Medicinrådet

Bilag til Medicinrådets vurdering af brexucabtagene autoleucel til behandling af R/R mantle celle lymfom efter minimum to tidligere behandlinger inkl. en BTKi

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. brexucabtagene autoleucel
2. Amgros' forhandlingsnotat vedr. brexucabtagene autoleucel
3. Ansøgning vedr. brexucabtagene autoleucel

December 15th, 2025

Gilead response to DMC regarding the assessment of Tecartus in R/R MCL

Patients' access to CAR T-cell therapies based on phase II data has been challenging in Denmark.

Denmark was among the last countries in Europe to see a positive recommendation for YESCARTA® in 3L+ DLBCL and approval awaited the 5-year data from the phase II ZUMA-1 trial.

Due to the historic challenges in convincing DMC of the long-term value of cell therapies, Gilead Sciences waited to submit Tecartus® (brexu-cel) until 5-year OS data was available and mature for both indications: R/R Mantle Cell Lymphoma (MCL) and R/R Acute Lymphoblastic Leukemia (ALL).Yet recently, Tecartus® for R/R ALL was rejected by DMC despite 5-year data from the phase II results from ZUMA-3 showing OS plateauing. DMC's focus on uncertainty in the 3-year data for the intermediary composite outcome RFS, rather than the 5-year OS data, led to the removal of a cure assumption. This led to a reduced perceived value of Tecartus® in R/R ALL as the health economic model underestimated the observed OS landmarks from ZUMA-3, and thereby the incremental QALYs.

Since its initial European marketing authorisation for R/R MCL 5 years ago, Tecartus® has been reimbursed across the vast majority of the European continent for both R/R MCL and R/R ALL based on the phase II data from ZUMA-2 and ZUMA-3, respectively.

We are pleased that the high severity and unmet need within R/R MCL is recognised by DMC

That being said, the main health economic analysis in the draft assessment report for Tecartus® in R/R MCL leads us to, once more, be concerned about DMC's approach to extrapolating OS and fear it will continue to substantially reduce the perceived value of Tecartus®, i.e. the incremental QALYs estimated.

It is concerning when DMC's main analysis produces 2.23 incremental QALYs; where other Nordic HTA bodies found 3.54 in Sweden, a range from 2.24 to 5.24 in Finland [1], and Norway skipped the formal health economics altogether and simplified their assessment.

However, in this specific assessment, DMC performed sensitivity analyses which shows the uncertainty on both sides of the point estimate in their main health economic analysis. Specifically, we agree that the sensitivity analysis put forward in the summary (OS extrapolation using LogNormal, in line with Gilead submission) is reasonable, especially given the properties of how the hazard is handled in the LogNormal distribution.

Further to this, it should be noted that outcomes can be even better than the scenario DMC presents with LogNormal extrapolation of trial OS data – data relevant to a Danish setting shows cell therapies provide better outcomes in a real world setting than observed in the trial.

As an example, in Figure 1, the left hand side of the figure shows the real-world survival outcomes of patients infused with YESCARTA® for the 3L+ DLBCL indication [2], and the right hand side shows the corresponding results from the pivotal trial for the indication: ZUMA-1 [3].

Figure 1: OS among YESCARTA® treated 3L+ DLBCL patients in Sweden [left], and in ZUMA-1 [right]

Jerkeman et al. note: "*...the Swedish data appear favorable in an international comparison. The encouraging results are most likely a result of national multidisciplinary conferences and cooperation between centers in addition to a strict selection of patients.*"

The evolution of patient selection criteria, practise (incl. options) for bridging, and adverse event management has evolved since the trial was conducted and all may play into expectations for real world outcomes.

Hospital contact for Tecartus® and Standard of Care (SoC)

DMC is assuming an additional 28 to 48 hospital contacts (out-patient visits, additional scans, or biopsies) during the first year after infusion (page 51 of 74). DMC may be correct that the number of outpatient contacts was underestimated for Tecartus® in the application but we argue this would also apply to the comparator, SoC.

According to Beck et al. 2025 [4] the annualized number of in-patient and out-patient days in 3L (DLBC)Lymphoma treated with SoC reach levels modelled for Tecartus® by DMC, see table below.

Table 1 standardized resource consumption for (DLBC)Lymphoma patients in the three lines of treatment

Assuming a similarity in hospital care for standard of care across 3L+ for MCL and DLBCL patients would entail a significant increase in cost in the comparator arm, not just to Tecartus® arm. Therefore, we request that DMC reconsider if the assumptions leading to a significant increase in hospital contacts for Tecartus® were balanced.

Sincerely,

Lars Oddershede

Gilead Sciences Denmark

References

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[3] S. S. Neelapu *et al.*, "Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma," *Blood*, vol. 141, no. 19, pp. 2307–2315, 2023, doi: 10.1182/blood.2022018893.

[4] C. G. Beck, M. L. Jørgensen, M. F. Kjaergaard, S. R. Bro, and T. Holm-Larsen, "Total costs of different lines of treatment in diffuse large B-cell lymphoma in Denmark – a real-world data analysis," *Eur. J. Heal. Econ.*, 2025, doi: https://doi.org/10.1007/s10198-025-01843-x.

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15.12.2025
MBA/MGK/CEH

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2026
Leverandør	Gilead/Kite Pharma
Lægemiddel	Tecartus (brexucabtagene autoleucel)
Ansøgt indikation	Voksne patienter med recidiveret eller refraktært mantle celle lymfom (MCL), efter de er blevet behandlet med to eller flere linjer systemisk behandling, inklusive en Bruton's Tyrosine Kinase-hæmmer.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel - ATMP

Prisinformation

Amgros har forhandlet følgende pris på Tecartus (brexucabtagene autoleucel):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP, (DKK)	Forhandlet rabat ift. AIP
Tecartus	én behandling – CAR-T	2.494.656,42	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.[redacted]

Aftaleforhold:

Amgros vil indgå en aftale med leverandøren, hvis Medicinrådet anbefaler Tecartus til den ansøgte indikation.

[redacted]

[redacted]

Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

[redacted]

Information fra forhandlingen

[redacted]

Konkurrencesituationen

På nuværende tidspunkt er der ikke konkurrence for behandling i tredjelinje af MCL. Breyanzi (lisocabtagene maraleucel) har for nyligt fået positive opinion på samme MCL-indikation som Tecartus. Leverandøren af Breyanzi har anmodet Medicinrådet om en vurdering af denne indikation.

[redacted]

For indikationen ALL blev Kymriah (tisagenlecleucel) anbefalet i 2019 af Medicinrådet til børn og unge ≤ 25 år. Indikationen for Tecartus omhandler behandling af ALL af patienter ≥ 26 år.

[redacted]

Tabel 2 viser lægemiddeludgifter for Tecartus og Kymriah, samt Yescarta og Breyanzi til sammenligning.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient for Tecartus, Kymriah, Yescarta og Breyanzi

Lægemiddel	Styrke (pakningsstørrelse)	Lægemiddeludgift pr. behandling (SAIP, DKK)
Tecartus	Én behandling – CAR-T	[redacted]

Kymriah*	Èn behandling – CAR-T	[redacted]
Yescarta	Én behandling – CAR-T	[redacted]
Breyanzi	Èn behandling – CAR-T	[redacted]

[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Anbefalet	Link til anbefaling

Opsummering

[redacted]

Application for the assessment of Tecartus® (brexucabtagene autoleucel, brexu-cel) for the treatment of adult patients with relapsed or refractory mantle cell lymphoma after two or more lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

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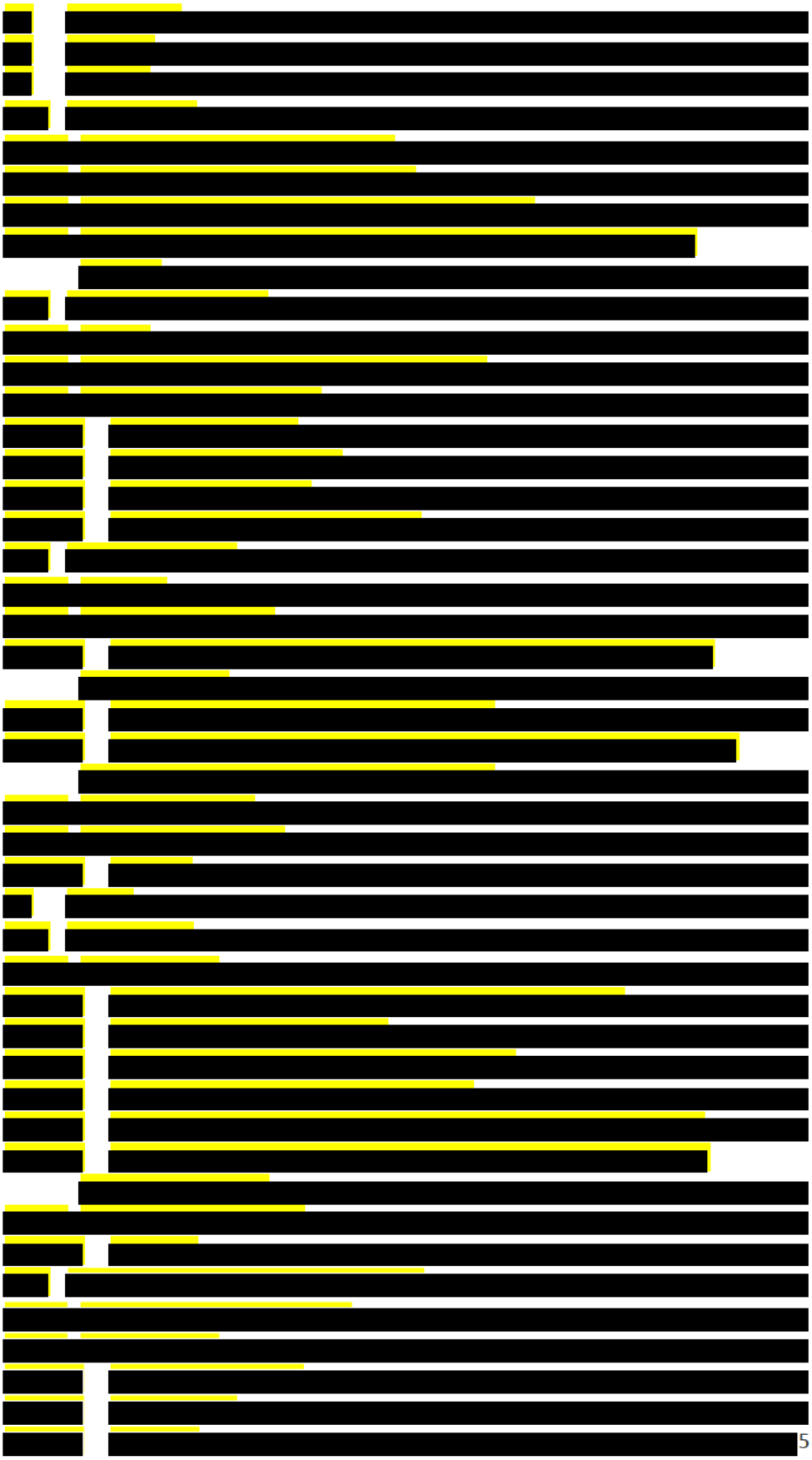
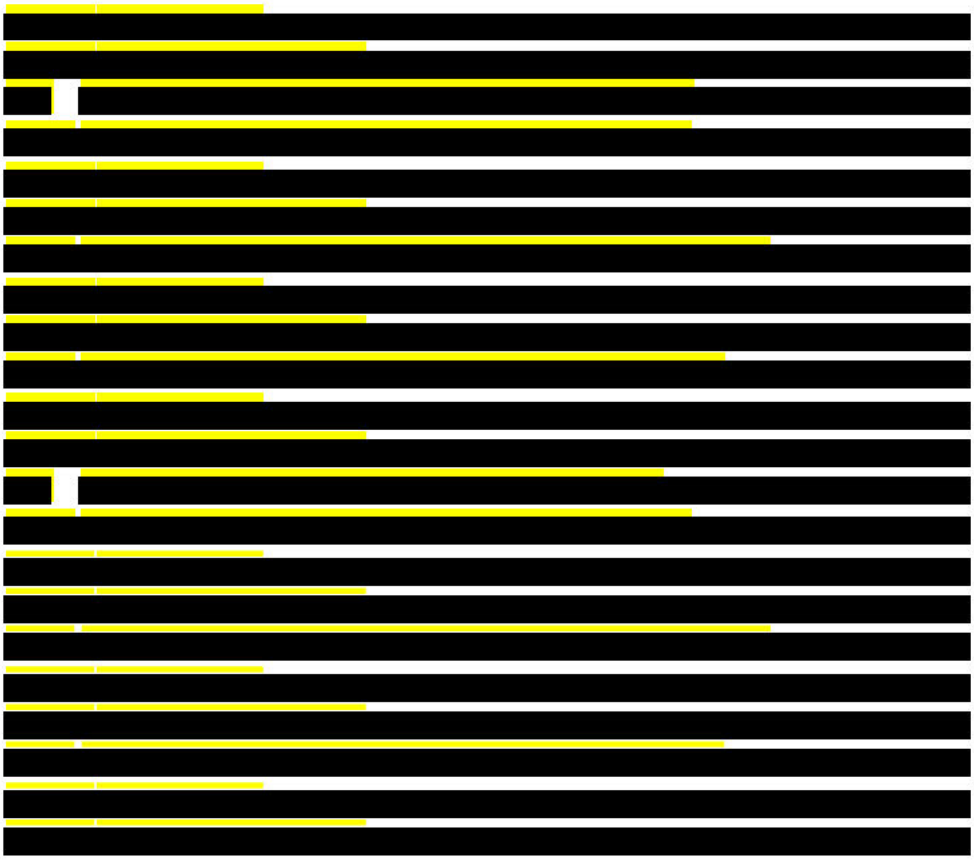
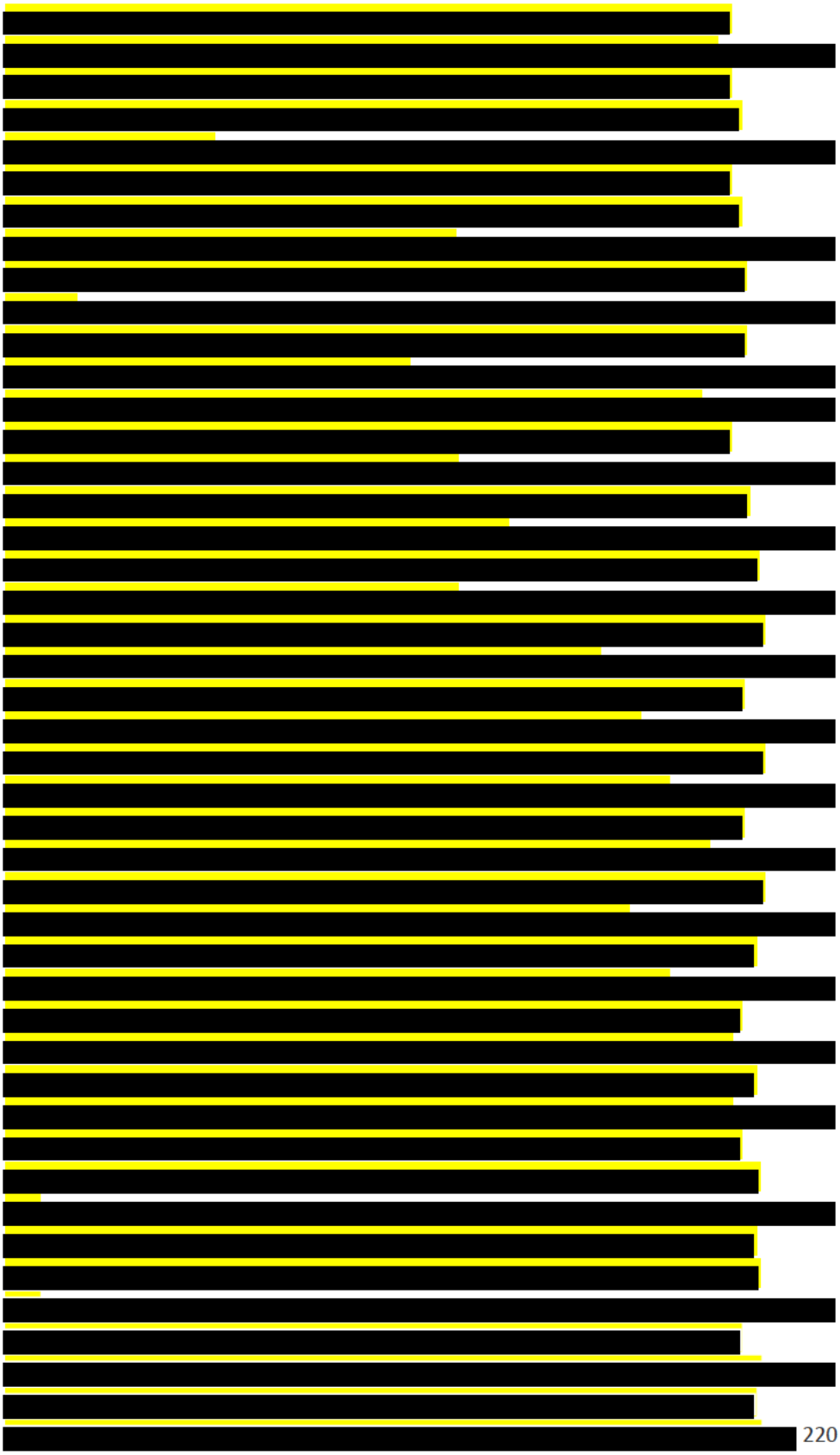




Tables and Figures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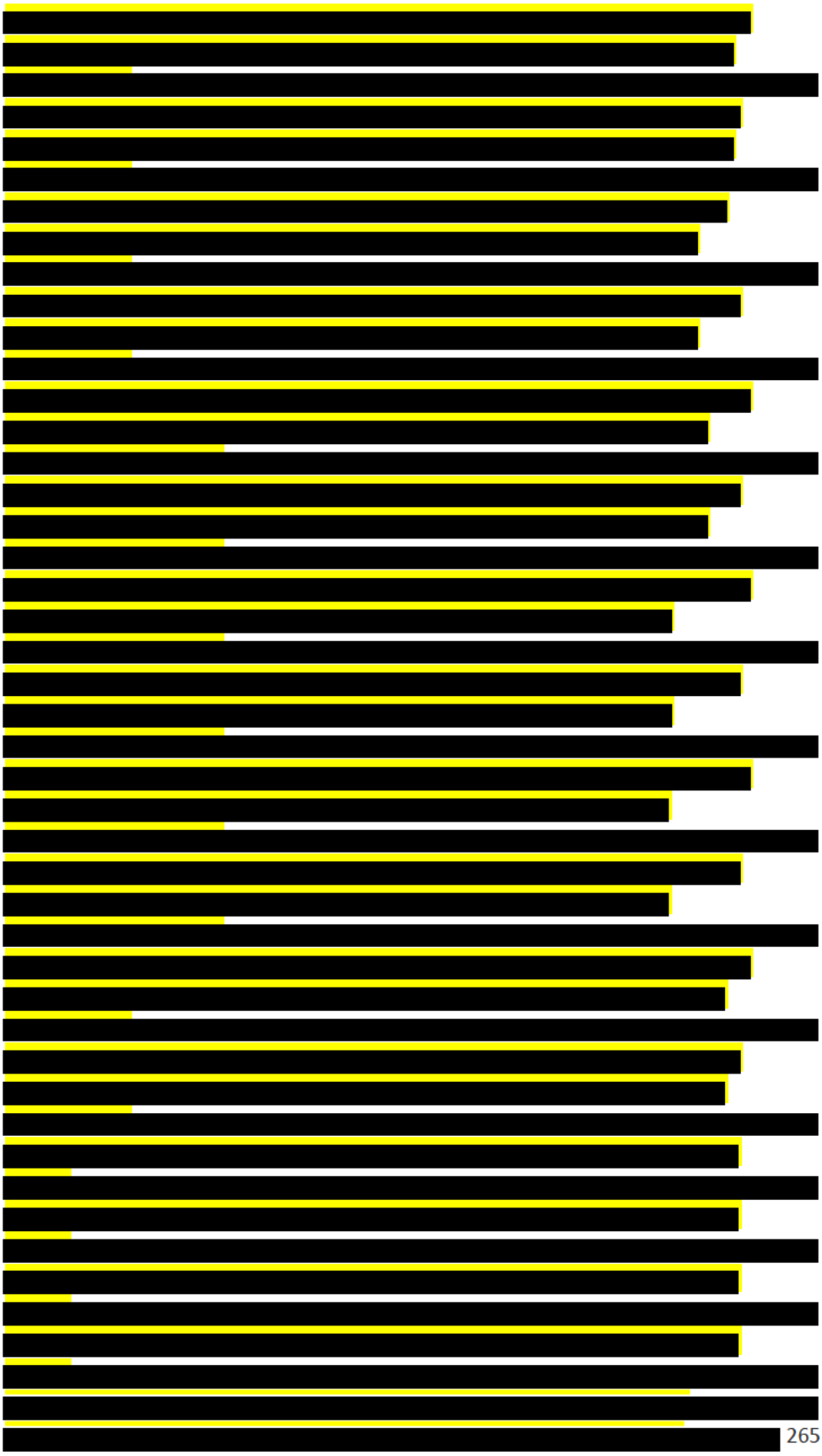
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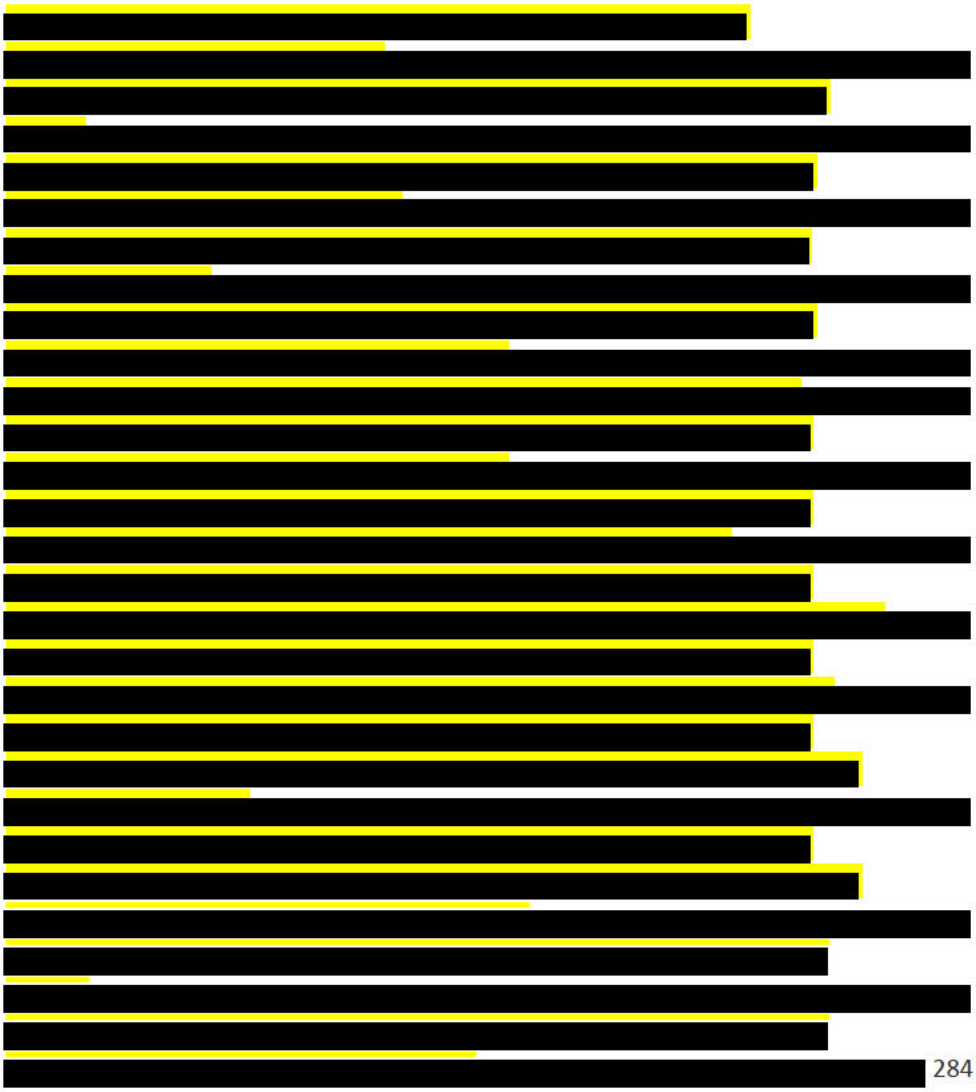

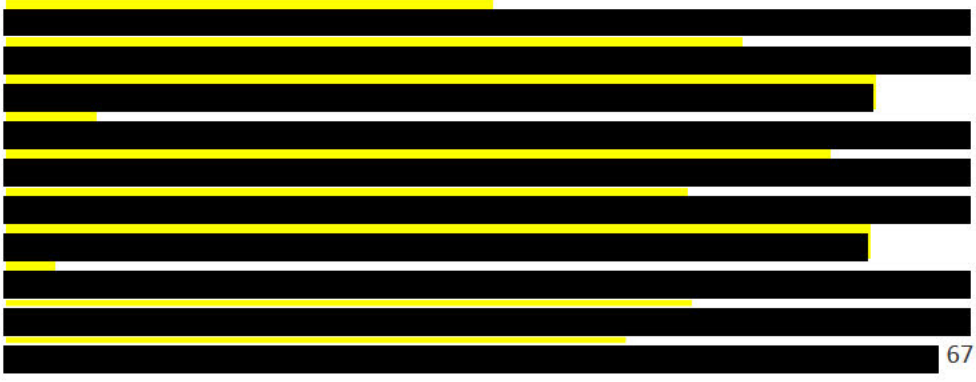

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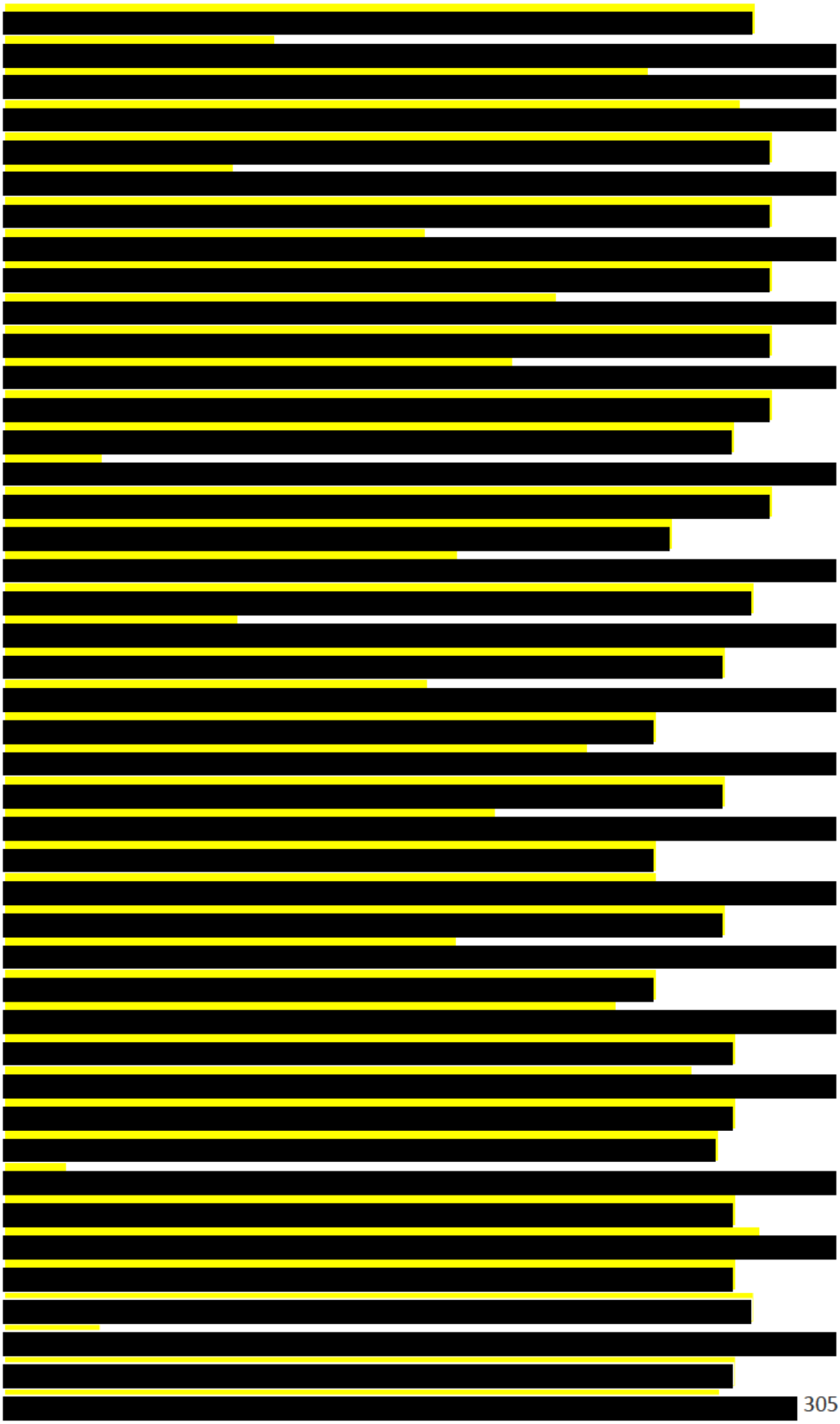
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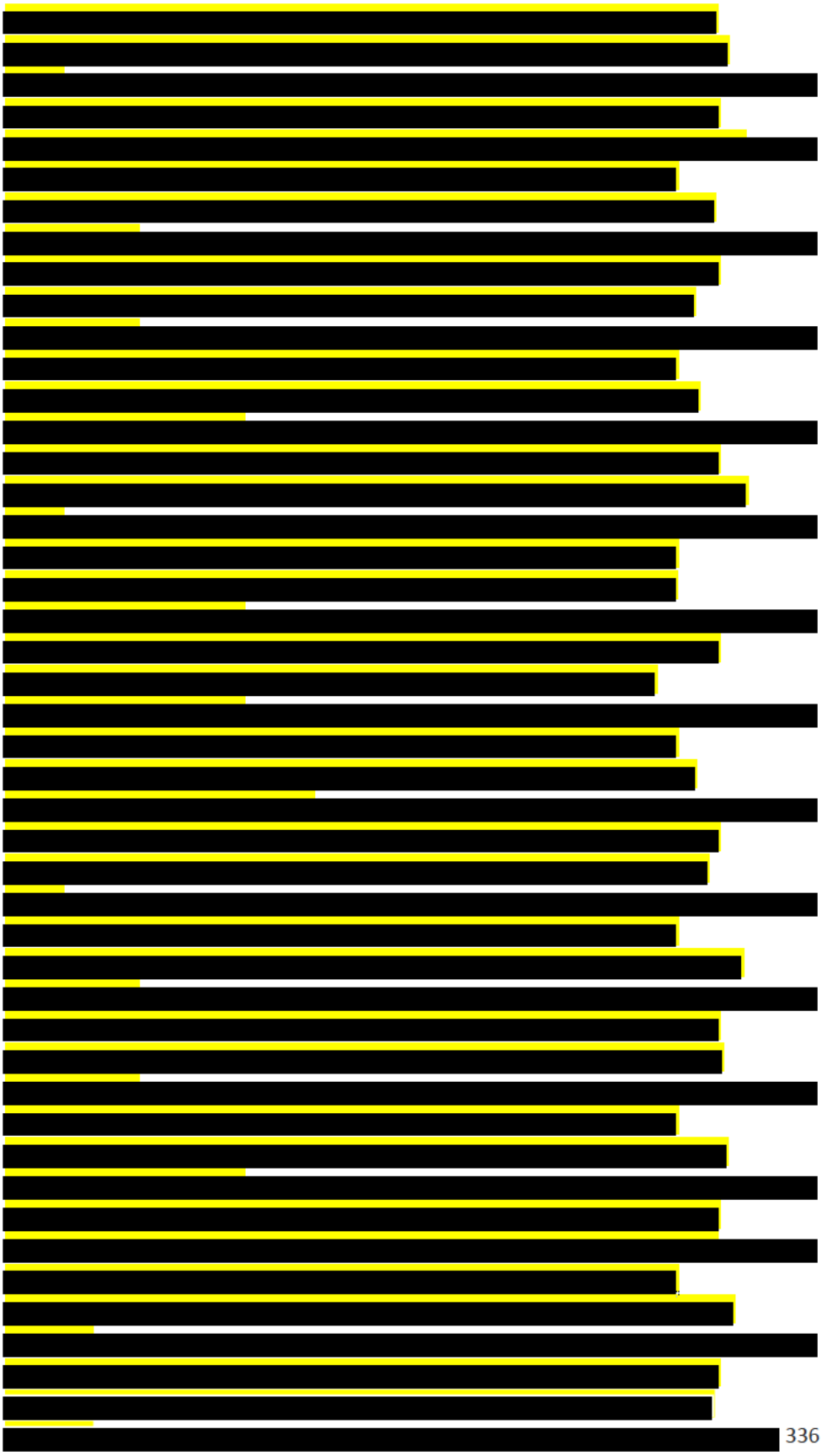
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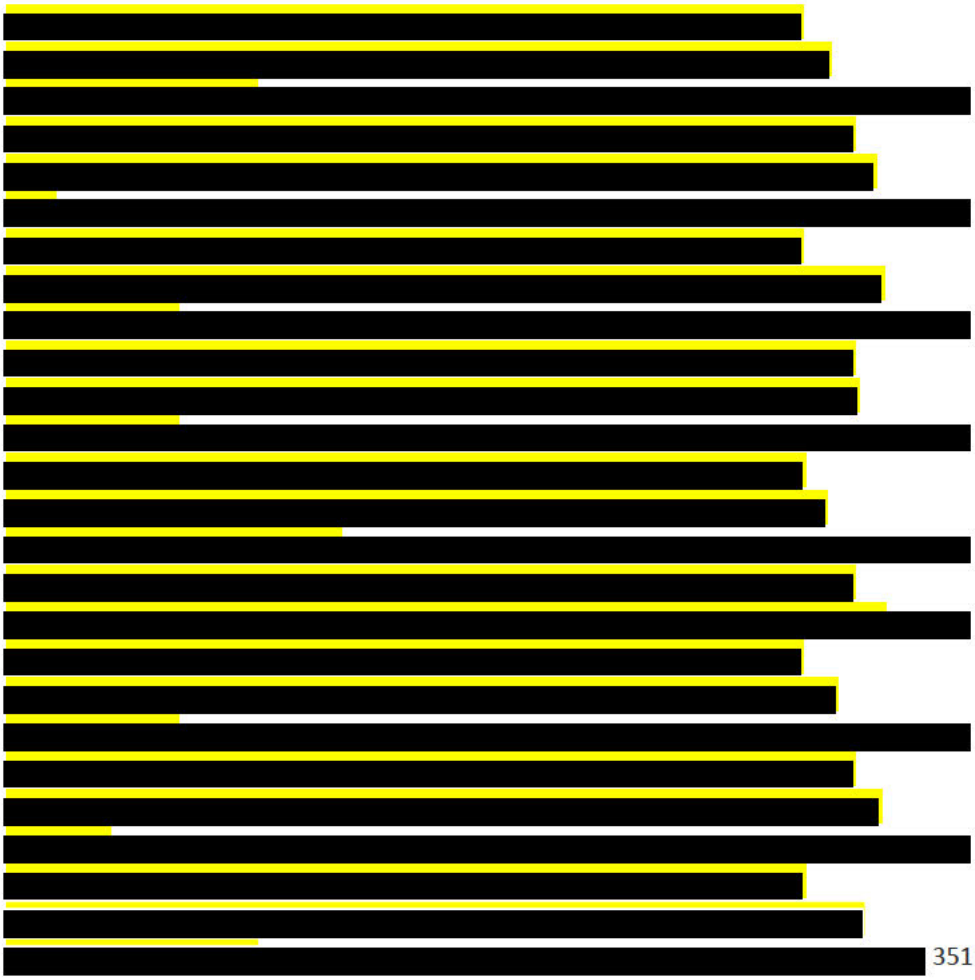


Abbreviations

Abbreviation	Explanation
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike Information Criterion
ALL	Acute lymphoblastic leukaemia
ATMP	Advanced therapy medicinal product
BIC	Bayesian Information Criterion
BTK	Bruton's tyrosine kinase

BTKi	Bruton's tyrosine kinase inhibitor
CAR	Chimeric antigen receptor
CCND1	Cyclin D1
CEAC	Cost-effectiveness acceptability curves
CNS	Central nervous system
CR	Complete response
CRS	Cytokine release syndrome
CI	Confidence interval
DCO	Data cut-off
df	Degrees of freedom
DKK	Danish krone
DLBCL	Diffuse large B-cell lymphoma
DLG	Danish lymphoma group
DMC	Danish Medicines Council
DMCG	Danish Multidisciplinary Cancer Group
DMP	Direktoratet For Medisinske Produkter
DOR	Duration of response
DSU	Decision support unit
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ESS	Effective sample size

FAS	Full analysis set
GvHD	Graft-versus-host disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUVs	Health state utility values
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
IWG	International Working Group
LYFO	Danish National Lymphoma Registry
MAH	Market Authorisation Holder
MCL	Mantle cell lymphoma
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
ORR	Overall response rate
OS	Overall survival

PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic sensitivity analysis
PSM	Partition survival model
QALYs	Quality-adjusted life years
RMSD	Root mean square deviation
RWE	Real-world evidence
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
TLS	Tumour lysis syndrome
VAS	Visual analogue scale

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Tecartus®
Generic name	Brexucabtagene autoleucel (brexu-cel)
Therapeutic indication as defined by EMA	Tecartus® is indicated for the treatment of adult patients with relapsed or refractory (R/R) mantle cell lymphoma (MCL) after two or more lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor (BTKi) [1].
Marketing authorization holder in Denmark	Kite Pharma EU B.V.
ATC code	L01XL06
Combination therapy and/or co-medication	Pre-treatment (lymphodepleting chemotherapy): A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously must be administered before infusing Tecartus®. The recommended days are on the 5th, 4th, and 3rd day before infusion of Tecartus® [1]. Pre-medication: Paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenously or orally (or equivalent medicinal products) approximately 1 hour before the infusion of Tecartus® [1]. At least one dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion [1].
Date of EC approval	14th of December 2020
Has the medicine received a conditional marketing authorization?	Yes, brexu-cel received a conditional marketing authorisation [2], when this indication (i.e. MCL) was approved. The specific obligations to complete post-authorisation measures for the conditional marketing authorisation, including due dates, are the following: • In order to confirm the long-term efficacy and safety of brexu-cel in adult patients with R/R MCL and the benefit/risk balance in the female, elderly and severely diseased patients, the market authorisation holder (MAH) shall submit the results of a prospective study investigating efficacy and safety based on data from the same registry used to characterise the long-term efficacy and safety of brexu-cel, according to an agreed protocol. Due date: 30 April 2027.

Overview of the medicine	
Accelerated assessment in the European Medicines Agency (EMA)	No. However, this medicine was granted entry to the EMA Priority Medicines (PRIME) scheme during its development. PRIME is a scheme launched by EMA to enhance support for developing medicines targeting unmet medical needs [3].
Orphan drug designation (include date)	Brexu-cel was designated as an orphan medicinal product (EU/3/20/2344) for MCL on 13 November 2019 and for acute lymphoblastic leukaemia (ALL) on 19 October 2020 [2].
Other therapeutic indications approved by EMA	In addition to the MCL indication, brexu-cel was approved with a condition for the treatment of adult patients 26 years of age or above with relapsed or refractory B-cell precursor ALL (R/R B-ALL) in 02/09/2022 (application number II/0008/G) [1]. In order to confirm the long-term efficacy and safety of brexu-cel in adult patients with R/R B-ALL, the MAH shall submit follow-up results of the ZUMA-3 clinical study (Part 1 and Part 2). Due date: 31 March 2025. In order to confirm the long-term efficacy and safety of brexu-cel in adult patients with R/R MCL, the MAH should conduct and submit the results of a prospective, observational study based on data from a registry, according to an agreed protocol. Due date: 31 December 2027.
Other indications that have been evaluated by the DMC (yes/no)	Yes, evaluation of brexu-cel for R/R B-ALL is ongoing at time of submission of this application.
Joint Nordic assessment (JNHB)	Brexu-cel in the adult R/R MCL indication is already recommended for use in Sweden [4], Norway [5], and Finland [6]. Hence, a joint Nordic assessment is not relevant. Moreover, the R/R B-ALL indication is also recommended in those three Nordic countries.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Infusion bag, cell dispersion for infusion brexucabtagene autoleucel (CAR+ viable T cells). Approximately 68 mL of cell dispersion [1].

2. Summary table

Summary	
Indication relevant for the assessment	Adult patients with R/R MCL after two or more lines of systemic therapy, including a BTKi [1].
Dosage regiment and administration	Brexu-cel is intended for autologous use only. Treatment consists of a single dose for intravenous infusion. One infusion bag containing a cell dispersion for infusion of a target dose of 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), with a maximum of 2×10^8 anti-CD19 CAR-positive viable T cells [1].
Choice of comparator	The relevant comparator is the current standard of care (SoC) in Denmark, which includes bendamustine ± rituximab, R-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone/prednisolone ± rituximab), R-BAC (rituximab, bendamustine and cytarabine) and lenalidomide ± rituximab.
Prognosis with current treatment (comparator)	Despite available therapies, almost all patients with MCL die from progressive disease, and prognosis worsens with each relapse and is particularly poor for patients with BTKi progression [7]. In a meta-analysis, median overall survival (OS) for post-BTKi standard therapies varied from 2.5 to 19.4 months, with a median OS of 9.1 months (95% CI: 7.3–11.3) [8]. In a SoC cohort (n = 59) closely matching ZUMA-2 patients (i.e., ECOG 0–1 and a minimum of 12-month potential follow-up from initiation of active therapy post-BTKi), the median OS was 15.7 months (95% CI: 10.0, 30.9).
Type of evidence for the clinical evaluation	ZUMA-2 (NCT02601313), a phase 2, single-arm, open-label, multicentre trial. The latest available data cut-off April 1st 2024, a median follow-up time of approximately five years [9]. SCHOLAR-2, a retrospective, observational, multicentre, international chart review of adults with R/R MCL, previously treated with a BTKi [10]. Individual patient data (IPD) from SCHOLAR-2 was used to form a SoC cohort (n = 59) closely matching ZUMA-2 patients (i.e., ECOG 0–1 and a minimum of 12-month potential follow-up from initiation of active therapy post-BTKi) [11]. A matched but naïve (unweighted) ITC between ZUMA-2 and SCHOLAR-2 forms the basis for the relative effectiveness of brexu-cel versus SoC [11].
Most important efficacy endpoints (Difference/gain compared to comparator)	The most important efficacy outcome is OS. In the unadjusted ITC for brexu-cel versus SoC, the median OS was 43.9 months (95% CI: 24.6, 59.2) for brexu-cel and 15.7 months (95% CI: 10.0, 30.9) for SoC. Hazard ratio (HR) = 0.46 (95% CI: 0.27, 0.78).

Summary	
Most important serious adverse events for the intervention and comparator	Serious AEs were reported in 49 patients (72%) treated with brexu-cel in ZUMA-2. Pyrexia occurred in 14 patients (21%), and pneumonia and encephalopathy in 12 (18%) patients each.
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L was used. Mean (SD) utility values were 0.930 (0.114) at baseline, 0.842 (0.227) at week 4, 0.871 (0.191) at month 3, and 0.904 (0.158) at month 6. Health economic model: health state-specific utilities for progression-free and progressed disease were used.
Type of economic analysis that is submitted	Type of analysis: Cost-utility analysis. Type of model: Partitioned survival model.
Data sources used to model the clinical effects	The estimation of OS was based on an unweighted ITC using IPD from ZUMA-2, the full analysis set (FAS)/intention-to-treat (ITT) population (n = 74), and the SCHOLAR-2 SoC cohort (n = 59). Data on progression-free survival (PFS) was not available in SCHOLAR-2, and a constant HR adjustment applied to the OS data was used for estimation of PFS, based on a meta-analysis on the available real-world (RW) OS data and PFS evidence from the literature [12].
Data sources used to model the health-related quality of life	Health state utility value (HSUV) for progression-free was calculated using EQ-5D-5L data from ZUMA-2 trial and Danish preference weights [13]. HSUV for progressed disease was calculated using proportions from the ibrutinib NICE submission in r/r MCL [14].
Life years gained	3.18 years
QALYs gained	2.67 QALY
Incremental costs	2,361,938DKK
ICER (DKK/QALY)	884,045DKK/QALY
Uncertainty associated with the ICER estimate	The cost of hospitalisation following conditioning chemotherapy had the major effects on the cost side. For QALYs, the largest uncertainty was the PFS utility values.
Number of eligible patients in Denmark	Incidence: 6 patients per year. Prevalence: N/A.
Budget impact (in year 5)	12,644,895 DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

MCL is a rare and aggressive type of B-cell non-Hodgkin's lymphoma (NHL), with US studies estimating an incidence of < 1 case per 100,000 persons and accounts for 2–10% of cases of newly diagnosed NHL [15-19]. Patients generally present with non-specific signs and symptoms common to B-cell malignancies, including lymphadenopathy (swelling of the lymph nodes), fever and night sweats, weight loss, fatigue, and discomfort related to splenomegaly (swelling of the spleen) [15, 17, 20]. MCL is more common in men (3:1), and the median age at diagnosis ranges from 60 to 70 years old [15, 17].

MCL is characterised by a chromosome translocation (11,14) that results in overexpression of the cyclin D1 (*CCND1*) gene and aberrant expression of cyclin D1 in lymphocytes [21, 22]. Cyclin D1 has a range of cellular effects, including cell cycle regulation, DNA repair and transcriptional regulation; overexpression of cyclin D1 leads to deregulation of these cellular events [23]. Cyclin D1 overexpression alone is insufficient for malignant transformation; secondary genetic alterations are also required to initiate and drive MCL pathogenesis. Due to this, MCL has a high number of recurrent genetic and molecular alterations upon diagnosis [23, 24].

MCL has a heterogeneous clinical course but is generally considered an aggressive NHL with poor prognosis, requiring prompt intervention. Most patients have advanced stage disease at diagnosis, where the lymphoma has spread beyond the diaphragm and potentially to extra-nodal sites, especially the gastrointestinal tract, spleen and bone marrow [15, 16].

Overall median survival in MCL is estimated to be between three and five years and is the lowest among the different NHL subtypes [17, 25].

Despite good potential for response to aggressive front-line therapy options, most patients with MCL eventually relapse; the same is true for first-relapse MCL patients receiving second-line treatment, including BTKi treatment, to which a subset of patients will inevitably develop resistance [7, 26].

With each subsequent treatment line, prognosis worsens, and the chance of complete remission and remission duration successively decreases from front- to later-line therapy [7]. Early relapse to front-line therapy (initiation of second-line treatment within 12 months) and progression of disease within 24 months of diagnosis (POD24) are

associated with a poor prognosis [16]. A retrospective chart review of patients with MCL treated in the post-rituximab era (2000–2014) showed complete remission rates decreasing from 81% with front-line therapy to 45% with second-line therapy and 30% with third-line therapy [7]. Associated PFS and OS rates similarly decreased from 87% and 95% at 1 year with front-line therapy to 56% and 83% with second-line therapy and to 35% and 72% with third-line therapy [7].

Outcomes after BTKi progression are particularly poor [26]. A recent Danish study by Trab et al. [27] reported inferior PFS and OS in a real-world setting in Denmark compared to clinical trials in patients with R/R MCL after receiving ibrutinib treatment.

Limited data from retrospective studies suggest that the R-BAC regimen (rituximab + bendamustine + cytosine arabinoside) results in favourable response rates in patients with R/R MCL after BTKi therapy but the optimal treatment strategy has not been established in prospective studies [16]. Moreover, despite favourable response rates, durable responses have not been observed with any regimen, with a median PFS of only 10.1 months (8.6 months with censoring for transplant) reported with the R-BAC regimen [28, 29]. In a retrospective, multicentre patient chart review that provides real-world data to reflect recent clinical practice across seven European countries (SCHOLAR-2), median OS from initiation of first post-BTKi therapy among 149 patients with R/R MCL was just 9.7 months (95% CI: 6.3, 12.7) [10]. A meta-analysis reported OS outcomes for post-BTKi standard therapies, where the median OS varied from 2.5 to 19.4 months with a lognormal distribution fitted estimated median OS of 9.1 months (95% CI: 7.3–11.3).

Compared to the expected population in Denmark for brexu-cel, as per ZUMA-2, the SCHOLAR-2 population at the start of post-BTKi treatments was slightly older, had more patients with Stage IV disease and included 34% patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2. When restricting to 59 patients with ECOG PS of 0/1 (to match ZUMA-2) and allowing for a minimum of 12-month follow-up, the median OS for SoC was 15.7 months (95% CI 10.0–30.9) with an estimated 12-month OS of 57.5% [10].

As with prognosis, symptoms tend to worsen with relapse and contribute to a worsening in the patient's quality of life. Common symptoms of fatigue, fever, night sweats and lymphadenopathy are among those reported to be of greatest impact to patients, and R/R MCL generally interferes with patients' quality of life and daily living, often preventing them from working, travelling, and performing simple day-to-day activities [30]. Such symptoms can often be exacerbated during treatment. Formal health-related quality of life (HRQoL) assessments clearly show an impaired HRQoL for patients with R/R MCL compared to the general population [31]. For those experiencing relapse and facing yet another line of treatment with limited expectation of benefit, there can be further emotional and physical trauma [32], not only for themselves but also for their families and close network.

3.2 Patient population

The population relevant to this application is adult patients with R/R MCL who have received two or more lines of systemic therapy, including a BTKi, reflecting the population of the ZUMA-2 pivotal trial [33]. Epidemiology data for patients with MCL in Denmark is collected in the Danish National Lymphoma Registry (LYFO), which the Danish Lymphoma Group (DLG) maintains. The 2023 annual report [34] stated that 90 patients were diagnosed with MCL in Denmark during 2023. Incidence for MCL for the years 2020 to 2023 are presented in Table 1.

Table 1 Incidence and prevalence in the past 5 years – MCL

Year	2020	2021	2022	2023	2024
Incidence in Denmark	84	86	92	90	N/A
Prevalence in Denmark	N/A	N/A	N/A	N/A	N/A

Source: Malignt Lymfom og CLL - National årsrapport 2023 [34]

A Danish population-based study of patients with R/R MCL treated with ibrutinib between 2010 and 2022 [27] reported that a total of 137 patients with R/R MCL received ibrutinib in second or later lines (63% and 37%, respectively) during the study period. To get an estimated annual number of patients over the study period (2010–2022, 13 years) or since KRIS approved the use of ibrutinib (2014–2022, 9 years), the 137 patients were divided either by 13 years or 9 years. This corresponds to 11–15 patients treated per year. In the same study [27], it was reported that 74% of the included patients experienced relapse or progression, corresponding to 8–11 patients per year. Finally, in the Norwegian assessment of brexu-cel [5], NOMA assumed that 50% of the described patients are eligible for brexu-cel. Thus, the estimated eligible patients for brexu-cel in Denmark is 4–6 per year (Table 2).

These estimates align well with the other Nordic countries. TLV in Sweden estimated [redacted] patients within label annually [4], Council for Choices in Health Care (COHERE, PALKO) in Finland estimated 2-4 patients annually [6], and NOMA in Norway estimated 7-10 eligible patients per year for brexu-cel [5]. Brexu-cel is available in these countries and since the launch in 2022 until March 18th, 2025, a total of [redacted] patients were treated for R/R MCL, supporting the estimation of 4-6 patients/year in Denmark.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	4-6	4-6	4-6	4-6	4-6

Source: Values estimated from Trab et al. 2024 [27], and brexu-cel assessment by NOMA [5].

3.3 Current treatment options

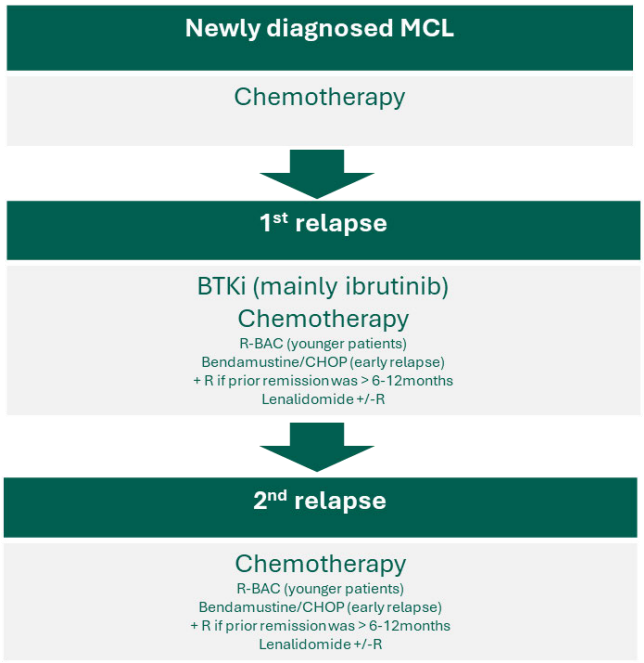
In Denmark, there are no DMC treatment guidelines for MCL. The DLG treatment guidelines for MCL were published by the Danish multidisciplinary cancer group (DMCG) [35] were approved in 2022, and a revision was planned for 2024. However, the DMCG has not yet published the revision. There is no single preferred treatment for this patient population, and treatment depends on the effect of the previously given therapy.

The current treatment in R/R MCL after two or more lines of systemic therapy, including a BTKi, consists of several treatments which will be referred to as SoC. Not all of the treatments mentioned in the DLG guideline "treatment of relapse" [35] will be relevant to patients who received two or more lines of systemic therapy, including a BTKi:

- Bendamustine ± rituximab or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab for early relapse (<12-24 months), the addition of rituximab is considered for patients with remission on prior immunochemotherapy (>6-12 months).
- R-BAC (rituximab, bendamustine, cytarabine/cytosine arabinoside [AraC]), for younger patients not previously treated with cytarabine.
- Ibrutinib or lenalidomide ± rituximab or temsirolimus. As ibrutinib is a BTKi, it is not relevant in the targeted population. Temsirolimus is less effective than ibrutinib, has limited use, and is not available in the Danish public price list.
- Radioimmunotherapy with ibritumomab tiuxetan is considered for older patients with co-morbidity who cannot tolerate dose intensification with chemotherapy.
- Allogeneic stem cell transplantation (allo-SCT), is a potentially curative treatment option for patients ≤70 years in 2nd/3rd CR/PR and may be considered in eligible patients, not relevant as expected after CAR-T.
- Brexu-cel, the intervention, is mentioned as an option in relapsed disease.

The current treatment algorithm and treatment options in Danish clinical practice is illustrated in Figure 1.

Figure 1 Current treatment algorithm and treatment options in Danish clinical practice



Abbreviations: B, bendamustine; BAC, bendamustine, cytosine arabinoside; BTKi, Bruton's tyrosine kinase inhibitor; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R, rituximab; R/R MCL, relapsed or refractory mantle cell lymphoma.

3.4 The intervention

Tecartus® (brexucabtagene autoleucel [brexu-cel]) is a genetically modified autologous cell-based product containing T cells transduced *ex vivo* using a retroviral vector expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single-chain variable fragment (scFv) linked to the CD28 co-stimulatory domain and the CD3-zeta signalling domain.

Brexu-cel binds to CD19-expressing cancer cells and normal B cells. Following anti-CD19 CAR-T-cell engagement with CD19-expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to the killing of CD19-expressing cells.

Brexu-cel is approved for the MCL indications with a condition by the EMA since December 2020. In addition to the MCL indication, brexu-cel was approved with a condition for the treatment of adult patients 26 years of age or above with relapsed or refractory B-cell precursor ALL in 02/09/2022 (application number II/0008/G) [1].

Brexu-cel is recommended in Sweden, Norway and Finland for both indications.

Table 3 provides an overview of brexu-cel.

Table 3 Overview of the intervention

Overview of intervention	
Indication relevant for the assessment	Adult patients relapsed or refractory MCL after two or more lines of systemic therapy including a BTKi.
ATMP	Brexu-cel was classified as a gene therapy medicinal product [36].
Method of administration	Intravenous infusion
Dosing	Brexu-cel is intended for autologous use only. Treatment consists of a single dose containing a dispersion for infusion of CAR-positive viable T cells in one bag. The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag. Brexu-cel is recommended to be infused 3 to 14 days after completion of the lymphodepleting chemotherapy for MCL patients. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.
Dosing in the health economic model (including relative dose intensity)	As above. Relative dose intensity does not apply to the intervention.
Should the medicine be administered with other medicines?	Pre-treatment (lymphodepleting chemotherapy): A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously must be administered prior to infusing brexu-cel. The recommended days are on the 5th, 4th, and 3rd day before infusion of brexu-cel. Pre-medication: Paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenously or orally (or equivalent medicinal products) approximately 1 hour before the infusion of brexu-cel. At least one dose of tocilizumab for use in the event of CRS and emergency equipment must be available prior to infusion.
Treatment duration / criteria for end of treatment	Brexu-cel is given in a single dose.

Overview of intervention	
Necessary monitoring, both during administration and during the treatment period	Monitoring prior to infusion: • In some patient groups at risk, a delay of the brexu-cel infusion may be indicated. Monitoring after infusion: • Patients must be monitored daily for the first 7 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians can consider hospitalisation for the first 7 days or at the first signs or symptoms of CRS and/or neurologic events. • After the first 7 days following the infusion, the patient is to be monitored at the physician's discretion. • Patients must remain within proximity of a qualified treatment centre for at least 4 weeks following infusion.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A.
Package size(s)	Brexu-cel is packaged in one infusion bag containing a cell dispersion for infusion of a target dose of 2×10^6 CAR-positive viable T cells per kg of body weight (range: 1×10^6–2×10^6 cells/kg), with a maximum of 2×10^8 anti-CD19 CAR-positive viable T cells.

Abbreviations: ATMP, Advanced Therapy Medicinal Product; BTKi, Bruton's tyrosine kinase; CRS, cytokine release syndrome; MCL, mantle cell lymphoma; N/A, not applicable.

3.4.1 Description of ATMP

Brexu-cel was designated as an advanced therapy medicinal product (ATMP) on July 1st, 2019 and it was classified as a gene therapy medicinal product [36]. Brexu-cel contains genetically modified autologous T cells - a patient's own T cells are harvested and genetically modified *ex vivo* by retroviral transduction using an MSCV based gamma-retroviral vector to express a CAR comprising an anti-CD19 single-chain variable fragment (scFv) linked to CD28 co-stimulatory domains and CD3-zeta signalling domain.

The transduced anti-CD19 CAR-T cells are expanded *ex vivo* and infused back into the patient, where they can recognise and eliminate CD19 expressing target cells [36]. As described in the summary of product characteristics of brexu-cel [1], special precautions for use include traceability, the fact that it is intended solely for autologous use, warnings and precautions of lymphodepleting chemotherapy must be considered, considering delaying the treatment if the patient has unresolved serious adverse

reactions, active uncontrolled infection or inflammatory disease or active graft-versus-host disease (GvHD).

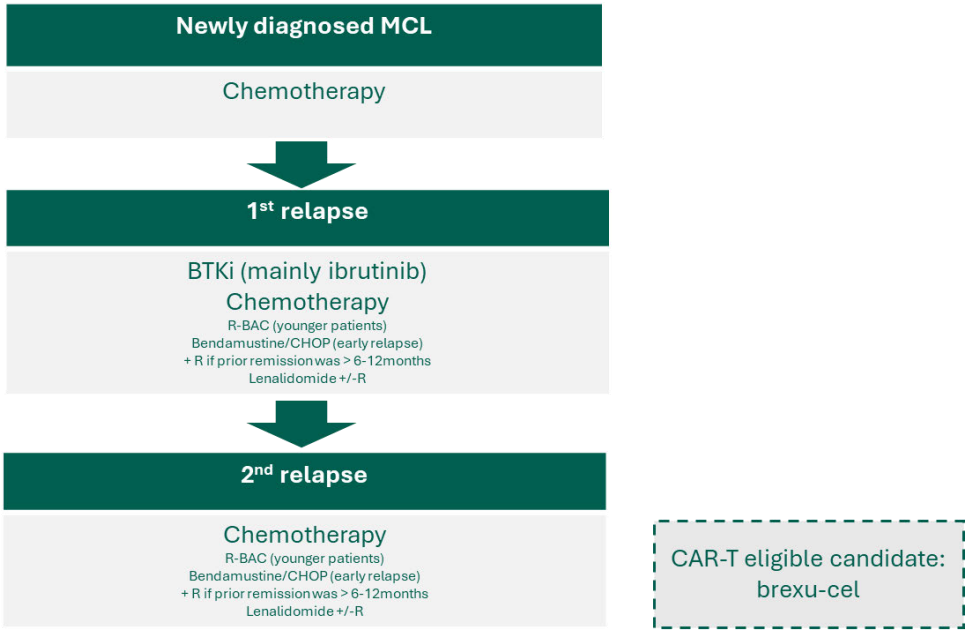
Screening for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) must be performed before collection of cells for manufacturing brexu-cel. In addition, patients need to be monitored daily for the first seven days following infusion. Nearly all patients experienced some degree of CRS. Severe neurologic adverse reactions (also known as immune effector cell-associated neurotoxicity syndrome [ICANS]) have been observed in patients treated with brexu-cel. Other special warnings include infections and febrile neutropenia, viral reactivation (e.g. HBV), prolonged cytopenias, hypogammaglobulinemia, development of secondary malignancies, and tumour lysis syndrome (TLS).

Brexu-cel is not recommended for patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD, who have relapsed with CD19-negative disease after prior anti-CD19 therapy or who have CD19-negative disease or an unconfirmed CD19 status.

3.4.2 The intervention in relation to Danish clinical practice

As described in section 3.3, there is no single established SoC regimen for the treatment of R/R MCL, rather a mix of chemotherapeutic options [16, 35, 37]. Considering the available evidence, brexu-cel may be positioned as an alternative to the current SoC in Denmark, as depicted in Figure 2.

Figure 2 Brexu-cel potential place in therapy, in relation to the Danish clinical practice



Abbreviations: B, bendamustine; BAC, bendamustine, cytosine arabinoside; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; R, rituximab; R/R MCL, relapsed or refractory mantle cell lymphoma.

3.5 Choice of comparator(s)

In this application, the comparator to brexu-cel is the current SoC chemotherapeutic options used in Denmark. The effectiveness was estimated through real-world evidence (RWE) regimens in SCHOLAR-2, assumed to reflect the effectiveness of regimens used in Danish clinical practice [35]: (R)-CHOP, R-BAC, (R)-lenalidomide, and (R)-bendamustine (see also section 3.3).

An overview of the comparator regimens is presented in the tables below.

Table 4 Overview of the comparator – (R)-CHOP

Overview of comparator	
Generic name	CHOP/R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ± rituximab.
ATC code	Rituximab: L01FA01 Cyclophosphamide: L01AA01 Doxorubicin: L01DB01 Vincristine: L01CA02 Prednisone: H02AB07
Mechanism of action	Rituximab binds to CD20 on pre-B and mature B lymphocytes resulting in B-cell lysis and apoptosis. Cyclophosphamide is an alkylating agent with antineoplastic and immunosuppressive activities. Doxorubicin is a cytotoxic anthracycline antibiotic, and its exact mechanism of the antitumour activity is unknown. It is generally believed that inhibition of DNA, RNA and protein synthesis is responsible for most cytotoxic effects. This is probably the result of the intercalation of the anthracycline between adjacent base pairs of the DNA double helix, thus preventing their unwinding for replication. Vincristine binds to the microtubular proteins of the mitotic spindle, leading to crystallisation of the microtubule and mitotic arrest or cell death. Prednisone is an exogenous glucocorticoid which is able to affect proliferation and apoptosis in malignant cells. In addition, it is effective when combined with chemotherapy but is also effective for treatment of cancer-related nausea, pain, anorexia, and other chemotherapy-related side effects.
Method of administration	Intravenous infusion: rituximab, cyclophosphamide, doxorubicin, vincristine. Oral administration: prednisone.

Overview of comparator	
Dosing	Rituximab: 375 mg/m^2 on day 1 of a 21-day cycle. Cyclophosphamide: 750 mg/m^2 on day 1 of a 21-day cycle. Doxorubicin: 50 mg/m^2 on day 1 of a 21-day cycle. Vincristine: 1.4 mg/m^2 (cap dose at 2 mg), on day 1 of a 21-day cycle. Prednisone: Tablet 50 mg/m^2 corresponding to 100 mg (two 50 mg tablets) once a day on days 1 to 5 of a 21-day cycle.
Dosing in the health economic model (including relative dose intensity)	The health economic model assumes dosing as above, with repeated 21-day cycles of CHOP, until disease progression or a maximum of six cycles. 100% RDI was assumed for all separate medicines in the R-CHOP regimen.
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or maximum six treatment cycles.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A

Overview of comparator	
Package size(s)	Rituximab: • 100 mg x 2 vials IV • 500 mg x 1 vial IV Cyclophosphamide: • 200 mg x 1 vial IV • 500 mg x 1 vial IV • 1000 mg x 1 vial IV Doxorubicin: • 2 mg/ml x 5 ml 1 vial IV • 2 mg/ml x 10 ml 1 vial IV • 2 mg/ml x 25 ml 1 vial IV • 2 mg/ml x 100 ml vial IV • 50mg x 1 vial IV Vincristine: • 1mg/ml x 1ml 1 vial IV • 1mg/ml x 2ml 1 vial IV Prednisone: • 5 mg x 100 tablets PO • 25 mg x 100 tablets PO

Source for dosing: Vårdprogramsgruppen för Lymfom (Kunskapsbanken), Rituximab-CHOP 21, 2023 [38], and Cancer Institute NSW, Mantle cell lymphoma R-CHOP, 2023 [39].

Table 5 Overview of the comparator – R-BAC

Overview of comparator	
Generic name	R-BAC (rituximab, bendamustine, cytosine arabinoside).
ATC code	Rituximab: L01FA01 Bendamustine: L01AA09 Cytosine arabinoside/cytarabine: L01BC01
Mechanism of action	Rituximab binds to CD20 on pre-B and mature B lymphocytes, resulting in B-cell lysis and apoptosis.

	Bendamustine causes intra- and inter-strand crosslinks between DNA bases, resulting in cell death. Cytarabine acts through direct DNA damage and incorporation into DNA.
Method of administration	Rituximab, bendamustine, and cytarabine are administered as intravenous infusions.
Dosing	Rituximab: 375 mg/m^2 on day 1 of a 28-day cycle. Bendamustine: 70 mg/m^2 on days 1 and 2 of a 28-day cycle. Cytarabine: 800 mg/m^2 on days 1 to 3 of a 28-day cycle.
Dosing in the health economic model (including relative dose intensity)	The health economic model assumes dosing as above of repeated 28-day cycles until progression or a maximum of six cycles. 100% RDI was also assumed for all separate treatments in the R-BAC regimen.
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until progression or a maximum of six cycles.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	Rituximab: • 100 mg x 2 vials IV • 500 mg x 1 vial IV Bendamustine: • 2.5 mg/ml 5 x 10 ml vials IV • 2.5 mg/ml 5 x 25 mg vials IV • 2.5 mg/ml 5 x 40 ml vials IV • 2.5 mg/ml 5 x 100 mg vials IV • 25 mg/ml 5 x 4ml vials IV Cytarabine: • 20mg/ml x 5ml vial IV • 20 mg/ml 5 x 5 ml vials IV • 100 mg/ml x 10 ml vials IV

- 100 mg/ml x 20 ml vials IV

Source for dosing: Vårdprogramsgruppen för Lymfom (Kunskapsbanken), R-BAC, 2023 [40].

Table 6 Overview of the comparator – Lenalidomide

Overview of comparator	
Generic name	Lenalidomide ± rituximab.
ATC code	Lenalidomide: L04AX04 Rituximab: L01FA01
Mechanism of action	Lenalidomide inhibits proliferation and enhances apoptosis of specific haematopoietic tumour cells, enhances T cell- and Natural Killer (NK) cell-mediated immunity and increases the number of NK and T cells. The mechanism of action of lenalidomide also includes anti-angiogenic and proerythropoietic properties. Rituximab binds to CD20 on pre-B and mature B lymphocytes, resulting in B-cell lysis and apoptosis.
Method of administration	Oral administration: lenalidomide. Intravenous infusion: rituximab.
Dosing	Lenalidomide monotherapy: 25 mg once daily on days 1 to 21 of repeated 28-day cycles. In combination with rituximab: 20 mg once daily on days 1 to 21 of repeated 28-day cycles and rituximab 375 mg/m^2, on day 1 of a 28-day cycle.
Dosing in the health economic model (including relative dose intensity)	The health economic model assumes a dose of 20 mg of lenalidomide (as per the R-lenalidomide dosing schedule), once daily on days 1 to 21, and rituximab 375 mg/m^2 on day 1 of repeated 28-day cycles until progression or a maximum of six cycles. 100% RDI was also assumed.
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until progression or a maximum six cycles.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A

Overview of comparator	
Package size(s)	Lenalidomide: • 2.5 mg x 21 tablets PO • 5 mg x 21 tablets PO • 7.5 mg x 21 tablets PO • 10 mg x 21 tablets PO • 15 mg x 21 tablets PO • 20 mg x 21 tablets PO • 25 mg x 21 tablets PO Rituximab: • 100 mg x 2 vials IV • 500 mg x 1 vial IV

Source for dosing: Lenalidomide SmPC, EMA, 2024 [41] and Vårdprogramsgruppen för Lymfom (Kunskapsbanken), Rituximab-Lenalidomide, 2024 [42].

Table 7 Overview of the comparator – Bendamustine

Overview of comparator	
Generic name	Bendamustine ± rituximab
ATC code	Bendamustine: L01AA09 Rituximab: L01FA01
Mechanism of action	Bendamustine causes intra- and inter-strand crosslinks between DNA bases, resulting in cell death. Rituximab binds to CD20 on pre-B and mature B lymphocytes resulting in B-cell lysis and apoptosis.
Method of administration	Intravenous infusion
Dosing	Bendamustine monotherapy: 100mg/m^2 once daily on day 1-2 of repeated 28-day cycles. In combination with rituximab: 90mg/m^2 one daily on days 1-2 of repeated 28-day cycles and rituximab 375 mg/m^2 on day 1 of a 28-day cycle.
Dosing in the health economic model (including relative dose intensity)	The health economic model assumes a dose of bendamustine of 70 mg/m^2 once daily (as per R-BAC dosing) on days 1-2 and rituximab 375 mg/m^2 on day 1 of repeated 28-day cycles until progression or a maximum of six cycles. 100% RDI was also assumed.

Overview of comparator	
Should the medicine be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until progression or a maximum of six cycles.
Need for diagnostics or other tests (i.e. companion diagnostics)	N/A
Package size(s)	Bendamustine: • 2.5 mg/ml 5 x 10 ml vials IV • 2.5 mg/ml 5 x 25 mg vials IV • 2.5 mg/ml 5 x 40 ml vials IV • 2.5 mg/ml 5 x 100 mg vials IV • 25 mg/ml 5 x 4ml vials IV Rituximab: • 100 mg x 2 vials IV • 500 mg x 1 vial IV

Source for dosing: Vårdprogramsgruppen för Lymfom (Kunskapsbanken), Bendamustin 100, 2021 [43], and Vårdprogramsgruppen för Lymfom (Kunskapsbanken), Rituximab-Bendamustin 90, 2023 [44].

3.6 Cost-effectiveness of the comparator(s)

In this application, the comparator to brexu-cel is the current SoC in Denmark, which is defined in the current Danish DLG treatment guidelines as (R)-CHOP, R-BAC, (R)-lenalidomide, and (R)-bendamustine treatment. The acquisition costs of comparators are low as they have generic competition. Thus, considering the comparator as an established standard Danish treatment practice and its low cost, no supplementary analysis for the comparator is presented in this application.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The most critical outcome for evaluating the relative efficacy of brexu-cel compared to SoC is OS (Table 8). OS with 60-month follow-up for brexu-cel was based on the ZUMA-2 trial for the ITT population (n = 74), which consisted of all enrolled patients (regardless of infusion with brexu-cel) [9] was compared to OS data from a subset of 59 patients from

SCHOLAR-2, which provided an external SoC control arm, selected to resemble the population of ZUMA-2 (referred to as the SoC cohort) [11].

PFS data for brexu-cel with a 60-month follow-up were available from ZUMA-2; however, not from SCHOLAR-2. Therefore, to obtain estimates of PFS for SoC, an HR adjustment was applied to the OS survival estimate for SCHOLAR-2; the method is explained in more detail in section 8.1.1.2.

At the most recent data cut-off (DCO), April 1 2024, a median follow-up of 67.8 months (range, 58.2-88.6) was reported in the mITT (n = 68) cohort and is therefore referred to throughout the document as the 60-month DCO. The 60-month DCO was made when all patients who remained in the study had completed 60-months of follow-up. The median follow-up for ITT is the same as for mITT because the index date for the actual and potential follow-up time calculation in subject disposition is based on infusion only.

The primary endpoint of ZUMA-2 was overall response rate (ORR) (complete response [CR] + partial response [PR]). SCHOLAR-2 does not have comparative data for ORR. ORR results from ZUMA-2 are presented in the clinical assessment with a three-year (35.6-month) follow-up.

Table 8 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
OS Included in ZUMA-2 and SCHOLAR-2	67.8 months ZUMA-2 27.3 months SCHOLAR-2	OS in ZUMA-2, in the FAS, was defined as the time from enrolment to the date of death from any cause. OS in SCHOLAR-2 was defined as the time from initiation of first post-BTKi therapy, for each patient, until death from any cause.	
PFS Included in ZUMA-2	67.8 months	In the FAS, PFS was defined as the time from the enrolment date to the date of disease progression or death from any cause.	PFS was evaluated using both central assessment and investigator assessment.
ORR Included in ZUMA-2	35.6 months	ORR was defined as the incidence of CR or PR, as assessed centrally, according to the Lugano Classification.	ORR (incidence of CR or PR) was evaluated using central assessment per the Lugano Classification.

* Time point for data collection used in analysis (follow-up time for time-to-event measures)

Validity of outcomes

OS and PFS are acceptable endpoints in the EMA guidelines on evaluating anticancer medicinal products [45]. According to these guidelines, convincingly demonstrated

favourable effects on survival are suggested to be the most persuasive outcome of a clinical trial. Prolonged PFS is considered to benefit the patient.

The Danish treatment guidelines for R/R MCL [35] aim to support decisions for treatment for this patient population. OS and PFS are used as indicators for efficacy in the guidelines [35] and were included as efficacy endpoints in the ZUMA-2 trial [33].

In addition, OS and PFS have been used in previous DMC submissions for other lymphomas. In a recent assessment of a treatment for diffuse large B-cell lymphoma (DLBCL), the DMC considered PFS and OS to be adequate for the evaluation of efficacy [46].

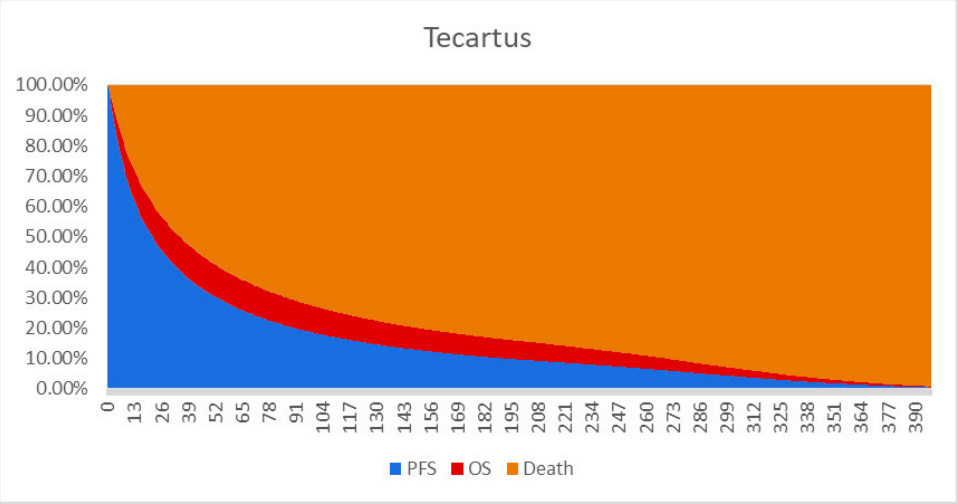
4. Health economic analysis

A previously developed health economic model in Microsoft® Excel was adapted to the Danish setting. The treatment effect of Tecartus® (brexu-cel) and SoC were based on ZUMA-2 (60 months DCO 1 April 2024) and SCHOLAR-2, respectively.

4.1 Model structure

The model is a standard three-state partition survival model (PSM): progression-free (pre-progression), progressed (post-progression), and death (Figure 3). The PSM framework depends on survival models to estimate the proportion of patients in each health state over time. Health state membership is derived directly from the OS and PFS survival models, with PFS restricted to ensure it does not exceed OS. Progression is calculated as the difference between OS and PFS. The pre-progression health state includes responders and patients who remain with stable disease.

Figure 3 PSM health state distribution over time



Abbreviations: OS: Overall survival; PFS: Progress-free survival. PSM: partition survival model

4.2 Model features

The main model features are presented in Table 9.

Table 9 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with R/R MCL who have received two or more lines of systemic therapy, including a BTK inhibitor.	This aligns with the ZUMA-2 trial population and the expected eligible population in Denmark.
Perspective	Limited societal perspective	According to DMC guidelines [47].
Time horizon	Lifetime (40 years)	To capture all health benefits and costs in line with DMC guidelines[47]. Based on the mean age at diagnosis in the ZUMA-2 population (63.7 years).
Cycle length	1 month	To achieve a balance between the sensitivity and complexity of the model, along with consistency with previous analyses in MCL assessed by NICE [14].
Half-cycle correction	Yes	According to DMC guidelines [47].
Discount rate	3.5%	Based on the established practice from the DMC [47], a discount rate of 3.5% for all years is applied.
Intervention	Tecartus® (brexu-cel)	
Comparator(s)	SoC based on SCHOLAR-2	SCHOLAR-2 is assumed to be a good representation of the effect of SoC in the eligible Danish population.
Outcomes	OS and PFS LY QALY's Cost	According to DMC guidelines [47].

Model features	Description	Justification
	ICER	

5. Overview of literature

5.1 Literature used for the clinical assessment

The efficacy and safety of brexu-cel are based on ZUMA-2 [33], a single-arm, phase 2, multicentre, international, pivotal trial in patients with R/R MCL who had received up to five prior therapies, including a BTKi [33]. The primary endpoint was ORR, and secondary endpoints included duration of response (DOR), PFS, OS, HRQoL, and safety [33]. The efficacy of the FAS, i.e. ITT population (n = 74), all enrolled patients (regardless of infusion of brexu-cel) with 60 months follow-up (DCO April 1, 2024) is presented here [9].

A comparison for efficacy was performed using SCHOLAR-2 to provide an external SoC control arm to ZUMA-2 with a subset selected to the criteria of ZUMA-2, with an ECOG performance status score of 0 or 1 who had received subsequent active therapy after a BTKi therapy and had a minimum of a 12-month potential follow-up from initiating a post-BTKi therapy (this SCHOLAR-2 subset is referred to as the SoC cohort, described further in section 6.1.1)[11]. SCHOLAR-2 was a retrospective, observational, multicentre patient chart review that provided RWE to reflect current clinical practice across seven European countries, including Denmark (n = 5), thus providing the efficacy for SoC. The study's primary objective was to estimate real-world OS among subjects with R/R MCL after treatment with a BTKi. The secondary objective was to describe treatment patterns and healthcare resource utilisation in this patient population. The SoC cohort from SCHOLAR-2 (n = 59) (DCO: December 18, 2020) is presented in Hess et al 2022 [10].

SCHOLAR-2 was selected as a targeted retrospective comparator study in preference to relying on a systematic literature review (SLR). SCHOLAR-2 was specifically designed to align with the ZUMA-2 trial's patient population, eligibility criteria, endpoints, and follow-up period, ensuring direct relevance to the decision problem. SCHOLAR-2 reflects contemporaneous SoC practice in Denmark and avoids the heterogeneity and outdated regimens commonly identified through an SLR. The harmonised data collection and alignment with the trial protocol minimise the need for extensive post-hoc adjustments, thereby reducing uncertainty in the comparative analysis and strengthening the validity of the cost-effectiveness results.

Table 10 below includes an overview of the literature used in the clinical assessment.

Table 10 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Wang, M., et al. (2023), Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. J Clin Oncol, 2023. 41(3): p. 555-567 [48]	ZUMA-2	NCT02601313	Start: July 24th, 2019 Completion: Latest available cut-off as below Data cut-off: July 24th, 2022	Efficacy (ORR) and safety for brexu-cel
Wang, M., et al. (2024), Five-Year Outcomes of Patients (Pts) with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Treated with Brexucabtagene Autoleucel (Brexu-cel) in ZUMA-2 Cohorts 1 and 2. Blood, 2024. 144: p. 4388. [9]	ZUMA-2	NCT02601313	Start: July 24th, 2019 Completion: Latest available cut-off as below Data cut-off: April 1st, 2024	Efficacy (OS and PFS) for brexu-cel
Data on file. ZUMA-2 (2025). Statistical output tables and figures (Five-year follow-up)	ZUMA-2	NCT02601313	Start: July 24th, 2019 Completion: cut-off as below Data cut-off: April 1st, 2024	Efficacy (OS and PFS) for brexu-cel
Hess, G., et al. (2022). Real-world experience among patients with relapsed/refractory mantle cell lymphoma after Bruton tyrosine	SCHOLAR-2	N/A	Data was collected between February 2020 until December 2020. However, this was a retrospective chart review study	Efficacy (OS) of the comparator SoC

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
kinase inhibitor failure in Europe: The SCHOLAR-2 retrospective chart review study. Br J Haematol, 2023;(202) 749–759 [10]			in which data was obtained according to the dates below. Start: Data collected from July 2012. Completion/data-cut: July 2018	
Hess, G., et al. (2022). A comparison of overall survival with brexucabtagene autoleucel (Brexu-cel) CAR-T-cell therapy (ZUMA-2) and SoC (SCHOLAR-2) in patients with Relapsed/Refractory mantle cell lymphoma (R/R MCL) previously treated with a covalent bruton tyrosine kinase inhibitor (BTKi). Blood, 2022. 140 (Supplement 1): p. 10296-10299 [11]	ZUMA-2/SCHOLAR-2	NCT02601313/N/A	Start ZUMA-2: July 24th, 2019 Start SCHOLAR-2: July 2012 Data-cut ZUMA-2: July 24th, 2021 Data- cut SCHOLAR-2: July 2018	Descriptive for ITC of brexu-cel versus SoC

5.2 Literature used for the assessment of HRQoL

The literature for utilities used in this assessment is presented in Table 11. Health state utilities for pre- and post-progression were derived from the ZUMA-2 clinical trial. EQ-5D-5L score with Danish value set applied from the 24-month follow-up, DCO 24 July 2021 [13].

Table 11 Relevant literature included for (documentation of) HRQoL (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Data on file. ZUMA-2 (2025) 24-month follow-up DCO: 24 July 2021	Pre-progression for brexu-cel: 0.882 [0.858- 0.908] Post-progression for brexu-cel: 0.805	Section 10

5.3 Literature used for inputs for the health economic model

The clinical inputs (OS and PFS) for the intervention brexu-cel, used in the health economic model, were retrieved from the pivotal ZUMA-2 trial and was extrapolated over time (see further section 8). For the comparator, SCHOLAR-2 was used as the efficacy source for estimating OS for the comparator and was extrapolated over time.

In the health economic model, unit cost inputs were based on publicly available literature and databases relevant to Denmark with 2025 prices, including medicinpriser.dk, the DMC "Valuation of unit costs" (Værdisætning af Enhedsomkostninger), and DRGs from Sundhedsdatastyrelsen.

Table 12 gives an overview of the literature used in the health economic model.

Table 12 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Wang, M., et al. (2024), Five-Year Outcomes of Patients (Pts) with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Treated with Brexucabtagene Autoleucel (Brexu-cel) in	OS and PFS	Pivotal registrational trial for the intervention	Section 8

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
ZUMA-2 Cohorts 1 and 2. Blood, 2024. 144: p. 4388. [9]			
Hess, G., et al. (2022). A comparison of overall survival with brexucabtagene autoleucel (Brexu-cel) CAR-T-cell therapy (ZUMA-2) and SoC (SCHOLAR-2) in patients with Relapsed/Refractory mantle cell lymphoma (R/R MCL) previously treated with a covalent bruton tyrosine kinase inhibitor (BTKi). Blood, 2022. 140 (Supplement 1): p. 10296-10299 [11]	OS	Best matching population for current SoC	Section 8
medicinpriser.dk	Drug acquisition cost	Targeted search, sources recommended in DMC guidelines and Værdisætning af Enhedsomkostninger 2025	Section 11
laeger.dk / rigshospitalet.dk	Costs of laboratory test		
sundhedsdatastyrelsen.dk	Resource use and AE cost using DRGs		
medicinraadet.dk	Administration cost and patient costs		

6. Efficacy

6.1 Efficacy of brexu-cel compared to SoC for adult MCL (R/R MCL) patients who have received two or more lines of systemic therapy, including a Bruton's tyrosine kinase (BTK) inhibitor

6.1.1 Relevant studies

The evidence base for the comparative efficacy consists of IPD from ZUMA-2 (n = 74 for the ITT set that included all enrolled/leukapheresed patients), and the SCHOLAR-2 (n = 59 SoC cohort).

An overview of both studies is presented in Table 13 and in Appendix A.

ZUMA-2 is a single-arm, phase 2, multicentre study evaluating the efficacy of brexu-cel in subjects with R/R MCL who have been treated with up to five prior regimens, including a BTKi. ZUMA-2 included patients aged ≥18 years with an ECOG performance status of 0 or 1 and histologically confirmed MCL that was R/R to up to five prior regimens, including an anthracycline-containing or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and BTKi therapy. The primary endpoint was ORR, and secondary endpoints included DOR, PFS, OS, HRQoL and safety. The latest available DCO was April 1, 2024, with a median follow-up of 67.8 months (range, 58.2-88.6) in the mITT (n = 68) cohort [9].

SCHOLAR-2 is a European retrospective, observational, multicentre, international chart review of patients aged at least 18 years with R/R MCL, previously treated with a BTKi, and with disease progression while on BTKi therapy or who discontinued due to intolerance. The primary outcome was OS. Secondary outcomes included patient demographics, disease characteristics, and treatment patterns [10].

Patients were eligible if they received BTKi therapy and active treatment after progressing or being intolerant to BTKi therapy. Patients were further selected for study inclusion based on the following eligibility criteria (to match baseline and disease characteristics of patients enrolled in the ZUMA-2 trial):

1. Aged ≥18 years;
2. Relapsed or refractory MCL;
3. Received BTKi therapy between July 2012 and July 2018 AND:
    a. While on BTKi therapy had progressive disease, OR
    b. Discontinued BTKi therapy due to intolerance;
4. Received active therapy post-BTKi for R/R MCL;
5. No current or history of central nervous system lymphoma;
6. Have not received CAR therapy or other genetically modified T-cell therapy.

The population of interest included the subset of patients who met the eligibility criteria of ZUMA-2 but received treatment in real-world clinical practice outside of a clinical trial. This requirement precluded the inclusion of SCHOLAR-2 patients who did not conform to the ZUMA-2 trial inclusion criteria, most notably patients with ECOG performance status >1, having prior allogenic SCT, having more than five prior lines of therapy, or not having previously received anthracycline or bendamustine-containing chemotherapy, and anti-CD20 monoclonal antibody therapy ([redacted]

From the 153 patients identified, only those with a reported ECOG performance status of 0 or 1 within six months prior to the initiation of post-BTKi therapy were considered in the analysis (n = 72). Exclusion based on the other criteria listed above was not planned, as it was anticipated that this would drastically reduce the sample size of the SCHOLAR-2 cohort. Three different approaches to construct a cohort from the SCHOLAR-2 dataset were planned in order to define a priori the index date for each cohort to minimize selection bias: 1) initial-line cohort, 2) period-prevalence cohort, and 3) bootstrap cohorts.

The initial-line cohort consisted of 59 patients with ECOG performance status of 0 or 1, and who had started a post-BTKi therapy no later than June 30th, 2019, to allow for a minimum of 12-month follow-up and is the cohort used in this application ([redacted]

The index date for this cohort was defined as the start of the initial line of therapy in the post-BTKi setting.

[redacted]

Source: Data on file [49]

Table 13 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ZUMA-2, NCT02601313 [9]	Single-arm, multicentre, phase 2 study	60 months Start: October 24th, 2016 Data-cut: April 1st, 2024.	≥18 years old, histologically confirmed MCL that is R/R and received 1-5 prior regimens. Must have received prior: anthracycline-containing or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody, and BTKi therapy (ibrutinib or acalabrutinib).	-On day 0, KTE-X19 was administered through IV at the target dose of 2*106 CAR-T cells/kg.-Conditioning chemotherapy (fludarabine 30 mg/m^2 per day; cyclophosphamide 500mg/m^2 once per day) was administered through IV on days -5, -4, and -3.-Before conditioning therapy and after leukapheresis, patients with high disease burden could receive bridging therapy with steroids or BTKi at investigators' discretion.	N/A	The median follow-up time for primary and all secondary outcomes was approximately 4 years (median follow-up for cohorts 1 and 2 were 67.8 months (58.2-88.6) and 72.3 months (70.1-74.3), respectively) **Primary:** ORR, defined as the incidence of CR or PR per central assessment as assessed by IRRC (Lugano classification). **Secondary:** DOR was defined as the time from the first objective response (CR or PR) to disease progression or death. PFS, was defined as the time from the brexu-cel infusion to the date of disease progression or death from any cause. OS was defined as the time from the KTE-X19 infusion date to the date of death from any cause. BOR (best objective response), Safety: AEs, any AE with an onset on or after the date of the initial KTE-X19 infusion, were monitored.

SCHOLAR- 2 [10]	Retrospective, observational, multicentre, international chart review study	Median follow-up of 27. years. Start: July 2012 End: July 2018.	≥18 years old with R/R MCL. Previous treatment with a BTKi, with disease progression while on BTKi therapy or who discontinued due to intolerance.	Subsequent systemic anticancer treatments administered to patients with R/R MCL following BTKi therapy failure. The most common treatments were lenalidomide-containing therapies (17.4%) and bendamustine+ rituximab (16.85%).	**Primary outcome:** The relevant outcome for this application is OS, defined as the time from the initiation of the first BTKi therapy to the date of death from any cause. The medium follow-up of the study was 27.6 months

Abbreviations: R/R MCL; refractory/relapsed multiple myeloma, ORR; objective response rate, DOR; duration of response, PFS; progression-free survival, OS; overall survival, BOR; best objective response, AE; adverse event, MRD; minimal residual disease.

6.1.2 Comparability of studies

The ZUMA-2 clinical trial was selected as it is the pivotal trial for the intervention brexucel in the relevant patients. For the comparator, the RWE study SCHOLAR-2 was used. The SCHOLAR-2 study was considered the most relevant source for the comparator, the population was selected to be aligned with that of ZUMA-2 in terms of inclusion criteria, including the median number of prior lines of therapy and prior BTKi ORR of 38% and 40.4%, respectively (see Table 14 for further baseline comparisons). In addition, the treatments in SCHOLAR-2 include the current SoC in Denmark: (R)-CHOP, R-BAC, (R)lenalidomide, and (R)-bendamustine, as described in chapter 3.5.

6.1.2.1 Comparability of patients across studies

As previously described, the ZUMA-2 ITT population (n = 74) was compared to the SoC cohort (n = 59) from SCHOLAR-2 (see Table 14). Both included patients aged ≥18 years with R/R MCL who had prior BTKi therapy. The comparison was based on a subset of the SCHOLAR-2 post-BTKi treated population that better resembled the patient population of ZUMA-2. This subset consisted of patients with an ECOG performance status score of 0 or 1 who had received subsequent active therapy after a BTKi therapy and had a minimum of a 12-month potential follow-up from initiating a post-BTKi therapy. The median follow-up for the SoC cohort was 27.6 months [10].

At baseline, patients in ZUMA-2 and SCHOLAR-2 were similar in median age, lines of prior therapy, and ORR to prior BTKi therapy. Differences were observed in median duration of prior BTKi therapy (7 vs 11 months), percentage of males, the percentage of patients with ECOG 0/1, and prior autologous SCT (42% vs 36%).

Table 14 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	ZUMA-2 Brexu-cel (N = 74)	SCHOLAR-2 SoC cohort (N = 59)
Mean age	63.7 (SD: 7.9)	64.3
Sex Male, n (%)	62 (83.8)	73%
Centre		
US	91.9%	0%
Netherlands	2.7%	0%
France	4.1%	30.5%
UK	0%	23.7%
Sweden	0%	5.1%
Denmark	0%	3.9%

Germany	1.4%	18.6%
Italy	0%	18.6%
Number of prior therapies (range)	3 (1-5)	3 (1-6)
1 prior, n (%)	1 (1.4)	3 (5.1)
2 prior, n (%)	13 (17.6)	21 (35.6)
3 prior, n (%)	34 (45.9)	19 (32.2)
4 prior, n (%)	15 (20.3)	6 (10.2)
5 prior, n (%)	11 (14.9)	9 (15.3)
6+ prior, n (%)	0 (0.0)	1 (1.7)
Prior ASCT, n (%)	31 (41.9)	21 (35.6)
Mean duration of prior BTKi therapy mo. (SD)	11.1 (11.0)	11.9 (12.2)
Prior BTKi ORR, n (%)	28 (37.8)	23/57 (40.4)
ECOG performance status		
0, n (%)	47 (63.5)	27 (45.8)
1, n (%)	27 (36.5)	32 (54.2)
Disease staging		
I, n (%)	0 (0.0)	5/49 (10.2)
II, n (%)	2 (2.7)	4/49 (8.2)
III, n (%)	8 (10.8)	9/49 (18.4)
IV, n (%)	64 (86.5)	31/49 (63.3)
Splenic involvement, n (%)	26 (35.1)	16/42 (38.1)
Extranodal disease, n (%)	43 (58.1)	11/42 (26.2)
Bone marrow involvement, n (%)	42/73 (57.5)	20/42 (47.6)
Type of prior BTKi therapy, Any BTKi, n (%)	74 (100)	59 (100)
Ibrutinib, n (%)	62 (83.8)	56 (94.9)

Presence of B symptoms, n (%)	6 (8.1)	6/42 (14.3)
Bulky disease, n (%)	10 (13.5)	5/42 (11.9)

Abbreviations: BTKi, Bruton tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; mo., months; ORR, objective response rate; OS, overall survival; SCT, stem cell transplantation; SD, standard

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The baseline characteristics selected for the health economic model were based on the ZUMA-2 ITT/FAS population that closely matched the real-world SCHOLAR-2 SoC cohort. The Danish LYFO yearly register reports do not contain granular data on patient characteristics for MCL and could not be used to validate the baseline characteristics as representative of the Danish population.

Table 15 Characteristics in the relevant Danish population and the health economic model

	Value in Danish population (assumed SCHOLAR-2)	Value used in health economic model (ZUMA-2)
Mean age (years)	64.3	63.7
Sex (male)	73%	84%
Mean bodyweight	81.8 kg (assumed as per ZUMA-2)	81.8 kg
Mean body surface area	1.98 m^2 (assumed as per ZUMA-2)	1.98 m^2

6.1.4 Efficacy – results per ZUMA-2

The efficacy results for the ITT/FAS population (n = 74) of the ZUMA-2 trial, for brexu-cel, are presented below using the latest DCO with 60 months follow-up (April 1, 2024) for OS and PFS [50].

The latest available DCO available for ORR was July 2022 (35.6 months follow-up). In the FAS population, the ORR was 84% (95% CI, 73.4 to 91.3), with a 62% CR rate (95% CI, 50.1 to 73.2) and a 22% PR rate (95% CI, 12.9 to 32.7).

At the time of the latest DCO for OS, April 1, 2024 (60 months), the maximum follow-up was [redacted] (Table 16 and [redacted] The Kaplan-Meier (KM) estimated median OS at this data-cut was [redacted] [9]. In the FAS population (n = 74), [redacted] of subjects had died, while [redacted] were alive at the time of analysis. [redacted] withdrew from the study, and [redacted] was lost to follow-up. The 12-month OS rate was [redacted] the 24-month OS rate was [redacted]

[redacted] the 60-month OS rate was [redacted] and the 87-month OS rate was [redacted]

Table 16 Overall Survival - FAS (n = 74) ZUMA-2

Outcome	Brexu-cel (N = 74)
OS[a]	
Number of subjects, n	[redacted]
Died, n (%)	[redacted]
Alive, n (%)	[redacted]
Withdrawal by subject, n (%)	[redacted]
Lost to follow up, n (%)	[redacted]
KM median (95% CI) OS time (months)	[redacted]
Min, max OS time (months)	[redacted]
Survival rate (% [95% CI]) by KM estimate	
12 months	[redacted]
24 months	[redacted]
36 months	[redacted]
42 months	[redacted]
60 months	[redacted]
72 months	[redacted]
87 months	[redacted]

[redacted]

Source: Data on file, DCO: 01APR2024

The maximum follow-up time for PFS was [redacted] at the DCO, April 1, 2024 (60 months) (Table 17 and [redacted] The KM estimated median PFS at this DCO was [redacted] 9]. In the FAS population [redacted] of subjects [redacted] experienced a PFS event, defined as either disease progression [redacted]) or death [redacted] The remaining [redacted] were censored at the time of data cut.

Censoring was applied for subjects without a documented event at the time of analysis. Reasons for censoring included, ongoing response [redacted] underwent SCT [redacted] initiated a non-SCT anticancer therapy [redacted], withdrew consent or were lost to follow-up [redacted] and no disease assessment [redacted] The PFS rate [redacted] for 12 months [redacted] at 24 months, [redacted] 3) at 60 months, and [redacted] at 84 months.

Table 17 Progression-free survival using investigator read per Cheson 2007 – FAS (n = 74)

Outcome	Brexu-cel (N = 74)
PFS[a]	[redacted]
Number of subjects, n	
Event, n (%)	
Censored, n (%)	
KM median (95% CI) PFS time (months)	

Min, max PFS time (months)	[redacted]
Type of event	
Disease progression, n (%)	[redacted]
Death, n (%)	
Censoring reason	
Response ongoing, n (%)	
SCT, n (%)	
Started non-SCT new anticancer therapy, n (%)	
Withdrawal of consent or lost to follow-up, n (%)	
No disease assessment, n (%)	
PFS rate (% [95% CI]) by KM estimation	
12 months	
24 months	
36 months	
42 months	
60 months	
72 months	
84 months	

[redacted]

Source: Data on file DCO: 01APR2024

[redacted]

6.1.5 Efficacy – results per SCHOLAR-2

The efficacy for the primary endpoint from the SCHOLAR-2 study was based on SoC cohort of 59 patients with a median follow-up of 27.6 months following initiation of therapy. The median OS was 15.7 months (95% CI 10.0-30.9), and the estimated 12-month OS of 57.5% [redacted] [10].

[redacted]

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

See section 6 for definitions of outcomes.

7.1.2 Method of synthesis

This assessment's comparative analysis of efficacy was based on a naïve (unweighted) comparison of OS in ZUMA-2 to OS in SCHOLAR-2. The ITT population in ZUMA-2 (60-month DCO) was compared to the matched SoC cohort (n = 59) of SCHOLAR-2. The unweighted approach was chosen as it is transparent and does not further reduce the sample size of the SoC cohort. Further, weighting the SCHOLAR-2 data to ZUMA-2 reduced the OS for patients treated with SoC, increasing the effect size for brexu-cel compared to SoC. The unweighted comparison is thus conservative compared to a weighted comparison.

