CLINICAL STUDY PROTOCOL

A Phase II Open-label Multicenter Study to Assess the Efficacy and Safety of AFM13 in Patients with Relapsed or Refractory CD30-positive Peripheral T-cell Lymphoma or Transformed Mycosis Fungoides (REDIRECT)

Protocol No.: AFM13-202

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Protocol V1.0 dated 20 February 2019
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PROTOCOL APPROVAL SIGNATURES

Sponsor's Approval:
This study will be conducted in compliance with International Council for Harmonization (ICH) guidelines on Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements, including data privacy laws.

This protocol, V6.0 dated 12 July 2021, has been approved by Affimed GmbH.

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Investigator's Declaration and Approval:
I have read this protocol and agree that it contains all the necessary details for carrying out this study. I will conduct the study as described in the current, approved protocol. I verify that I am suitably qualified by education, scientific and medical training and experience to conduct the study. Documentation of my qualifications and professional affiliations are contained in my up-to-date curriculum vitae provided to the Sponsor.

I will provide the supplied copies of the protocol, including future protocol amendments, and all information relating to non-clinical and clinical experience when available (eg, in updated editions of the Investigator's Brochure), to all staff involved in the conduct of this study. I will discuss this material with them to ensure that they are fully conversant with the investigational medicinal product and study design, and that they will handle the data and information generated in the study confidentially.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. I acknowledge that the study will be conducted in accordance with the relevant laws and regulations relating to clinical studies and the protection of subjects, including data privacy laws. I confirm it is my duty and the duty of my study staff to ensure participating subjects are informed comprehensively about the nature of the study and will give their written consent to participate before entry into the study. Subjects will be informed that they may withdraw from the study at any time without jeopardizing their future care. I will use only the subject informed consent form approved by the Sponsor and the Ethics Committee/Institutional Review Board for this study. I will supply the Sponsor with any material written prepared by myself or my study staff eg, summary of study, which is given to the Ethics Committee/Institutional Review Board in support of the application.

Where applicable, the subject information contained in clinic records, reports and manuscripts will be transcribed to the study case report forms. I (or my delegates as described in my Study File) will attest to the authenticity of the data and accuracy and completeness of the transcription by signing the case report forms. I agree to the audit and monitoring procedures to verify study records against original records. Should it be requested by government regulatory agencies, I will make available additional background data from my records and from the hospital or institution where the study was conducted (as permitted by the hospital or institution).

I understand that the case report forms and other data pertinent to this study are the property of Affimed GmbH and are confidential. I agree to only supply Affimed GmbH (or their delegates) with subject study data in such a way that the subject cannot be personally identified.

Investigator: …… ……
Signature Date

Print Name: ……

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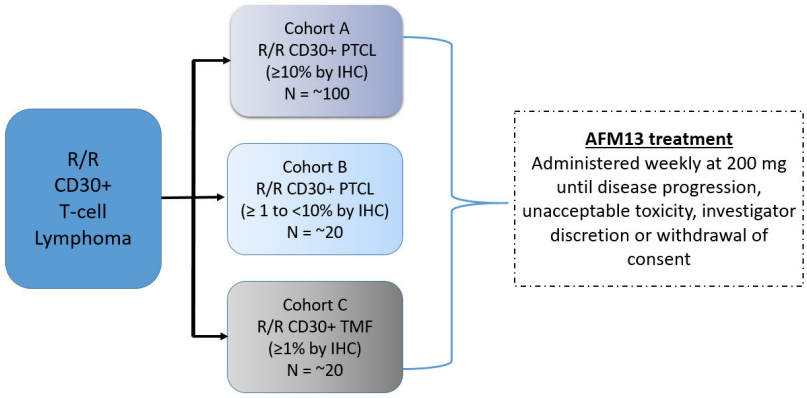
OTHER CONTACT INFORMATION

Full contact details for each Investigational site, the Sponsor, the Medical Monitor(s), and key coordinating and operational personnel will be maintained in the Trial Master File and in each site's Study File throughout the course of the study.

PROTOCOL SYNOPSIS

Study Title	A Phase II Open-label Multicenter Study to Assess the Efficacy and Safety of AFM13 in Patients with Relapsed or Refractory CD30-positive Peripheral T-cell Lymphoma or Transformed Mycosis Fungoides (REDIRECT)
Investigational Product	AFM13
Protocol Number	AFM13-202
EudraCT Number	2019-001003-20
IND Number	107652
Sponsor and Contract Research Organization	Sponsor: Affimed GmbH Contract Research Organization : ICON plc
Study Phase	2
Study Regions	North America, Europe and Asia Pacific.
Number of Subjects	Up to 150 subjects in total: approximately 100 (maximum of 103) subjects in Cohort A (peripheral T-cell lymphoma [PTCL]; defined as CD30-positive ≥10% by centrally assessed Ber-H2 targeted immunohistochemistry [IHC]), 20 subjects (maximum of 25) in Cohort B (PTCL; defined as CD30-positive ≥1% to <10% by centrally assessed Ber-H2 targeted IHC), and approximately 20 (maximum of 22) subjects in Cohort C (transformed mycosis fungoides [TMF]; defined as CD30-positive ≥1% by centrally assessed Ber-H2 targeted IHC).
Study Objectives	**PRIMARY:** • To assess the antitumor activity of AFM13 by Independent Review Committee confirmed positron emission tomography-computed tomography (PET-CT)-based objective response rate (ORR) **SECONDARY:** • To assess the antitumor activity of AFM13 by Independent Review Committee -confirmed complete response (CR) and partial response (PR) rates and CT scan-based ORR • To assess the antitumor activity of AFM13 by Investigator-assessed ORR (defined as ORR-2) • To assess the duration of response (DOR) to AFM13 • To assess the safety and tolerability of AFM13 • To assess the pharmacokinetics (PK) of AFM13

	• To assess the immunogenicity of AFM13 • To assess Quality of Life of subjects while on treatment with AFM13 **EXPLORATORY:** [redacted]
Methodology	This is an open-label, multicenter, Phase 2 study in subjects with relapsed or refractory (R/R) CD30-positive PTCL or TMF to investigate the efficacy and safety of AFM13 dosed weekly at 200 mg until disease progression, unacceptable toxicity, Investigator discretion or withdrawal of consent. A select group of subjects who achieve an objective response (at least PR) and experience persistent infusion-related reactions will have the option to be dosed every other week (Q2W) after Week 16 at the discretion of the Investigator. Subjects who express CD30 (≥10% CD30 expression for PTCL subjects in Cohort A, ≥ 1% to <10% CD30 expression for PTCL subjects in Cohort B, and ≥1% for TMF subjects in Cohort C) by centrally assessed Ber-H2 targeted IHC (Section 5.4.2), and who meet all of the inclusion criteria and none of the exclusion criteria, will be enrolled in this study. After the planned Interim Analyses (IA), Cohorts A and B may be combined to include PTCL subjects with ≥1% CD30 expression. The specific subtypes of PTCL allowed for Cohorts A and B are listed in the Inclusion Criteria. A summary of the study design is provided below.