A previous ITC between ZUMA-2 and SCHOLAR-2 has been published by Hess et al. 2024 [51] using a prior data-cut for ZUMA-2, with a median follow-up of 35.8 and 27.6 months for ZUMA-2 and SCHOLAR-2, respectively. Three different weighting methods were used to adjust for differences in baseline characteristics between ZUMA-2 and SCHOLAR-2. The ITC reported similar results for the naïve comparison and weighting methods. The authors conclude that '[t]*he consistency of the results across the naive and various adjustment methods and the high concordance across the various sensitivity analyses provide compelling evidence for the validity and robustness of the study findings.'*

7.1.3 Results from the comparative analysis

Table 18 below presents the naïve comparison between ZUMA-2 [9] and SCHOLAR-2 [10].

Table 18 Results from the comparative analysis of brexu-cel vs. SoC in adults with R/R MCL who have received two or more lines of systemic therapy, including a BTKi

Outcome measure	Brexu-cel (N = 74)	SoC (N = 59)	Difference
Median overall survival	[redacted]	15.7 months (95% CI 10.0, 30.9)	[redacted]
12-month OS rate	[redacted]	57.5% (95% CI 44.8%, 69.3%)	[redacted]

7.1.4 Efficacy – results per [outcome measure]

Please refer to Table 18 above for OS and section 6 for PFS and ORR from ZUMA-2.

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

8.1.1 Extrapolation of efficacy data

Clinical data from ZUMA-2 and the real-world study SCHOLAR-2 were used to extrapolate PFS and OS for Tecartus® and SoC, respectively. In the base case, standard survival models (exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, and generalised gamma) were fitted to the individual trial data. Distribution selection followed the guidance from the DMC and NICE Decision Support Unit guidance (DSU) [52]. Extrapolations were compared visually against Kaplan-Meier curves, and statistical fit was evaluated using Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Additionally, clinical plausibility was assessed based on the shape of the hazard function and estimated PFS in relation to expected OS. Mortality estimates were bound by age- and gender-specific natural mortality rates from Danish life tables [53].

For Tecartus®, the effectiveness was based on the OS and investigator-assessed PFS estimates from the 60-month data-cut of the ZUMA-2 trial (data on file), using the ITT population (the FAS [n = 74] population).

For SCHOLAR-2, a propensity score weighted analysis was initially performed to ensure comparability with the intervention group, as represented by the population in the ZUMA-2 trial. However, using the FAS of the ZUMA-2 trial, including n = 74 patients (60-month data for OS; 60-month data for investigator-assessed PFS) and weighted to the updated meta-analysis as described, this population gives an effective sample size (ESS) of only 36.2 for OS and 16.3 for PFS. The reduced ESS meant insufficient data to run robust survival analyses on the weighted data directly. Therefore, the base case analysis uses the unweighted KM curves. The unweighted approach is transparent and requires fewer assumptions. Finally, weighting the SCHOLAR-2 data to the ZUMA-2 trial introduced minor changes to the KM curve, with the unweighted curve indicating somewhat better survival in SoC patients; that is, the unweighted comparison is more conservative in its estimate of the relative effect.

The extrapolation of PFS was undertaken as the initial step in the survival modelling process, as PFS represents a direct, and earlier clinical endpoint with more mature and less confounded data than OS. OS is inherently bounded by PFS (i.e. as disease-related death must be preceded by progression), as such modelling OS first, risk generating PFS curves that are biologically implausible.

Anchoring the OS extrapolation to a clinically plausible PFS function, ensure logical consistency realistic post-progression survival, and alignment with both trial data and clinical expectations. The most pessimistic OS curves were excluded because they implied crossover with PFS or unrealistically short post-progression survival, which is not clinically credible (see section below 8.1.1.1 for PFS and 8.1.1.2 for OS).

8.1.1.1 Extrapolation of PFS

A summary of assumptions associated with PFS extrapolation is shown in Table 19.

Table 19 Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	ZUMA-2 and SCHOLAR-2
Model	The seven standard survival models were fitted to the individual subject data in ZUMA-2. The survival times are assumed to have one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, or generalised gamma. SCHOLAR-2 did not report PFS. Therefore, an HR adjustment was applied to the OS survival estimate for each time point for the SCHOLAR-2 data (see below).
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: Lognormal Comparator: Not applicable
Function with best BIC fit	Intervention: Lognormal Comparator: Not applicable
Function with best visual fit	Intervention: Lognormal Comparator: Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Lognormal Comparator: Not applicable
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Intervention: Lognormal Comparator: Constant HR adjustment of 0.727 applied to OS function

Method/approach	Description/assumption
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure-point	No

Further details concerning the extrapolations are described in Appendix D. [redacted] shows the standard parametric distributions together with the KM data for PFS.

Abbreviations: KM: Kaplan-Meier; PFS: Progression-free survival.

PFS data from ZUMA-2 were mature, due to the extensive follow-up, which allows for the use of goodness-of-fit statistics to guide the extrapolation. Therefore, in line with NICE TSD 14 guidelines, the goodness-of-fit statistics could be used to inform the model selection. Furthermore, the model selection considered clinical plausibility, by assessing the hazard shape, and visual fit to the KM data. Visually, the lognormal distribution provided the best fit to the KM data. This is supported by a lower root mean square deviation (RMSD) between the parametric and KM curves compared to alternative distributions. The exponential distribution had the worst visual fit with the KM data.

The lognormal exhibited the best fit with the lowest AIC and BIC values, as shown in Table 53, closely followed by the log-logistic. The remaining distributions showed a ΔAIC and ΔBIC, calculated from the lognormal minimum, larger than three, with the exponential and the generalised gamma showing a distance larger than six. This is

reflected in the share of predicted survival at different landmarks, with the exponential being a clear outlier with the lowest survival at 10 and 20 years (Table 53). The hazard from the trial ([redacted] is reasonably well represented by the lognormal, log-logistic and generalised gamma models. The exponential shows the worst fit due to its assumption of a constant hazard with time. Given these findings, the lognormal was selected for the base case. Appendix D presents predicted landmark PFS rates, median, and estimated mean for each survival model. Therefore, based on all the criteria evaluated, in line with the guidance of NICE TSD 14, the lognormal consistently proves to be the best possible candidate for extrapolation of PFS in the Tecartus® arm.

For SCHOLAR-2, PFS estimates were not available. Therefore, an HR adjustment was applied to the OS survival estimate to derive it. That is, PFS is defined to be:

$$S_{PFS}(t) = S_{OS}(t)^{HR}$$

A literature-based meta-analysis was conducted for comparator analysis for post-BTKi, R/R MCL patients. This meta-analysis was carried out for both OS and PFS. Therefore, the HR adjustment applied to the OS can be estimated using the meta-analysis results under the assumption that the relationship between OS and PFS would be similar in the SCHOLAR-2 data [12]. Exponential models estimated from the literature-based meta-analysis have been used for both OS and PFS. As the exponential model assumes a constant hazard over time, this means that the HR between OS and PFS is constant. Therefore, the HR can be estimated for each time point, t, as:

$$HR(t) = \frac{h_{PFS}(t)}{h_{OS}(t)}$$

where $h_{PFS}(t)$ and $h_{OS}(t)$ are estimated using the parameters estimated for the exponential distribution for the PFS and OS, respectively. [redacted] shows the results of applying this hazard ratio adjustment to the proposed base case for the OS extrapolation, the Weibull distribution, fitted to the SCHOLAR-2 data. The predicted PFS landmarks for the SoC are shown in Table 54.

[redacted]

8.1.1.2 Extrapolation of OS

A summary of assumptions associated with OS extrapolation is shown in Table 20.

Table 20 Summary of assumptions associated with the extrapolation of OS

Method/approach	Description/assumption
Data input	ZUMA-2 SCHOLAR-2
Model	The seven standard survival models were fitted to the individual subject data in ZUMA-2 and SCHOLAR-2. The survival times are assumed to have one of the following distributions: exponential, Weibull, Gompertz, log-logistic, lognormal, gamma, or generalised gamma.
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	Intervention: Weibull Comparator: Gamma
Function with best BIC fit	Intervention: Exponential Comparator: Exponential
Function with best visual fit	Intervention: Weibull Comparator: Generalised gamma
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Lognormal Comparator: Log-logistic
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Intervention: Lognormal Comparator: Weibull
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No

Method/approach	Description/assumption
Assumptions of cure-point	No

In line with the PFS analysis, for Tecartus®, OS extrapolation in this section used the FAS population from the ZUMA-2 study (n = 74). The KM curves are presented for the OS and PFS curves in [redacted] and [redacted]6, respectively. For the SoC, SCHOLAR-2 was used, as shown in [redacted]. KM estimates from ZUMA-2 and SCHOLAR-2 were mature, with extensive follow-up. Therefore, the goodness-of-fit statistics can be used to guide the selection of the base case. However, the distributions supported by the clinical evidence were also assessed based on clinical plausibility and visual fit to the non-parametric survival data (KM estimates and smoothed non-parametric hazard). Moreover, the selection should align with the chosen PFS distribution, which has already been identified as the most suitable candidate across all the metrics. Therefore, when choosing the OS distribution, the decision was guided by a combination of goodness-of-fit, clinical plausibility, in relation to the shape of the hazard function, and consistency with the selected PFS curve. This ensures that the OS projection does not fall below the PFS, which would imply a clinically implausible result.

For Tecartus®, all the fitted models are shown in [redacted]. Additional details on the survival landmarks, AIC and BIC, mean and median endpoints are presented in Appendix D.

[redacted]

Abbreviations: KM: Kaplan-Meier; OS: Overall survival.

The best fit curve to the KM data was assessed visually and through RMSD between the parametric curves and the KM estimate. The Weibull distribution had the best visual fit.

All the extrapolated curves follow the KM data relatively well, except for the exponential distribution.

AIC and BIC values were comparable between the different survival distributions (Table 55). The Weibull model has the lowest AIC, but all distributions demonstrated similar statistical fit. For BIC, the lowest value was achieved with the exponential, followed closely by the Weibull and the gamma. With the choice of lognormal for PFS, only Gompertz, log-logistic and lognormal OS curves avoid crossing the PFS curve. While the model adjusts for the curve crossing, this implies that when selected, these models predict lower OS than PFS (a clinically implausible scenario. The remaining distributions are relatively comparable in terms of statistical fit and landmarks, respectively (Table 55), but the lognormal distribution combined a statistical fit with a good visual fit to both the KM curve and the smoothed trial hazard (and was thus selected for the base case.

The parametric survival models fitted to the SCHOLAR-2 data are shown in

Abbreviations: KM: Kaplan-Meier

The OS data from SCHOLAR-2 were relatively mature, and the choice of distribution was mainly informed by goodness-of-fit and clinical plausibility. The generalised gamma was the best visual fit to the KM estimate. The Gompertz, log-logistic, and lognormal models were the most optimistic regarding extrapolated OS. The exponential distribution was the most conservative, with the lowest predicted future OS.

The Weibull model, closely followed by gamma and exponential, had the best statistical fit. AIC/BIC goodness-of-fit and related landmarks are shown in Table 56.

The hazard shape from SCHOLAR-2 was monotonically decreasing [redacted] Among the best candidates based on the AIC/BIC values, Weibull and gamma follow the smoothed study hazard. Due to the better overall statistical fit, the Weibull distribution was selected as the base case for the analysis.

8.1.2 Calculation of transition probabilities

Not applicable.

Table 21 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence		
	Death		
Recurrence	Death		
Health state/Transition			

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

In ZUMA-2, 26 subjects (35%) received one or more subsequent therapies after brex-cel. These included not only the Danish SoC regimens, but also a wide range of other chemotherapies, TKIs, and experimental agents. Similarly, SCHOLAR-2 included a broad range of post-BTKi therapies (as presented in Hess et al. 2022, Supplementary Appendix) [10] including Danish SoC, but also other chemotherapeutic combinations, targeted or experimental therapies [10].

The clinical effects of subsequent treatments are captured within the efficacy outcomes of ZUMA-2 and SCHOLAR-2, as subjects received subsequent lines of therapy following disease progression. As the effect of subsequent therapy are included in the observed trial outcomes, no additional treatment effect for subsequent treatments is modelled separately in the economic analysis.

As outlined in section 11.6, cost of subsequent therapies was included, with the same post-BTKi SoC regimens assumed in both treatment arms (based on SCOLAR-2 adjusted to reflect Danish SoC).

8.4 Other assumptions regarding efficacy in the model

Not applicable.

8.5 Overview of modelled average treatment length and time in model health state

The estimates for the modelled average and modelled median are shown in Table 22.

Table 22 Estimates in the model

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
Tecartus®	60 months [PFS] ('Survival chart'!F5) 83.1 months [OS] ('Survival chart'!F6)	21.5 months [PFS] ('Survival chart'!E5) 35.5 months [OS] ('Survival chart'!E6)	PFS: [redacted] months OS: [redacted] months
SoC	19.3 months [PFS] ('Survival chart'!K5) 28.4 months [OS] ('Survival chart'!K6)	11.5 months [PFS] ('Survival chart'!J5) 16.5 months [OS] ('Survival chart'!J6)	PFS: N/A OS: 15.7 months

Table 23 shows the modelled average treatment length and time in the model health state. Tecartus® is given as a one-off treatment, while for SoC, treatment is given until progression, except for treatments which are given up to 6 cycles. PFS for SoC was derived with an HR adjustment as described in section 8.1.1.1. For each of the SoC treatments, the average time on treatment was calculated either as PFS (for treatments that are used until progression) or as the PFS over the first six cycles (for treatments that are used for six cycles or to progression). For rituximab, as it is present in both regimens that are treated to progression and capped at six cycles, it was calculated as the weighted mean of these two, the weights being the proportion of patients on R-CHOP and R-BAC, respectively. Total mean treatment duration in the SoC arm was then calculated as the weighted sum of the above by the share of patients on each respective treatment.

Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half-cycle correction

Treatment	Treatment length [months]	PFS [months]	OS [months]
Tecartus®	N/A	60.0	83.1

SoC	13.0	19.3	28.4

9. Safety

9.1 Safety data from the clinical documentation

The primary source for the safety data comes from the ZUMA-2 clinical trial, which used the DCO 5 October, 2023 for the safety analysis set (SAS n = 68) [54]. All subjects (n = 68) in the SAS population experienced at least one treatment emergent adverse event (TEAE). Furthermore, 49 patients (72%) experienced serious TEAEs, and grade 3 or 4 TEAEs were reported in [redacted]

The overview of the safety events from ZUMA-2 are presented in Table 24.

Table 24 Overview of safety events – SAS (n=68) ZUMA-2

	Brexu-cel (N = 68)	Comparator (N=x) (source)- N/A	Difference, % (95 % CI)-N/A
Number of adverse events, n	N/A		
Number and proportion of patients with ≥1 adverse events, n (%)	68 (100%)		
Number of serious adverse events*, n	N/A		
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	49 (72%)		
Number of CTCAE grade ≥ 3 events, n	N/A		
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events[§], n (%)	[redacted]		
Number of adverse reactions, n	N/A		

	Brexu-cel (N = 68)	Comparator (N=x) (source)- N/A	Difference, % (95 % CI)-N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	N/A		
Number and proportion of patients who had a dose reduction, n (%)	N/A		
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	N/A		
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	N/A		

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

Source: Data on file, safety analysis set DCO: 05OCT2023.

Serious TEAEs occurring in ≥5% of patients, as reported in the ZUMA-2 trial SAS population at DCO 5 October 2023, are included in Table 25. Serious AEs were reported for 49 patients (72%), with pyrexia reported in 14 patients (21%), and pneumonia and encephalopathy reported in 12 (18%) patients each. The full list of serious AEs for ZUMA-2 is provided in Appendix E.

Table 25 Serious AEs - SAS (N = 68) ZUMA-2

Adverse events	Brexu-cel (N = 68)[55]		Comparator (N=x)-N/A	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	49 (72%)	N/A		
Anaemia	4 (6%)	N/A		

Adverse events	Brexu-cel (N = 68)[55]		Comparator (N=x)-N/A
Pyrexia	14 (21%)	N/A	
Pneumonia	12 (18%)	N/A	
Sepsis	4 (6%)	N/A	
Encephalopathy	12 (18%)	N/A	
Confusional state	5 (7%)	N/A	
Acute kidney injury	5 (7%)	N/A	
Hypoxia	7 (10%)	N/A	
Respiratory failure	4 (6%)	N/A	
Hypotension	11 (16%)	N/A	

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Source: Data on file, safety analysis set DCO:05OCT2023

In the health economic model, the AEs were based on the SAS (n = 68) with the DCO 5 October, 2023, from the ZUMA-2 trial [54]. Only TEAEs of grade 3 or 4 and those occurring in ≥5% of patients were considered as per MedDRA preferred term, as these are often associated with CAR-T therapy and can result in severe or life-threatening outcomes (see Table 26). Cytokine release syndrome (CRS) is an AE that is specific to treatment with Tecartus®. Grade 3/4 CRS was reported in [redacted]. Among the [redacted] the median duration of CRS was [redacted] No subject experienced CRS after the primary analysis (DCO 24 July 2019). As of the primary DCO, CRS had resolved in all subjects.

Table 26 AEs used in the health economic model

Adverse events	Brexu-cel (N = 68)	Comparator N/A		
Adverse event (%)*	**Frequency used in economic model for intervention**	**Frequency used in economic model for comparator**	**Source**	**Justification**
Neutrophil count decreased	[redacted]	N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%

Anaemia	[redacted]	N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
White blood cell count decreased		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Platelet count decreased		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Neutropenia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Hypophosphatemia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Hypotension		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Hypoxia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Encephalopathy		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Pneumonia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Thrombocytopenia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Any CRS*		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Leukopenia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%
Hypertension		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Pyrexia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Confusional state		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Aspartate aminotransferase increased		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Hyponatraemia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Alanine aminotransferase increased		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Febrile neutropenia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Lymphocyte count decreased		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.

Acute kidney injury	[redacted]	N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Hypokalaemia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Hypocalcaemia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Lymphopenia		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Respiratory failure		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%.
Sepsis		N/A	ZUMA-2	TEAEs of grade ≥3 in ≥5%

Note: *CRS events are graded per the revised grading system of Lee et al 2014. All other events are graded per CTCAE version 4.03 coded using MedDRA version 26.0 and graded. TEAE is defined as any adverse event with onset on or after the anti-CD19 CAR T cells infusion. AEs occurred on/after retreatment are not included. Multiple incidences of the same AE in 1 subject are counted once at the highest grade for that subject. Percentages are calculated using the total number of subjects in the treatment group as the denominator.

Source: Data on file, cohort 1 - safety analysis set n = 68, DCO: 05OCT2023.

9.2 Safety data from external literature applied in the health economic model

N/A

Table 27 AEs that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n								

10. Documentation of HRQoL

HRQoL was assessed using the EQ-5D questionnaire from ZUMA-2 study, at screening (for baseline scores), Week 4 (± 3 days), Month 3 (± 1 week), and Month 6 (during the long-term follow-up period) before any other assessments or procedures were performed (see Table 28).

The EQ-5D questionnaire included the EQ-5D-5L and a visual analogue scale (VAS) in which subjects rated their overall health status from 0 (representing "the worst health you can imagine") to 100 (representing "the best health you can imagine").

Table 28 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-questionare	ZUMA-2 study	EQ-5D-5L and EQ-5D VAS was collected for individual patients as part of ZUMA-2. EQ-5D-5L was used to estimate the pre-progression utility. Descriptive statistics were used to summarise the EQ-5D-5L utility index using the Danish value set. The VAS subjects rated their overall health status from 0 (representing "the worst health you can imagine") to 100 (representing "the best health you can imagine")

10.1 Presentation of the HRQoL EQ-5D-5L and EQ-5D-VAS

10.1.1 Study design and measuring instrument

HRQoL was assessed in the ZUMA-2 trial safety population (n = 68) using the EQ-5D questionnaire [56, 57]. The QoL survey (EQ-5D) is a comprehensive and widely used patient-reported outcome questionnaire designed to measure HRQoL in the general population, as well as in subject groups with diverse chronic diseases. This questionnaire has well established reliability and validity [58, 59]. For each health dimension in the EQ-5D questionnaire, subjects were instructed to select the severity level (no problems, slight problems, moderate problems, severe problems, or extreme problems) that best described their health status on the day that the questionnaire was administered. The EQ-5D also included a visual analogue scale (VAS) in which subjects rated their overall health status from 0 (representing "the worst health you can imagine") to 100 (representing "the best health you can imagine") [56].

10.1.2 Data collection

In the ZUMA-2 trial, participants completed the EQ-5D-5L questionnaire including VAS at screening (for baseline scores), week 4 (± 3 days), month 3 (± 1 week), and month 6 (during the long-term follow-up period) before any other assessments or procedures were performed [56].

The pattern of missing data and completion of the questionnaire for EQ-5D-5L overall is presented in Table 29. The completion rate for the five domains in the questionnaire; mobility, self-care, usual activity, pain/discomfort, anxiety/depression and also VAS are presented in Table 58- Table 63. Available data rates and completion rates was assessed within the safety analysis population (n = 68) and remained above 70% at all visits through month 6 [57].

Table 29 Pattern of missing data and completion – EQ-5D-5L overall

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomisation	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	68	6 (8.8%)	68	62 (91.2%)
Week 4	68	17 (25.0%)	68	51 (75.0%)
Month 3	68	13 (19.1%)	64	55 (85.9%)
Month 6	68	25 (36.8%)	58	43 (74.1%)

Source: Data of file – ZUMA-2 utility analysis Denmark, 2025 [57].

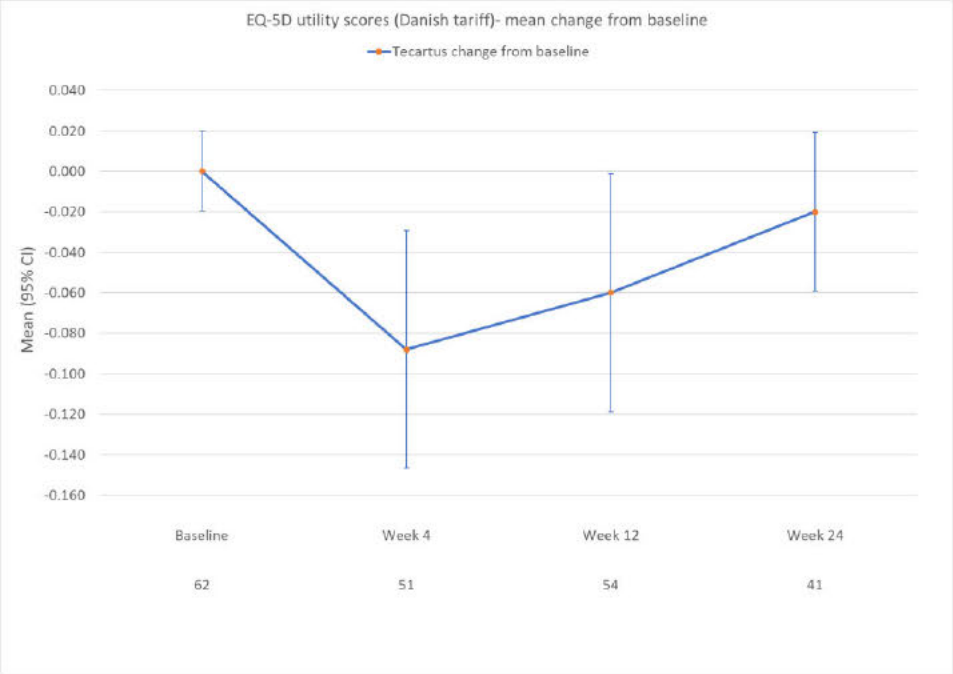
10.1.3 HRQoL results

Descriptive statistics were used to summarise the EQ-5D-5L utility index using the Danish value set for each visit. The EQ-5D-5L index score mean change from baseline through the different data collection time points for brexu-cel is presented in Figure 12 [57]. The mean EQ-5D-5L index was highest at screening and lowest at week 4, with slight and gradual increases at month 3 and 6 (Table 30). Utility values in week 4 and month 3 were significantly lower than those in screening. No significant difference in utility values was observed between screening and month 6.

The EQ-5D-VAS mean change from baseline through the different data collection time points for brexu-cel is presented in Figure 13. For the VAS, the mean score was 82.0 (range: 45 to 100) at screening and 74.5 (range: 38 to 100) at week 4, with higher mean

scores of 80.2 (range: 40 to 100) at month 3 and 84.3 (range: 20 to 100) at month 6 (Table 31).

Figure 12 EQ-5D-5L index score mean change from baseline through the different data collection time points for the brexu-cel



Abbreviations: CI, confidence interval.

Source: Data of file – ZUMA-2 utility analysis Denmark, 2025 [57].

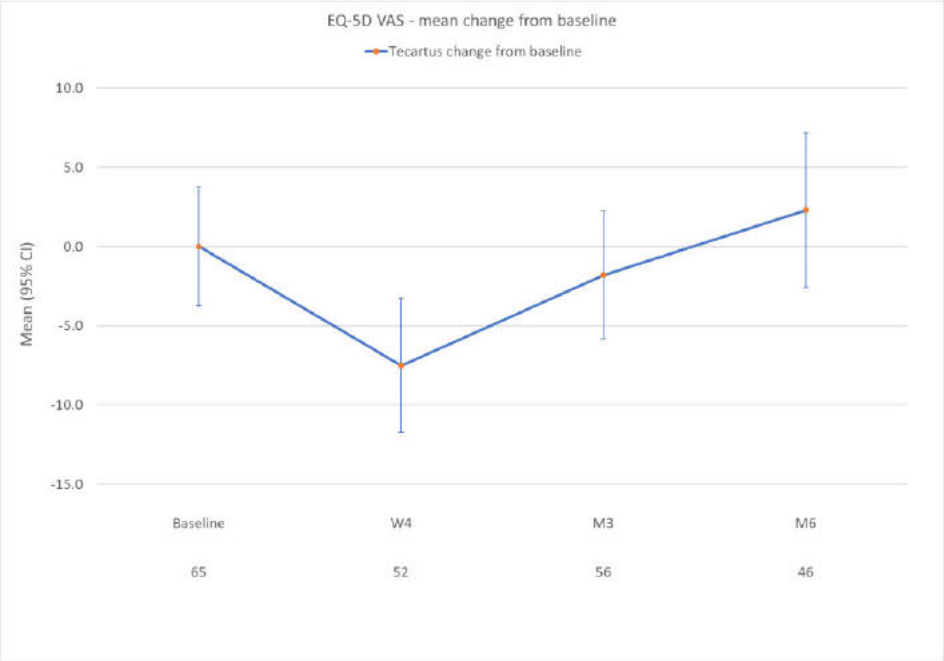
Table 30 HRQoL EQ-5D-5L summary statistics

	Intervention (brexu-cel)	Comparator (SoC)		Intervention vs. comparator
	Mean (SD)	N	Mean (SD)	Difference (95% CI) p value
Baseline	0.930 (0.114)	N/A	N/A	N/A
Week 4	0.842 (0.227)	N/A	N/A	N/A
Month 3	0.871 (0.191)	N/A	N/A	N/A
Month 6	0.904 (0.158)	N/A	N/A	N/A

Abbreviations: CI, confidence interval; SD, standard deviation; SoC, standard of care.

Source: Data of file – ZUMA-2 utility analysis Denmark, 2025 [57].

Figure 13 EQ-5D-VAS mean change from baseline through the different data collection time points for the brexu-cel



Abbreviations: CI, confidence interval.

Source: Data of file – ZUMA-2 CSR

Table 31 HRQoL EQ-5D-VAS summary statistics

	Intervention (brexu-cel)		Comparator (SoC)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (95% CI) p value
Baseline	65	82.0 (15.4)	N/A	N/A	N/A
Week 4	52	74.5 (15.6)	N/A	N/A	N/A
Month 3	55	80.2 (15.5)	N/A	N/A	N/A
Month 6	42	84.3 (16.9)	N/A	N/A	N/A

Abbreviations: CI, confidence interval; SD, standard deviation; SoC, standard of care.

Source: Data of file – ZUMA-2 CSR

10.2 HSUVs used in the health economic model

10.2.1 HSUV calculation

HSUVs used in the health economic model were calculated using EQ-5D-5L data from ZUMA-2 trial and Danish preference weights [57], or using proportions obtained from

the literature (ibrutinib NICE submission in r/r MCL [14]). In addition, HSUVs in the model were age-adjusted according to DMC guidelines[47].

EQ-5D-5L data collected for individual patients as part of ZUMA-2 was used to estimate the pre-progression utility (progression-free state [PF]) using the Danish value set. The Danish value set proposed by Cathrine Elgaard Jensen et al. (2021) [13] was used to convert dimension scores from trial EQ-5D-5L data into a utility value at the following time points: screening (within 28 days of enrolment), post-treatment week 4, month 3 and month 6 [57].

The analysis population was the safety analysis set of ZUMA-2. Linear mixed models were used to estimate the mean EQ-5D-5L index values at each visit. The mixed model included fixed effects for age (continuous), sex (dummy variable) and visit (dummy variable) and a random effect for subject as per the equation below [57].

$$U_{it} = \alpha + \beta_1 * age_i + \beta_2 * sex_i + \beta_3 * visit\_2_i + \beta_4 * visit\_3_i + \beta_5 * visit\_4_i + \varepsilon_{it}$$

Due to lack of data, the post-progression (progressed disease [PD]) utility could not be estimated using the trial data. Therefore, it was calculated applying the proportional difference between PD and PF UK EQ-5D-5L utility values in the ibrutinib NICE submission (2016) [14], corresponding to 0.680/0.780 = 8.7% difference, directly to the Danish PF value (0.882) resulting in 0.882-0.882*0.087 = 0.805.

10.2.1.1 Mapping

Not applicable, since the HRQoL in this application is based on the measuring instrument EQ-5D-5L.

10.2.2 Disutility calculation

Not applicable.

10.2.3 HSUV results

The descriptive statistics of the Danish EQ-5D-5L index values over time from individuals in the PFS state are summarised in Table 32 [57]. Observations from individuals with post-progression, or retreatment were excluded. Out of [redacted] PF utility observations in [redacted] individuals, there were 92 observations with a perfect EQ-5D-5L state (11111; 1.000) and zero observations with the worst EQ-5D-5L state (55555; -0.758) [57].

Table 32 Descriptive EQ-5D-5L index (PF observations only)

EQ-5D-5L Index (Danish)	PF
N	[redacted]
Mean	0.882

95% CI	0.858, 0.908
Median (min, max)	0.952 (-0.212, 1)

Abbreviations: CI, confidence interval.

Source: Data of file – ZUMA-2 utility analysis Denmark, 2025 [57].

An overview of the HSUV used in the health economic model, based on ZUMA-2, are presented in Table 33. Disutilities for AE's were not included, as disutilities for AE's are captured in the health state specific utilities. The DMC has previously accepted the assumption that disutilities for AE are captured within the HSUV [60].

Table 33 Overview of health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
PF	0.882 [0.858-0.908]	EQ-5D-5L	DK	ZUMA-2 trial. Estimate is based on descriptive EQ-5D-5L Index (PF observations only) [57], visits classified as unscheduled at screening and week 4 were included in this analysis. Post-progression visits were excluded.
PD	0.805	EQ-5D-5L	DK	Difference in pre-progression and post-progression utilities from ibrutinib NICE submission in R/R MCL **[14]** applied to the pre-progression utility estimated from ZUMA-2 [57].

Abbreviations: CI, confidence interval; CRS, cytokine release syndrome; N/A, not available; PD, progressed disease; PF, progression-free; TTO, time-trade-off; SG, standard gamble; VAS, visual analogue scale.

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable

10.3.1 Study design

Not applicable

10.3.2 Data collection

Not applicable

10.3.3 HRQoL results

Not applicable

10.3.4 HSUV and disutility results

Not applicable

Table 34 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A		EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
HSUV B		EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
...				
[Disutilities]				
...				

Table 35 Overview of literature-based health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1		EQ-5D-5L	DK	EQ-5D-5L data was collected in X trial. Estimate is based on mean of both trial arms.
Study 2				
Study 3				
HSUV B				
...				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
[Disutility A]				
...				

11. Resource use and associated costs

11.1 Medicines - intervention and comparator

Tecartus® is administered as a one-time treatment, with a total treatment cost of 2,374,981 DKK. This cost includes the expected list price of Tecartus® (2,494,656.42 DKK, applied to infused patients only, 91.9%), bridging therapy (n = 28, 37.8%, total 4,156 DKK including administration), apheresis (25,006 DKK, DRG takster 2025, 16MP05), conditioning chemotherapy (n = 69, 93.2%, 1,533 DKK, including administration), and hospitalisation associated with the administration of Tecartus® [1].

Non-elective hospitalisation is required following infusion to monitor for signs and symptoms of potential CRS, neurologic events and other toxicities. This was costed as per DRG, with a one-off cost of 51,697 DKK (DRG takster 2025: 17MA01 see section 11.4).

[redacted]

For the comparator arm, all the drugs identified from the Danish SoC in section 3.5 are included in the analysis and listed in Table 36. Drug prices, strengths, and pack sizes were sourced from Medicinpriser.dk in May 2025.

In ZUMA-2, 37.8% (n = 28) of patients were given bridging chemotherapy after leukapheresis and completed at least 5 days before initiating conditioning chemotherapy before the infusion with Tecartus® [33]. In the Danish setting, bridging therapy with R-BAC was assumed (Rituximab 375 mg/m^2 day 1; Bendamustine 70 mg/ m^2 days 2, 3; Cytarabine 800 mg/ m^2 days 2-4) [40]. For Tecartus®, 93.2% (n = 69) patients received conditioning chemotherapy with fludarabine (30 mg/m^2, IV) and cyclophosphamide (1,000 mg/m^2, IV), three to five days before infusion [33]. The treatment duration for the SoC arm follows the treatment regimen for each drug, but it is constrained by progression, i.e., patients discontinue treatment at disease progression or according to the posology of the regimen.

The share of patients assigned to each therapy was based on what was observed in SCHOLAR-2 for the post BTKi therapies (full list of therapies from SCHOLAR-2 are available in Hess et al (2022) supplementary Appendix [10]. The proportions for each regimen used in clinical practice in Denmark in SCHOLAR-2 were redistributed to equal 100% of the cohort (all other therapies from SCHOLAR-2 were not considered). The treatments included were; R-BAC, R-CHOP, CHOP, BR, R-lenalidomide, bendamustine, and lenalidomide monotherapy. In the CE-model, the comparators are included as single drugs, and each single drug was therefore assigned the proportion of each of the regimens. As an example, rituximab was assigned the proportion of R-BAC, BR, R-CHOP and R-lenalidomide. As drugs were included in more than one regimen, the total use will exceed 100% (the proportions assumed for each drug are shown in Table 37).

All the treatments, with the exception of rituximab, were given in 21- or 28-day cycles. The frequency of rituximab in the SoC was weighted to accommodate patients receiving a 21-day cycle (R-CHOP, 39.5%) and a 28-day cycle (R-BAC, 61.5%).

Table 36 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Tecartus®	N/A	N/A	Once	No
Rituximab	375 mg/m²	100%	SoC: Q3W (R-BAC, 39.5%), on day 1 of 21-day cycles or Q4W for six cycles (R-CHOP,61.5%), on day 1 of 28 days cycles	No
			Bridging: Q4W for six cycles, on day 1 of 28 cycles	
Cyclophosphamide	750 mg	100%	SoC: Q3W day 1 of 21 days cycle	No
	1,000 mg	100%	Conditioning: One-off	
Fludarabine	30 mg/m²	100%	Conditioning: One-off	No
Doxorubicin	50 mg/m²	100%	Q3W day 1 of 21 days cycle	No
Vincristine	1.4 mg/m²	100%	Q3W day 1 of 21 days cycle	No

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Prednisone	50mg/m^2 corresponding to 100mg day	100%	On day 1-5 Q3W, 21 days cycle	No
Bendamustine	70 mg/m^2	100%	SoC: Q4W for six cycles, on day 1 and 2 of 28 days cycle	No
			Bridging: Q4W for one cycle, on day 1 and 2 of 28 days cycle	
Cytarabine	800 mg/m^2	100%	SoC: Q4W for six cycles, on day 1-3 for 28 days cycle	No
			Bridging: Q4W for one cycle, on day 1-3 of 28 days cycle	
Lenalidomide	25 mg	100%	Q4W, on day 1 to 21 of 28 days cycle	No

Notes: Q3W: every three weeks; Q4W: every four weeks.

Table 37 SoC Treatment distributions

Treatment	Distributions	Comment/Reference
Rituximab	72%	Included in R-CHOP, R-BAC, BR and R-lenalidomide. reweighted based on SCHOLAR-2
Bendamustine	59%	Included in R-CHOP, R-BAC, BR, and bendamustine mono. Reweighted based on SCHOLAR-2
Lenalidomide	33%	Included in R-lenalidomide and lenalidomide mono. Reweighted based on SCHOLAR-2
Cytarabine	16%	Included in R-BAC, reweighted based on SCHOLAR-2
Vincristine	7%	Included in R-CHOP, reweighted based on SCHOLAR-2
Prednisone	7%	Included in R-CHOP, reweighted based on SCHOLAR-2
Doxorubicin	7%	Included in R-CHOP, reweighted based on SCHOLAR-2
Cyclophosphamide	7%	Included in R-CHOP, reweighted based on SCHOLAR-2

Note: As some single drugs are included in more than one SoC regimen, the total will exceed 100%.

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Administration costs for all the listed medicines were included in the analysis and are shown in Table 38. The unit cost of administration was sourced from the relevant Danish DRG code for IV administration [61]. The IV administration cost for conditioning was applied with frequency as per the Tecartus® SmPC. For SoC and bridging, the frequency of administration was included for the different treatment regimens, per model cycle, which differs from the treatment cycle. To avoid double-counting administrations for each single treatment, patients receiving multiple drugs simultaneously, such as those with R-BAC or R-CHOP regimens, are assumed to incur one single administration cost, inclusive of all the drugs administered on the same day.

In the SoC, all the IV treatments are administered on a maximum of two days per dosing cycle (Table 36), with the exception of cytarabine, which has a three-day treatment schedule per dosing cycle. Therefore, for that IV treatment, the number of administrations per model cycle is calculated based on a weighted average. This is based on the maximum administration per treatment cycle for those drugs administered on day 1 and day 2, and the maximum administration of the patients receiving cytarabine (day 1, day 2 and day 3) as per SCHOLAR-2 (6%).

Table 38 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Intravenous administration (IV)	Based on the different posology as shown in Table 36	2,136	DRG taster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	DRG 2025 [61]
Oral	Based on the different posology as shown in Table 36	0	Assumption	Assumption

11.4 Disease management costs

Disease management costs per health state were included in the analysis (Table 39). The costs were based on Danish DRG weights. [61]. The frequency was based on those reported in the NICE technology appraisal for ibrutinib for R/R MCL [TA502][14]. For

Tecartus® monitoring for CRS symptoms is assumed for 7 days, as per the SmPC, costing as hospitalisation after infusion [1].

Table 39 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Initial Hospitalisation: Inpatient Day (Non-ICU)	One-off, assumed 7 days of hospital stay	51,697	DRG takster 2025: 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år. The cost is assumed to cover the 7 days monitoring required on Tecartus® SmPC	DRG 2025 [61], NICE TA502[14] and SmPC [1]
Office visit (medical)	Pre-progression: every 5 to 6 weeks. Post-progression: every 3 weeks.	2,136	DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	DRG 2025[61] and NICE TA502 [14]
X ray	Pre-progression: Twice per year. Post-progression: Twice per year.	1,731	DRG takster 2025: 30PR18 Røntgenundersøgelse (alm), ukompliceret	DRG 2025[61] and NICE TA502 [14]
Bone marrow exam	Pre-progression: Twice per year. Post-progression: Every 3 months.	16,156	DRG takster 2025: 17PR01 Udtagning af knoglemarv til diagnostisk undersøgelse	DRG 2025[61] and NICE TA502 [14]
Inpatient stay	Pre-progression: Every year and half. Post-progression: every 3 months	3,802	DRG takster 2025: 17MA02 trim point 15 days (57027/15 to get an average cost per day)	DRG 2025[61] and NICE TA502 [14]

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Biopsy	Pre-progression: Once per year Post-progression: None	5,879	DRG takster 2025: 09PR04 Biopsi og væskeudsugning, overfladisk	DRG 2025[61] and NICE TA502 [14]
Blood transfusion	Pre-progression: Twice per year Post-progression: Every month and half	4,218	DRG takster 2025: 16PR02 Transfusion af blod, øvrig	DRG 2025[61] and NICE TA502 [14]

11.5 Costs associated with management of AEs

Costs of AE management were included in the analysis (Table 40). Frequencies for Tecartus®, were based on the TEAEs by MedDRA preferred term of grade ≥3 and in ≥5% of the SAS (n = 68) from ZUMA-2, using the DCO 5 October 2023, (see section 9). The costs were sourced from Danish DRG weights, using the Sundhedsdatastyrelsen interactive DRG with MCL as main diagnosis and the ICD-10 diagnosis code for the respective AE as procedure code/secondary diagnosis [61]. All AEs were assumed to be acute and some managed within a day visit (<12 hours) or as an inpatient stay (>12 hours) (Table 40).

CRS was assumed to be managed during the administration of Tecartus®, and therefore, CRS event costs were calculated assuming only the acquisition cost of tocilizumab, which was applied to the proportion of patients experiencing CRS. Treatment with tocilizumab was assumed to be given at a dose of 8 mg/kg. The cost for one dose of tocilizumab is 7,143.11 DKK, according to medicinpriser.dk (sourced in January 2025). The mean weight (82.7 kg) reported in ZUMA-2 is used to calculate the cost per dose for an average patient. The AEs related to CRS were assumed to be managed within the CRS-related monitoring at infusion.

For SoC, no AEs have been included in the base case, due to that there are no available AE event rates from SCHOLAR-2. As such, they were conservatively excluded from the analysis.

Table 40 Cost associated with the management of adverse events

	DRG code/Reference	Unit cost/DRG tariff
Neutrophil count decreased	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD709) Neutropeni UNS Duration: Acute <12 hours DRG: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136.00 DKK
Anaemia	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD649) Anæmi UNS Duration: Acute <12 hours DRG: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136.00 DKK
White blood cell count decreased	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD729) Sygdom i hvide blodlegemer UNS, Duration: Acute <12 hours DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Platelet Count decreased	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD696) Trombocytopeni UNS Duration: Acute <12 hours DRG: 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	2,136 DKK
Neutropenia	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD709) Neutropeni UNS Duration: Acute <12 hours DRG: 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	2,136 DKK

	DRG code/Reference	Unit cost/DRG tariff
Hypophosphataemia	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DE833A) Hypofosfatæmi Duration: Acute <12 hours DRG: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Hypotension	Hypotension, is a CRS symptom and assumed to be covered within the CRS related monitoring at infusion	0 DKK
Hypoxia	Hypoxia, is a CRS symptom and assumed to be covered within the CRS related monitoring at infusion	0 DKK
Encephalopathy	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DG934) Encefalopati UNS Duration: Acute <12 hours DRG: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Pneumonia	Diagnosis code: Mantle celle lymfom (MCL) (DC831) and (DJ189) Pneumoni UNS Duration: Acute <12 hours DRG: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Thrombocytopenia	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD696) Trombocytopeni UNS Duration: Acute <12 hours DRG: 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	2,136 DKK
CRS	Medicinpriser.dk. 1 dose of tocilizumab, 162 mg for infusion, 4pcs, RoActemra inj.væske, opl., pen, 577505, Roche Pharmaceuticals A/S. Based on Tecartus® INN the	7,143 DKK

	DRG code/Reference	Unit cost/DRG tariff
	recommended dose is 8 mg/kg and the mean body weight in ZUMA-2---> 8 mg*82 kg-->656 mg needed = approximately four pens at 162 mg	
Leukopenia	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD728H) Leukopeni Duration: Acute <12 hours DRG: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Hypertension	Diagnosis code: (DC831) Mantle cell lymphoma (MCL) and (DI109) Essentiel hypertension Duration: Acute < 12 hours DRG: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Pyrexia	Pyrexia is a CRS symptom and assumed to be covered within the CRS-related monitoring at infusion	0 DKK
Confusional state	Confusional state is a CRS symptom and is assumed to be covered within the CRS-related monitoring at infusion	0 DKK
Aspartate aminotransferase increased	Assumed not to incur additional costs in Danish clinical practice	0 DKK
Hyponatraemia	Diagnosis code: (DC831) and (DE871A) Hyponatriæmi Duration: Acute <12 hours DRG: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Alanine aminotransferase increased	Assumed not to incur additional costs in Danish clinical practice	0 DKK
Febrile Neutropenia	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD709) Neutropeni UNS Duration: Acute <12 hours	2,136 DKK

	DRG code/Reference	Unit cost/DRG tariff
	DRG: 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	
Lymphocyte count decreased	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DD729) Sygdom i hvide blodlegemer UNS, Duration: Acute <12 hours DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Acute kidney injury	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DN179) Akut nyreinsufficiens UNS. Duration: Acute >12 hours DRG: 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	51,697 DKK
Hypokalaemia	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DE876) Hypokaliæmi Duration: Acute <12 hours DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Hypocalcaemia	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DE835D) Hypokalcæmi UNS Duration: Acute <12 hours DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	2,136 DKK
Lymphopenia	Diagnosis code: Mantle celle lymfom (MCL) and (DD728D) Lymfopeni Duration: Acute <12 hours	2,136 DKK

	DRG code/Reference	Unit cost/DRG tariff
	DRG takster 2025: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år	
Respiratory failure	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DJ960) Akut respirationsinsufficiens Duration: Acute >12 hours DRG: 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	51,697 DKK
Sepsis	Diagnosis code: (DC831) Mantle celle lymfom (MCL) and (DA419) Sepsis UNS Duration: Acute >12 hours DRG: 17MA01 Malign hæmatologisk sygdom uden specifik behandling, pat. mindst 18 år	51,697 DKK

11.6 Subsequent treatment costs

In ZUMA-2, 26 subject (35%) had one or more subsequent treatments after brexu-cel. These included lenalidomide, anti-CD20 (rituximab, obinutuzumab, and antineoplastic monoclonal antibodies), chemotherapies (bendamustine, methotrexate, cytarabine, cyclophosphamide, fludarabine, melphalan, gemcitabine, oxaliplatin, carmustine, etoposide, doxorubicin, prednisone, vincristine, other antineoplastic agents, busulfan, and decitabine), TKI's (acalabrutinib, abemaciclib, copanlisib, ibrutinib, and pirtobrutinib), radiotherapy, bortezomib, steroids (dexamethasone and prednisone), venetoclax, ASCT and experimental drugs. Also, SCHOLAR-2 included several lines of post BTKi therapies (all post BTKi therapies in SCHOLAR-2 are presented in Hess et al (2022) Supplementary Appendix)[10].

As described previously, the SoC in Denmark post BTKi includes the chemotherapeutic options (R)-CHOP, R-BAC, (R)-lenalidomide, and (R)-bendamustine. These regimens are recommended after two or more lines of systemic therapy, and as such subsequent therapy includes the same regimens as the first regimens recommended after BTKi.

In the cost effectiveness analysis, 35% of subjects in each arm were assumed to receive subsequent therapy (the proportion based on ZUMA-2). The distribution of each subsequent therapy was applied in the same way as for the comparator, using the SCHOLAR-2 post-BTKi therapies, adjusted to reflects Danish SoC and re-distributed to each single drug (see Table 37 for the proportion used).

Table 41 below present the subsequent therapies included in the cost effectiveness analysis with the dosing schedule and frequency, RDI and vial sharing applied, also consistent with what was applied with the comparator. The subsequent therapy costs (drug acquisition and administration cost) were then applied as a one-off cost at progression, based on the average number of administrations per drug times the cost per drug administration for each single drug and applied to an average treatment duration, based on the modelled duration for each drug.

Monitoring and AE costs for subsequent treatments are not included, only drug acquisition costs and administration cost.

Table 41 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Rituximab	375 mg/m^2	100%	SoC: Q3W (R-BAC, 39.5%), on day 1 of 21-day cycles or Q4W for six cycles (R-CHOP,61.5%), on day 1 of 28 days cycles	No
Cyclophosphamide	750 mg	100%	SoC: Q3W day 1 of 21 days cycle	No
Fludarabine	30 mg/m^2	100%	Conditioning: One-off	No
Doxorubicin	50 mg/m^2	100%	Q3W day 1 of 21 days cycle	No
Vincristine	1.4 mg/m^2	100%	Q3W day 1 of 21 days cycle	No
Prednisone	50mg/m^2 corresponding to 100mg day	100%	On day 1-5 Q3W, 21 days cycle	No
Bendamustine	70 mg/m^2	100%	SoC: Q4W for six cycles, on day 1 and 2 of 28 days cycle	No
Cytarabine	800 mg/m^2	100%	SoC: Q4W for six cycles, on day 1-3 for 28 days cycle	No

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Lenalidomide	25 mg	100%	Q4W, on day 1 to 21 of 28 days cycle	No

11.7 Patient costs

The analysis adopts a limited societal perspective, accounting for other costs such as patient costs for time spent receiving treatment, e.g., administration of the drug and transportation costs. Patient and transportation costs are presented in Table 43, and they apply to both treatment arms.

For patient time related to administration, this was calculated based on the weighted IV administration frequency per model cycles, taking into account the average time patients on SoC are treated (around 13.0 months). It was assumed that a total of 2 hours were lost per administration, and the average administration per model cycle was calculated. As a result, the average hour lost per cycle was calculated to be 1.66.

For the resource use, a similar approach was used. The maximum resource use frequency was calculated for both PFS and PD, and the same 2-hour assumption of time lost was used. For PFS in SoC, on top of the resource use, the drug-related time was added, since the analysis assumes they are treated until progression. On top of patient time, travel costs were also included. The travel costs were measured based on the resource use and drug administration frequencies, and differ from PFS, PD and PFS in SoC.

The cost of patient time was applied to the patients, and it was estimated using the hourly wage of DKK 188, as reported in *Værdisætning af Enhedsomkostninger* [62]. Transportation costs were also derived from *Værdisætning af Enhedsomkostninger* and set to DKK 3.79 per km [62], which was calculated based on the number of visits per cycle in each health state. The average distance to health care provider was assumed to be 20 km.

Table 42 Patient costs used in the model

Activity	Time spent [minutes, hours, days]	Unit cost
Patient time	Patient hours per cycle in PFS: 0.8 hours Patient hours per cycle in PD: 1.6 hours Patient hours per cycle in PFS in SoC: 4.1 hours	188 DKK
Travel cost - Average distance to	20 km.	3.79 DKK

Activity	Time spent [minutes, hours, days]	Unit cost
health care provider (round trip, km)		
Number of visits	No. of visits PFS: 0.4 No. of visits PD: 0.8 No. of visits PFS SoC: 2.1	75.80 DKK

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not applicable.

12. Results

12.1 Base case overview

Table 43 shows the base case overview and the main features.

Table 43 Base case overview

Feature	Description
Comparator	SoC
Type of model	PSM
Time horizon	40 years (lifetime)
Treatment line	Two or more lines of systemic therapy
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in ZUMA-2. Danish population weights were used to estimate health-state utility values
Costs included	Medicine costs Hospital costs Monitoring Subsequent treatments Costs of AEs Patient costs

Feature	Description
Dosage of medicine	Based on weight
Average time on treatment	Intervention: N/A Comparator: Based on different regimens. Average time is of 13.0 months, taking into account both PFS time and PFS time conditioned on six cycles.
Parametric function for PFS	Intervention: Lognormal Comparator: HR adjustment based on OS
Parametric function for OS	Intervention: Lognormal Comparator: Weibull
Inclusion of waste	No
Average time in model health state	Intervention / Comparator
PFS	60.0 months /19.3 months
OS	83.1 months/ 28.4 months

12.1.1 Base case results

Table 44 presents the discounted base case results for Tecartus® against SoC. The base case's ICER is 884,045 DKKDKK per QALY.

Table 44 Base case results, discounted estimates

	Tecartus®	SoC	Difference
Medicine costs – with the inclusion of conditioning and bridging chemotherapies	2,374,981 DKK	124,360 DKK	2,250,622 DKK
Medicine costs – co-administration	- DKK	- DKK	- DKK
Administration	4,347	21,201	-16,854 DKK
Disease management costs	204,629 DKK	85,413 DKK	119,216 DKK
Costs associated with management of AEs	18,707 DKK	- DKK	18,707 DKK
Subsequent treatment costs	51,217 DKK	55,967 DKK	-4,750 DKK

	Tecartus®	SoC	Difference
Patient costs	14,136 DKK	19,138 DKK	-5,002 DKK
Palliative care costs	- DKK	- DKK	- DKK
Total costs	**2,668,017 DKK**	**306,079 DKK**	**2,361,938 DKK**
Life years gained PFS	3.95	1.49	2.46
Life years gained PD	1.37	0.66	0.72
Total life years	**5.32**	**2.14**	**3.18**
QALYs (PFS)	3.43	1.31	2.12
QALYs (PD)	1.08	0.53	0.55
QALYs (adverse reactions)	0.00	0.00	0.00
Total QALYs	**4.51**	**1.84**	**2.67**
Incremental costs per life year gained			**743,478.01 DKK**
Incremental cost per QALY gained (ICER)			**884,045.30 DKK**

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

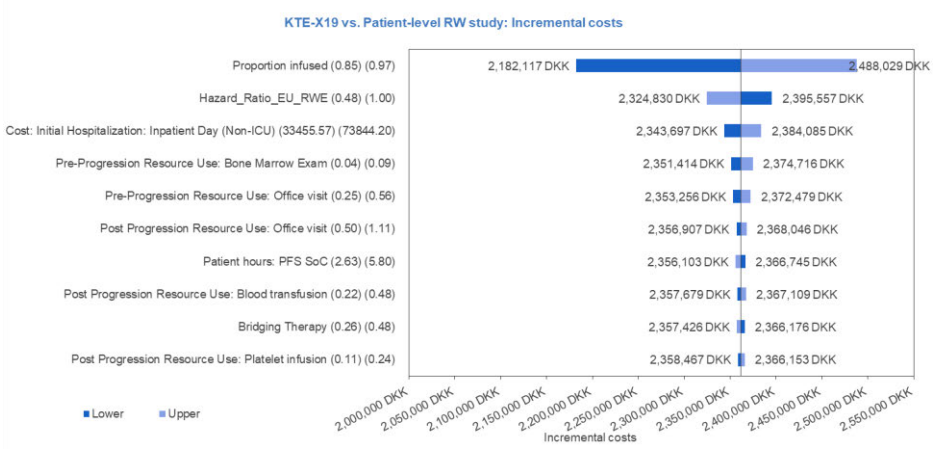
The result from the deterministic one-way sensitivity analyses is shown in Table 45. Tornado diagrams for the ten most influential parameters with respect to costs and QALYs are shown in Figure 14 and Figure 15. Since only utilities have a direct impact on the QALYs, only two parameters are shown in Figure 15. For the Tornado diagram, upper and lower values correspond to the lower and upper bounds of the 95% CI of the given parameter or a 20% variation if the confidence interval was unavailable.

Table 45 One-way sensitivity analyses results

	Change	Reason / rational / source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	N/A	N/A	2,361,938 DKK	2.67	884,045
Drug acquisition cost Tecartus®	20% increase	Specified in DMC	2,820,456/1,903,420	2.67/2.67	1,055,663

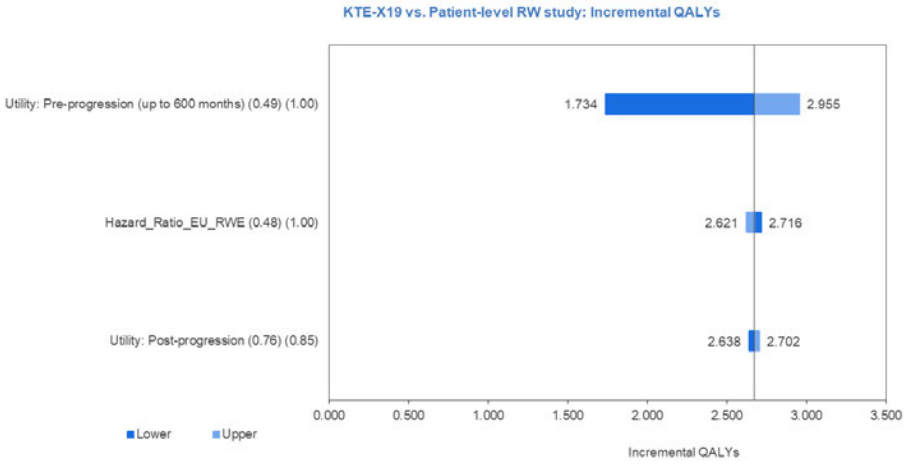
	Change	Reason / rational / source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
	and 20% decrease	guidelines[47]			/712,428
Time horizon (years)	20 and 30 years	Specified in DMC guidelines[47].	2,344,393/2,360,635	2.41/2.65	972,547/889,170
Discount rate - costs	1.5% and 5%	To see the impact of discounting on the cost	2,390,891/2,345,941	2.67/2.67	894,882/878,058
Discount rate - benefits	1.5% and 5%	To see the impact of discounting on the benefits	2,361,938/2,361,938	3.23/2.35	731,080 /1,005,379
PFS Tecartus®	Log-logistic	A suitable candidate distribution for the PFS extrapolations	2,361,431	2.67	883,776
OS Tecartus®	Log-logistic	A suitable candidate distribution for the OS extrapolations	2,358,827	2.64	895,010

Figure 14 Tornado diagram – Costs



Abbreviations: ICU: intensive care unit; IV: intravenous injection; KTE-X19: Tecartus®; PFS: progression-free survival.

Figure 15 Tornado diagram – QALYs



Abbreviations: KTE-X19: Tecartus®. Note that since only utilities and HR have a direct effect on the QALYs in the DSA, only these three parameters are shown in the tornado diagram.

12.2.2 Probabilistic sensitivity analyses

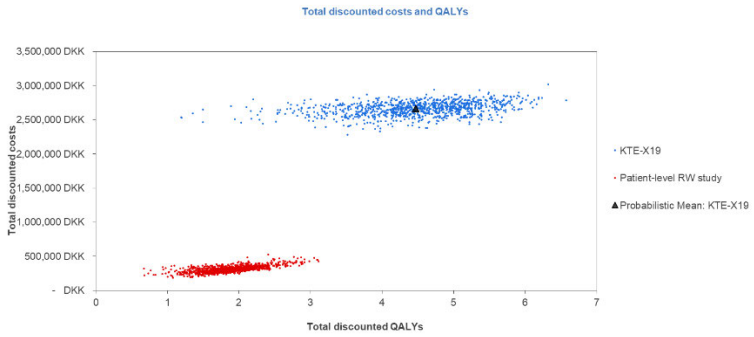
Probabilistic sensitivity analysis (PSA) involves drawing values for each parameter from its individual uncertainty distribution. The distribution itself is selected to reflect the known bounds for the parameter e.g., a beta distribution has been used for parameters bounded between 0 and 1. These were informed by the standard health economic practice. Contrary to the univariate sensitivity analysis, PSA is performed for all selected parameters simultaneously, with the resulting

incremental results recorded. This constitutes one 'simulation'. When the SE were unknown, 20% of the mean value was assumed.

In total, one thousand simulations have been performed, which gives a distribution of incremental results and, consequently, an estimate of the overall uncertainty surrounding the cost-effectiveness results. The results are presented on a cost-effectiveness plane in Figure 16 and the probability that each treatment is cost-effective at different levels of willingness to pay per QALY is presented using a cost-effectiveness acceptability curve (CEAC), Figure 17. Figure 18 presents the convergence plot for the estimated mean.

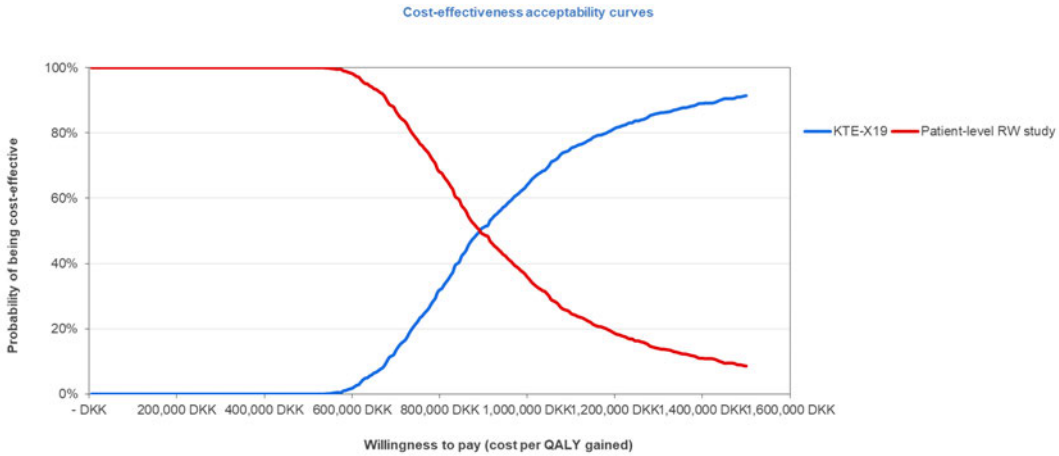
Not all parameters are included in the PSA. Time horizon, cycle length, discount rates, and drug costs are fixed settings, and, as such, are not included. The result of the PSA is a probabilistic ICER of 1,025,298 DKK, in line with the deterministic one.

Figure 16 Cost-effectiveness scatter plot



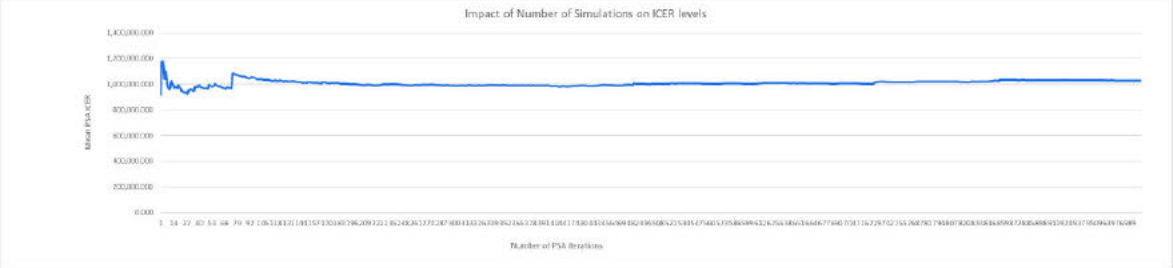
Abbreviations: KTE-X19: Tecartus®; QALY: Quality-adjusted life years; RW: Real-world.

Figure 17 Cost-effectiveness acceptability curve (CEAC)



Abbreviations: KTE-X19: Tecartus®; QALY: Quality-adjusted life years; RW: Real-world.

Figure 18 Convergence plot of PSA ICERs



Abbreviations: KTE-X19: Tecartus®; PSA: probabilistic sensitivity analysis.

13. Budget impact analysis

The budget impact analysis has been performed following the population described in section 3.2. An estimated four to six patients are assumed to be eligible and to receive treatment with Tecartus® if recommended as standard care. A total of six patients was used in the calculations. In the scenario in which DMC does not recommend Tecartus®, the market share is assumed to be 0%, as shown in Table 46.

The budget impact has been calculated with undiscounted costs, as per DMC guidelines. [47]. The results are shown in Table 47.

Number of patients (including assumptions of market share)

Table 46 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Tecartus®	6	6	6	6	6
SoC	0	0	0	0	0
			Non-recommendation		
Tecartus®	0	0	0	0	0
SoC	6	6	6	6	6

Note: *Numbers are presented rounded to sum up to the eligible patients.

Budget impact

Table 47 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	14,665,180 DKK	14,865,397 DKK	15,019,241 DKK	15,146,607 DKK	15,256,160 DKK
The medicine under consideration is NOT recommended	1,065,021 DKK	1,613,169 DKK	2,013,149 DKK	2,335,072 DKK	2,611,265 DKK
Budget impact of the recommendation	13,600,159 DKK	13,252,228 DKK	13,006,092 DKK	12,811,535 DKK	12,644,895 DKK

14. List of experts

Not applicable.

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Appendix A. Main characteristics of studies included

A.1 ZUMA-2

Table 48 Main characteristics of ZUMA-2

Trial name: ZUMA-2	NCT number: NCT02601313
Objective	The objective of the ZUMA-2 trial was to evaluate the efficacy and safety of brexu-cel in patients with R/R MCL, in terms of ORR, OS, and PFS.
Publications – title, author, journal, year	Hess et. al (2020). KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med. 2020 April; (382):1331-42 [33] Hess et. al (2022). Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. J Clin Oncol. 2022 June; (41):555-567 [48]. Hess et. al. (2024). Five-Year Outcomes of Patients (Pts) with Relapsed/Refractory Mantle Cell Lymphoma (R/R MCL) Treated with Brexucabtagene Autoleucel (Brexu-cel) in ZUMA-2 Cohorts 1 and 2. The 66th ASH Annual Meeting Abstracts, Blood, 2024; (144) 4388–4390 [9]
Study type and design	Single-arm, open-label, multicentre, phase 2 clinical trial
Sample size (n)	N = 74 (ITT)
Main inclusion criteria	• Up to five prior regimens for MCL. Prior therapy must have included: -Anthracycline or bendamustine-containing chemotherapy and -Anti-CD20 monoclonal antibody therapy and -Ibrutinib or acalabrutinib • At least one measurable lesion • Platelet count ≥ 75,000/uL • Creatinine clearance (as estimated by Cockcroft Gault) > or = to 60 mL/min • Cardiac ejection fraction ≥ 50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings • Baseline oxygen saturation >92% on room air.

Trial name: ZUMA-2		NCT number: NCT02601313
Main exclusion criteria	• Known history of infection with HIV or hepatitis B (HBsAG positive) or HCV (anti-HCV positive). A history of hepatitis B or hepatitis C is permitted if the viral load is undetectable per standard serological and genetic testing • History of a seizure disorder, cerebrovascular ischemia/haemorrhage, dementia, cerebellar disease, cerebral edema, posterior reversible encephalopathy syndrome, or any autoimmune disease with central nervous system (CNS) involvement • Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management.	
Intervention	-On day 0, Brexu-cel was administered through IV at the target dose of $2*10^6$ CAR-T cells/kg. Brexu-cel was administered to 68 patients (92%). -Conditioning chemotherapy (fludarabine 30 mg/m^2 per day; cyclophosphamide 500mg/m^2 once per day) was administered through IV on days -5, -4, and -3. -Before conditioning therapy and after leukapheresis, patients with high disease burden could receive bridging therapy with steroids or BTKi at the investigators' discretion.	
Comparator(s)	N/A	
Follow-up time	Median follow-up for cohort 1 (mITT, n = 68) was 67.8 months, 95% CI (58.2-88.6).	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	**Primary outcome:** • ORR, defined as the incidence of CR or PR per central assessment, as assessed by IRRC (Lugano classification). **Secondary outcomes:** • DOR was defined as the time from the first objective response (CR or PR) to disease progression or death, as per investigator response. • PFS was defined as the time from the brexu-cel infusion to the date of disease progression or death from any cause. Assessed as per the investigator's response. • OS was defined as the time from the KTE-X19 infusion date to the date of death from any cause. • BOR (best objective response) consists of CR (complete response), PR (partial response), SD (stable disease), PD (progressive disease),	

Trial name: ZUMA-2	NCT number: NCT02601313
	and unknown. Assessed as per the investigator, determined by the international working group (IWG). • Safety: AEs, any AE (including TEAEs) with an onset on or after the date of the initial KTE-X19 infusion were monitored. **Outcomes included in this application:** • ORR, PFS, and OS.
Method of analysis	The efficacy analyses were performed on the ITT/FAS population (n = 74). The Kaplan-Meier survival was used to estimate and assess the primary outcome, ORR, and the secondary outcomes OS and PFS.
Subgroup analyses	N/A
Other relevant information	N/A

A.2 SCHOLAR-2

Table 49 Main characteristics of SCHOLAR-2

Trial name:	NCT number:
Objective	To characterise real-world treatment patterns and clinical outcomes among European patients with R/R MCL following failure of BTKI therapy.
Publications – title, author, journal, year	Hess et al. (2022). Real- world experience among patients with relapsed/refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor failure in Europe: The SCHOLAR- 2 retrospective chart review study. Br J Haematol, 2023;(202) 749–759 [10] Hess, G., et al. (2022). A comparison of overall survival with brexucabtagene autoleucel (Brexu-cel) CAR-T-cell therapy (ZUMA-2) and SoC (SCHOLAR-2) in patients with Relapsed/Refractory mantle cell lymphoma (R/R MCL) previously treated with a covalent bruton tyrosine kinase inhibitor (BTKi). Blood, 2022. 140 (Supplement 1): p. 10296-10299 [11]
Study type and design	A retrospective, observational, multicentre, international chart review study. Randomisation and crossover were not applicable.
Sample size (n)	A total of 240 patients, of which a subset of n = 59 patients had an ECOG performance status of 0 or 1, and had started a post-BTKi therapy no later than June 30th, 2019.

Trial name:	NCT number:
Main inclusion criteria	Patients were enrolled in the study who were treated at the eligible centres which met all of the following criteria: inpatient diagnostic and treatment facilities for patients with B- cell lymphomas; belonged to a network of oncologists or haematologists who treated patients with R/R B- cell lymphomas; had been operational and treating patients with B- cell lymphoma for ≥24 months; and had clinical records available for review.
Main exclusion criteria	• Did not receive BTKi between July 2012 and July 2018 (n = 30) • Did not progress while on BTKi or discontinue BTKi due to intolerance (n = 3) • Current or history of CNS lymphoma (n = 14) • Received CAR-T cell therapy (n = 2)
Intervention	SoC regimens
Comparator(s)	N/A
Follow-up time	The median follow-up time of the entire SCHOLAR-2 cohort is 11.1 years; however, the subpopulation we use in this application (n = 59) has a medium follow-up of 27.6 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary outcome:** • OS, defined as the time from the initiation of the first BTKi therapy to the date of death from any cause. **Secondary outcomes:** • Patient demographics • Disease characteristics • Treatment patterns in the population
Method of analysis	The efficacy analyses were carried out on the subpopulation (n = 59, post-BTKi therapy before July 2019). The Kaplan-Meier survival was used to estimate and assess the primary outcome OS.
Subgroup analyses	N/A
Other relevant information	No

Appendix B. Efficacy results per study

B.1 Efficacy results ZUMA-2

Table 50 Results per study ZUMA-2

Results of ZUMA-2 (NCT02601313)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR	brexu-cel	74	62 (84%) (95% CI: 73.4%, 91.3%)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[48]
OS											
mOS	brexu-cel	74	43.9 months (95% CI: 24.6-59.2)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[9]
12-month OS	brexu-cel	74	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[50]

Results of ZUMA-2 (NCT02601313)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
24-month OS	brexu-cel	74	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[50]
60-month OS	brexu-cel	74		N/A	N/A	N/A	N/A	N/A	N/A	N/A	[50]
87-month OS	brexu-cel	74		N/A	N/A	N/A	N/A	N/A	N/A	N/A	[50]
PFS											
mPFS	brexu-cel	74	24.2 months	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[9]
12-month PFS	brexu-cel	74	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[50]
24-month PFS	brexu-cel	74		N/A	N/A	N/A	N/A	N/A	N/A	N/A	[50]

Results of ZUMA-2 (NCT02601313)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
60-month PFS	brexu-cel	74	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[50]
84-month PFS	brexu-cel	74		N/A	N/A	N/A	N/A	N/A	N/A	N/A	[50]

B.2 Efficacy results SCHOLAR-2

Table 51 Results per study SCHOLAR-2

Results of [trial name (NCT number)]												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS											

Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
mOS	SoC	59	15.7 months (95% CI 10.0-30.9)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[10, 11]
12-month OS	SoC	59	57.5%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	[10, 11]

Appendix C. Comparative analysis of efficacy

Table 52 Comparative analysis of studies comparing brexu-cel to SoC for adult MCL (R/R MCL) patients who have received two or more lines of systemic therapy including a BTK inhibitor

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Median overall survival	ZUMA-2 and SCHOLAR-2	28.2 months	(95% CI 10.0–30.9)		179.6			Indirect, unadjusted comparison	No
12-month OS	ZUMA-2 and SCHOLAR-2	[redacted]						Indirect, unadjusted comparison	No

Appendix D. Extrapolation

All standard parametric models—including exponential, Weibull, Gompertz, gamma, lognormal, log-logistic, and generalised gamma—were evaluated using both statistical and visual assessment methods. Goodness-of-fit was assessed using AIC and BIC, while root mean square deviation (RMSD) was used to quantify the fit to the Kaplan–Meier estimate in addition to visually assessing the fit. Clinical plausibility, including alignment with expected hazard shapes and the potential for curve crossing, was also taken into account in the selection of the most appropriate model.

The lognormal survival model was selected for both OS and PFS for the Tecartus® arm. For the comparator SoC, PFS estimates were not available, and an HR adjustment of 0.727 derived from literature was applied to the OS to model PFS (see section 8.1.1.1 for the details). For OS of SCHOLAR-2, the Weibull distribution was selected. The choices were motivated by good statistical fit to the observed data and the clinical plausibility of extrapolation over the model's time horizon, with no crossing of the OS and PFS curves.

Graphical representations (see [redacted] and [redacted] include the KM survival curves and the fitted parametric distributions for OS and PFS, plotted together with the general background mortality in Denmark over the analysis's time horizon.

D.1 Extrapolation of PFS

D.1.1 Data input

For Tecartus®, the PFS was extrapolated from ZUMA-2 data [redacted]

D.1.2 Model

Standard parametric models were tested and are included in the health economic model. These include exponential, Weibull, Gompertz, gamma, lognormal, log-logistic, and generalised gamma.

D.1.3 Proportional hazards

The model does not rely on proportional hazards, and the assumption was not tested for PFS due to unavailable PFS data from SCHOLAR-2.

D.1.4 Evaluation of statistical fit (AIC and BIC)

Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for Tecartus® are described in Table 53. The lognormal showed the lowest AIC and BIC values, and it was also estimated to have the closest visual fit to the KM data among the standard models. Log-logistic followed closely, with a ΔAIC and ΔBIC smaller than 2.

Table 53 Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for Tecartus® PFS

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1 year	3 years	5 years	10 years	20 years	Mean PFS (months)	Median PFS (months)
Exponential	461.43	463.73	9.51	7.21	73.80%	41.14%	22.57%	5.03%	0.25%	39.97	28.50
Gamma	457.98	462.59	6.07	6.07	69.11%	41.21%	26.00%	8.90%	1.18%	44.82	26.50
Generalised gamma	453.63	460.54	1.72	4.02	62.94%	38.23%	28.27%	17.49%	9.39%	64.32	21.50
Gompertz	455.52	460.13	3.61	3.61	66.16%	37.21%	26.79%	19.27%	12.02%	70.04	22.50
Log-logistic	453.97	458.58	2.05	2.05	**64.67%**	**37.80%**	**26.83%**	**15.64%**	**8.12%**	60.35	21.50
Lognormal	**451.92**	**456.52**	**0.00**	**0.00**	**64.10%**	**38.32%**	**27.47%**	**15.72%**	**7.67%**	**59.98**	**21.50**
Weibull	456.63	461.24	4.71	4.71	67.61%	40.33%	26.32%	10.58%	2.30%	47.80	25.50

Goodness-of-fit data were not available for SCHOLAR-2 as PFS was not measured. The estimated PFS landmarks, mean, and median are shown in Table 54.

Table 54 Landmark survival rates, estimated median, and estimated mean survival for SoC, PFS

PFS	1 year	3 years	5 years	10 years	20 years	Mean (months)	Median (months)
Exponential HR adjustment based on Weibull OS.	49.10%	16.47%	6.31%	0.73%	0.02%	19.3	11.5

D.1.5 Evaluation of visual fit

Visual fit for Tecartus® PFS was evaluated using the RMSD distance from the KM data. A close-up of the distributions is shown [redacted] The distribution with the best fit to the KM estimate was the lognormal.

D.1.6 Evaluation of hazard functions

The smoothed hazard, together with parametric hazards for Tecartus® PFS are shown in [redacted] The observed hazard from the trial is decreasing at the beginning, and it reaches a plateau up until the very end of the follow-up period.

When compared to the smoothed hazard function, most parametric models broadly reflect the observed hazard shape, except the exponential, Gompertz, and gamma distributions, which deviate notably. Among the remaining models, the lognormal and log-logistic distributions demonstrate a closer alignment with the empirical hazard, with slightly better concordance than the Weibull and generalised gamma. Taking into account the overall fit—statistically, visually, and in relation to the hazard shape—the lognormal distribution was selected as the most appropriate model.

D.1.7 Validation and discussion of extrapolated curves

The lognormal distribution was identified as the most suitable distribution for extrapolating Tecartus® PFS, supported by both statistical goodness-of-fit criteria and visual inspection. It reflects the observed hazard profile from the trial and produces a gradually declining PFS trajectory over time, consistent with evidence from ZUMA-2.

D.1.8 Adjustment of background mortality

The PFS was adjusted for Danish background mortality.

D.1.9 Adjustment for treatment switching/cross-over

Not applicable

D.1.10 Waning effect

Not applicable

D.1.11 Cure-point

Not applicable

D.2 Extrapolation of OS

D.2.1 Data input

For Tecartus®, the OS was extrapolated from ZUMA-2 data [redacted] For the SoC comparator, the OS was extrapolated from the unweighted SCHOLAR-2 data [redacted] as explained in section 8.1.

D.2.2 Model

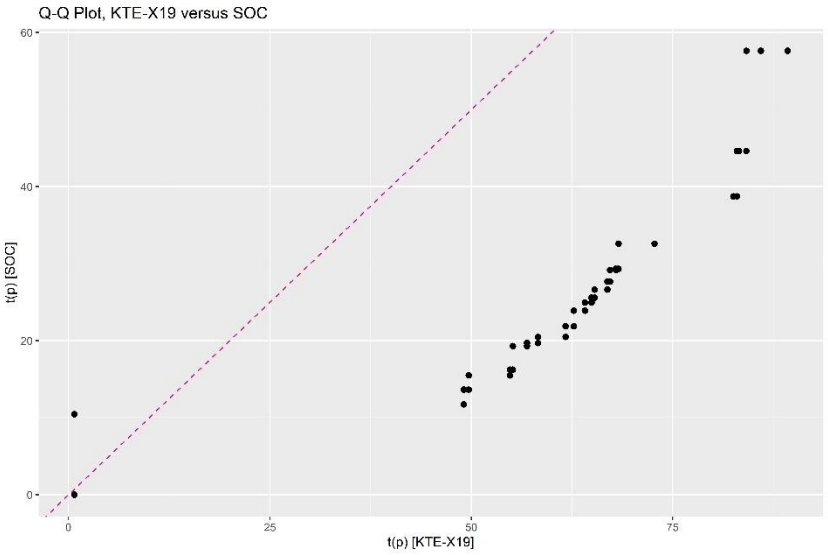
Standard parametric models were tested and included in the health economic model for both intervention and comparator. These are exponential, Weibull, Gompertz, gamma, lognormal, log-logistic, and generalised gamma.

D.2.3 Proportional hazards

The model does not rely on the proportional hazard assumption. Diagnostic plots assessing whether Accelerated Failure Time (AFT) or PH assumptions hold between the two treatment arms for OS are presented in Figure 23 to Figure 25.

The Q-Q plot in Figure 23 shows a deviation from the reference line, with a concave pattern at the lower quantiles and a convex tail at the upper quantiles. This indicates that the observed values are more dispersed than expected under the assumed model. In the context of an AFT model, this suggests that the assumed distribution poorly captures the actual survival time distribution, possibly due to heavier tails in the data. If interpreted under a PH framework, this pattern indicates that the residuals do not follow the expected exponential distribution, pointing to potential violations of the proportional hazard assumption.

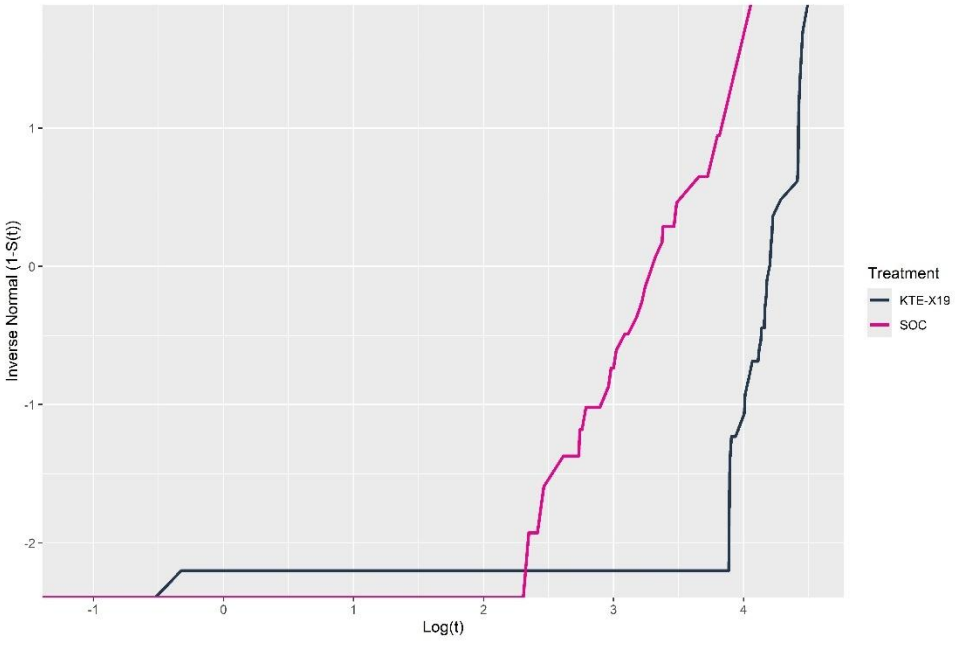
Figure 23 Q-Q Plot, Tecartus® vs SoC



Abbreviations: KTE-X19: Tecartus®; SoC: Standard of care.

The log-cumulative hazard plot shows the two curves crossing (Figure 24). Non-parallel and differently shaped hazard curves may indicate a violation of the PH assumption.

Figure 24 Inverse log-cumulative hazard plot, Tecartus® vs SoC

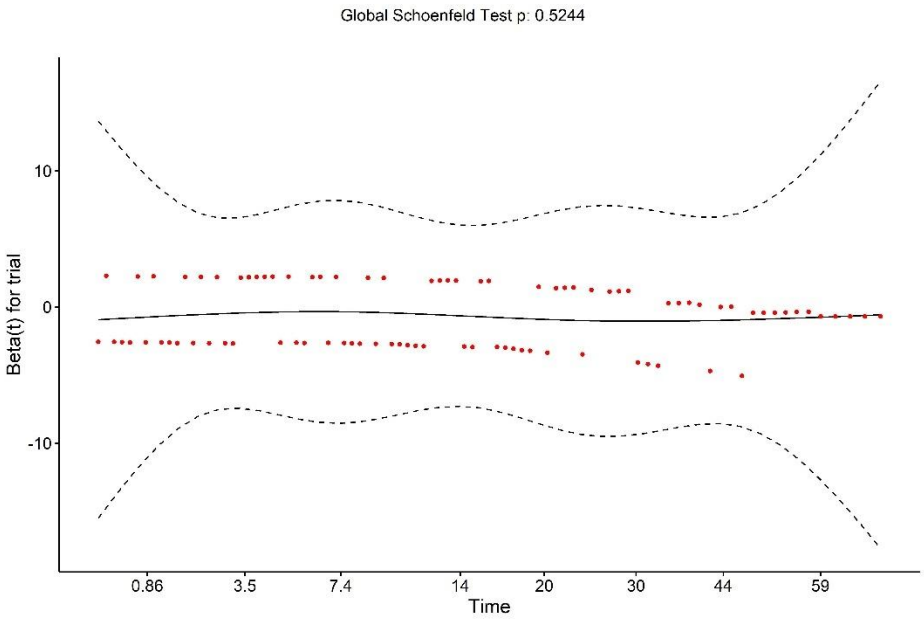


Abbreviations: KTE-X19: Tecartus®; SoC: Standard of care.

Finally, Schoenfeld residuals were also evaluated (Figure 25). The residuals appear random and centred, and the time-varying coefficient remains stable over time, lending credibility to the use of a Cox PH model. Moreover, the p-value of 0.5244 from the global

Schoenfeld test fails to reach statistical significance, implying no evidence of time-dependent effects and thus supporting the validity of the PH assumption.

Figure 25 Schoenfeld residuals plot



Nevertheless, combined with the other diagnostic plots, the PH assumption was rejected, and independent parametric distributions were fitted to the model OS data.

D.2.4 Evaluation of statistical fit (AIC and BIC)

Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for OS Tecartus® are described in Table 53. The Weibull distribution showed the lowest AIC values; however, most distributions have ΔAIC values smaller than 2, which suggests that all models have support from the available evidence. The exponential distribution has the lowest BIC, and while the ΔBIC are slightly larger compared to the ΔAIC, Weibull, gamma, and the log-logistic, lognormal distributions have a reasonably close statistical fit. In terms of landmarks, the exponential distribution is a clear outlier, with the lowest predicted OS rates at 10 and 20 years. The Weibull and gamma distributions show similar trends, while the lognormal and log-logistic distributions exhibit larger OS rates at 10 and 20 years, which align better with the plateau observed in the KM of the clinical trial.

Table 55 Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for Tecartus® OS

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1 yr	3 yrs	5 yrs	10 yrs	20 yrs	Mean OS (months)	Median OS (months)
Exponential	**497.62**	**499.92**	**0.76**	**0.00**	**81.96%**	**54.12%**	**35.73%**	**12.66%**	**1.59%**	**57.8**	**40.5**
Gamma	497.09	501.70	0.23	1.78	77.62%	52.59%	36.91%	16.04%	3.28%	62.7	39.5
Generalised gamma	498.54	505.45	1.68	5.53	76.11%	50.85%	36.99%	19.65%	7.58%	72.1	37.5
Gompertz	497.49	502.10	0.63	2.18	77.98%	50.70%	36.33%	21.17%	11.82%	80.0	36.5
Log-logistic	497.42	502.03	0.56	2.11	75.98%	50.32%	37.54%	22.91%	12.09%	81.9	36.5
Lognormal	497.67	502.28	0.82	2.36	73.80%	49.53%	37.86%	23.86%	12.64%	83.3	35.5
Weibull	**496.86**	**501.47**	**0.00**	**1.55**	**77.10%**	**52.02%**	**36.90%**	**17.15%**	**4.45%**	**65.4**	**38.5**

Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for OS SoC are described in Table 56. SCHOLAR-2 OS data were mature; therefore, the selection of distributions can be guided by the statistical fit. Concerning AIC, the Weibull and gamma distributions had close values, although the latter had the absolute minimum value. None of the distributions but lognormal has a ΔAIC larger than 2; therefore, most distributions were

suitable candidates. For BIC, the best fitting model was the exponential, followed by both gamma and Weibull with a ΔBIC closer to two. The remaining distributions have inferior fits.

Table 56 Goodness-of-fit statistics and landmark survival rates, estimated median, and estimated mean survival for SoC, OS

Distribution	AIC	BIC	ΔMin AIC	ΔMin BIC	1 yr	3 yrs	5 yrs	10 yrs	20 yrs	Mean OS (months)	Median OS (months)
Exponential	**330.71**	**332.79**	**0.08**	**0.00**	**62.99%**	**24.01%**	**9.15%**	**0.82%**	**0.01%**	**24.9**	**17.5**
Gamma	**330.634**	**334.789**	**0.000**	**2.00**	**60.20%**	**26.60%**	**12.41%**	**1.99%**	**0.06%**	**27.1**	**17.5**
Generalised gamma	332.63	338.86	2.00	6.07	**59.95%**	**26.76%**	**12.87%**	**2.34%**	**0.10%**	27.6	17.5
Gompertz	331.92	336.07	1.28	3.29	60.17%	26.15%	14.36%	6.07%	3.09%	36.1	16.5
Log-logistic	332.43	336.59	1.80	3.80	57.81%	30.38%	20.52%	11.28%	5.64%	47.4	16.5
Lognormal	332.75	336.91	2.12	4.12	55.94%	30.95%	21.37%	11.63%	5.45%	47.4	15.5
Weibull	**330.638**	**334.793**	**0.004**	**2.01**	**59.64%**	**26.96%**	**13.43%**	**2.81%**	**0.18%**	**28.4**	**16.5**

D.2.5 Evaluation of visual fit

Visual fit for Tecartus® OS was evaluated using the RMSD distance from the KM data. A close-up of the distributions is shown in [redacted] The distribution closer to the KM data was Weibull.

To guide the selection of the best candidate for the OS extrapolation of Tecartus®, additional attention was given to the curve crossing between OS and the selected, lognormal PFS. All the curves, except lognormal, log-logistic and Gompertz, crossed with the PFS (F[redacted] implying that the predicted OS rate was lower than that of PFS survival. Crossing of OS and PFS curves is clinically implausible, as it contradicts the observed clinical data and introduces unwarranted uncertainty in the survival estimates. Consequently, all OS extrapolations that intersected the selected lognormal PFS curve, identified as the most appropriate based on available evidence, were excluded from consideration.

Visual fit was evaluated for SoC OS as well, using the same methodology. A close-up of the distributions is shown in [redacted] The curve closer to the KM in the trial period is the generalised gamma. Most curves diverge significantly at the end of the trial period, and the fit is generally poor. Lognormal and log-logistic are predicting high OS rates and were the worst visual fit to the KM data.

D.2.6 Evaluation of hazard functions

Hazard functions for Tecartus® OS are shown in [redacted] The observed hazard from the trial initially decreases and then flattens out at approximately 24 months. An increase is observed towards the end of the parametric hazard, starting at 36 months. However, this should be interpreted with caution because as follow-up time increases, the number of patients at risk decreases ([redacted] With few remaining individuals and events, random variation becomes more pronounced, making the smoothed hazard estimates unstable and more susceptible to fluctuations. Furthermore, the kernel smoothing can overfit noise in the tail of the data.

The log-logistic, lognormal, and generalised gamma distributions closely follow the smoothed hazard function but do not project an increase in hazard over time. Among these, the lognormal distribution provides the best overall fit. In contrast, the Gompertz, exponential, and Weibull models demonstrate poor alignment with the observed hazard pattern. Taking into account the visual and statistical goodness-of-fit, as well as the clinical plausibility, particularly the avoidance of curve crossing between the selected lognormal PFS and extrapolated OS, the lognormal distribution was chosen as the most appropriate model for the base case.

For SCHOLAR-2, the observed hazard with the parametric distributions is shown in [redacted] The observed trial hazard drops to zero towards the end of the follow-up, which is not clinically plausible. This is most likely an effect of a few patients still at risk and kernel smoothing at the end of follow-up.

Most parametric distributions align with the initial period of the observed hazard, except for the Gompertz and exponential models, which deviate significantly. Among the better-fitting models, the Weibull distribution was considered to provide the most clinically plausible and reliable extrapolation and was therefore selected for the base case.

D.2.7 Validation and discussion of extrapolated curves

Using the available evidence in the form of statistical fits and clinical plausibility, the lognormal is the most suitable candidate for the extrapolation of Tecartus® OS. For the SoC, Weibull was selected as base case due to its better statistical fit and closer approximation of the hazard shape at the beginning of the observed period.

D.2.8 Adjustment of background mortality

The OS was adjusted for Danish background mortality.

D.2.9 Adjustment for treatment switching/cross-over

Not applicable

D.2.10 Waning effect

Not applicable

D.2.11 Cure-point

Not applicable

Appendix E. Serious AEs

Table 57 Overview of all serious adverse events from ZUMA-2

Adverse events	Brexu-cel (N = 68)	
	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	49 (72%)	N/A
CRS	62 (91%)	N/A
Blood and lymphatic system disorders	7 (10%)	N/A
Anaemia	4 (6%)	N/A
Febrile neutropenia	1 (1%)	N/A
Neutropenia	1 (1%)	N/A
Thrombocytopenia	1 (1%)	N/A
Cardiac disorders	4 (6%)	N/A
Tachycardia	2 (3%)	N/A
Atrial fibrillation	1 (1%)	N/A
Atrial flutter	1 (1%)	N/A
Gastrointestinal disorders	5 (7%)	N/A
Autoimmune colitis	1 (1%)	N/A
Colitis	1 (1%)	N/A
Dysphagia	1 (1%)	N/A
Pancreatic haemorrhage	1 (1%)	N/A
Pancreatitis	1 (1%)	N/A
Rectal haemorrhage	1 (1%)	N/A

Adverse events	Brexu-cel (N = 68)	
Stomatitis necrotising	1 (1%)	N/A
Vomiting	1 (1%)	N/A
General disorders and administration site conditions	15 (22%)	N/A
Pyrexia	14 (21%)	N/A
Chills	1 (1%)	N/A
Fatigue	1 (1%)	N/A
Generalised oedema	1 (1%)	N/A
Multiple organ dysfunction syndrome	1 (1%)	N/A
Hepatobiliary disorders	1 (1%)	N/A
Hypertransaminasaemia	1 (1%)	N/A
Infections and infestations	23 (34%)	N/A
Pneumonia	12 (18%)	N/A
Sepsis	4 (6%)	N/A
Staphylococcal bacteraemia	2 (3%)	N/A
Appendicitis	1 (1%)	N/A
Arthritis infective	1 (1%)	N/A
Bronchitis	1 (1%)	N/A
Cytomegalovirus infection reactivation	1 (1%)	N/A
Device related infection	1 (1%)	N/A
Enterococcal infection	1 (1%)	N/A
Influenza	1 (1%)	N/A

Adverse events	Brexu-cel (N = 68)	
Pneumonia bacterial	1 (1%)	N/A
Respiratory syncytial virus infection	1 (1%)	N/A
Salmonella bacteraemia	1 (1%)	N/A
Septic shock	1 (1%)	N/A
Skin infection	1 (1%)	N/A
Soft tissue infection	1 (1%)	N/A
Upper respiratory tract infection	1 (1%)	N/A
Urinary tract infection	1 (1%)	N/A
Injury, poisoning and procedural complications	1 (1%)	N/A
Femur fracture	1 (1%)	N/A
Investigations	6 (9%)	N/A
Blood creatinine increased	2 (3%)	N/A
Platelet count decreased	2 (3%)	N/A
Alanine aminotransferase increased	1 (1%)	N/A
Aspartate aminotransferase increased	1 (1%)	N/A
Ejection fraction decreased	1 (1%)	N/A
International normalised ratio increased	1 (1%)	N/A
Urine output decreased	1 (1%)	N/A
White blood cell count decreased	1 (1%)	N/A

Adverse events	Brexu-cel (N = 68)	
Metabolism and nutrition disorders	3 (4%)	N/A
Dehydration	1 (1%)	N/A
Hypernatraemia	1 (1%)	N/A
Malnutrition	1 (1%)	N/A
Musculoskeletal and connective tissue disorders	2 (3%)	N/A
Joint effusion	1 (1%)	N/A
Myopathy	1 (1%)	N/A
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (10%)	N/A
Acute myeloid leukaemia	2 (3%)	N/A
B-cell lymphoma	2 (3%)	N/A
Lung neoplasm malignant	1 (1%)	N/A
Myelodysplastic syndrome	1 (1%)	N/A
Plasma cell myeloma	1 (1%)	N/A
Nervous system disorders	20 (29%)	N/A
Encephalopathy	12 (18%)	N/A
Aphasia	3 (4%)	N/A
Immune effector cell-associated neurotoxicity syndrome	3 (4%)	N/A
Lethargy	2 (3%)	N/A
Seizure	2 (3%)	N/A
Brain oedema	1 (1%)	N/A

Appendix F. HRQoL

Table 58 Pattern of missing data and completion – Mobility domain

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomisation	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	68	6 (8.8%)	68	62 (91.2%)
Week 4	68	17 (25.0%)	68	51 (75.0%)
Month 3	68	13 (19.2%)	64	55 (80.8%)
Month 6	68	24 (35.3%)	58	44 (64.7%)

Source: Data of file – ZUMA-2 CSR DCO

Table 59 Pattern of missing data and completion – Self care domain

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomisation	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	68	6 (8.8%)	68	62 (91.2%)
Week 4	68	16 (23.5%)	68	52 (76.5%)
Month 3	68	13 (19.2%)	64	55 (80.8%)
Month 6	68	24 (35.3%)	58	44 (64.7%)

Source: Data of file – ZUMA-2 CSR

Table 60 Pattern of missing data and completion – Usual Activity domain

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomisation	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	68	3 (4.4%)	68	65 (95.6%)
Week 4	68	17 (25.0%)	68	51 (75.0%)
Month 3	68	12 (17.6%)	64	56 (82.4%)
Month 6	68	23 (33.8%)	58	45 (66.2%)

Source: Data of file – ZUMA-2 CSR

Table 61 Pattern of missing data and completion – Pain / Discomfort domain

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomisation	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	68	3 (4.4%)	68	65 (95.6%)
Week 4	68	14 (20.6%)	68	54 (79.4%)
Month 3	68	12 (17.6%)	64	56 (82.4%)
Month 6	68	22 (32.4%)	58	46 (67.6%)

Source: Data of file – ZUMA-2 CSR

Table 62 Pattern of missing data and completion – Anxiety / Depression domain

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomisation	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	68	3 (4.4%)	68	65 (95.6%)
Week 4	68	14 (20.6%)	68	54 (79.4%)
Month 3	68	12 (17.6%)	64	56 (82.4%)
Month 6	68	22 (32.4%)	58	46 (67.6%)

Source: Data of file ZUMA-2 CSR

Table 63 Pattern of missing data and completion – EQ-5D-VAS

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomisation	Number of patients for whom data is missing (% of patients at randomisation)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	68	3 (4.4%)	68	65 (95.6%)
Week 4	68	16 (23%)	68	52 (76.5%)
Month 3	68	12 (17.6%)	64	56 (82.4%)
Month 6	68	22 (32.4%)	58	46 (67.6%)

Source: Data of file ZUMA-2 CSR

Appendix G. Probabilistic sensitivity analyses

Table 64 shows the point estimates and the related distributions in the model, which form the basis for the PSA.

Table 64 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Patient population				
Body weight	81.8	77.97226809	85.62773191	Normal
BSA	1.978	1.92508671	2.03091329	Normal
Resource use for disease management per health state				
Pre-Progression Resource Use: Full blood count	0.39	0.252387437	0.557077522	Beta
Pre-Progression Resource Use: X ray	0.06	0.040446705	0.089275244	Gamma
Pre-Progression Resource Use: Blood glucose	0.02	0.011864367	0.026187405	Gamma
Pre-Progression Resource Use: Lactate dehydrogenase	0.26	0.168258291	0.371385015	Gamma
Pre-Progression Resource Use: Lymphocyte counts	0.39	0.252387437	0.557077522	Gamma
Pre-Progression Resource Use: Bone Marrow Exam	0.06	0.040446705	0.089275244	Gamma
Pre-Progression Resource Use: Office visit	0.39	0.252387437	0.557077522	Gamma
Pre-Progression Resource Use: Inpatient stay	0.03	0.018335839	0.040471444	Gamma
Pre-Progression Resource Use: Biopsy	0.04	0.028582338	0.063087839	Gamma

Pre-Progression Resource Use: Blood transfusion	0.07	0.042603862	0.09403659	Gamma
Pre-Progression Cured: Resource Use: Office visit	0.17	0.107857879	0.238067317	Gamma
Post-Progression Resource Use: Full blood count	0.78	0.503157005	1.110584035	Gamma
Post-Progression Resource Use: X ray	0.06	0.040446705	0.089275244	Gamma
Post-Progression Resource Use: Lactate dehydrogenase	0.44	0.287441247	0.634449401	Gamma
Post-Progression Resource Use: Lymphocyte counts	0.78	0.503157005	1.110584035	Gamma
Post-Progression Resource Use: Platelet infusion	0.17	0.107857879	0.238067317	Gamma
Post-Progression Resource Use: Office visit	0.78	0.503157005	1.110584035	Gamma
Post-Progression Resource Use: Inpatient stay	0.17	0.107857879	0.238067317	Gamma
Post-Progression Resource Use: Blood transfusion	0.33	0.215715758	0.476134635	Gamma
Utilities				
Utility: Pre-progression (up to 600 months)	0.882	0.492393483	0.999843237	Beta
Utility: Pre-progression, cured (beyond 600 months)	0.824	0.47665635	0.992420931	Beta
Utility: Post-progression	0.805	0.755906404	0.849839763	Beta
KTE-X19 Treatment shares				
Infused patients with KTE-X19	0.919	0.846917563	0.969544249	Beta
Bridging Therapy	0.37	0.313295819	0.423718714	Beta

Conditioning chemotherapy	0.932	0.864499013	0.97735441	Beta
Costs				
Admin cost: IV	2,136.00	1382.306577	3051.070738	Gamma
Admin cost: Conditioning Chemotherapy	2,136.00	1382.306577	3051.070738	Gamma
Cost: Initial Hospitalisation: Inpatient Day (Non-ICU)	51,697.00	33455.57262	73844.19661	Gamma
Cost: Stem cell transplant, Total from Mobilization through 100 Days Post-SCT	1,035,036.00	669820.7258	1478449.463	Gamma
Cost: Office visit	2,136.00	1382.306577	3051.070738	Gamma
Cost: X ray	1,731.00	1120.211931	2472.567157	Gamma
Cost: Bone Marrow Exam	16,156.00	10455.31136	23077.29347	Gamma
Cost: Inpatient stay	3,801.80	2460.324506	5430.505961	Gamma
Cost: Biopsy	5,879.00	3804.578823	8397.58655	Gamma
Cost: Blood transfusion	4,218.00	2729.667201	6025.007666	Gamma
Cost: Platelet infusion	6,876.00	4449.784655	9821.705242	Gamma
Cost: CT Scan	2,401.00	1553.800605	3429.597773	Gamma
Cost: PET Scan	1,731.00	1120.211931	2472.567157	Gamma
Hourly wage	188	121.6636875	268.5399339	Gamma
Patient hours: PFS	0.78	0.504774874	1.114155045	Gamma
Patient hours: PD	1.555	1.006314011	2.22116807	Gamma
Patient hours: PFS SoC	4.012	2.596354863	5.730756462	Gamma
Distance to health care provider	20	12.94294548	28.56807808	Gamma

Travel costs per km	3.79	2.452688168	5.413650795	Gamma
Travel: No. of visits PFS	0.39	0.252387437	0.557077522	Gamma
Travel: No. of visits PD	0.7775	0.503157005	1.110584035	Gamma
Travel: No. of visits PFS SoC	2.006	1.298177431	2.865378231	Gamma
AE cost: CRS	7,143.00	4622.572978	10203.08908	Gamma
AE cost: Pyrexia	0.00	0	0	Gamma
AE cost: Anaemia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Platelet Count decreased	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Hypotension	0.00	0	0	Gamma
AE cost: Neutrophil count decreased	2,208.00	1428.901181	3153.915819	Gamma
AE cost: White blood cell count decreased	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Hypoxia	0.00	0	0	Gamma
AE cost: Hypophosphatemia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Neutropenia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Hyponatraemia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Alanine aminotransferase increased	0.00	0	0	Gamma
AE cost: Encephalopathy	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Hypokalaemia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Hypocalcaemia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Thrombocytopenia	2,136.00	1382.306577	3051.070738	Gamma

AE cost: Aspartate aminotransferase increased	0.00	0	0	Gamma
AE cost: Confusional state	0.00	0	0	Gamma
AE cost: Hypertension	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Acute Kidney Injury	51,697.00	33455.57262	73844.19661	Gamma
AE cost: Leukopenia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Lymphocyte count decreased	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Pneumonia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Respiratory Failure	51,697.00	33455.57262	73844.19661	Gamma
AE cost: Sepsis	51,697.00	33455.57262	73844.19661	Gamma
AE cost: Febrile Neutropenia	2,136.00	1382.306577	3051.070738	Gamma
AE cost: Lymphopenia	2,136.00	1382.306577	3051.070738	Gamma
AE frequencies				
KTE-X19 AE incidence: Cytokine release syndrome (CRS)	15.0%	0.054637799	0.282200908	Beta
KTE-X19 AE incidence: Pyrexia	13.0%	0.058245273	0.224867326	Beta
KTE-X19 AE incidence: Anaemia	51.0%	0.391313896	0.62812052	Beta
KTE-X19 AE incidence: Platelet Count decreased	38.0%	0.268310308	0.498494398	Beta
KTE-X19 AE incidence: Hypotension	22.0%	0.129916448	0.325925149	Beta
KTE-X19 AE incidence: Neutrophil count decreased	53.0%	0.410903854	0.647398375	Beta

KTE-X19 AE incidence: White blood cell count decreased	41.0%	0.295974173	0.529124448	Beta
KTE-X19 AE incidence: Hypoxia	21.0%	0.122510329	0.313621059	Beta
KTE-X19 AE incidence: Hypophosphatemia	22.0%	0.129916448	0.325925149	Beta
KTE-X19 AE incidence: Neutropenia	34.0%	0.232492924	0.456532801	Beta
KTE-X19 AE incidence: Hyponatraemia	10.0%	0.040183221	0.182850803	Beta
KTE-X19 AE incidence: Alanine aminotransferase increased	9.0%	0.034754905	0.167812136	Beta
KTE-X19 AE incidence: Encephalopathy	18.0%	0.098876792	0.278891924	Beta
KTE-X19 AE incidence: Hypokalaemia	7.0%	0.011547553	0.174617746	Beta
KTE-X19 AE incidence: Hypocalcaemia	6.0%	0.011868882	0.142983931	Beta
KTE-X19 AE incidence: Thrombocytopenia	16.0%	0.082813528	0.256521979	Beta
KTE-X19 AE incidence: Aspartate aminotransferase increased	10.0%	0.040183221	0.182850803	Beta
KTE-X19 AE incidence: Confusional state	12.0%	0.054679453	0.206320459	Beta
KTE-X19 AE incidence: Hypertension	13.0%	0.060787121	0.22035462	Beta
KTE-X19 AE incidence: Acute Kidney Injury	7.0%	0.021629922	0.143485442	Beta
KTE-X19 AE incidence: Leukopenia	15.0%	0.076186853	0.243207296	Beta

KTE-X19 AE incidence: Lymphocyte count decreased	9.0%	0.034754905	0.167812136	Beta
KTE-X19 AE incidence: Pneumonia	16.0%	0.088150015	0.248196759	Beta
KTE-X19 AE incidence: Respiratory Failure	6.0%	0.017182776	0.126852608	Beta
KTE-X19 AE incidence: Sepsis	6.0%	0.017182776	0.126852608	Beta
KTE-X19 AE incidence: Febrile Neutropenia	9.0%	0.042338208	0.15316785	Beta
KTE-X19 AE incidence: Lymphopenia	6.0%	0.017182776	0.126852608	Beta
Extrapolations				
PFS_KTE-X19_Lognormal mu	3.061	N/A	N/A	Cholesky
PFS_KTE-X19_Lognormal Log_Sigma	0.538	N/A	N/A	Cholesky
OS_KTE-X19_Lognormal mu	3.549	N/A	N/A	Cholesky
OS_KTE-X19_Lognormal Log_Sigma	0.552	N/A	N/A	Cholesky
OS_SOC_Weibull_LogScale	3.242	N/A	N/A	Cholesky
OS_SOC_Weibull_LogShape	-0.192	N/A	N/A	Cholesky

Appendix H. Literature searches for the clinical assessment

Not applicable.

H.1 Efficacy and safety of the intervention and comparator(s)

Table 65 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	E.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm.yyyy
CENTRAL	Wiley platform		dd.mm.yyyy

Abbreviations:

Table 66 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
e.g. EMA website			dd.mm.yyyy

Abbreviations:

Table 67 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Manual search	List individual terms used to search in the conference material:	dd.mm.yyyy
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

H.1.1 Search strategies

Table 68 of search strategy table for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

H.1.2 Systematic selection of studies

Table 69 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population			
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

Table 70 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1						
Study 2						

H.1.3 Excluded fulltext references

H.1.4 Quality assessment

H.1.5 Unpublished data

Appendix I. Literature searches for HRQoL

Not applicable.

I.1 Health-related quality-of-life search

Table 71 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

Table 72 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
CEA Registry	Tufts CEA - Tufts CEA		dd.mm.yyyy

Table 73 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the congress material:	dd.mm.yyyy

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies

Table 74 Search strategy for [name of database]

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

I.1.2 Quality assessment and generalizability of estimates

I.1.3 Unpublished data

Appendix J. Literature searches for input to the health economic model

Not applicable.

J.1 External literature for input to the health economic model

J.1.1 Example: Systematic search for […]

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

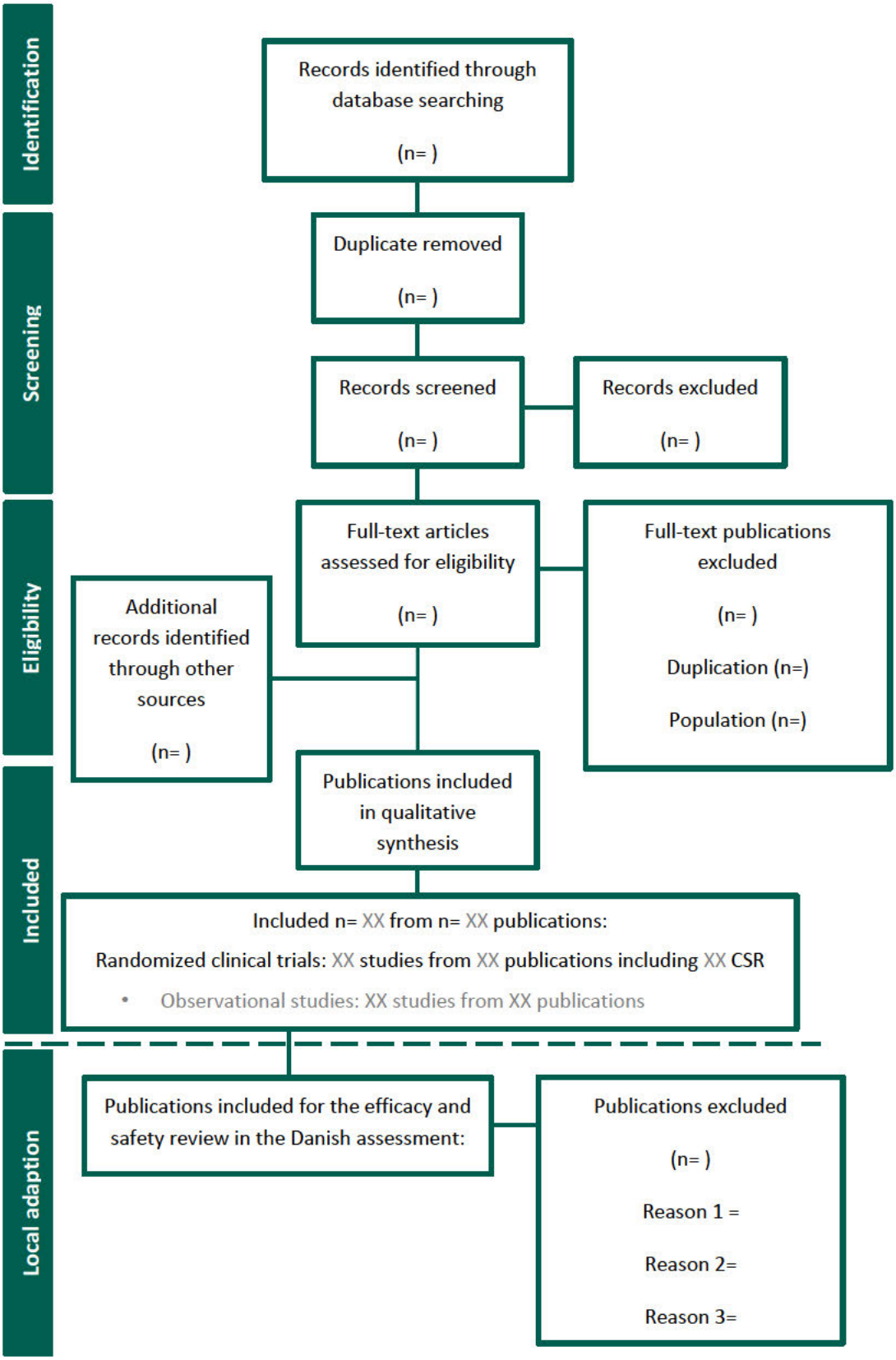
J.1.2 Example: Targeted literature search for [estimates]

Table 52 Sources included in the targeted literature search

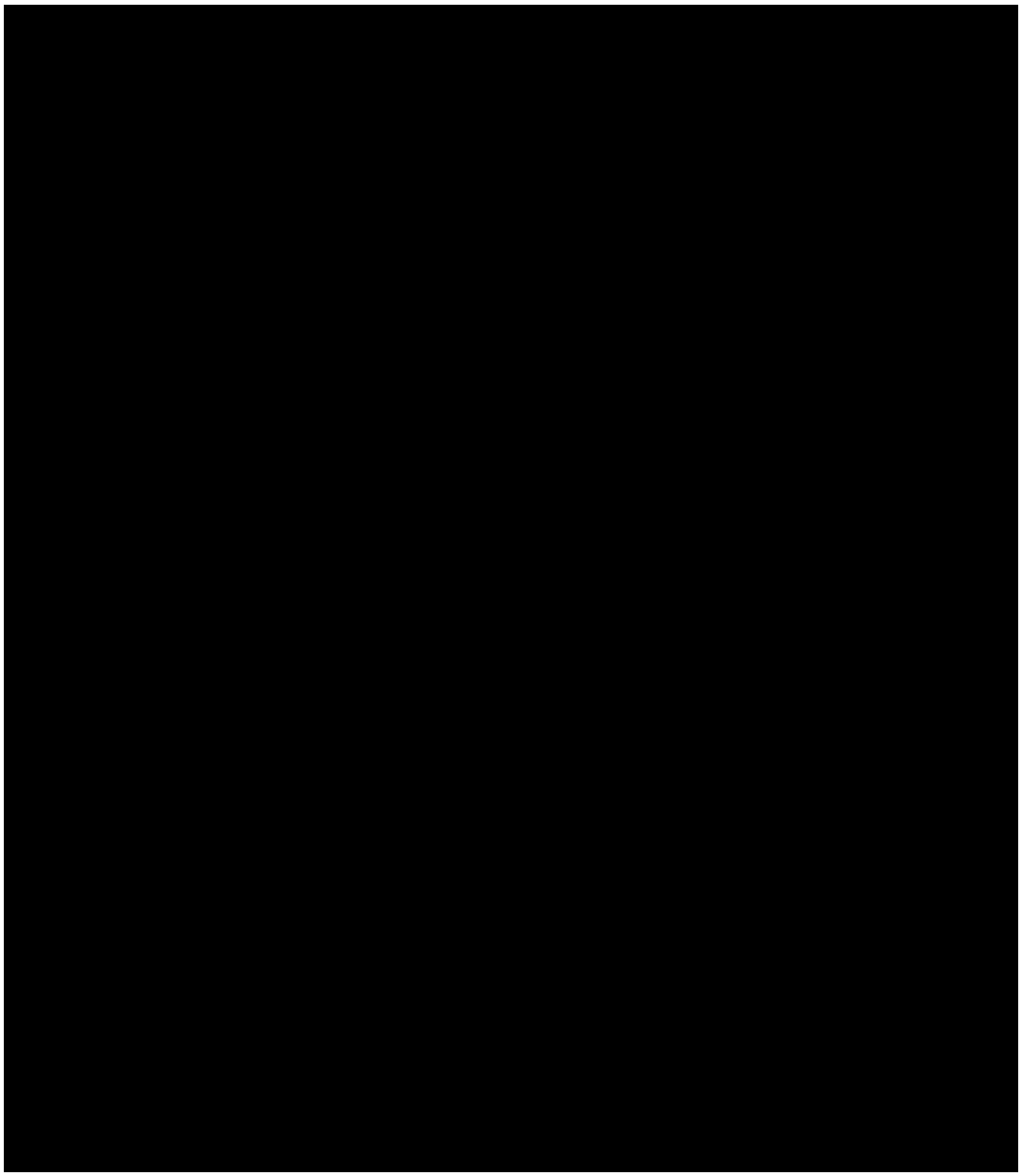
Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

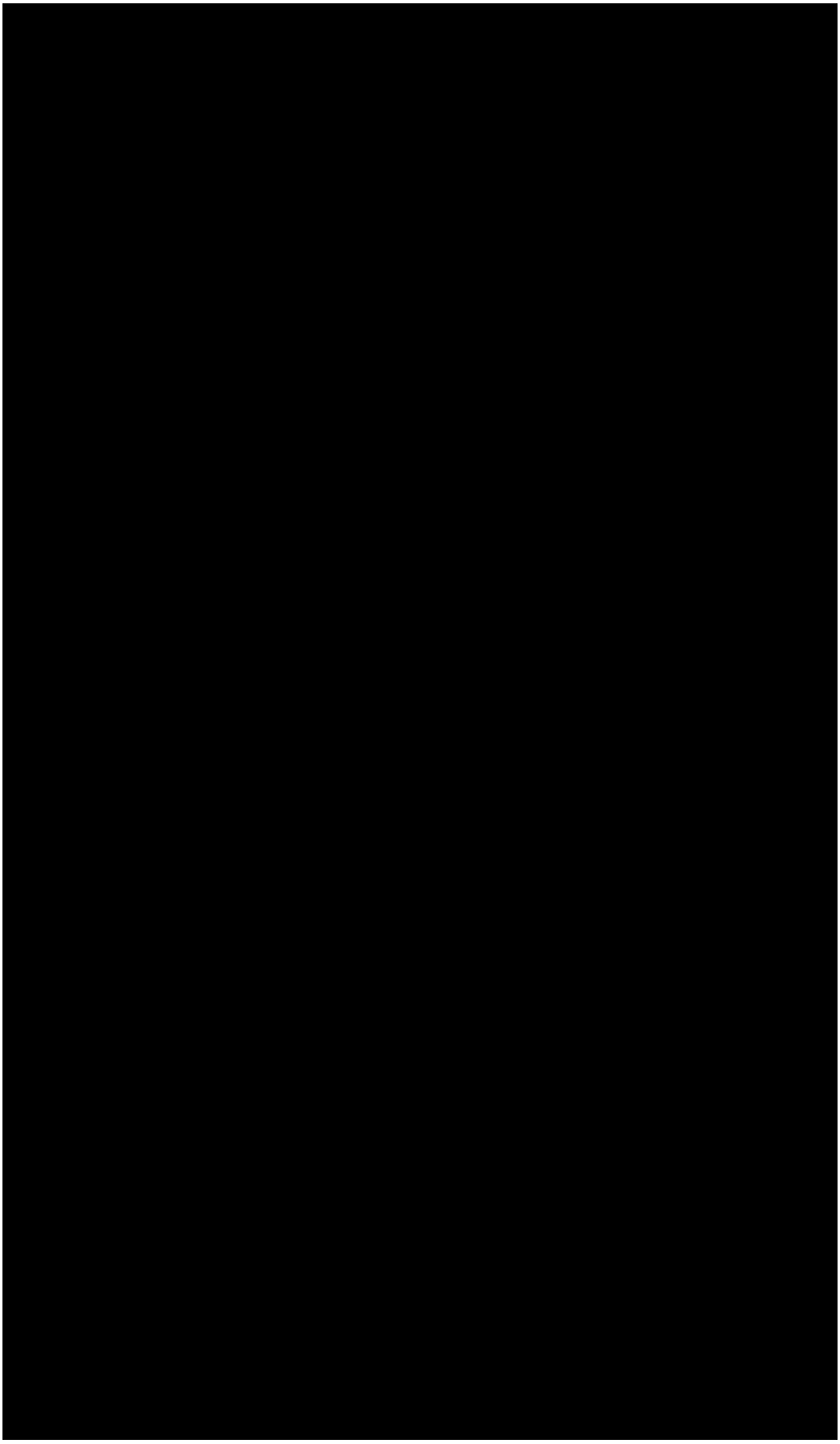
Abbreviations:

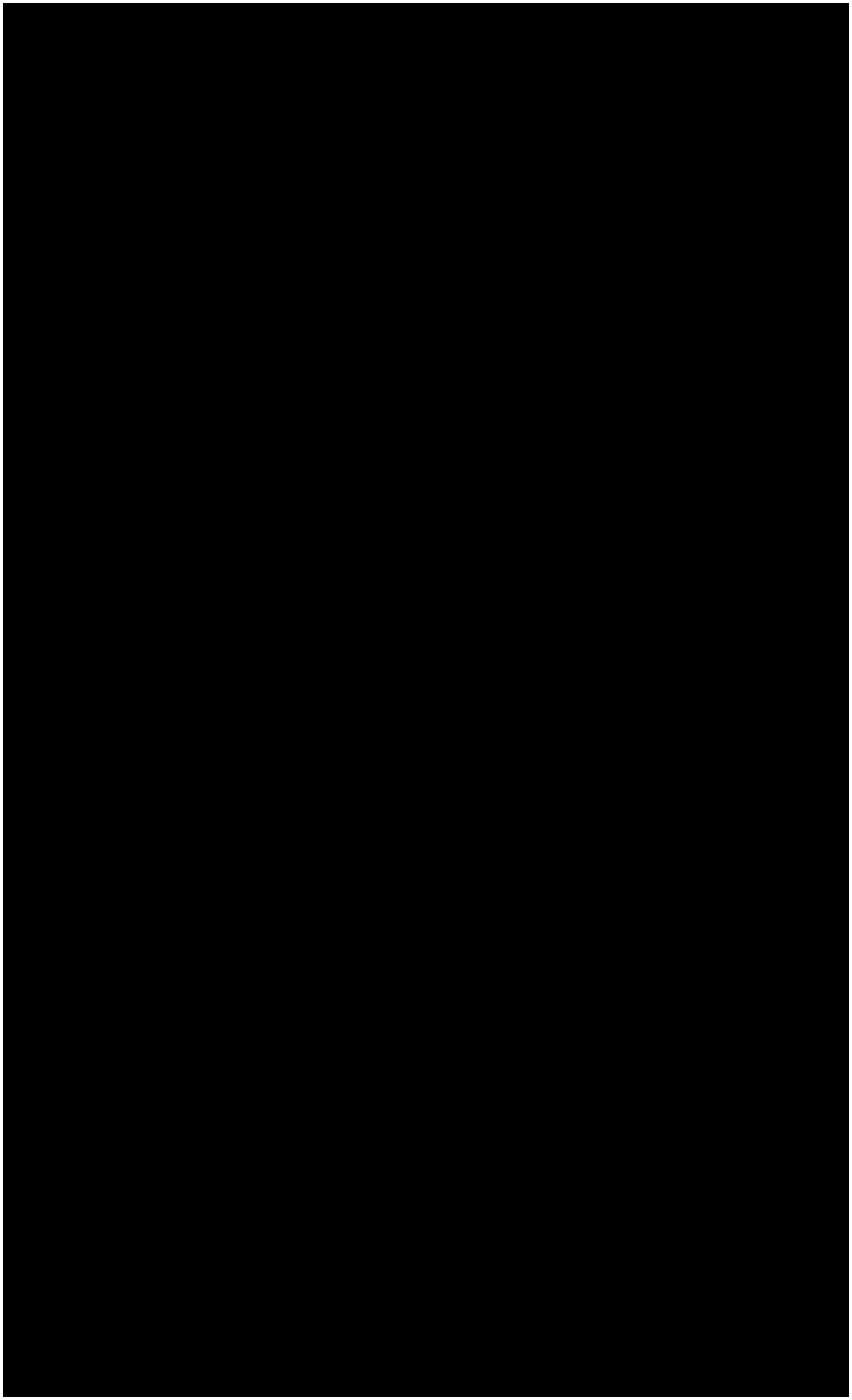
Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.

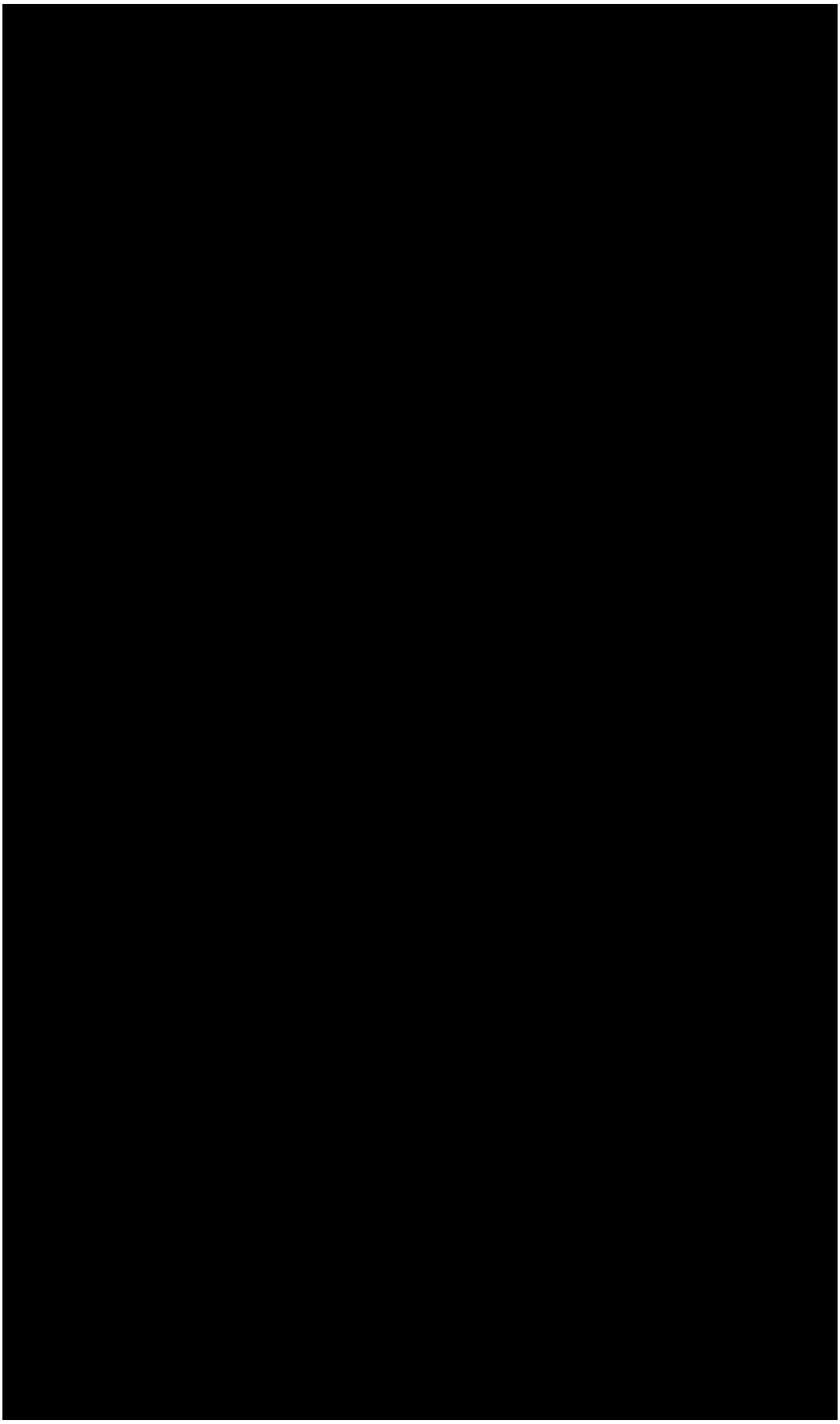


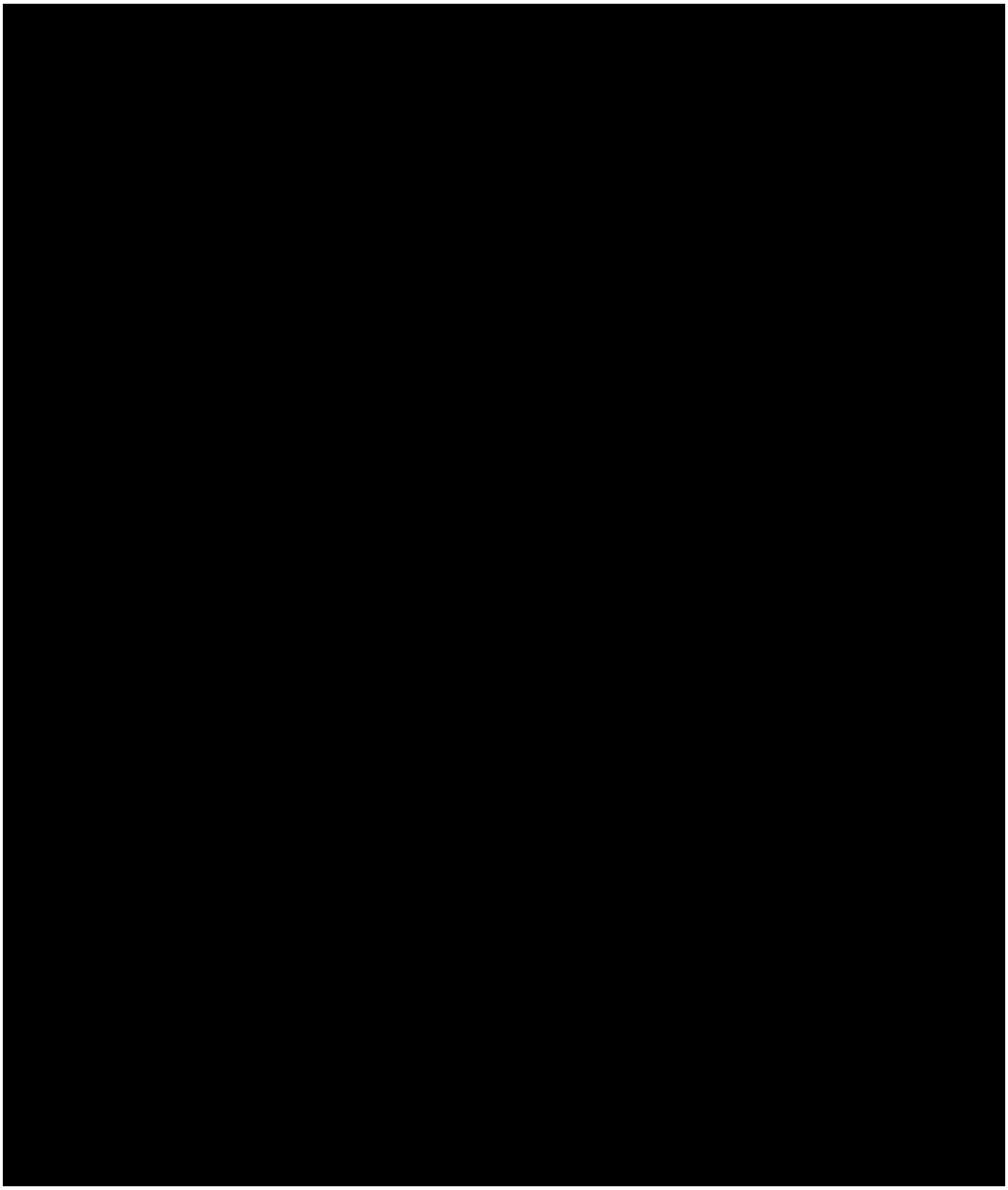
Appendix K. Updated Meta-Analysis and Indirect Comparison of Interventions for Relapsed or Refractory Mantle Cell Lymphoma Previously Treated with Bruton Tyrosine Kinase Inhibitors

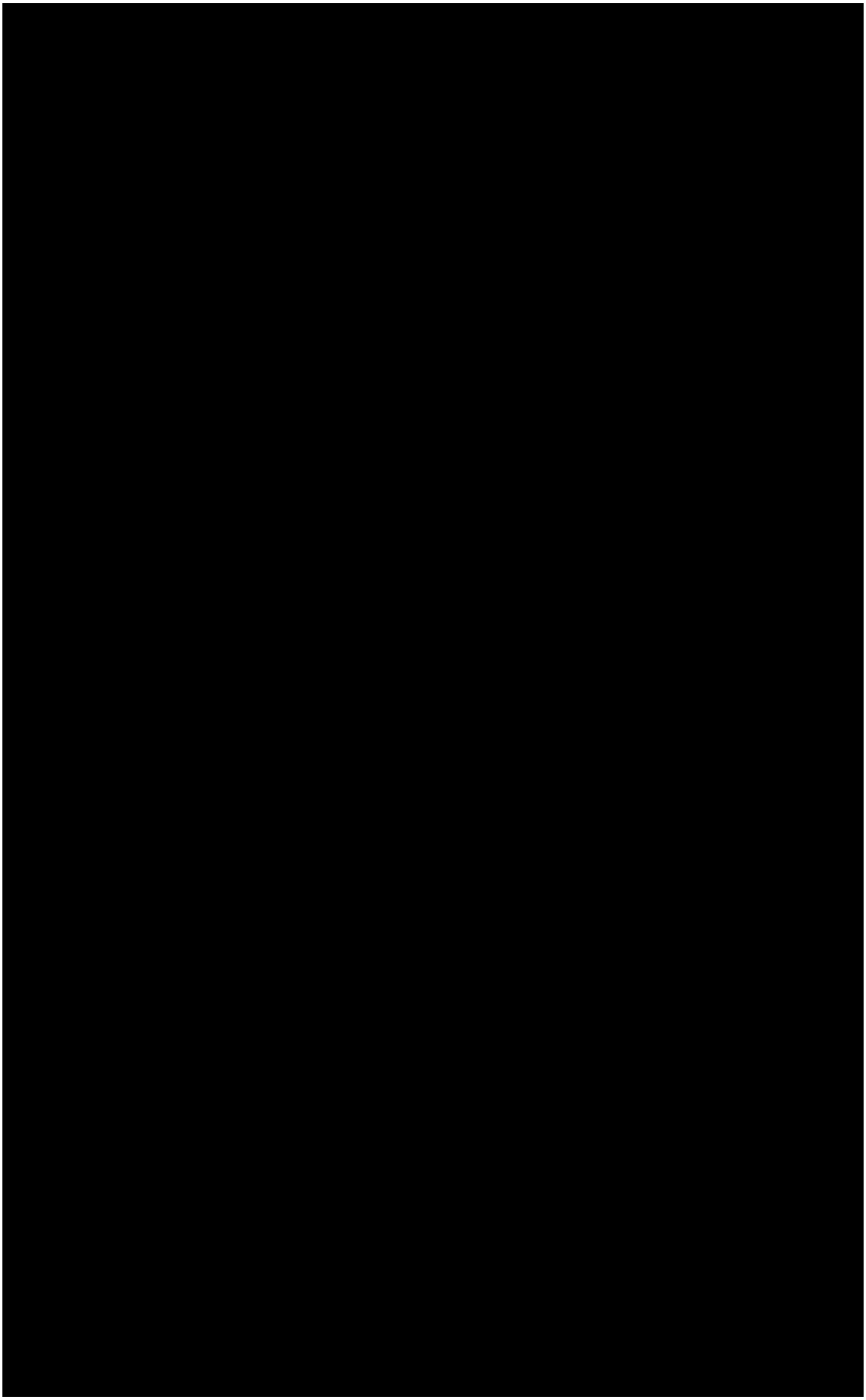


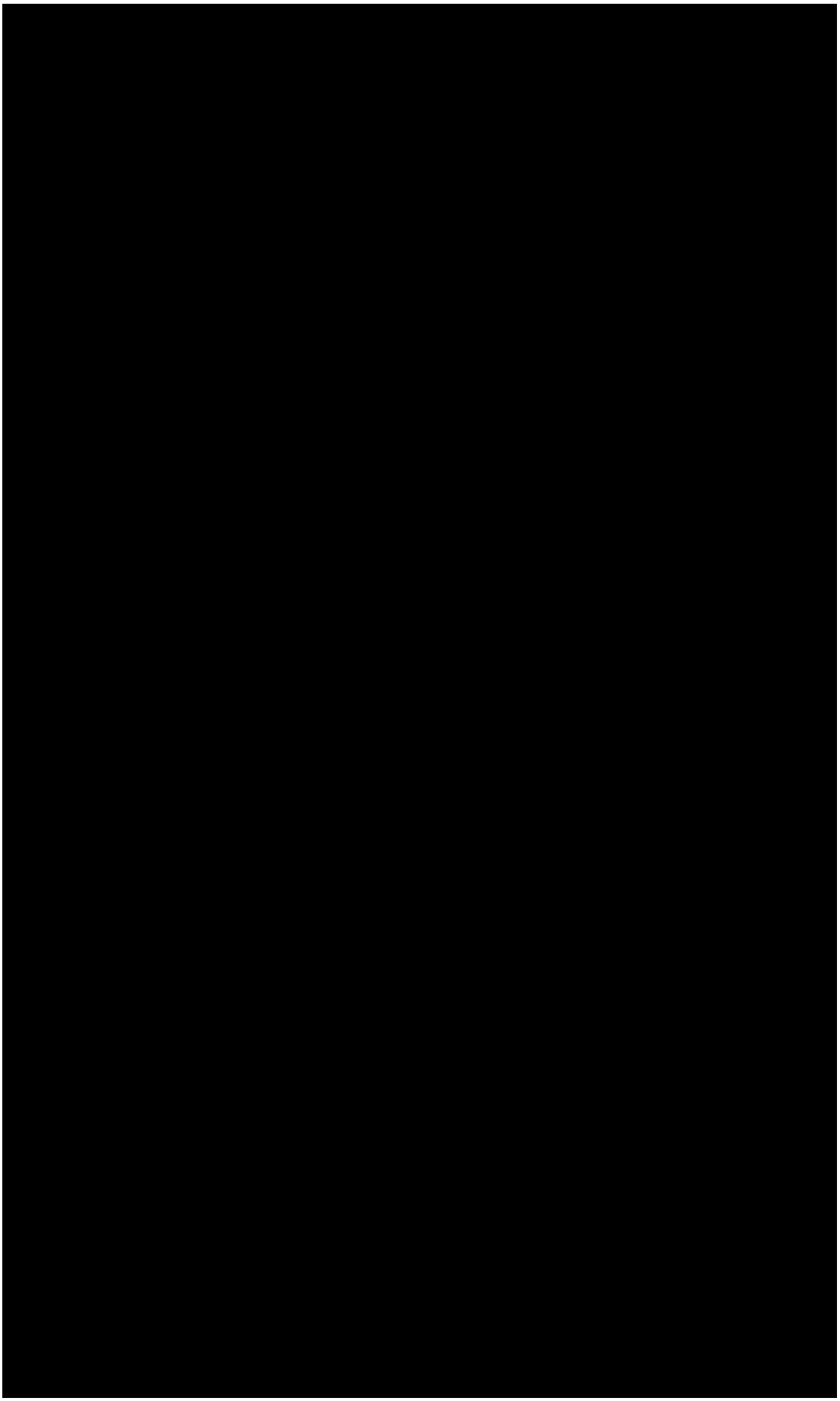


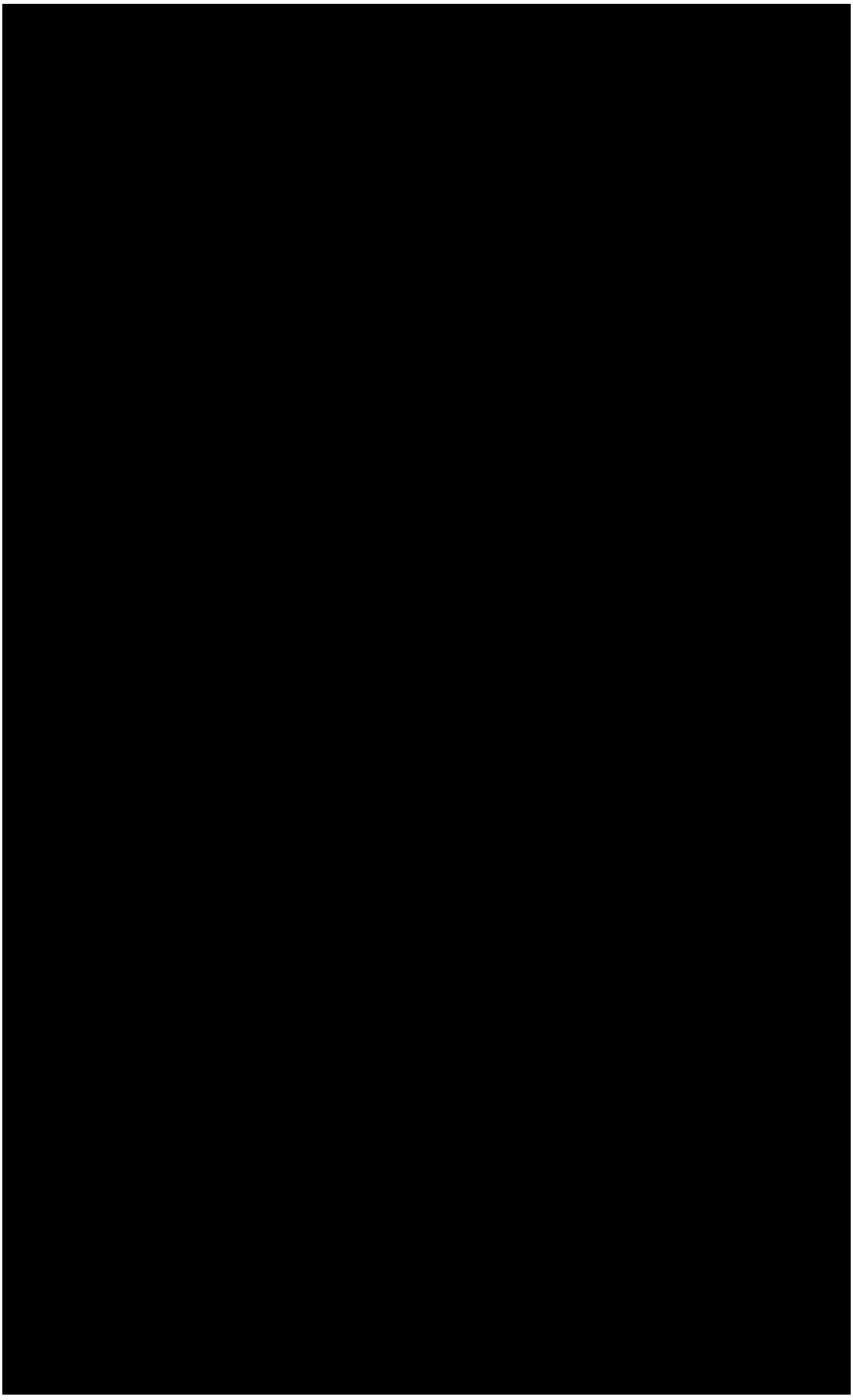


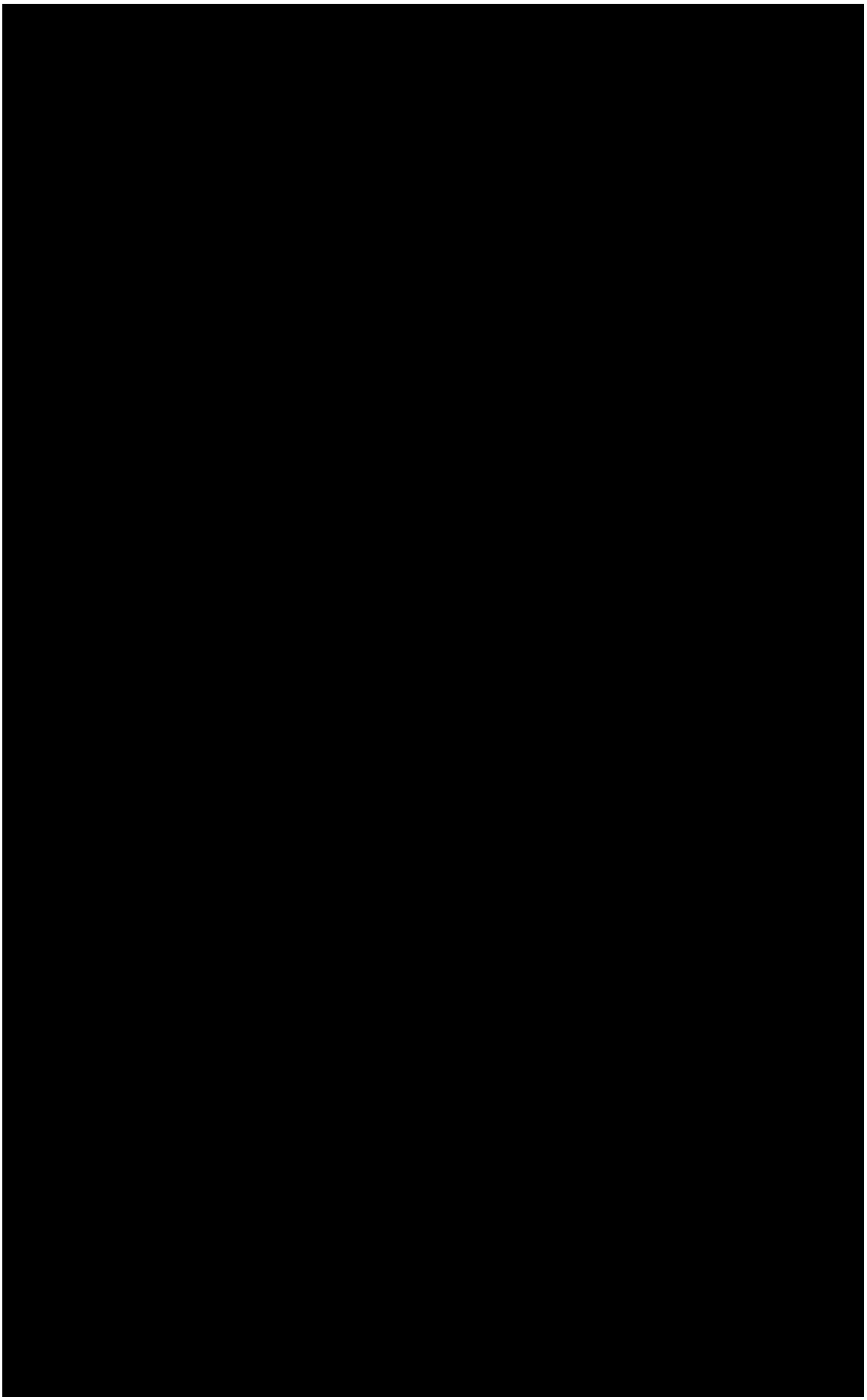


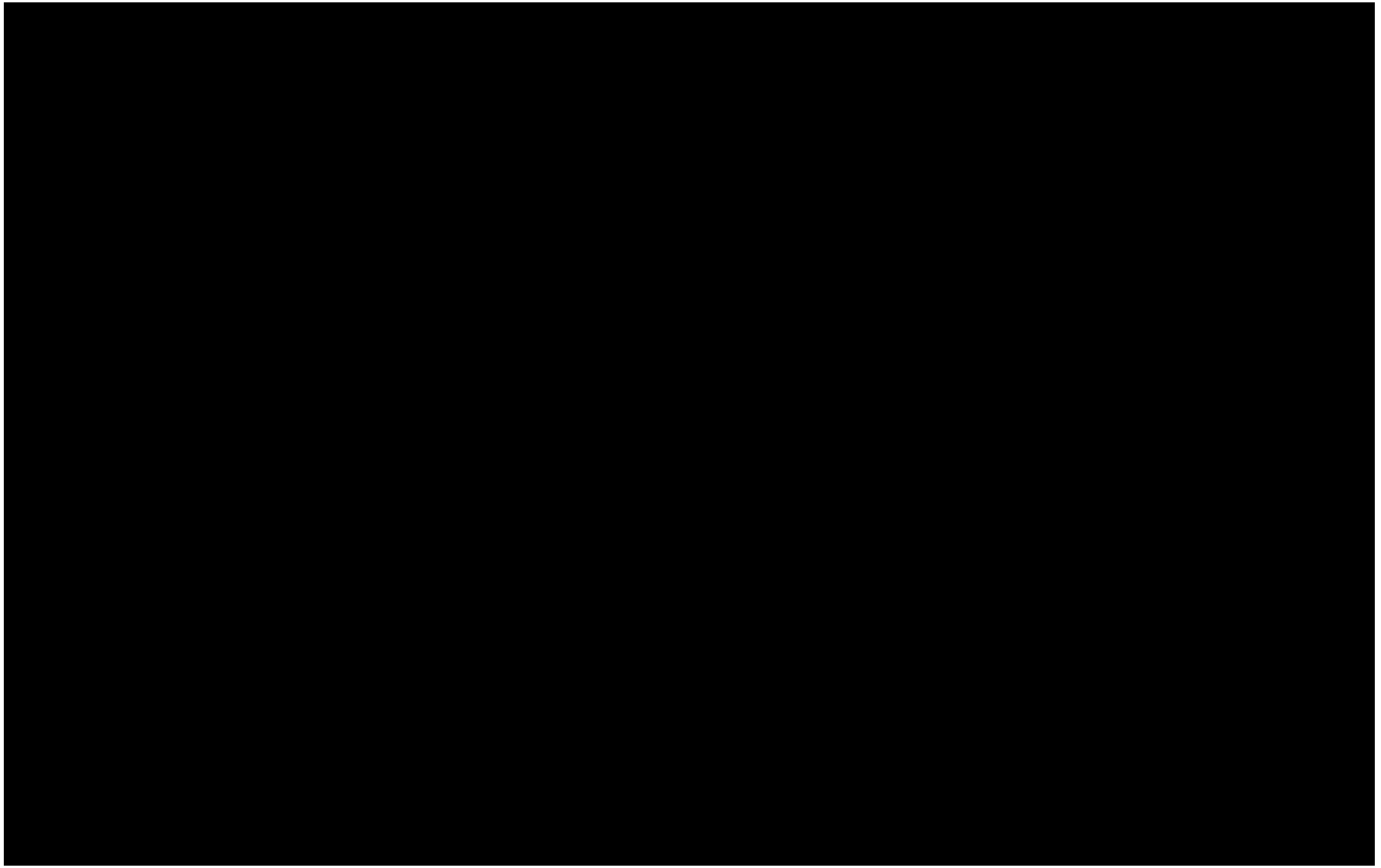












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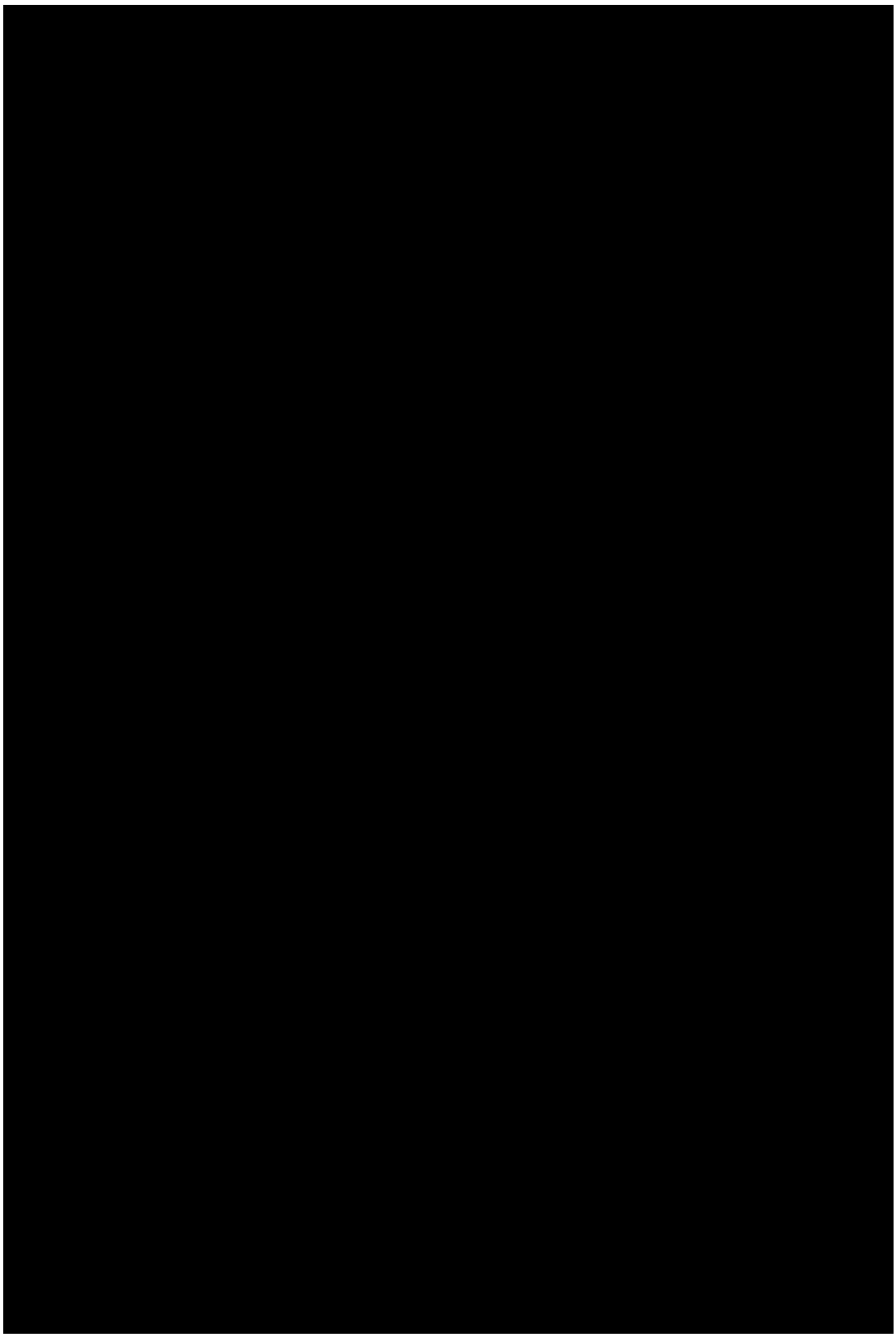