	
Inclusion and Exclusion Criteria	**INCLUSION CRITERIA:** 1. Written informed consent in accordance with federal, local, and institutional guidelines. 2. Age ≥18 years at time of provision of informed consent. 3. Histologically confirmed CD30-positive (via centrally assessed Ber-H2 targeted IHC; cut-offs listed below) PTCL (allowed subtypes listed below) or TMF per the revised World Health Organization 2016 classification (Swerdlow, 2016). (Note: Subjects must wait for central results before first dose of study drug) The PTCL subtypes allowed for Cohorts A and B: • Enteropathy-associated T-cell lymphoma • Monomorphic epitheliotropic intestinal T-cell lymphoma • Hepatosplenic T-cell lymphoma • Subcutaneous panniculitis-like T-cell lymphoma • Peripheral T-cell lymphoma, not otherwise specified • Angioimmunoblastic T-cell lymphoma • Follicular T-cell lymphoma • Nodal peripheral T-cell lymphoma with T-follicular helper phenotype • Anaplastic large-cell lymphoma, anaplastic lymphoma kinase (ALK)-positive • Anaplastic large-cell lymphoma, ALK-negative • Breast implant–associated anaplastic large-cell lymphoma The required cut-offs for the CD30-positivity are: • Cohort A (PTCL): ≥10% by IHC • Cohort B (PTCL): ≥1% to <10% by IHC • Cohort C (TMF): ≥1% by IHC Note: After the planned Interim Analyses, Cohorts A and B may

	be combined with the CD30-positivity defined as ≥1% by centrally assessed IHC. See Section 5.4.1 for additional details on definition of CD30-positivity. Measurable disease will be defined as below for each cohort: • Cohorts A and B (PTCL cohorts): measurable by the modified Lugano Classification (Cheson, 2014); measurable disease of >1.5 cm diameter by CT, assessed locally for eligibility • Cohort C (TMF cohort): measurable by the Olsen Criteria (Olsen, 2011) including at least 1 cutaneous lymphoma lesion ≥2 cm in diameter, assessed locally for eligibility. 4. Subjects must have relapsed or refractory disease AND the following: • [redacted]

8. Eastern Cooperative Oncology Group performance score of 0 or 1 ([redacted]).

[redacted]

	[redacted] **EXCLUSION CRITERIA:** 1. Subjects with the following subtypes of lymphoma: • T-cell prolymphocytic leukemia • T-cell large granular lymphocytic leukemia • Chronic lymphoproliferative disorder of NK cells • Aggressive NK-cell leukemia • Extranodal NK-/T-cell lymphoma • Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract • Adult T-cell leukemia/lymphoma [redacted]

	[redacted]
Investigational product, dosage and mode of administration	AFM13 will be administered intravenously at a dose of 200 mg. Subjects will be treated weekly until disease progression, unacceptable toxicity, Investigator discretion, or withdrawal of consent.
Criteria for evaluation	**Anti-tumor Activity:** • Cohorts A and B (PTCL): FDG-PET and CT scans • Cohort C (TMF): peripheral blood samples, CT scans (or

	magnetic resonance imaging), skin exam by whole-body photography and modified Severity Weighted Assessment Tool and Composite Assessment of Index Lesions Severity Disease assessment (including all components of the assessment criteria for each cohort) will be conducted at Screening and every 8 weeks for the first 3 assessments (Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4, Day 1), then every 12 weeks thereafter, regardless of any treatment/cycle delays that may occur. Additional assessments will be performed at the time of suspected clinical progression. **Safety:** Includes adverse events (AE) reports (number and severity), physical examinations, 12-lead resting electrocardiograms, which will be performed predose and at the end of each infusion (EOI), and laboratory safety evaluations. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 (or higher). Cytokine levels in blood samples will be tested predose and EOI on Cycle 1 Day 1 and is also recommended if the subject experiences an infusion-related reaction during the first AFM13 infusion. **Pharmacokinetics:** Serum trough levels of AFM13 in all subjects, plus PK profiling [redacted] **Immunogenicity:** Blood samples will be taken [redacted] for assessment of anti-drug antibodies against AFM13. All study assessments will be performed at the time points described in Schedule of Assessments [redacted]
Statistical methods	The study will have three separate cohorts: Cohort A (PTCL) subjects with CD30 positive ≥10% by IHC, Cohort B (PTCL)

	subjects with CD30 positive ≥ 1% to <10% by IHC, and Cohort C (TMF) subjects with CD30 expression ≥1% by IHC. All three cohorts will be analyzed independently as described below. **Analysis Sets:** The full analysis set (FAS) following the intent to treat principle will consist of all subjects who received at least one dose of AFM13. The FAS will be the primary population for all efficacy related endpoints and the primary objective; an additional sensitivity analysis for all subjects who received at least one dose of AFM13 and had at least one post-baseline efficacy assessment will be conducted to support the results of the primary analysis. The safety set will consist of all subjects who received at least one dose of AFM13 and had at least one post-baseline safety assessment, where the statement that a subject had no AE on the AE Case Report Form constitutes a safety assessment. The safety set will be the primary population for all safety related endpoints. Additional analysis sets for sensitivity analyses may be introduced in the statistical analysis plan due to the coronavirus disease-2019 pandemic. **Missing Data/Discontinuation:** As this is a non-randomized study design, no missing imputation of missing values will be done for any analysis except for partial/missing AE dates and concomitant medication dates. Reasons for discontinuation of the study and the study drug will be listed and summarized. **Efficacy Analyses:** ORR (CR+PR) N will be summarized using descriptive statistics and 95% confidence limits. In addition, CR and PR will be presented separately. [redacted] **Safety Analyses:** AEs, related AEs, serious AEs (SAEs) and related SAEs, AEs with NCI CTCAE Grades ≥3, related AEs of NCI CTCAE Grades ≥3, AEs leading to premature discontinuation, interruptions or discontinuation of study drug or dose modification will be analyzed

	descriptively utilizing corresponding Medical Dictionary for Regulatory Activities System Organ Classes and Preferred Terms. Safety laboratory results will be graded by NCI CTCAE v5.0 (or higher). If no grading exists, then values will be classified into low/normal/high based on laboratory normal ranges. Each parameter will be presented by descriptive statistics at each visit including change from baseline (Screening). Shift tables for CTCAE grades and reference ranges will be presented. All laboratory values will be listed. A separate listing for abnormal lab values (≥Grade 3, and low/high values) will be presented. Vital signs will be summarized by descriptive statistics at each visit including change from baseline will be presented and a listing will be provided. **Interim Analysis:** An interim analysis will be performed for Cohorts A and B independently, with all subjects enrolled at or prior to the cut-off date defined as the completion of the 20th subject for each cohort. [redacted] **Sample Size:** [redacted]

	[redacted]

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LIST OF ABBREVIATIONS

ADA	anti-drug antibodies
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
AUC	area under the concentration versus time curve
$AUC_{0-\infty}$	AUC from time zero to infinity
AUC_{0-t}	AUC from time zero to time t
BSA	body surface area
BV	brentuximab vedotin; brentuximab; Adcetris®
CAILS	Composite Assessment of Index Lesions Severity
CD	cluster of differentiation
CHOP	cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CR	complete response/remission
CRA	Clinical Research Associate
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTCL	cutaneous T-cell lymphoma
DLT	dose limiting toxicity
DOR	duration of response
EC	Ethics Committee(s)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOI	end of infusion
EPOCH	etoposide phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide, and doxorubicin hydrochloride (hydroxydaunorubicin)
EQ-5D	European Quality of Life 5-Dimensional
FAS	full analysis set
FDA	(US) Food and Drug Administration
FDG	fluorodeoxyglucose
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GvHD	graft versus host disease
H1/H2	histamine 1/histamine 2
HCT	hematopoietic stem cell transplantation
HIV	Human Immunodeficiency Virus
HL	Hodgkin lymphoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IND	Investigational New Drug

IPI	International Prognostic Index
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MF	mycosis fungoides
MRI	magnetic resonance imaging
mSWAT	modified Severity Weighted Assessment Tool
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
NK	natural killer
NYHA	New York Heart Association
ORR	objective (or overall) response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PS	performance score
PT	preferred term
PTCL	peripheral T-cell lymphoma
QxW	every x weeks
QOL	quality of life
R/R	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCD30	soluble CD30
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TEAE	treatment emergent adverse event
TMF	transformed mycosis fungoides
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States (of America)
V_{ss}	volume of distribution at steady state
WHO	World Health Organization

1 INTRODUCTION

1.1 Targeting Unique Cell Surface Proteins in Lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoproliferative malignancies with multiple histological subtypes. It is estimated that approximately 65,540 new cases of NHL were diagnosed in 2010 and 20,210 patients died of their disease (Jemal, 2010). Based on the World Health Organization (WHO) classification of hematological and lymphoid tumors, NHL can be broadly classified as B or T/natural killer (NK)-cell neoplasms (Campo, 2011). In the United States of America (US), about 85% of cases are categorized as B-cell lymphomas and 15% are categorized as T/NK-cell lymphomas (Jemal, 2010).