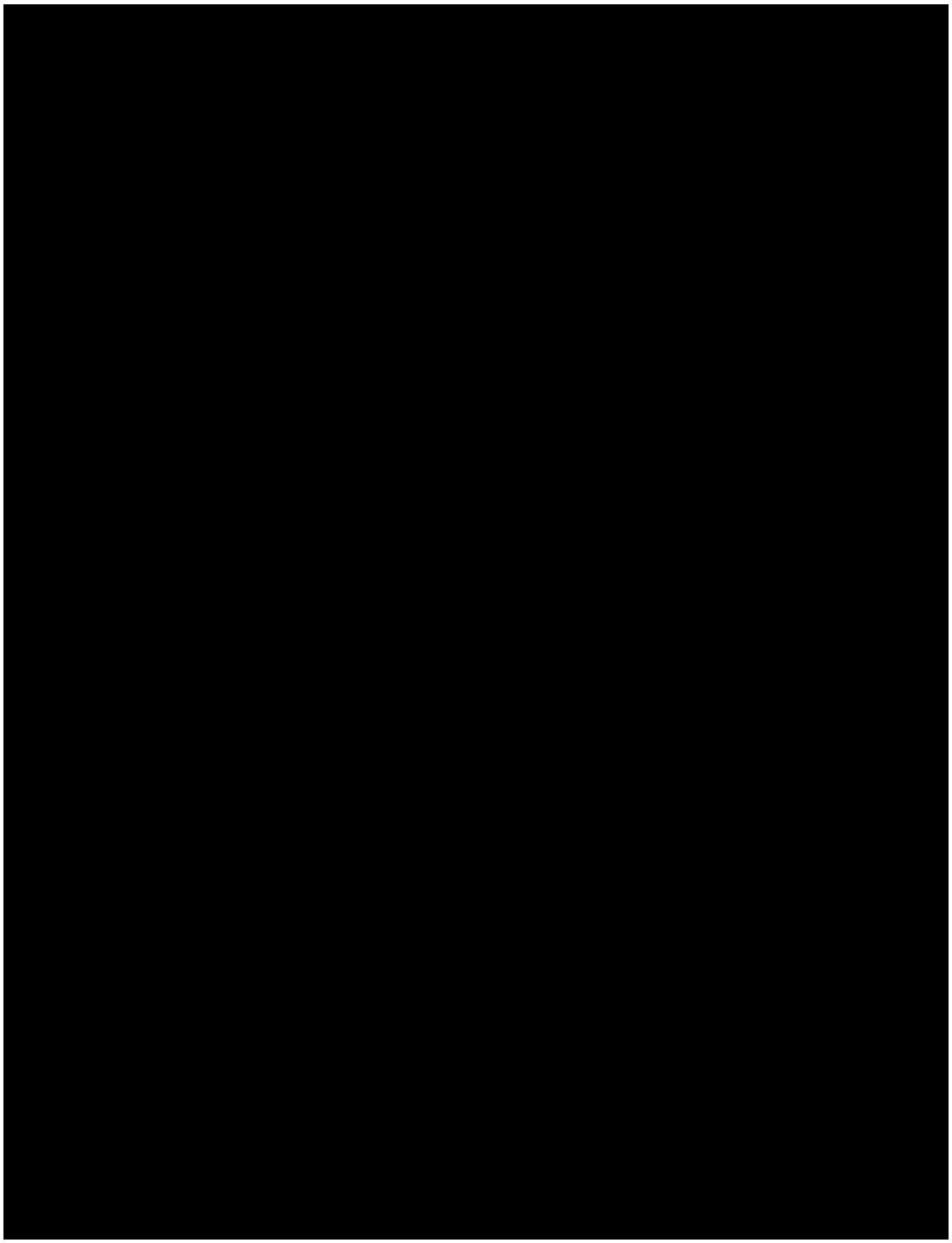

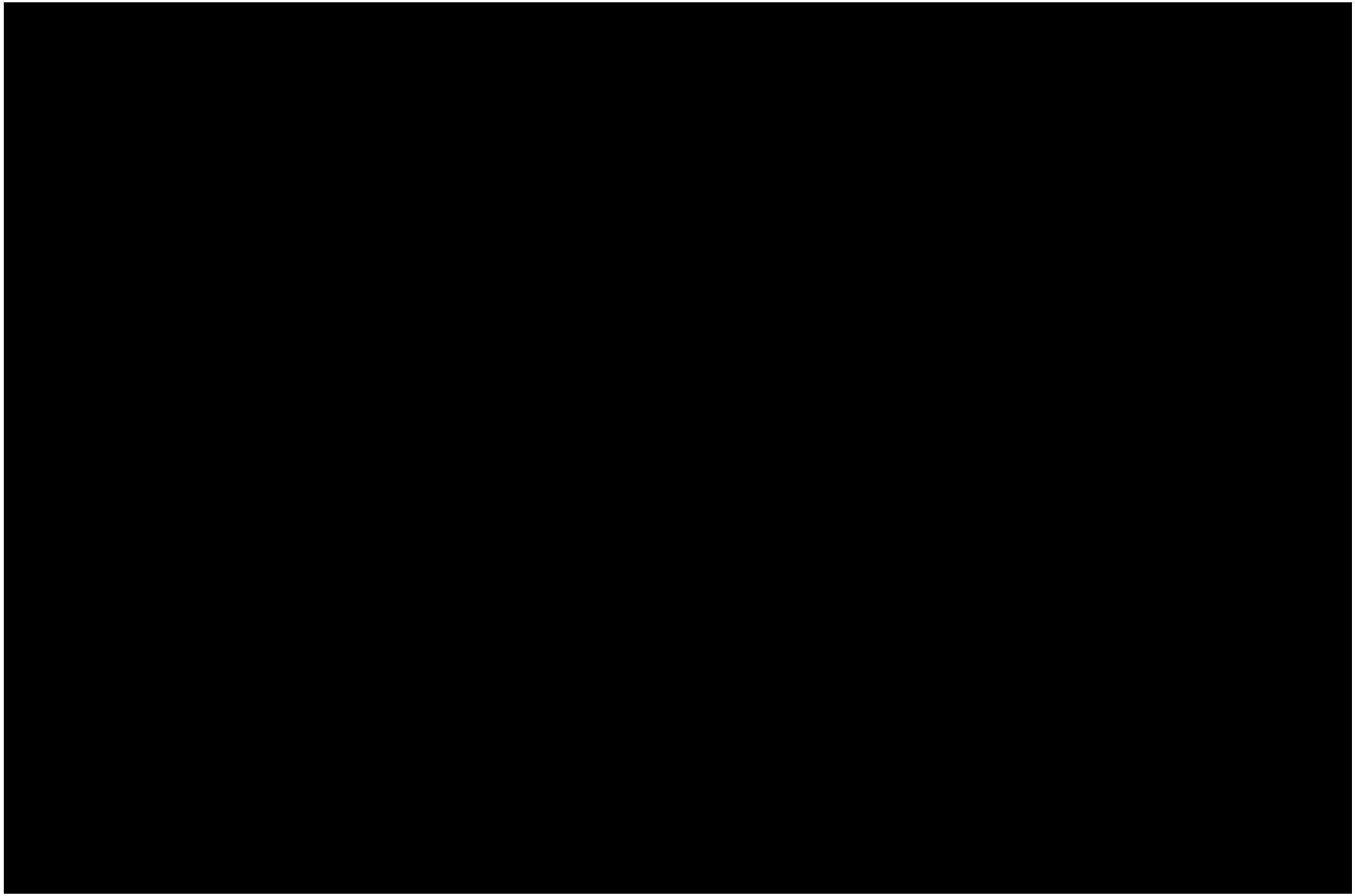

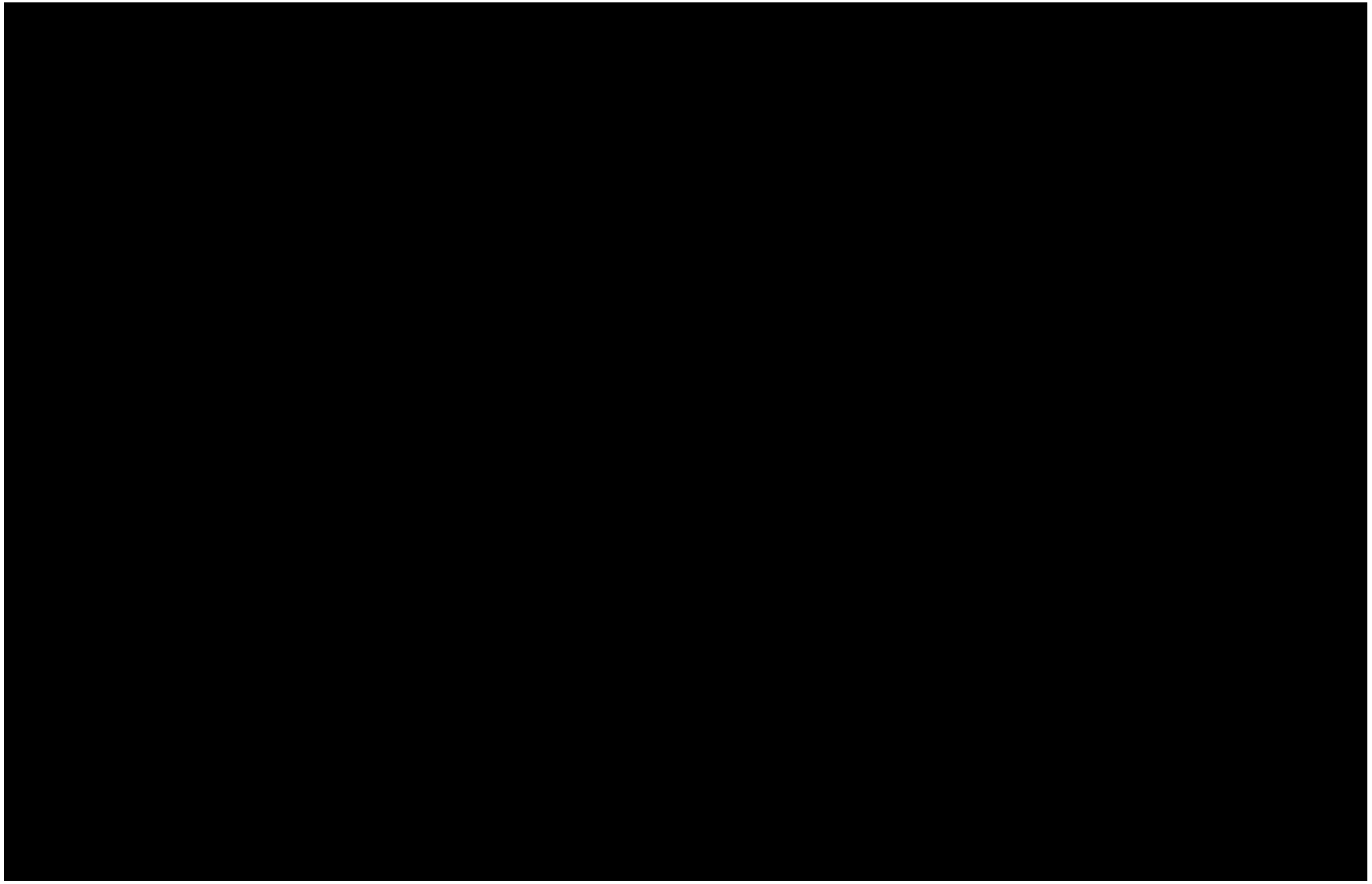

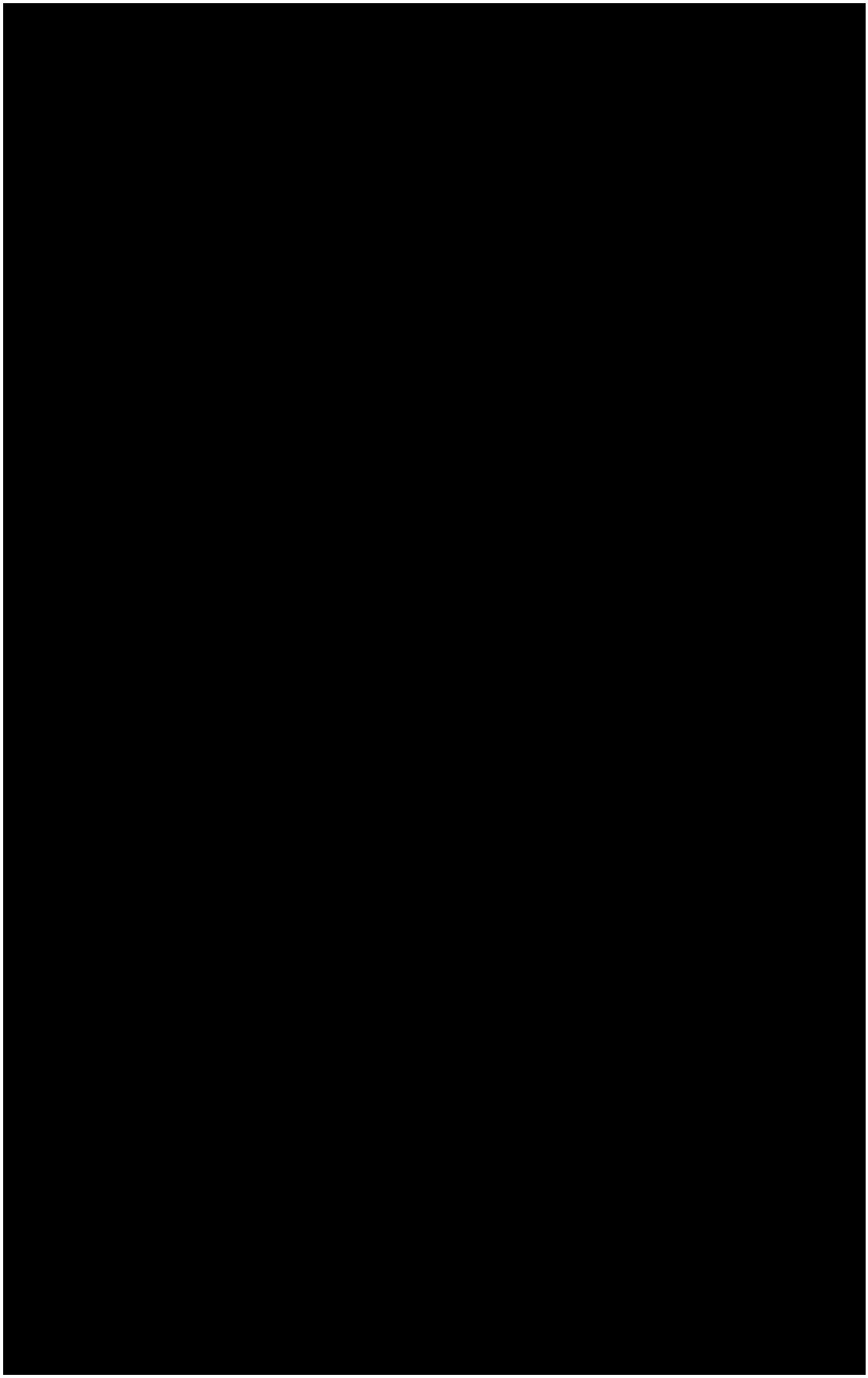

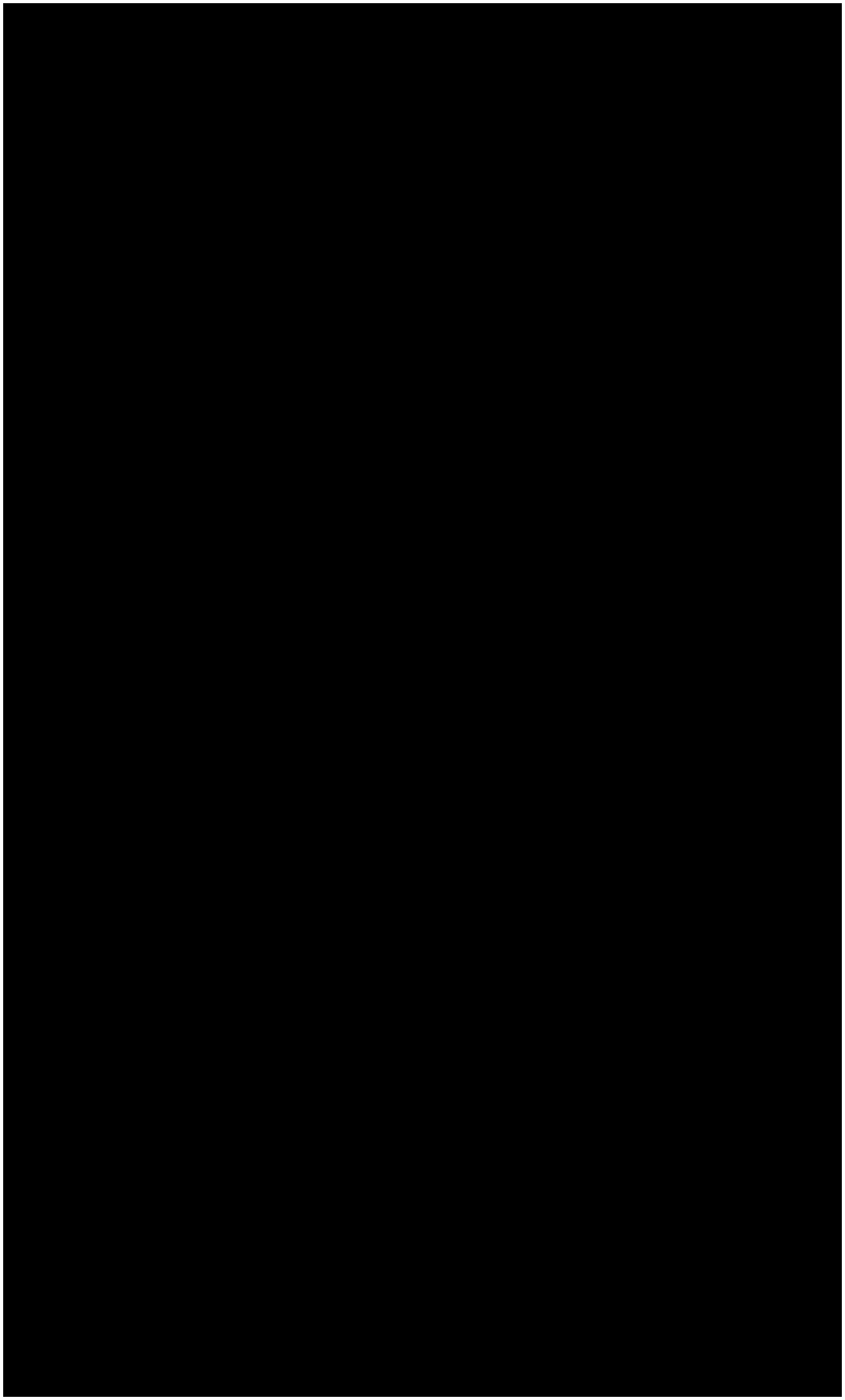

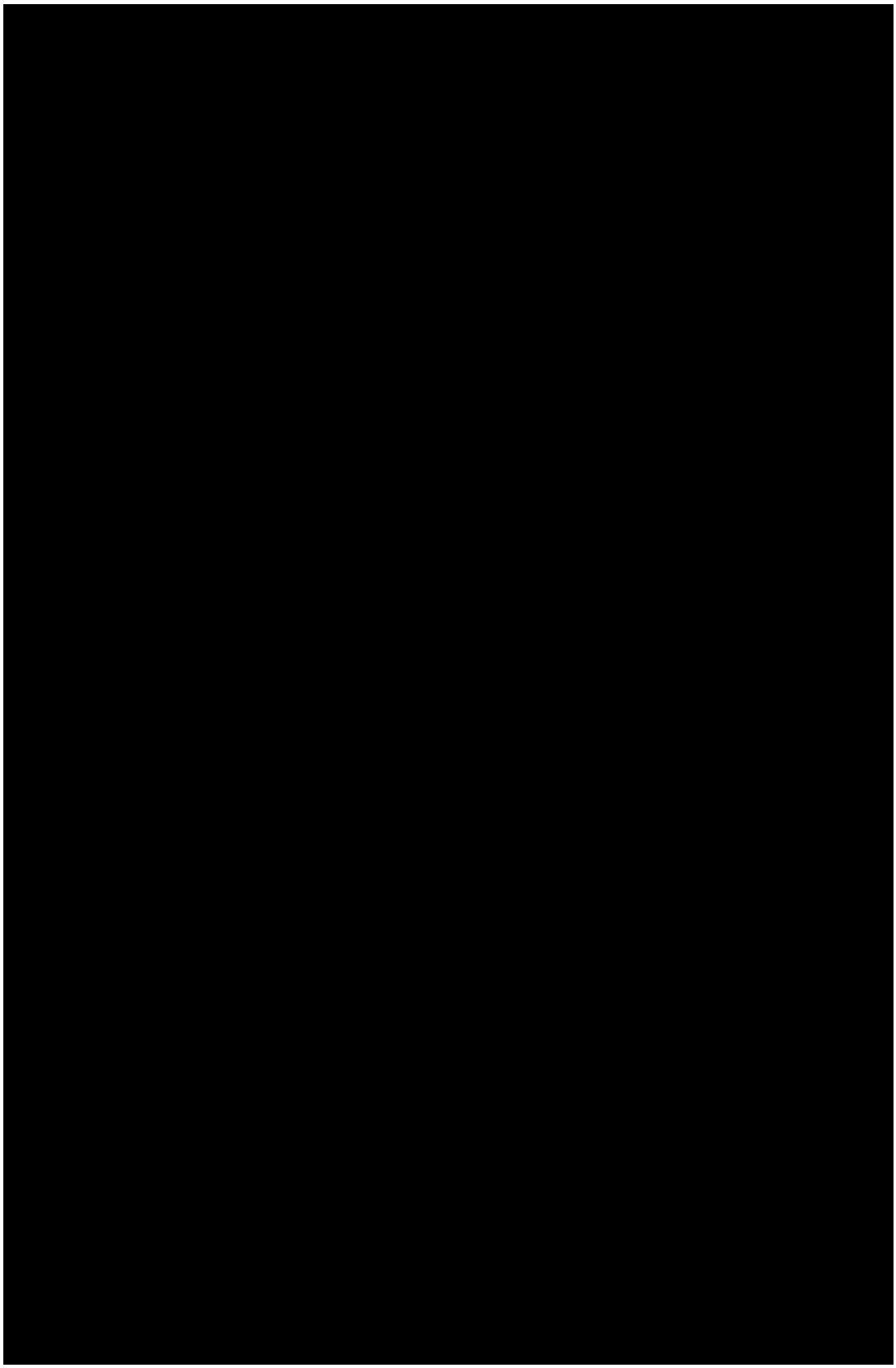

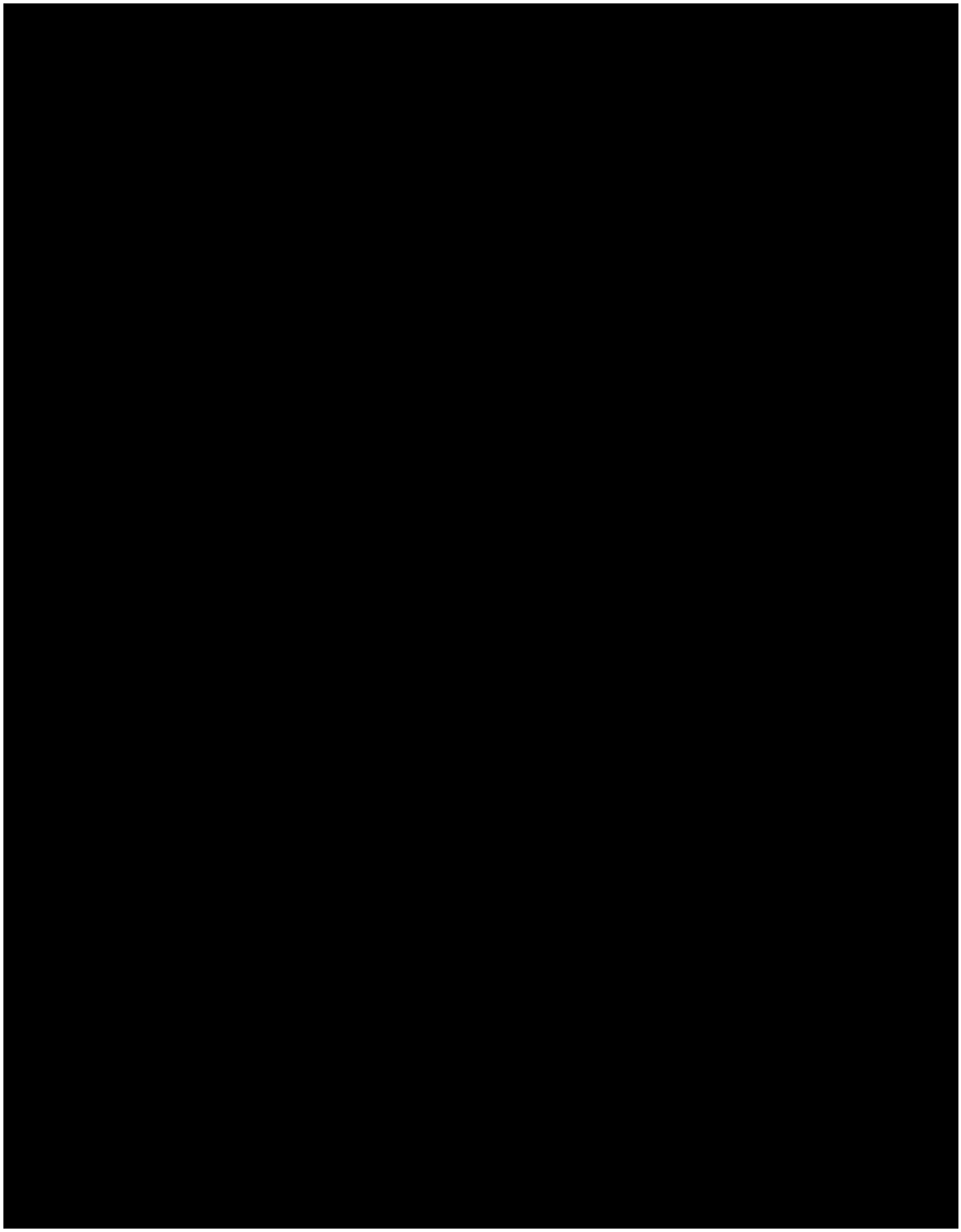

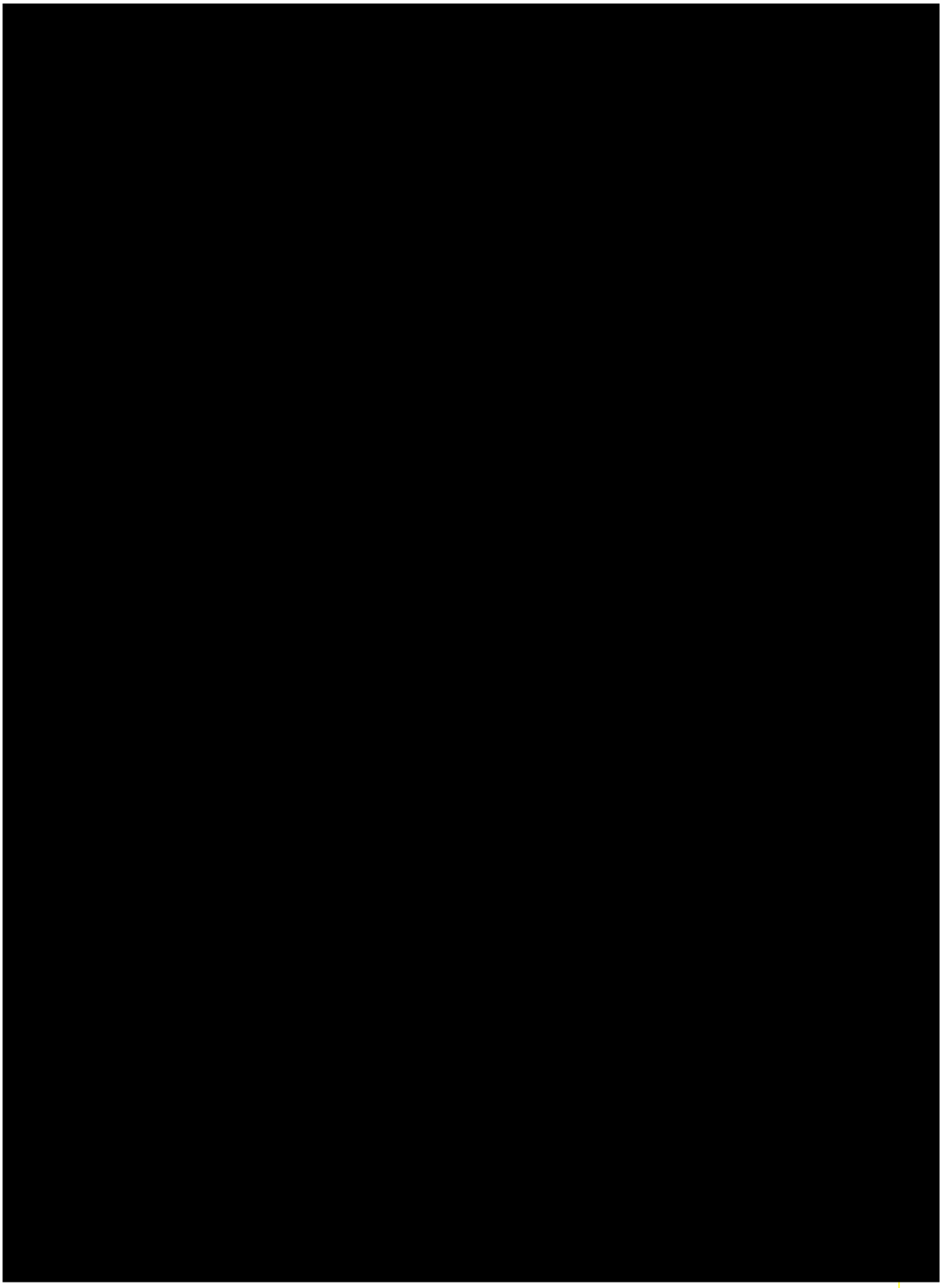

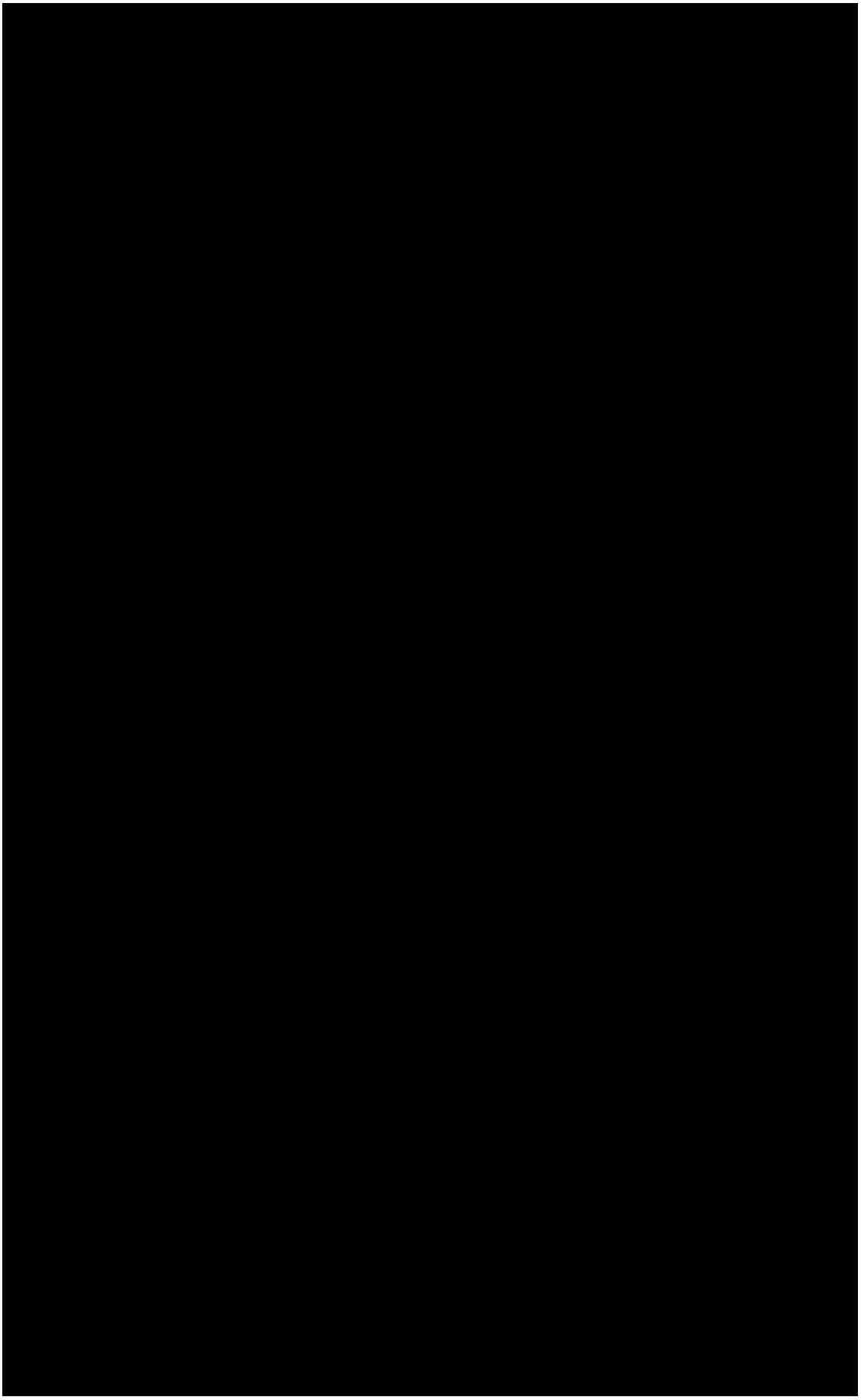

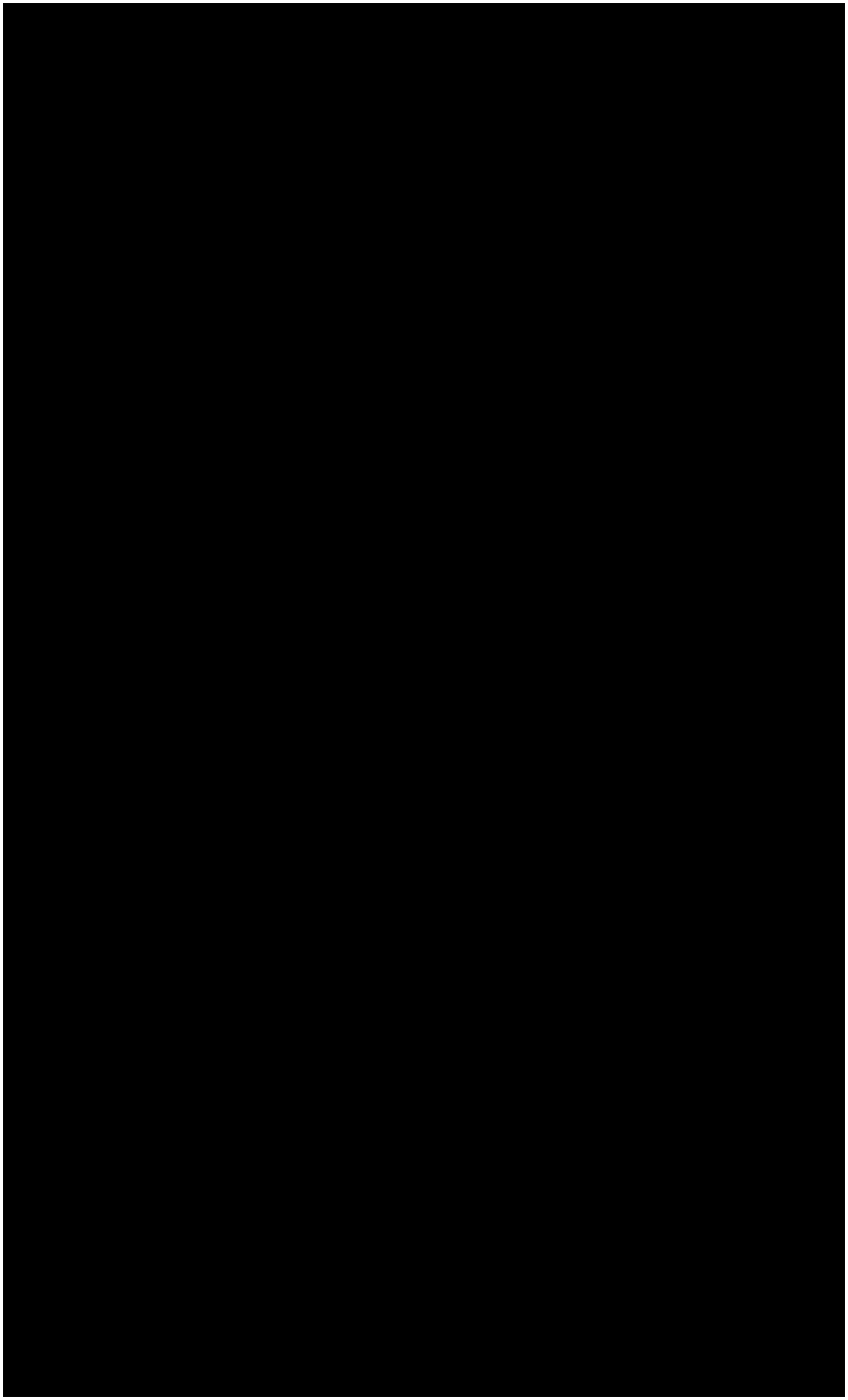

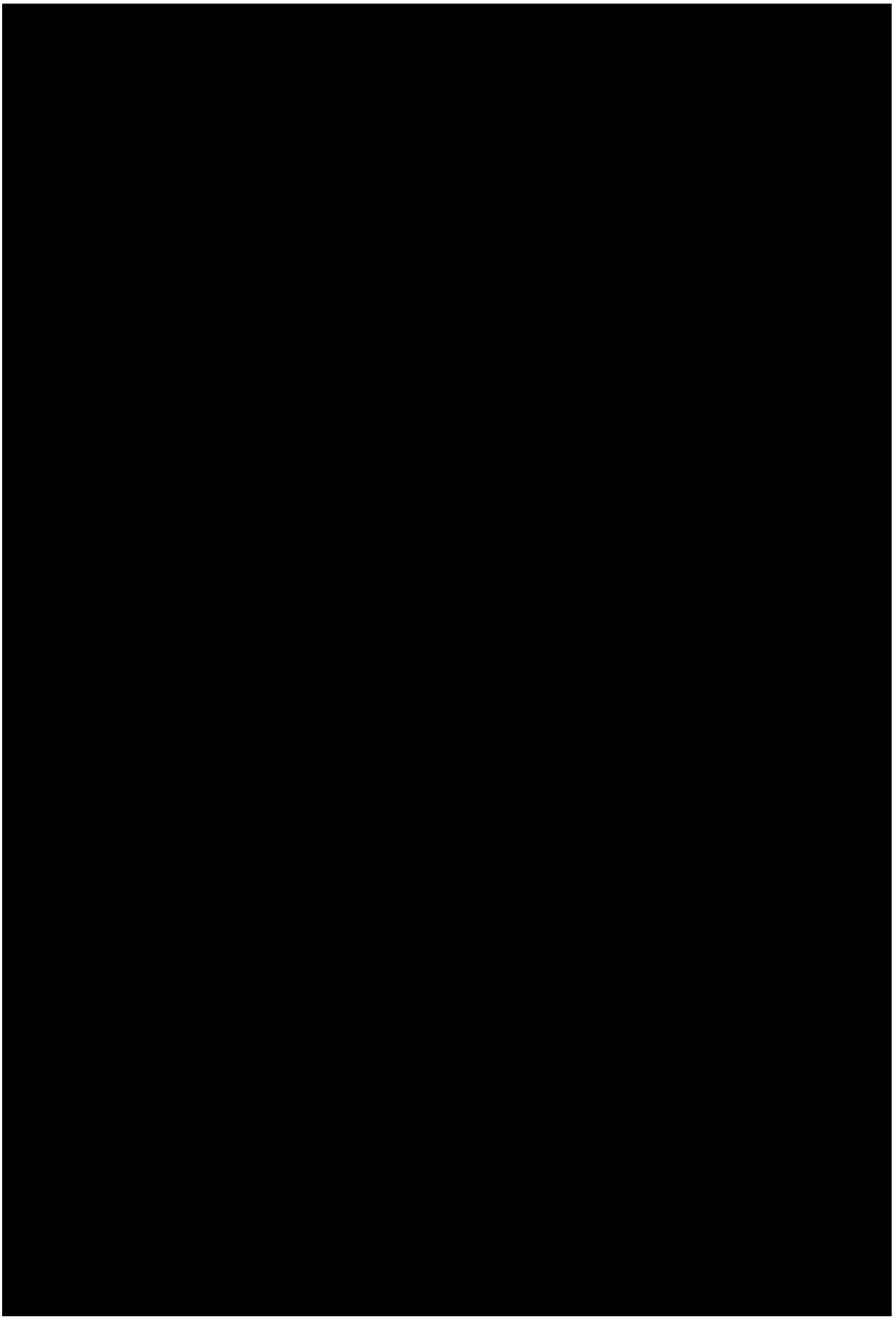

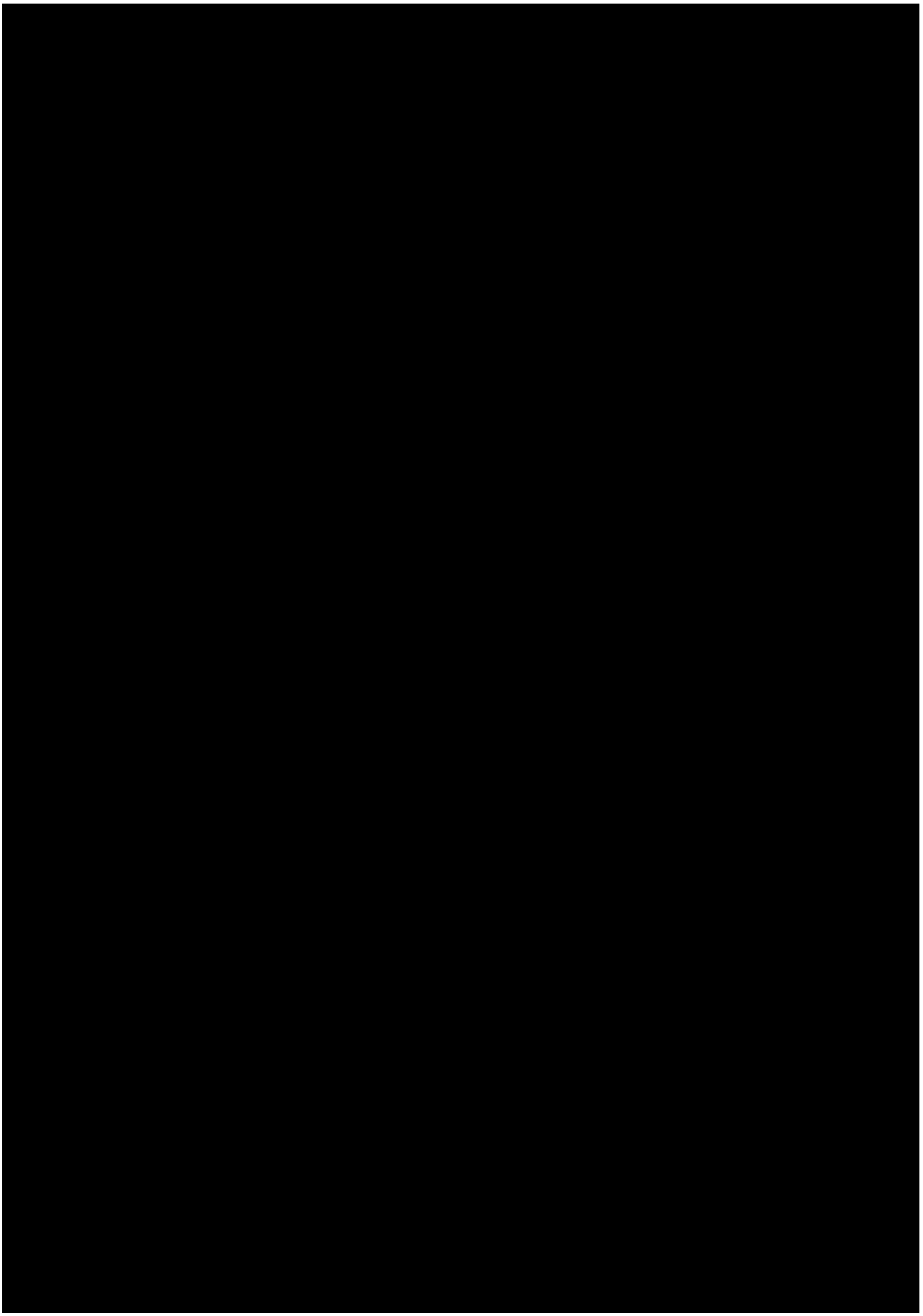

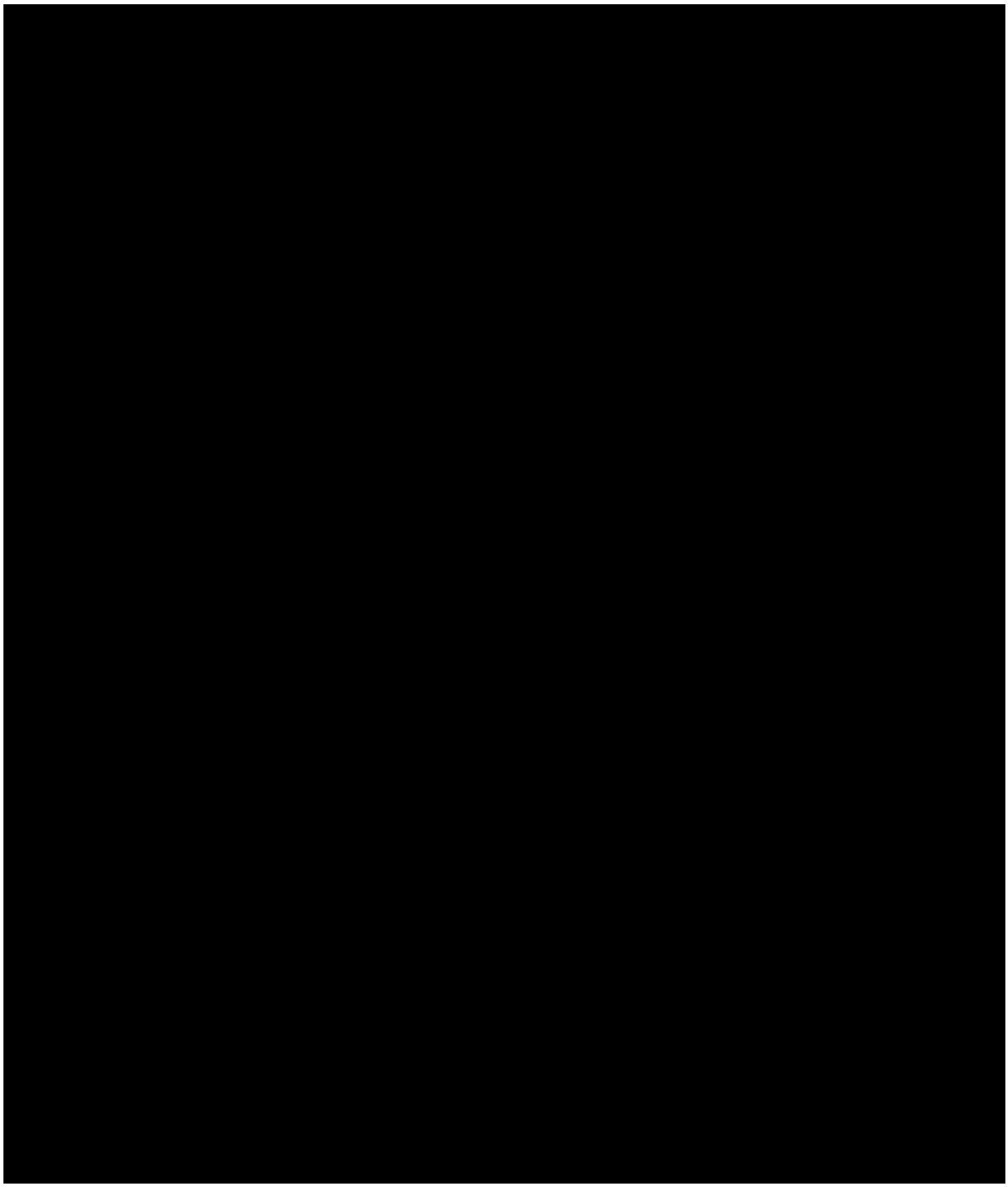

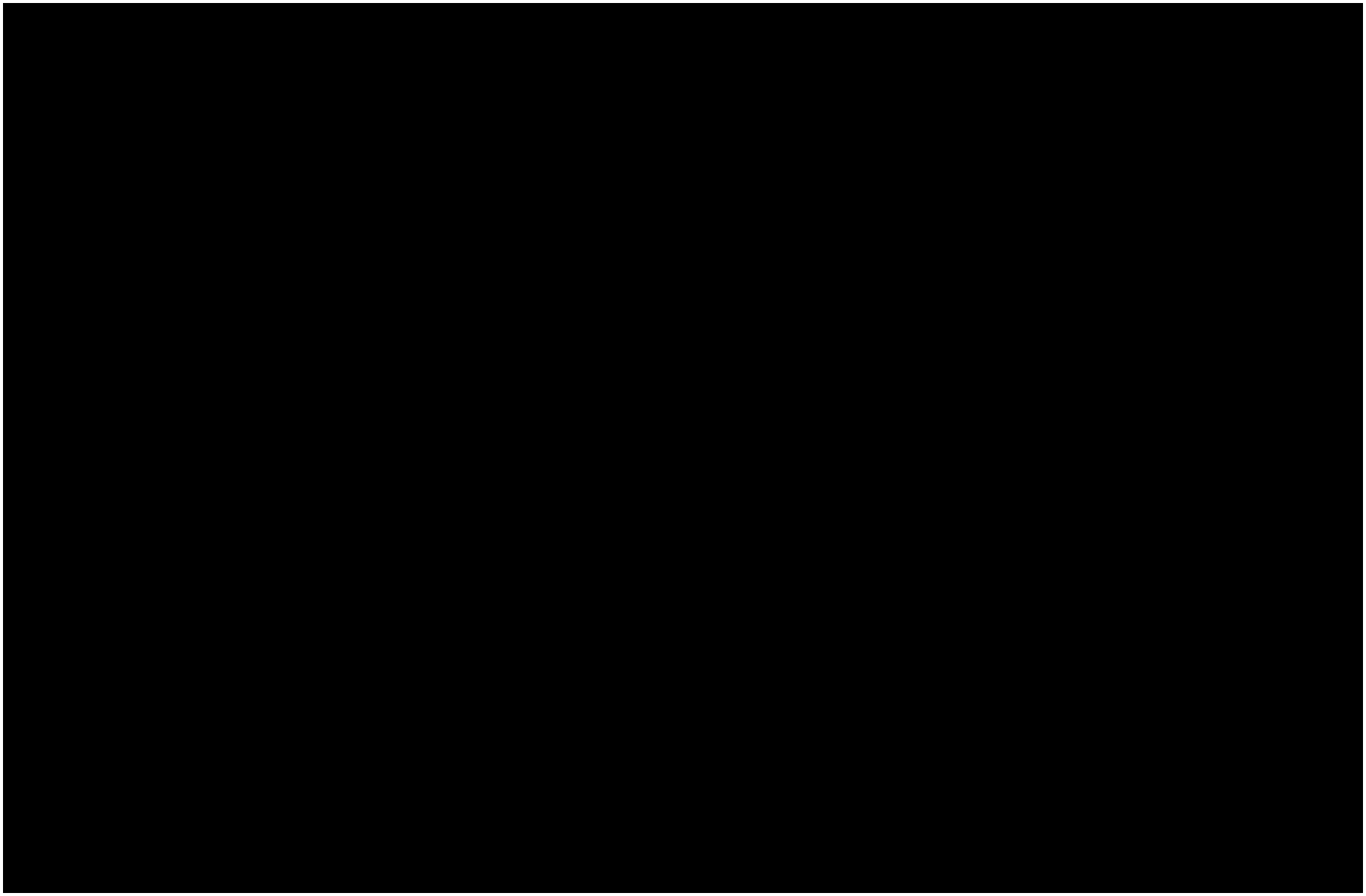

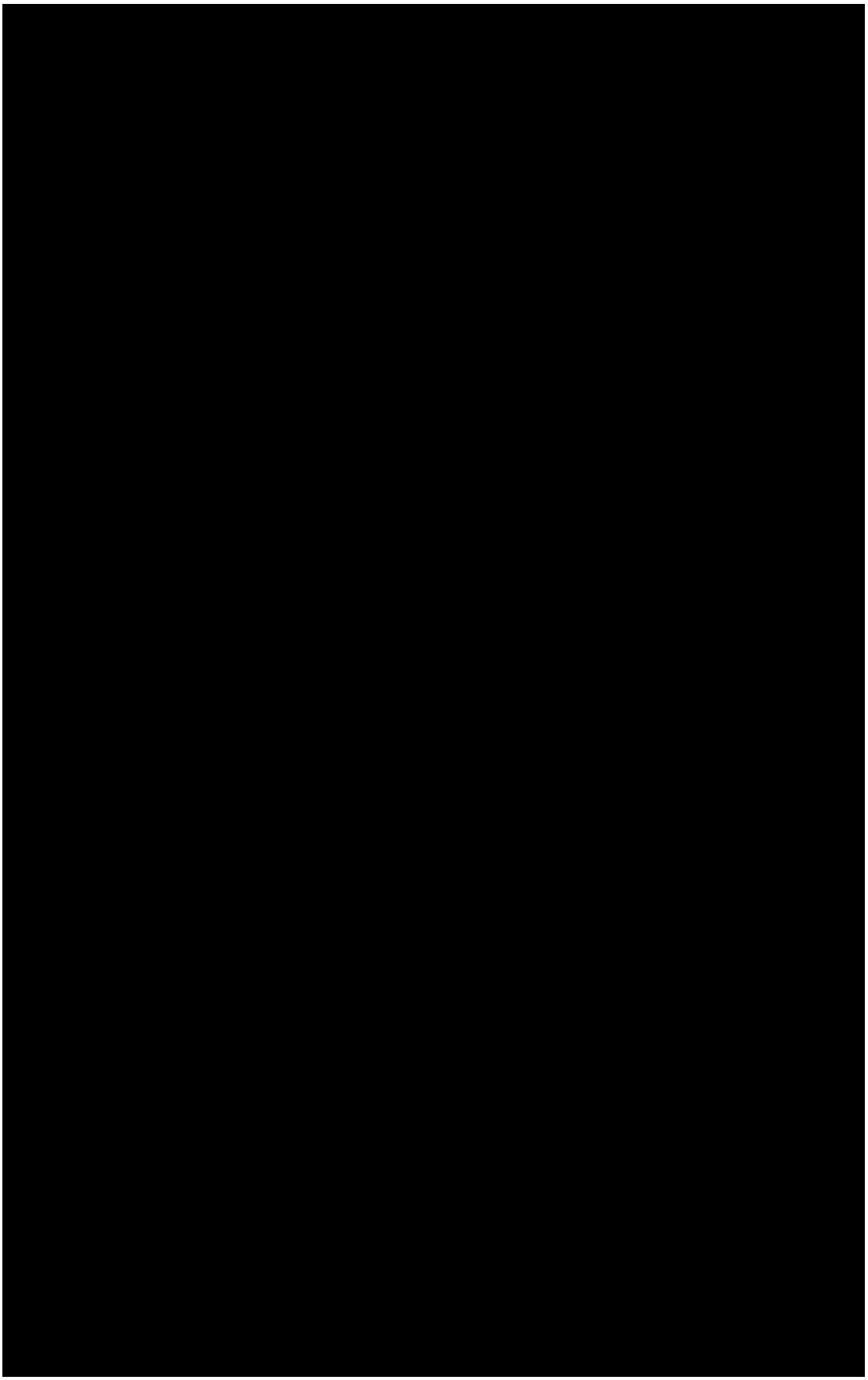

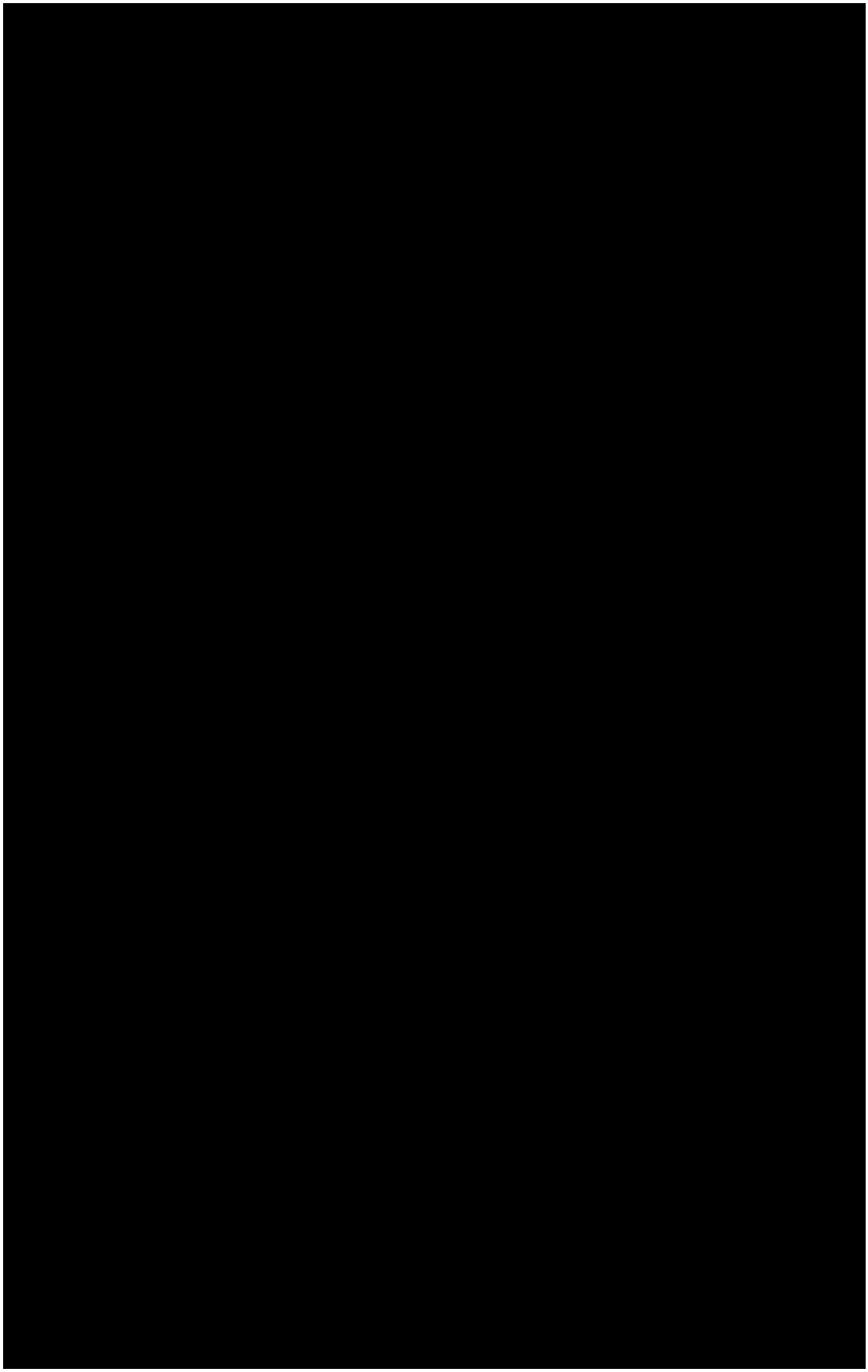

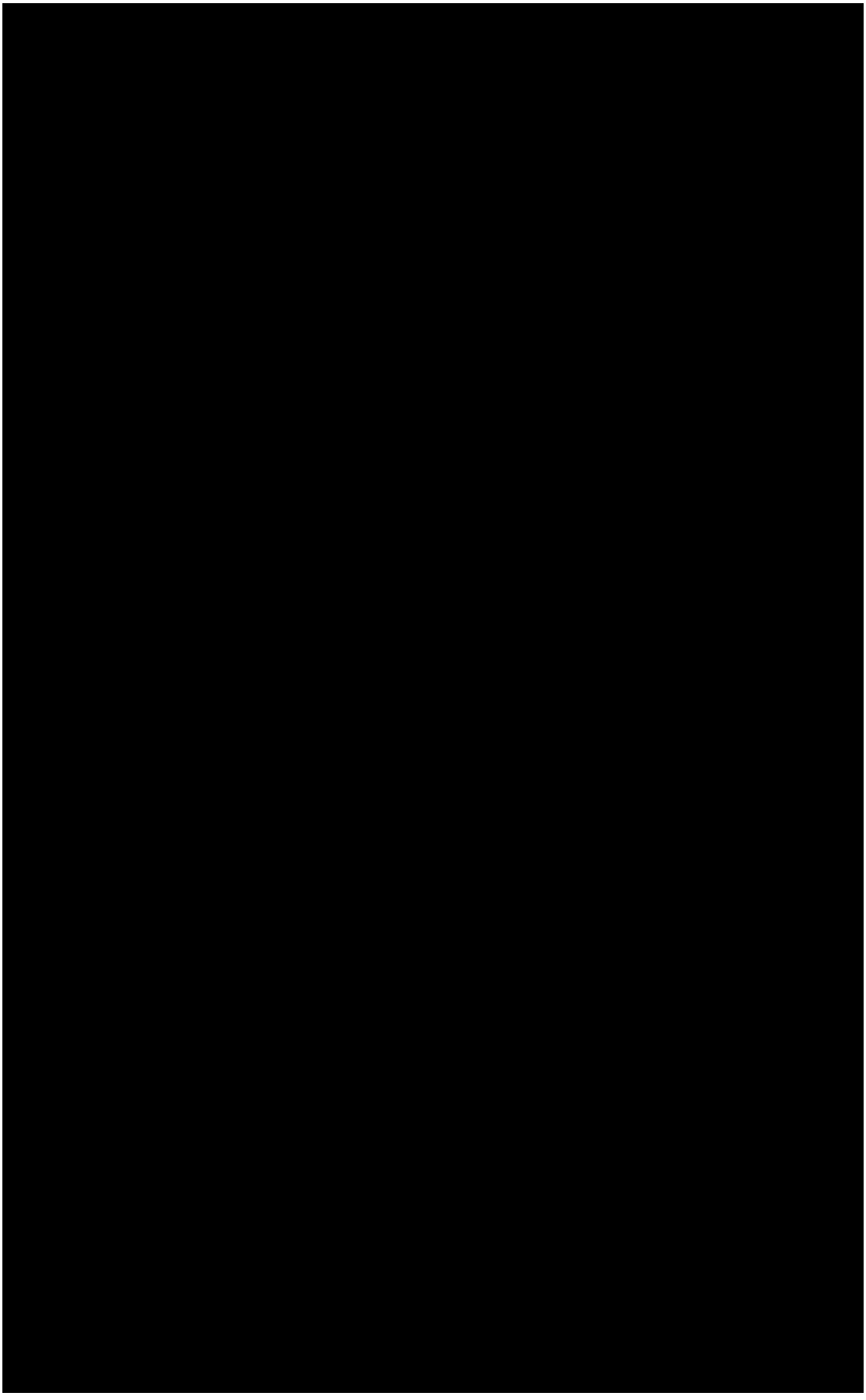

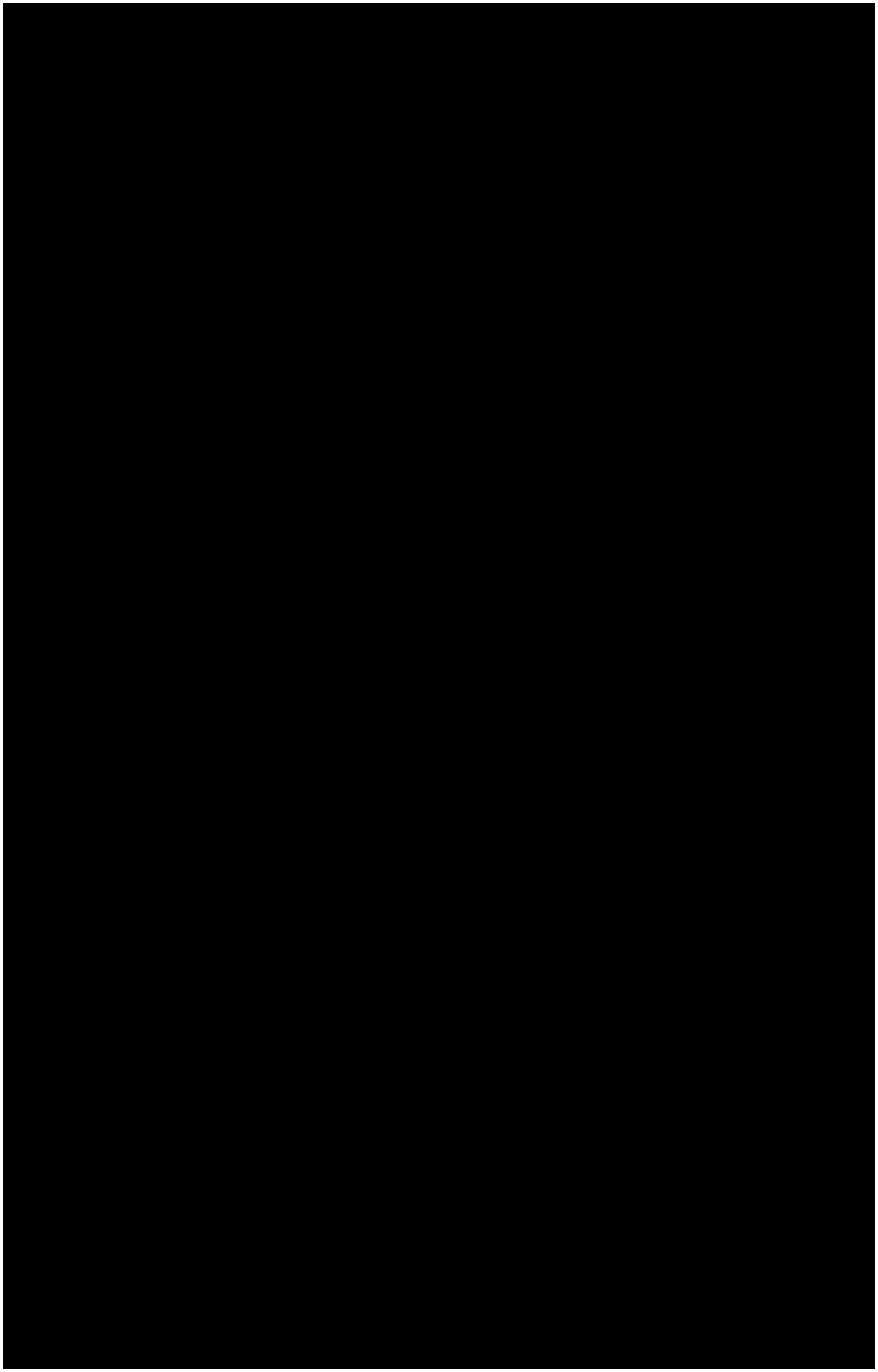

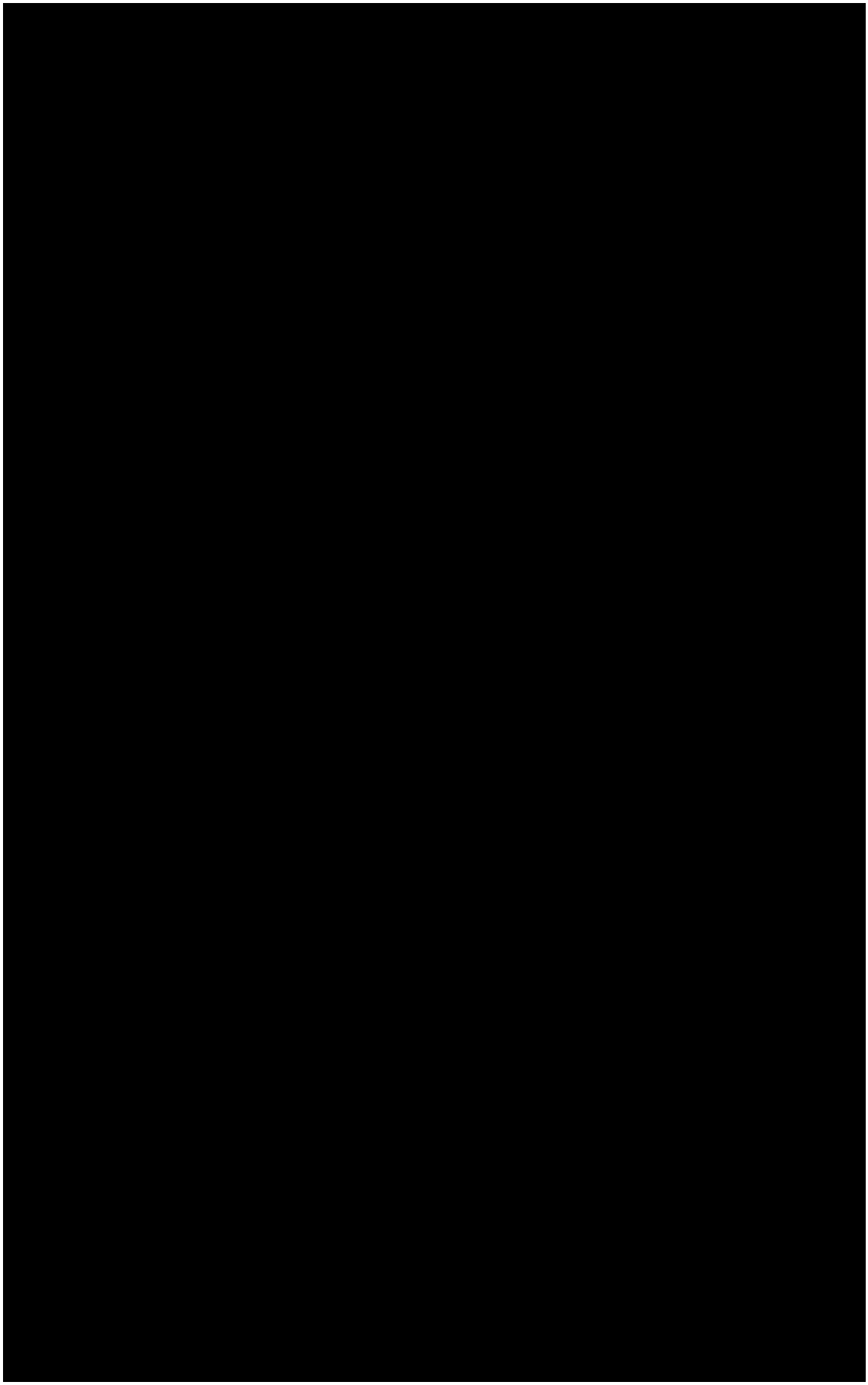

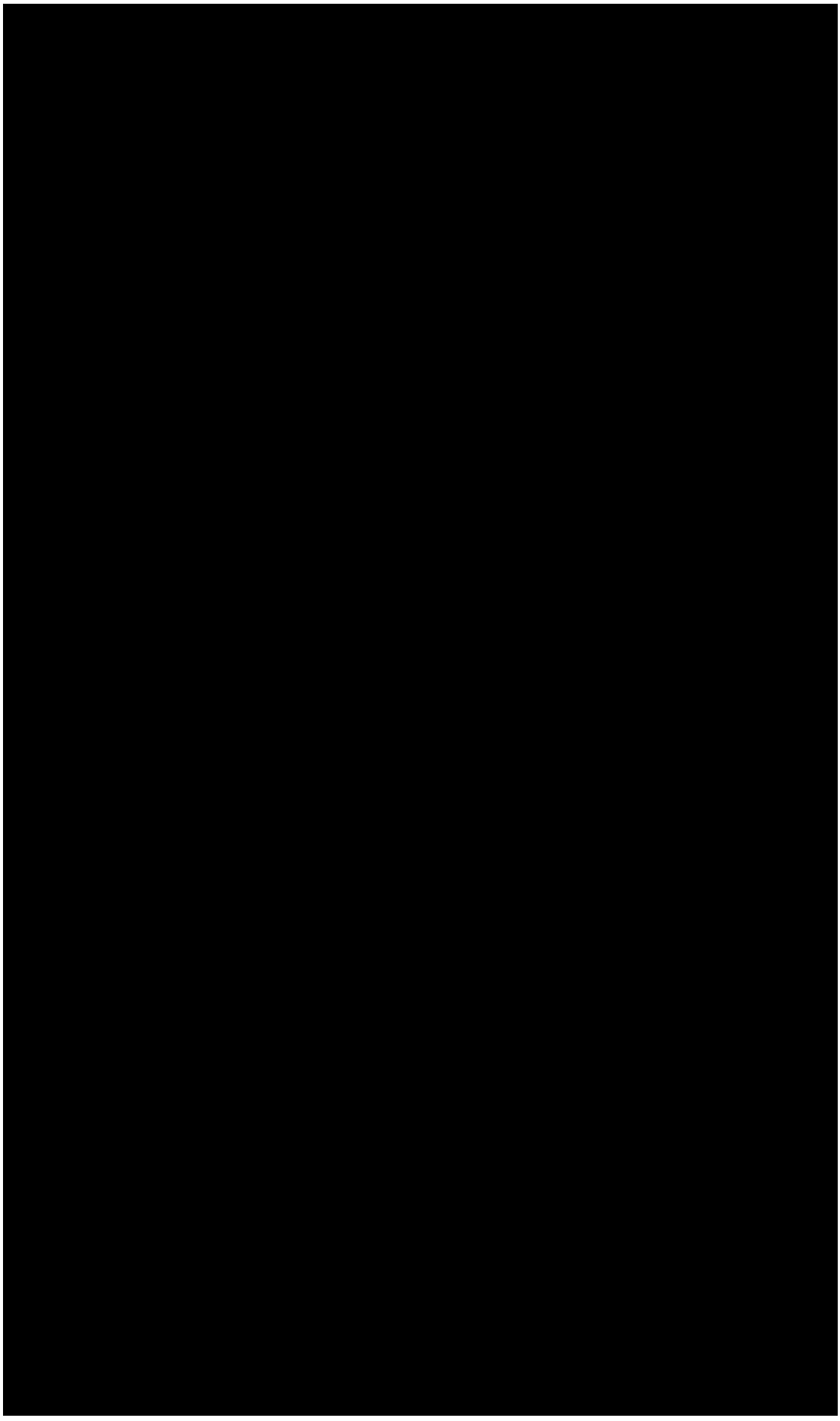

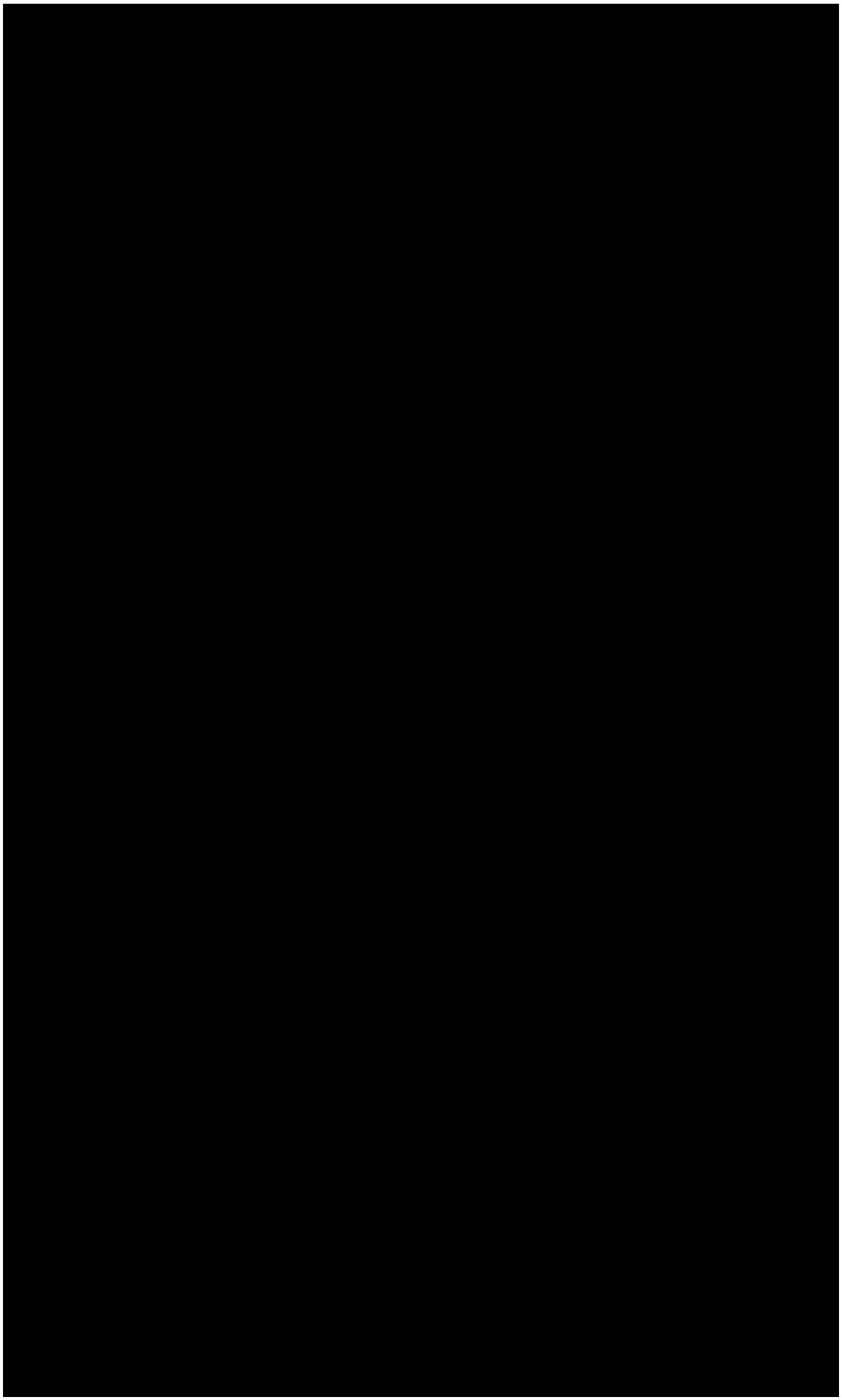

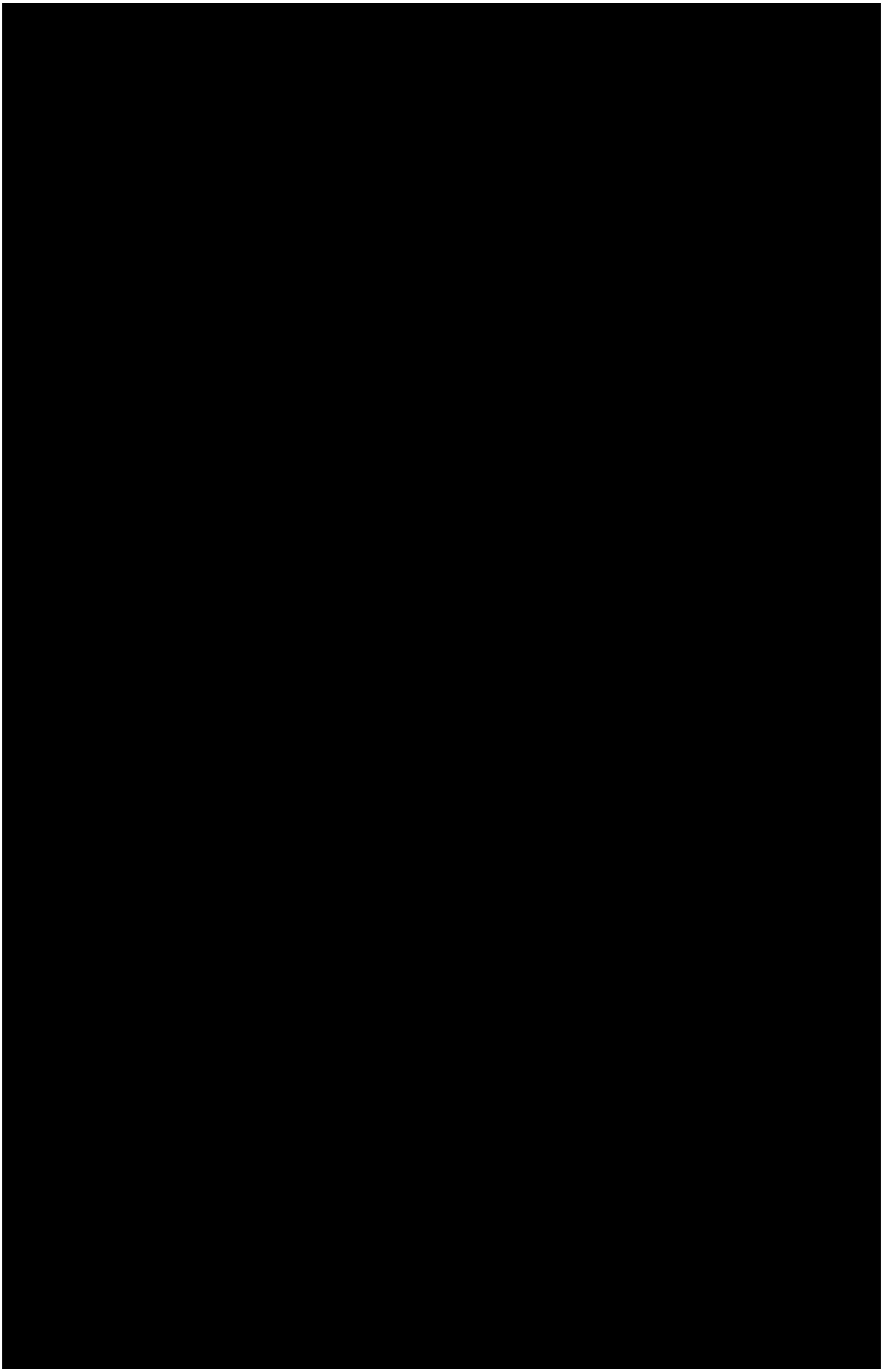

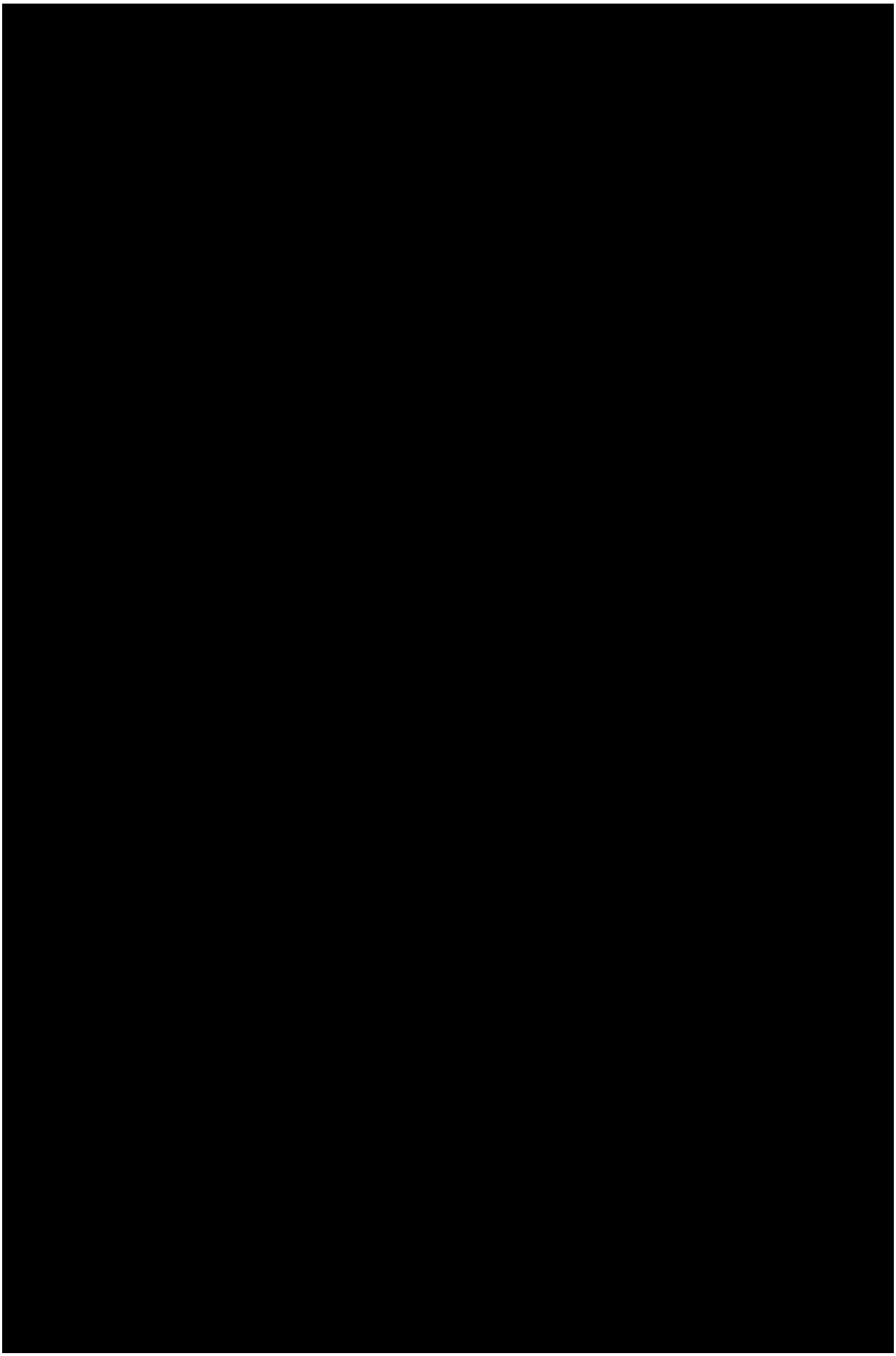

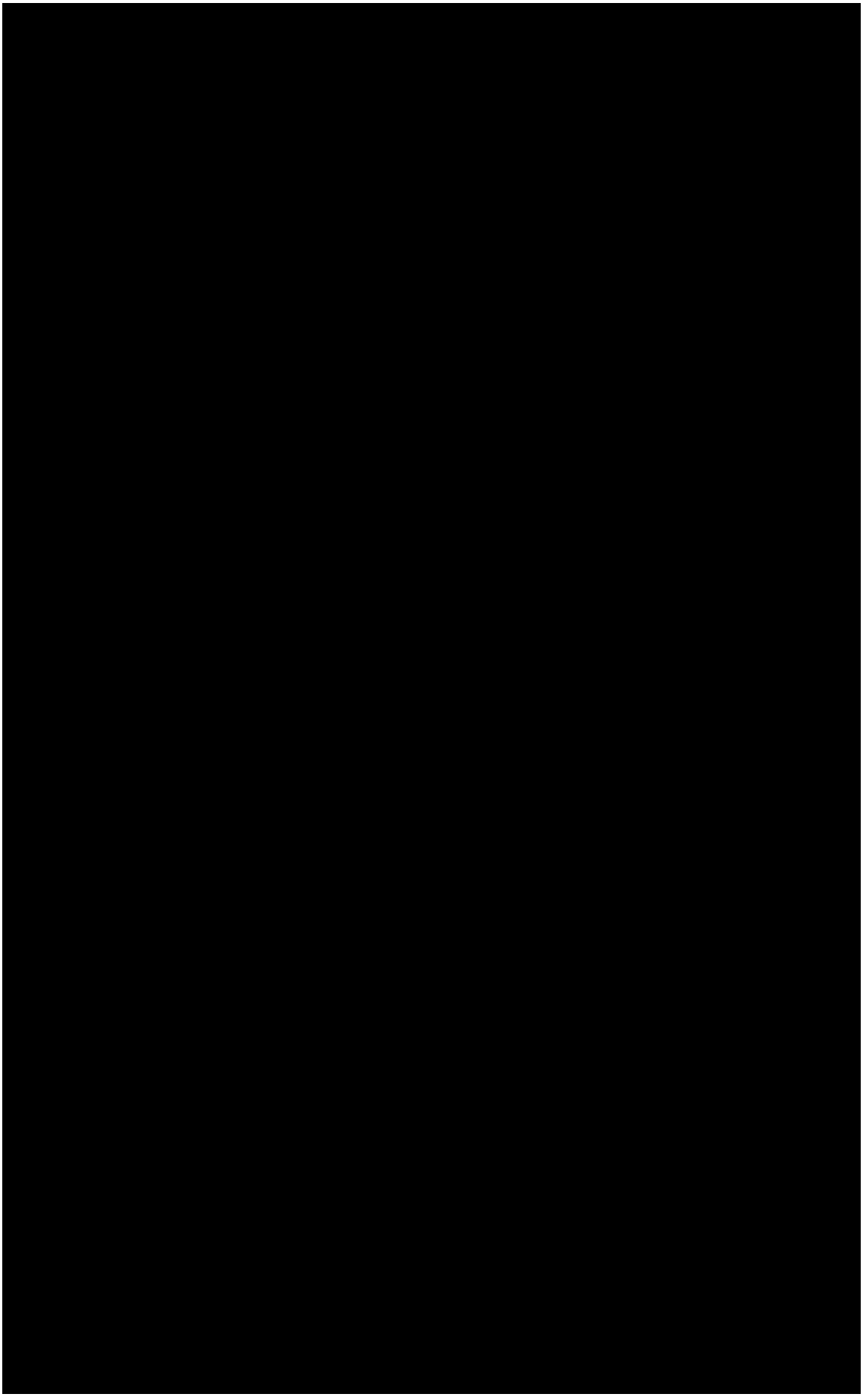

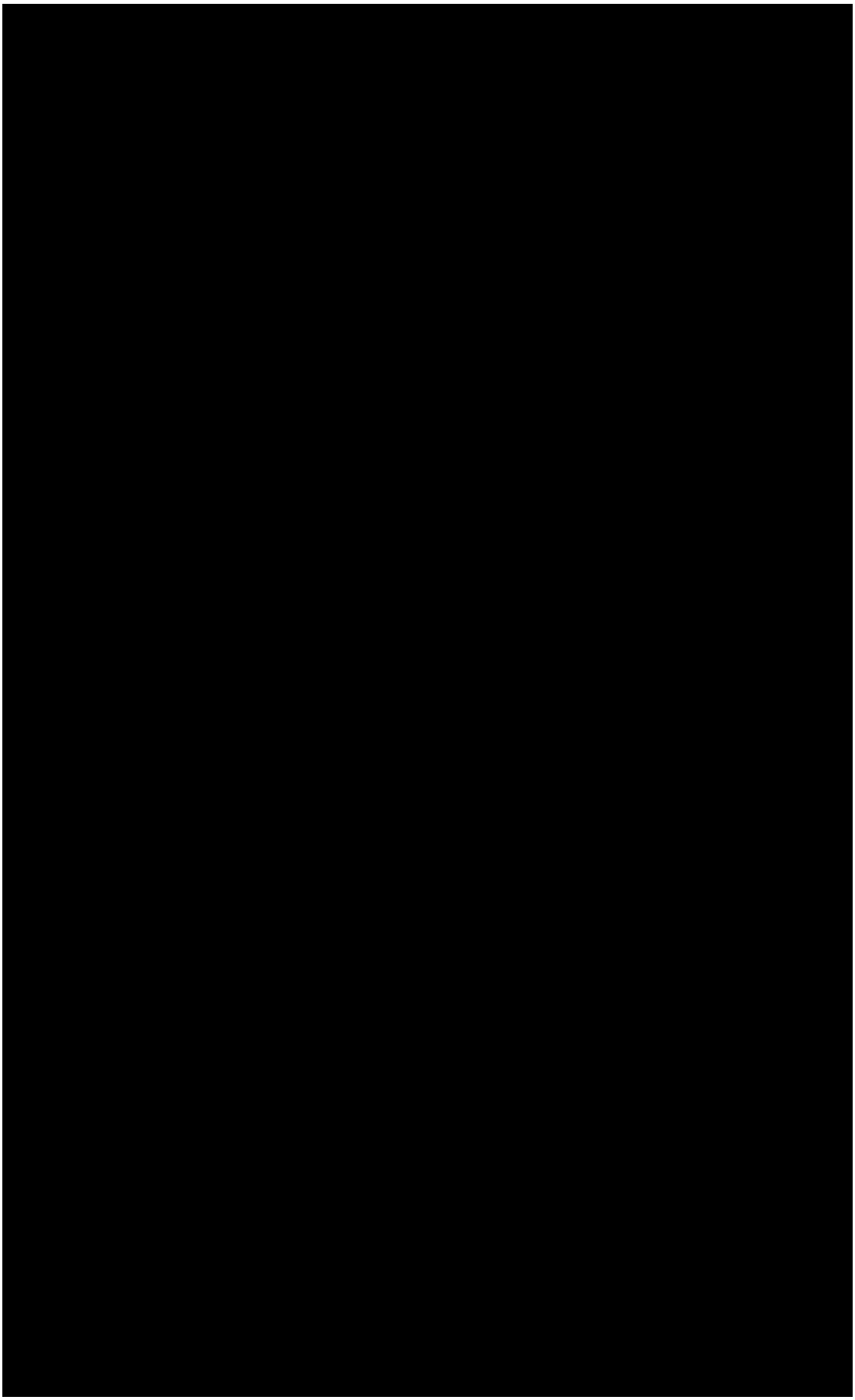

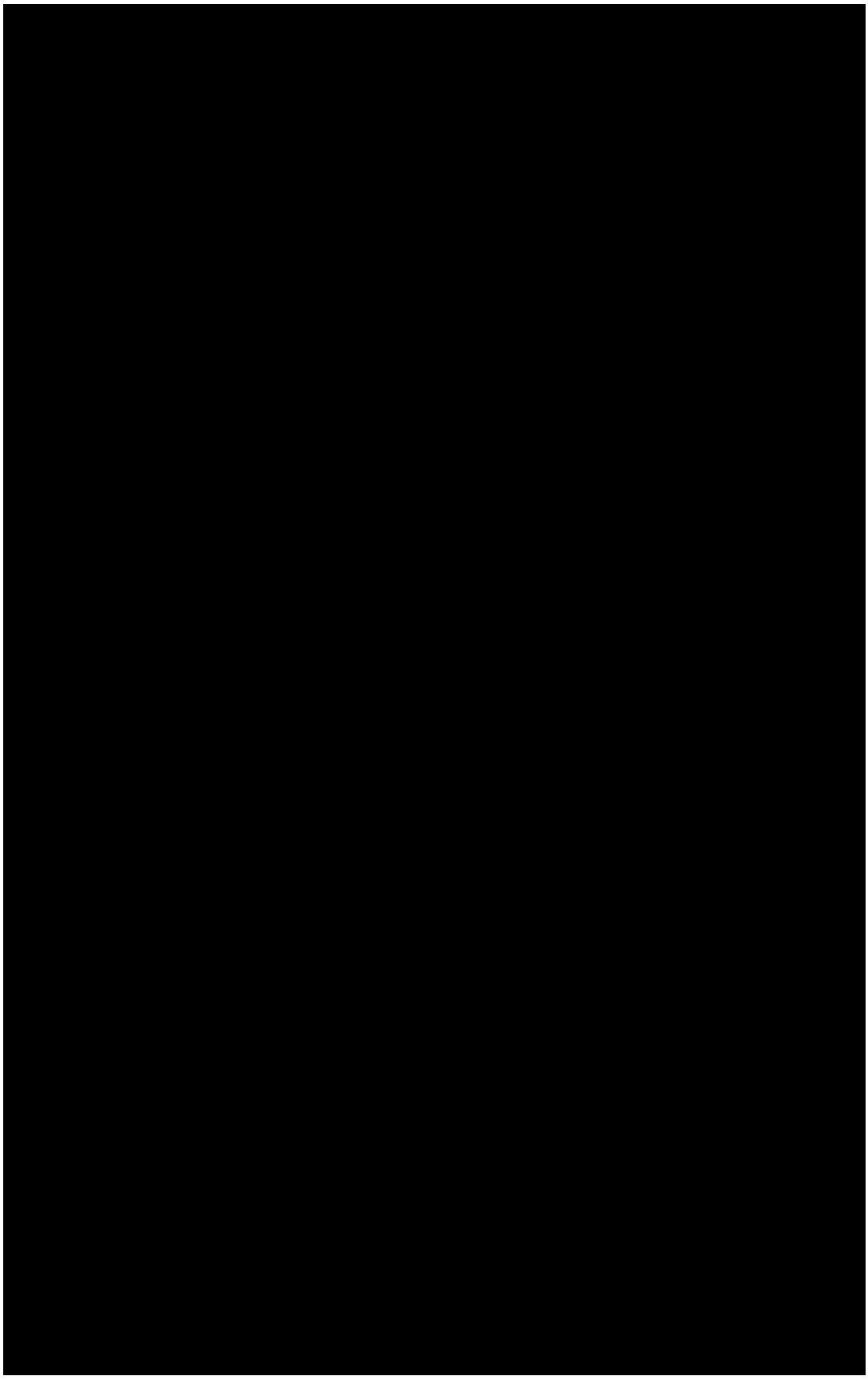

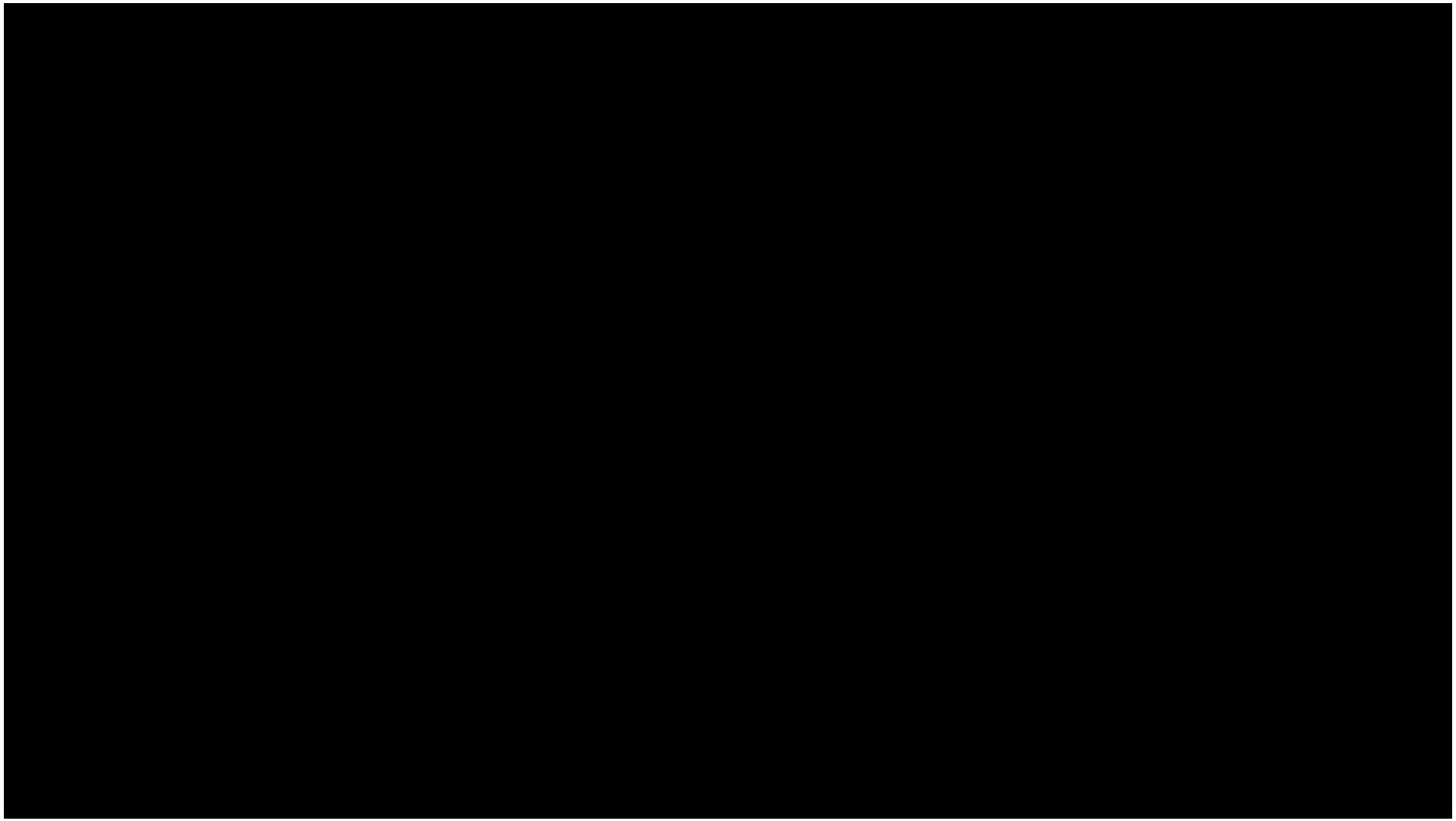

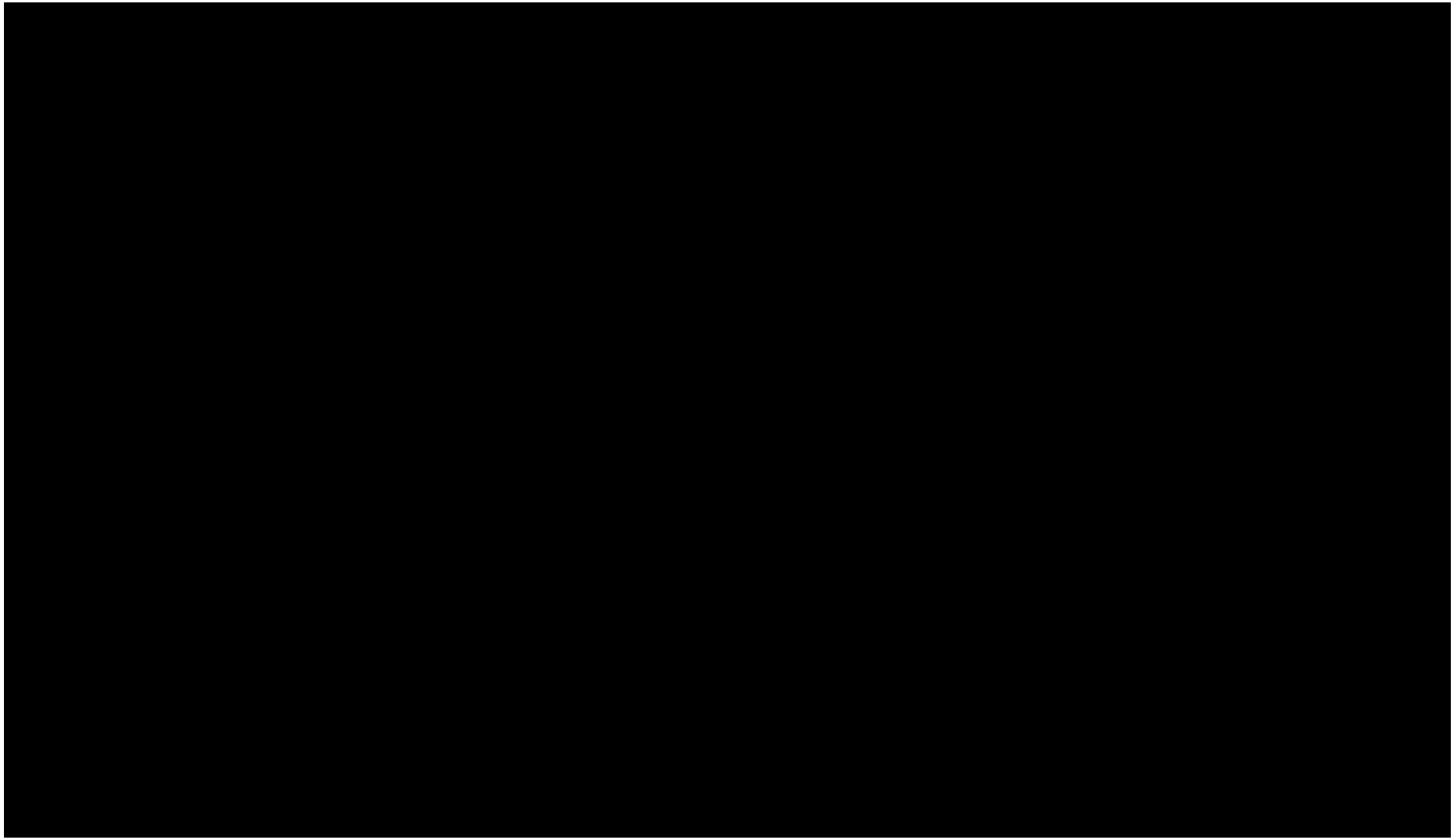

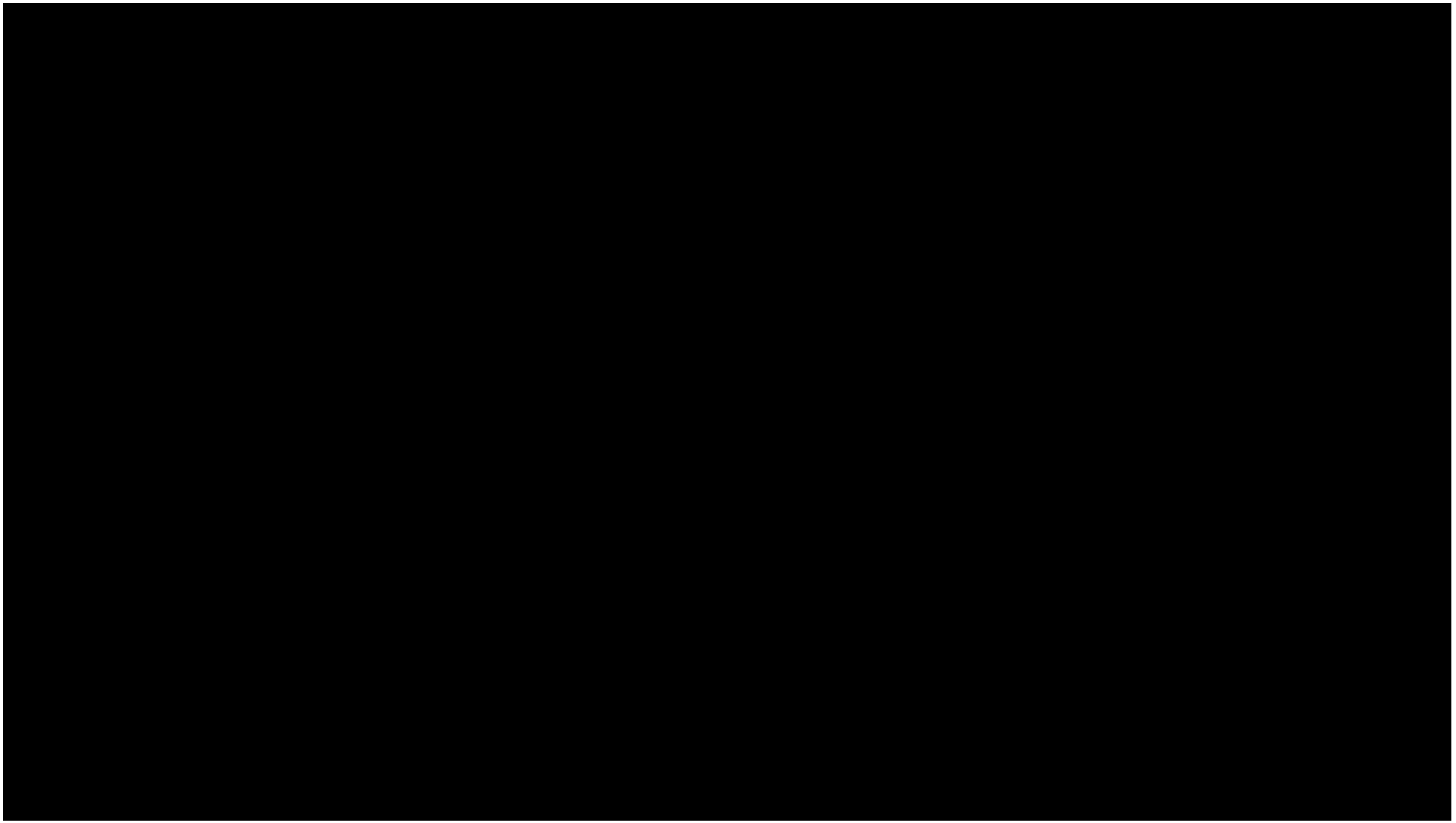

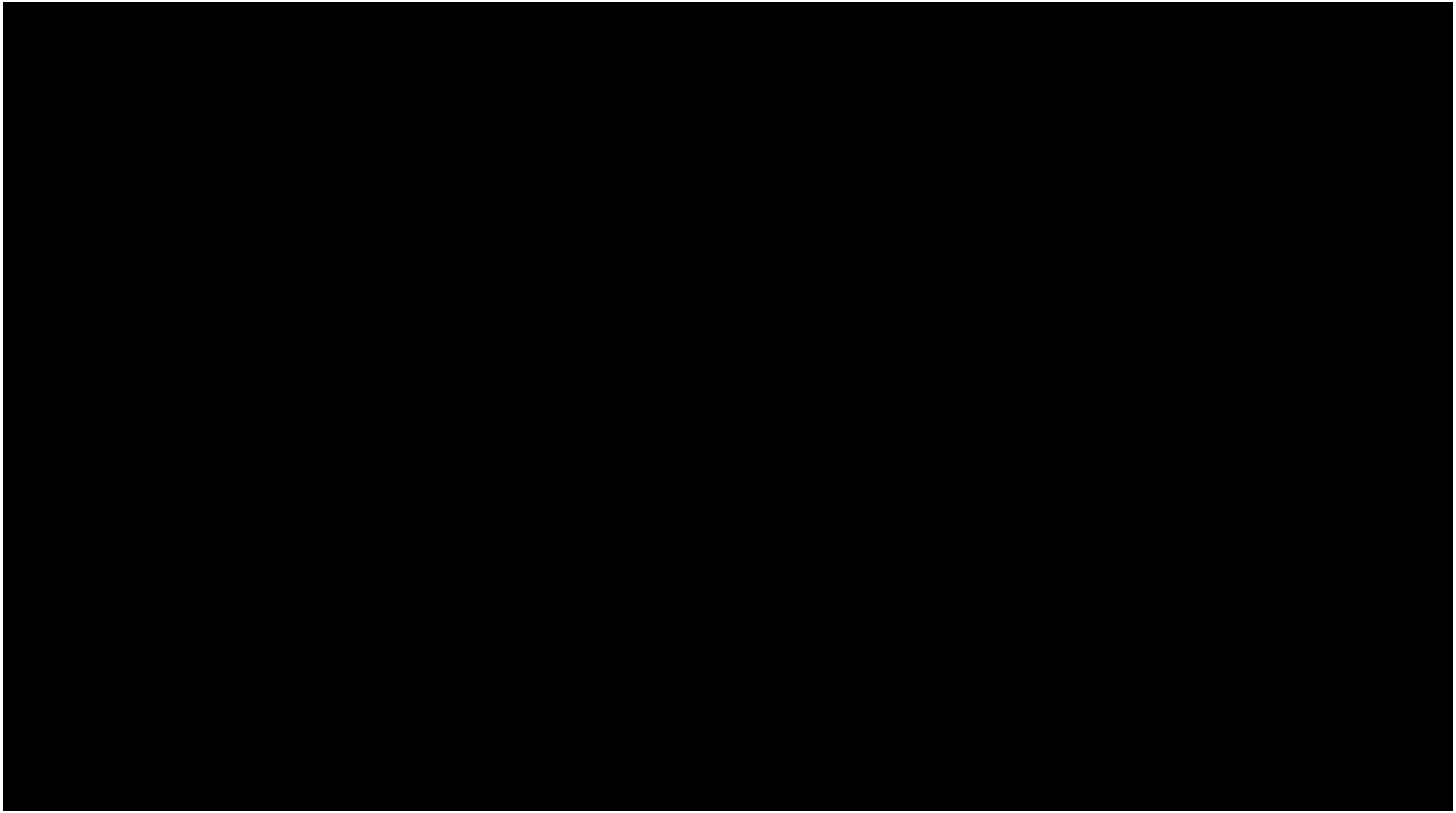

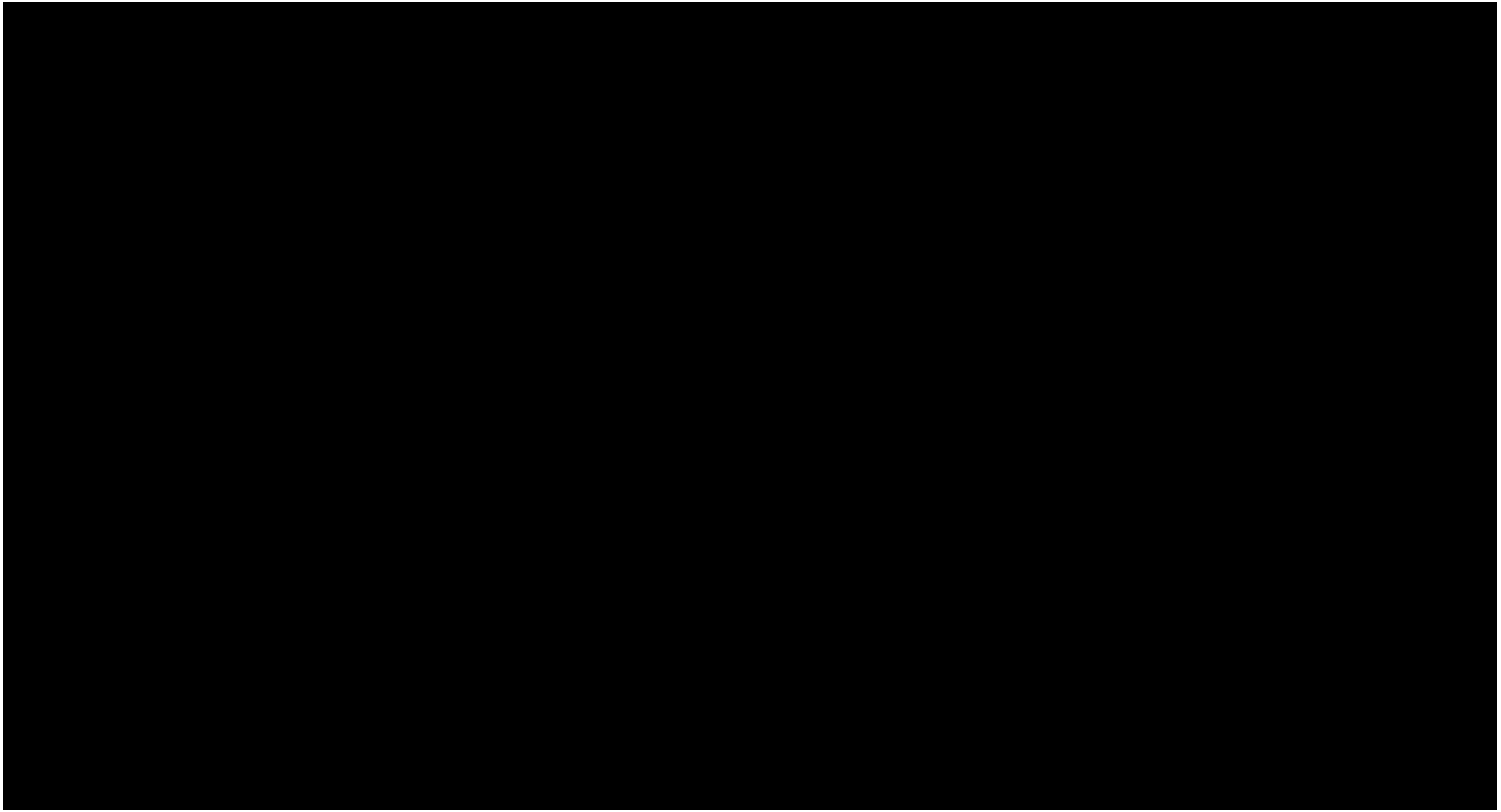

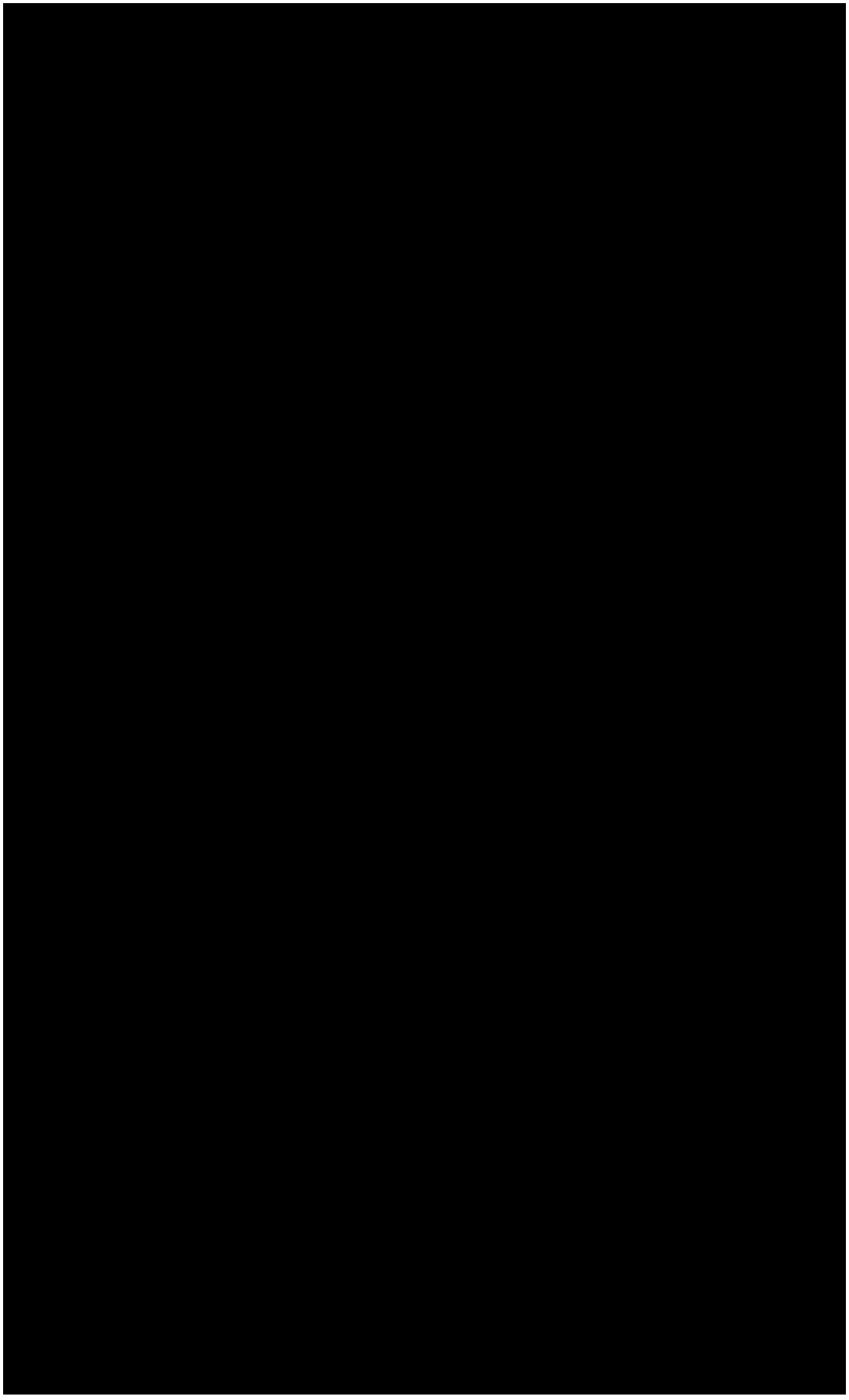