The expression of unique proteins on the cell surface allows for the identification and differential diagnosis of lymphoid malignancies. Several cell markers have been exploited as treatable targets by immunotherapeutics, such as rituximab, a genetically-engineered chimeric immunoglobulin G1 monoclonal antibody that targets cluster of differentiation (CD)20, and brentuximab vedotin ([BV] Adcetris®), an antibody drug conjugate targeting CD30. CD30, a member of the tumor necrosis factor (TNF)-receptor superfamily, has pleiotropic biologic functions, and antibodies targeting CD30 and other TNF family receptors can exhibit both agonistic and antagonistic signaling functions. CD30 was identified in the early 1980s as a protein recognized by monoclonal antibody Ki-1 (Schwab, 1982) and abundantly and selectively expressed on the surface of Hodgkin and Reed-Sternberg cells. Later, its expression in other neoplastic cells such as anaplastic large cell lymphoma (ALCL), and other lymphoid malignancies as well as on several non-lymphoid malignancies including selected germ cell tumors was demonstrated. Expression of CD30 on normal cells is highly restricted, thereby allowing differential targeting of malignant cells. Brentuximab vedotin has shown striking efficacy in Phase 1, 2, and 3 trials, with manageable toxicity, and is approved for the treatment of classical Hodgkin lymphoma (HL), systemic ALCL and in primary cutaneous ALCL or CD30-expressing mycosis fungoides (MF). These results provide clinical validation for therapeutic targeting of CD30 in the setting of HL, ALCL, and cutaneous T-cell lymphoma (CTCL).

1.2 CD30-positive Lymphoid Malignancies

In hematologic malignancies, CD30 expression is strongly increased in HL and ALCL, but has also been noted in other lymphoid malignancies, such as diffuse large B-cell lymphoma , including primary mediastinal (thymic) large B-cell lymphoma , peripheral T-cell lymphoma (PTCL), lymphomatoid papulosis, MF, and Epstein-Barr virus -driven clonal lymphoproliferative disease enteropathy-associated T-cell lymphoma type I, human T-cell lymphotropic virus type 1-associated adult T-cell leukemia/lymphoma, and primary effusion lymphoma harboring human herpes virus-8 (Bhatt, 2013; Sibon, 2016; Hu, 2013; Lunning, 2012; de Leval, 2010). Additionally, primary CTCL represents a heterogeneous group of neoplasms derived from skin-homing T-cells that also regularly expresses CD30.

1.2.1 Peripheral T-cell Lymphoma

Peripheral T-cell lymphomas are a heterogeneous group of aggressive lymphomas that make up ~15% of all NHLs in adults. Some of the many known subtypes include PTCL, not otherwise specified, ALCL, and angioimmunoblastic T-cell lymphoma.

While the identified subtype of the PTCL can lead to different survival rates and initial treatment options, in general without treatment the survival of PTCL patients is measured in months. With combination chemotherapy (eg, cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin®), and prednisone [CHOP] or etoposide phosphate, prednisone, vincristine sulfate (Oncovin), cyclophosphamide, and doxorubicin hydrochloride (hydroxydaunorubicin) [EPOCH]), 5-year overall survival (OS) rates range from 49 to 74% for those patients with low to intermediate scores (scores 0 to 2) on the International Prognostic Index (IPI); however, such low-intermediate risk patients are not common and the 5-year OS after combination chemotherapy for the more common patients with the IPI scores of 3 or 4 to 5 are 21 and 6%, respectively (Sonnen, 2005).

The poor outcomes with chemotherapy have led to more aggressive approaches such as autologous hematopoietic stem cell transplantation (HCT) or radiation therapy as consolidation. The use of autologous HCT may depend on the subtype of PTCL and the IPI score.

In general, most if not all patients undergoing treatment for PTCL will not achieve remission or will relapse with very poor long-term survival, especially in absence of HCT, with estimates as low as a median progression-free survival (PFS) and OS of 3 and 6 months, respectively (Mak, 2013; Biasoli, 2015; Bellei, 2018).

No optimal therapy is defined for relapsed or refractory (R/R) PTCL with the exception of BV for the ALCL subtype and there is sparsity of data regarding long term outcomes for these patients. For those patients who are potential candidates for autologous or allogeneic HCT, achieving an objective response as a bridge to transplant is vitally important (Laribi, 2018; Corradini, 2004; Le Gouill, 2008; Jacobsen, 2011; Goldberg, 2012).

1.2.2 Transformed Mycosis Fungoides

Mycosis fungoides is the most common subtype of primary CTCL and is a mature T-cell lymphoma with cutaneous presentation but with potential systemic involvement.

Advanced stage is considered to be a persistent disease with multiple relapses. Due to the chronic nature of the condition, the choice of therapy depends on the goals of therapy, including long-term disease control, symptom relief to increase quality of life and addressing more clinically aggressive disease.

Once the disease is widespread, systemic therapies are needed as skin-directed therapies are insufficient for treatment (Whittaker, 2003; Trautinger, 2006; Willemze and Dreyling, 2010; NCCN Clinical Practice Guidelines in Oncology V2.2021; Sugaya, 2013; Olsen, 2011). Such systemic approaches include single agent or combination therapies; with agents considered to be

immune-preserving (eg, retinoids, low dose methotrexate) or immunostimulatory (eg, interferon) being utilized first (Jawed, 2014a; Jawed, 2014b). Other systemic therapies include phototherapy, histone deacetylase inhibitors, BV, and alemtuzumab.

Large cell transformation, which is the histopathological transformation of neoplastic lymphocytes to a clonally identical large cell phenotype (Wolfe, 1995, Wood, 1993), occurs in 20 to 50% of patients with advanced MF. Such transformation is often associated with poor prognosis and is associated with mean 5-year OS of less than 20% (Salhany, 1988). CD30 expression is also associated with a reduced survival and often seen in diseases with large cell transformation leading to a more aggressive clinical course (Benner, 2012).

Currently the only known curative therapy for patients with transformed mycosis fungoides (TMF) is allogeneic HCT and the patients are in dire need for other therapeutic options.

1.3 AFM13

Please refer to the Investigator's Brochure (IB) for additional details of non-clinical and clinical studies conducted with AFM13.

1.3.1 Pharmaceutical and Therapeutic Background

The investigational medicinal product AFM13 is a tetravalent bispecific chimeric (anti-human CD30 x anti-human CD16A) recombinant antibody construct that is being developed for the indication of HL (Reusch, 2014) and other CD30-postive T-cell malignancies.

[redacted]

[redacted]

[redacted]

1.3.2 Nonclinical Studies

Due to the lack of an appropriate animal model of HL, most primary and secondary pharmacodynamic data of AFM13 have been generated *in vitro*.

The pharmacokinetic (PK) behavior of AFM13 has been investigated in stand-alone studies in mice, and in cynomolgus monkeys as the only relevant species. Furthermore, toxicokinetic data were generated in cynomolgus monkeys in parallel with the toxicological assessment of AFM13.

1.3.2.1 Characterization of Affinity and Specificity

[redacted]

1.3.2.2 Primary Pharmacodynamics Activity

[redacted]

1.3.2.3 Secondary Pharmacodynamics Activity

[redacted]

[redacted]

[redacted]

1.3.2.4 Safety Pharmacology

[redacted]

1.3.2.5 Tissue Cross Reactivity

[redacted]

1.3.3 AFM13 Clinical Experience

A first-in-human Phase 1 study with AFM13 was conducted and completed in patients with R/R HL (AFM13-101). Currently, there are three ongoing clinical studies with AFM13 in patients with CD30-positive lymphoid malignancies, namely, AFM13-102 (R/R T-cell lymphoma), AFM13-103 (R/R HL), and AFM13-201 (R/R HL). Data from the clinical studies AFM13-101 and AFM13-103 which informed this study design are provided below.

1.3.3.1 Phase 1 First-in-Human Clinical Trial in Relapsed/Refractory Hodgkin Lymphoma

The clinical first-in-human study, AFM13-101, was conducted in patients with heavily pre-treated R/R HL (Rothe, 2015). Escalating doses of AFM13 were administered to determine the safety and tolerability of AFM13. Twenty-eight patients (16 males, 12 females) were enrolled and received treatment with AFM13 in 8 dose cohorts. Twenty-four patients received increasing doses of AFM13 ranging from 0.01 to 7.0 mg/kg on a weekly dosing schedule for 4 weeks. In addition, 4 patients were treated with 4.5 mg/kg twice weekly for 4 weeks.

The median age was 38.5 years (range 19 to 72 years). Fourteen of the 28 patients (50%) had refractory disease and the remainder had relapsed disease; all were CD30-positive. Patients had received a median of 6 (range 3 to 11) previous lines of therapy for HL. Twenty-four patients

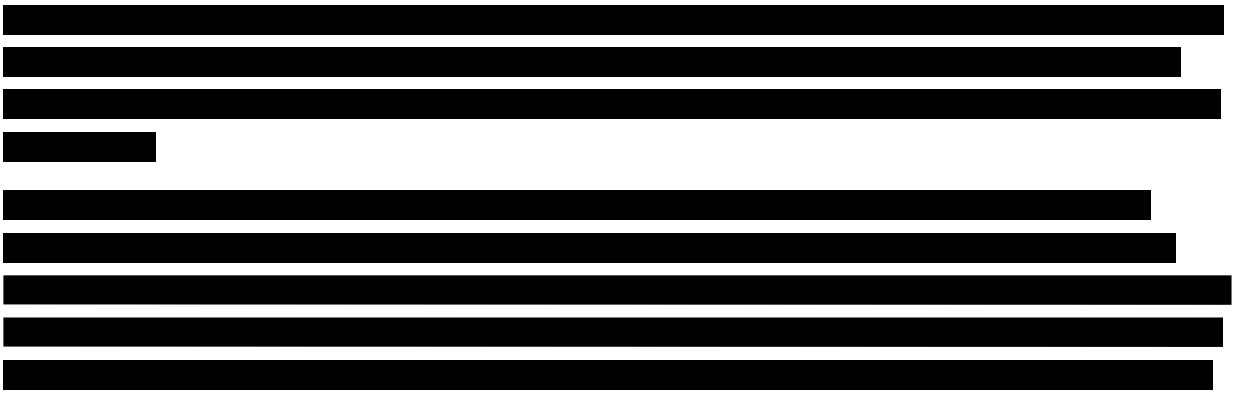
(85.7%) had previously received radiotherapy and 22 patients (78.6%) had previously undergone stem cell transplantation. Nine patients had previously received BV.

All 28 patients were included in the Safety population, 2 patients had to be excluded from the Efficacy population: 1 patient withdrew the informed consent; 1 patient discontinued due to adverse events (AEs) of pneumonia and multi-organ failure. Twenty-three of the 28 patients experienced at least one AE which was evaluated as treatment-related by the Investigator. Most AEs were mild or moderate; only 18 of 196 (9.2%) of documented AEs were National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3. One dose limiting toxicity (DLT) was documented; Grade 4 hemolytic anemia considered possibly related to AFM13. The patient subsequently died due to aspergillus pneumonia and multi-organ failure which was assessed as not/unlikely to be related to study drug. The most frequent AEs were symptoms associated with infusion-related reactions including pyrexia, chills, headache and nausea. Treatment-associated infections were rare; nasopharyngitis and pneumonia was documented in 5 and 4 patients, respectively.

After review of the safety data, the Independent Data Monitoring Committee concluded that the maximum feasible dose of 7 mg/kg following a weekly dose schedule was reached without toxicity concerns or reaching the maximum tolerated dose. Additionally, the 4 patients treated with 4.5 mg/kg twice weekly completed the treatment without toxicity concerns of the Independent Data Monitoring Committee. Apart from the DLT event, administration of AFM13 was not associated with clinically significant changes in any laboratory parameters, nor was it associated with clinically significant changes in any vital signs or electrocardiogram (ECG) parameters.

Twenty-six of 28 patients were eligible for efficacy evaluation. No patients had a complete response (CR) and 3 of 26 patients had a partial response (PR) at the final study visit. The objective response rate (ORR) (CR + PR) was 11.5%. At the end of study assessment 13 patients (50%) had stable disease and 10 patients (38.5%) had disease progression.

Overall, the effect of AFM13 treatment was more pronounced in patient cohorts with AFM13 doses ≥1.5 mg/kg with an ORR of 23% (3/13).



[redacted]

This study concluded that AFM13 is safe and well tolerated at weekly doses of up to 7 mg/kg, and 4.5 mg/kg dosed twice a week.

1.3.3.2 Phase 1b/2a Clinical Trial in CD30-positive Lymphoma with Cutaneous Involvement

AFM13-102 is an open-label, Phase 1b/2a, Investigator-sponsored study conducted by Investigators at Columbia University Medical Center in patients with R/R (≥1 prior therapy) CD30-positive lymphomas with cutaneous involvement. The primary objective of this trial is to study the biologic and immunologic effects induced by AFM13 as a single agent. As of 24 July 2018 cut-off date, the study enrolled 9 patients with 3 patients being assigned to each of the following 3 dose cohorts, all dosed over 8 weeks: 1.5 mg/kg weekly, 7.0 mg/kg weekly and 7.0 mg/kg (1 mg/kg administered as a loading dose and 6 mg/kg administered as a continuous infusion over 5 days of each week; Table 1).

Table 1: AFM13 Dose and Schedule for Study AFM13-102

Cohort	AFM13 Dose and Schedule	Cycle Duration
1	1.5 mg/kg over 4 hours, administered weekly	8 weeks
2	7 mg/kg over 4 hours, administered weekly	8 weeks
3	7 mg/kg (1 mg/kg loading dose followed by 6 mg/kg CIV over 5 days, administered weekly)	8 weeks

Abbreviations: CIV = continuous intravenous infusion

As of the data cut-off, 8 of the 9 enrolled patients were evaluable for efficacy. Of the 3 patients with either systemic or cutaneous ALCL, there were 3 objective responses: 1 CR and 2 PRs (100% ORR). Of the remaining 5 evaluable patients all of whom had MF or TMF, there was one PR (20% ORR) in a patient with TMF. [redacted]

[redacted]

The most commonly observed AE has been rigors, a symptom known to be associated with infusion-related reaction (IRR), which occurred during AFM13 infusions and was considered related to AFM13. These AEs were all Grade 1 in severity.

1.3.3.3 Phase 1b Clinical Trial of AFM13 in Combination with Pembrolizumab in Patients with Relapsed or Refractory Classical Hodgkin Lymphoma

AFM13-103 was an open label Phase 1b dose escalation study to assess the safety of AFM13 in combination with pembrolizumab in patients with R/R classical HL. The study consisted of Part 1 (dose escalation) and Part 2 (extension study). Part 1 was 3+3 dose escalation design and Part 2 was dose extension study with optional translational substudy. Treatment duration for AFM13 was until Week 25 and treatment duration for pembrolizumab was up to Week 52. In Part 1 (dose escalation), the AFM13 was escalated in sequential cohorts, while the dose of pembrolizumab was fixed at 200 mg once every 3 weeks (Q3W).