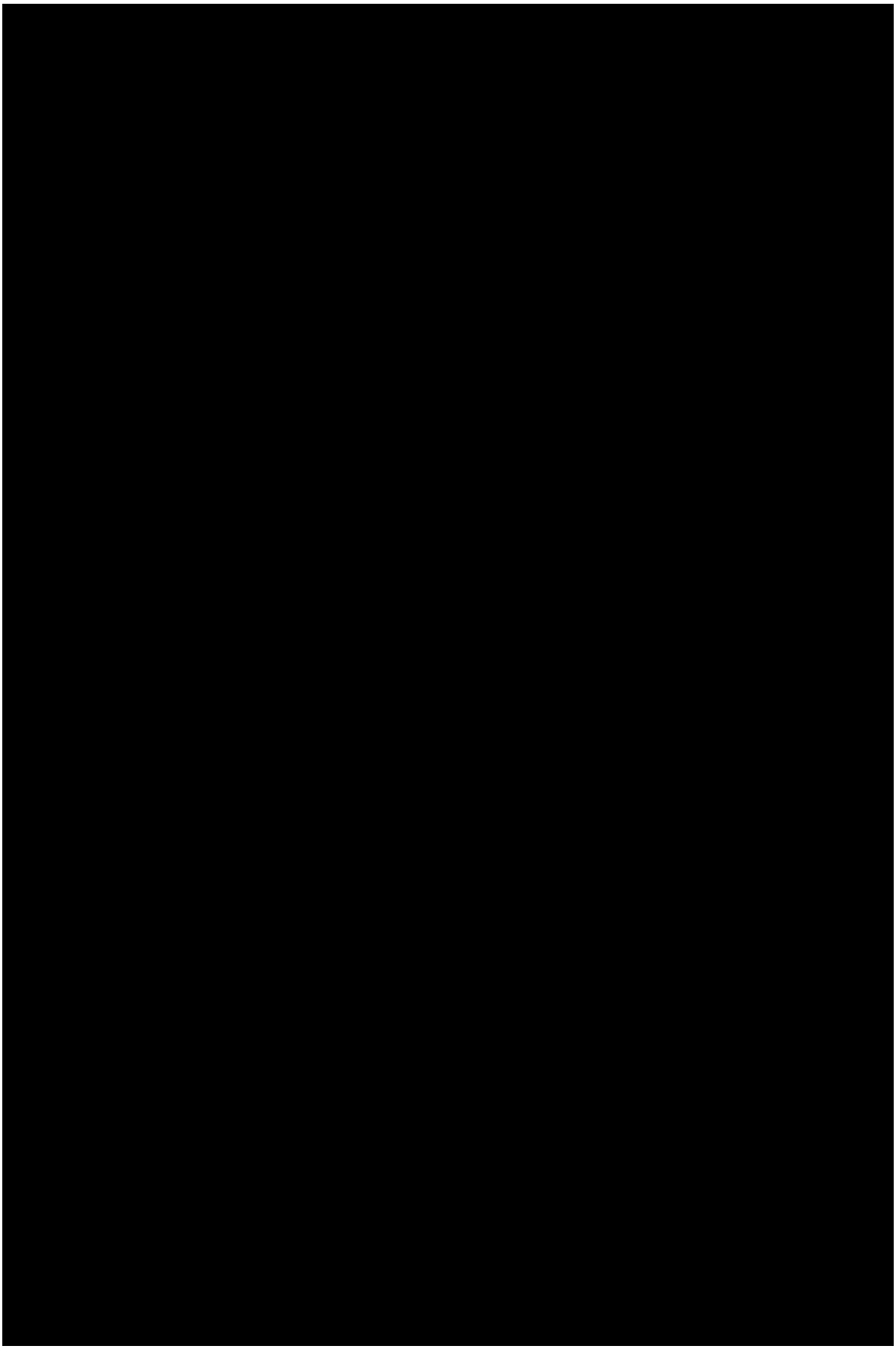

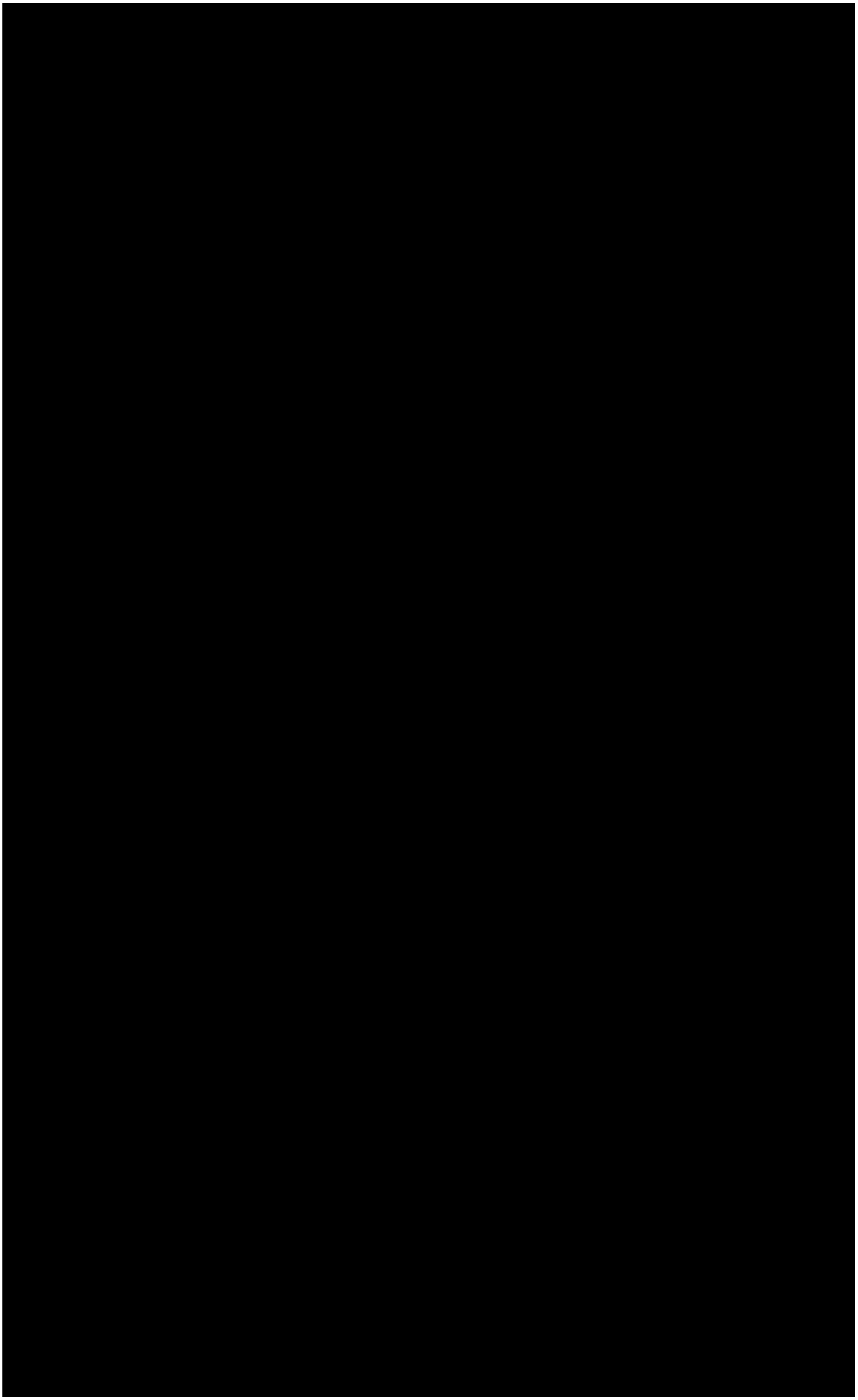

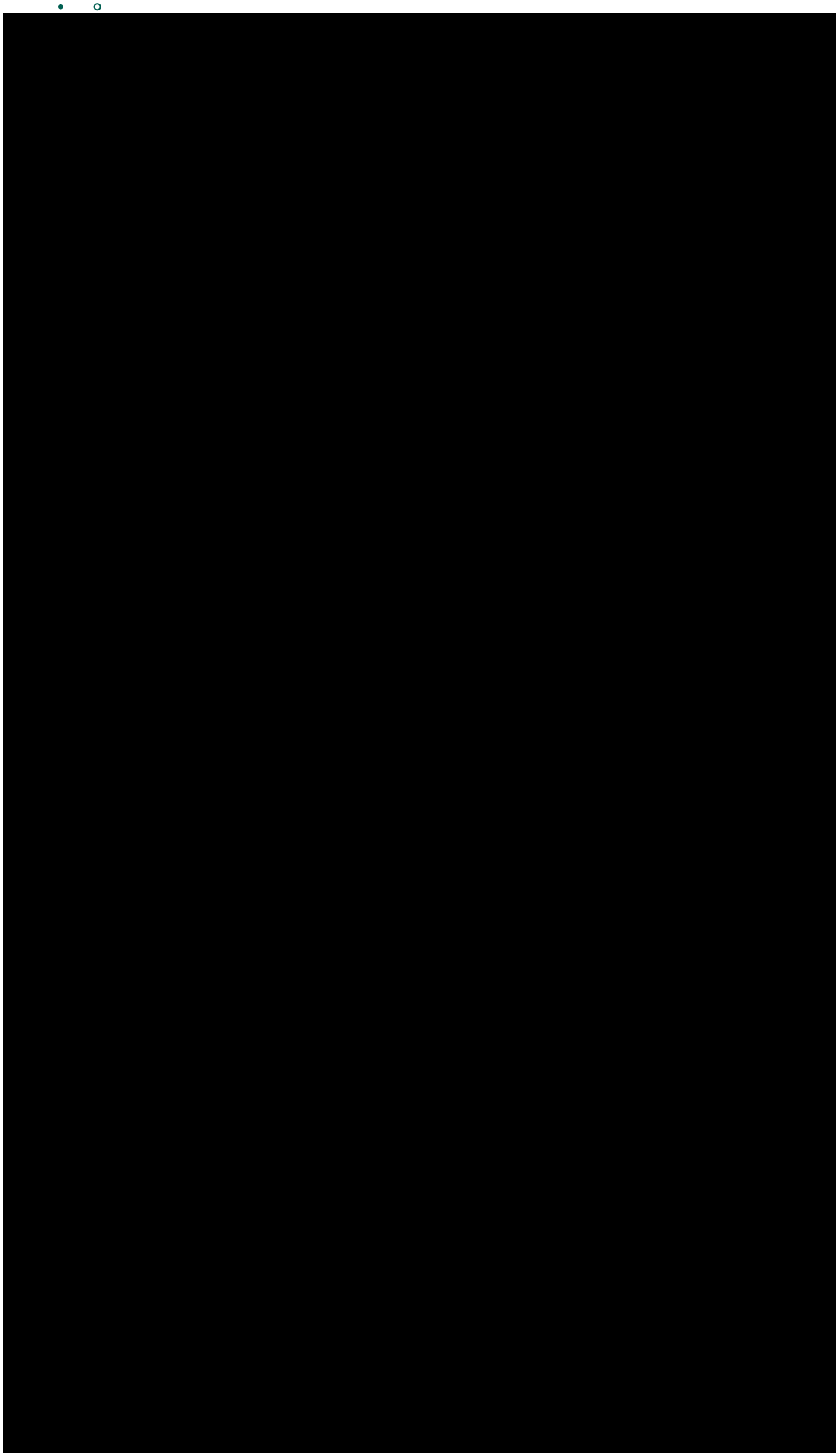

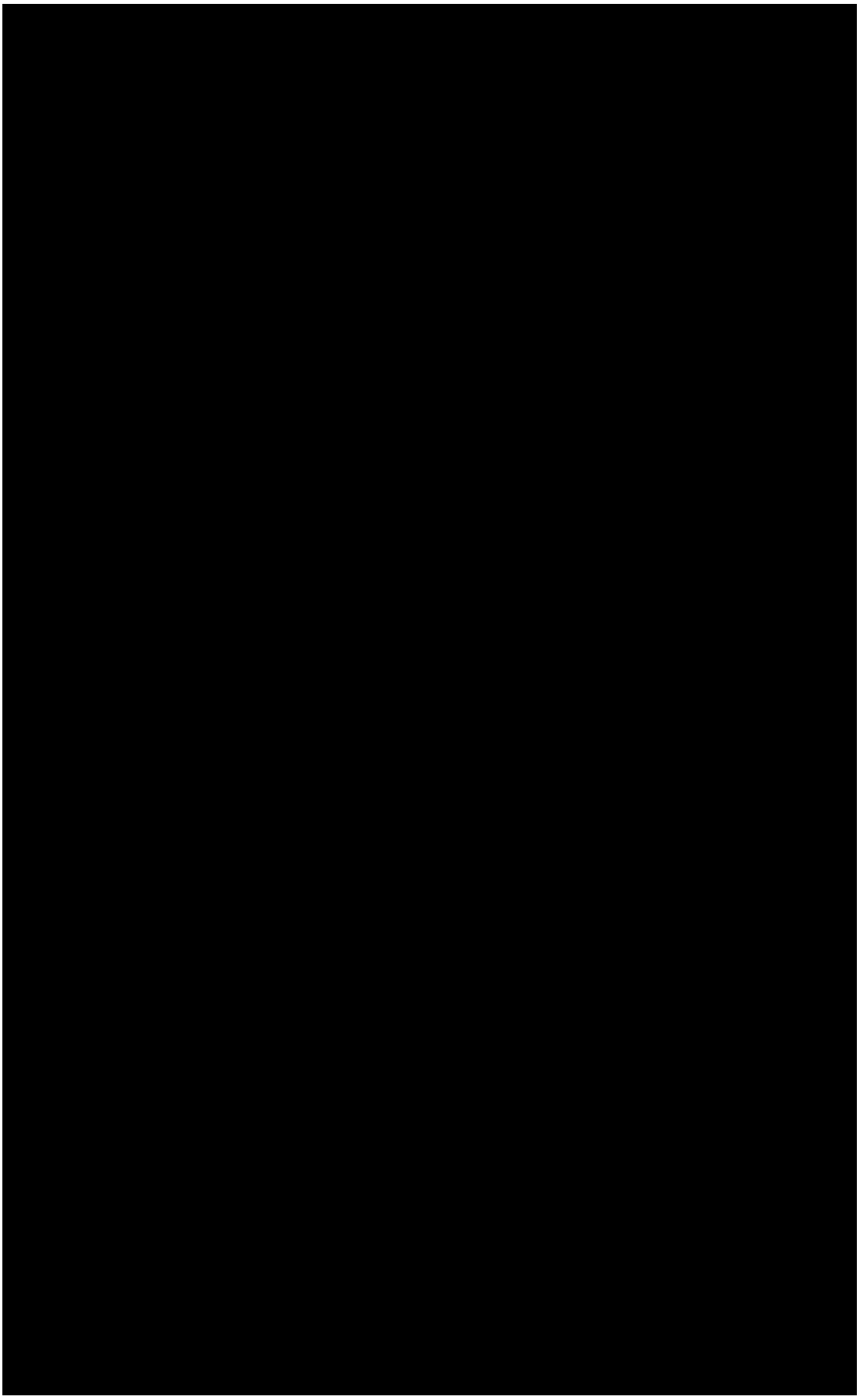

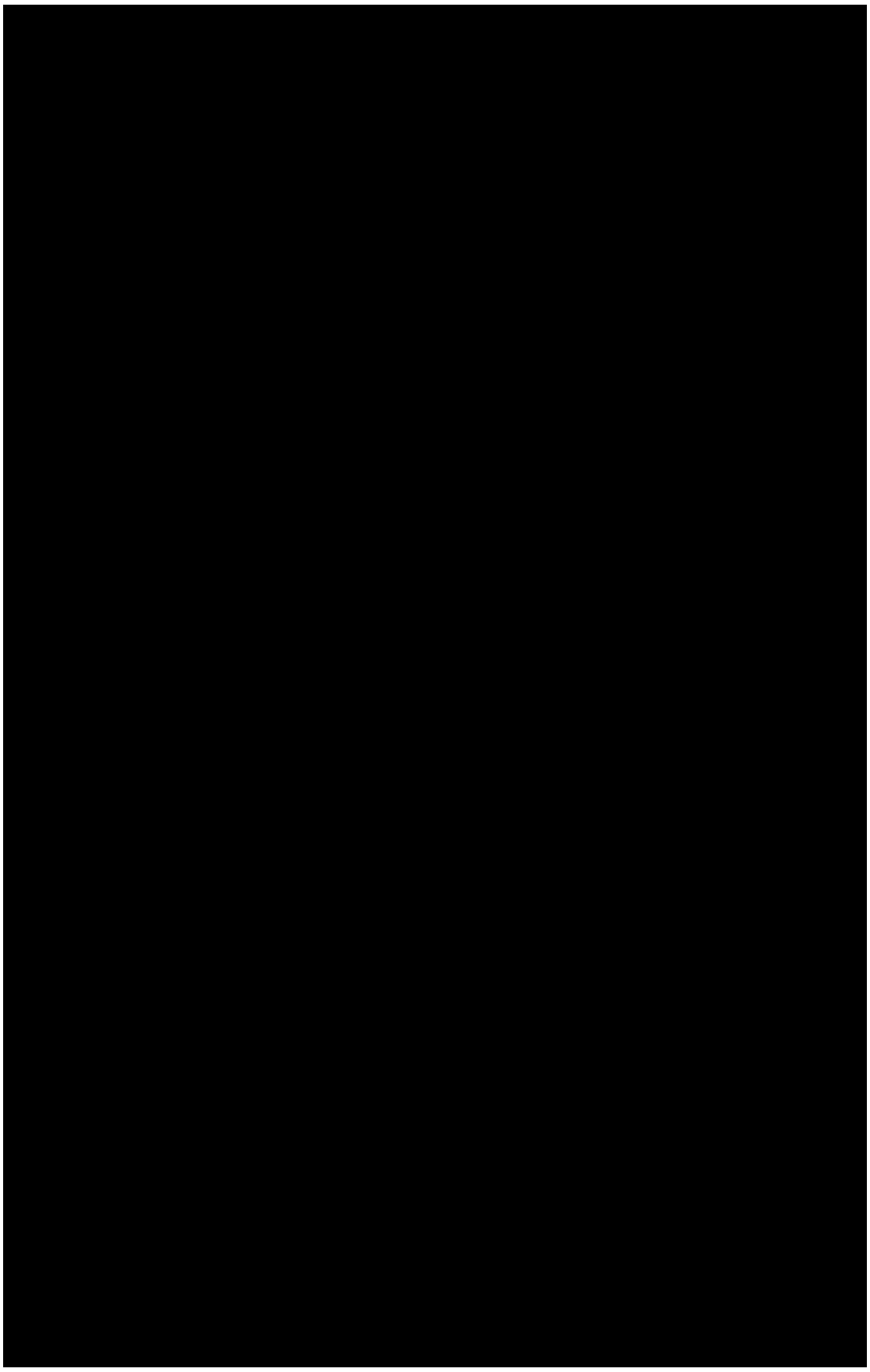

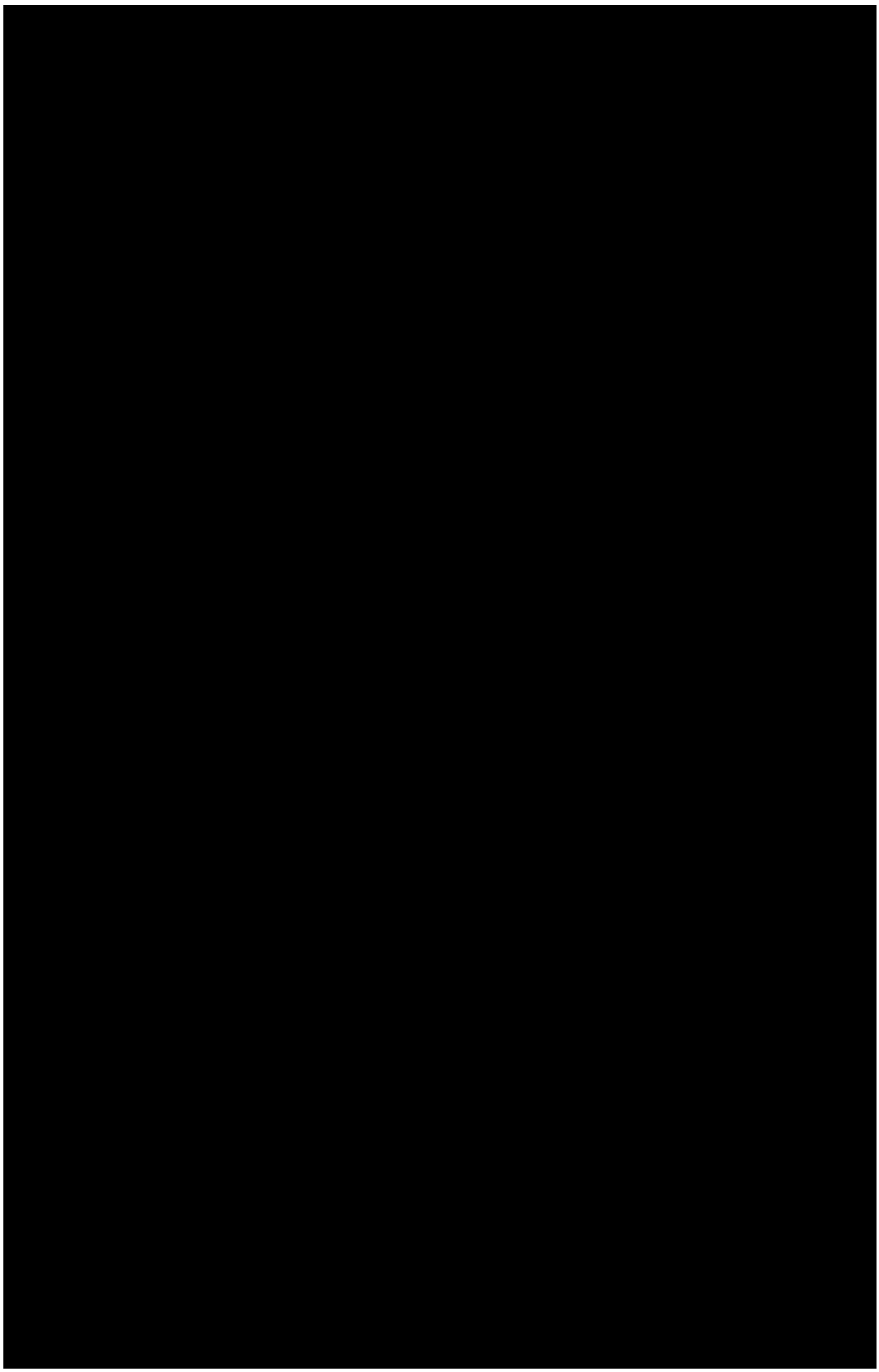

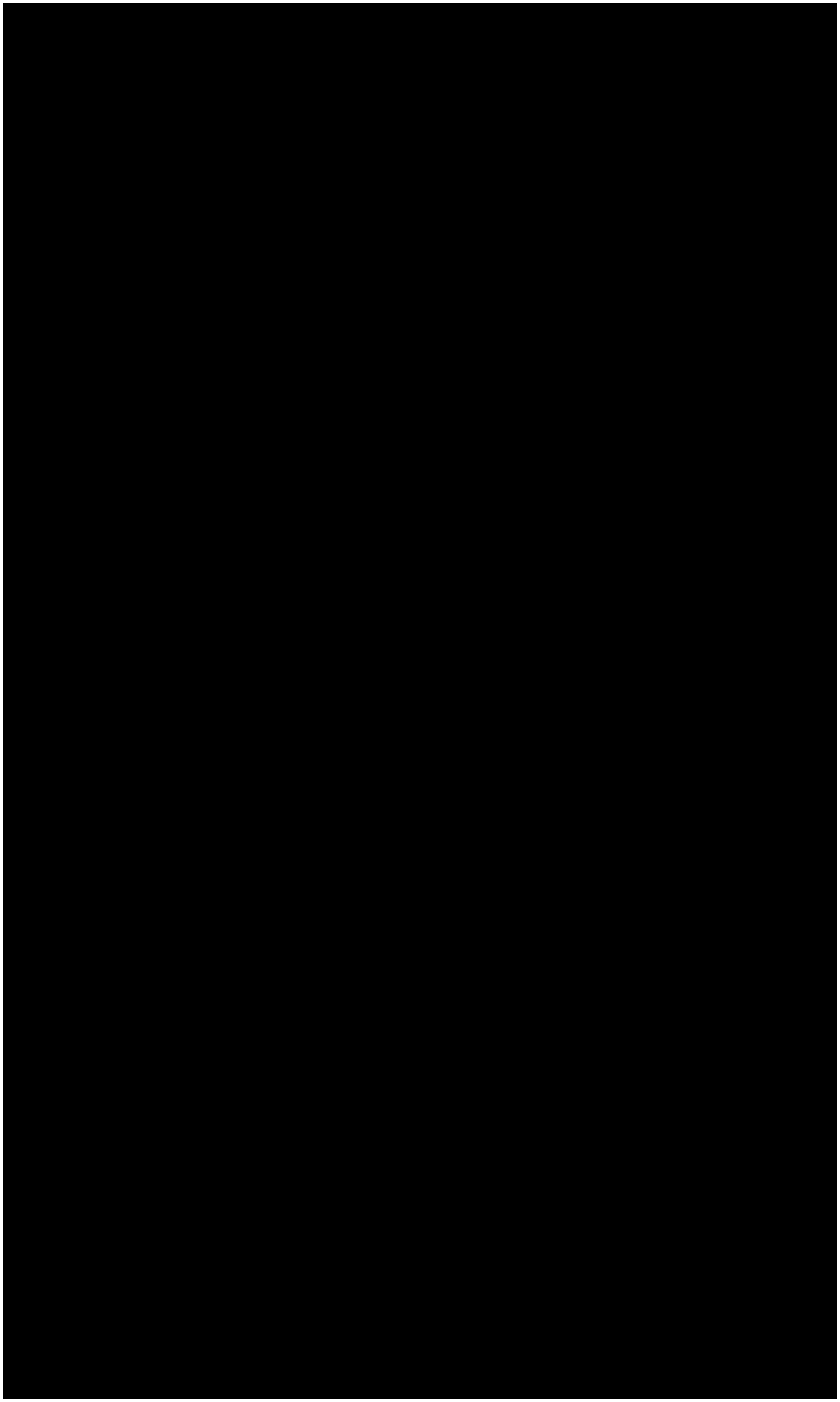

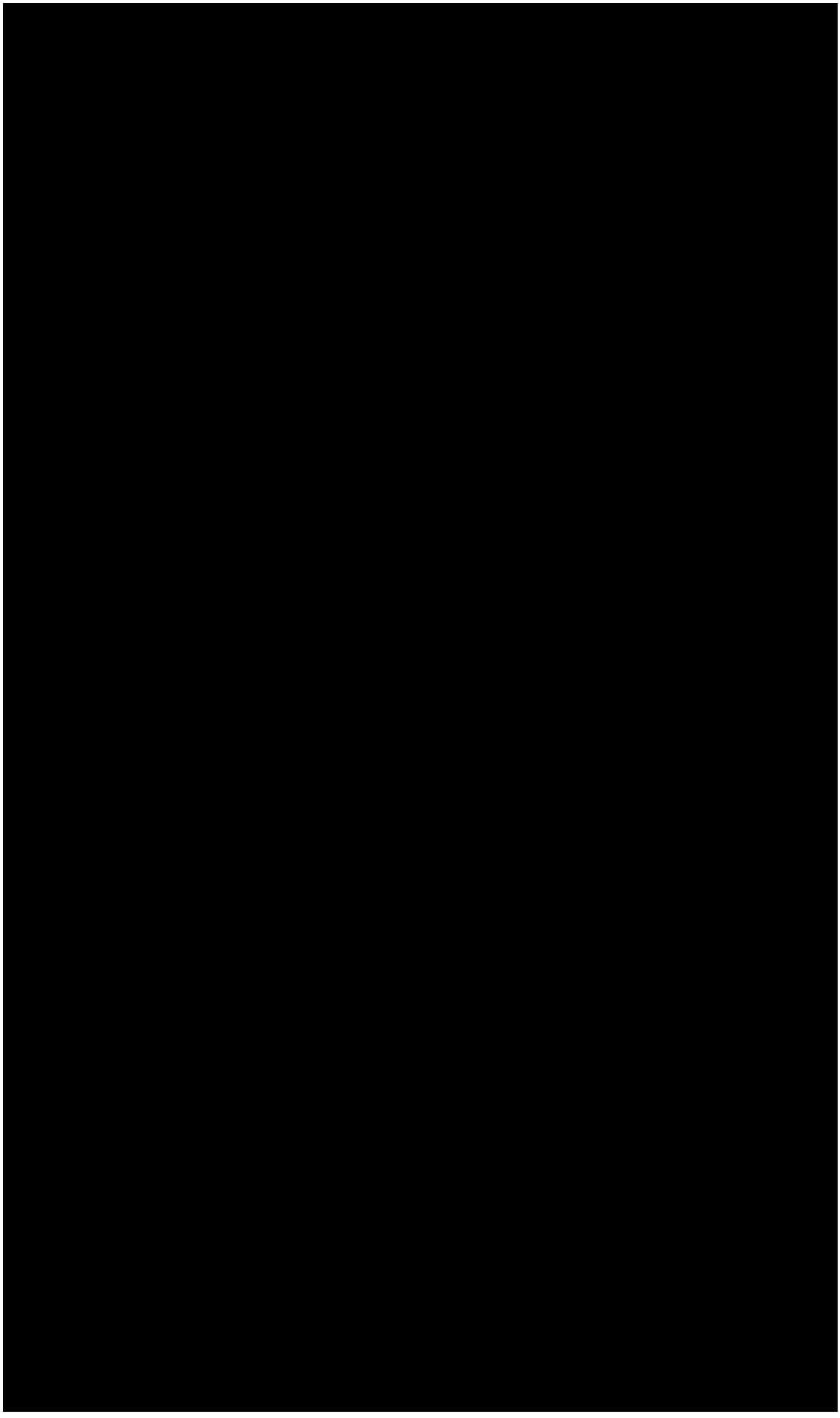

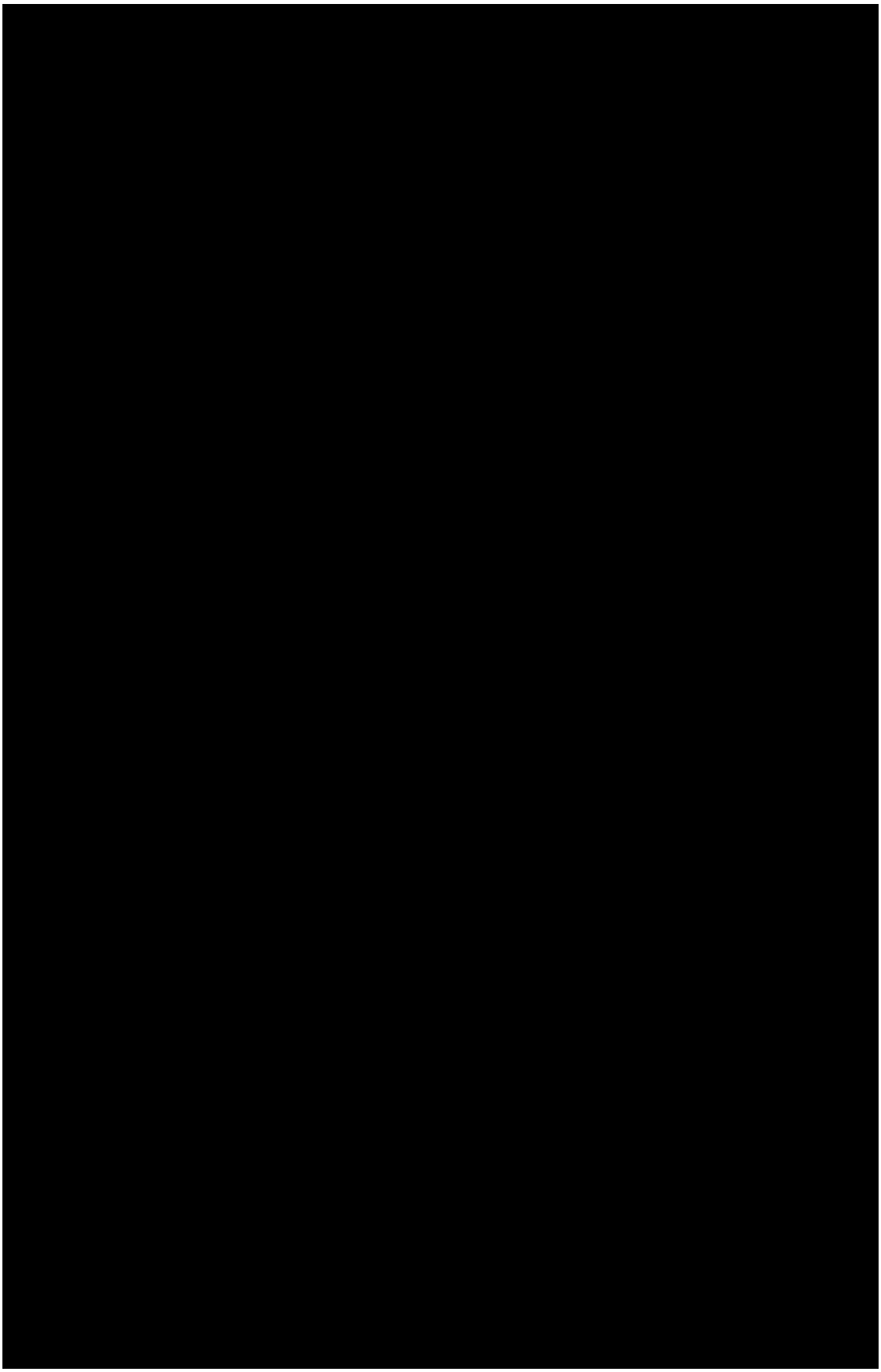

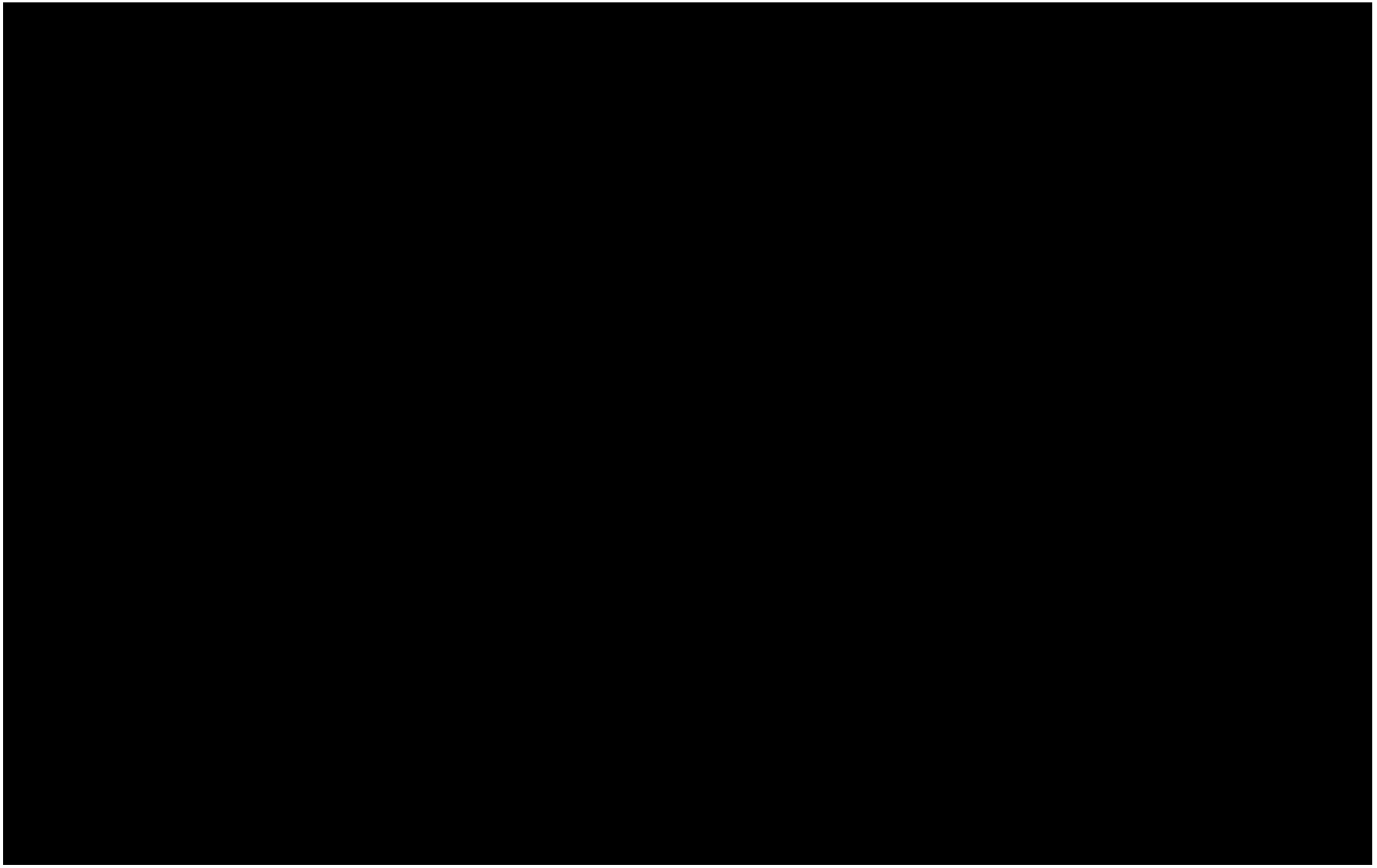

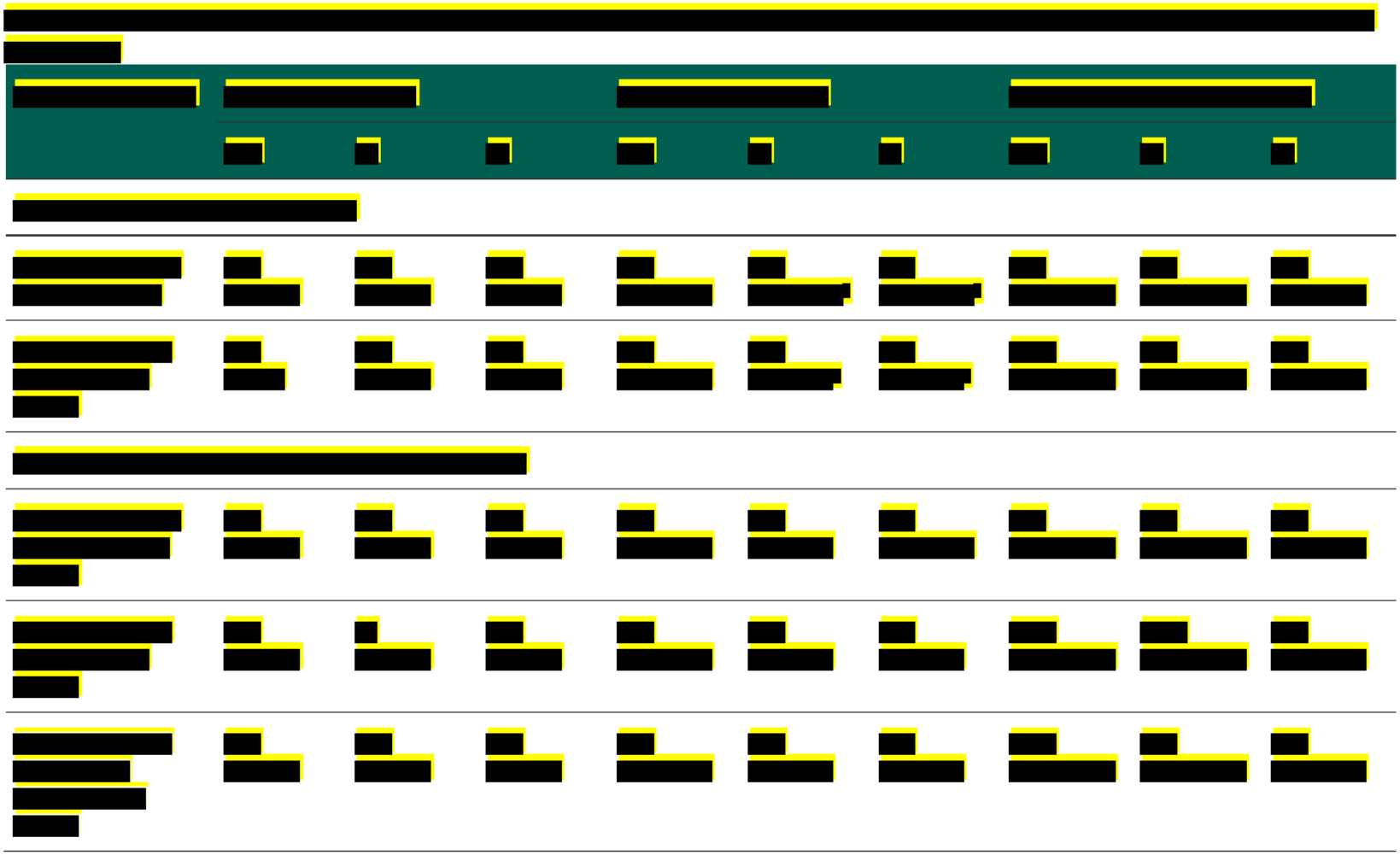

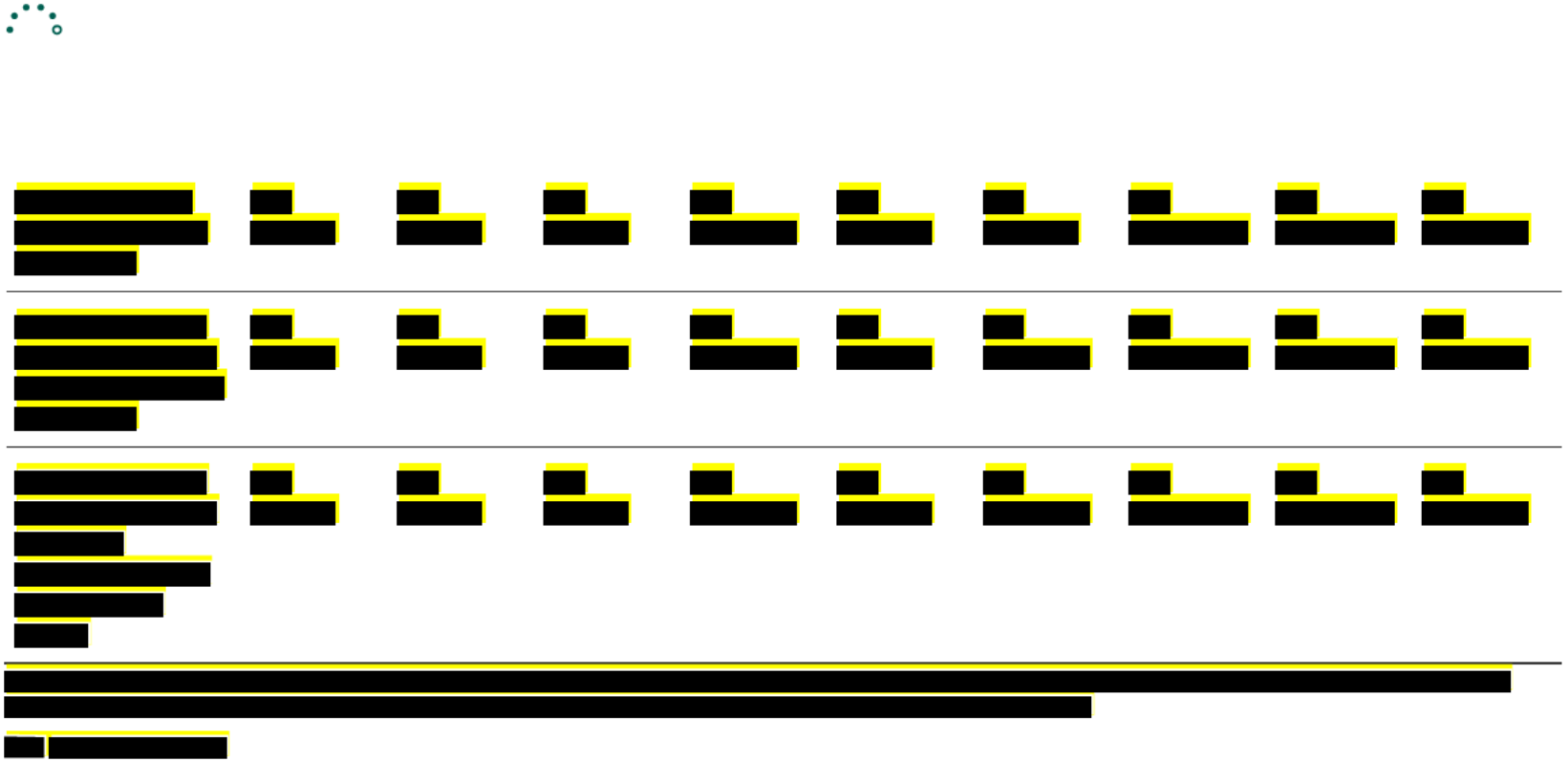

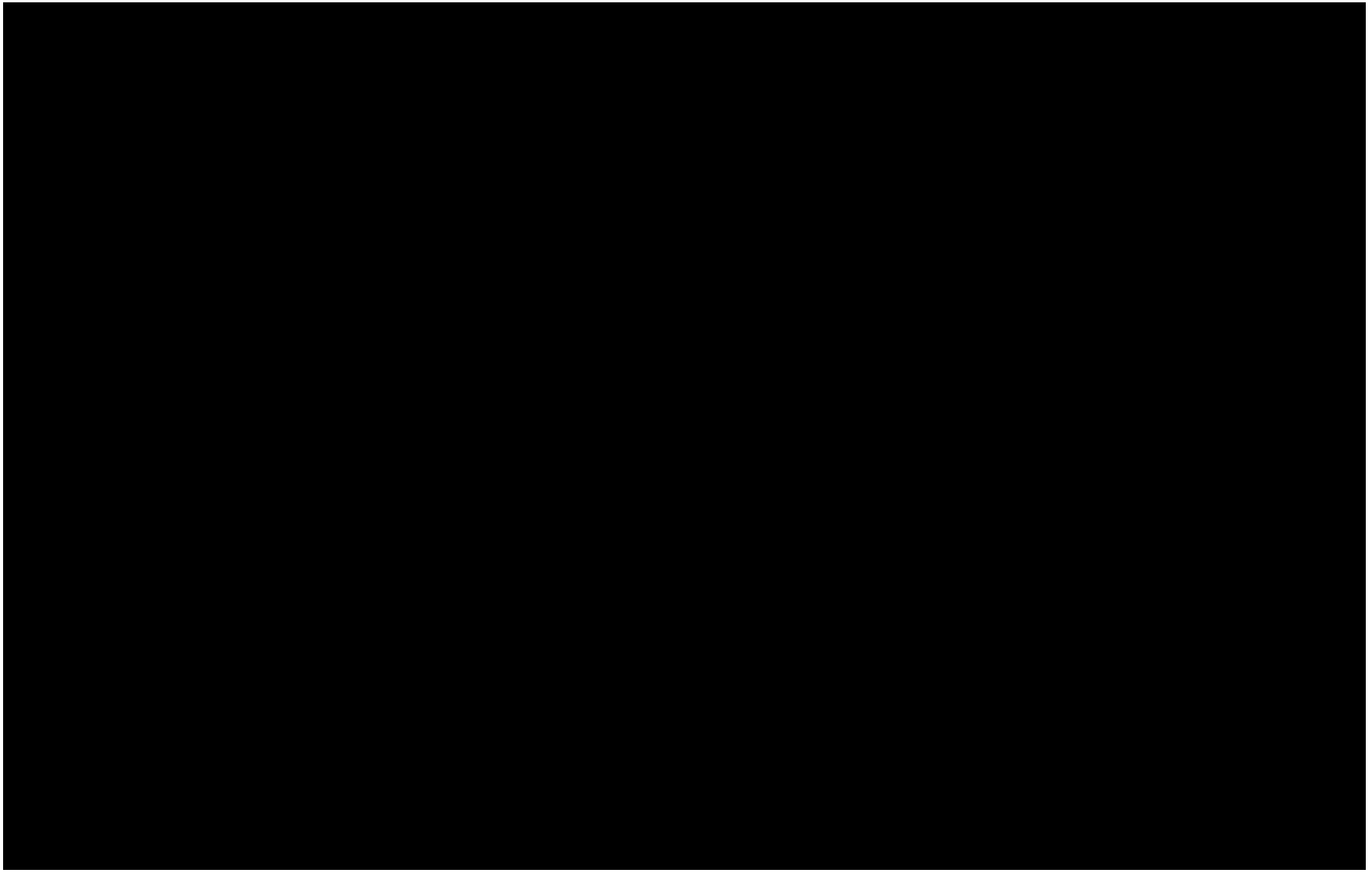

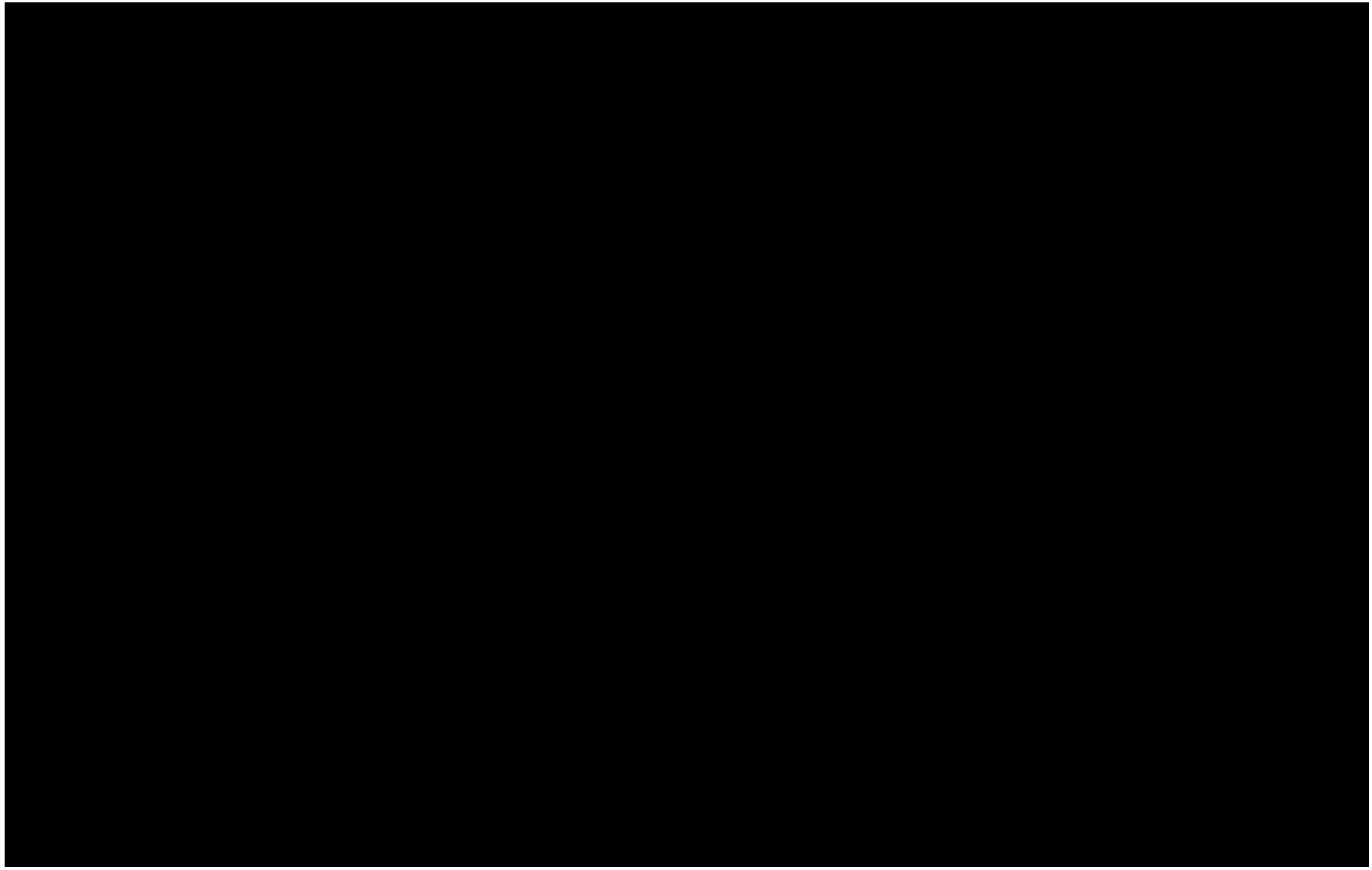

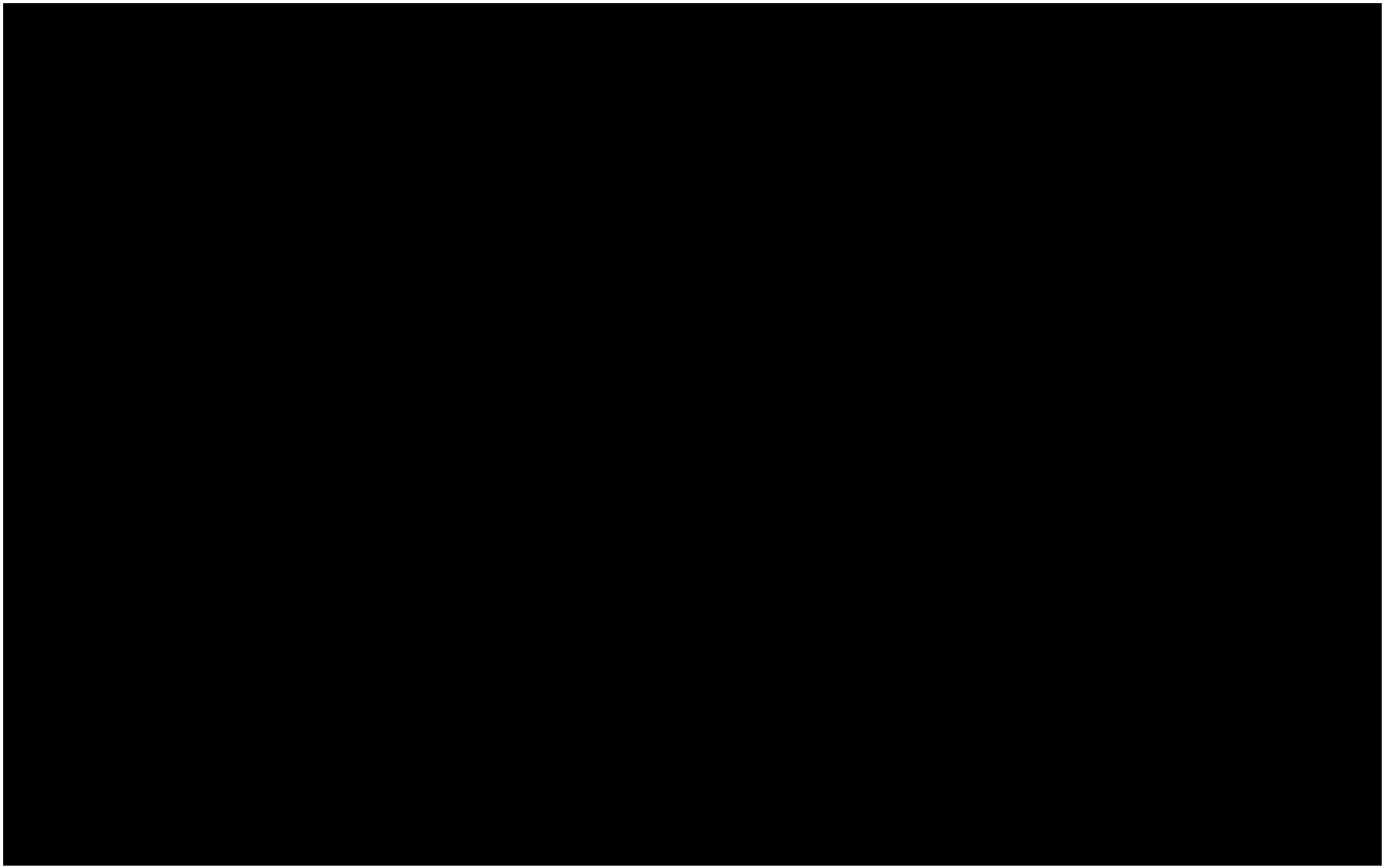

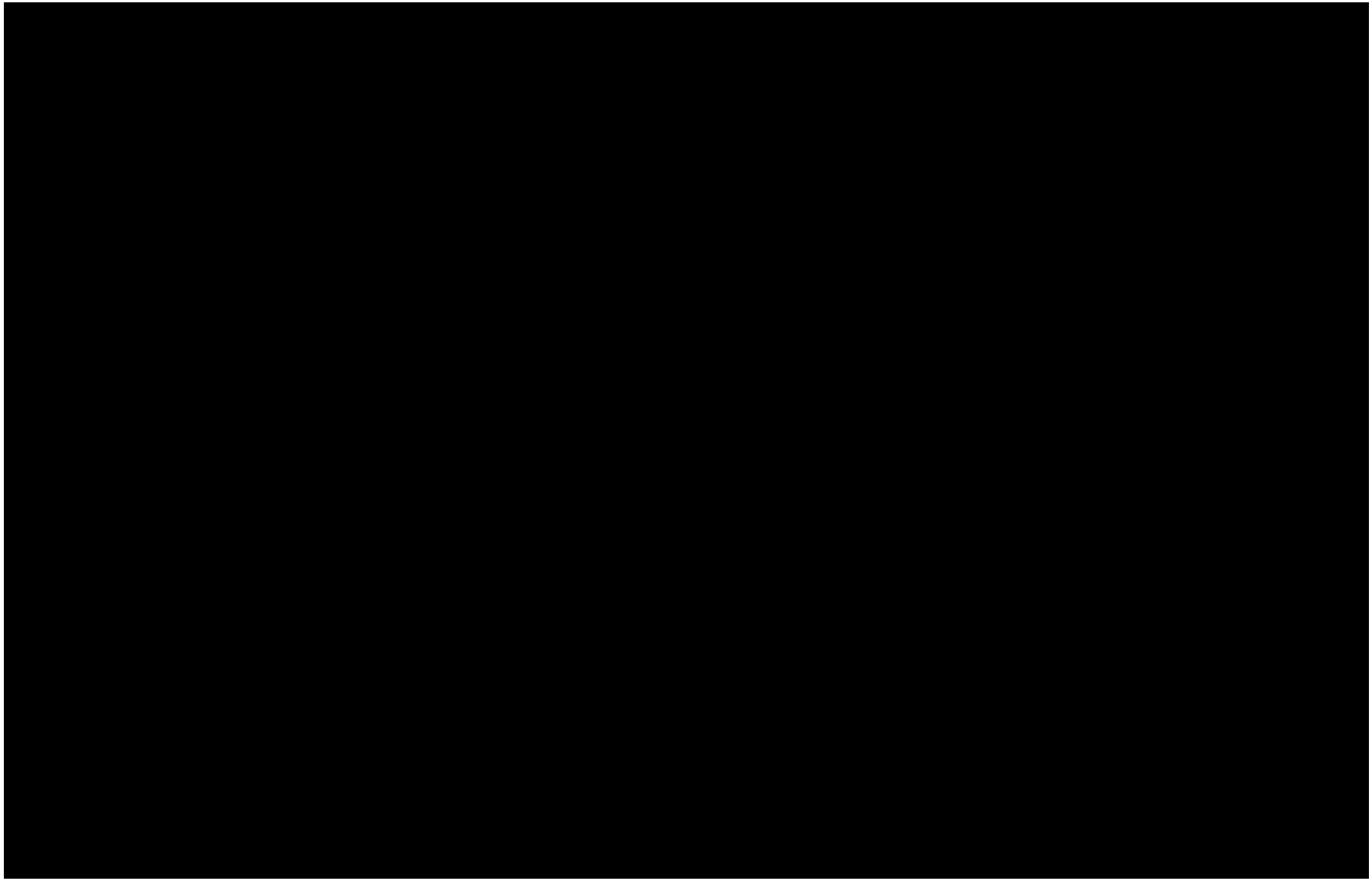

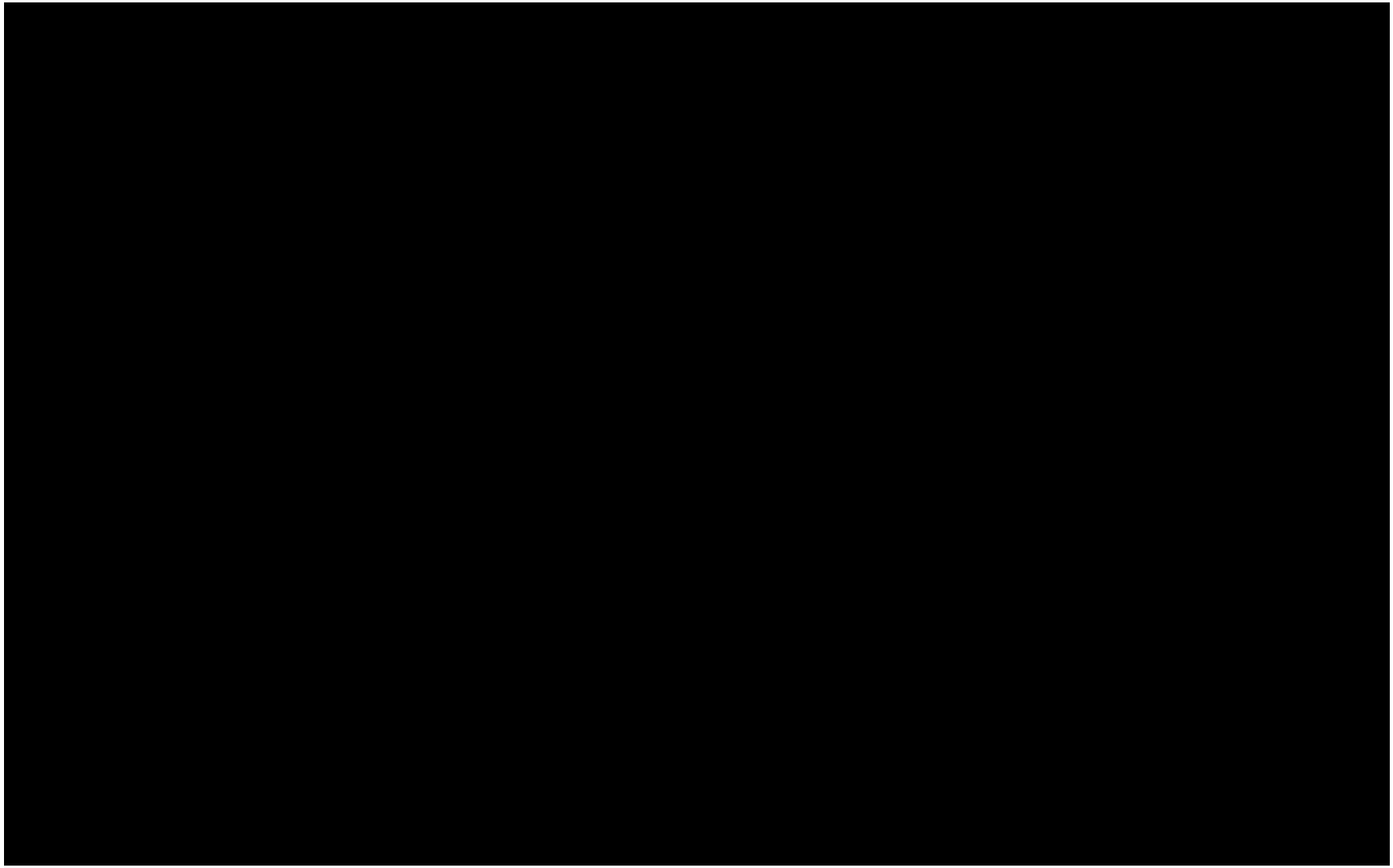

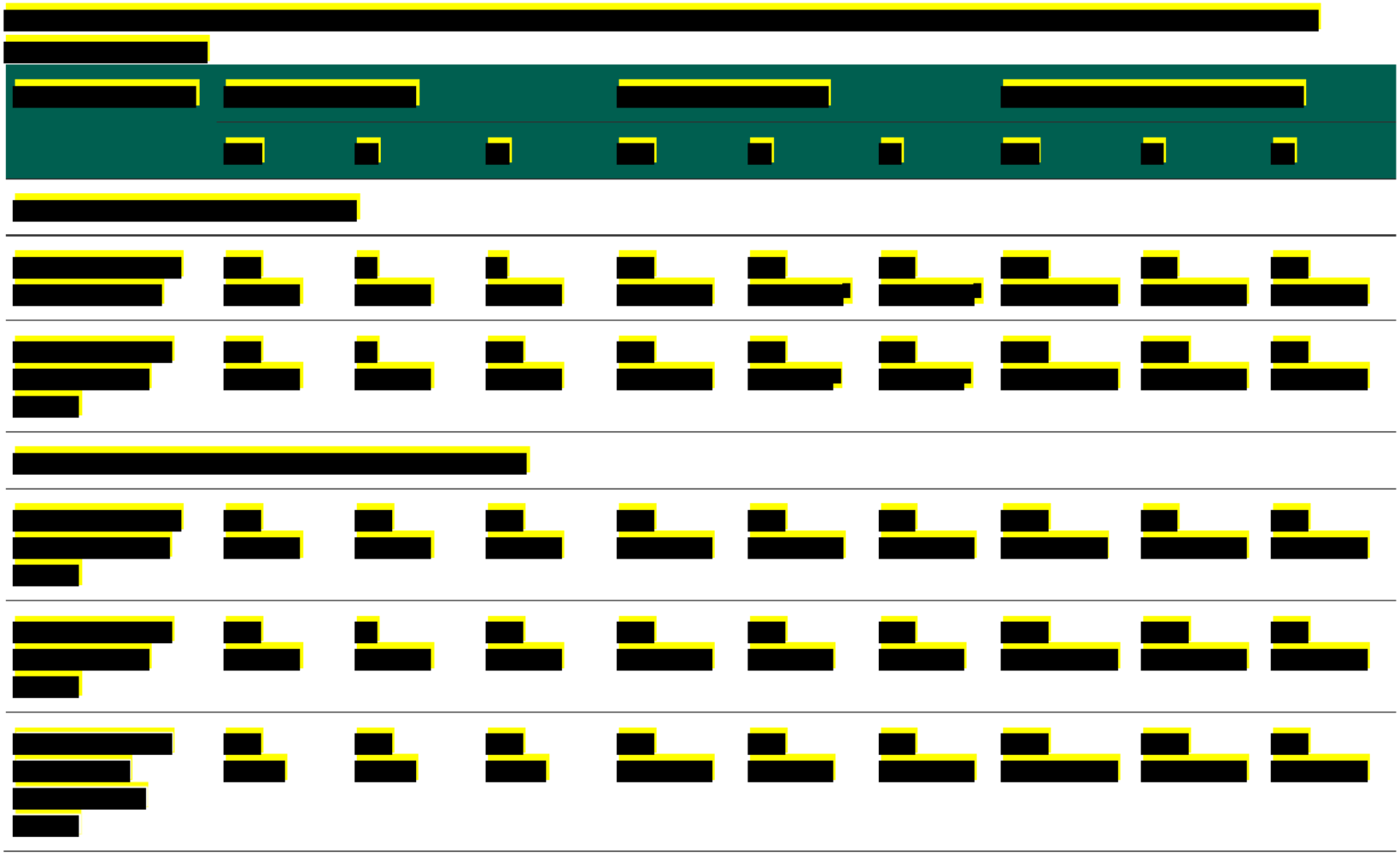

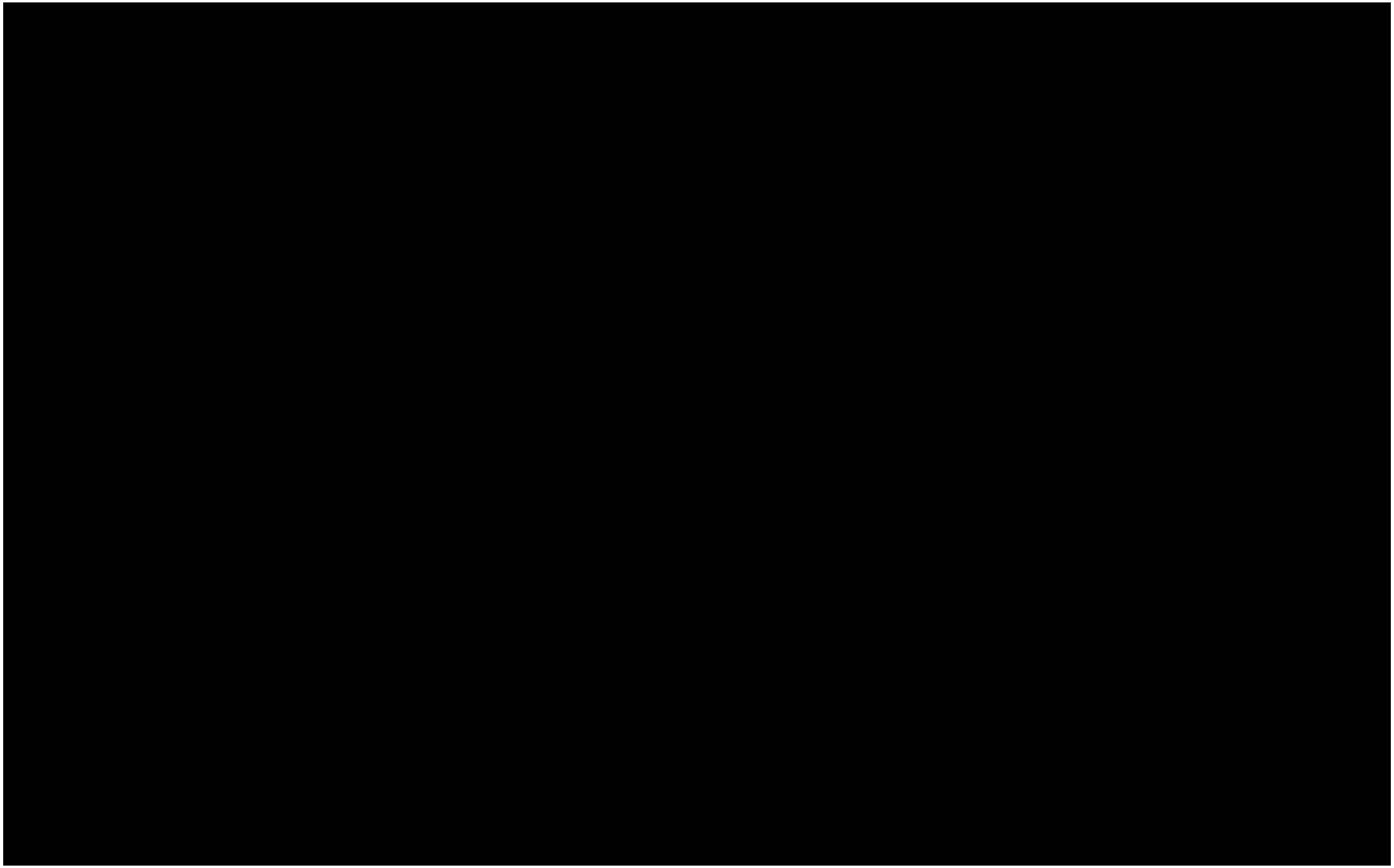

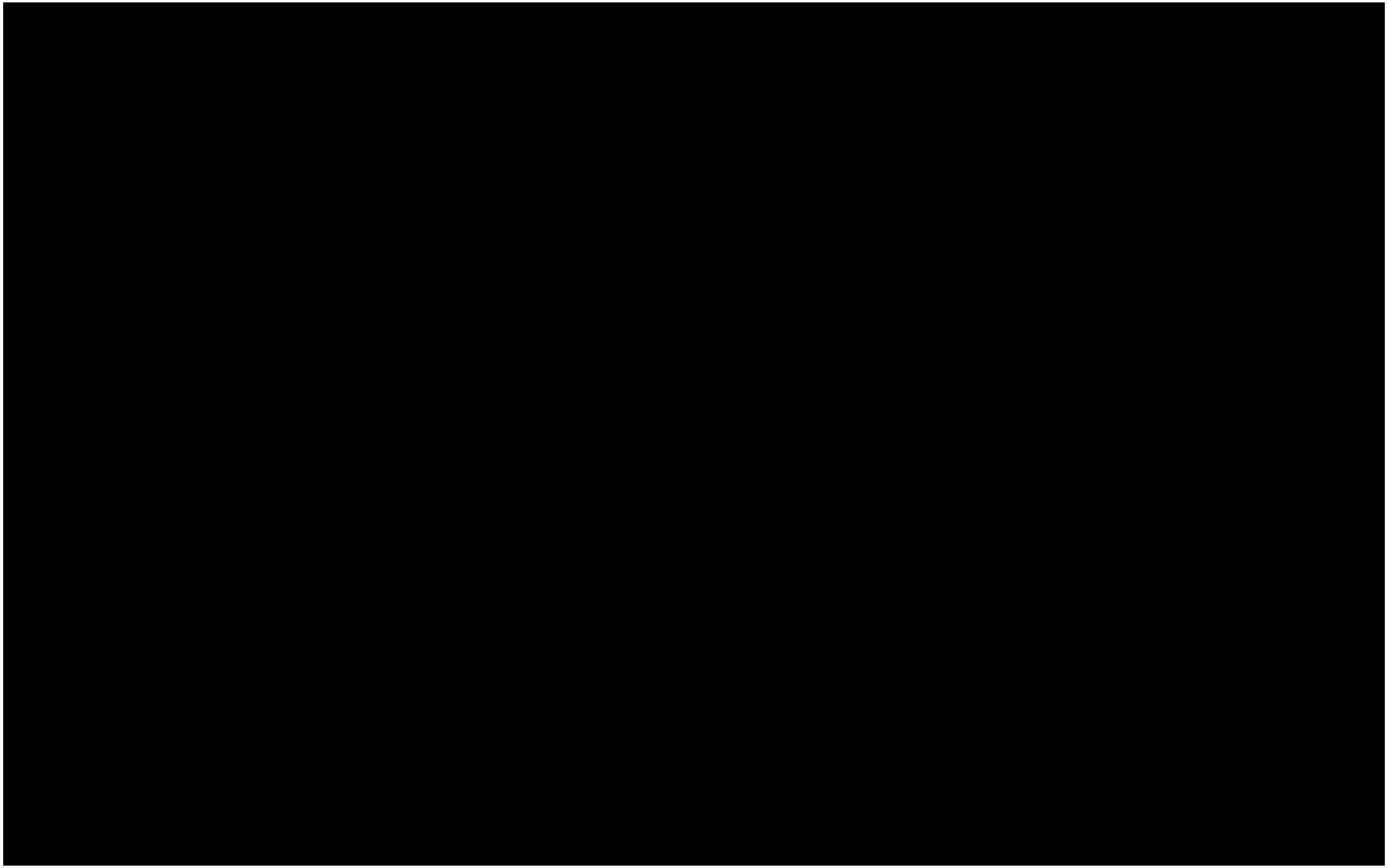

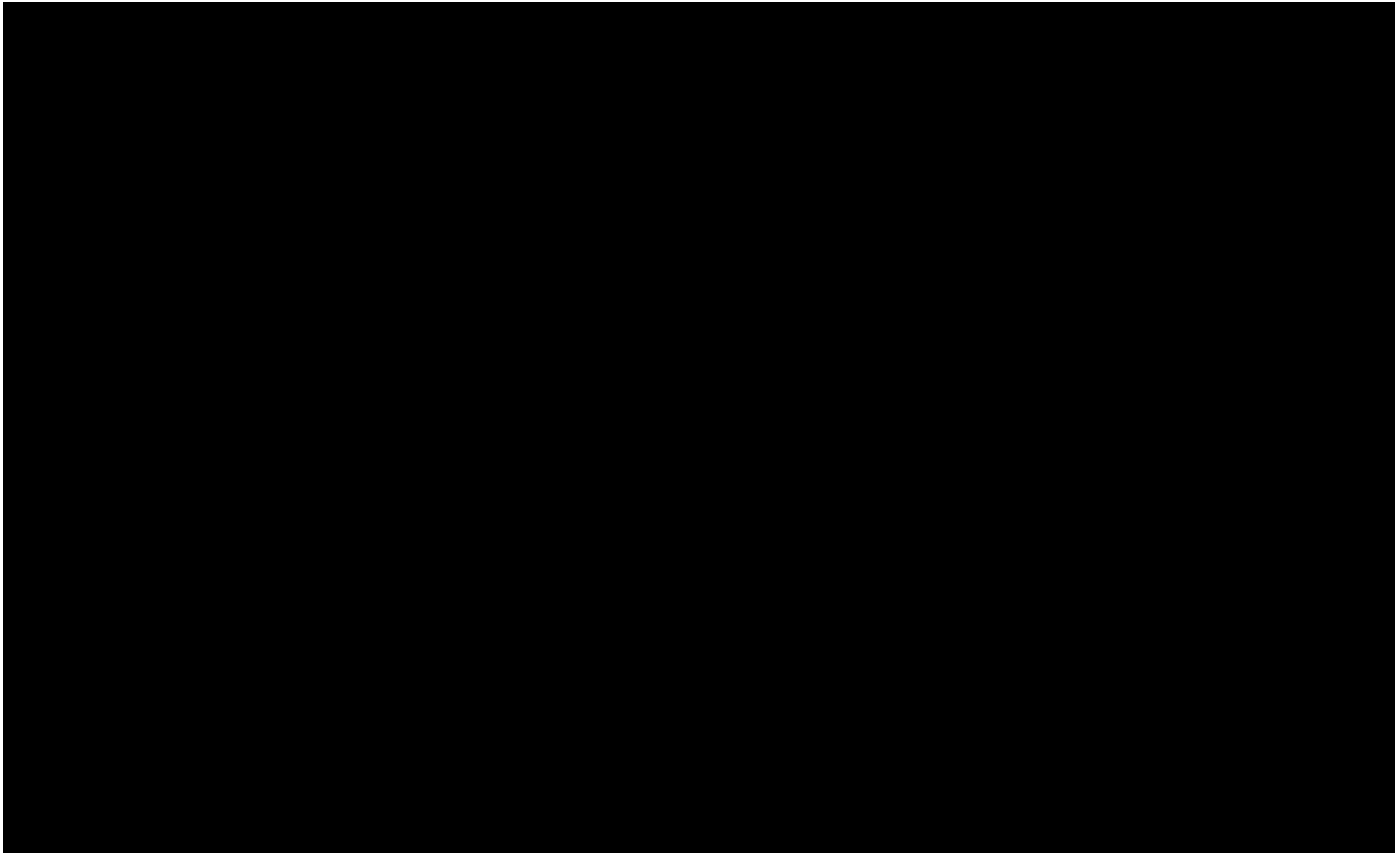

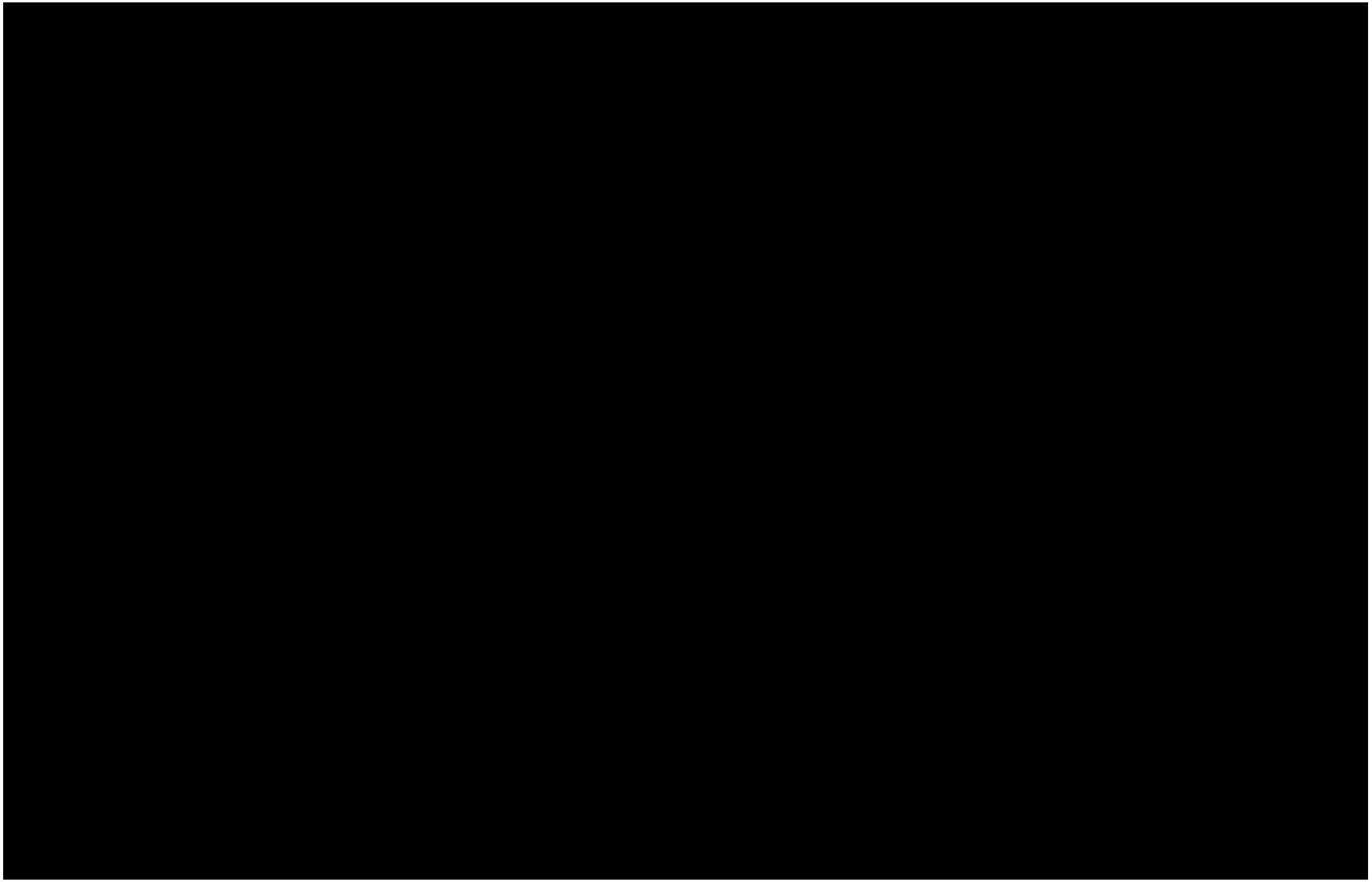

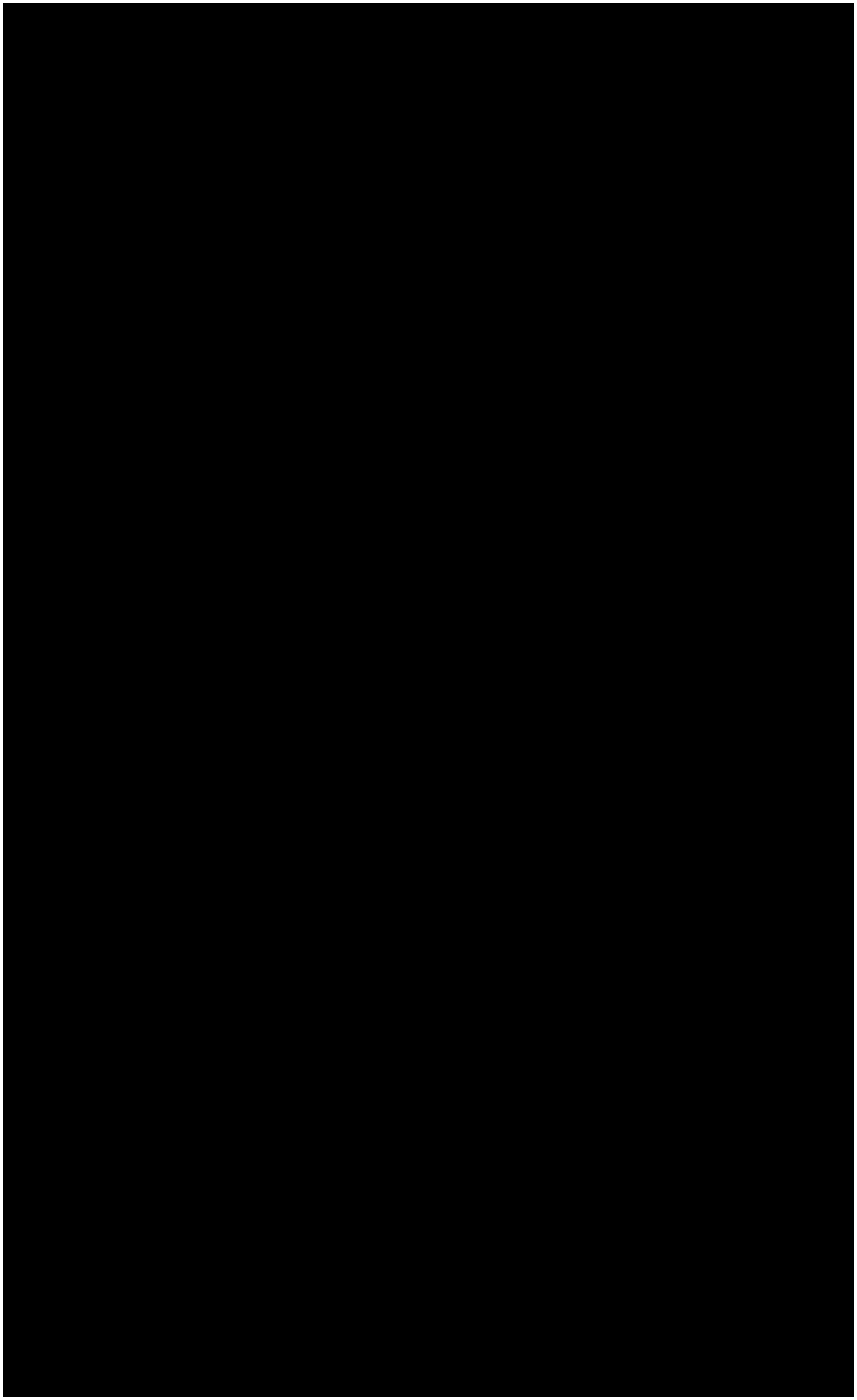

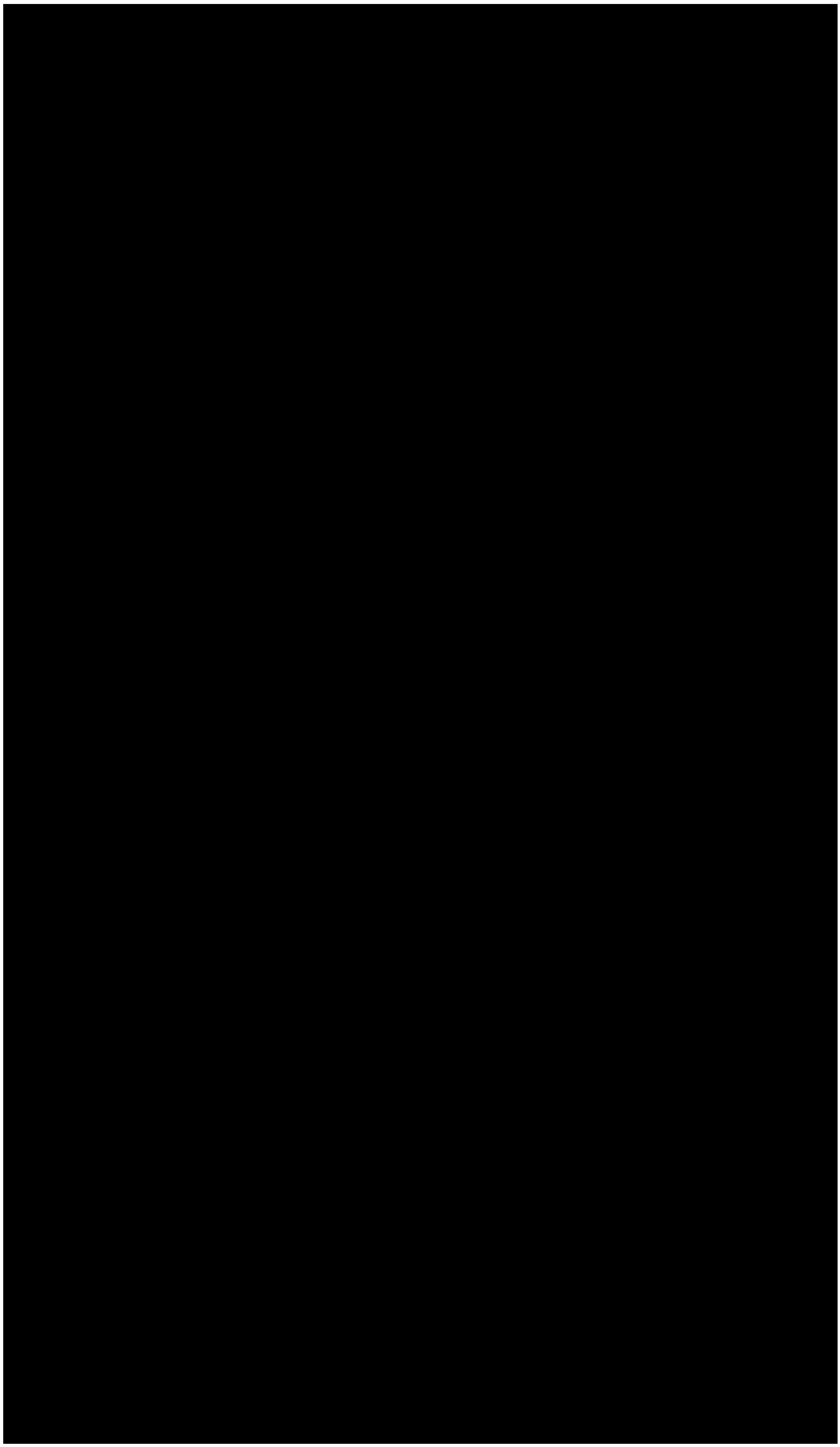

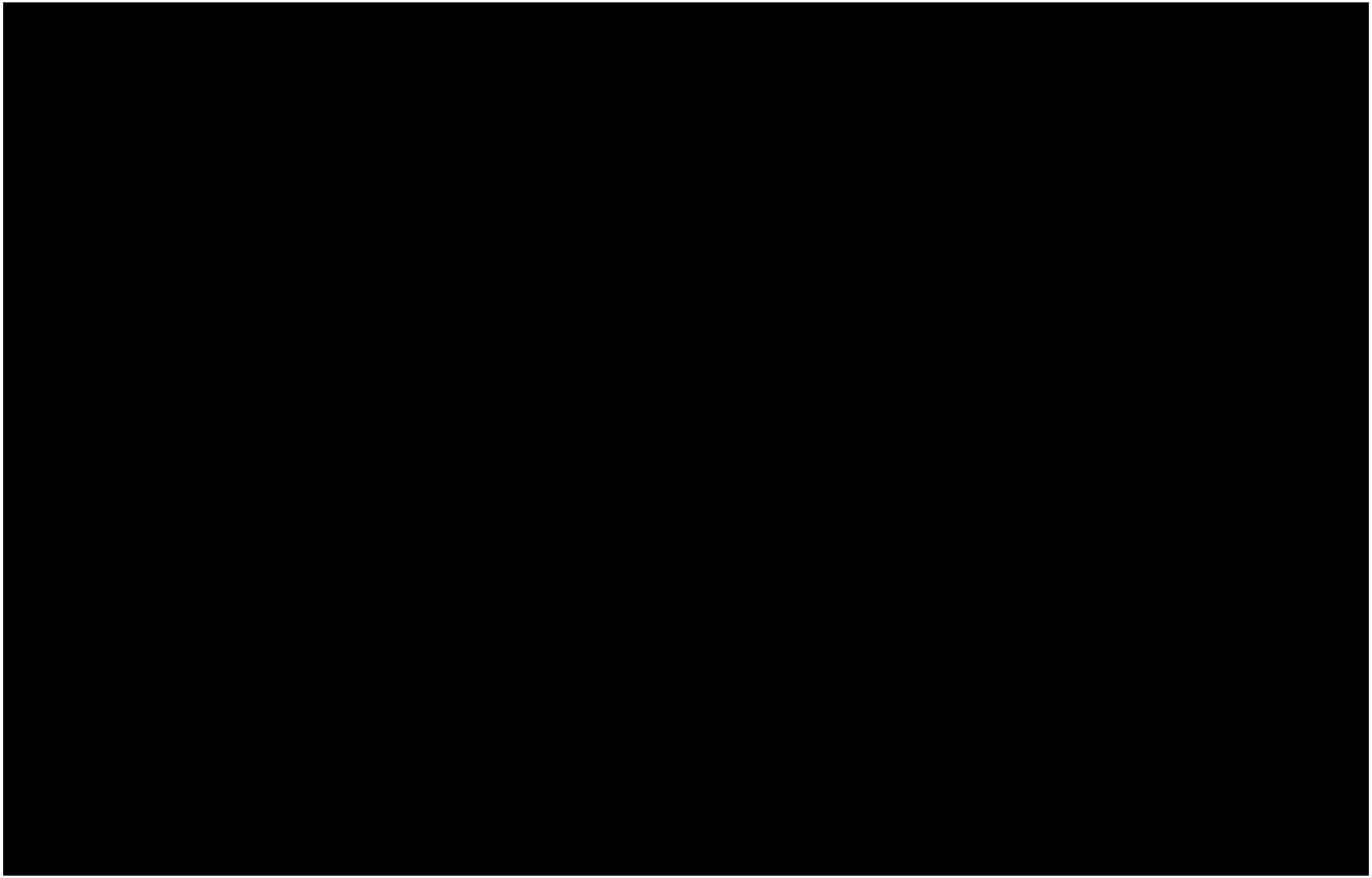

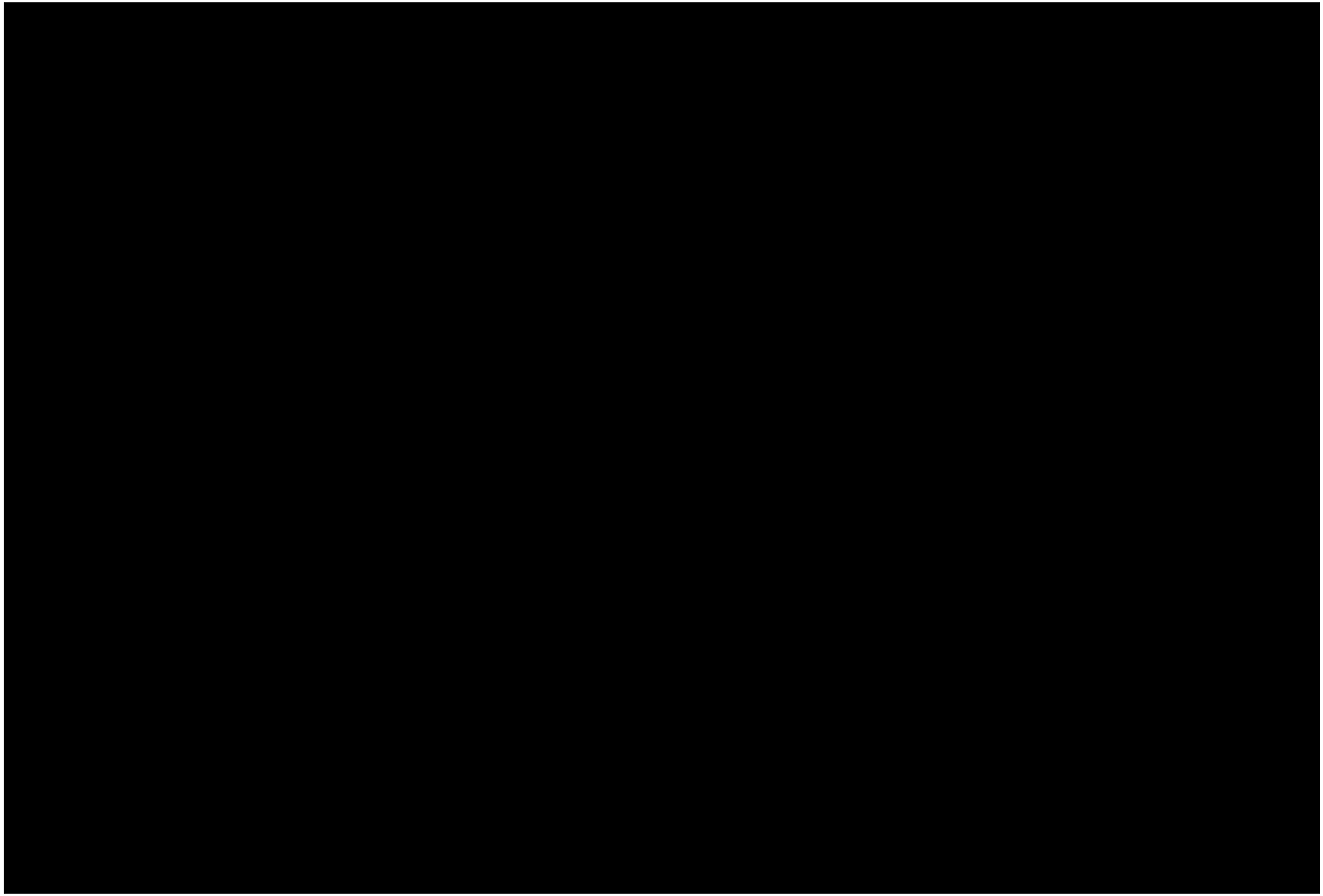

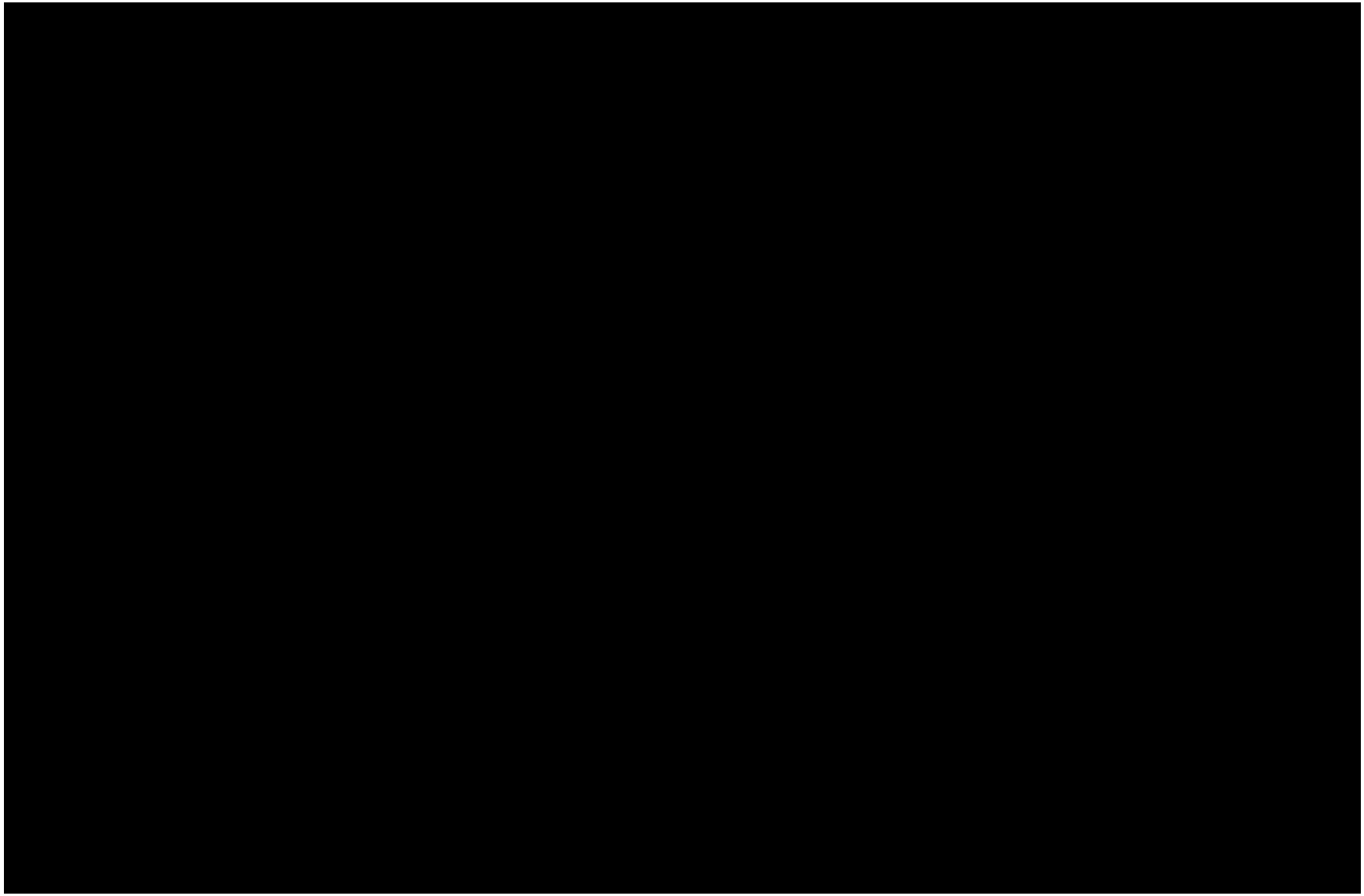

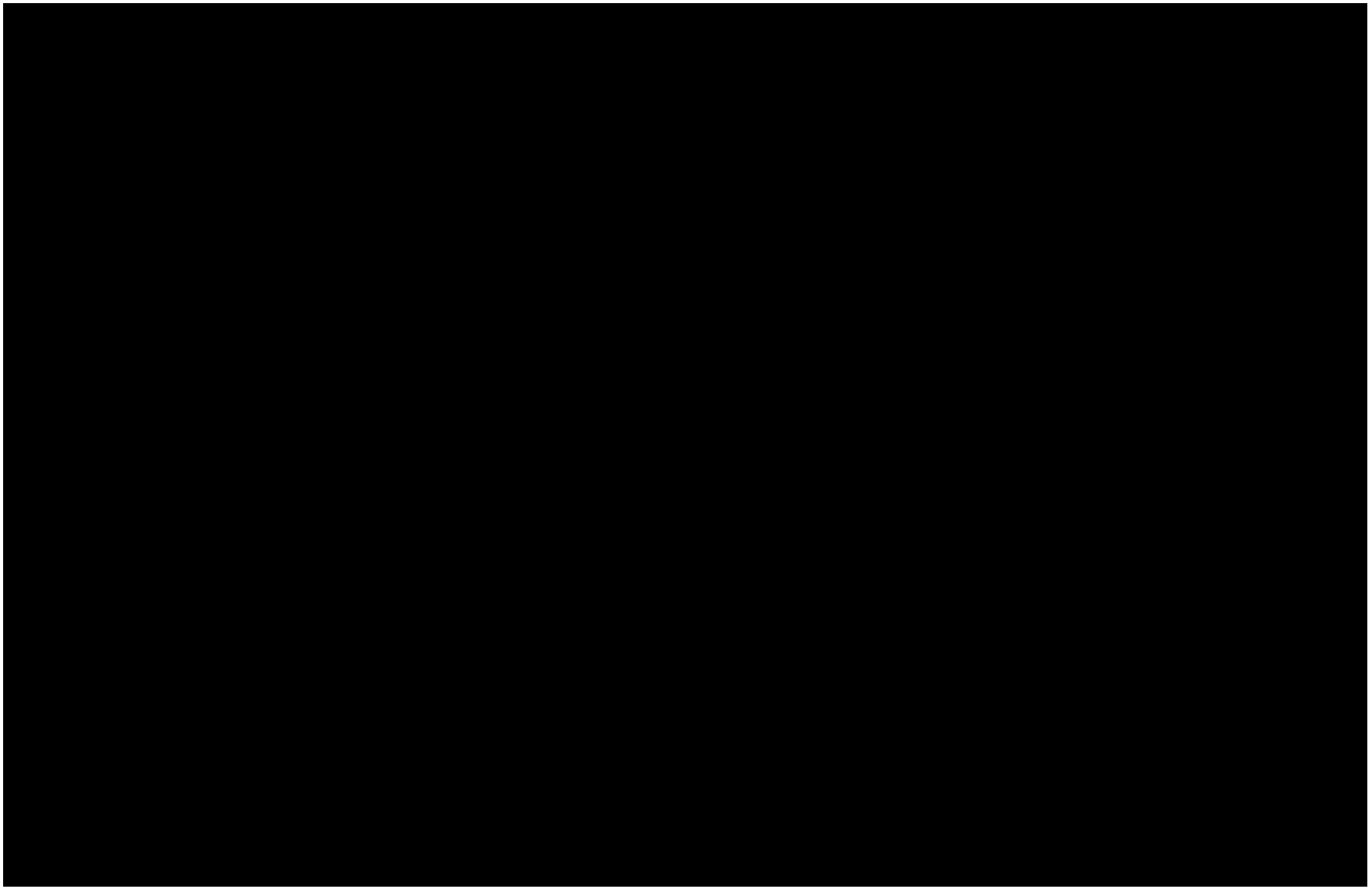

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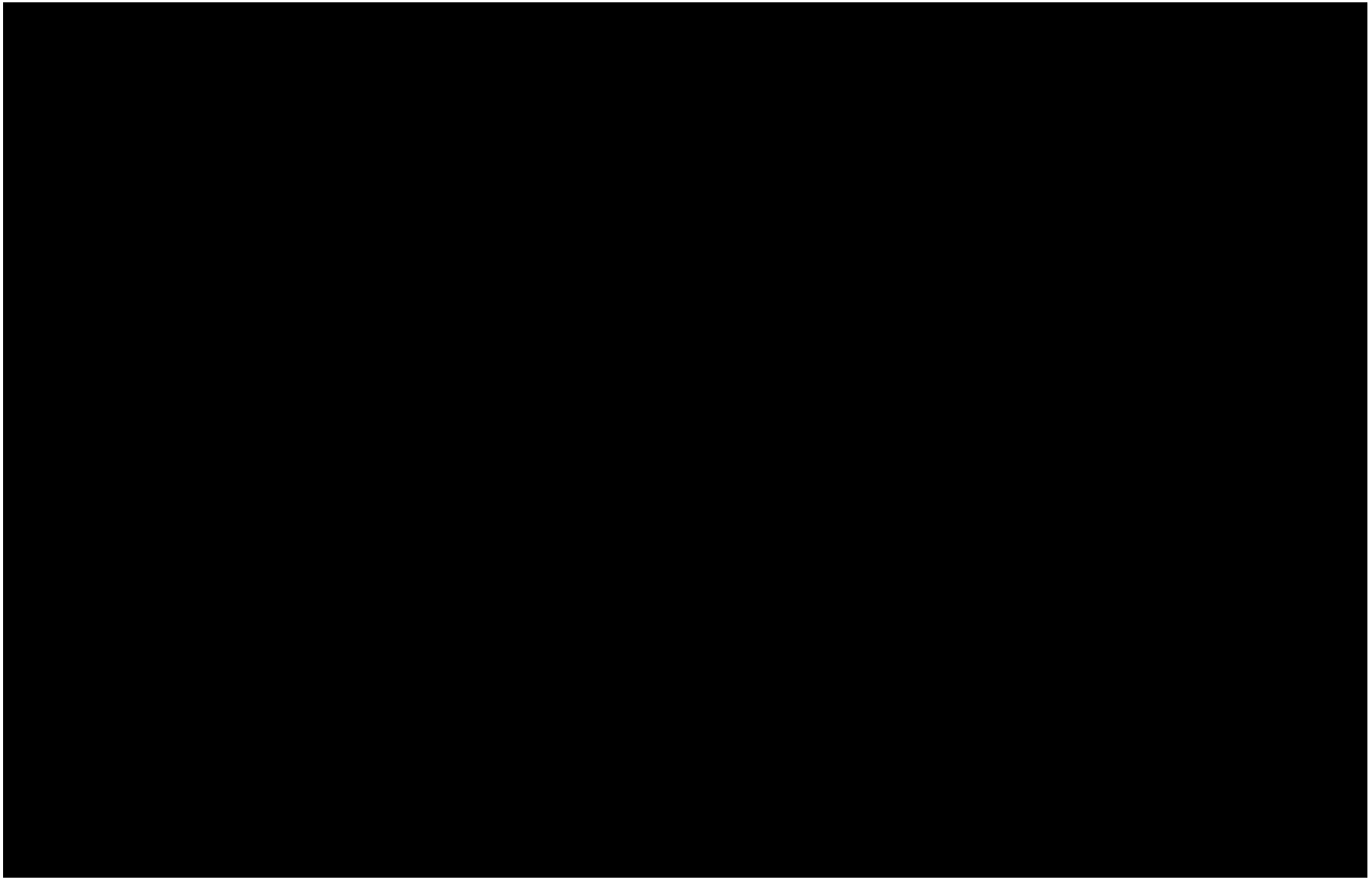

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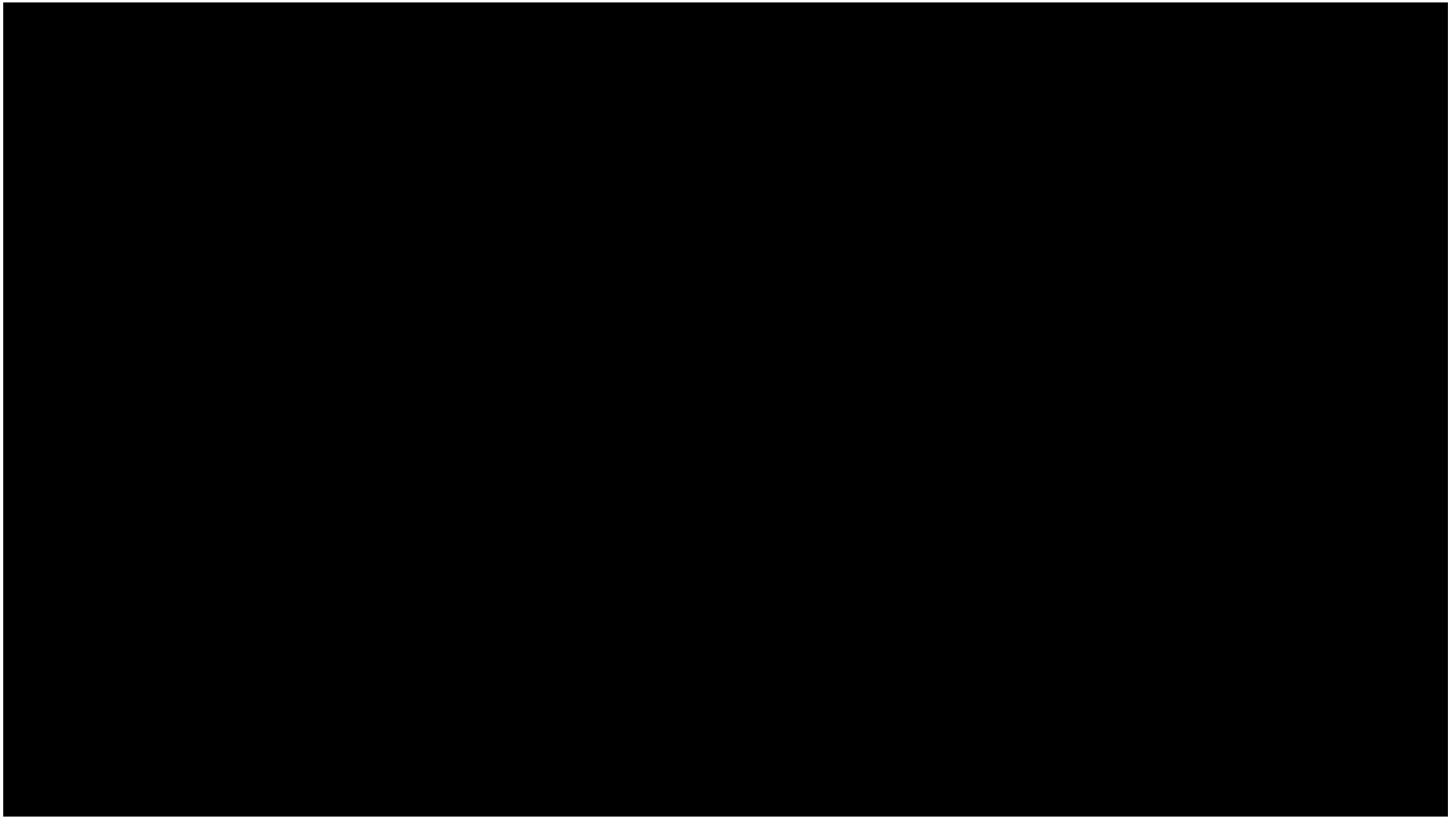