A total of 30 patients (12 in Part 1 [dose escalation] and 18 in Part 2 [extension study]) were analyzed for safety and efficacy; 10 patients completed all 52 weeks of study drug.

The maximum tolerated dose was not exceeded and the minimal activation dose was determined to be 7 mg/kg. Overall, all 30 patients experienced at least one treatment emergent adverse events (TEAEs). The most frequently reported events by preferred terms (PTs) were infusion related reaction (28 [93.3%] patients), nausea (12 [40.0%] patients), pyrexia (12 [40.0%] patients), diarrhea (10 [33.3%] patients), rash (10 [33.3%] patients), upper respiratory tract infection (9 [30.0%] patients), cough (8 [26.7%] patients), fatigue (8 [26.7%] patients), headache (7 [23.3%] patients), pruritus (7 [23.3%] patients), alanine aminotransferase increased (6 [20.0%] patients), and vomiting (6 [20.0%] patients). [redacted]

The ORR was 83.3% (25/30 patients) with 95% CI of 65.3, 94.4. CR was observed in 11 (36.7%) patients and partial response was observed in 14 (46.7%) patients: Stable disease was observed in 2 (6.7%) patients and progressive disease was observed in 10.0% (3 patients).

1.4 Rationale for Dose Selection

[redacted]

[redacted]

1.5 Safety Guidance Information for Investigators

Throughout the study, Investigators should refer to the current edition of the IB for a full review of the potential risks associated with treatment with AFM13 and details of expected AEs.

2 STUDY OBJECTIVES AND ENDPOINTS

This is a Phase 2 study to evaluate the antitumor activity and safety of AFM13 given as monotherapy in subjects with CD30-positive T-cell lymphoma. The study objectives and their respective endpoints for assessment are described in Table 2.

Table 2: Study Objectives and Endpoints

Objective	Endpoint (Assessment)
PRIMARY: • To assess the antitumor activity of AFM13 by an IRC-PET-CT based ORR	• ORR (CR + PR) as confirmed by an IRC as assessed by the modified Lugano Classification (Cheson, 2014) for Cohorts A and B (PTCL) based on PET-CT and after at least 8 weeks from the first assessment as assessed by Olsen Criteria (Olsen, 2011) for Cohort C (TMF) ([redacted]
SECONDARY: • To assess the antitumor activity of AFM13 by IRC-confirmed CR and PR rates and CT scan-based ORR	• CR rate, PR rate, and CT-based ORR as confirmed by an IRC as assessed by the modified Lugano Classification (Cheson, 2014) for Cohorts A and B (PTCL) and after at least 8 weeks from the first assessment by Olsen Criteria (Olsen, 2011) for Cohort C (TMF) ([redacted]
• To assess the antitumor activity of AFM13 by Investigator-assessed ORR (defined as ORR-2)	• ORR-2 confirmed by Investigator assessment as assessed by the modified Lugano Classification (Cheson, 2014) for Cohorts A and B (PTCL) and after at least 8 weeks from the first assessment by Olsen Criteria (Olsen, 2011) for Cohort C (TMF) ([redacted]
• To assess the DOR to AFM13	• DOR as assessed by the modified Lugano Classification (Cheson, 2014) for Cohorts A and B (PTCL) and after at least 8 weeks from the first assessment by Olsen Criteria (Olsen, 2011) for Cohort C (TMF) based on IRC assessment [redacted]
• To assess the safety and tolerability of AFM13	• Number and frequency of treatment-related AEs
• To assess the PK of AFM13	• Assessment of non-compartmental PK parameters including C_{max}, AUC, V_{ss}, $t_{1/2}$

Objective	Endpoint (Assessment)
• To assess the immunogenicity of AFM13	• Incidence of subjects who develop ADA during treatment and their neutralizing potential
• To assess QOL of subjects while on treatment with AFM13	• QOL as measured by EQ-5D for Cohorts A and B; and by Skindex-29 for Cohort C
EXPLORATORY: [redacted]	[redacted]

Abbreviations: [redacted]

2.1 Estimand for the Primary Objective

The estimand is the target of estimation to address the scientific question of interest posed by the trial objective (International Council for Harmonisation [ICH] E9[R1], 2020). Attributes (A.3.3. of ICH E9[R1]) of an estimand include the population of interest, the treatment of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable.

The estimand corresponding to the primary objective consists of:

- Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted subject population for approval.
- Variable: Response assessment from the first assessment as assessed by the modified Lugano Classification (Cheson, 2014) for Cohorts A and B (PTCL) and after at least 8 weeks from the first assessment as assessed by Olsen Criteria (Olsen, 2011) for Cohort C (TMF) [redacted]
- Intercurrent event strategy will follow the treatment policy strategy: subjects non-evaluable for efficacy will not be replaced.

Subjects with missing post-baseline response assessment will be classified as non-responders regardless of the reason.

[redacted]

- Population-level summary: Percentage of subjects achieving an overall response.

Estimator: Best objective response rate assessed via positron emission tomography (PET)-computed tomography (CT) and evaluated by independent central review, for all subjects in the full analysis set (FAS).

Sensitivity estimand: [redacted]

3 SUBJECT ELIGIBILITY AND ENROLLMENT

For Cohorts A, B and C, subjects who meet all the following inclusion criteria and none of the exclusion criteria will be enrolled into the study.

Subjects who express CD30 (≥10% CD30 expression for PTCL subjects in Cohort A, ≥1% to <10% CD30 expression for PTCL subjects in Cohort B, and ≥1% CD30 expression for TMF subjects in Cohort C) by centrally assessed Ber-H2 targeted immunohistochemistry (IHC) (Section 5.4.1), and who have received at least one prior line of systemic therapy and have progressed on, or are not eligible for all standard approved therapy, will be enrolled in this study. Subjects with PTCL will be enrolled to Cohorts A or B and subjects with TMF will be enrolled to Cohort C. The specific subtypes for the PTCL cohorts are listed under the Inclusion Criteria (Section 3.1). After the planned Interim Analyses, Cohorts A and B may be combined to include subjects with ≥1% CD30 expression.

3.1 Inclusion Criteria

1. Written informed consent in accordance with federal, local, and institutional guidelines.

2. Age ≥18 years at time of provision of informed consent.

3. Histologically confirmed CD30-positive (via centrally assessed Ber-H2 targeted IHC; cut-offs listed below) PTCL (allowed subtypes listed below) or TMF per the revised WHO 2016 classification (Swerdlow, 2016) (Note: Subjects must wait for central results before first dose of study drug).

   The PTCL subtypes allowed for Cohorts A and B:

   - Enteropathy-associated T-cell lymphoma
   - Monomorphic epitheliotropic intestinal T-cell lymphoma
   - Hepatosplenic T-cell lymphoma
   - Subcutaneous panniculitis-like T-cell lymphoma
   - Peripheral T-cell lymphoma, not otherwise specified
   - Angioimmunoblastic T-cell lymphoma
   - Follicular T-cell lymphoma
   - Nodal peripheral T-cell lymphoma with T-follicular helper phenotype
   - Anaplastic large-cell lymphoma, anaplastic lymphoma kinase (ALK)-positive
   - Anaplastic large-cell lymphoma, ALK-negative
   - Breast implant–associated anaplastic large-cell lymphoma

The required cut-offs for the CD30-positivity are:

   - Cohort A (PTCL): ≥10% by IHC
   - Cohort B (PTCL): ≥1% to <10% by IHC
   - Cohort C (TMF): ≥1% by IHC

   Note: After the planned Interim Analyses, Cohorts A and B may be combined with the CD30-positivity defined as ≥1% by centrally assessed IHC.

See Section 5.4.1 for additional details on definition of CD30-positivity.

Measurable disease will be defined as below for each cohort:

- Cohorts A and B (PTCL cohorts): measurable by the modified Lugano Classification (Cheson, 2014); measurable disease of >1.5 cm diameter by CT, assessed locally for eligibility.
- Cohort C (TMF cohort): measurable by the Olsen Criteria (Olsen, 2011) including at least 1 cutaneous lymphoma lesion ≥2 cm in diameter, assessed locally for eligibility.

4. Subjects must have R/R disease AND the following:

[redacted]

[redacted]

3.2 Exclusion Criteria

1. Subjects with the following subtypes of lymphoma

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
- Chronic lymphoproliferative disorder of NK cells
- Aggressive NK-cell leukemia
- Extranodal NK-/T-cell lymphoma
- Indolent T-cell lymphoproliferative disorder of the gastrointestinal tract
- Adult T-cell leukemia/lymphoma

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.3 Process for Subject Enrollment

Prior to completion of any study-related activities, written informed consent form (ICF) needs to be obtained from all subjects. After signing the Pre-screening ICF, subjects will have their tumors assessed for CD30 expression. In order to start the main screening period, the subject will have to sign the Main study ICF. During this period it has to be confirmed that all subjects meet all of the Inclusion Criteria (Section 3.1) and do not meet any of the Exclusion Criteria (Section 3.2).

Please refer to the guidance document 'Enrollment process' for specific details about the enrollment process.

3.4 Definition of Evaluable Subject and Replacement of Subjects

All subjects who have received at least one dose of AFM13 will be considered evaluable for the primary endpoint. Subjects who withdraw from the study for any reason prior to their first post-baseline disease assessment will not be replaced. [redacted]

3.5 Reasons for Withdrawal of Subject from Study

Throughout the study, treatment with AFM13 may continue until the occurrence of one of the following events, whichever comes first:

- Subject withdrawal of consent.
- Disease progression.
- Occurrence of an unacceptable toxicity (see also Section 6.8).
- Requirement for treatment with prohibited medication (see Section 6.9.2).
- Treatment or study non-compliance (see Section 3.6) and the need for withdrawal for this reason as assessed by the Investigator.
- Subject withdrawal due to COVID-19 pandemic (directly or indirectly impacted and if in the opinion of the Investigator the risk(s) of participation exceeds any potential benefit)
- Investigator decision that it is in the subject's best interest to withdraw from the study (eg, subject transitioning to a stem cell transplant after achieving a durable objective response on the current study).

Note: *Each subject's continued willingness to attend study visits and undergo study assessments will be assessed by the Investigator on a case-by-case basis.*

3.6 Subject Compliance, Lost to Follow-up, and Procedures for Subject Discontinuation

Please refer to Section 6.8 for details of permitted AFM13 dose delays or interruptions.

A subject will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. The following actions must be taken if a study subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

All situations of non-compliance will be reviewed on a case-by-case basis with the Sponsor and the site will be provided guidance on subject withdrawal from treatment and/or the study, where appropriate.

Per Section 5.1.2, subjects who discontinue treatment due to achieving CR, are still considered to be on study and are required to undergo study assessments per the Schedule of Assessments [redacted]. Such subjects may resume treatment where there is subsequent radiological evidence of disease progression, following a *documented discussion* with the Sponsor.

Upon withdrawal from study drug, the reason for withdrawal should be sought and recorded in the subject file and the electronic case report form (eCRF). Every effort will be made to complete the Final Study Visit and for the subject to be followed up every 3 months thereafter to check for disease progression and survival status. Where a subject withdraws his/her consent to participate in the study, such follow-up assessments cannot be conducted. The management and holding of data around subject withdrawal will be described in the subject ICF.

3.7 Study or Site Termination

If the Sponsor or their representatives, Investigator, or Competent Authority discover conditions during the study that indicate that the study or site involvement should be terminated, this action may be taken after appropriate consultation with the Sponsor and the Investigator. Conditions that may warrant termination of the study or a study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study.
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the study drug.

- Failure of an Investigator(s) to comply with pertinent clinical trial regulations.
- Submission of knowingly false information from the study site to the Sponsor, clinical research associate (CRA), or Competent Authority.
- Insufficient adherence to protocol requirements.

Study termination and/or site close out will be performed in accordance with applicable local regulations.

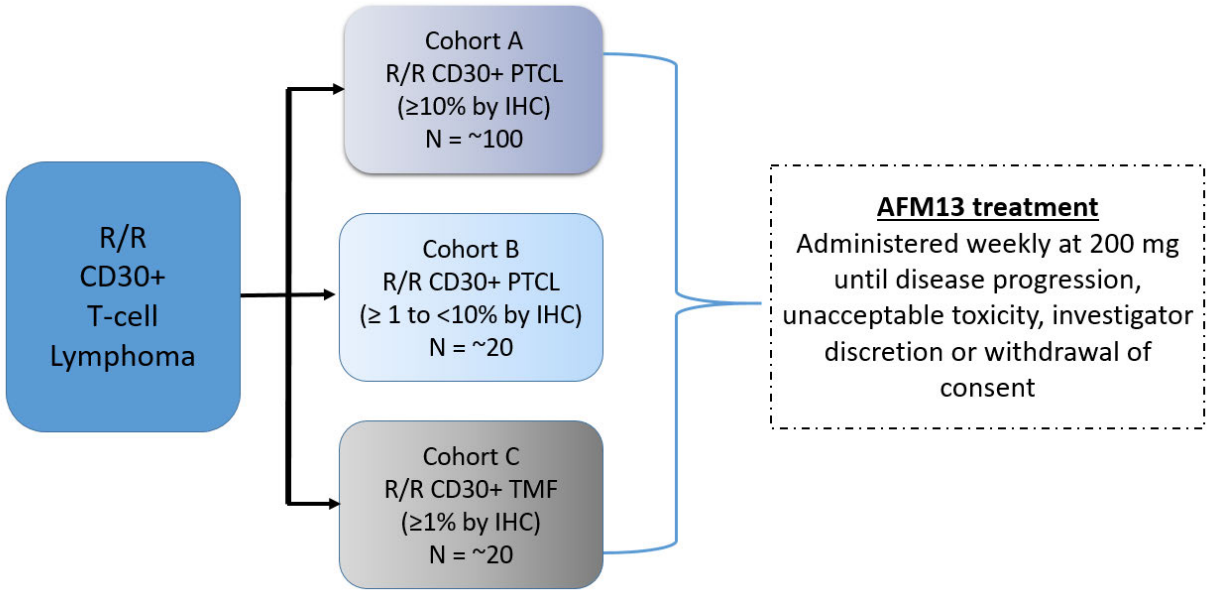
4 STUDY DESIGN

This is an open-label, multicenter, Phase 2 study in subjects with R/R CD30-positive PTCL or TMF to investigate the antitumor activity and safety of AFM13 dosed weekly at 200 mg until disease progression, unacceptable toxicity, Investigator discretion or withdrawal of consent.

Subjects with PTCL or TMF who express CD30 (ie, are confirmed to have ≥1% CD30 expression) as determined by centrally assessed Ber-H2 targeted IHC (Section 3.1), and who meet all of the inclusion criteria and none of the exclusion criteria, will be allowed for this study. Subjects with PTCL will be enrolled to Cohort A and Cohort B based on the centrally determined CD30 expression levels of ≥10% and ≥1% to <10%, respectively, and subjects with TMF will be enrolled to Cohort C based on the centrally determined CD30 expression of ≥1%. After the planned Interim Analyses, Cohorts A and B may be combined to include subjects with ≥1% CD30 expression. The specific subtypes of PTCL allowed for Cohorts A and B are listed in the Inclusion Criteria (Section 3.1). A summary of the study design is provided in Figure 2.

Subjects will receive AFM13 until disease progression, intolerable toxicity, or withdrawal of consent. Reasons for withdrawing a subject from the study are described in Section 3.5.