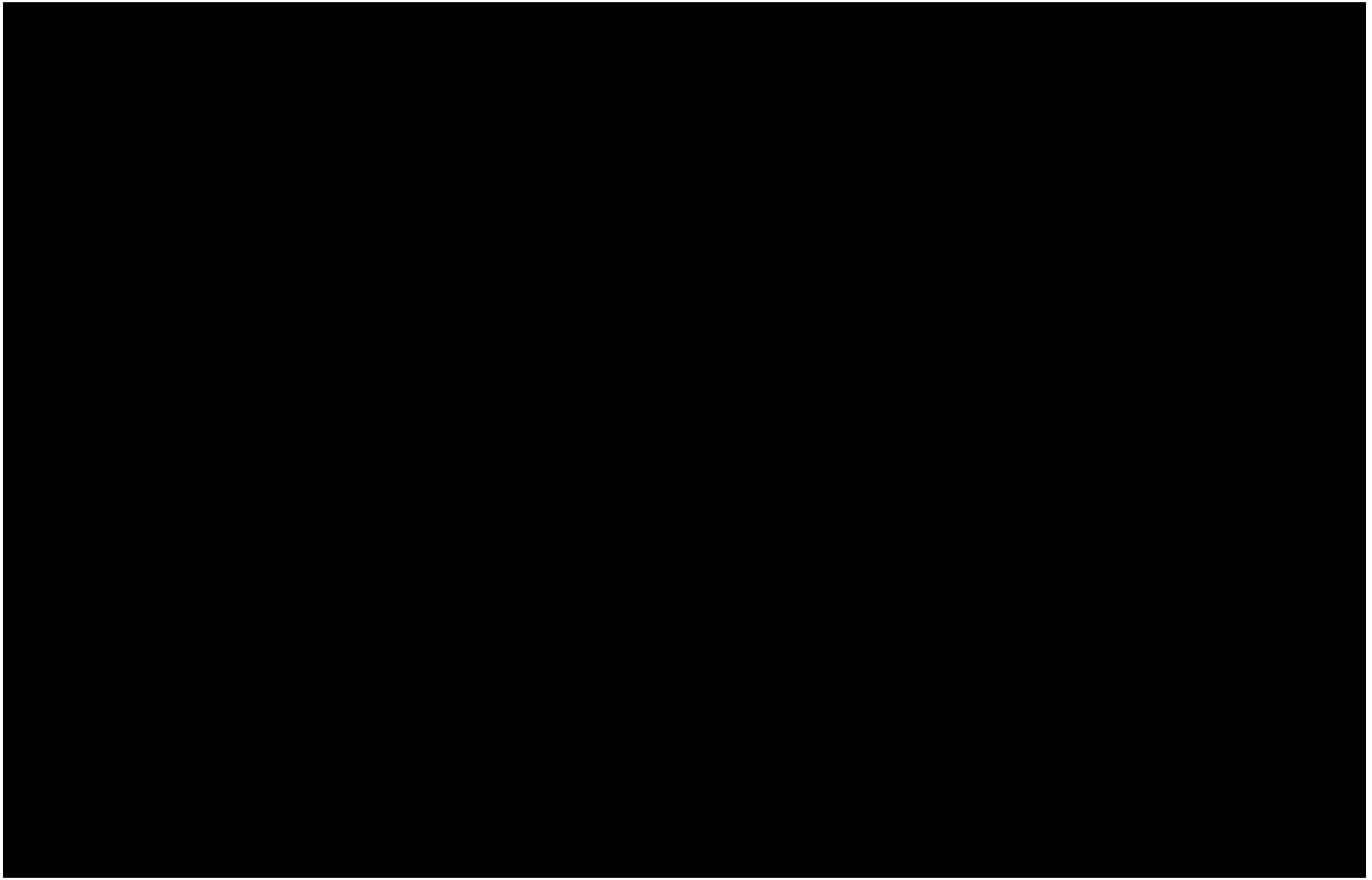

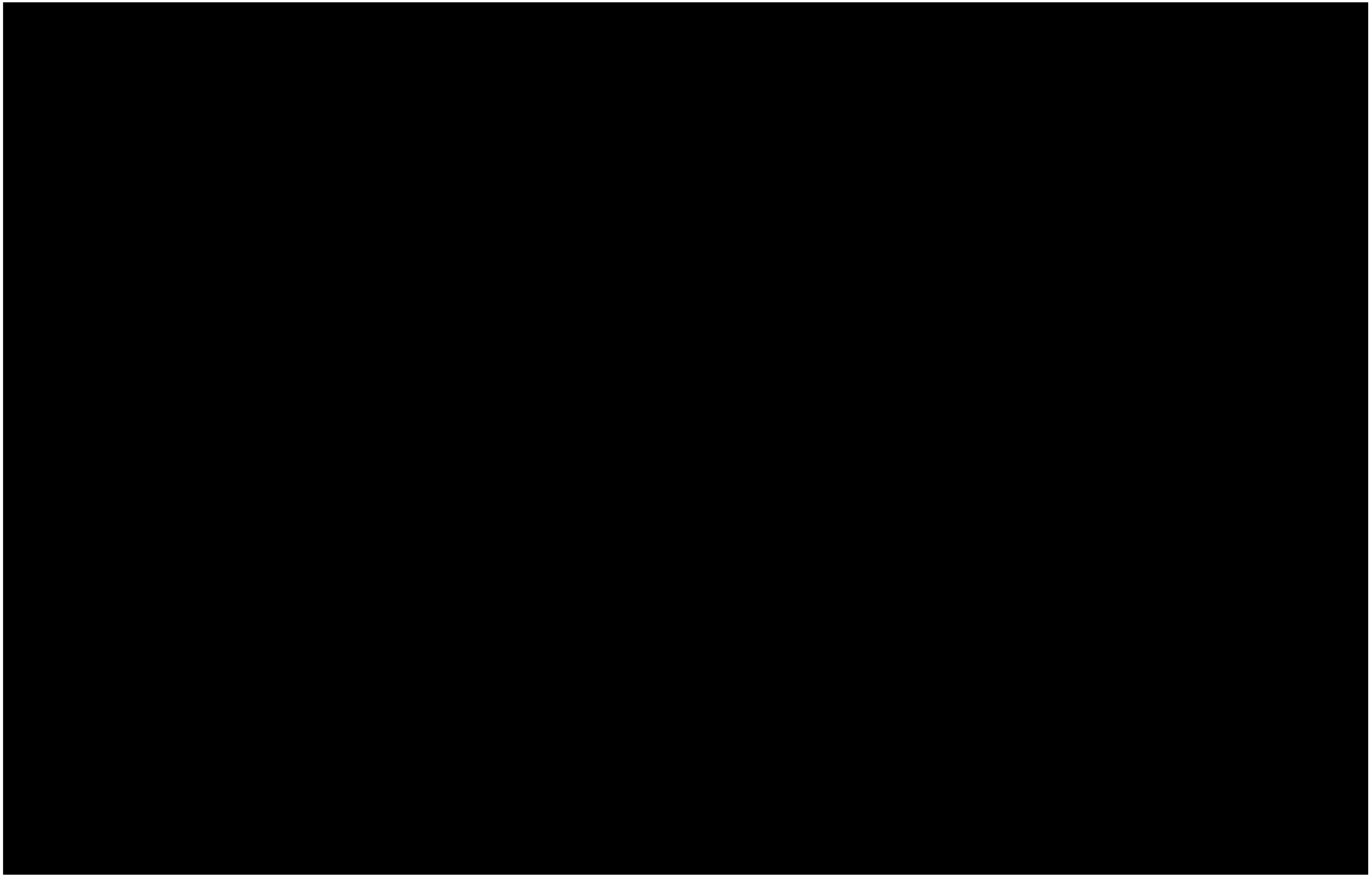

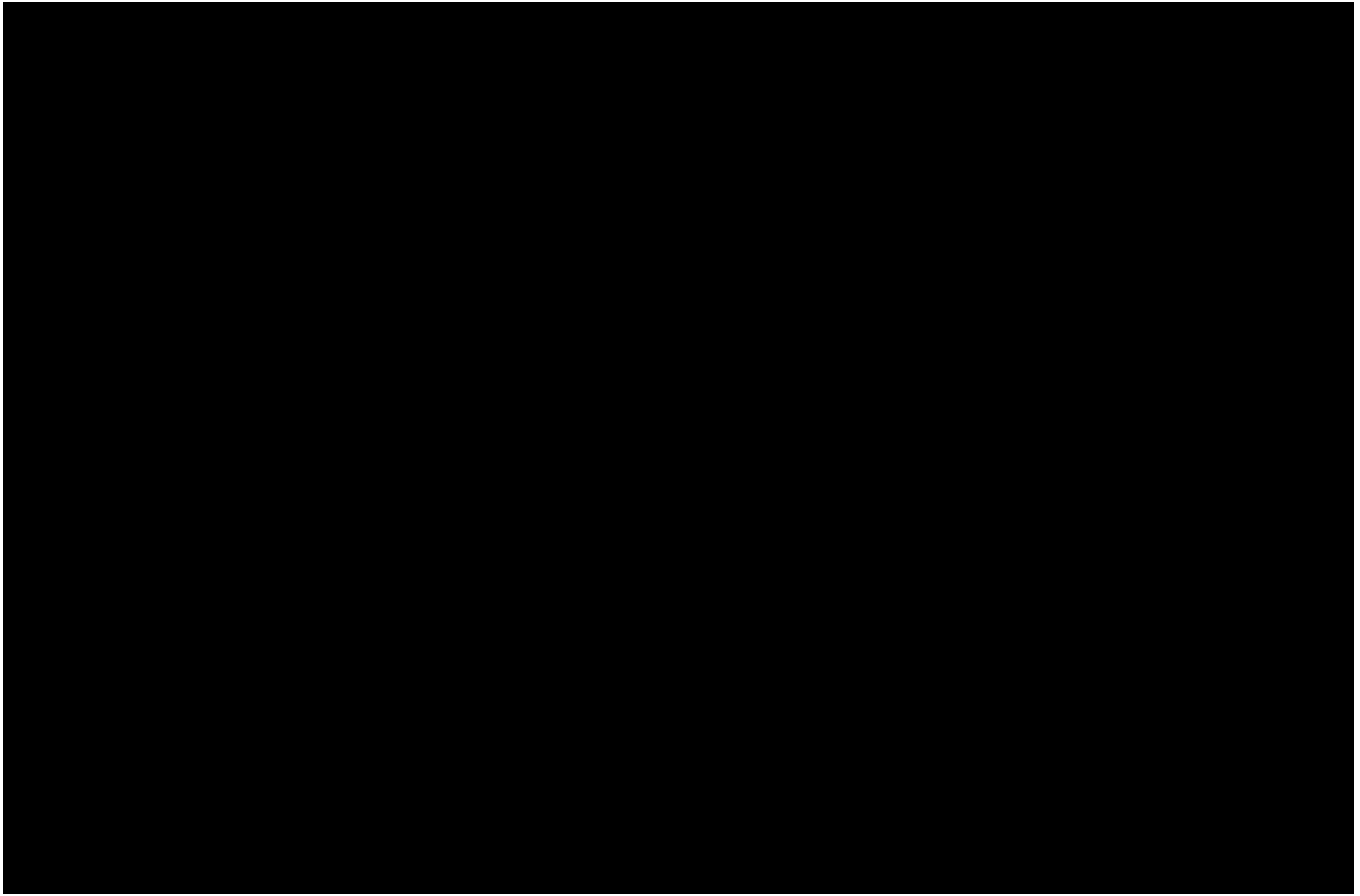

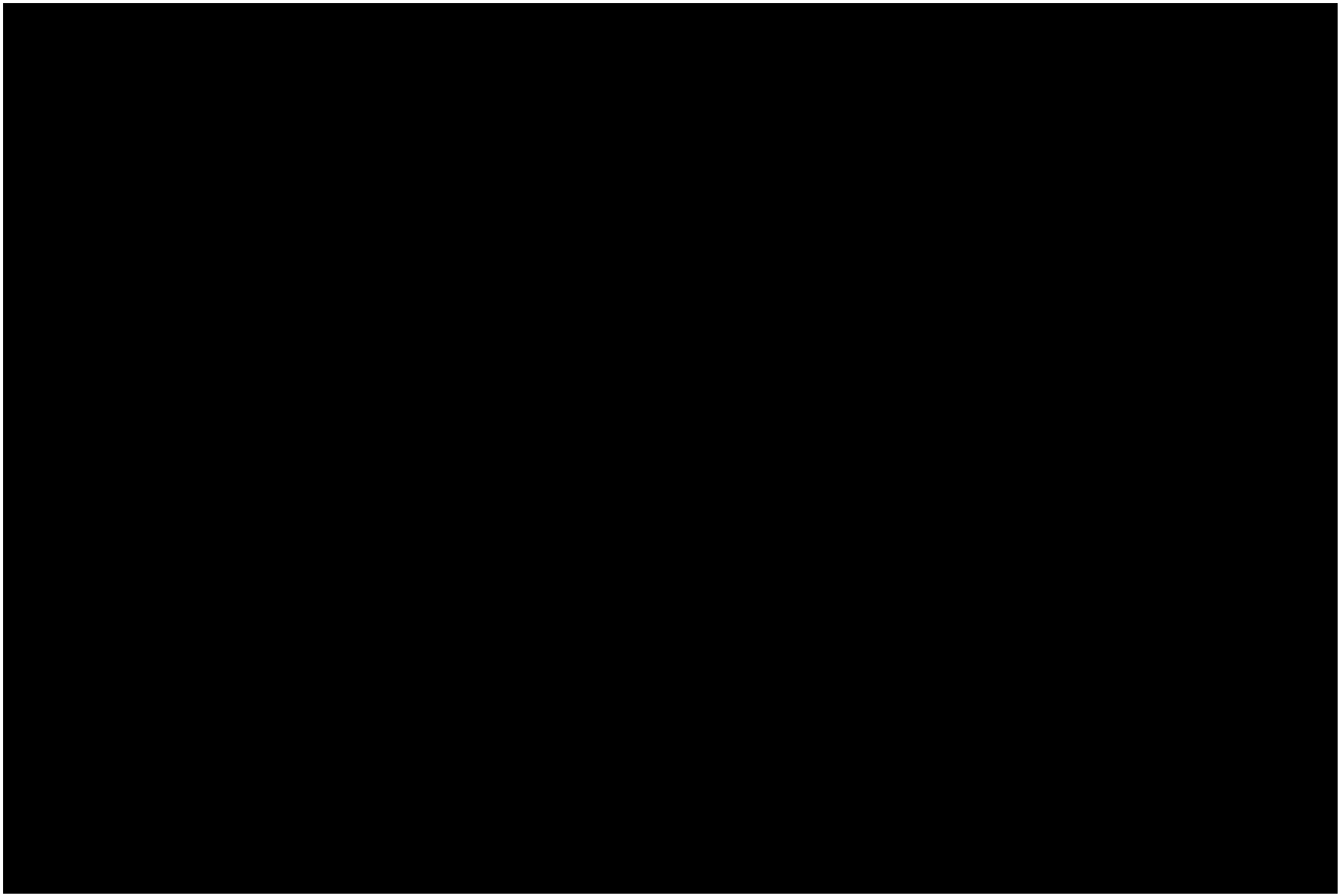

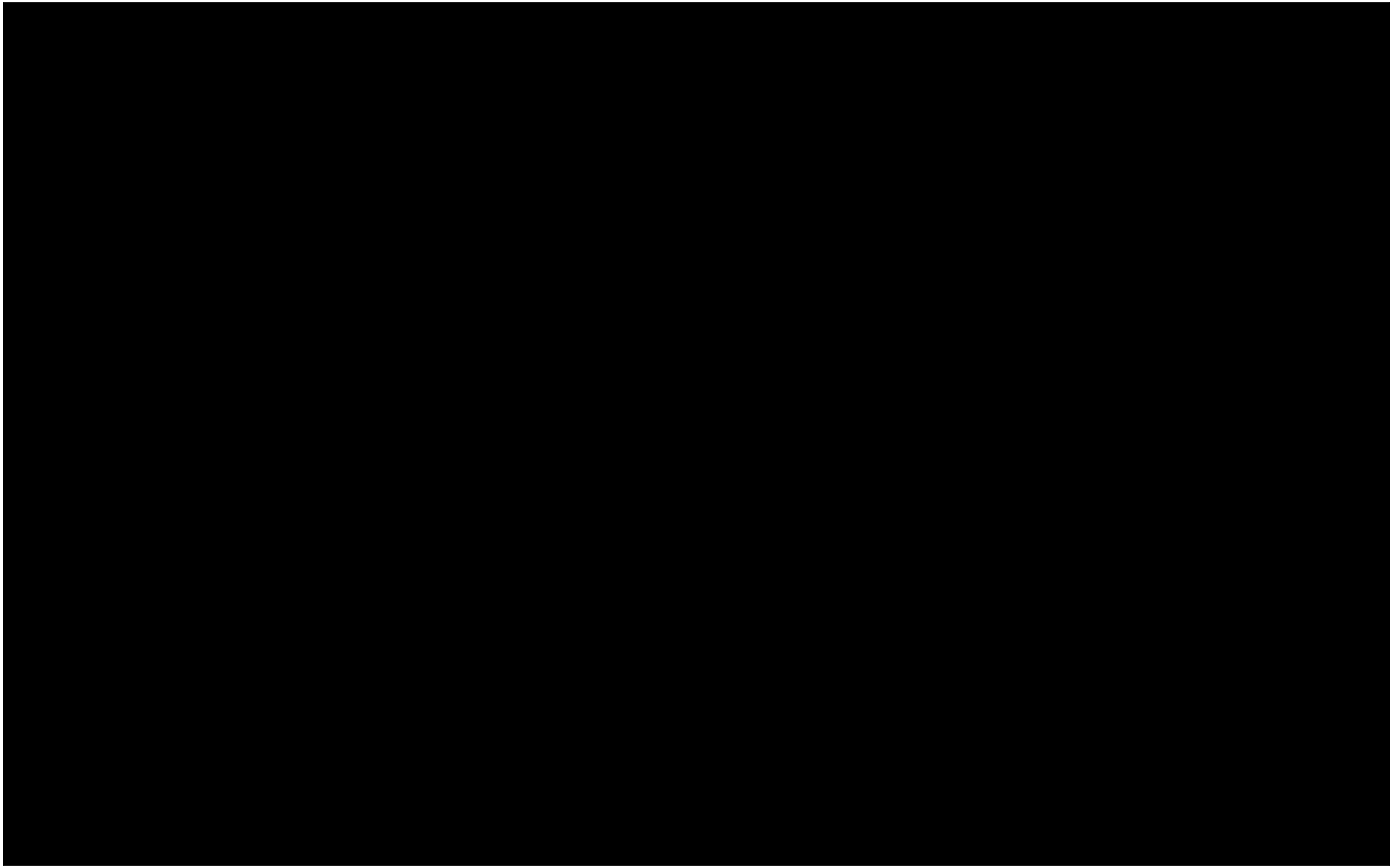

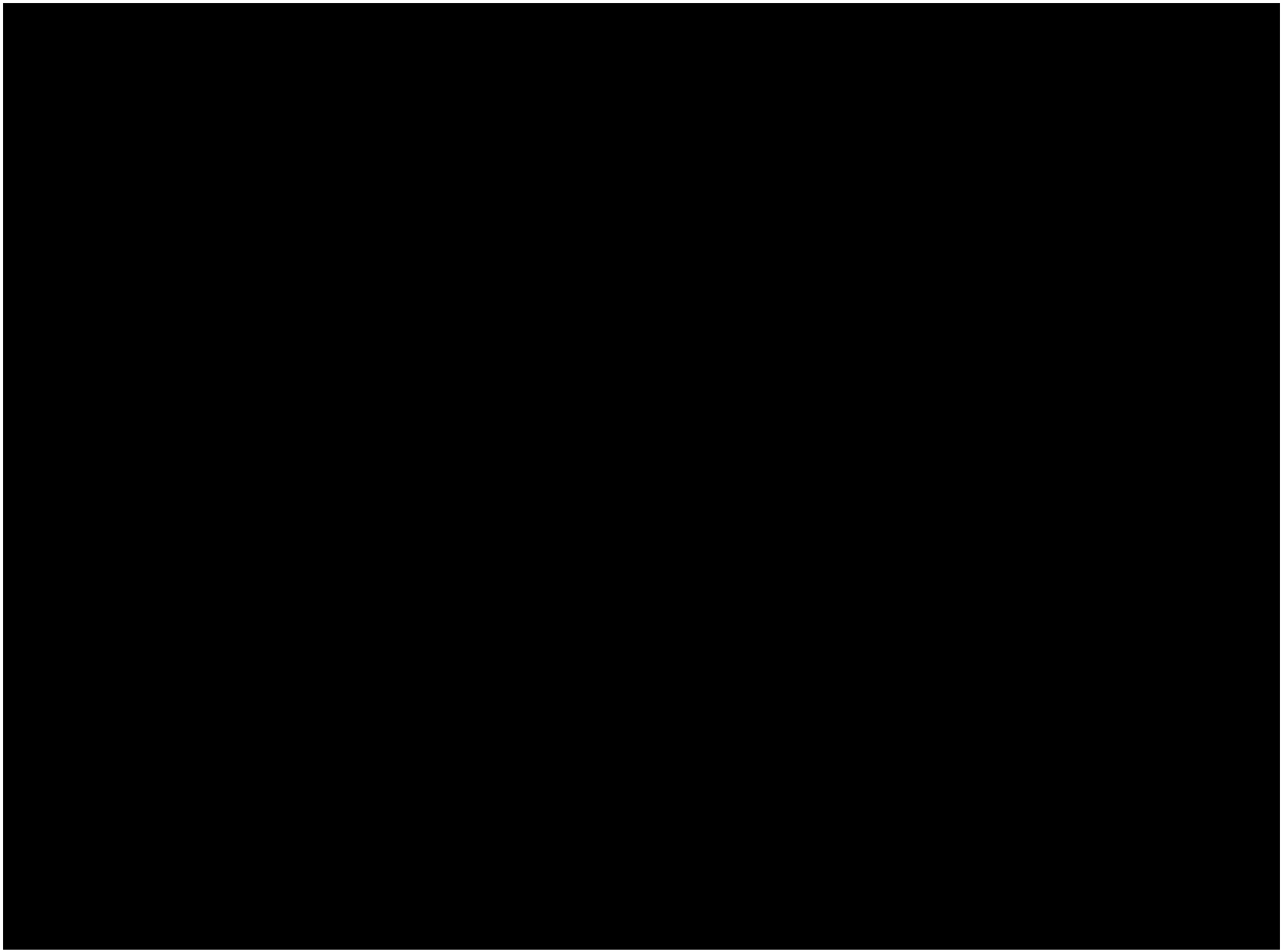

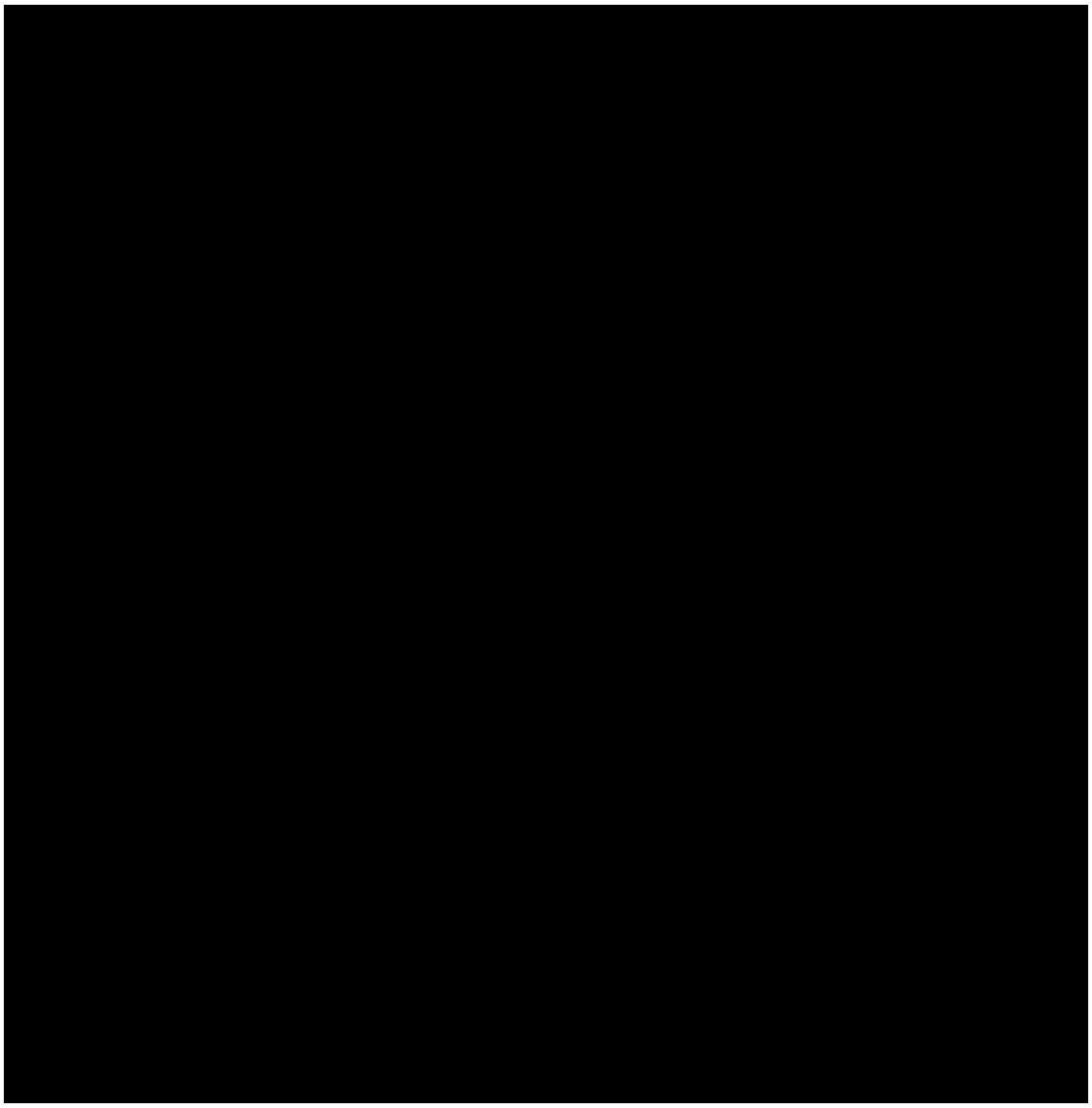

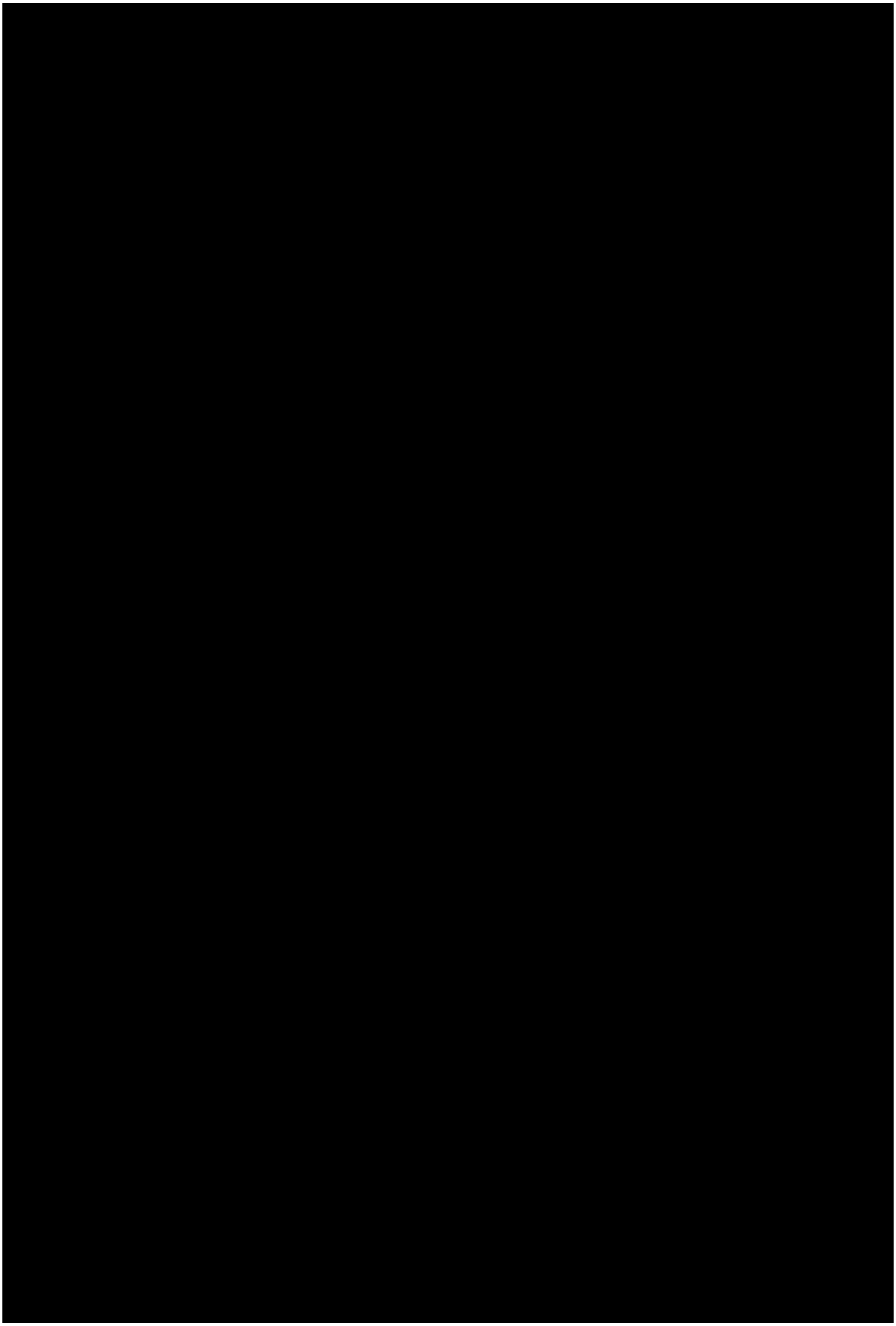

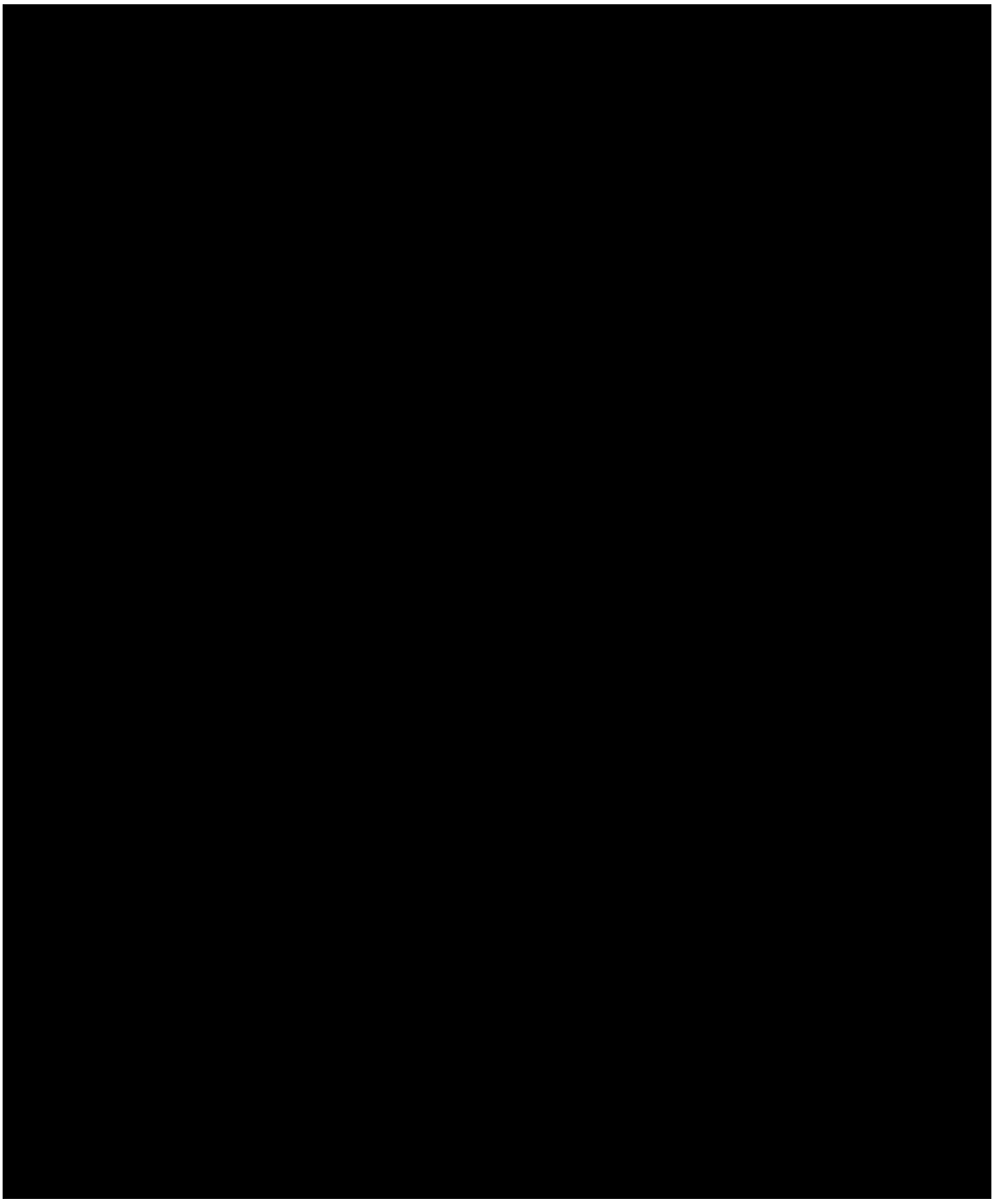

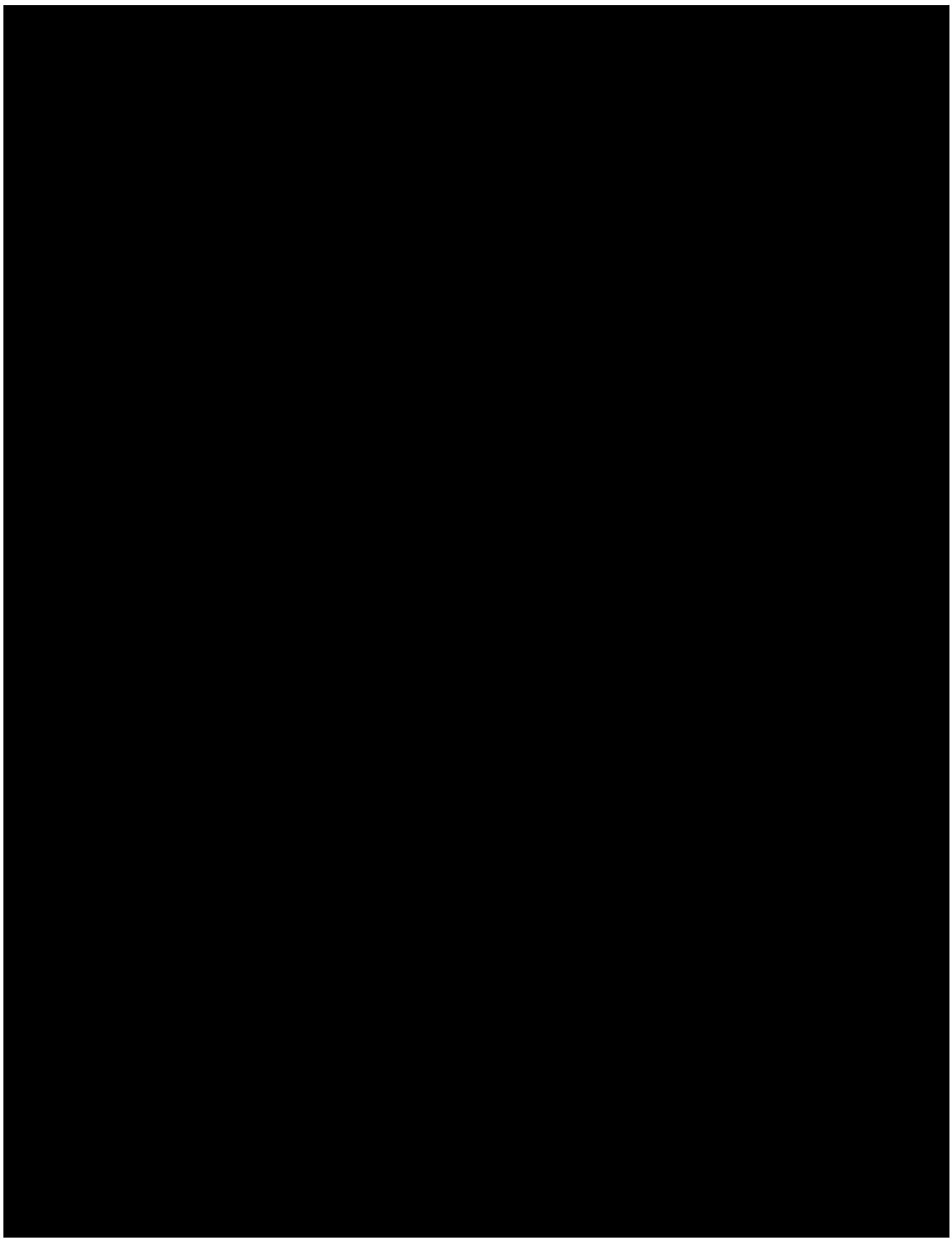

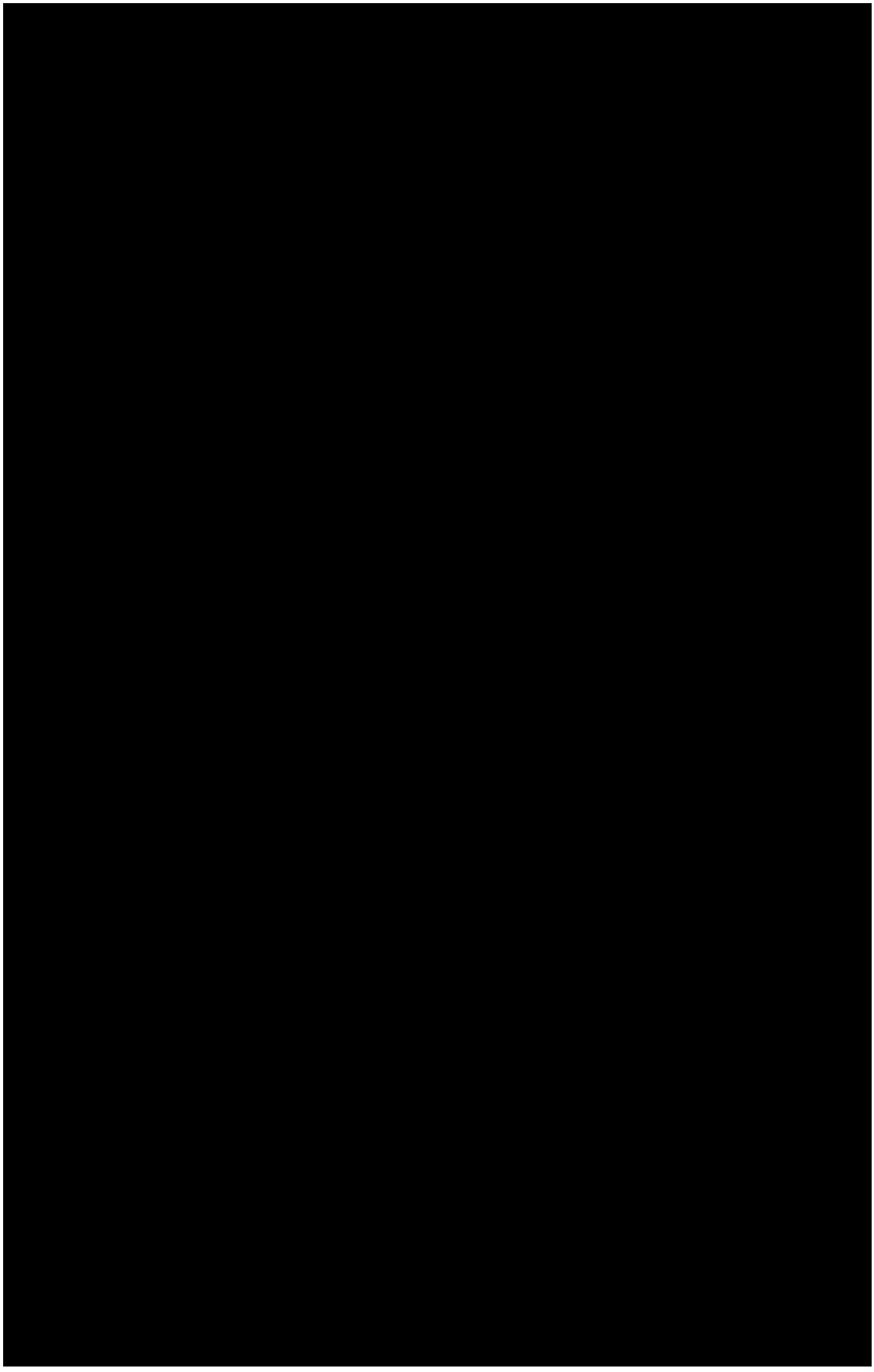

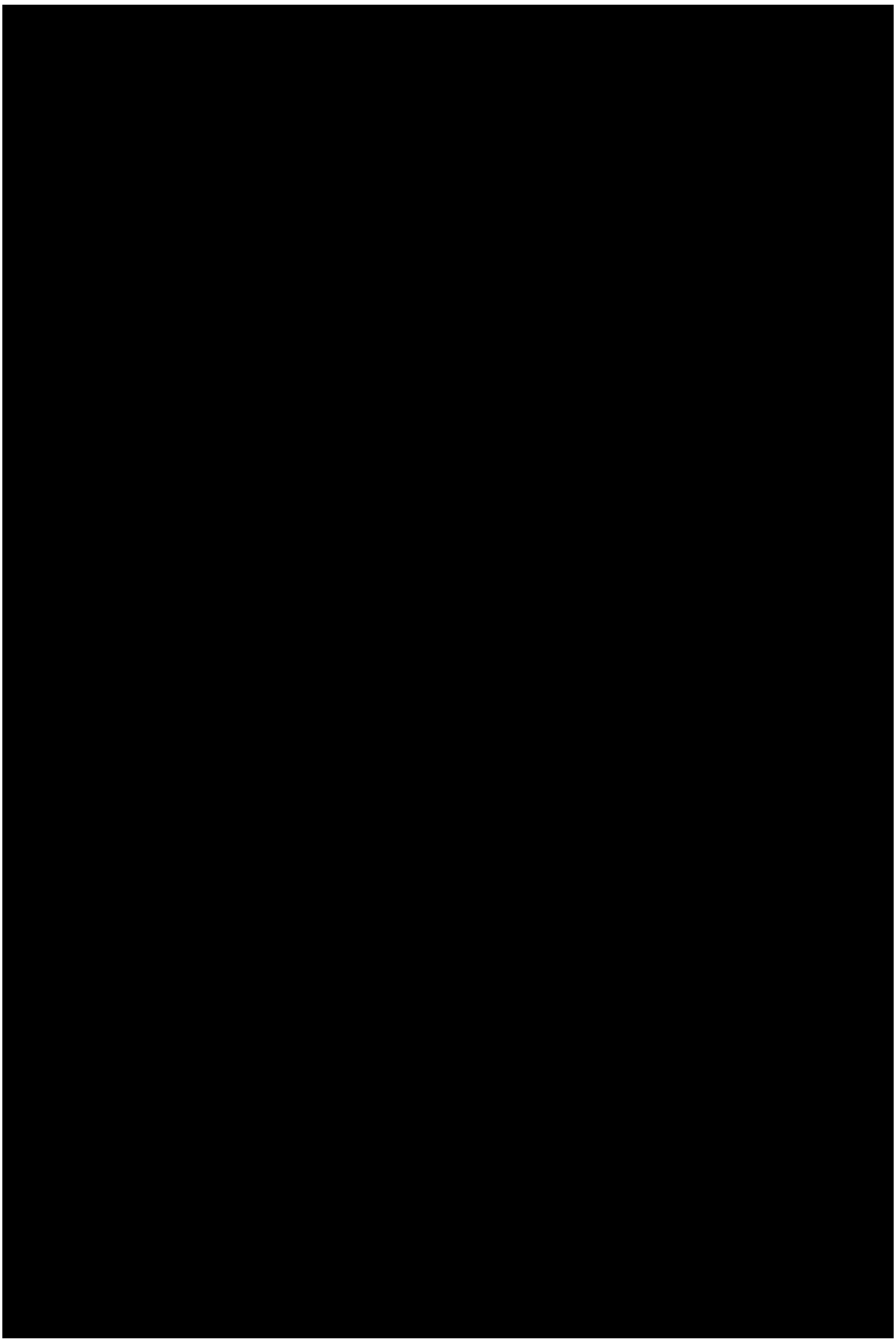

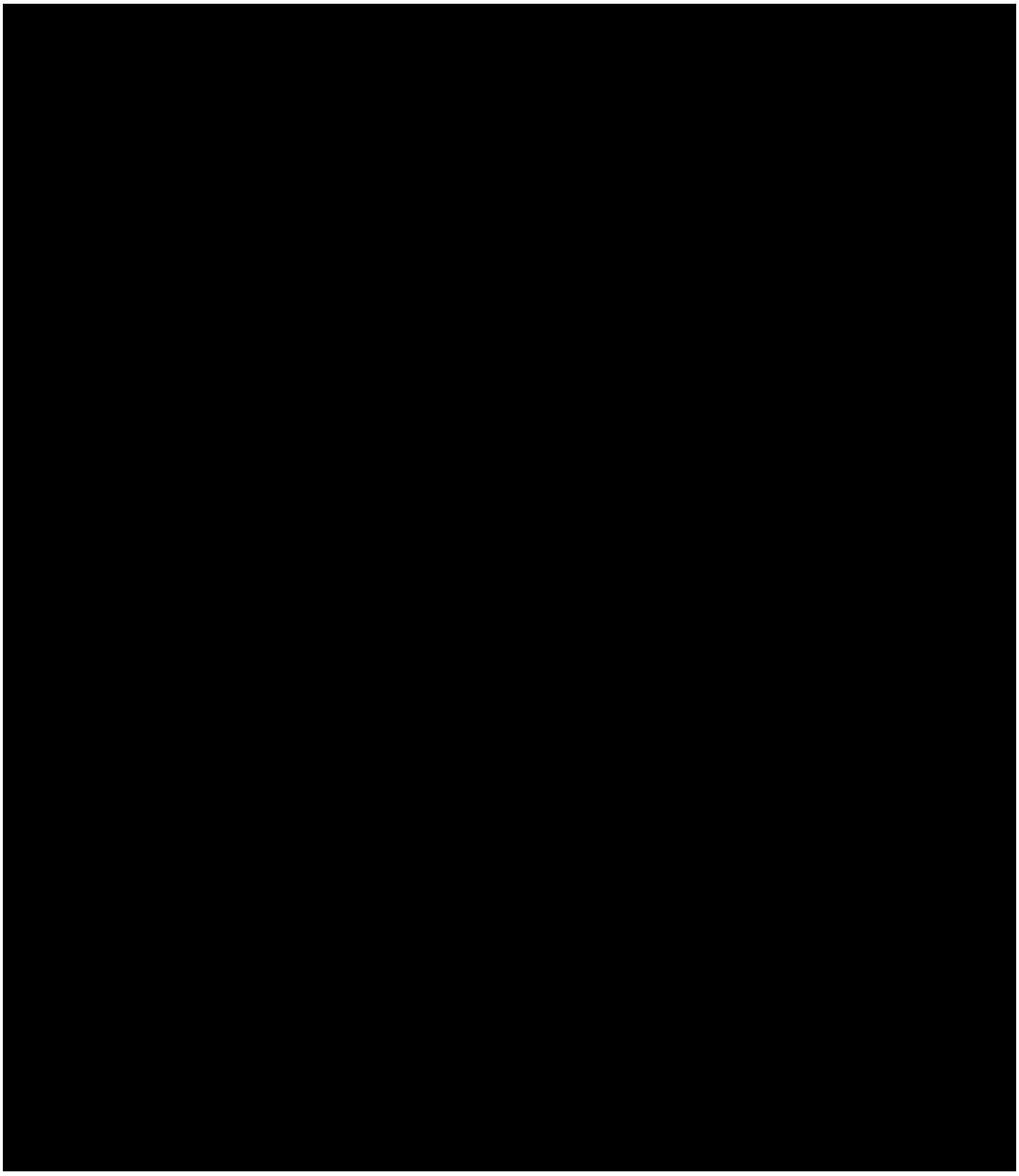

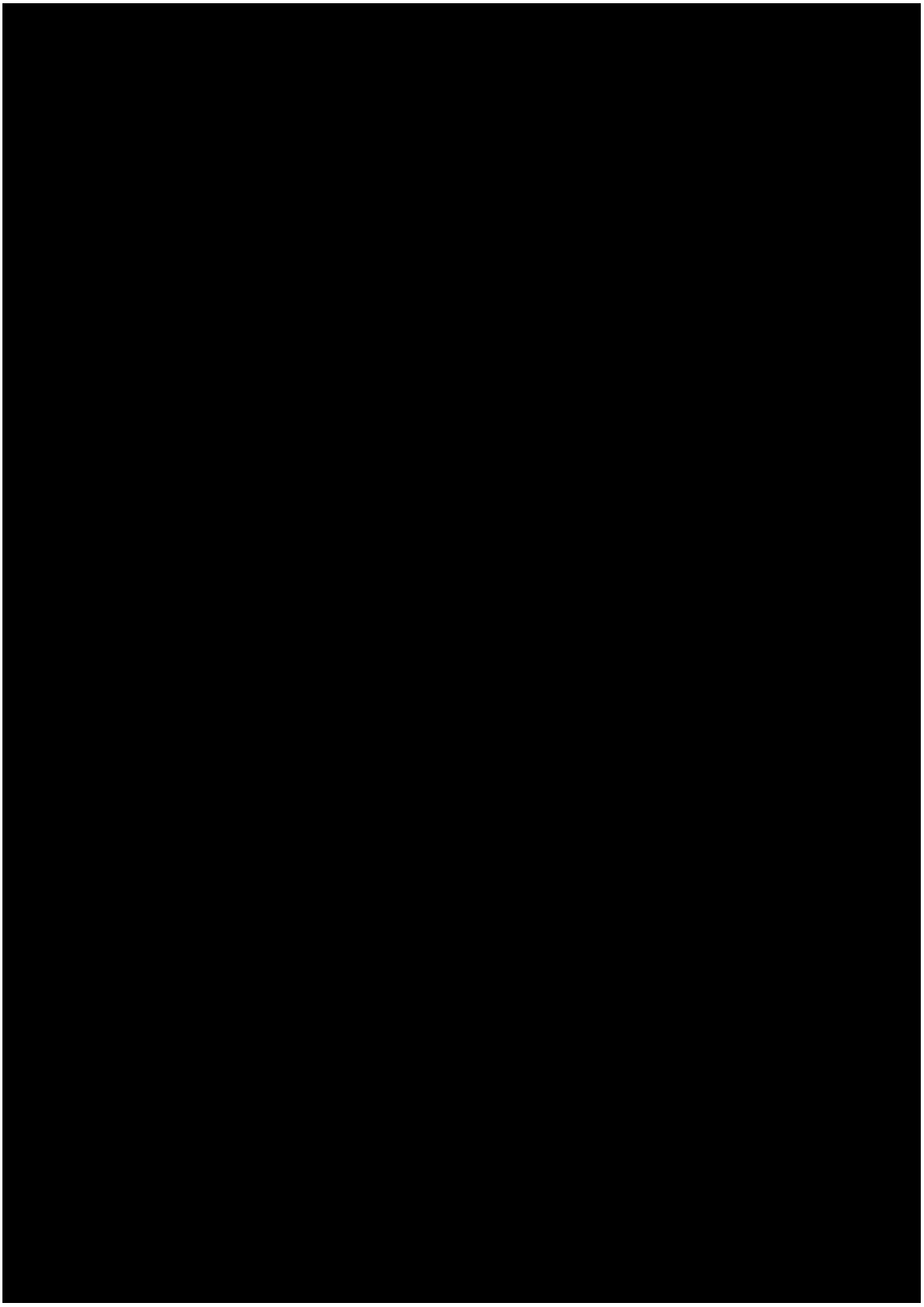

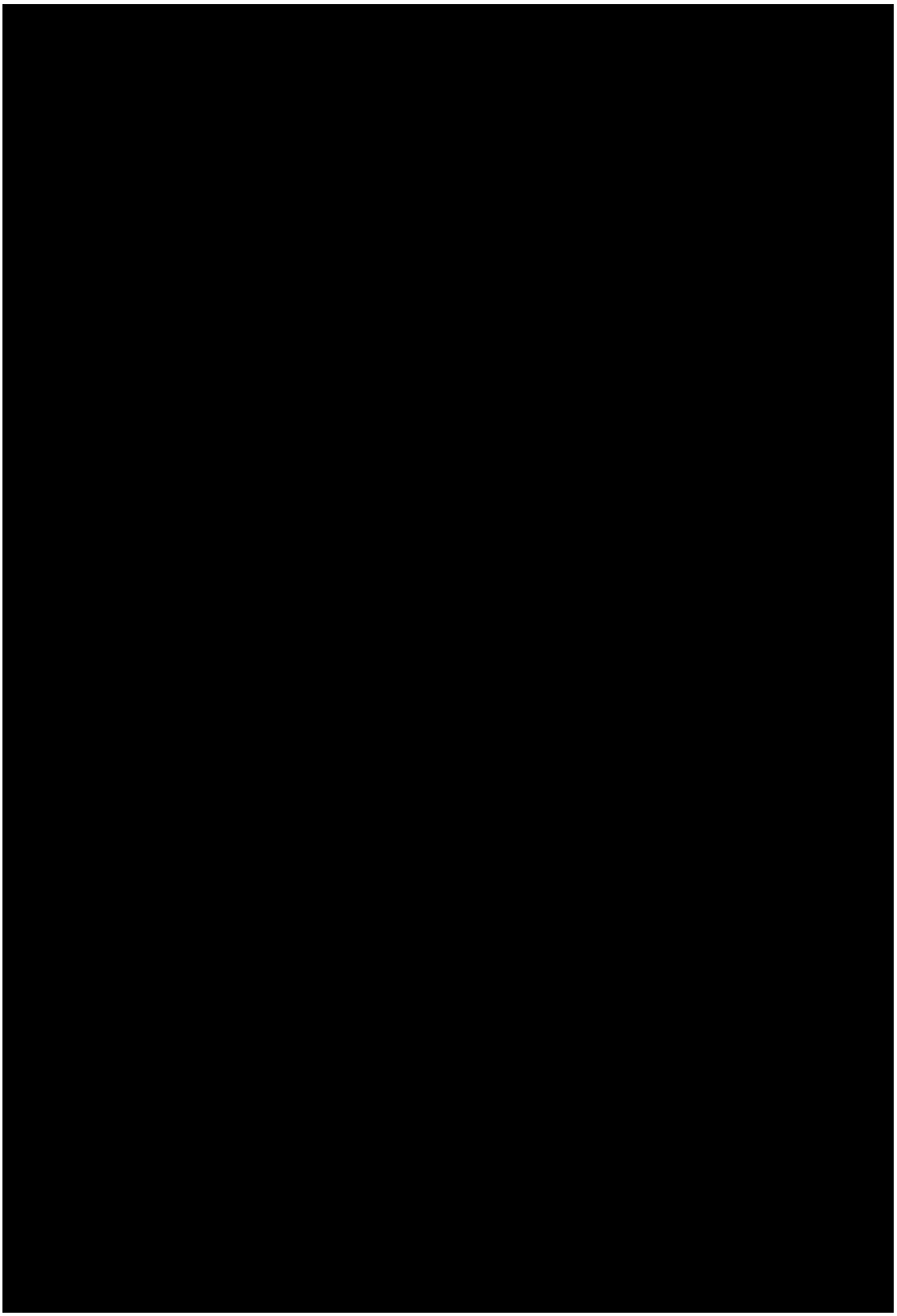

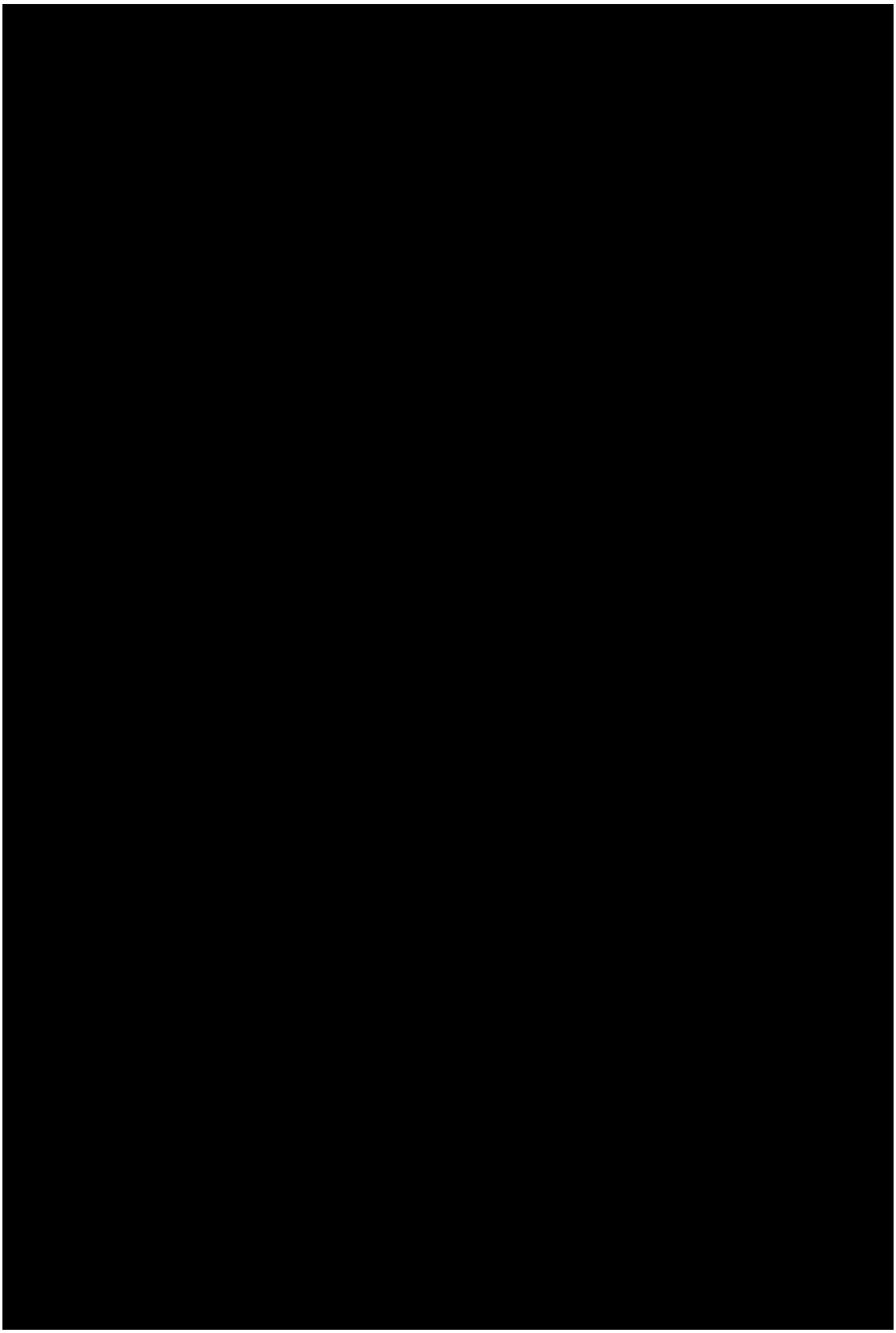

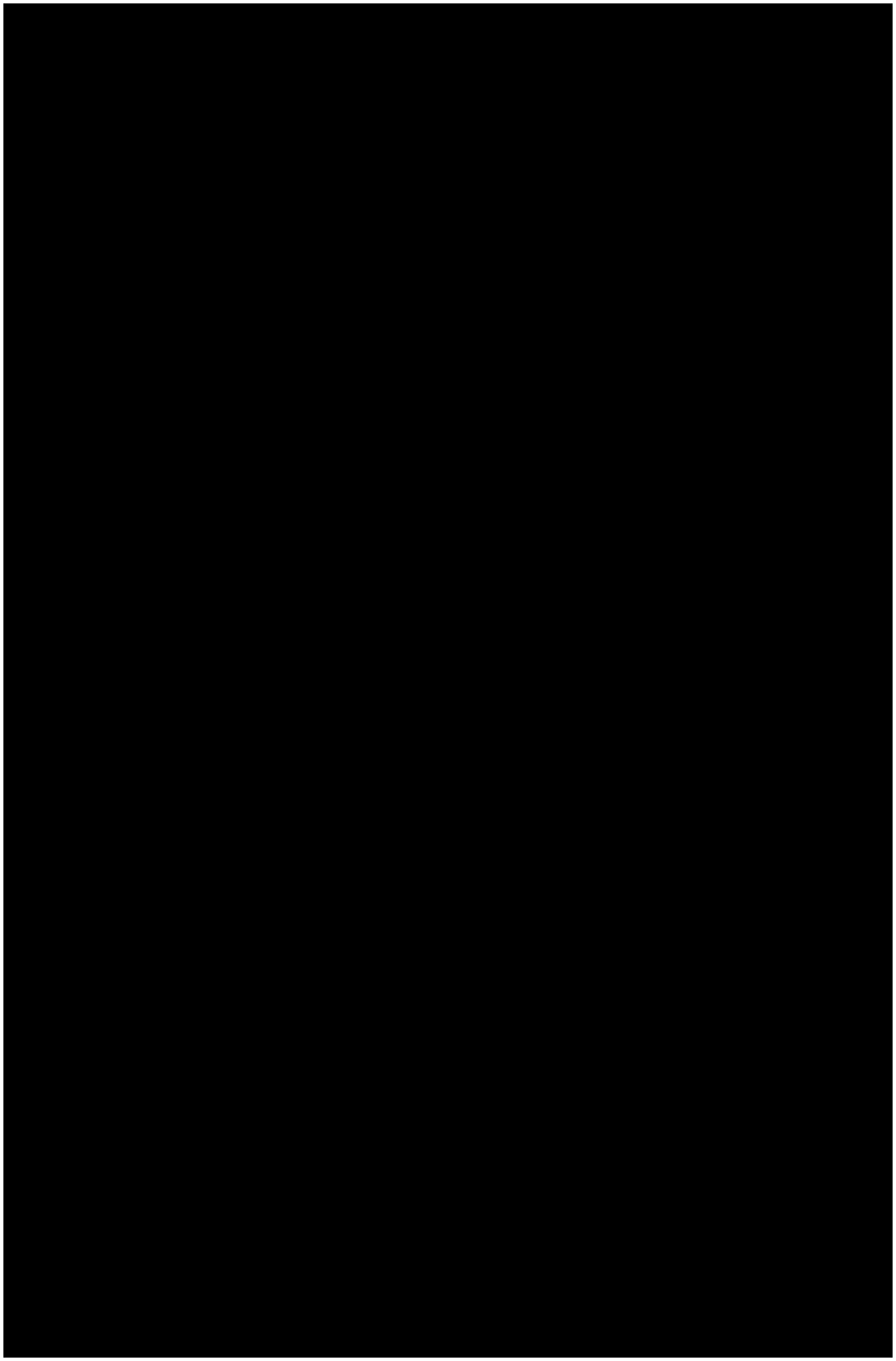

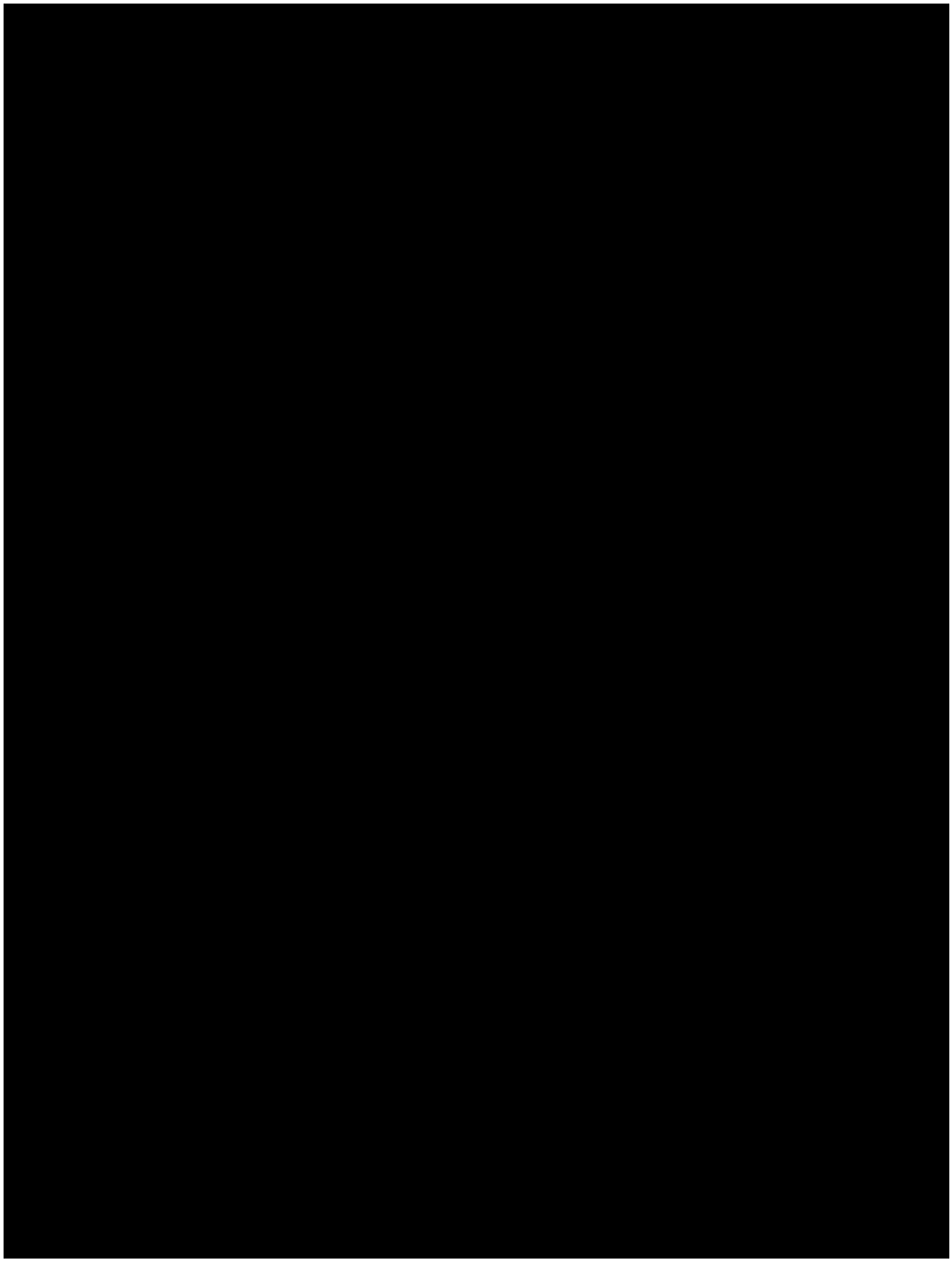

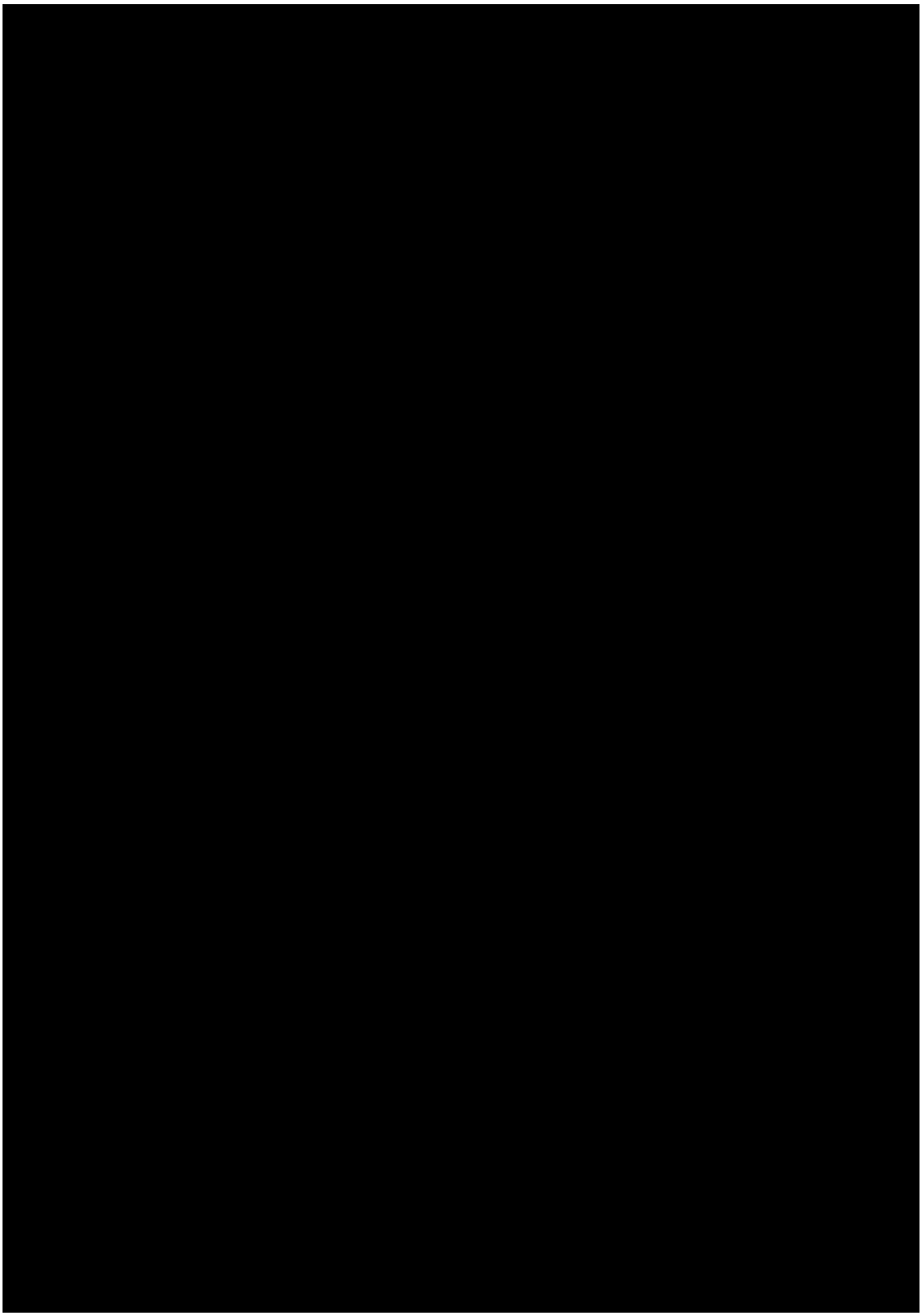

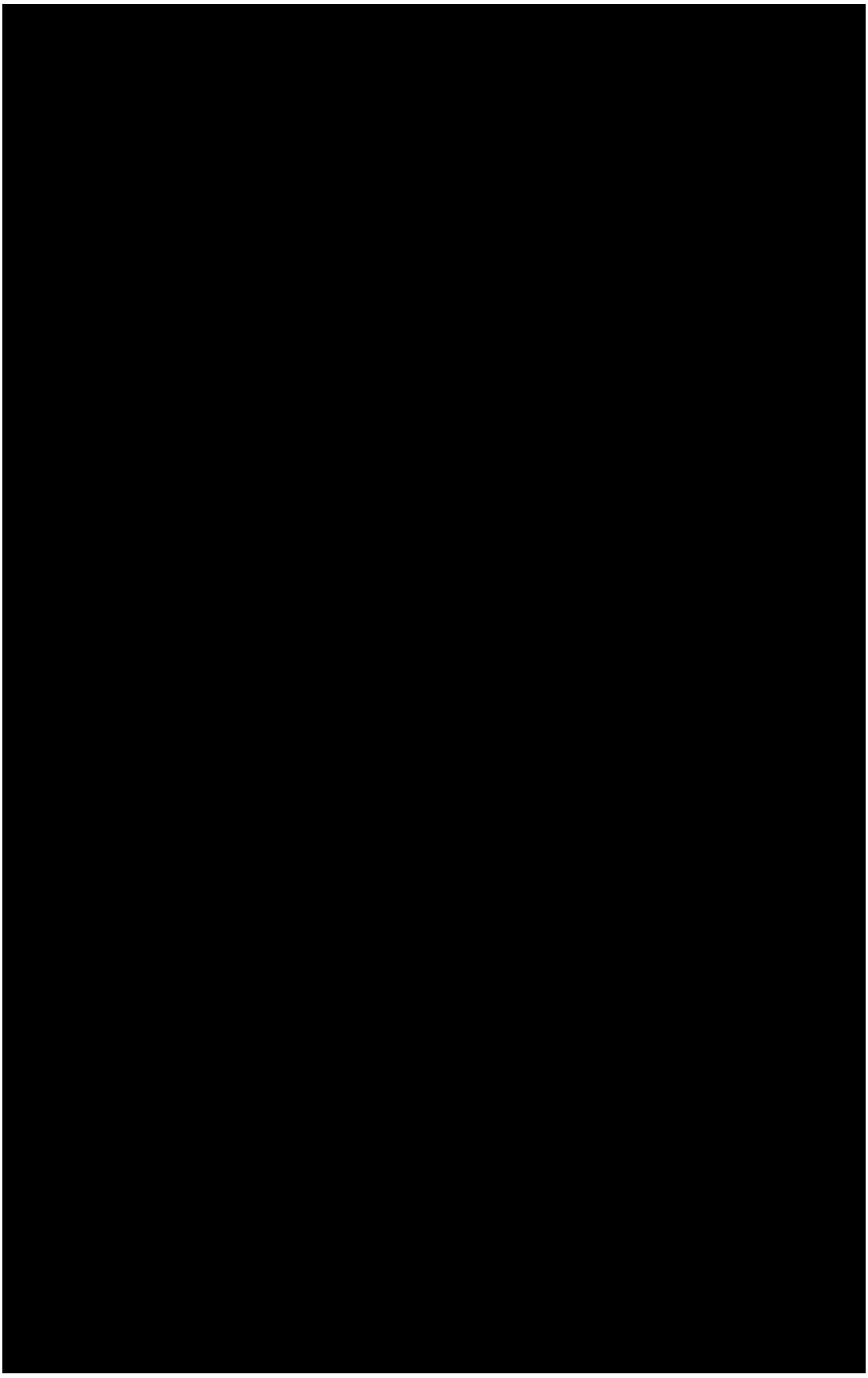

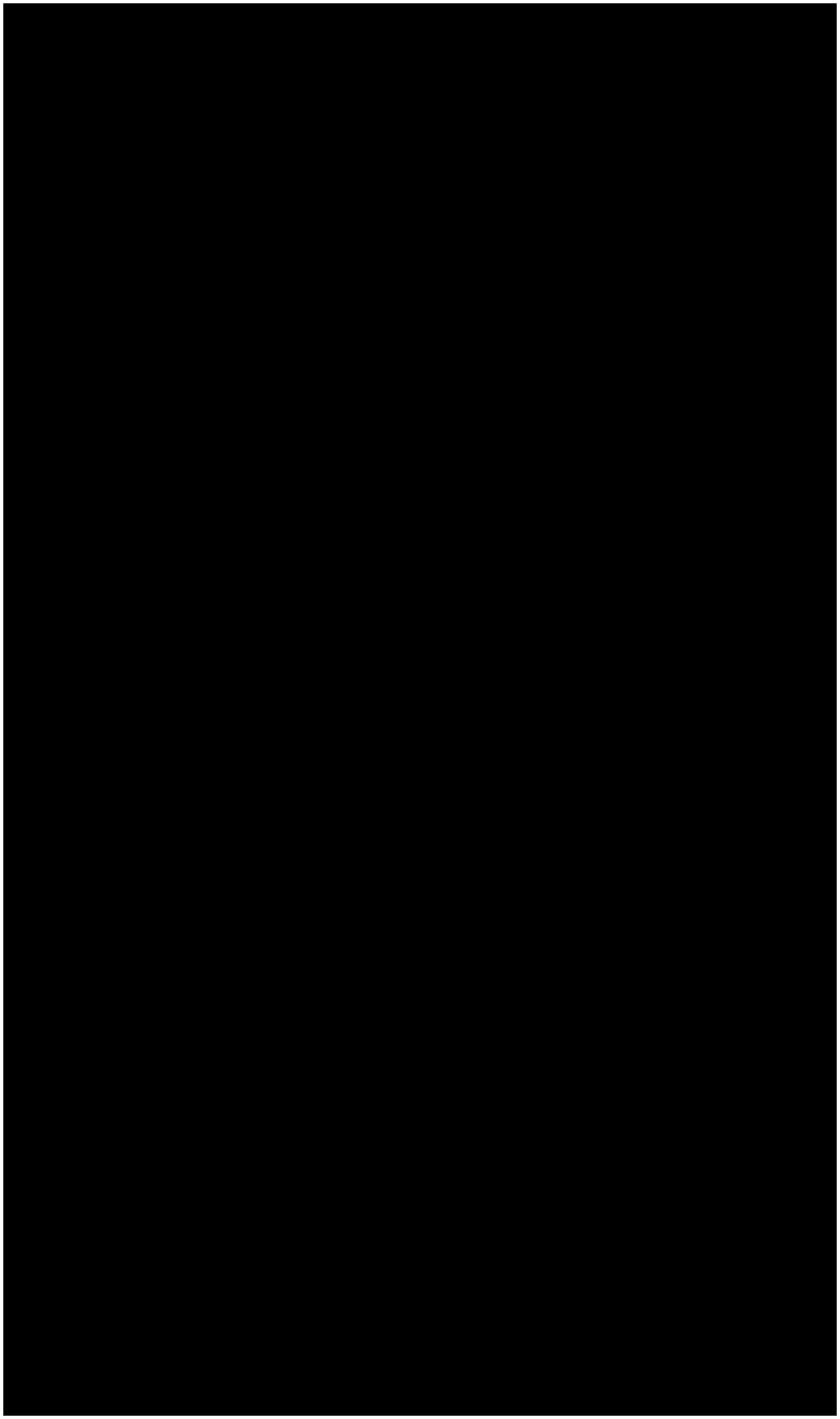

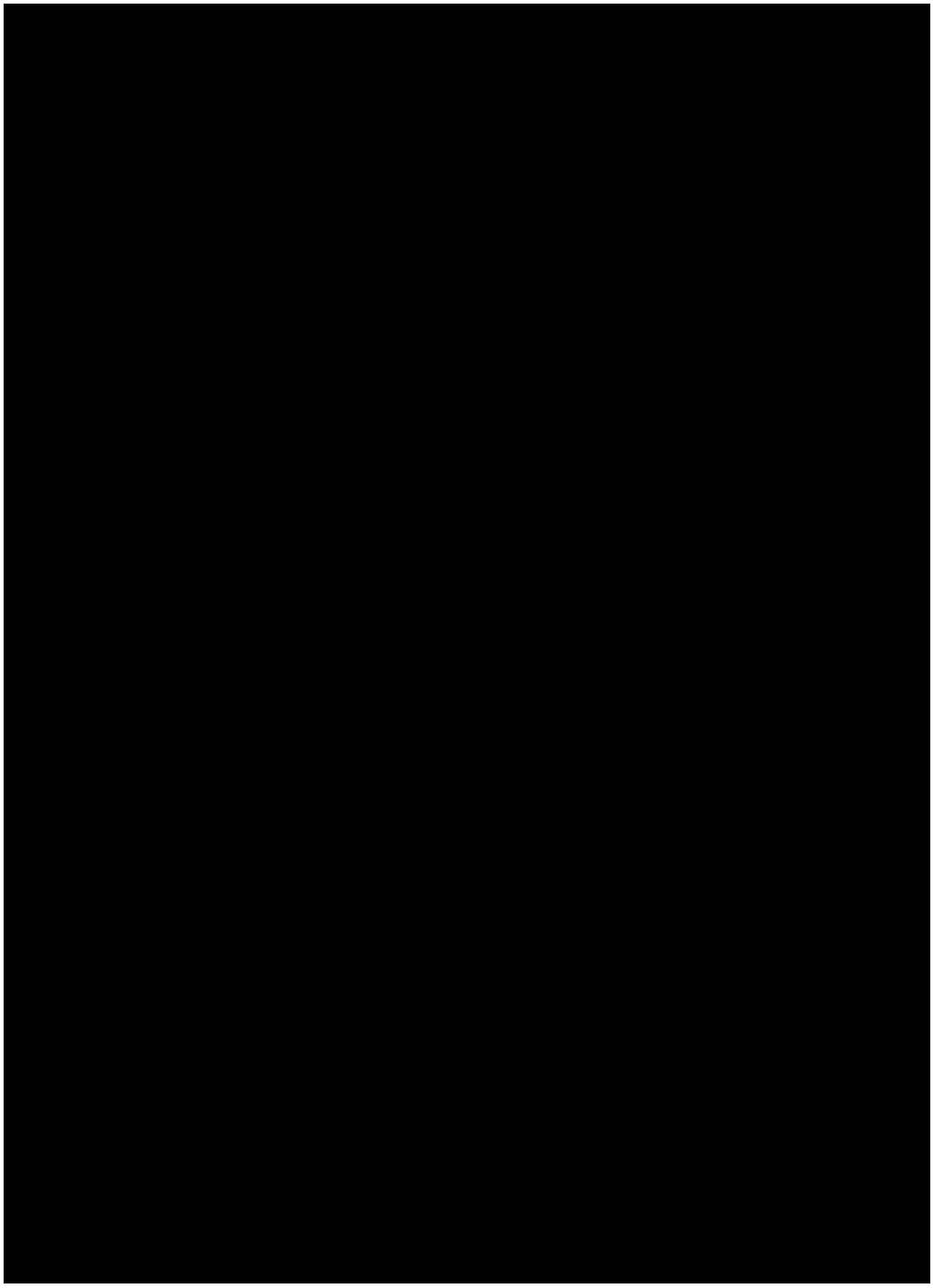

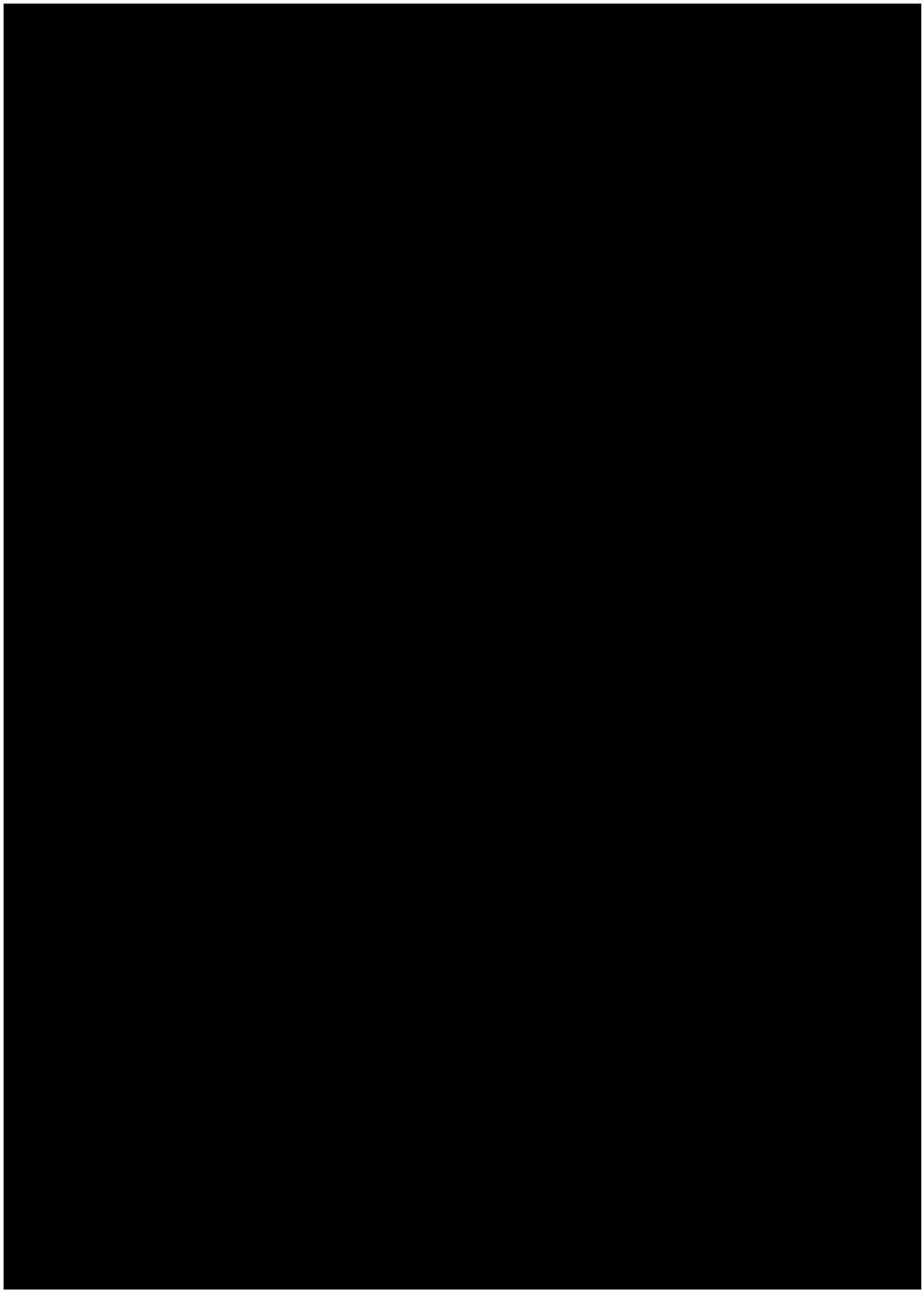

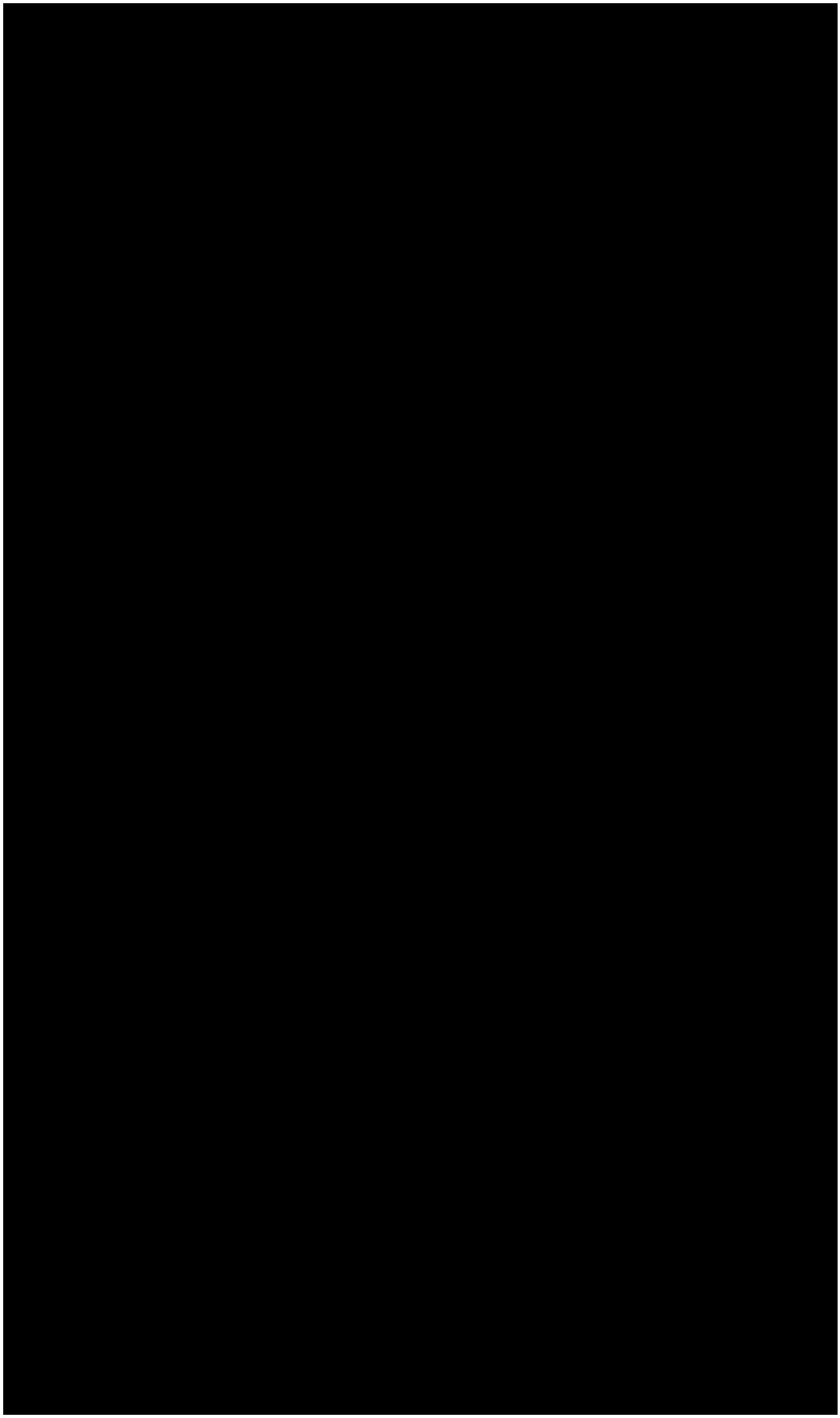

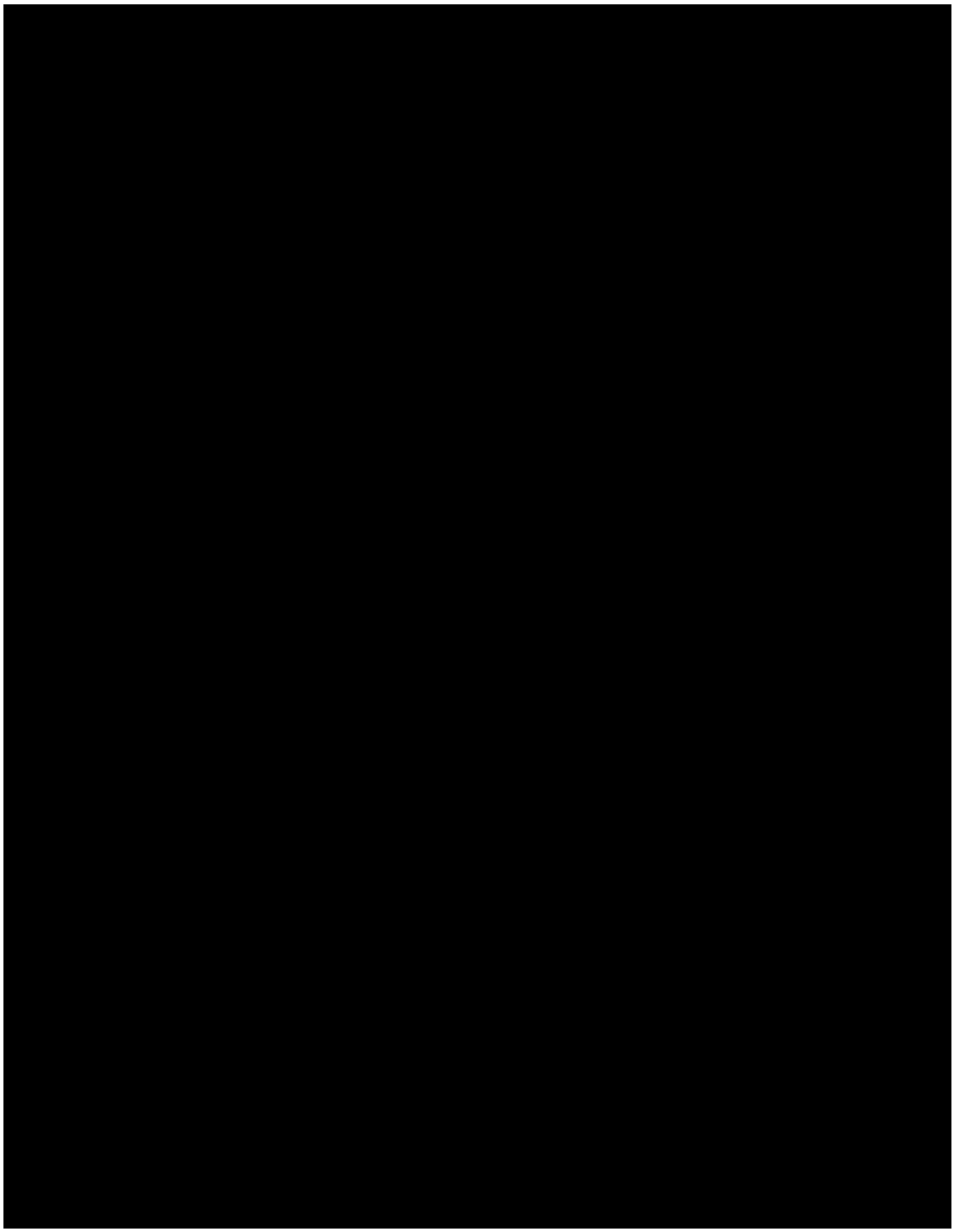

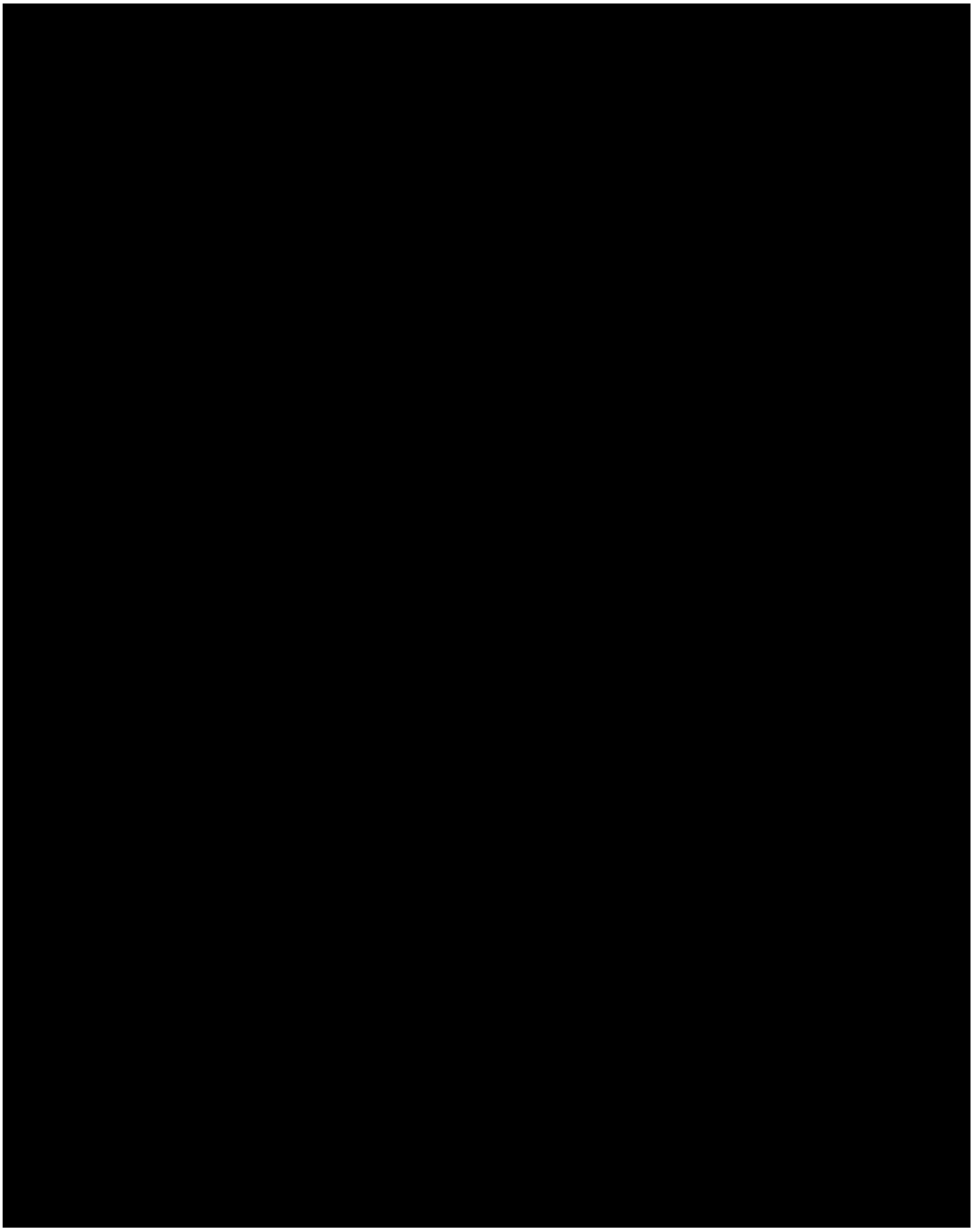

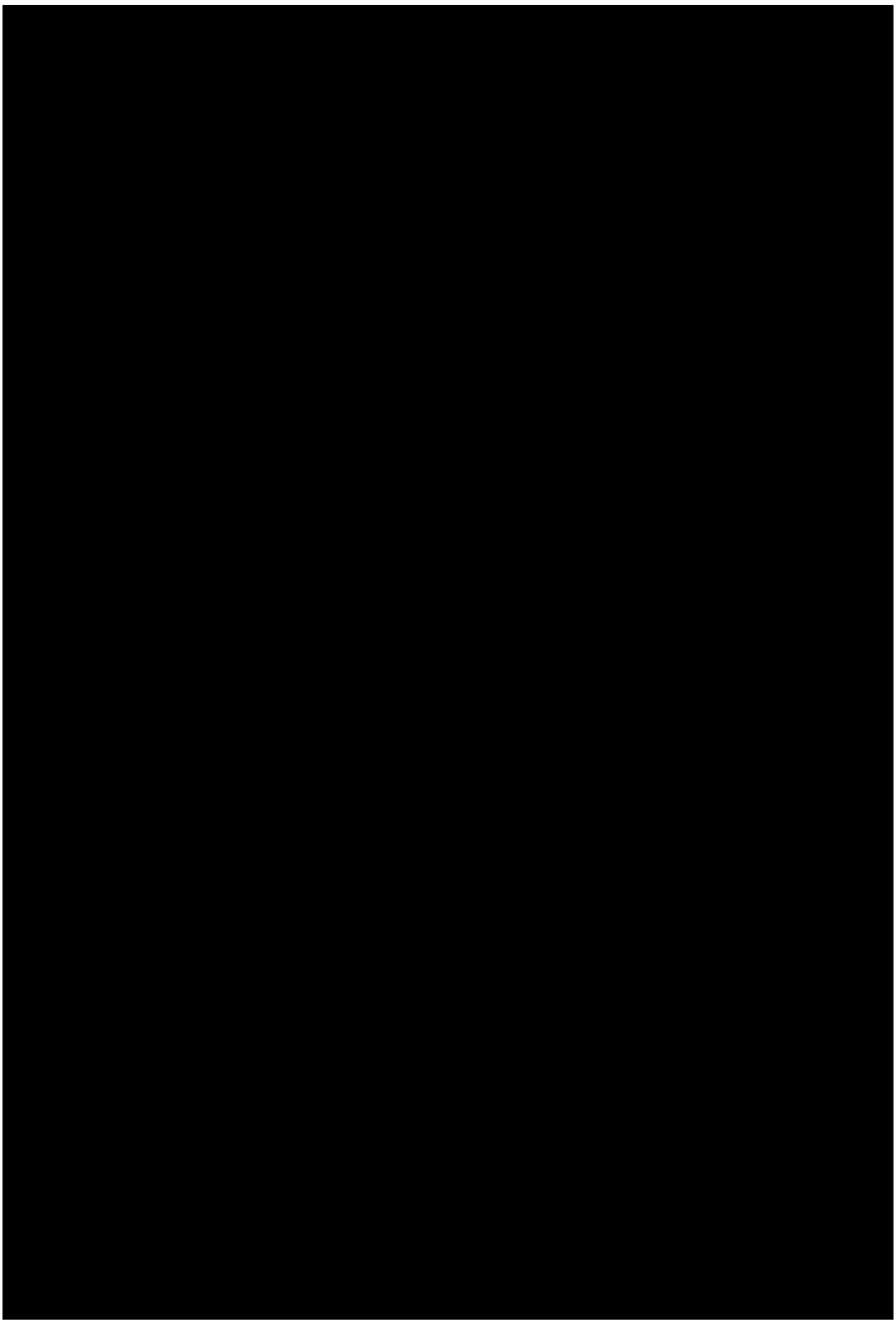

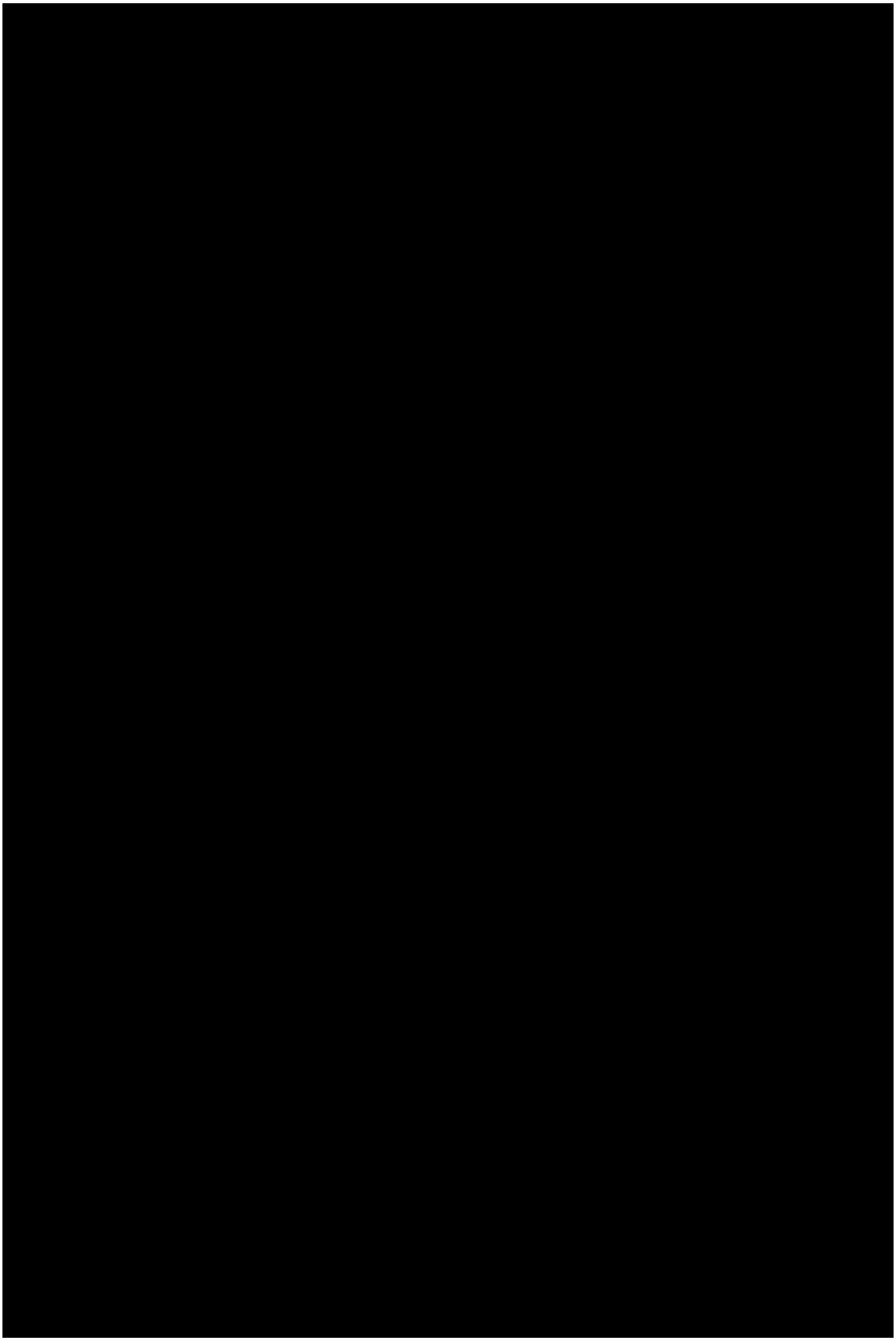

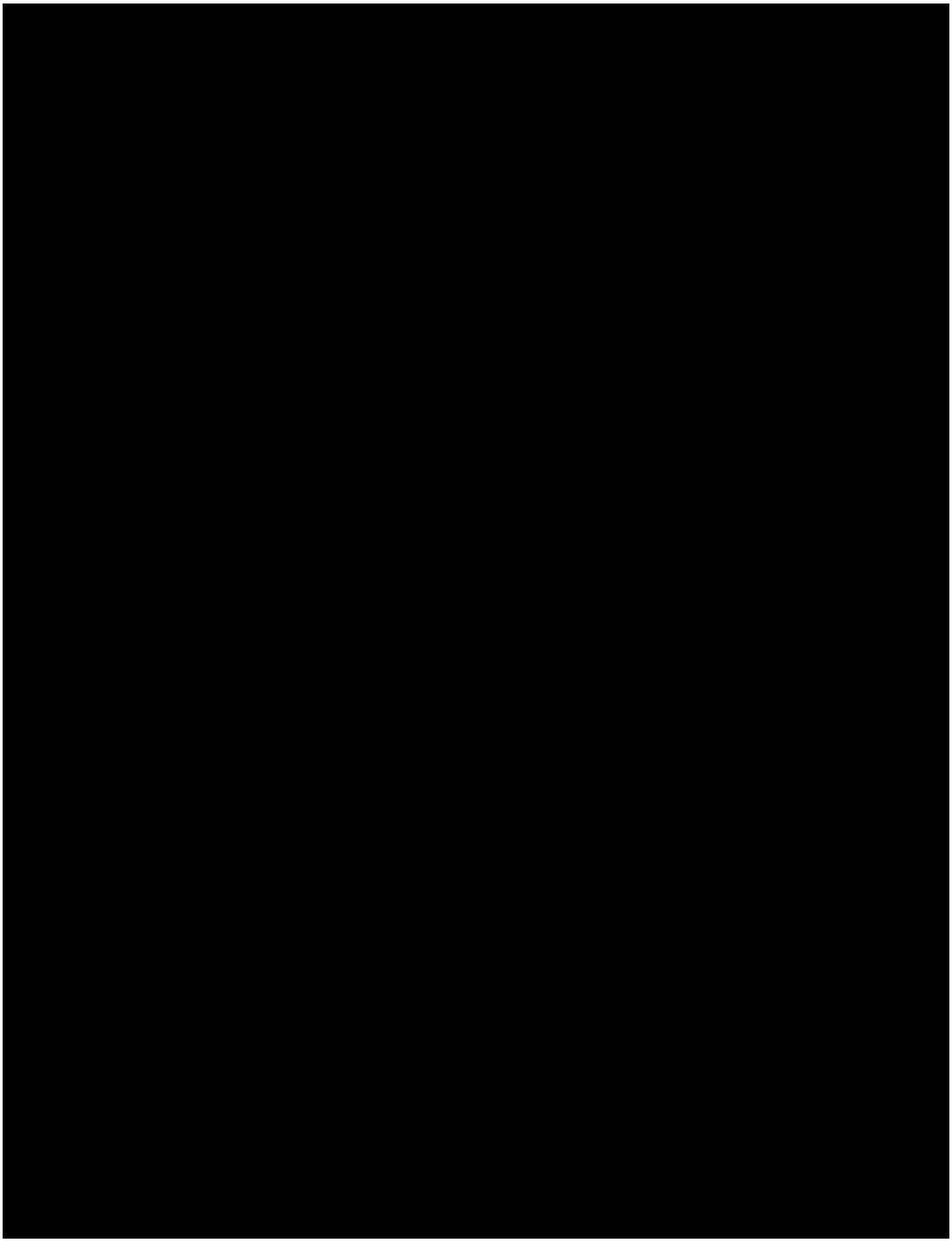

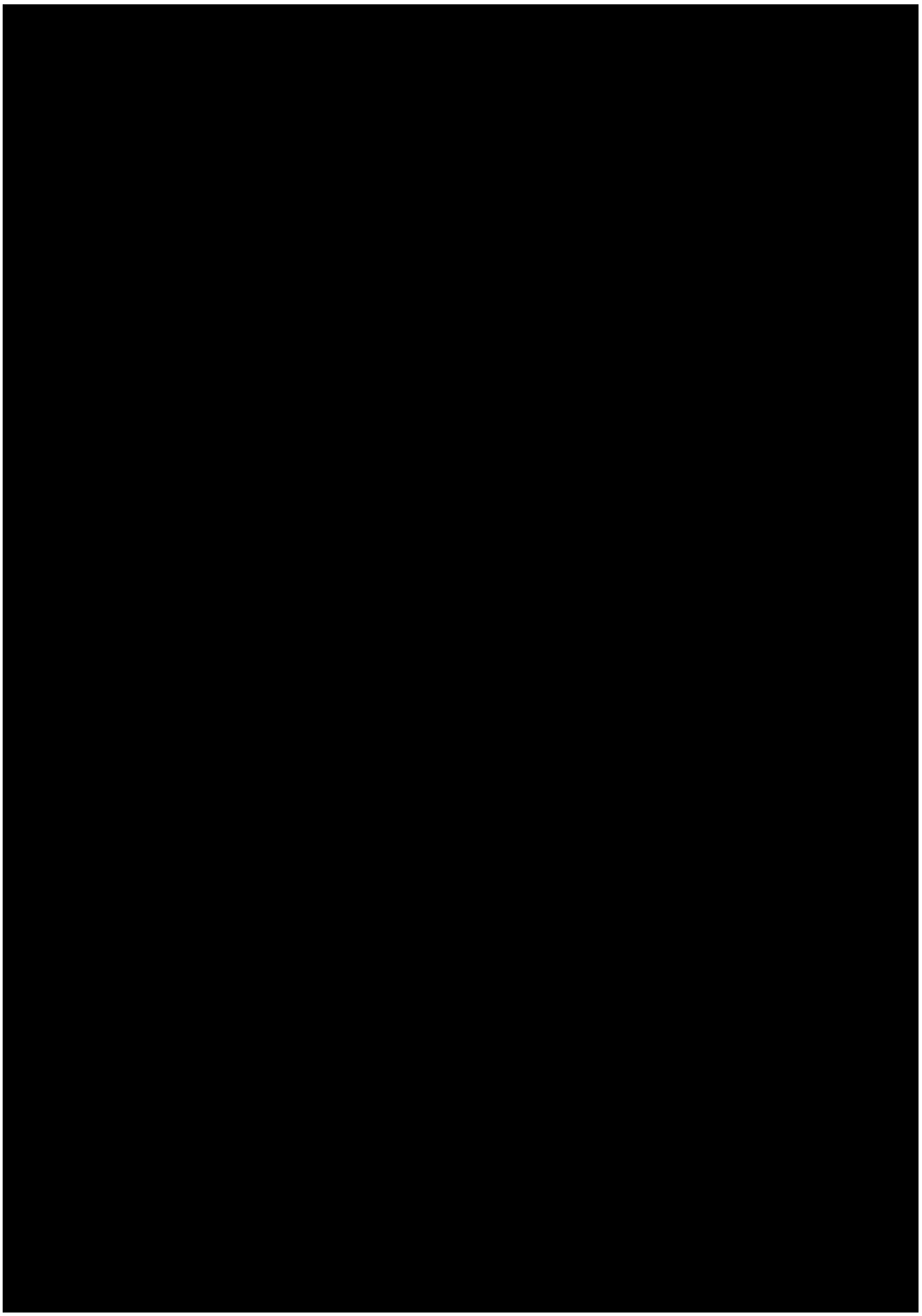

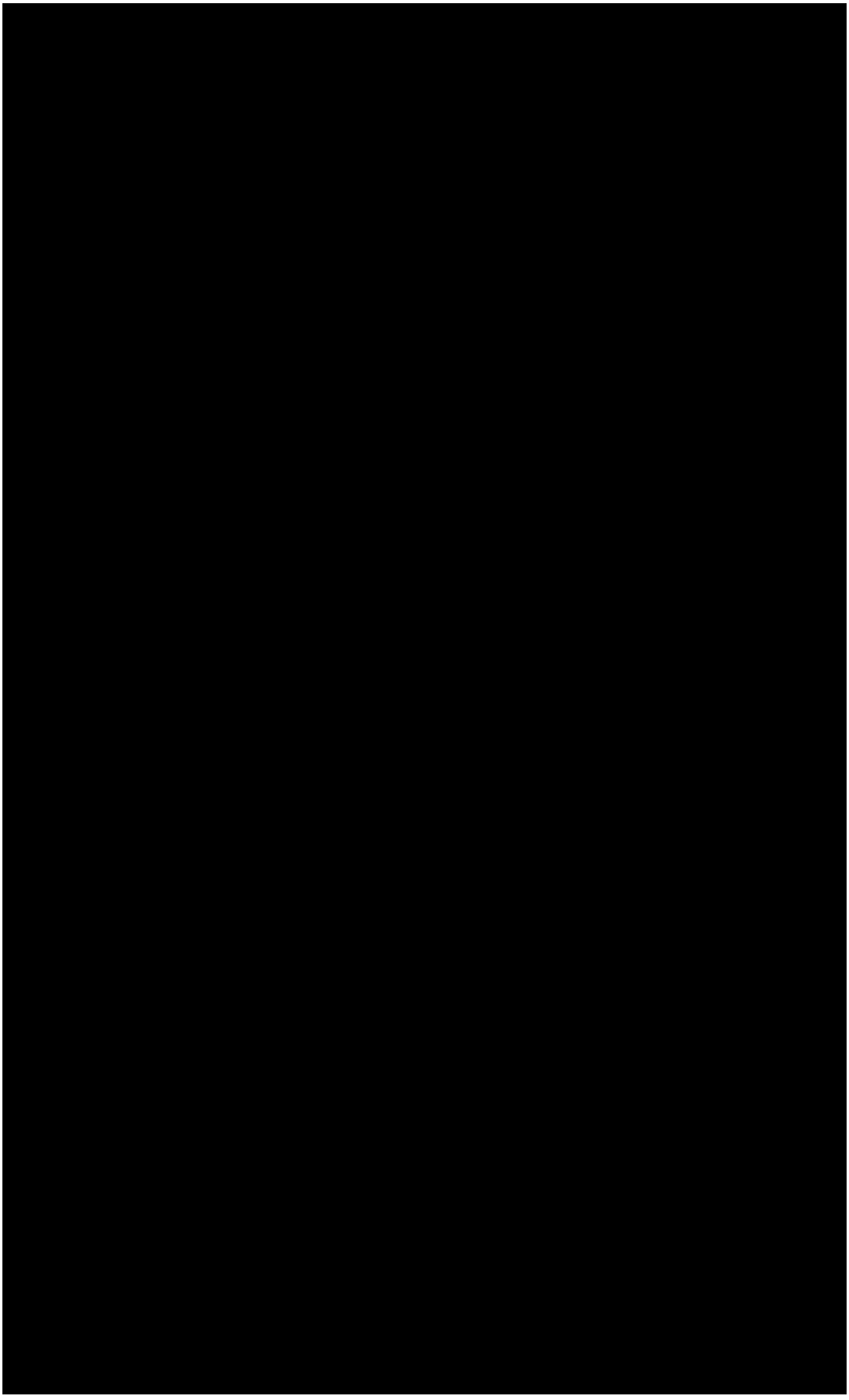

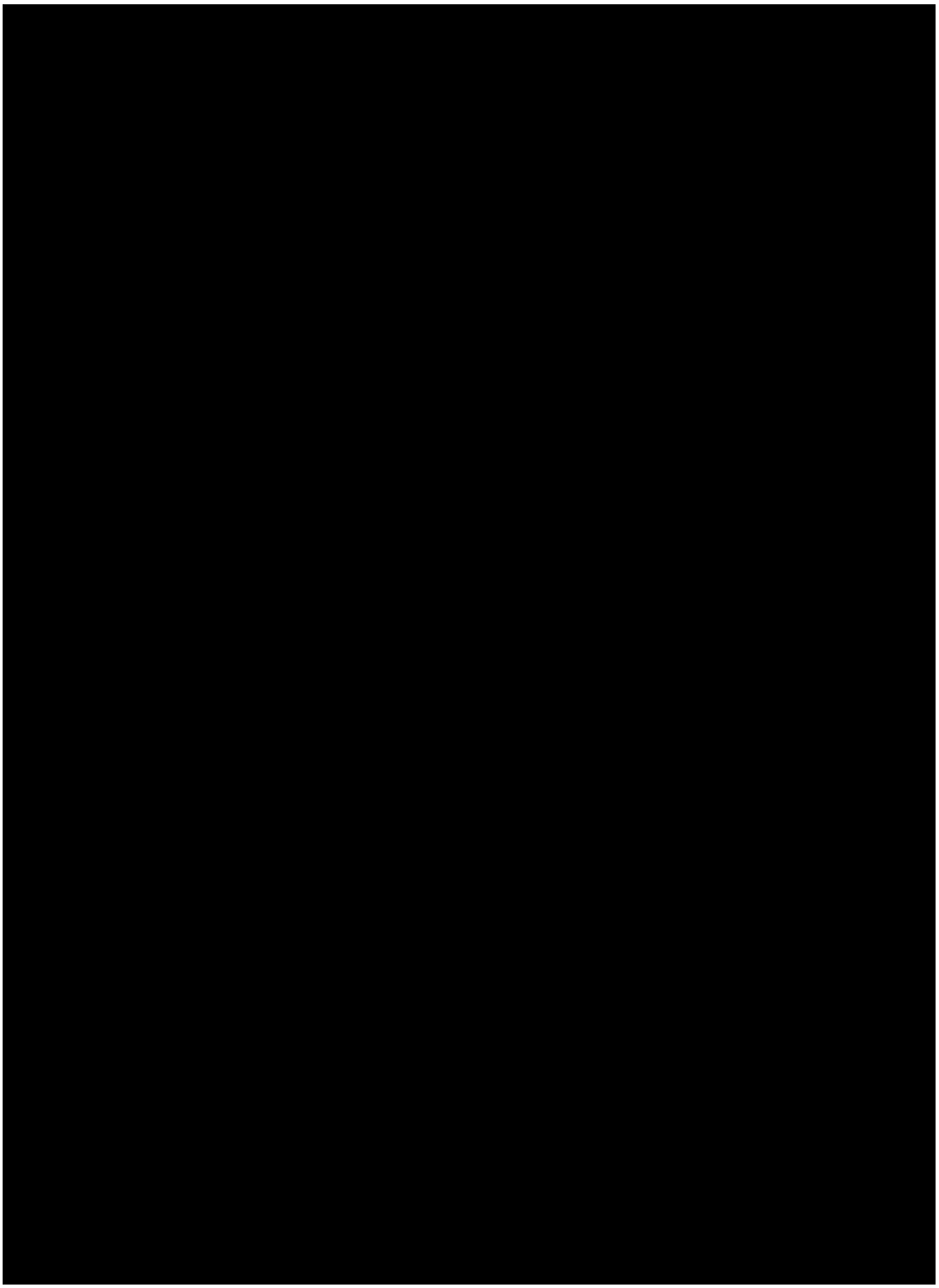

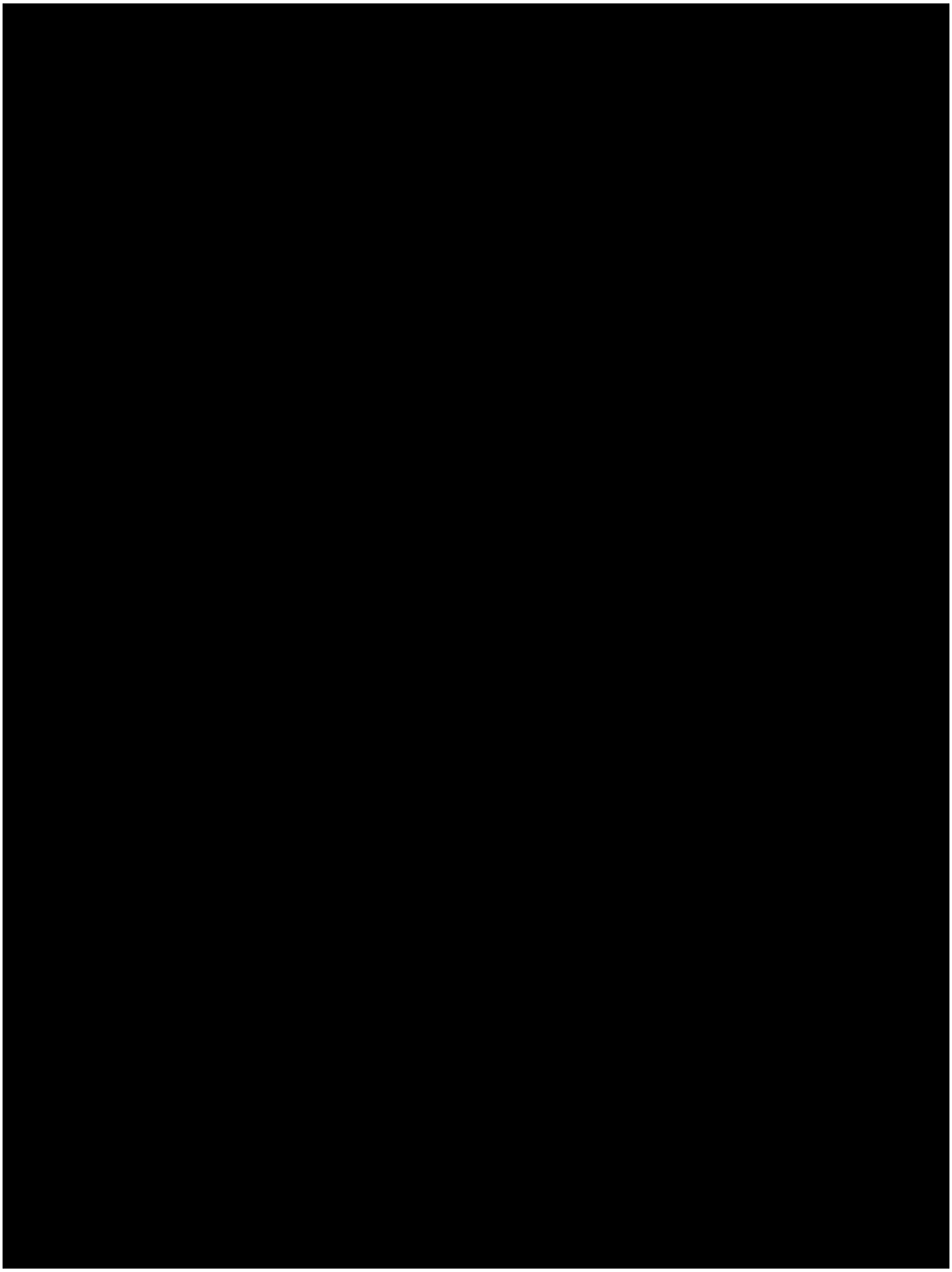

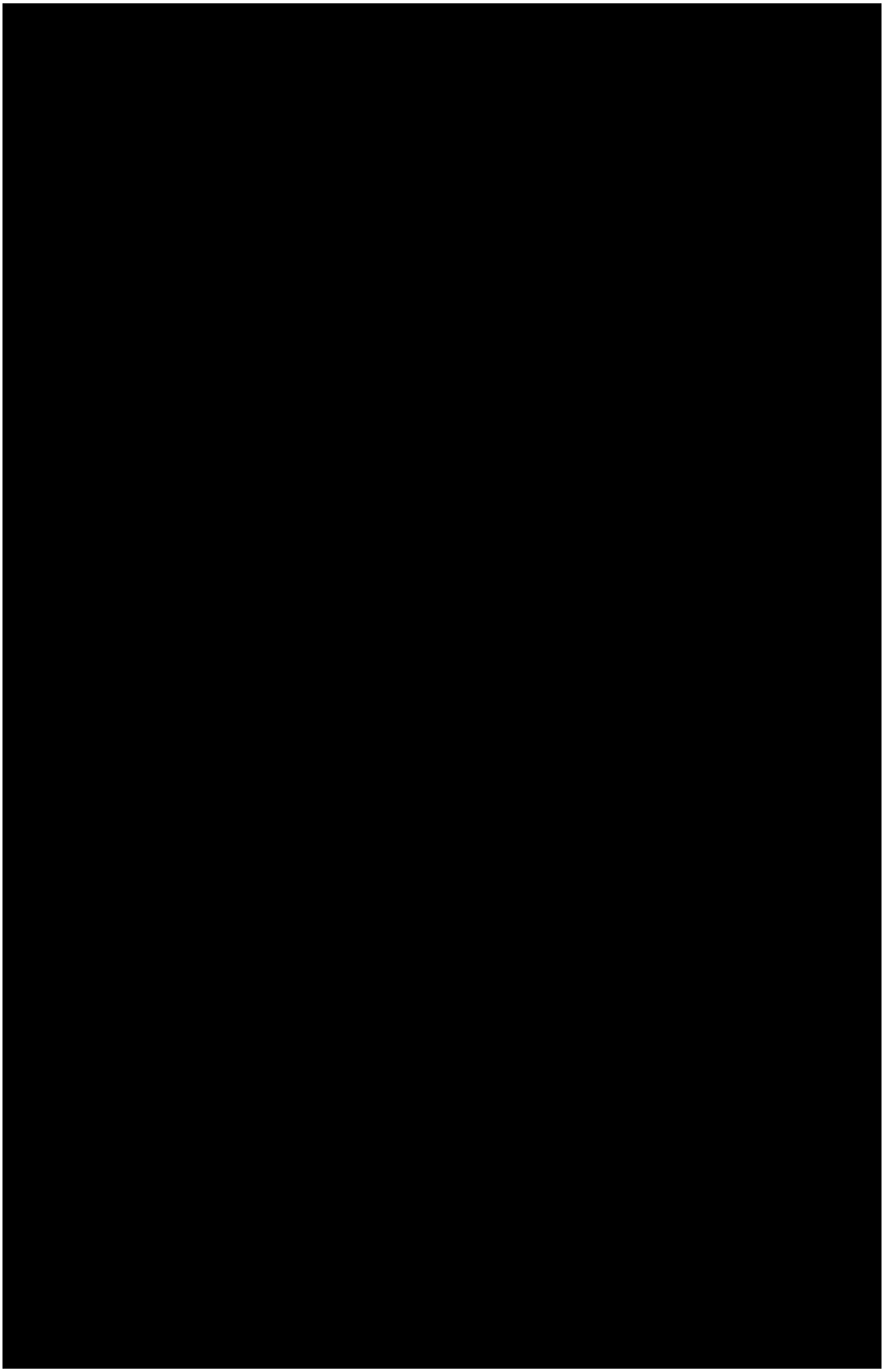

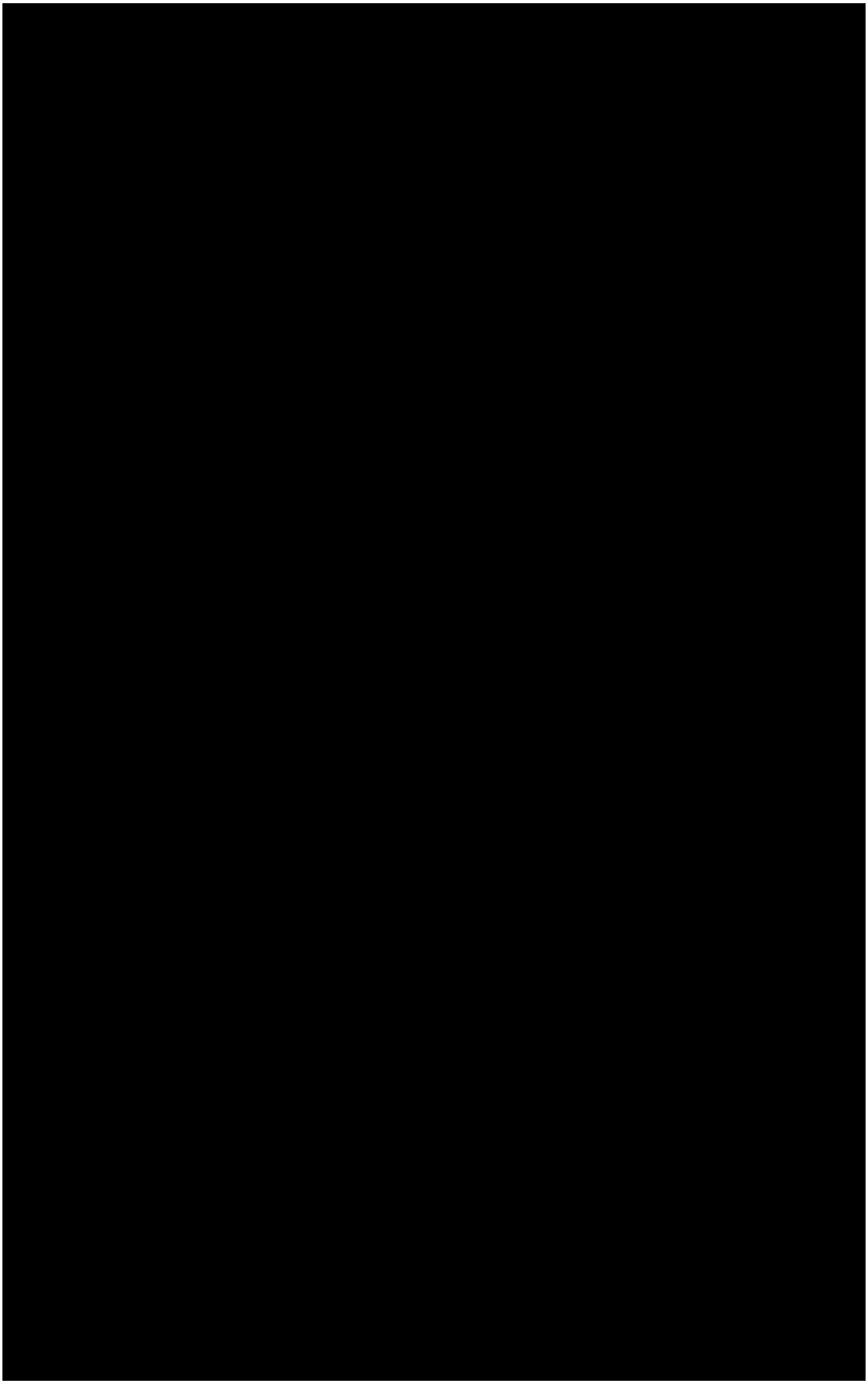

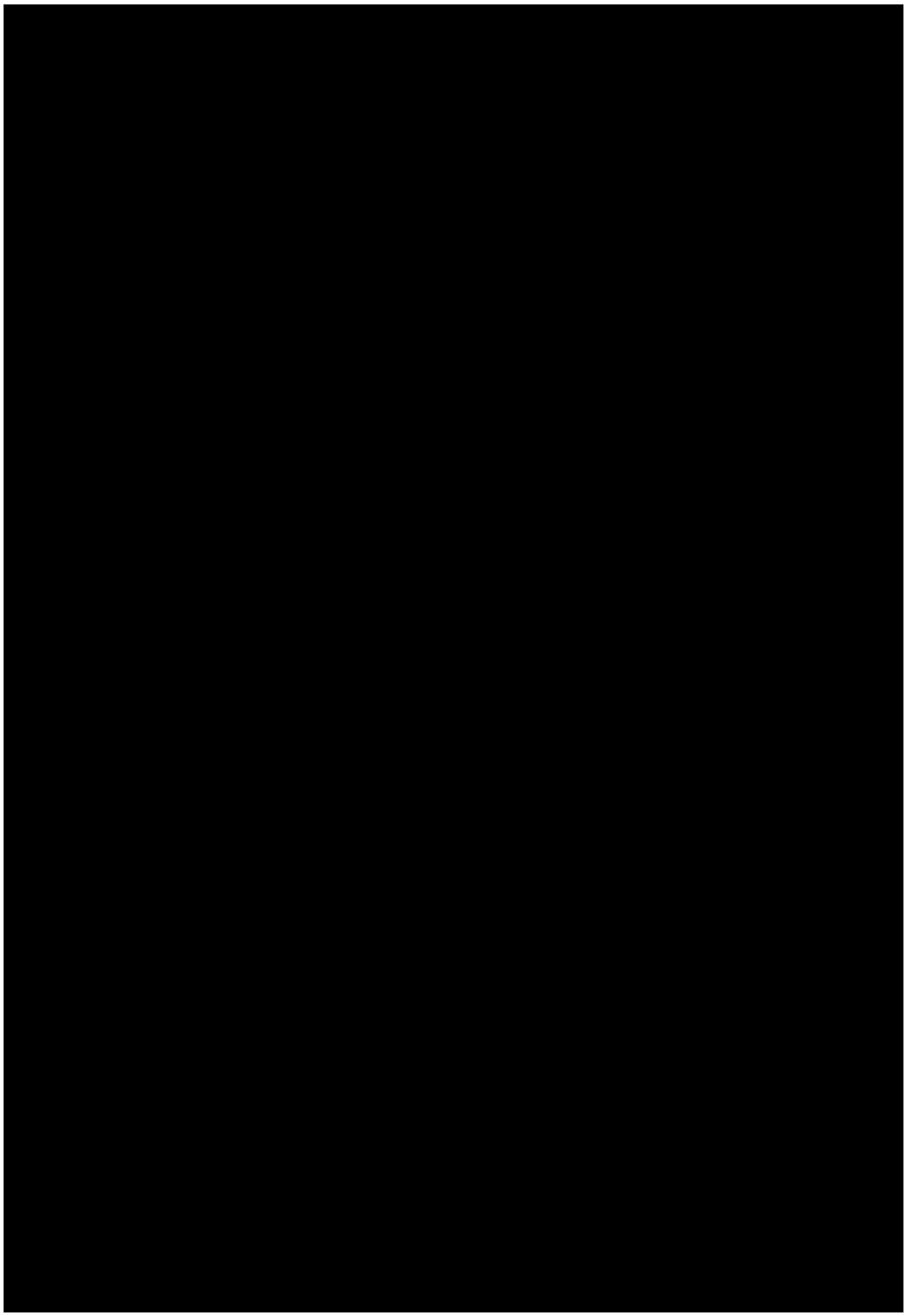

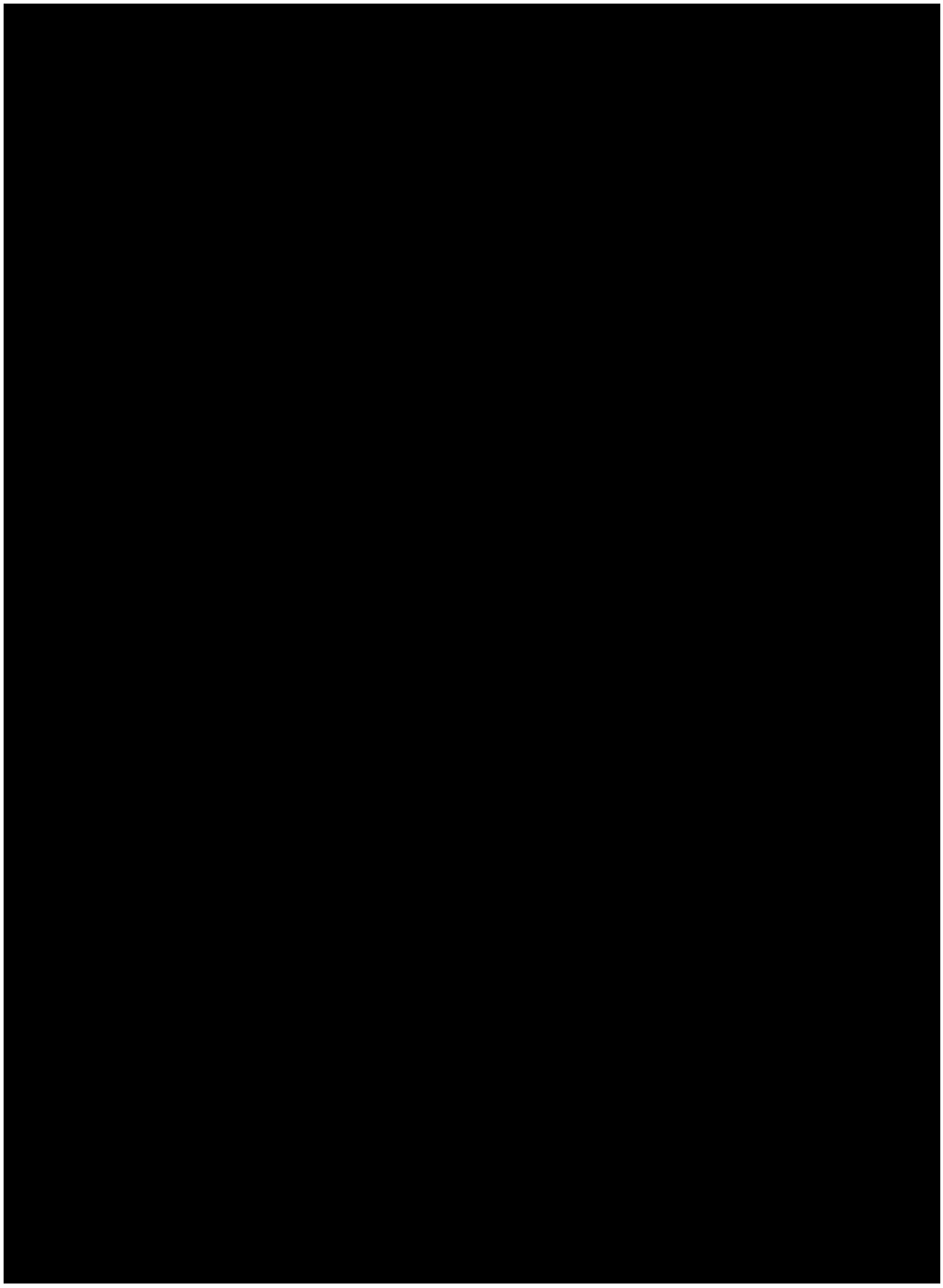

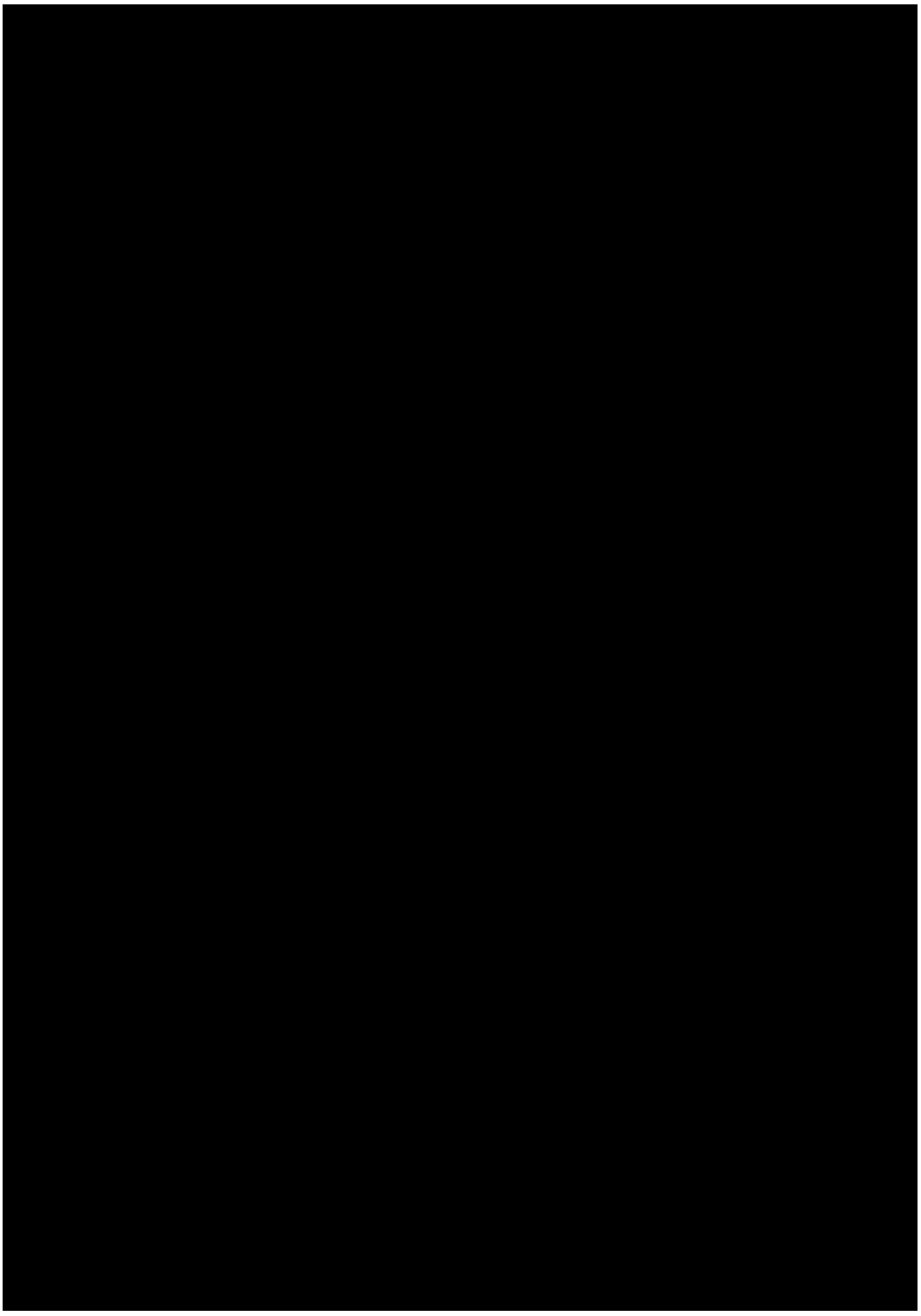

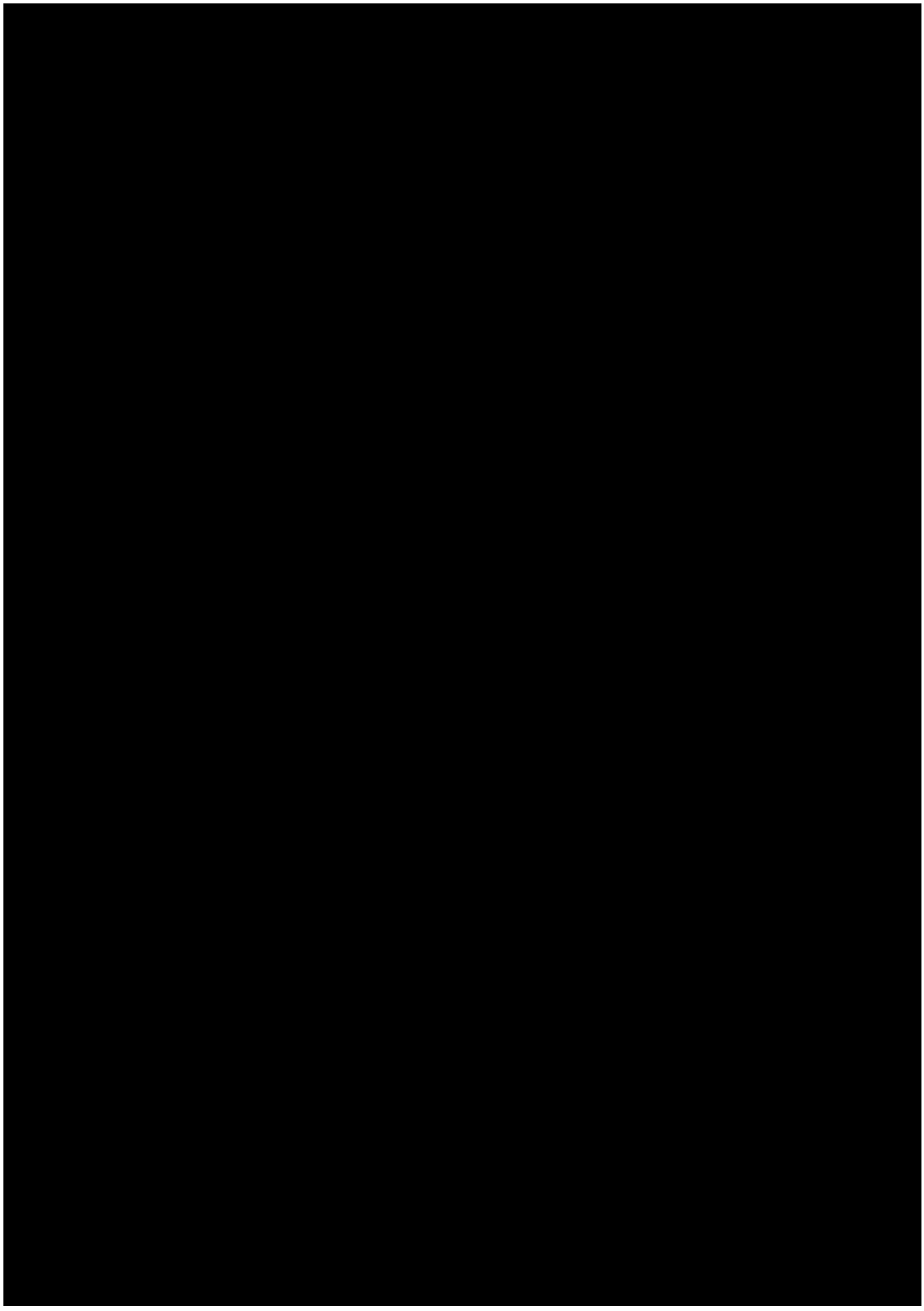

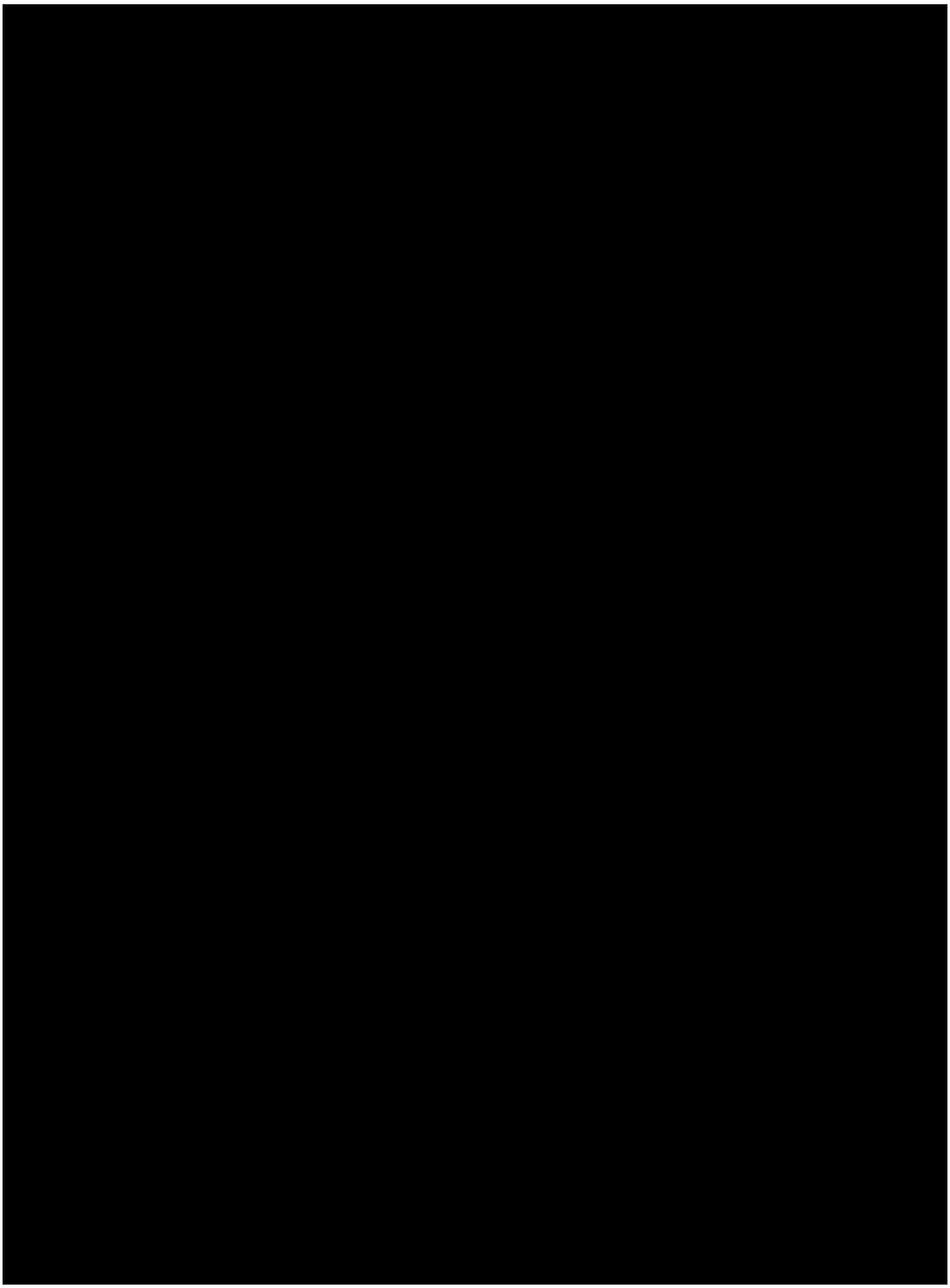

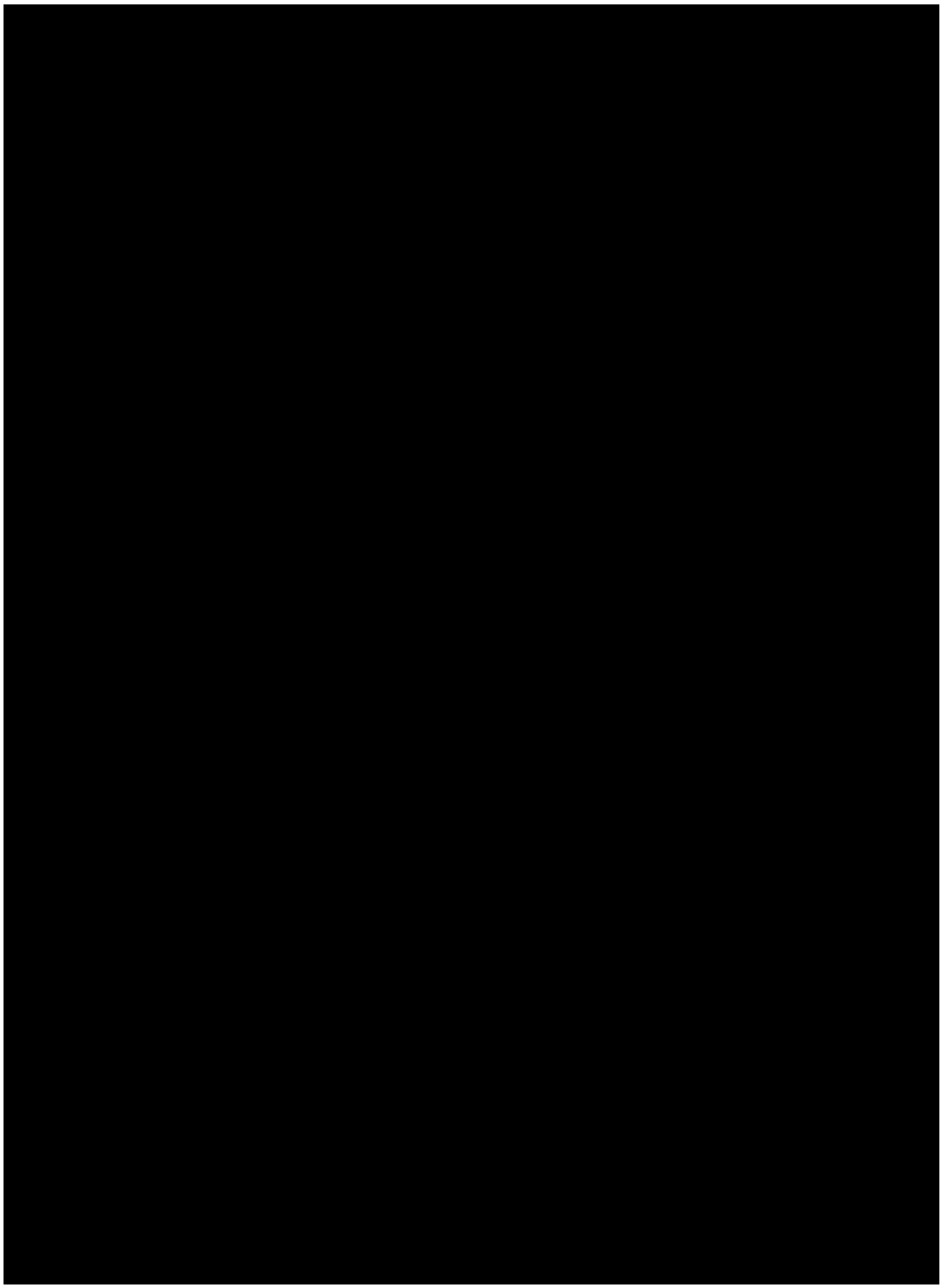

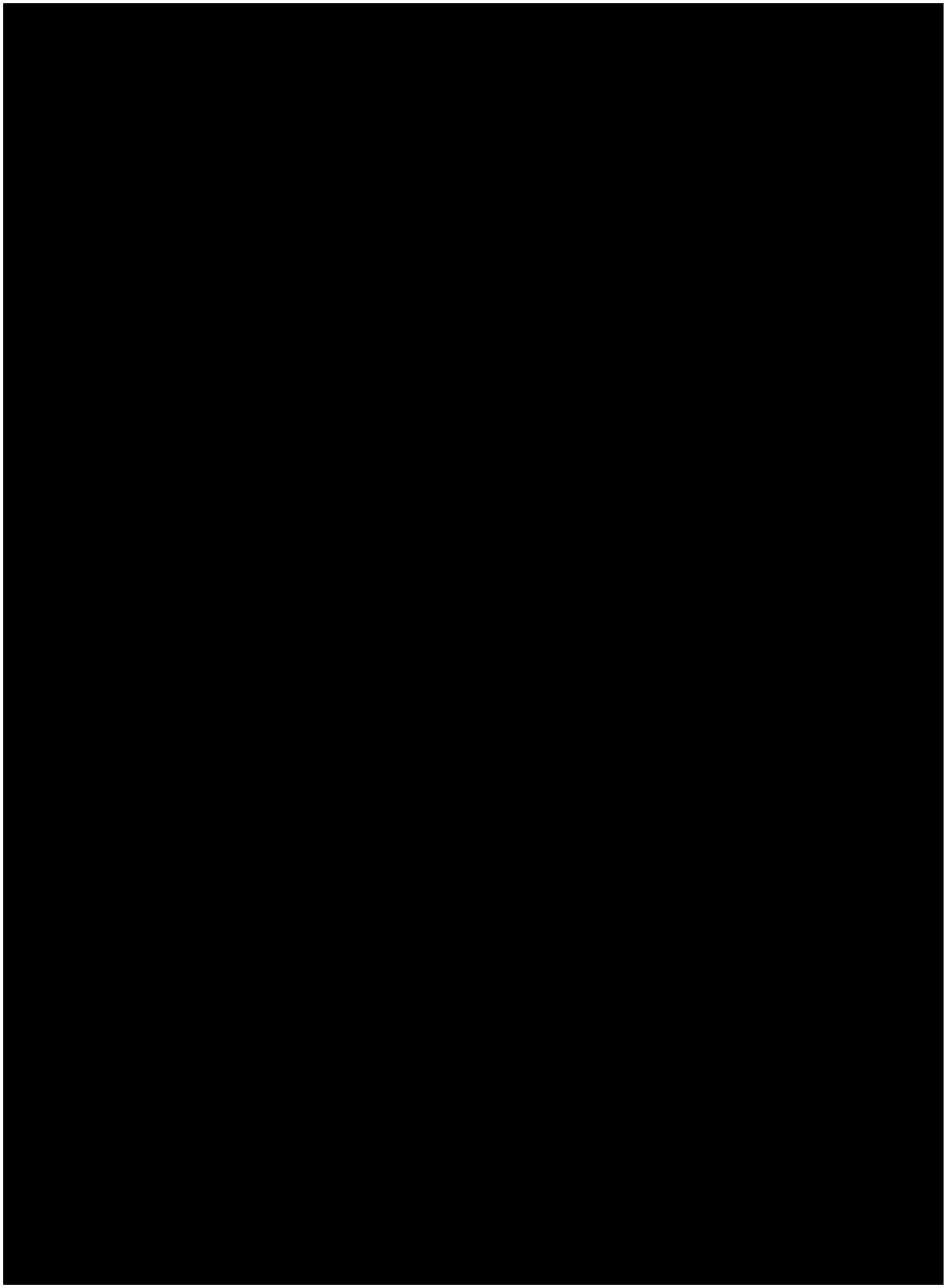

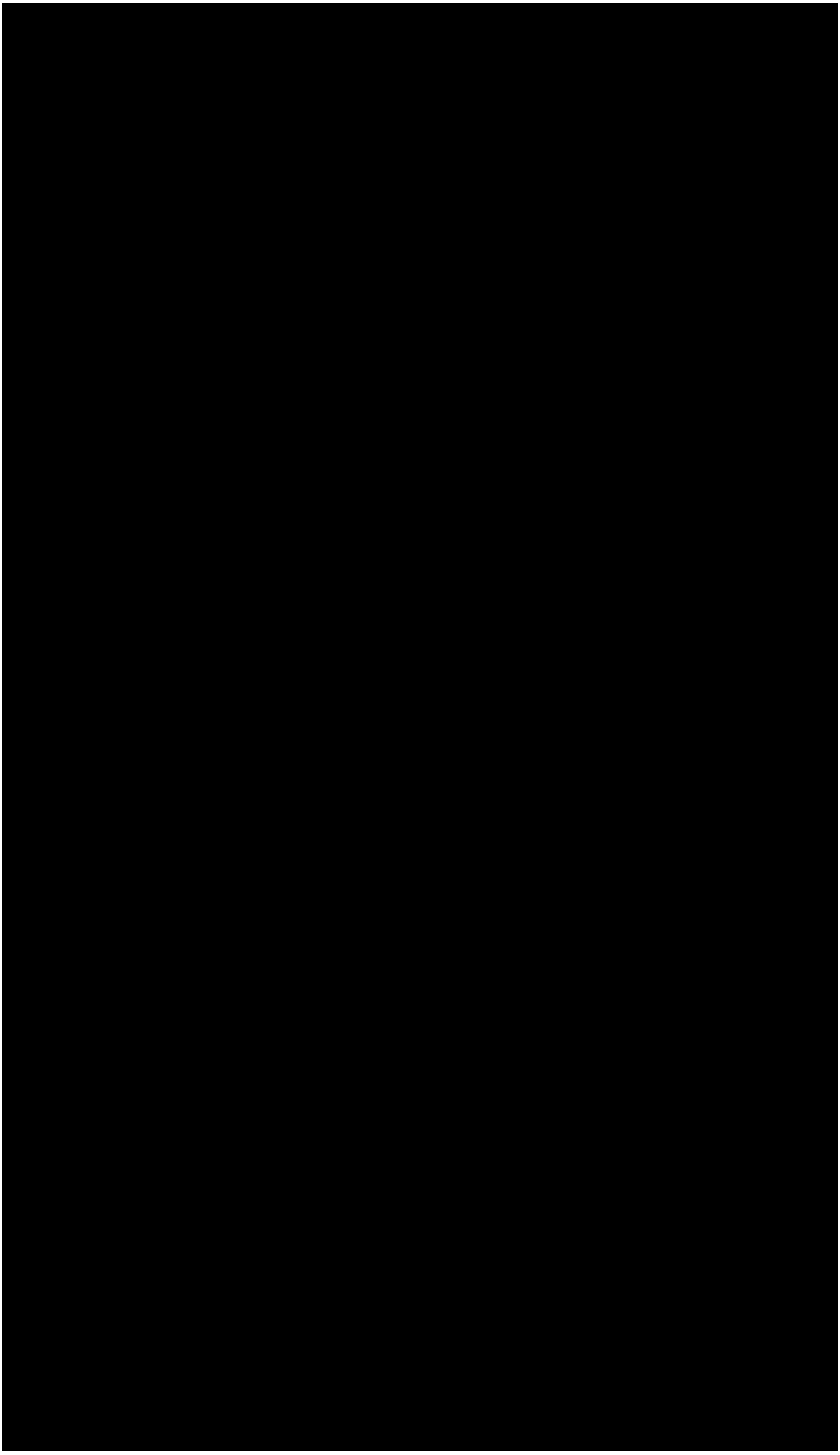

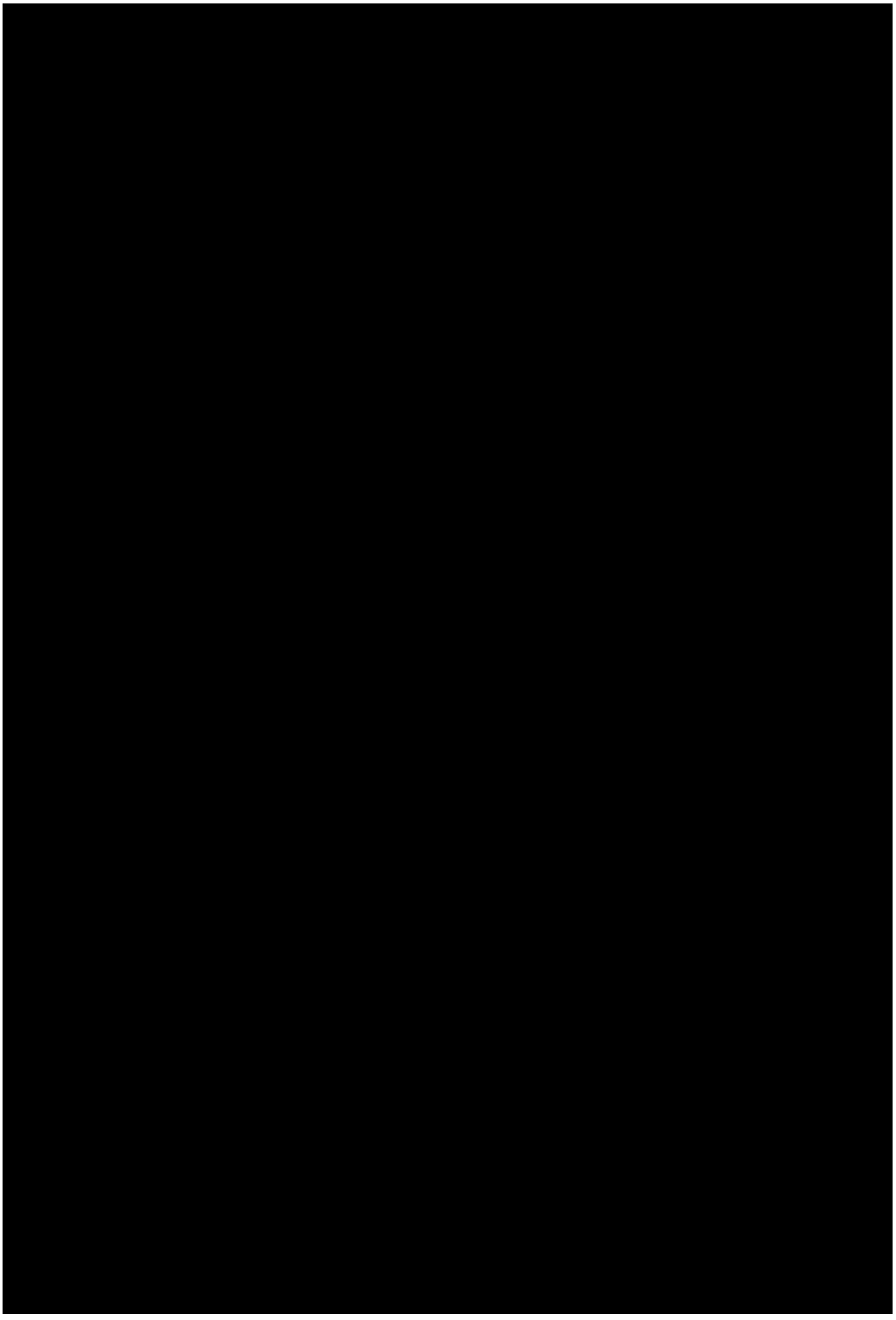

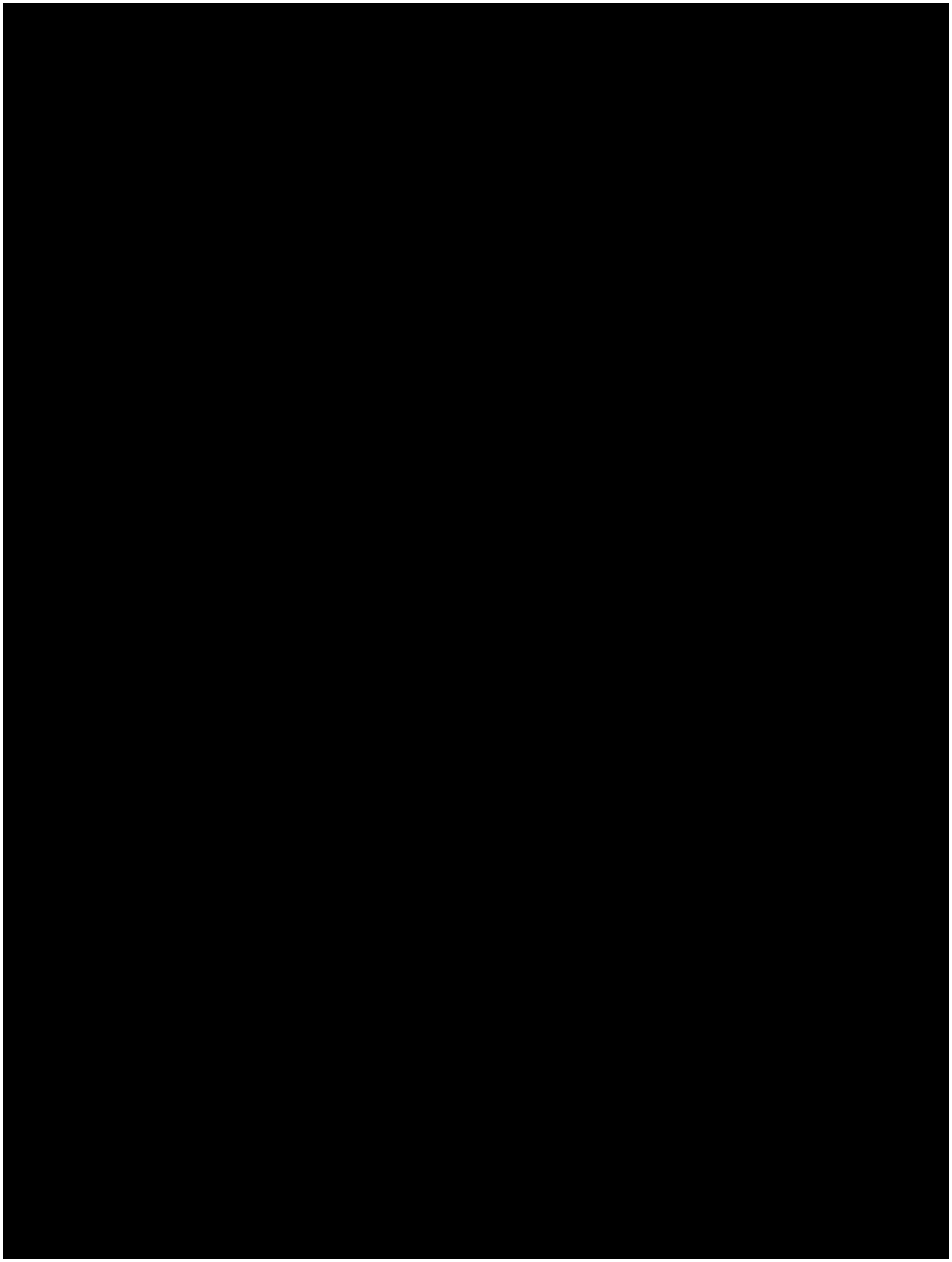

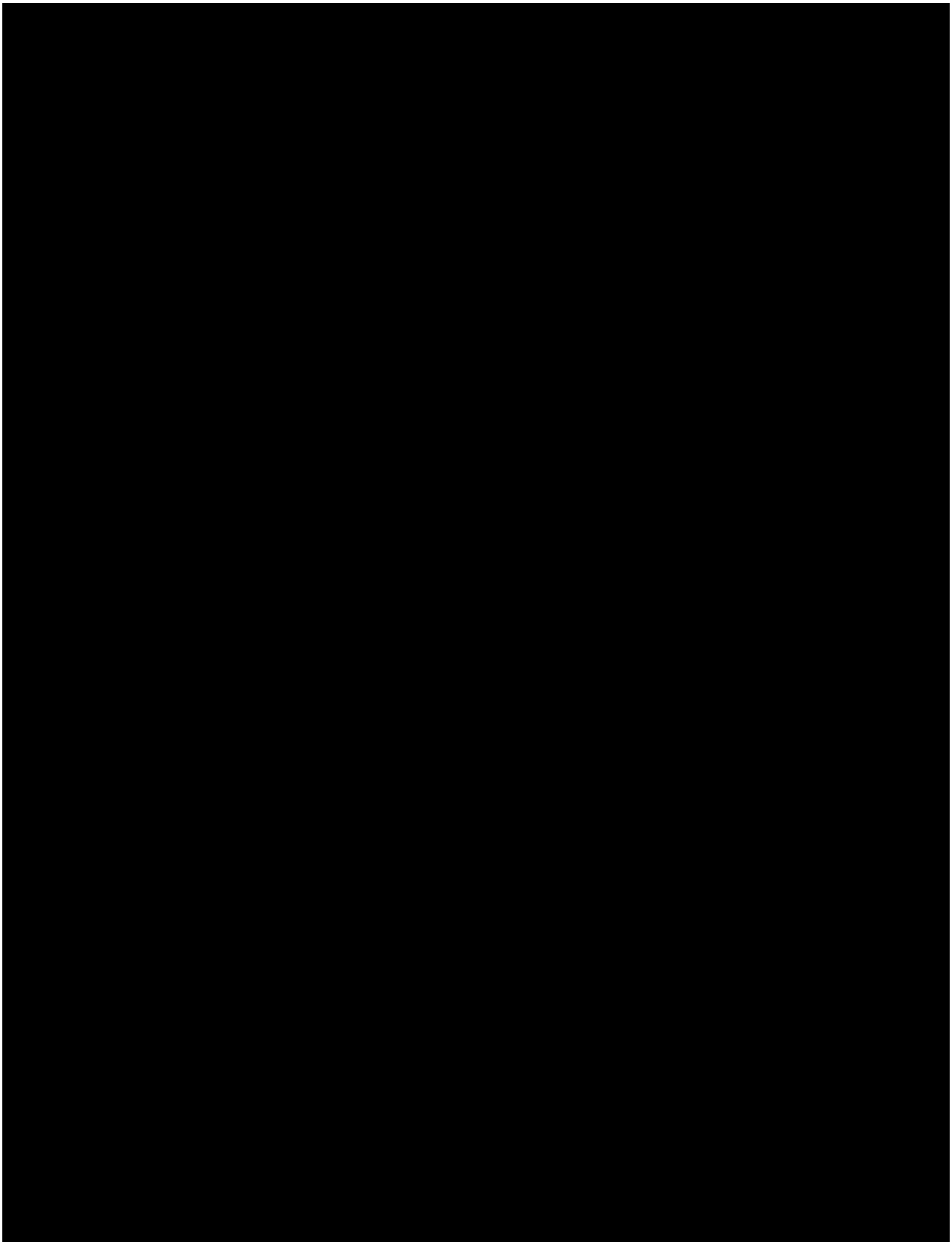

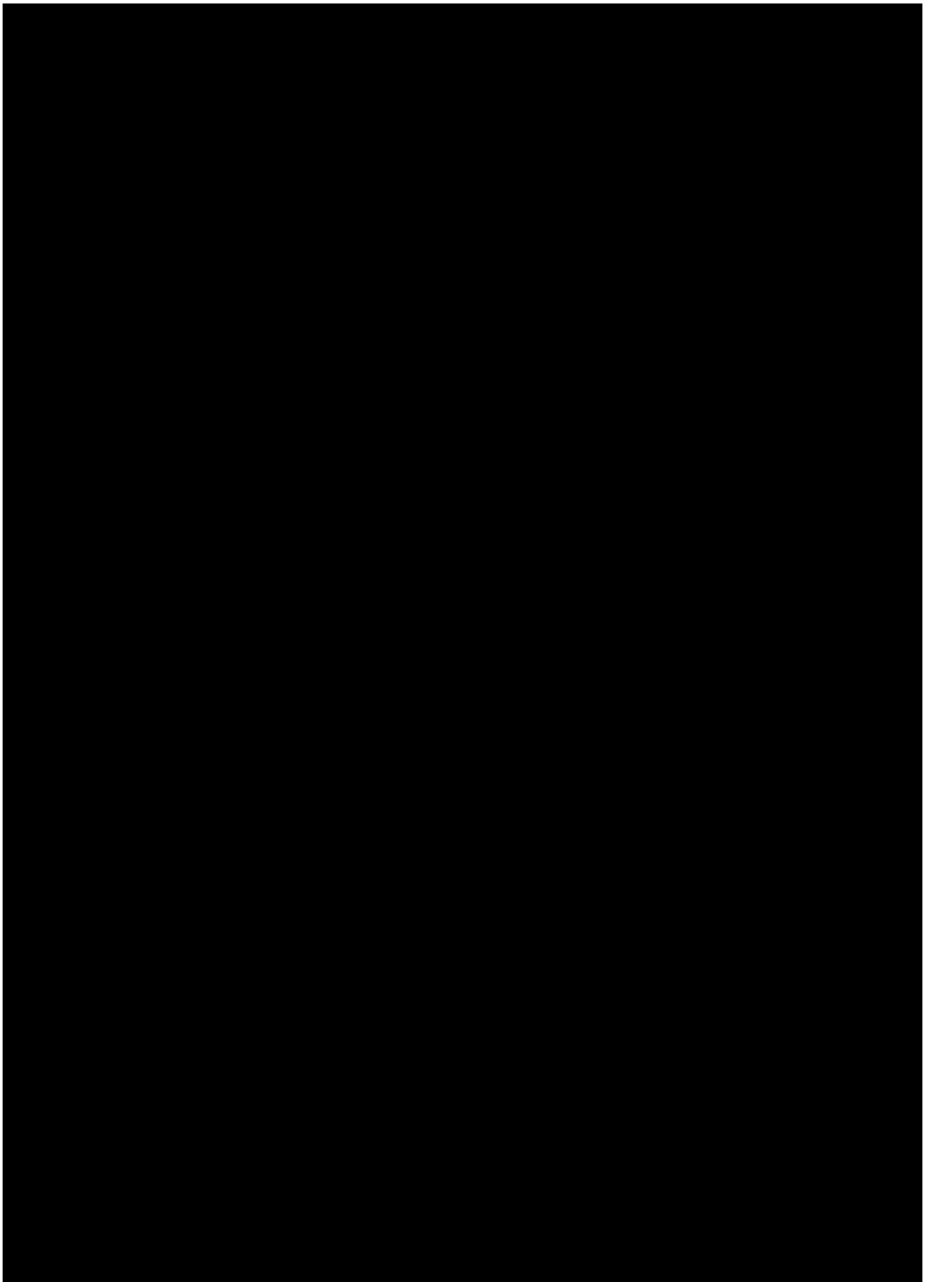

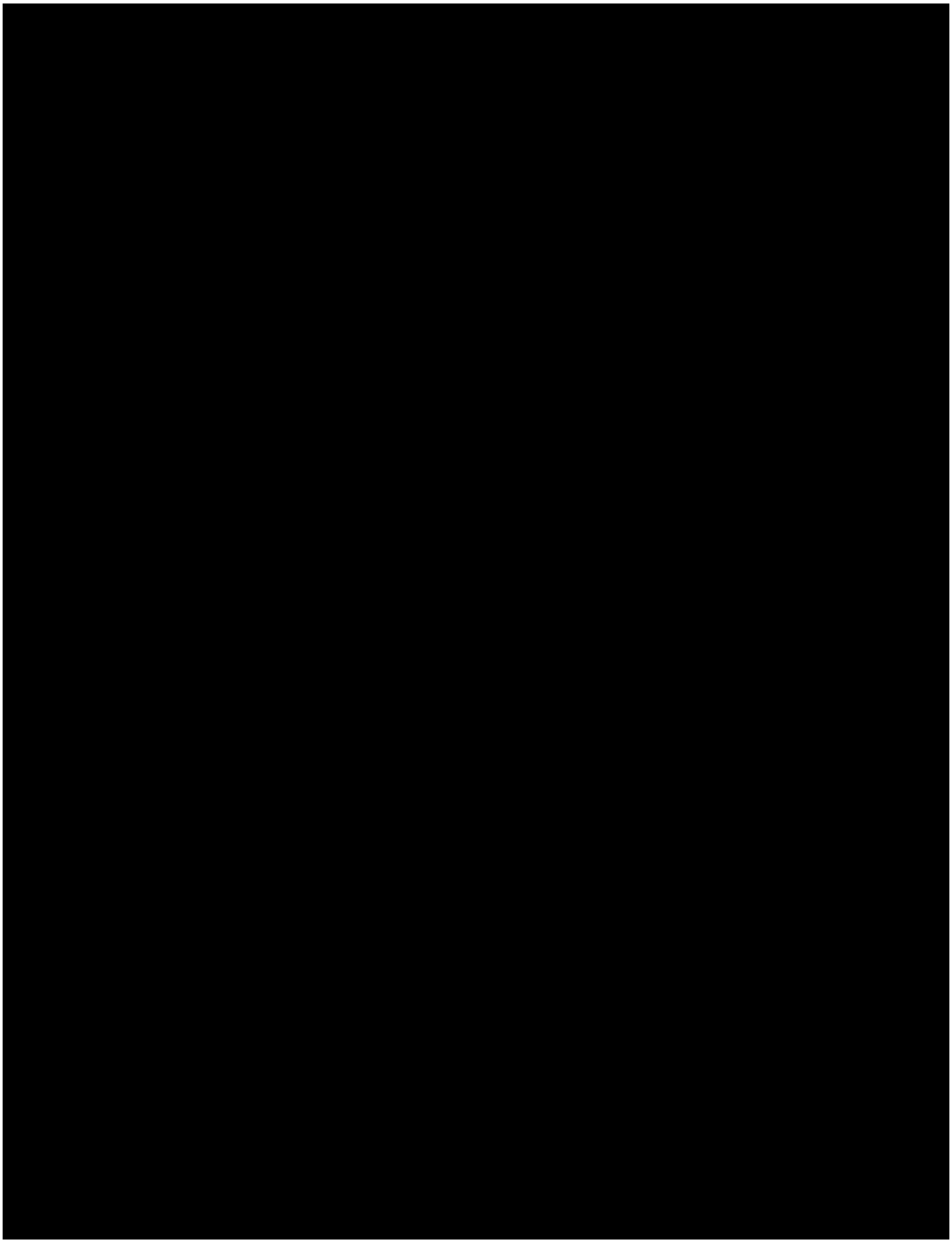

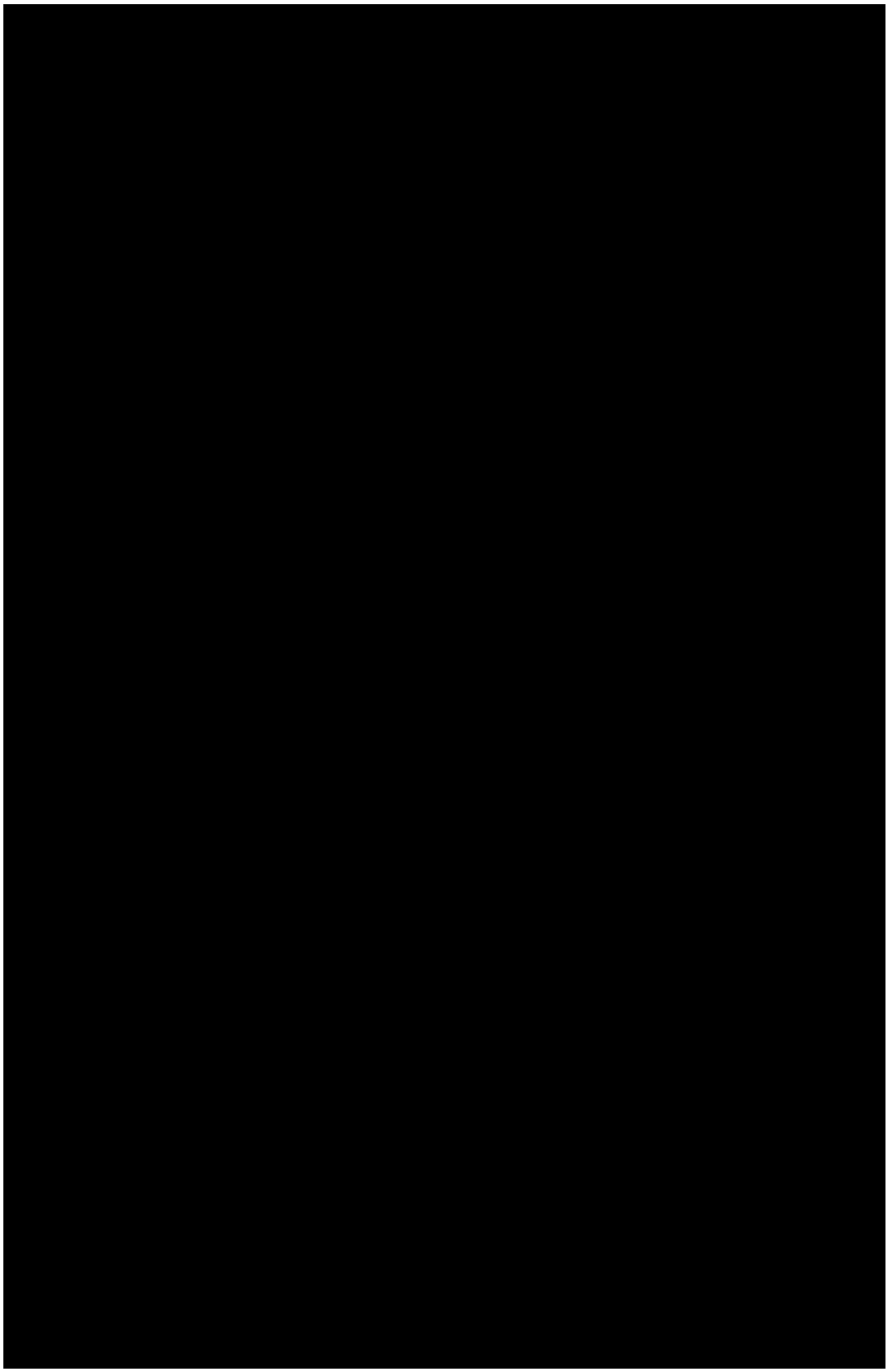

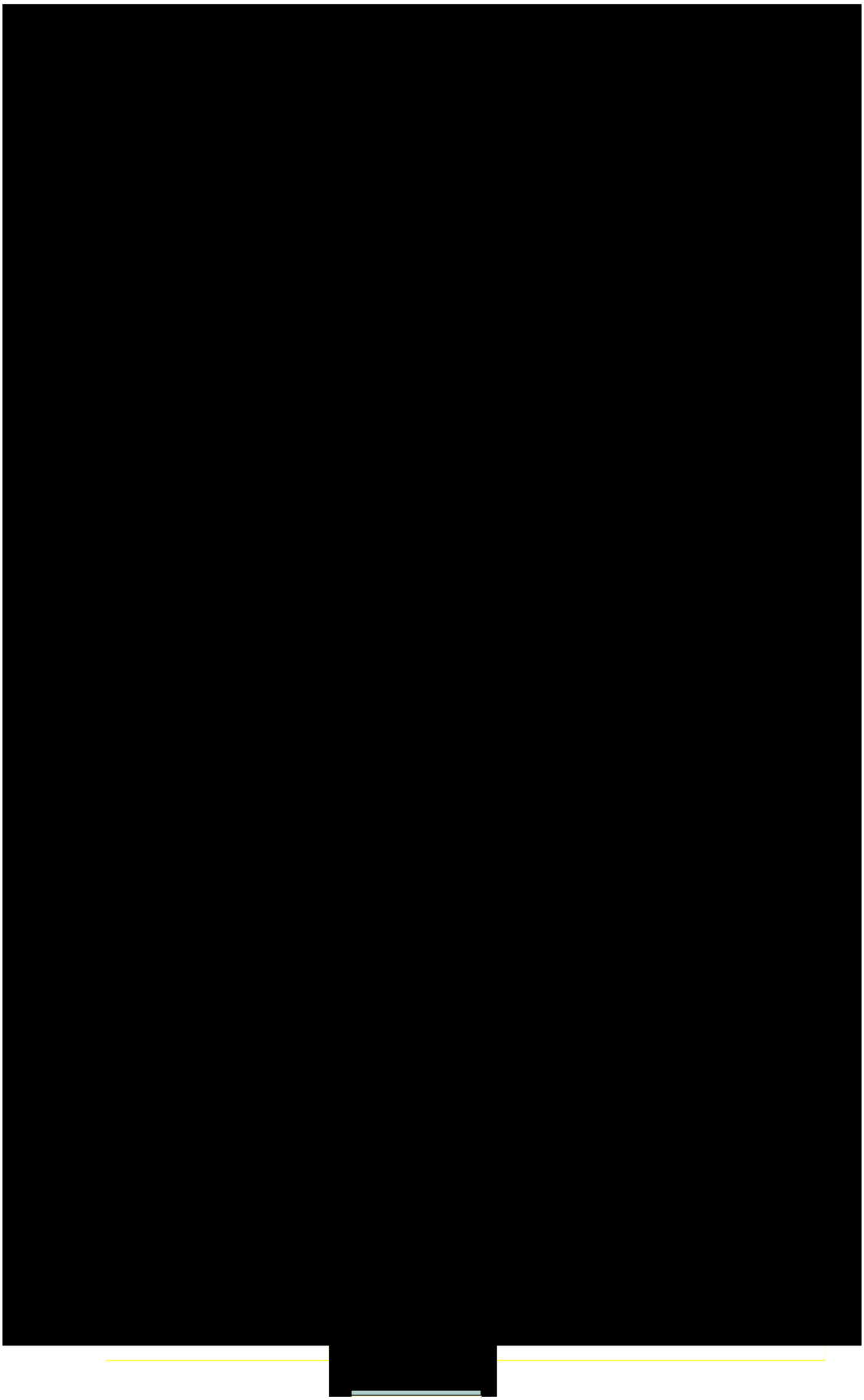

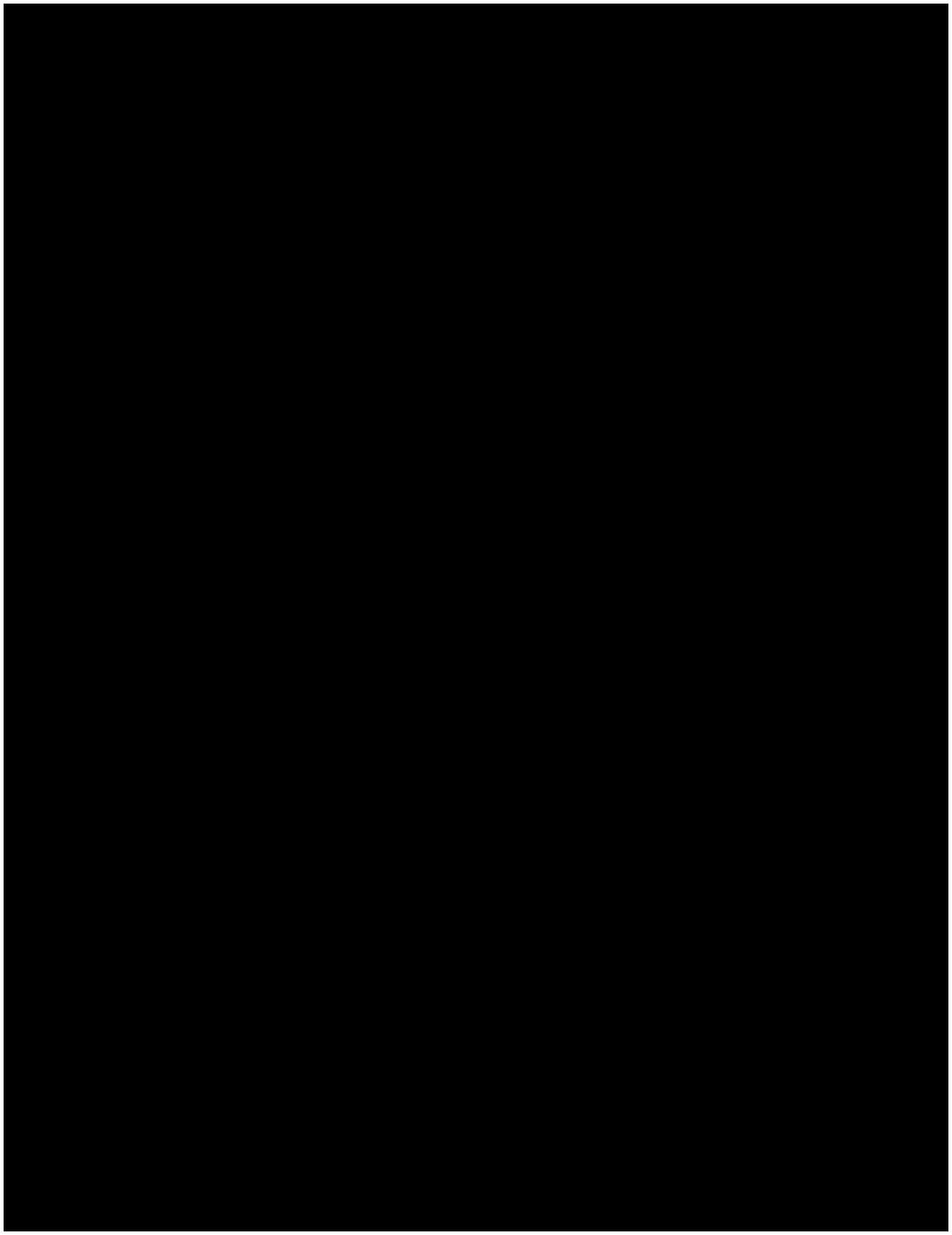

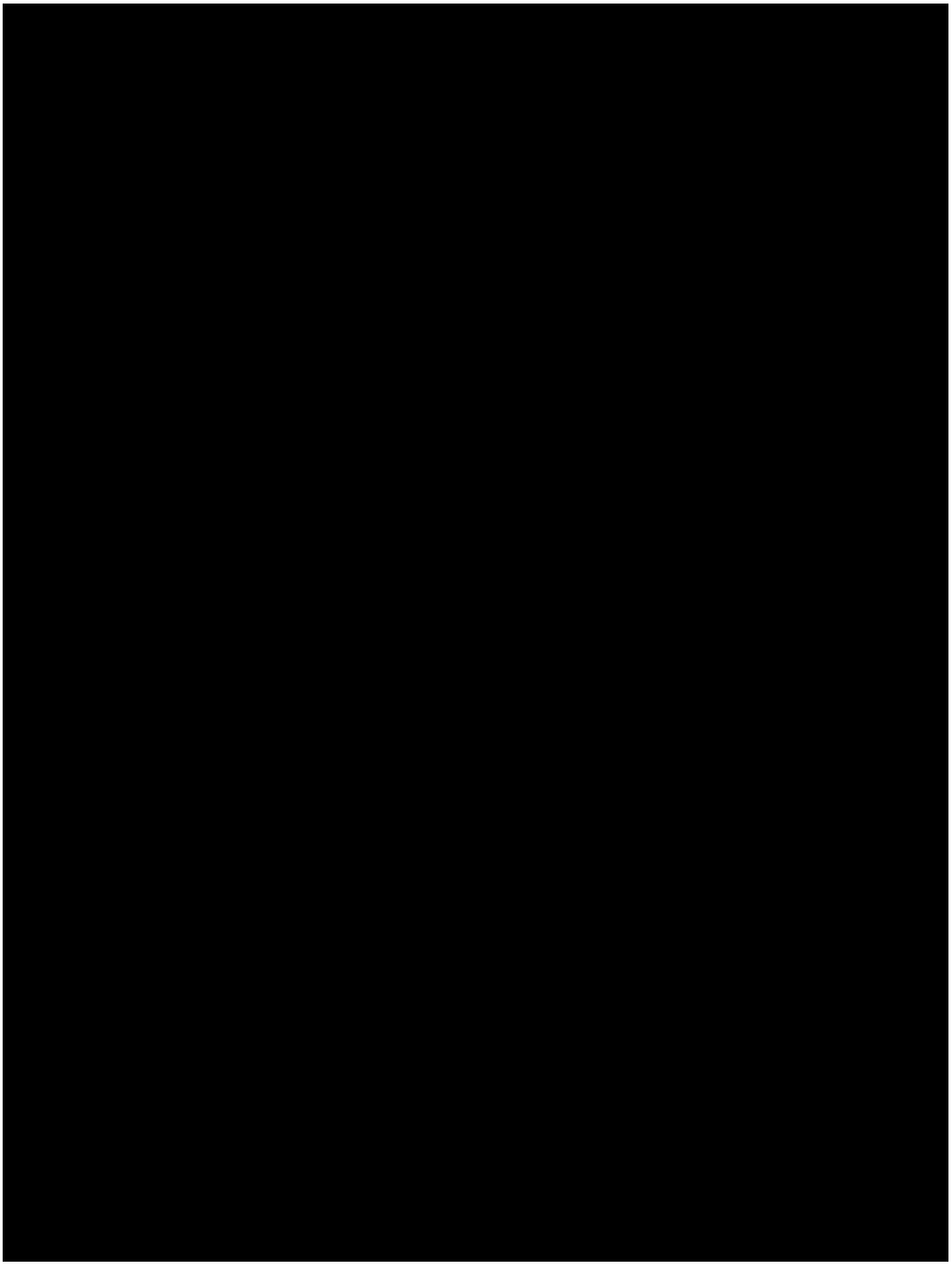

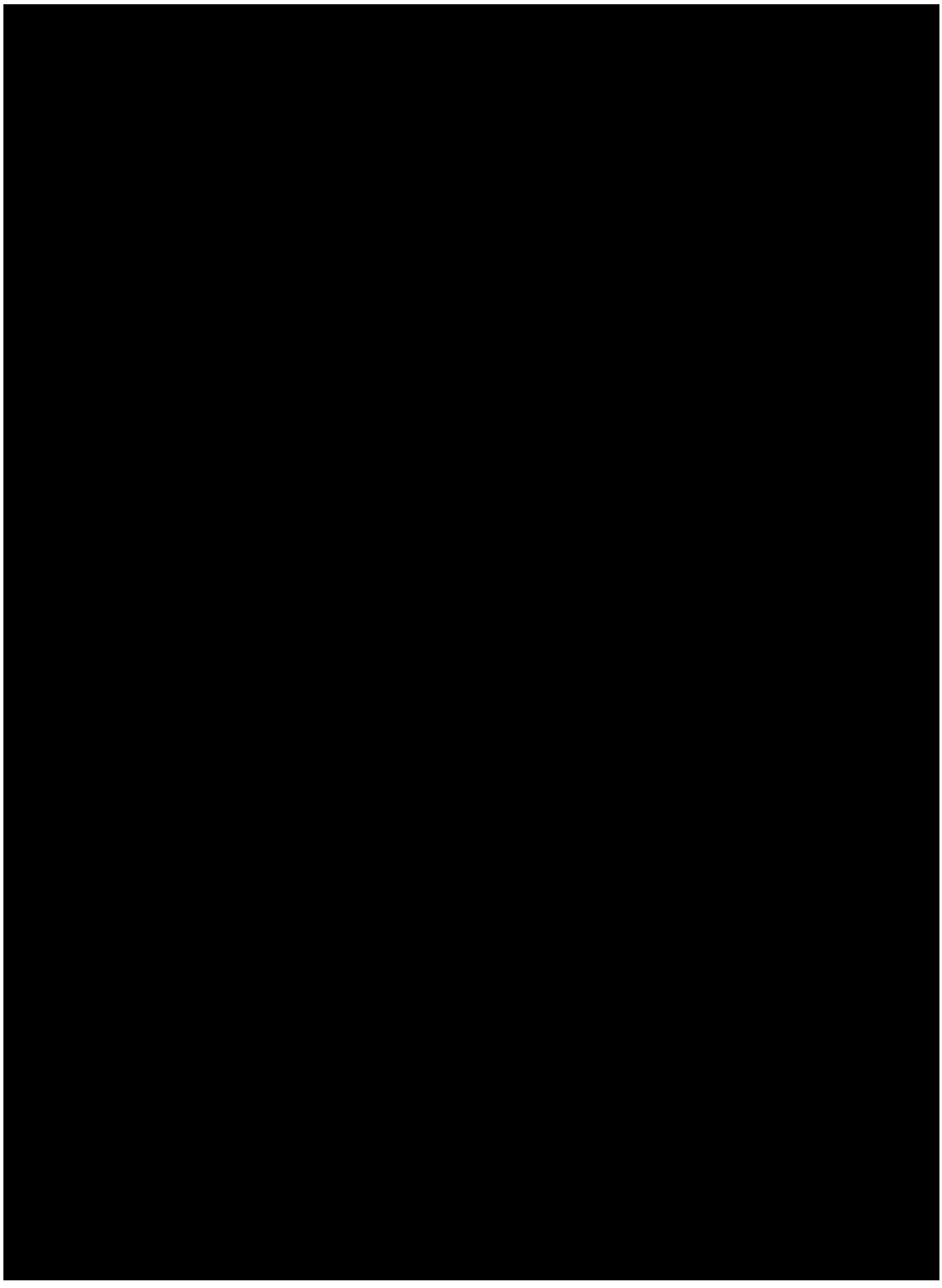

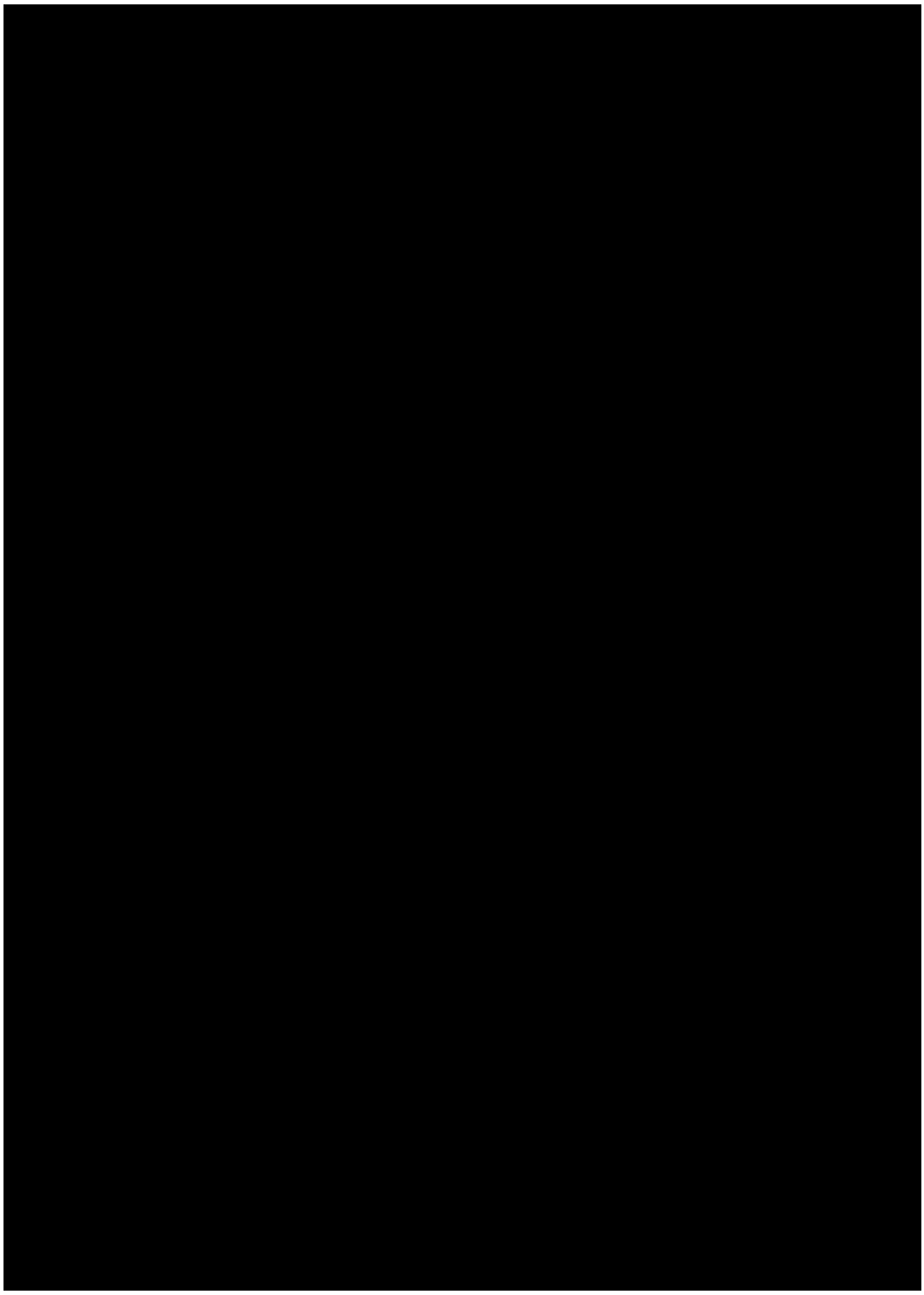

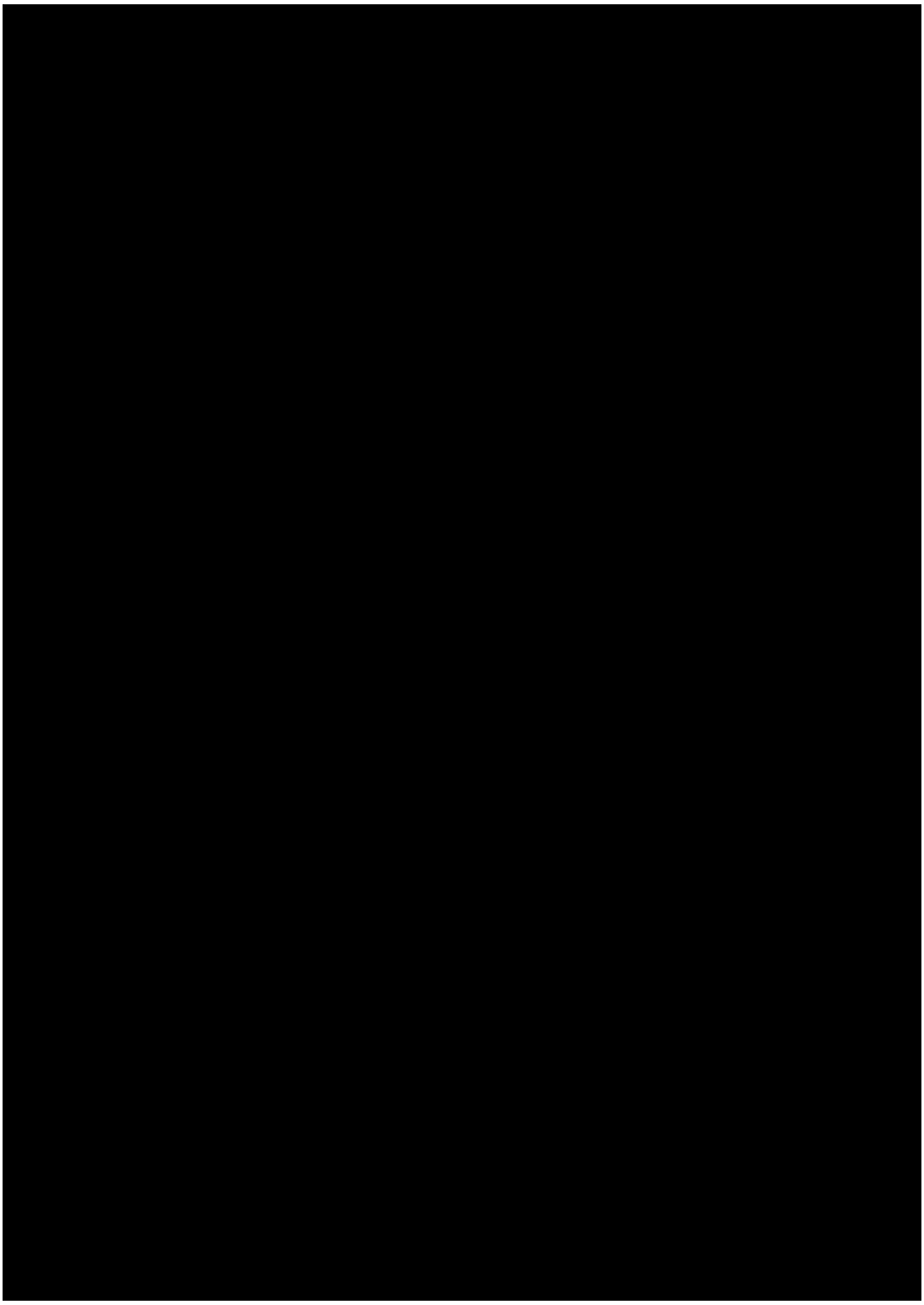

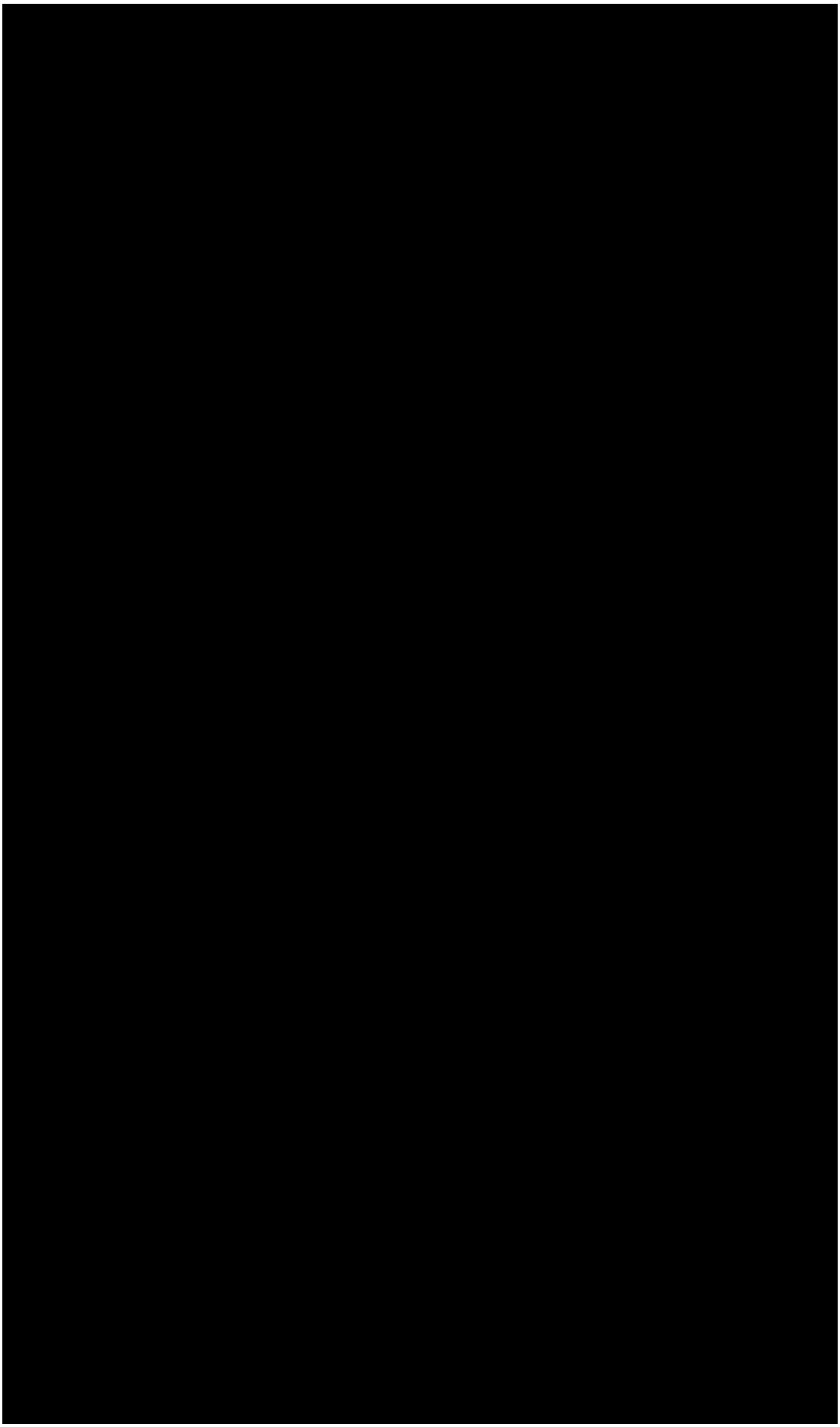

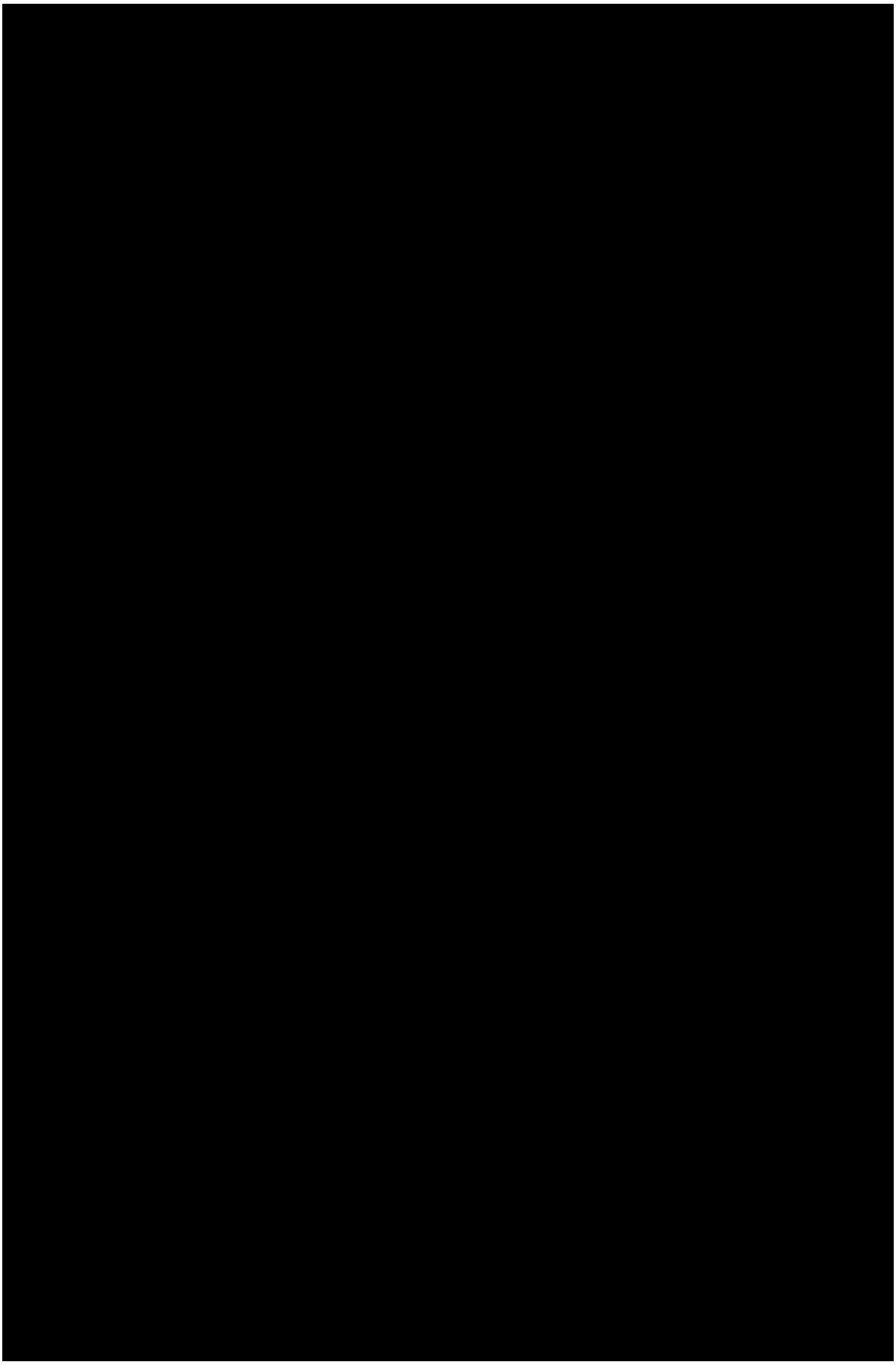