Figure 2: Study Design



Abbreviations: CD = cluster of differentiation; IHC = immunohistochemistry; PTCL = peripheral T-cell lymphoma; R/R = relapsed/refractory; TMF = transformed mycosis fungoides

5 STUDY SCHEDULE

The study consists of a Pre-screening Period, a Screening Period, a Treatment Period, an Efficacy and Safety Follow-up Period (Final Study Visit), plus Survival Follow-up. Informed consents (one for Pre-screening and a second one for the main study after the confirmation of CD30-expression) must be obtained using the current, approved versions of the ICF prior to commencing Pre-screening and Screening, respectively. Subjects will undergo a Pre-screening for CD30 expression up to 28 days before Screening and, if confirmed, will start Screening assessments up to 21 days before receiving the first dose of AFM13. Due to the nature of the diseases being studied, Screening assessments may, in practice, be carried out over a shorter time-period. The Efficacy and Safety Follow-up Period (Final Study Visit) assessments may be conducted between 30 to 37 days after the subject has permanently discontinued AFM13 study drug; however, a final AE and concomitant medication review must take place 30 days after the last dose of AFM13. Where applicable, disease progression and survival status will be checked every 3 months by telephone interview, or during the subject's routine clinic visits, following completion of the Final Study Visit assessments.

5.1 Study Periods

All subjects enrolled may participate in the following study periods:

- Pre-screening Period
- Screening Period
- Treatment Period
- Efficacy and Safety Follow-up Period (Final Study Visit)
- Survival Follow-up (after completion of the study)

Each study period is described below. Subjects will undergo study assessments from the Screening Period to the Efficacy and Safety Follow-up Period (Final Study Visit) at scheduled site visits as described in the Schedule of Assessments table [redacted] All subjects are considered "on-study" until they complete the Efficacy and Safety Follow-up Period (Final Study Visit), withdraw consent, are lost to follow up, or die.

5.1.1 Pre-screening and Screening Period

The study includes a Pre-Screening and a Screening Period. The maximum number of days from the time of informed consent for Pre-Screening to the Main study ICF is 28 days.

During this Pre-Screening Period the subject will be tested for CD30 expression. In addition, the ALK status for subjects with systemic ALCL will also be determined.

The main screening period can last up to 21 days to assess the subject's full eligibility to move to the treatment period of the trial (ie, the subject cannot start dosing until all screening assessments confirm the subject's eligibility).

Please refer to the guidance document 'Enrollment process' for specific details about the enrollment process.

5.1.2 Treatment Period

The Treatment Period will begin following the Screening Period, on Cycle 1 Day 1. Study drug will be administered only if the subject meets all inclusion criteria and none of the exclusion criteria as defined in Section 3.1 and Section 3.2.

[redacted]

If a subject permanently discontinues study drug, they should continue to the Efficacy and Safety Follow-up Period (Final Study Visit).

5.1.3 Efficacy and Safety Follow-up Period

[redacted]

5.1.4 Follow-up

[redacted]

5.1.5 End of Study

End of study is defined as the point when all subjects have completed their Efficacy and Safety Follow-up Period (Final Study Visit) assessments following permanent discontinuation of study drug. On completion of the study, data will be reconciled, and the database will be locked for analysis.

5.2 Schedule of Assessments

[redacted]

[redacted]

Pre-screening:

[redacted]

- [redacted]
- [redacted]

[redacted]

Screening Period:

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Treatment Period:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.3 Volume of Blood Sampling

Total blood volumes required during study participation will be provided in the ICF provided to each subject. The Lab Manual will also describe unit and total blood volumes and provide examples based on various durations on study. Efforts will be made to limit blood sampling to avoid any redundancy. Any such reductions in requirements for blood sampling will be described and maintained in the Lab Manual.

5.4 Description of Study Interventions and Assessments

Details of the procedures to be followed for specified study assessments are provided. During the study, additional assessments may be carried out as clinically indicated.

[redacted]

5.4.2 Medical History

There will be a baseline assessment of relevant medical history conducted at Screening to confirm eligibility and to record significant medical history and concurrent illnesses in the eCRF. Concurrent illnesses recorded at Screening (excluding the primary disease under evaluation), that worsen in severity or frequency from this baseline assessment during the study, should be reported as AEs (see Section 7).

5.4.3 Pregnancy and Follicle Stimulating Hormone Tests

Female subjects of reproductive potential will have a pregnancy test carried out at Screening. This test must be carried out within 3 days prior to first AFM13 administration. A urine test is acceptable; however, where a urine test is equivocal, a blood test must be performed to confirm the result. Subjects confirmed as pregnant will be excluded from participation in the clinical study.

Female subjects of reproductive potential with a negative pregnancy test at Screening will continue to have pregnancy tests conducted at least every 4 weeks during the study and at the Final Study Visit [redacted]

Female subjects who require documented confirmation of post-menopausal status will have their FSH levels assessed at Screening. A urine test is acceptable; however, where a urine test is equivocal, a blood test must be performed to confirm the result. Where post-menopausal status is not confirmed, subjects will be required to undergo pregnancy testing per protocol to confirm suitability to proceed.

5.4.4 Eastern Cooperative Oncology Group Performance Score

ECOG Performance Score (PS) will be assessed at the times given in Schedule of Assessments [redacted] Details of the ECOG PS categories are presented in [redacted] Subjects must be confirmed as ECOG PS 0 or 1 at Screening to be eligible for study participation.

5.4.5 Vital Signs

Vital sign parameters will be taken at the times given in Schedule of Assessments [redacted] The date and time of collection will be recorded in the source data and in the eCRF.

Vital sign parameters will consist of measurements of temperature, resting heart rate, seated blood pressure (systolic/diastolic) and respiratory rate.

If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

5.4.6 Physical Examinations

A physical examination, including measurement of weight, will be taken at the times given in Schedule of Assessments [redacted] The subject's height will be measured at Screening. The subject's weight will also be assessed at Screening and prior to each AFM13 administration. Height and body weight will be obtained while the subject is wearing light clothing (without shoes).

A full physical examination will include assessment of the following categories: head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, musculoskeletal, extremities, neurological, lymph nodes, and 'other'. After the Screening assessment, the physical examination may be reduced to a symptom-directed assessment.

If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

5.4.7 Clinical Chemistry, Hematology, Coagulation, and Urinalysis

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis parameters will be taken at the times given in Schedule of Assessments [redacted] and recorded in the source data and in the eCRF. Coagulation will be assessed at Screening and Final Study Visit only and may be assessed from the hematology sample.

The laboratory variables to be measured are described in [redacted]

Copies of laboratory accreditation certificates and reference ranges will be obtained from each study site prior to analysis of their first subject sample and maintained over the course of the trial.

If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

5.4.8 Electrocardiogram

A resting 12-lead ECG will be performed at the times given in Schedule of Assessments [redacted] For those occasions when both an ECG and peripheral blood sample collection are required at the EOI of AFM13, the blood draw must be completed first as close to the EOI as possible, followed by the ECG. Both procedures should be completed within 10 minutes after the EOI (+10 minutes, note plus only).

All 12-lead ECGs should be recorded while the subject is in the supine position. ECGs will be recorded at 25 mm/sec. All efforts should be made to ensure that an identical ECG machine is used to collect traces for individual subjects. The Investigator or designated physician will review the ECG results. If any clinically significant findings are identified during the study, the Investigator will record these as an AE, where the finding represents a change from baseline.

5.4.9 Disease Assessment

Imaging assessments, including FDG-PET and CT assessments for Cohorts A and B (PTCL) and CT scan or MRI for Cohort C (TMF), will be performed at Screening and every 8 weeks for the first 3 assessments, then every 12 weeks thereafter, as well as at the time of suspected clinical progression, as described in Schedule of Assessments [redacted] This scheduling is regardless of any treatment/cycle delays that may occur. All imaging assessments will be conducted according to local institutional practice and the same modality should be used for initial staging at Screening and all restaging assessments.

[redacted]

Further details of the conduct and processing of imaging assessments will be described in the Imaging Manual for the study.