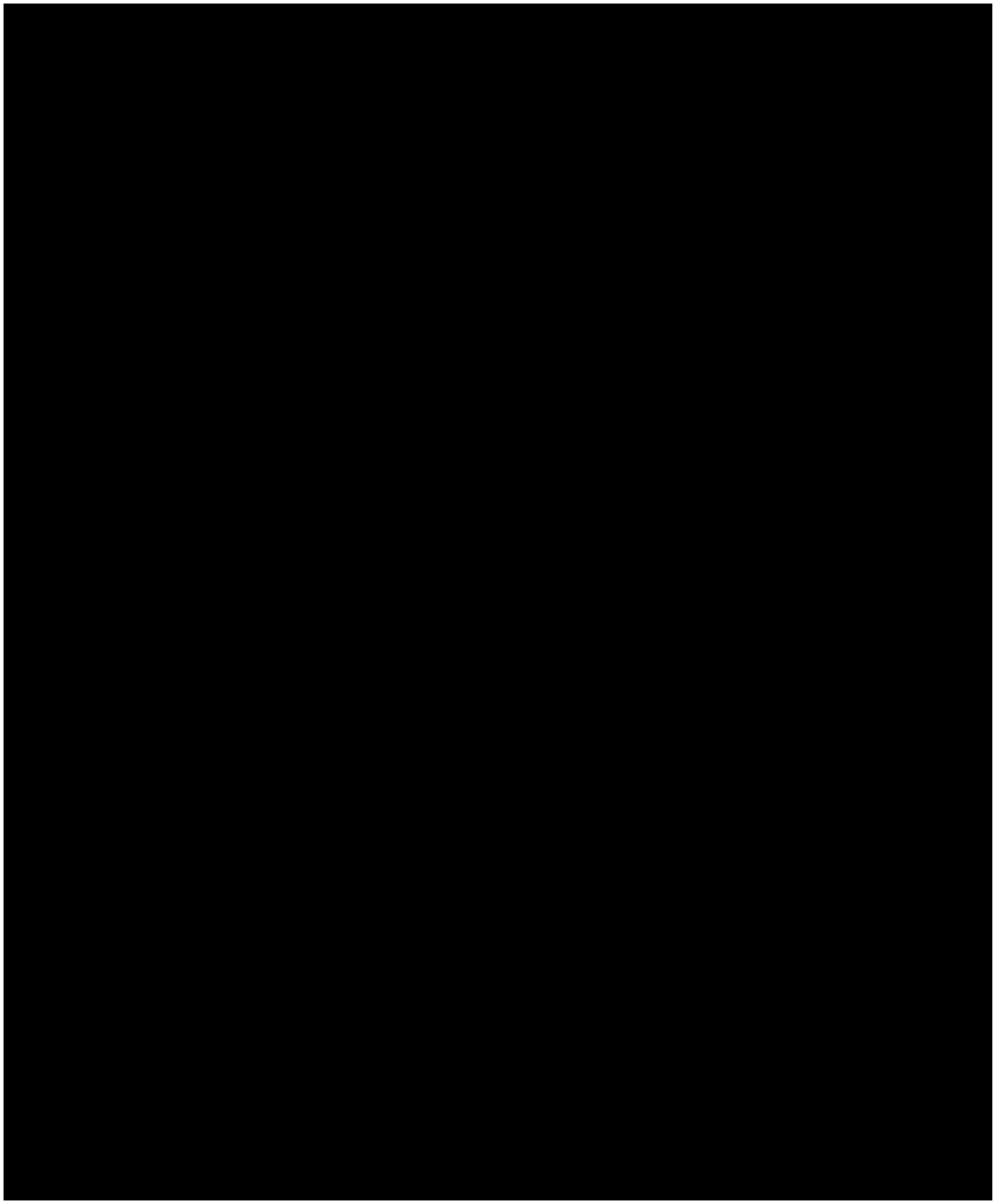

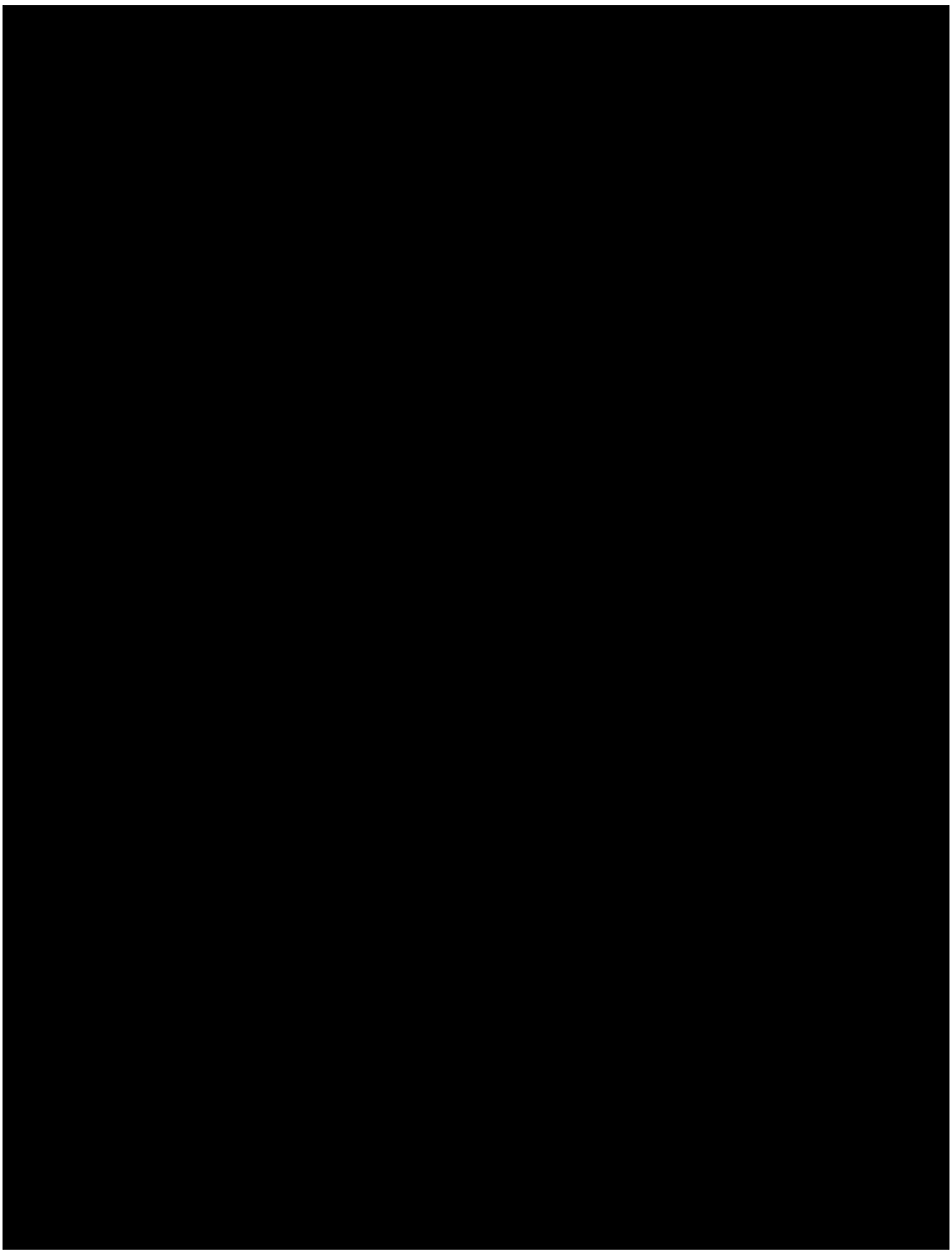

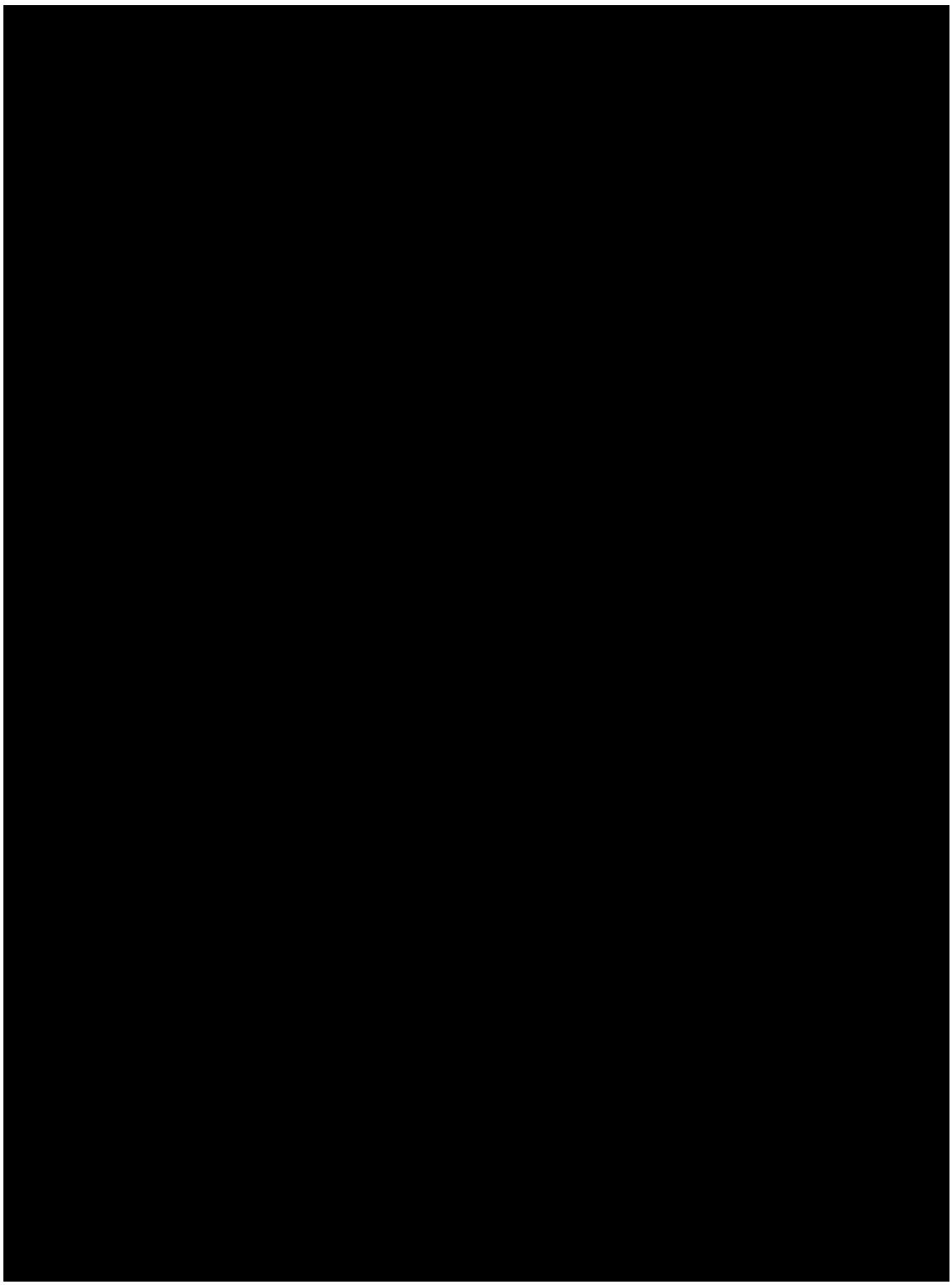

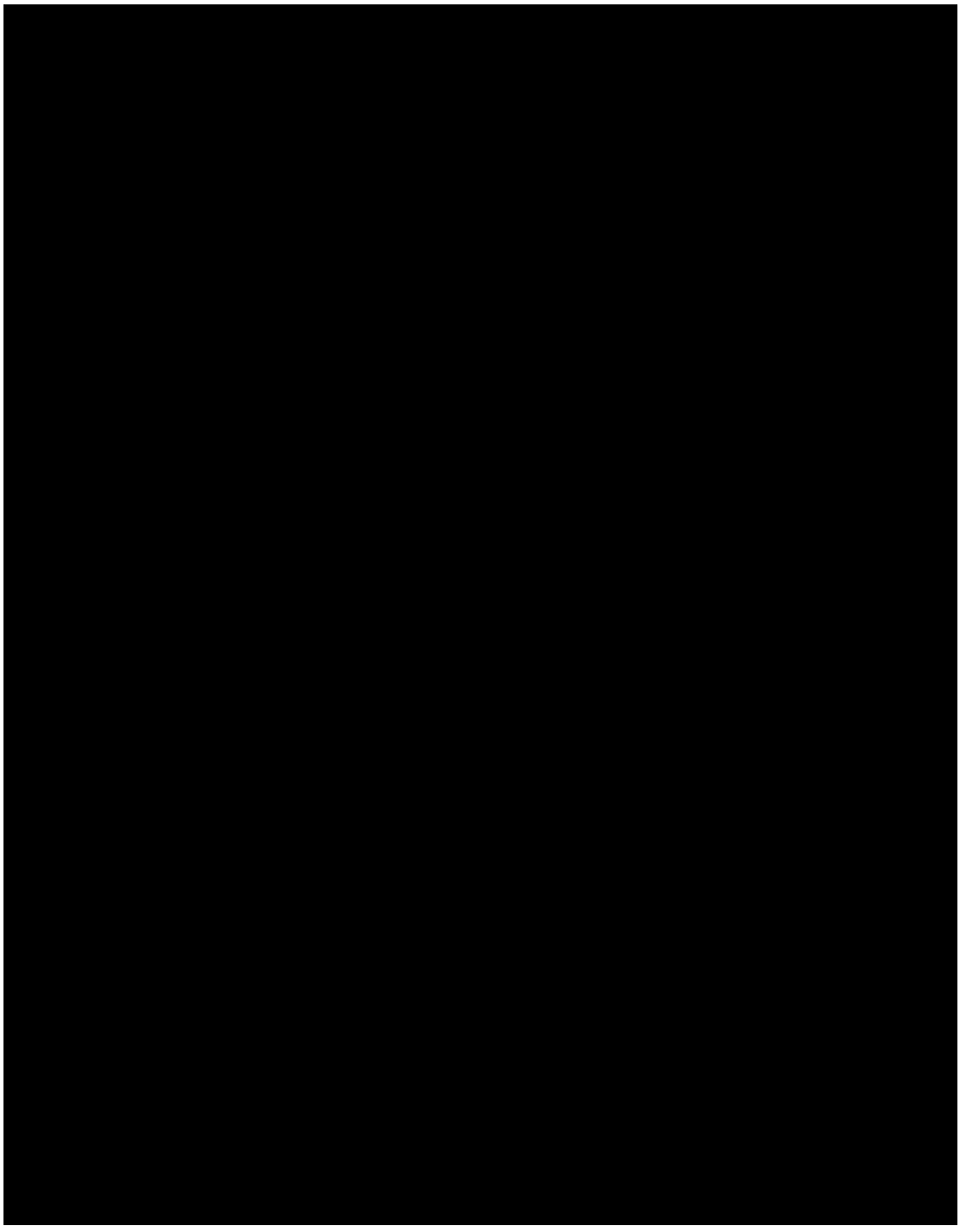

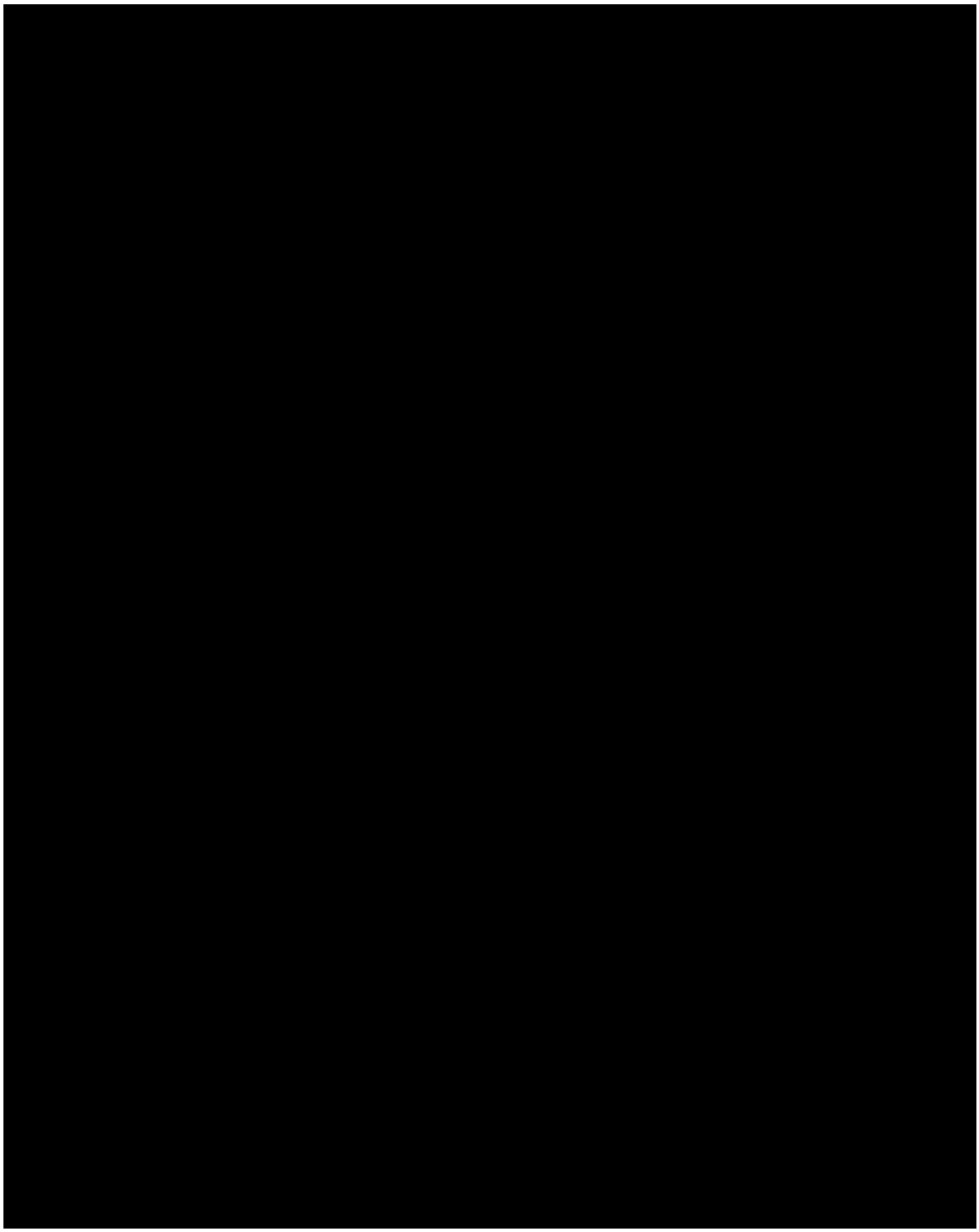

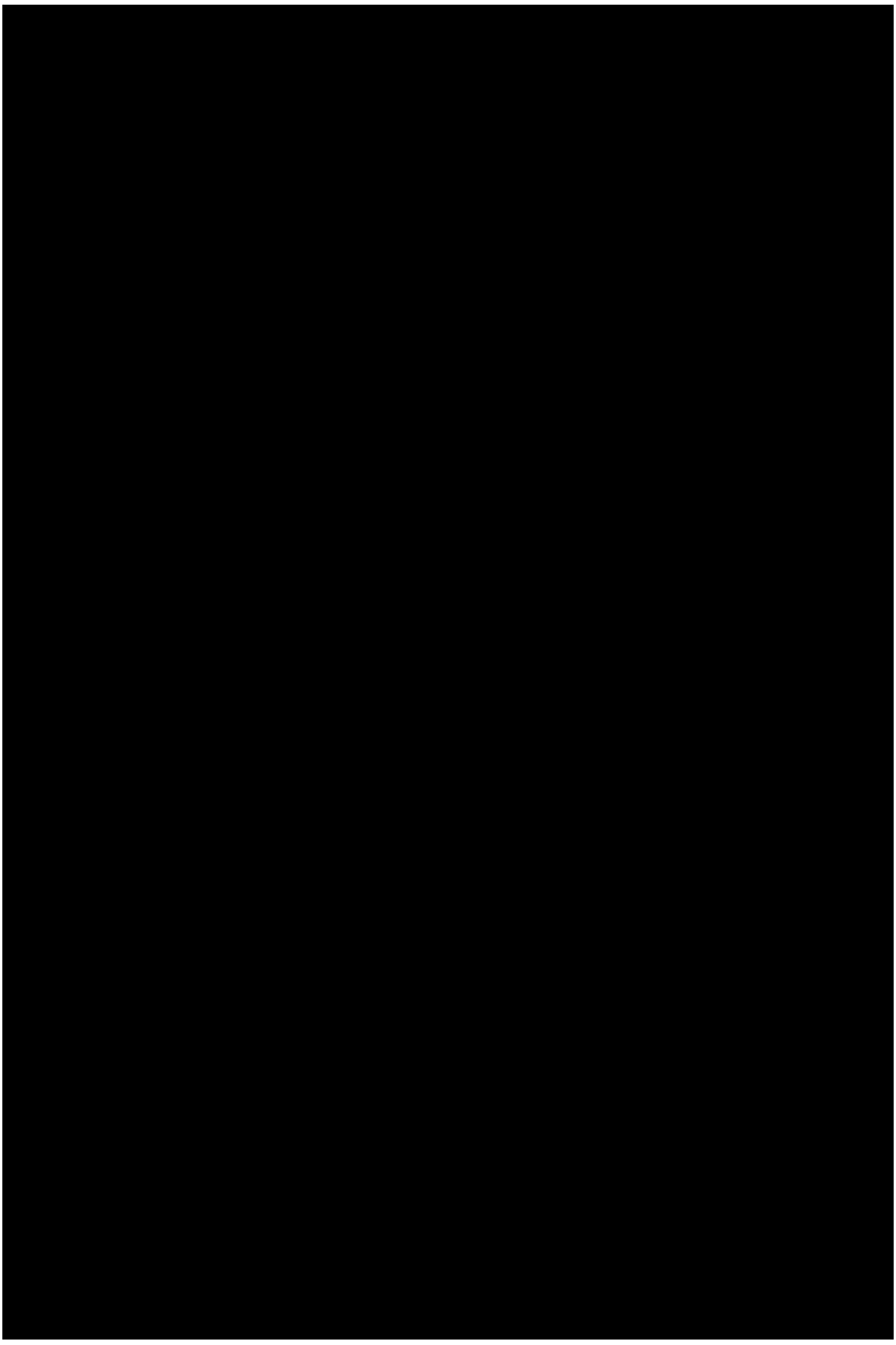

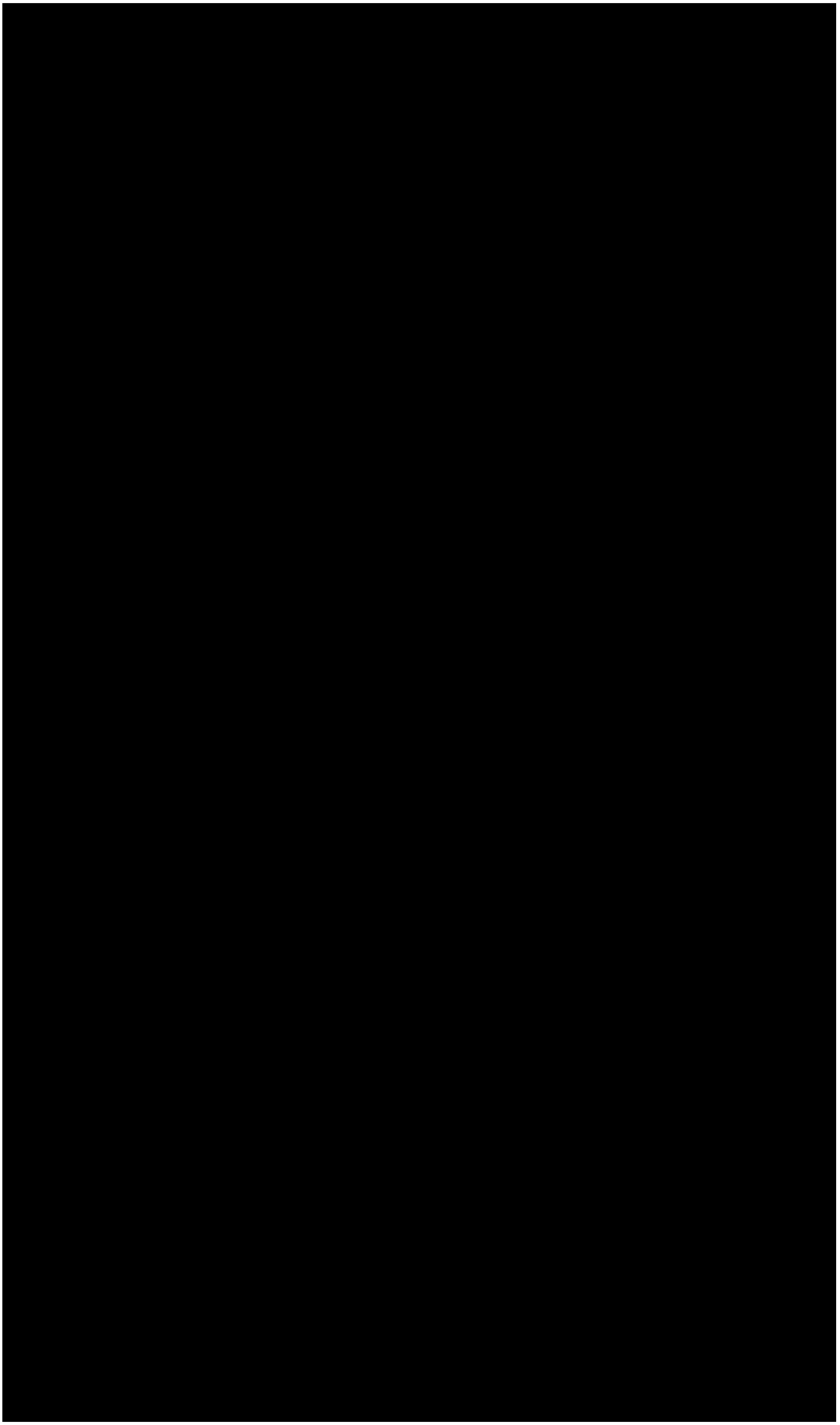

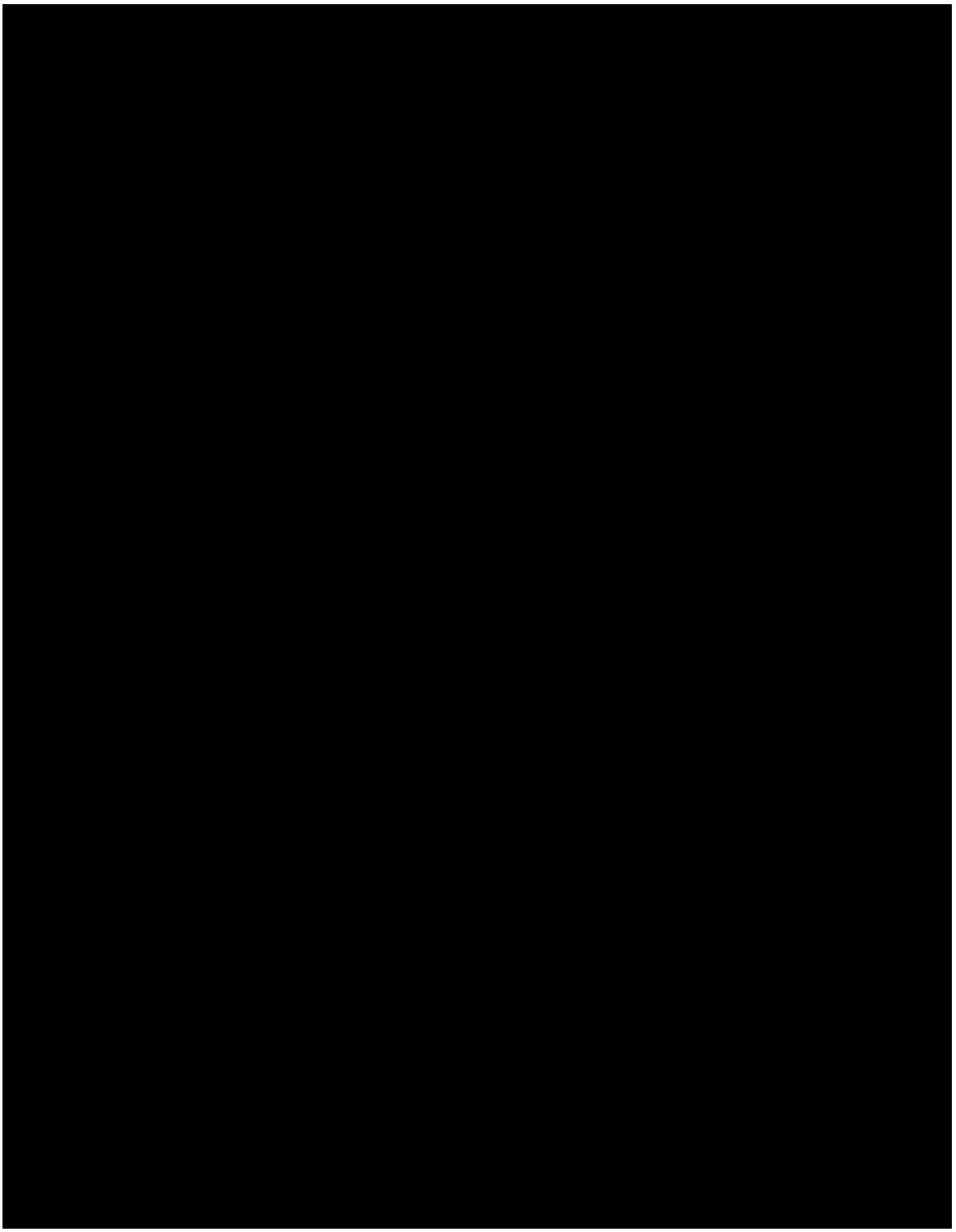

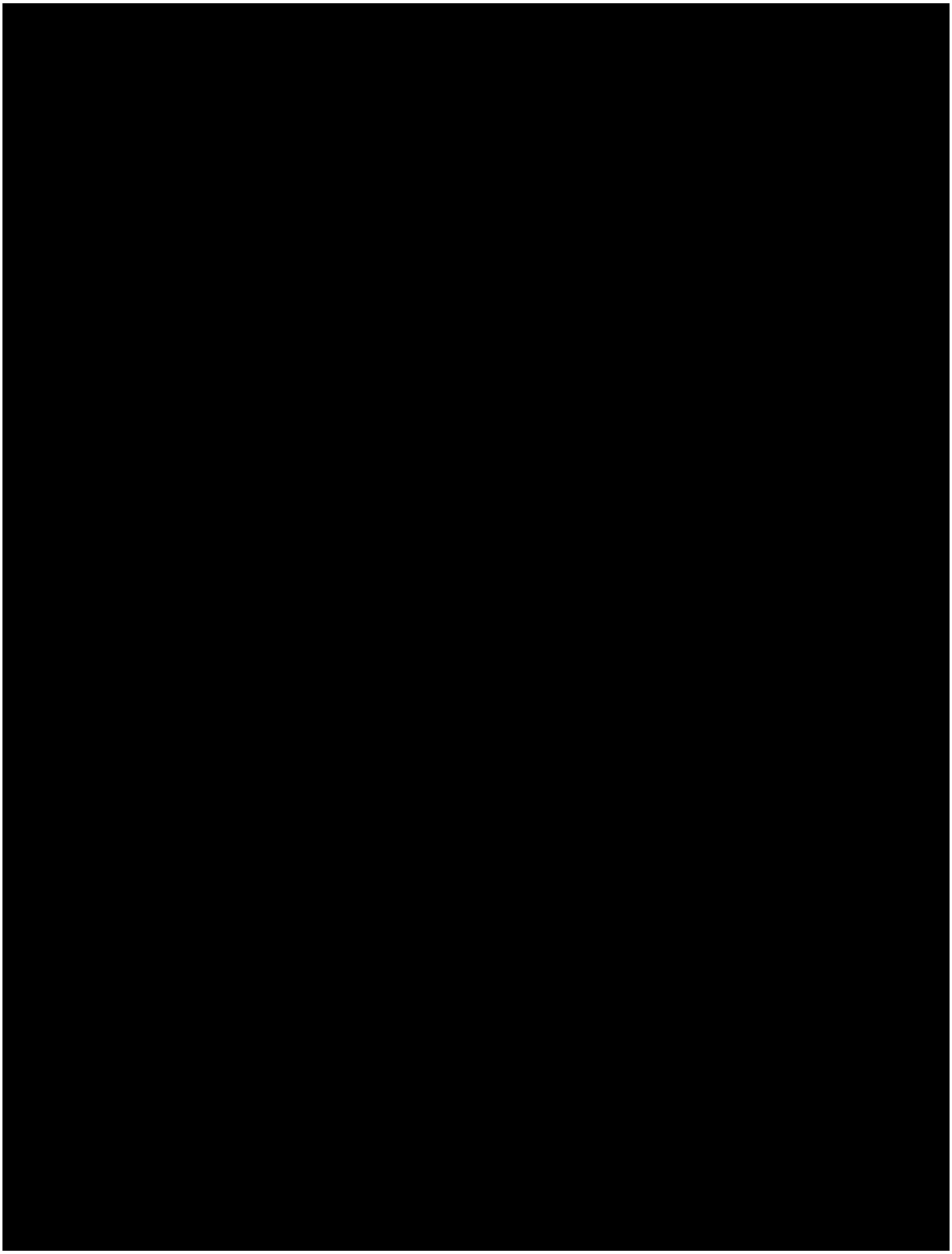

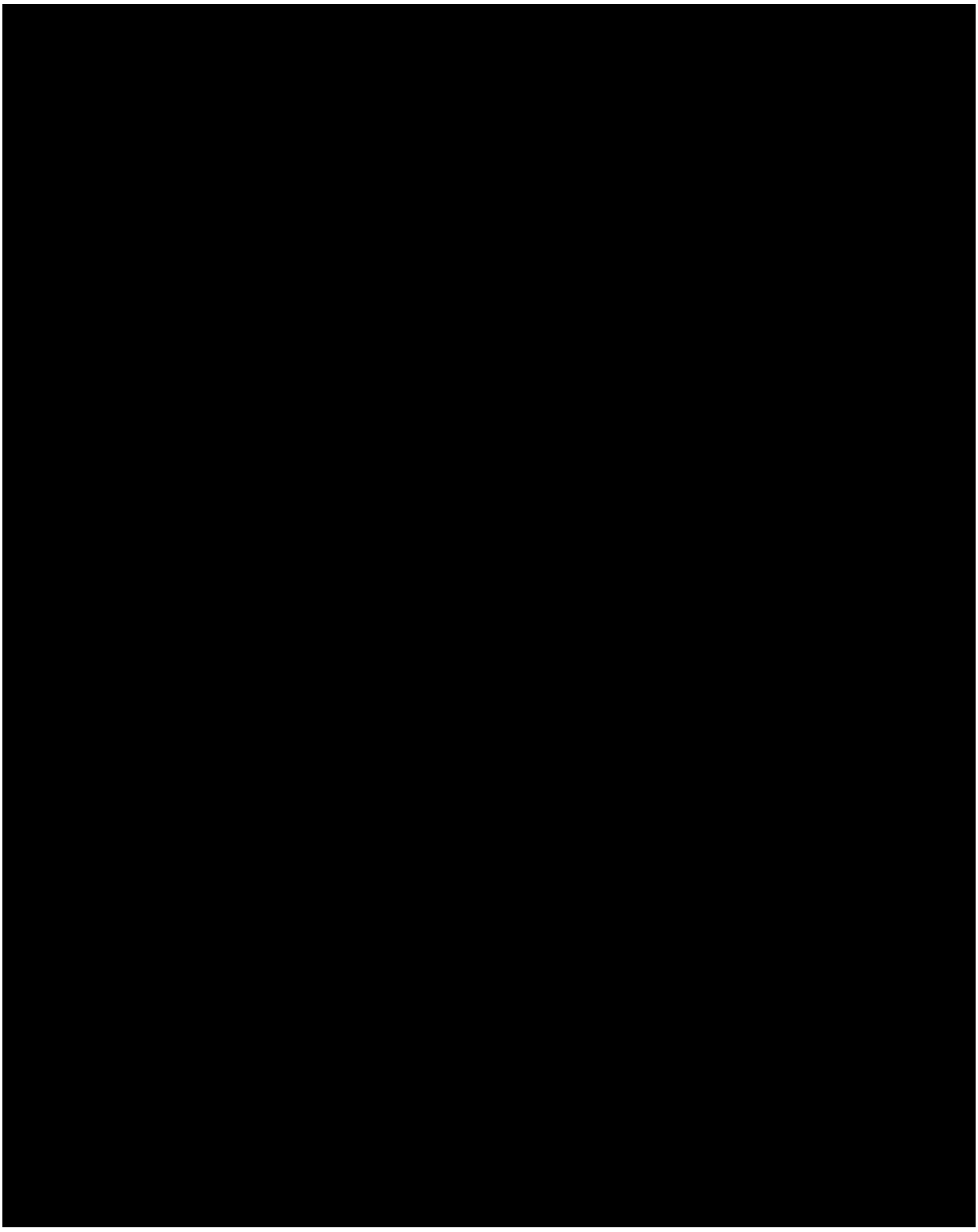

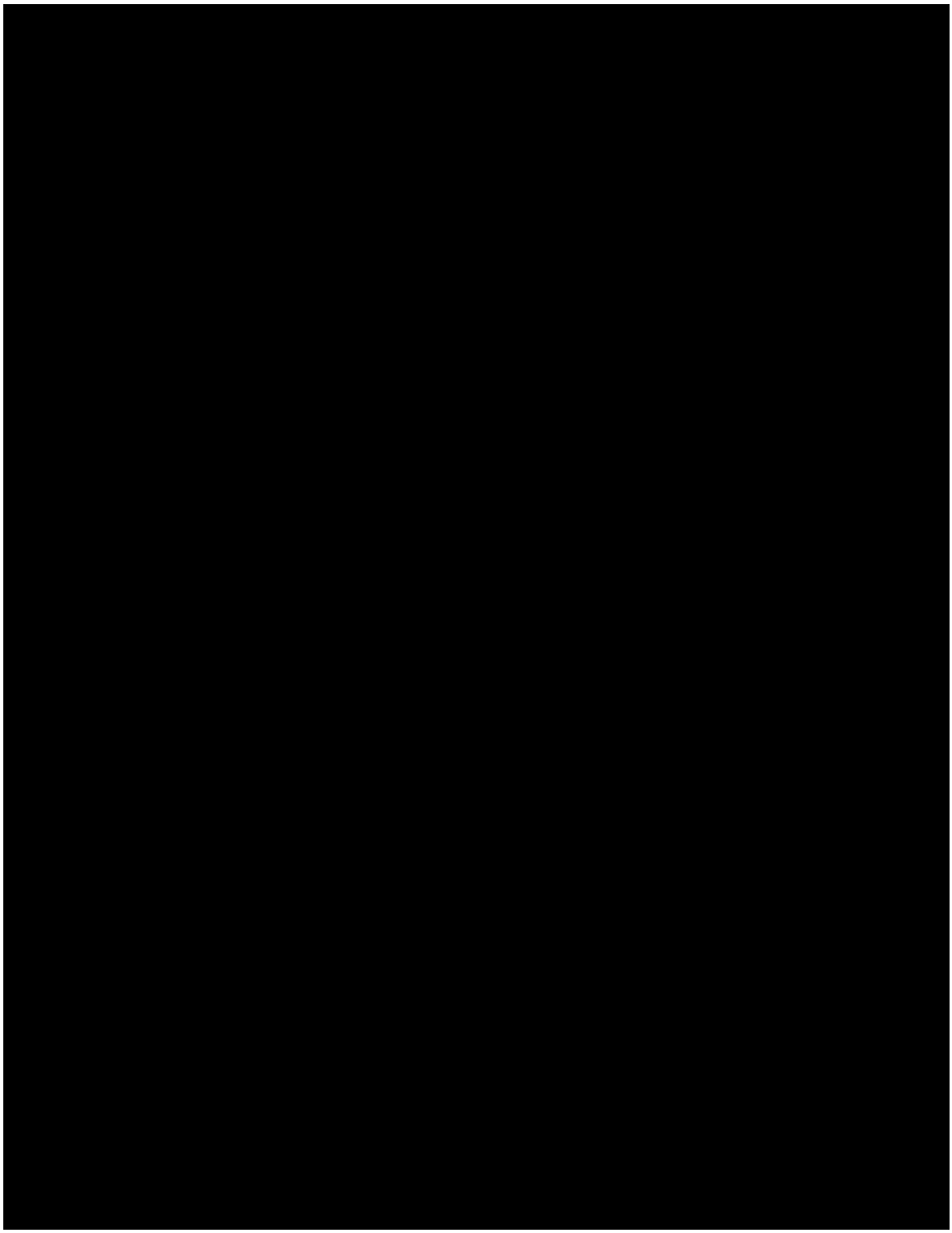

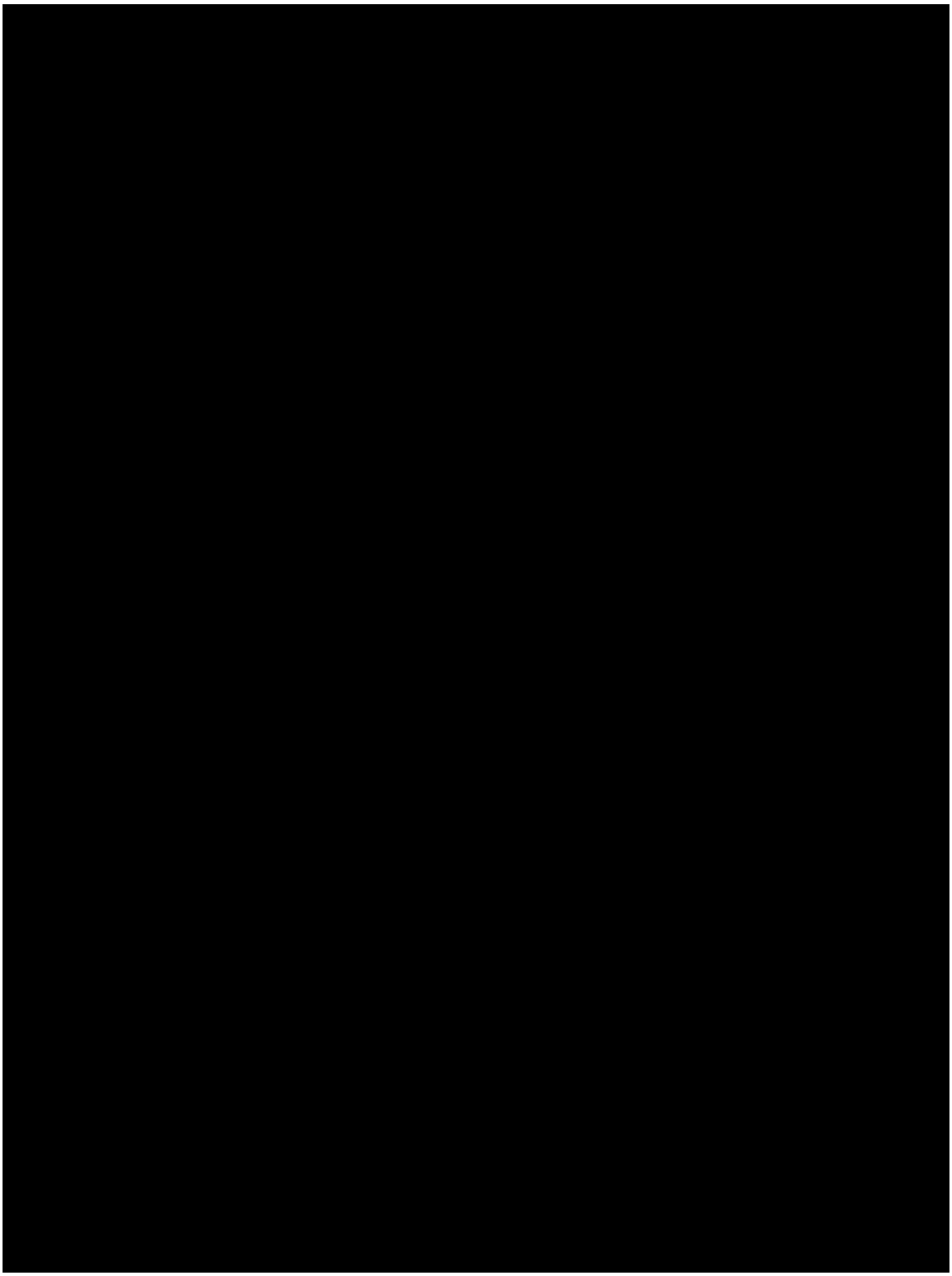

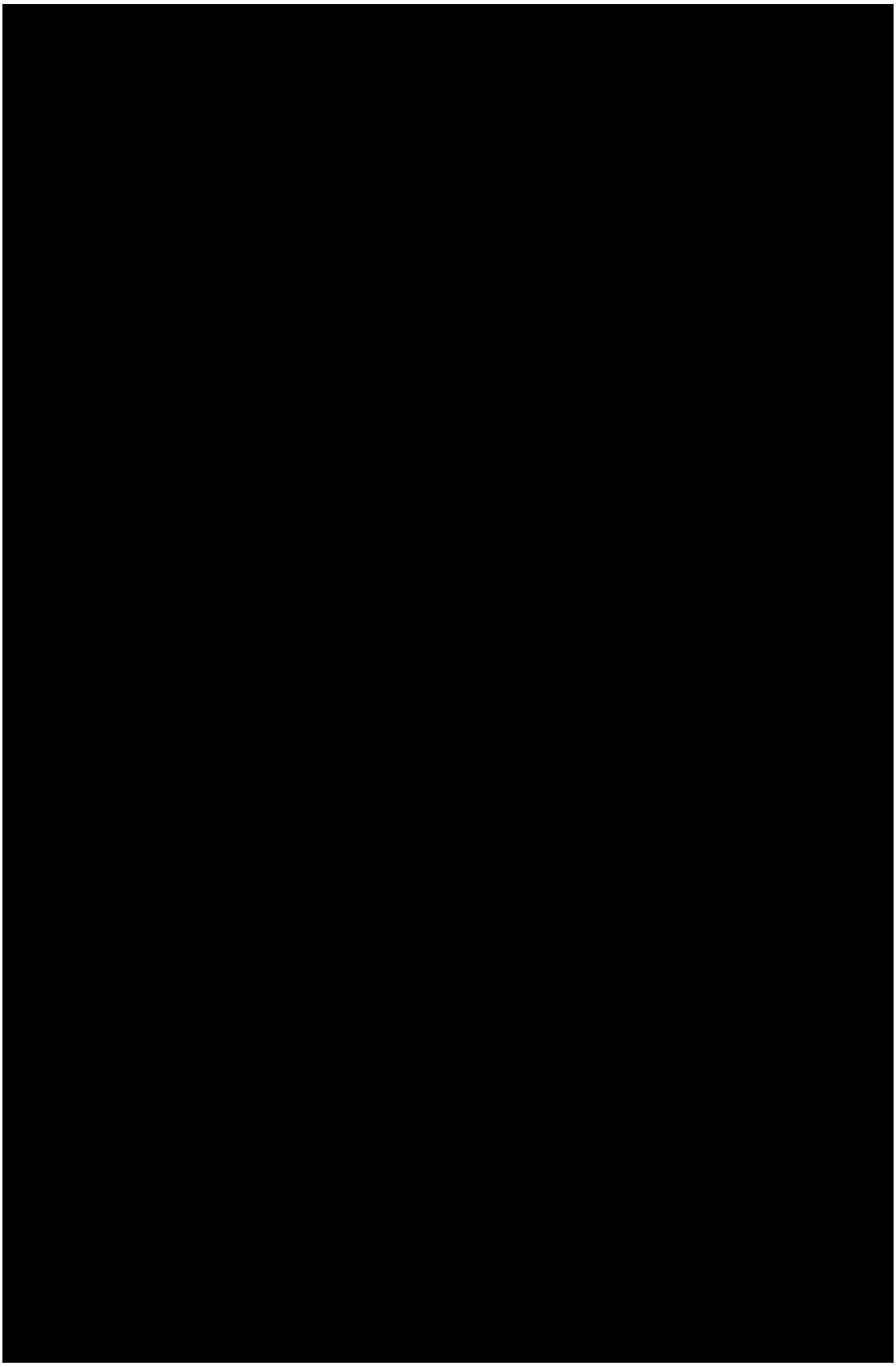

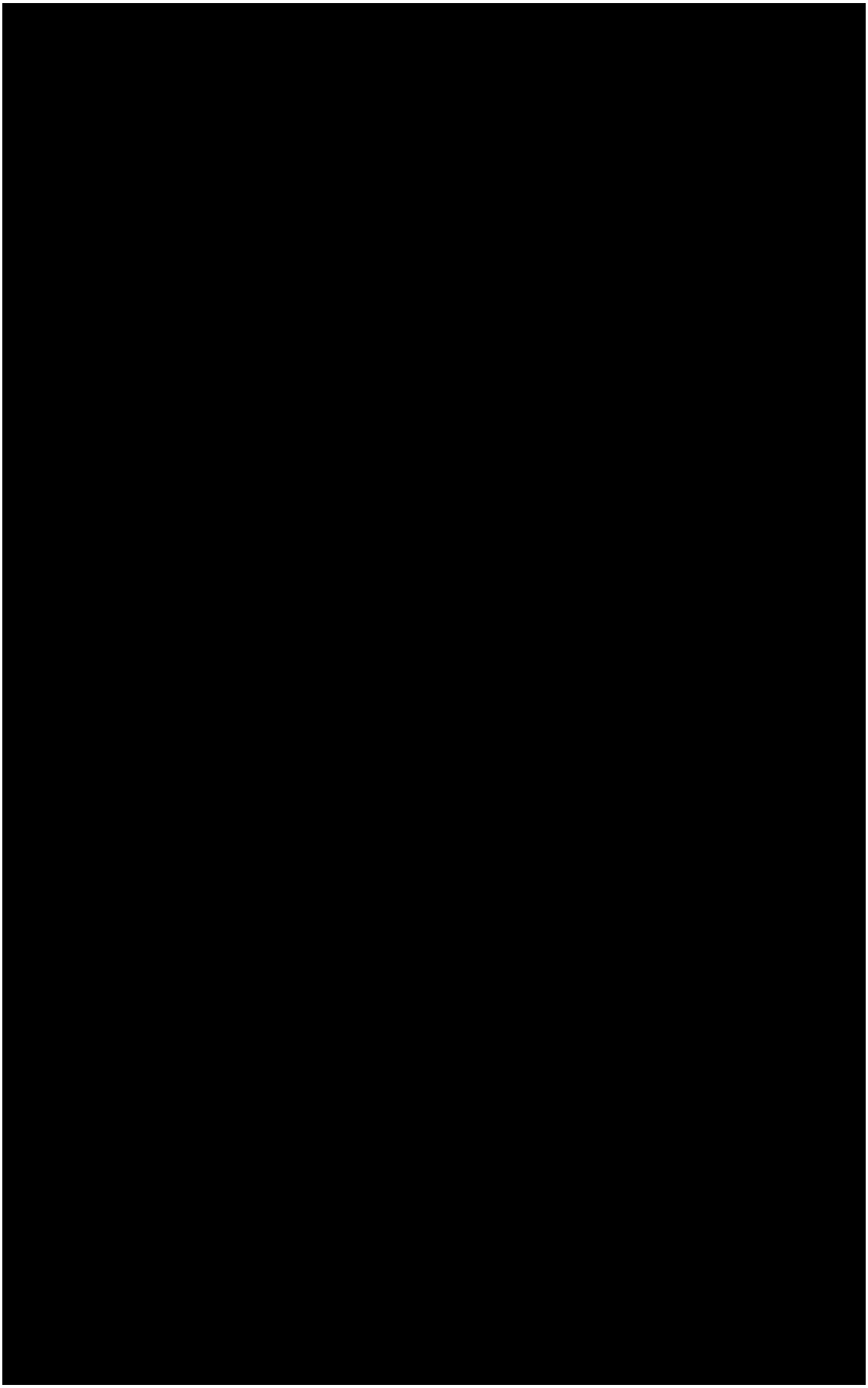

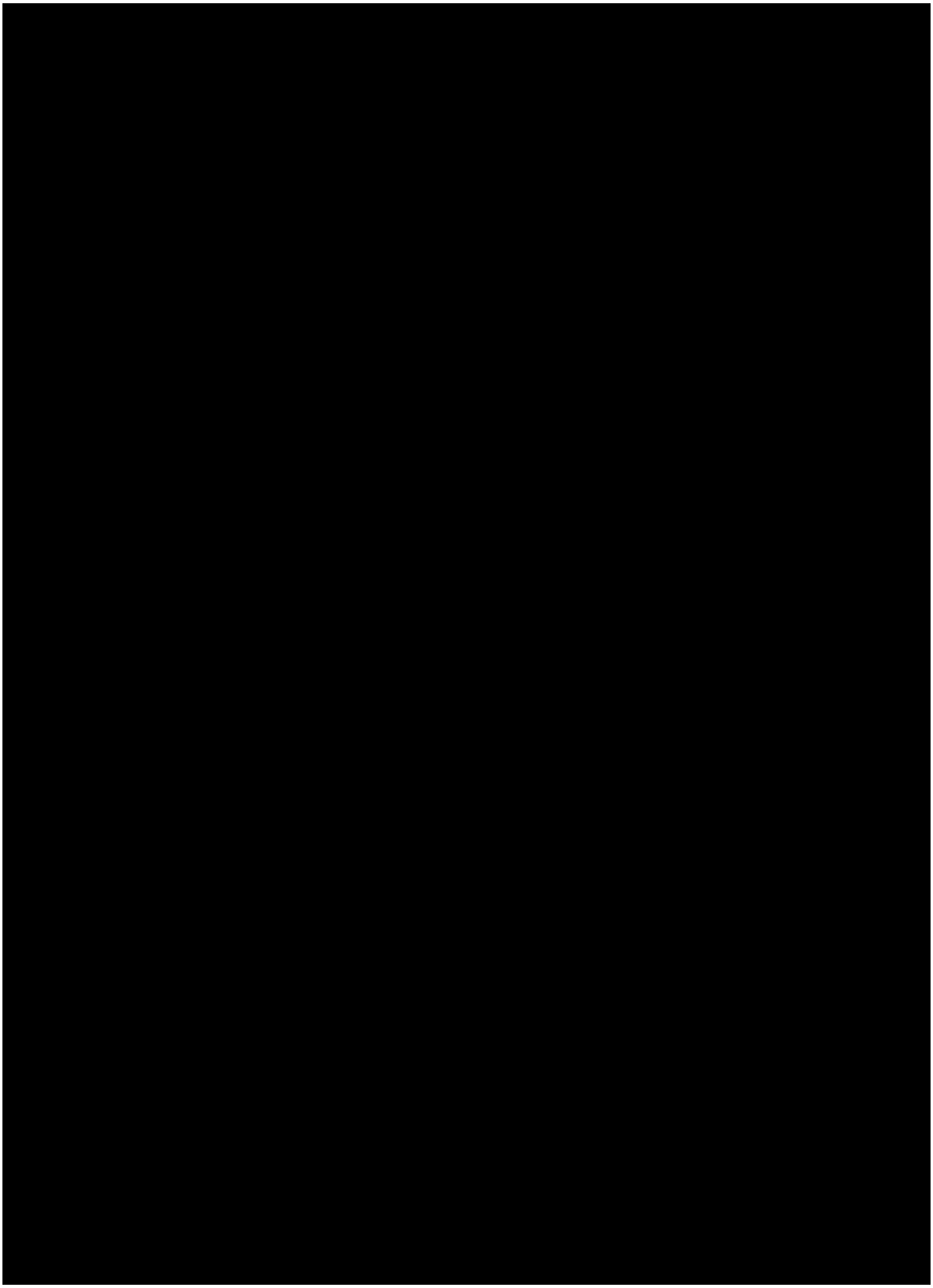

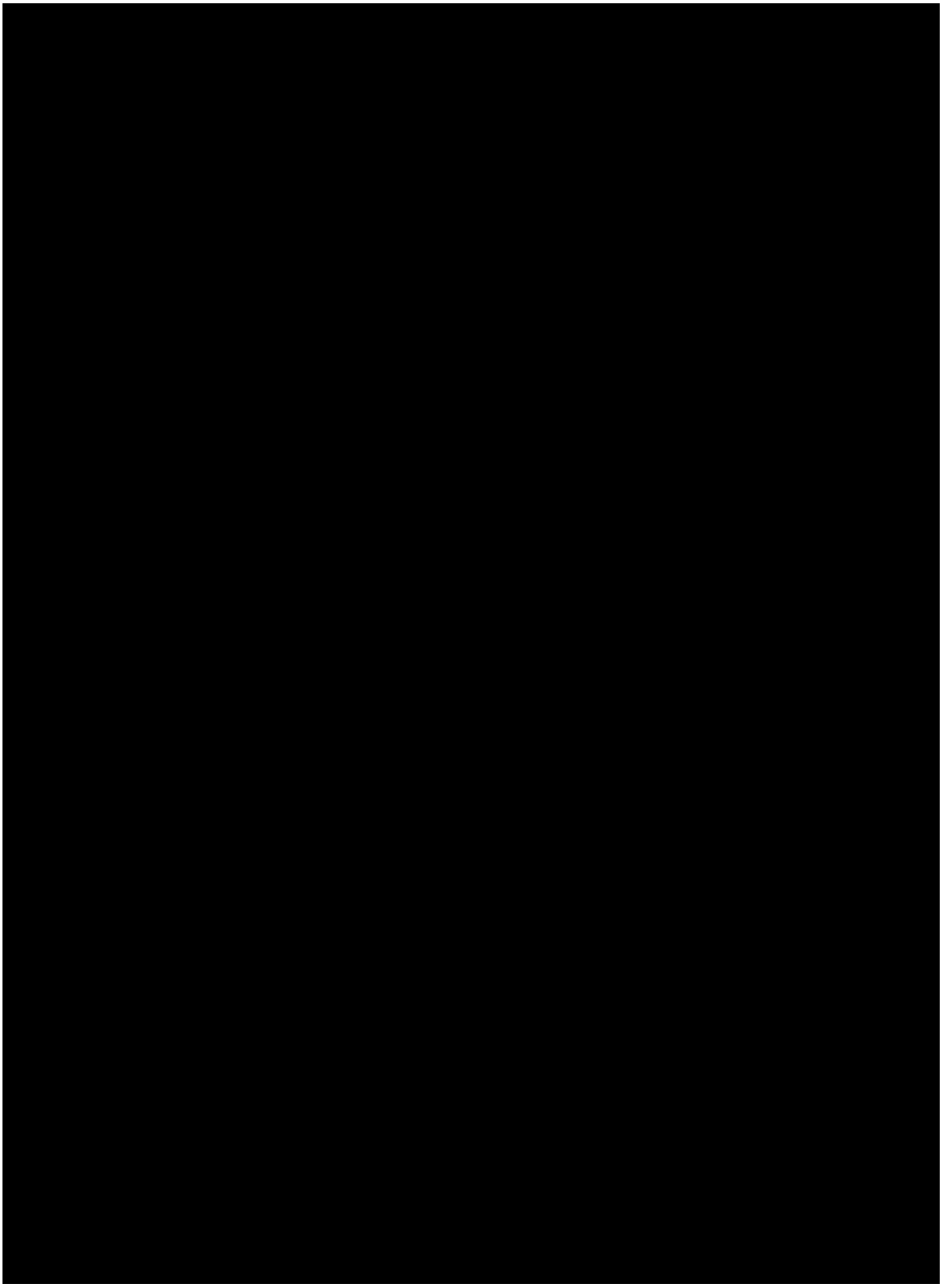

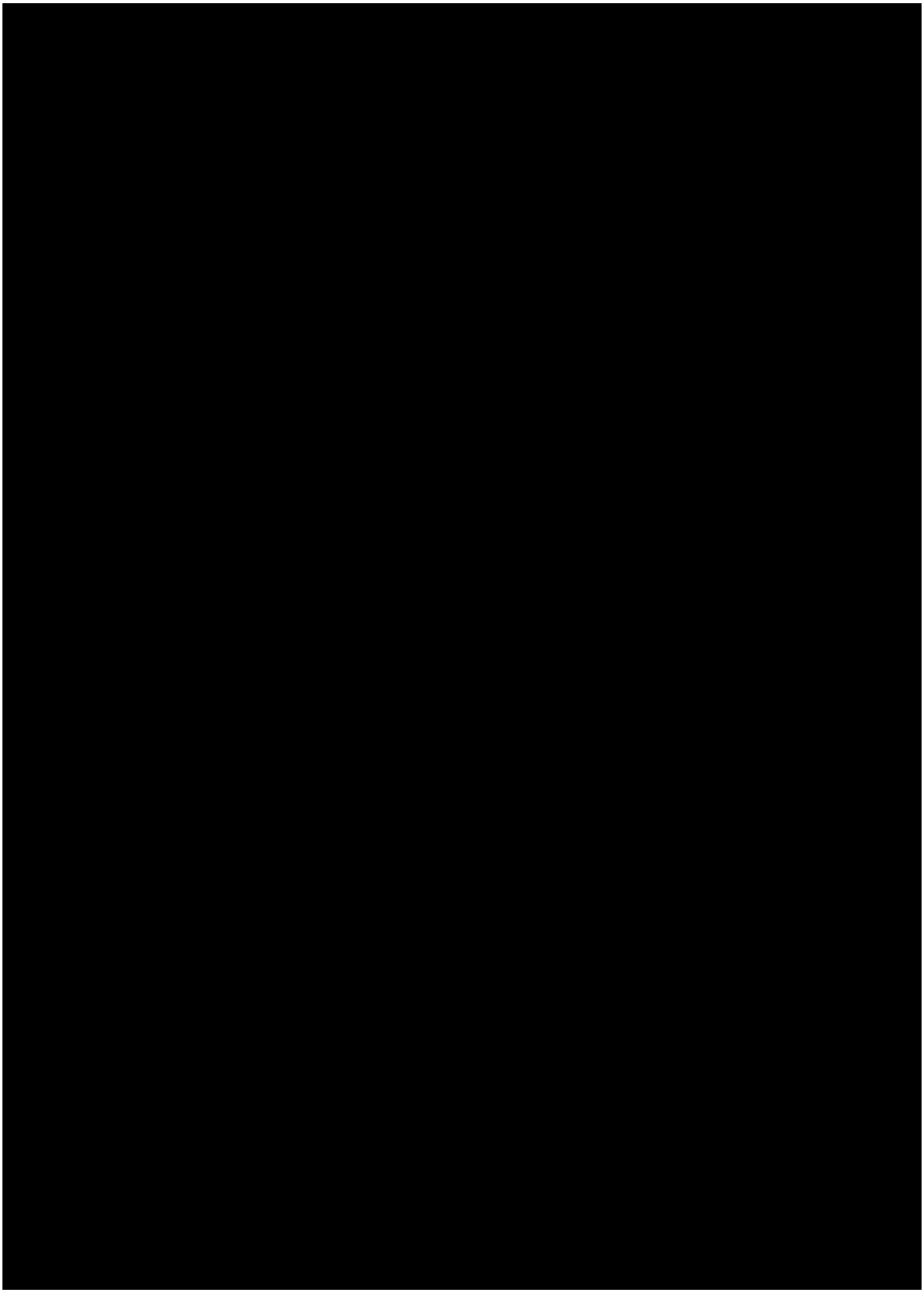

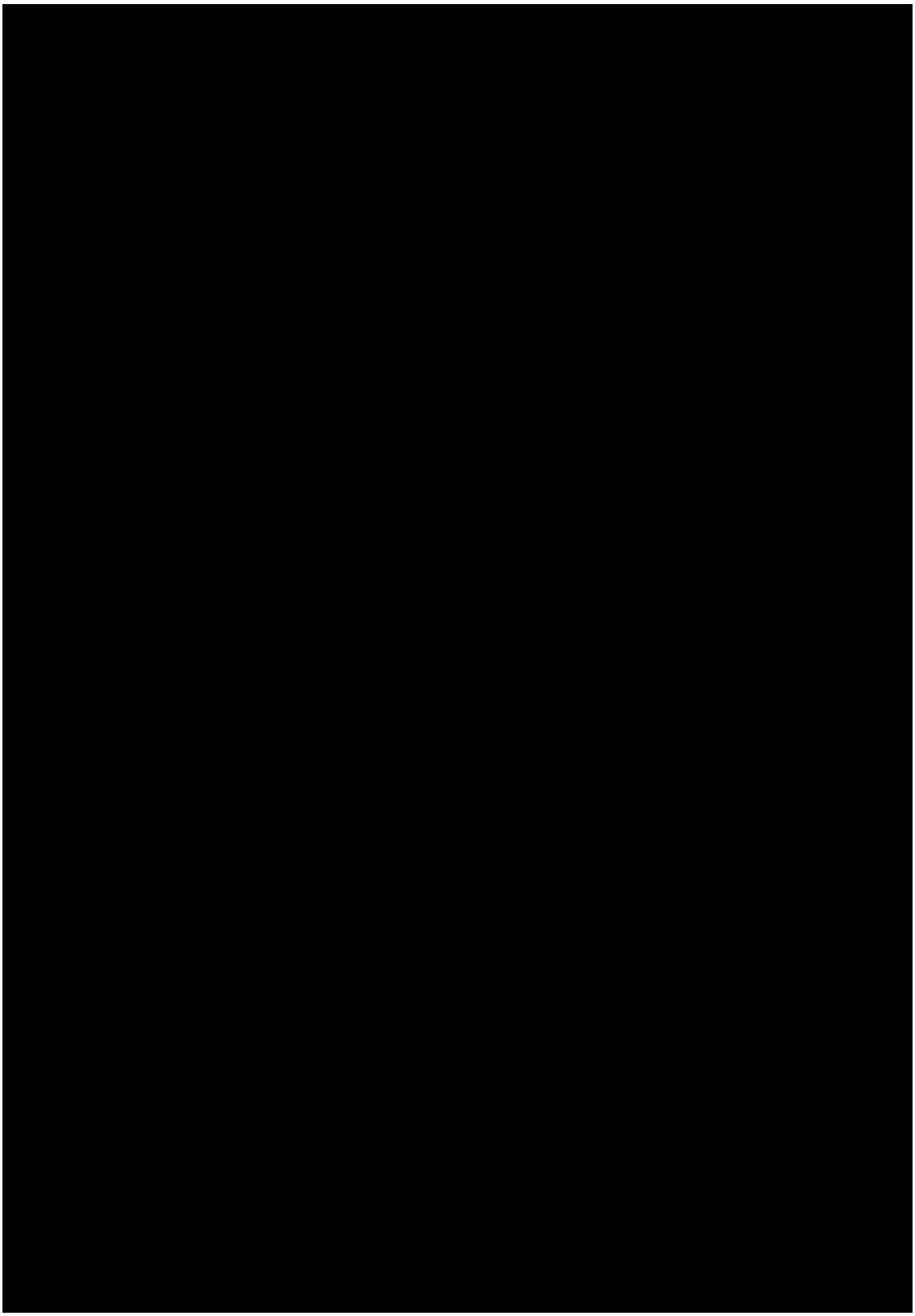

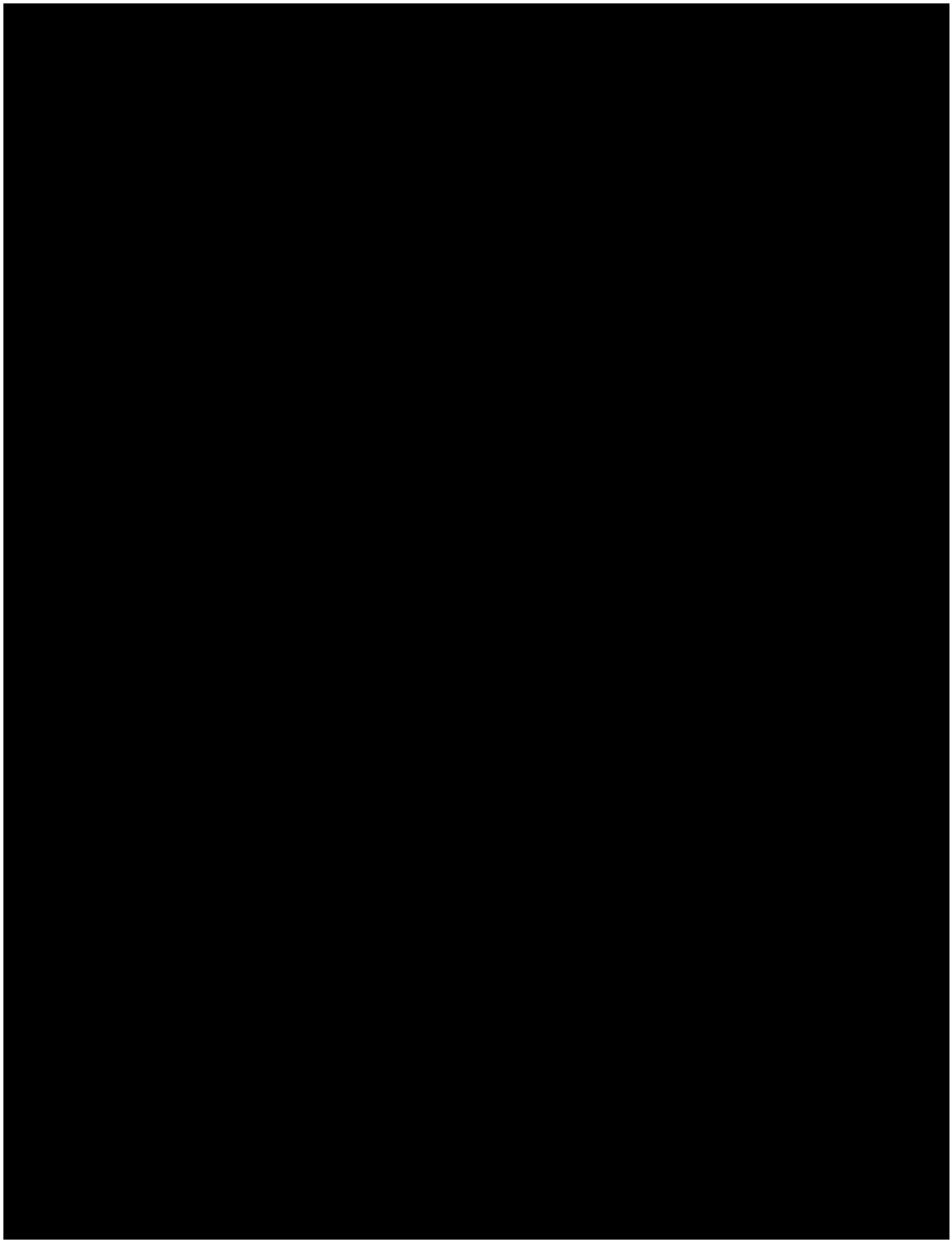

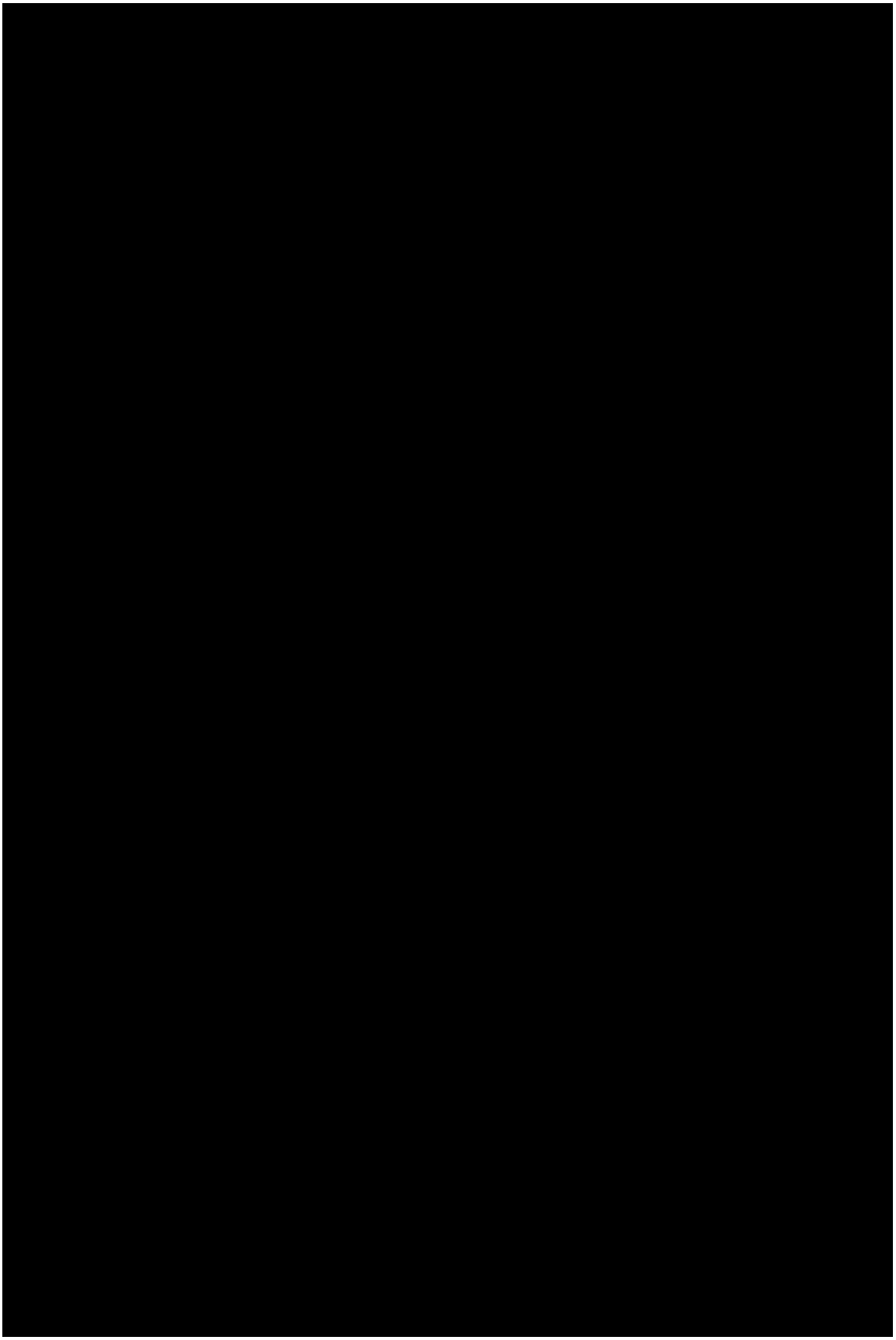

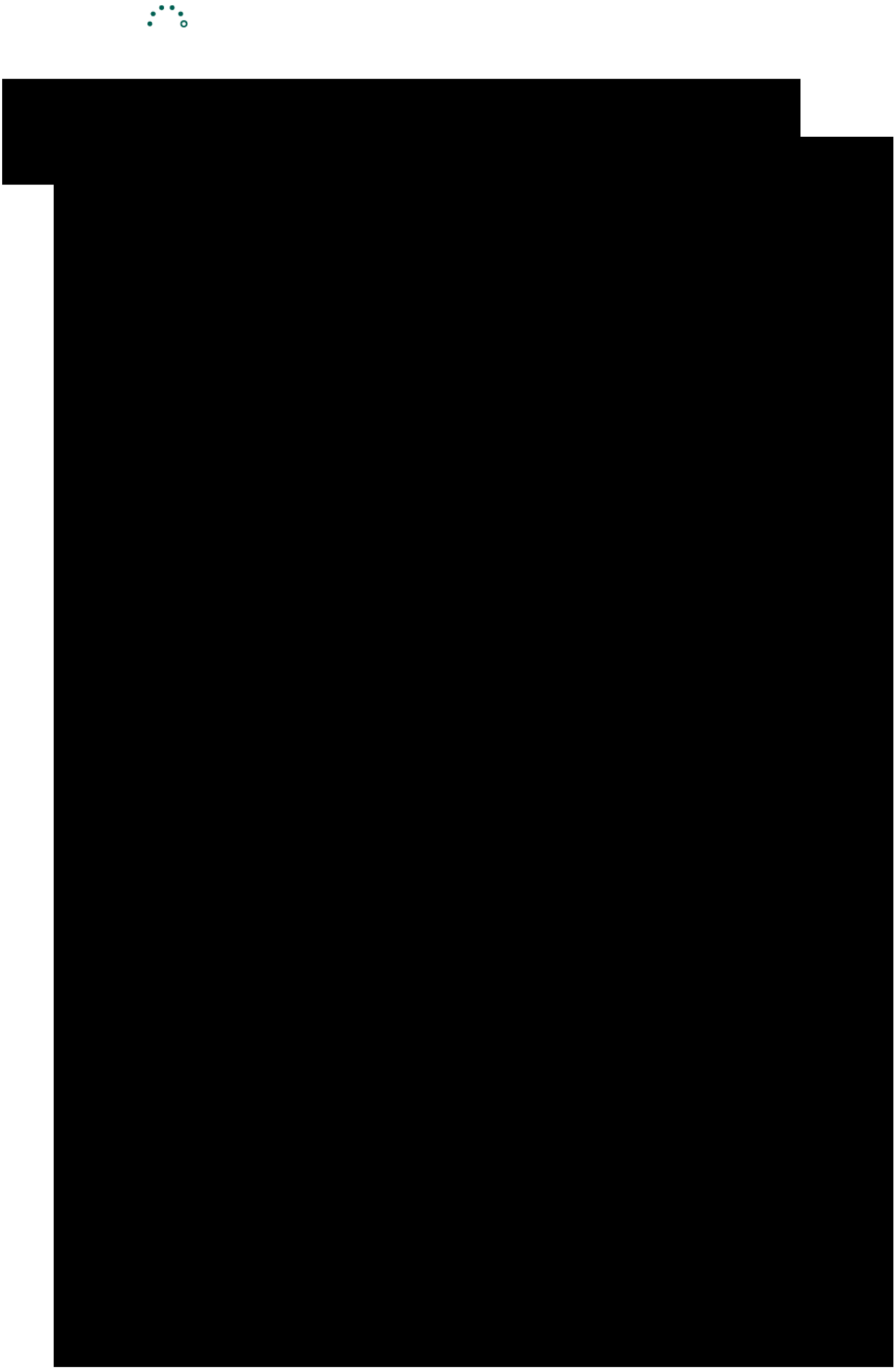

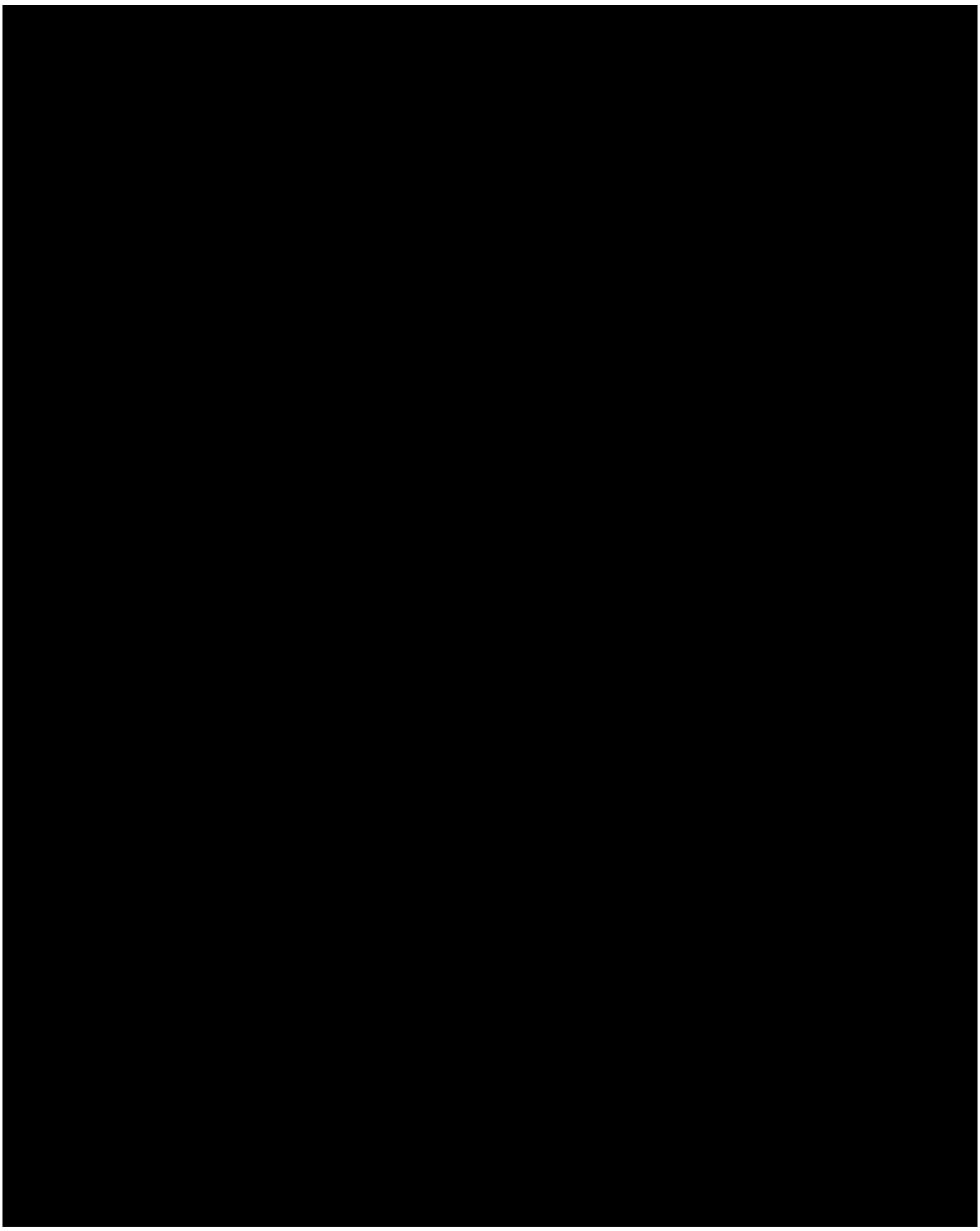

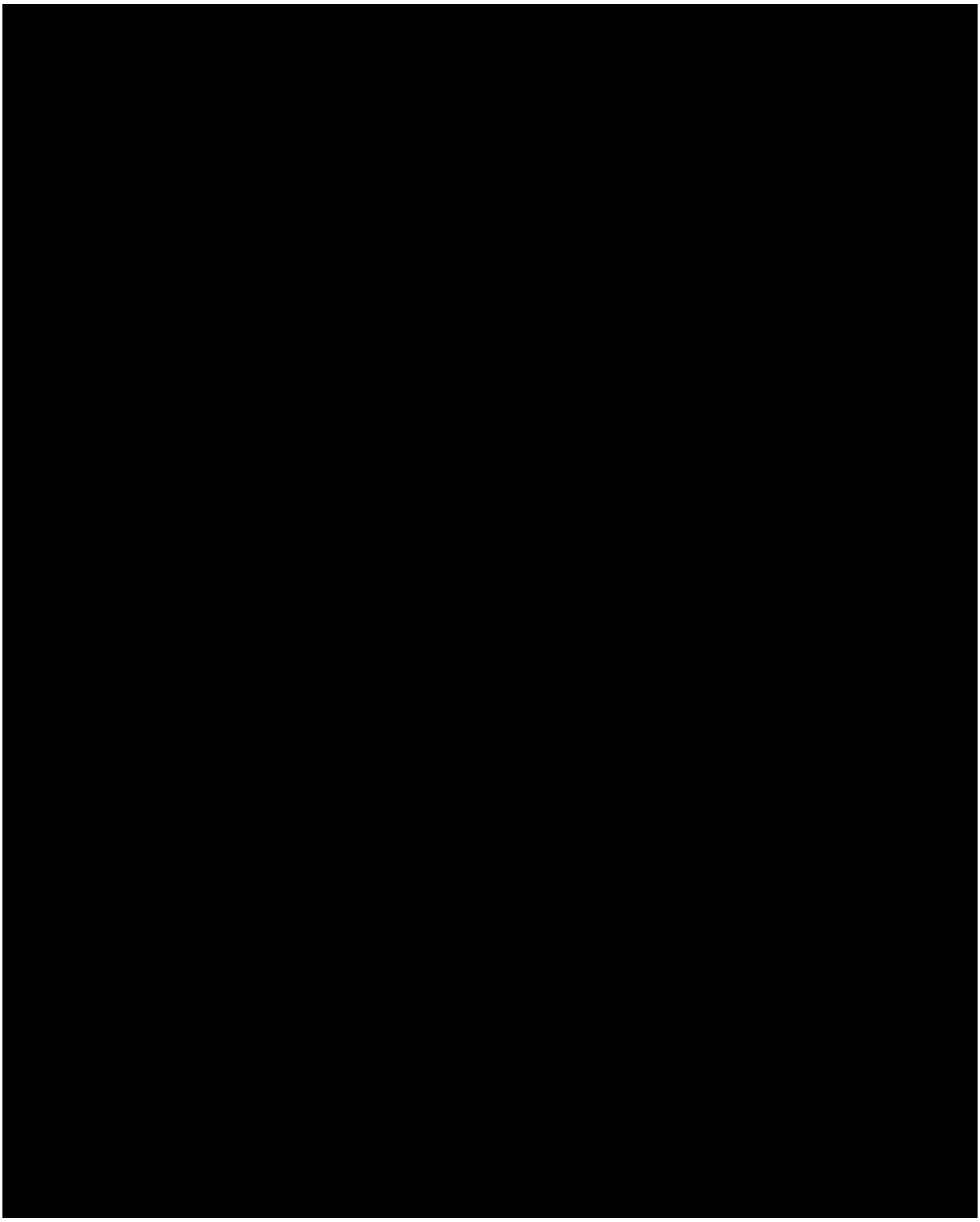

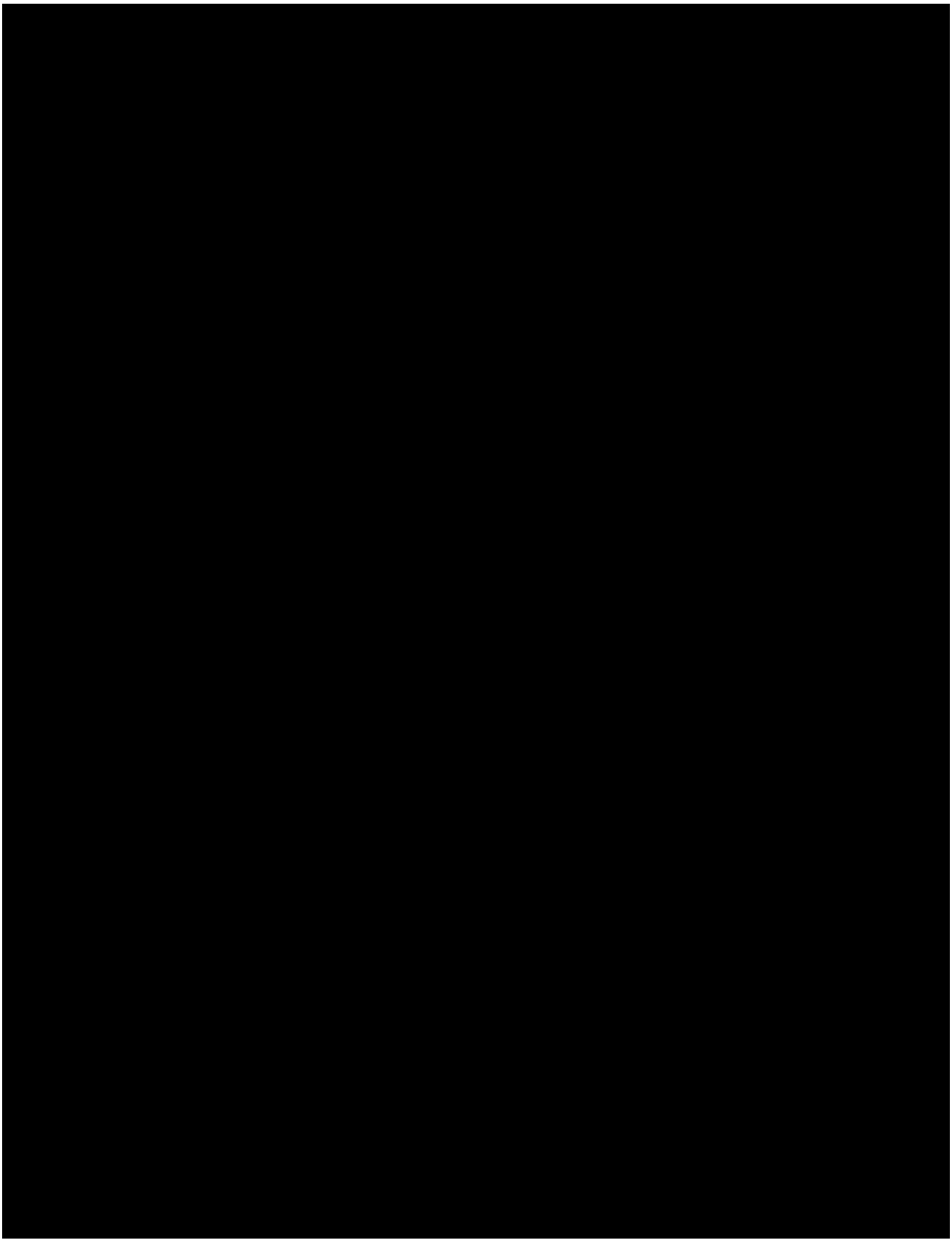

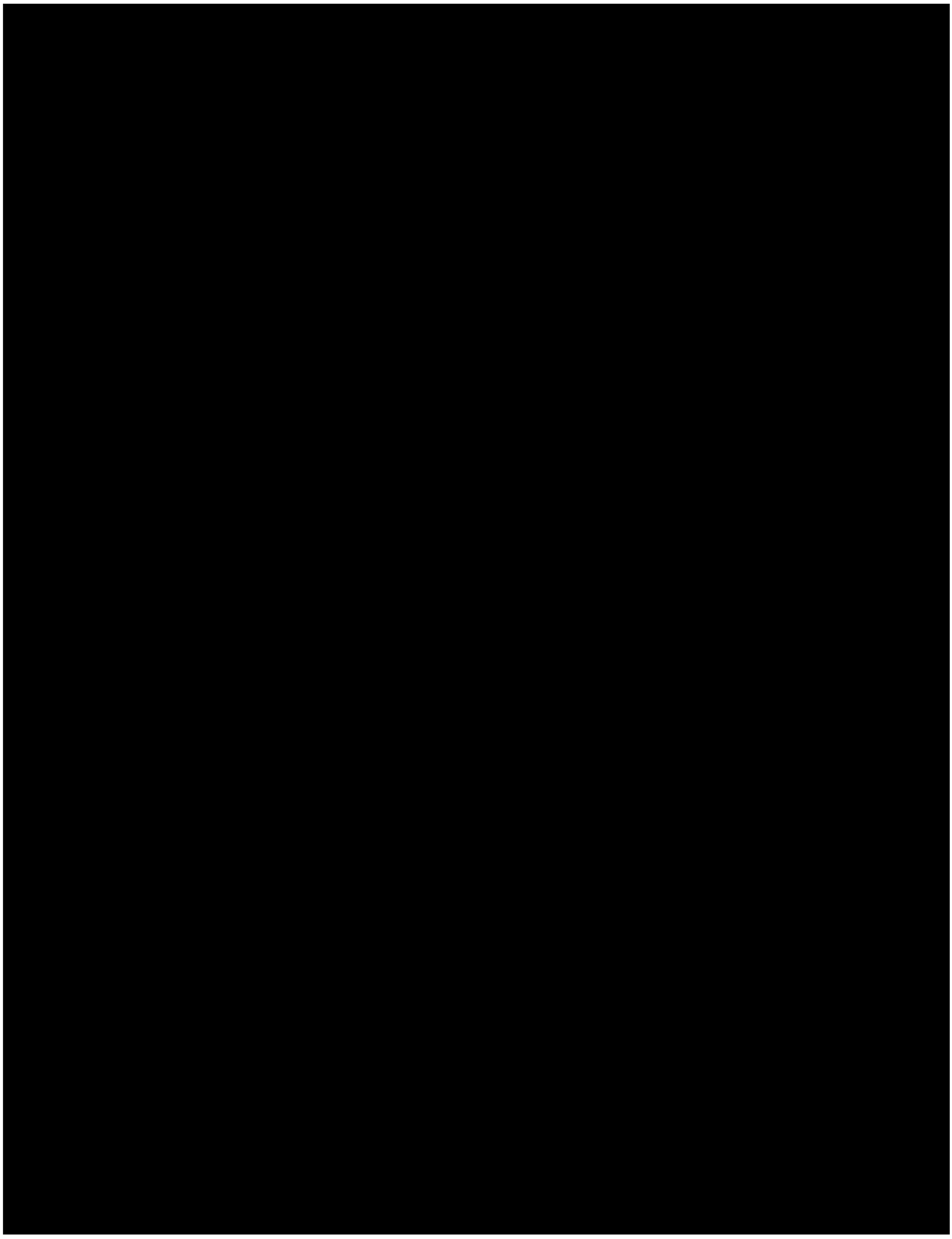

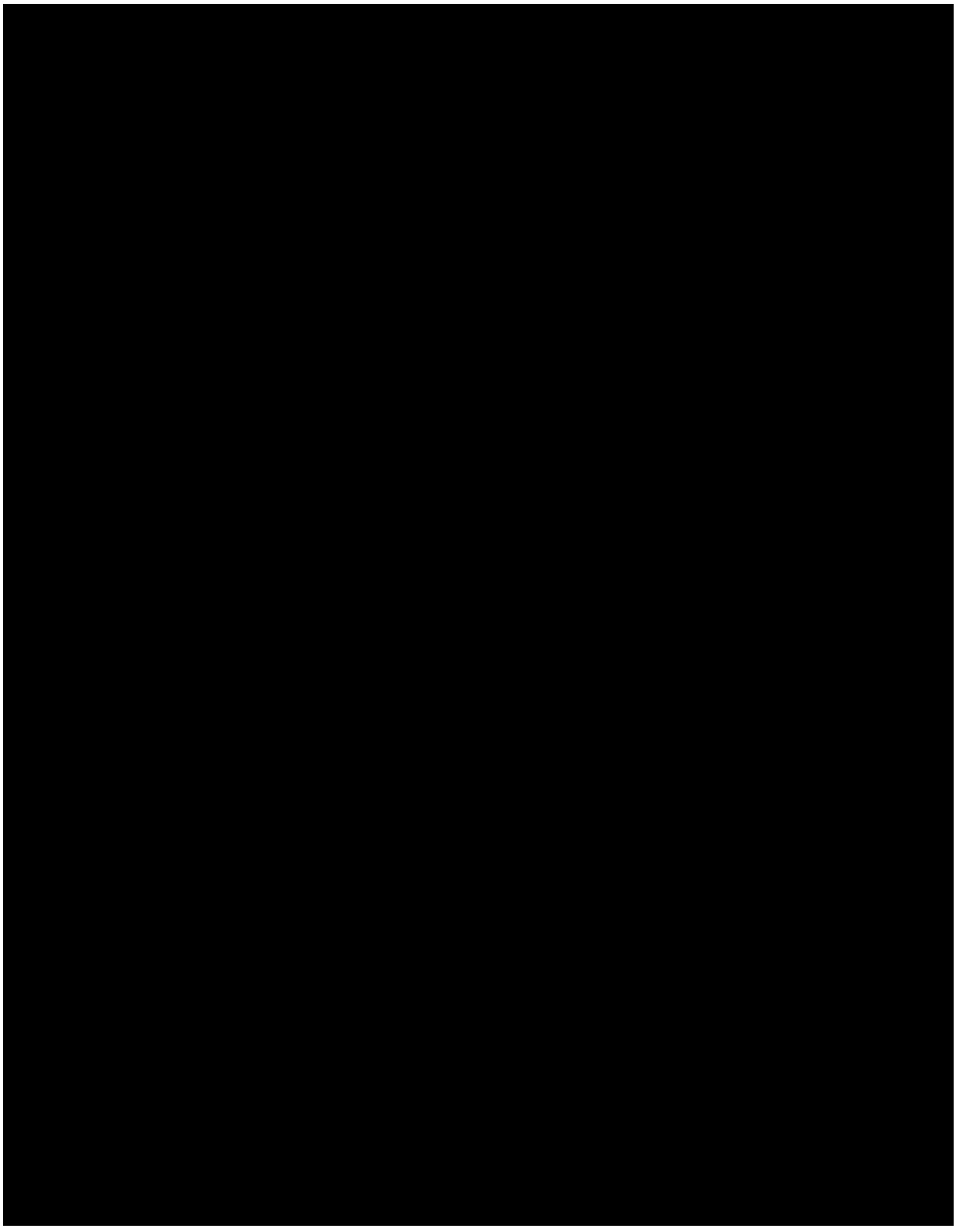

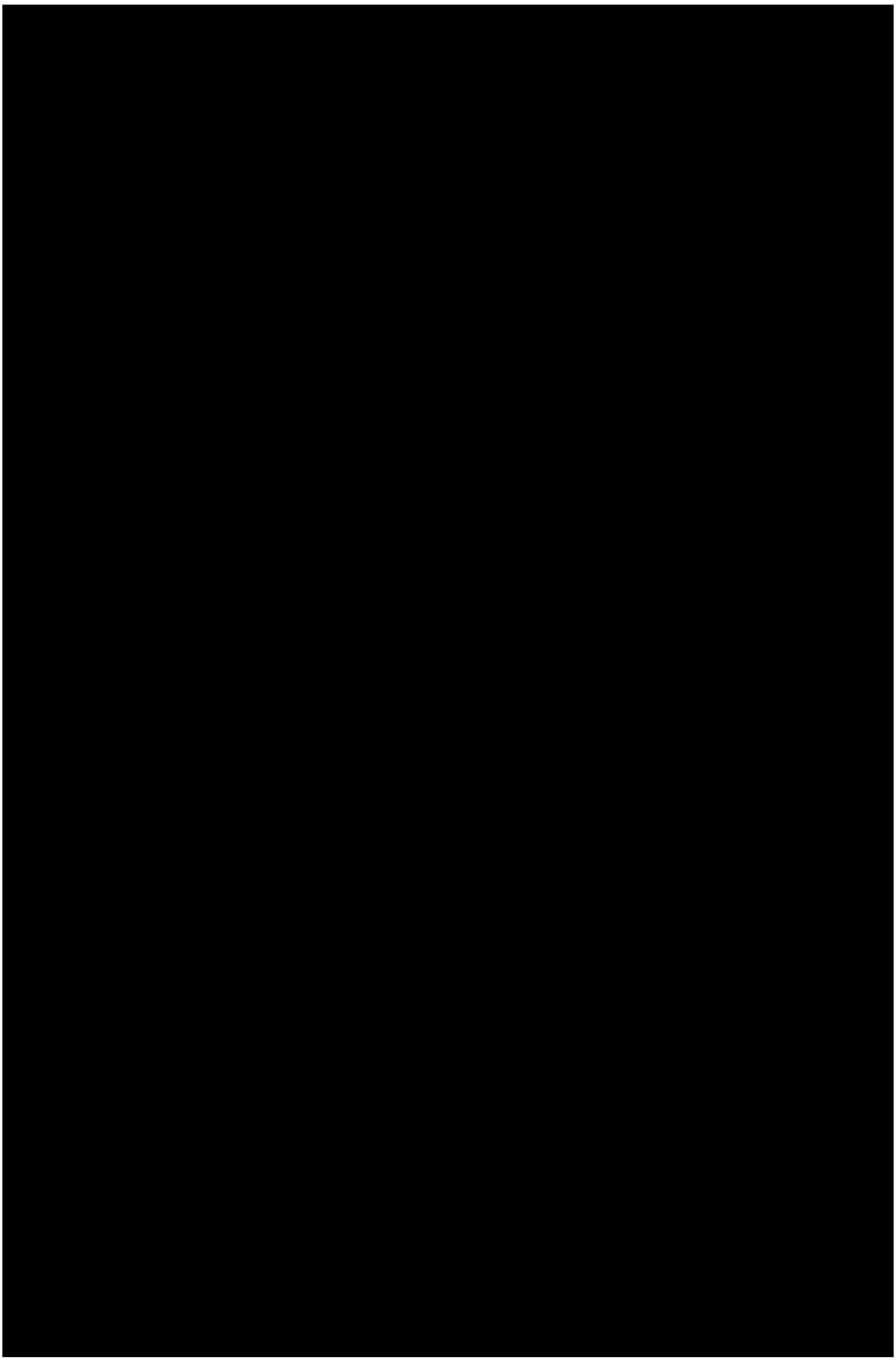

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