5.4.10 Response Assessment

Response assessment will be performed in conjunction with the post dose disease assessments ie, every 8 weeks for the first 3 assessments, then every 12 weeks thereafter, as well as at the time of suspected clinical progression, as described in Schedule of Assessments [redacted] Response assessment will follow the modified Lugano Classification Revised Staging System for malignant lymphoma (Cheson, 2014) for subjects with PTCL (Cohorts A and B) and the Olsen Criteria (Olsen, 2011) for subjects with TMF (Cohort C) [redacted]

The modified Lugano Classification refers to the protocol's separate use of PET-CT based response criteria from CT-based response criteria from the Lugano Classification to guide clinical decisions and assessment of overall response. The CT-based overall response will be one of the secondary endpoints.

For Cohort C (TMF), the Olsen Criteria determines the global response (GR) based on the following:

- skin assessment by the modified Severity Weighted Assessment Tool (mSWAT) and Composite Assessment of Index Lesions Severity (CAILS)
- lymph node assessment by CT (or MRI)
- visceral disease assessment by CT (or MRI)
- blood assessment by flow cytometry (ie, CD4-positive/CD7-negative and CD4-positive/CD26-negative subsets)

[redacted]

Assessments will be performed both locally and centrally, and all imaging scans (PET-CT for Cohorts A and B, CT or MRI for Cohort C) will be collected for independent review. Treatment decisions should be based on the local disease assessment.

5.4.11 Exploratory Biomarkers

[redacted]

5.4.12 Cytokines

All subjects will have blood samples taken to assess cytokine levels at the time points described in Schedule of Assessments [redacted]

[redacted]

Full details of sample collection and handling of cytokine samples will be described in Lab Manual for the study.

5.4.13 Anti-drug Antibodies

All subjects will have blood samples taken to assess for ADA at the time points described in Schedule of Assessments [redacted]

Full details of sample collection and handling of ADA samples will be described in Lab Manual for the study.

5.4.14 Pharmacokinetic Sampling

Evaluation of the levels of AFM13 in serum will be performed at the time points described in Schedule of Assessments [redacted]

[redacted]

Full details of the blood sample collection, processing and handling for PK samples will be described in Lab Manual for the study.

5.4.15 Quality of Life Assessment

Evaluation of QOL parameters will be performed at the time points described in Schedule of Assessments [redacted]

Subjects in Cohorts A and B (PTCL) will be evaluated using the EQ-5D, and subjects in Cohort C (TMF) will be evaluated using Skindex 29.

Example templates of both QOL evaluation tools are provided in [redacted]

6 STUDY MEDICATION AND ADMINISTRATION

Affimed will supply AFM13 study drug as a sterile lyophilized powder for reconstitution for intravenous (IV) infusion (Table 3). Full details on the preparation and administration of AFM13 are provided in the Pharmacy Manual for the study.

The Investigator shall take responsibility for the study drug and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study drug in accordance with the protocol and any applicable laws and regulations.

The Quality Control Standards and requirements for AFM13 study drug are described in separate release protocols/Certificate of Analysis.

Please refer to the current version of the IB for additional information on the physical, chemical, and pharmaceutical properties of AFM13.

6.1 Provision and Replacement of AFM13

Sufficient doses of AFM13 study drug will be supplied. Where study drug supplies (or packaging) are apparently damaged on receipt or considered unfit for use by the study site, the Sponsor (or their delegate) must be notified immediately. Where required, clinical trial supplies will be replaced. Further details on the handling of AFM13 study drug at site will be described in the Pharmacy Manual.

6.2 Labelling of AFM13

AFM13 clinical trial supplies will be labeled in compliance with Good Manufacturing Practice Annex 13 requirements, US Food and Drug Administration (FDA) requirements, and any other applicable local regulatory guidelines.

6.3 Storage of AFM13

AFM13 study drug will be shipped to the site and must be stored at the site in a secure location under controlled conditions and in the required temperature range (Table 3).

6.4 Drug Accountability

The Investigator is obliged to keep sufficient documentation of the delivery, use and destruction or return of unused, used or partially used AFM13 study drug. The documentation must include dates, quantities, subject numbers, batch numbers or other identification number. The Investigator may assign some or all of the Investigator's duties for drug accountability to an appropriate pharmacist. Roles and responsibilities of site staff will be recorded in the Investigator Site File.

The Investigator should maintain records that document adequately that the subjects were administered the doses specified in the protocol and reconcile all AFM13 study drug received for the trial. The local CRA will be responsible for checking the drug accountability records maintained by the site during study monitoring visits.

AFM13 provided for this study is for use only as directed in the protocol. It is the Investigator and their institution's responsibility to establish a system for handling study drug so as to ensure that:

- Deliveries of AFM13 are correctly received by a responsible person;
- Such deliveries are recorded;
- Study drug is handled and stored safely and properly as stated on the label;
- Study drug is only dispensed to study subjects in accordance with the protocol; and
- Any unused study drug is destroyed locally or returned for destruction in liaison with the CRA.

Certificates of delivery and return must be signed by the responsible pharmacist, and copies retained in the Pharmacy File. Throughout the study, it must be possible to reconcile delivery records with records of usage and any destroyed/returned stock of AFM13. To help with compliance checks, records of usage should include an appropriate form of identification of the subject to whom the study drug was dispensed (using an indirect form to allow cross reference to the subjects' identity), plus the quantity and date of dispensing.

The return or destruction of unused drug will be conducted after written approval by the Sponsor, with appropriate documentation and drug accountability procedures completed following destruction.

6.5 Premedication Regimen and Post Dose Observation

[redacted]

6.6 AFM13 Dosing Instructions

AFM13 will be administered at a dose of 200 mg. Subjects will be treated weekly until disease progression, unacceptable toxicity, Investigator discretion or withdrawal of consent.

[redacted]

6.7 Duration of Treatment

Treatment with AFM13 should continue until disease progression, unacceptable toxicity, Investigator discretion or withdrawal of consent.

[redacted]

6.8 AFM13 Dose Delays or Interruptions

The dosing schedule for Study visits that include AFM13 administration permit a tolerance window of ±1 day at Cycle 1 Day 8, then a ±3-day tolerance window for all visits thereafter. However, the minimum time period between any two consecutive AFM13 administrations cannot be less than 3 days.

AFM13 dosing delays may be permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation and/or holidays) after obtaining approval from the Sponsor.

[redacted]

[redacted]

6.9 Permitted and Restricted Concomitant Medications

Medications specifically prohibited in the exclusion criteria (Section 3.2) are not allowed during the ongoing trial. If there is a clinical indication for any medication specifically prohibited during the trial, discontinuation from trial therapy may be required. The final decision on any supportive therapy rests with the Investigator and/or the subject's primary physician. However, in such cases, the decision to continue the subject on AFM13 study drug requires the mutual agreement of the Investigator, Sponsor and the subject.

6.9.1 Acceptable Concomitant Medications

All treatments and supportive care that the Investigator considers necessary for a subject's welfare may be administered at the discretion of the Investigator in keeping with the study site's standards of medical care except for the prohibited concomitant medications listed in Section 6.9.2. All concomitant medication will be recorded in the eCRF including all prescription, over-the-counter, herbal supplements, and iv medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included in the eCRF. All concomitant medications received within 30 days before the first dose of study drug and 30 days after the last dose of study drug should be recorded. Concomitant medications administered >30 days after the last dose of study drug should be recorded for serious adverse events (SAEs) that are considered related to study drug (Section 7.10).

6.9.1.1 Highly Effective Contraception

Both sexually active females of childbearing potential and non-vasectomized male subjects with female partners of childbearing potential are required to use highly effective methods of contraception, initiated prior to first dose of study drug, continued during study drug, and for at least 60 days after the last dose of study drug. Note that for non-vasectomized male subjects, some of these methods are applicable to their female partners.

Highly effective methods of contraception, including abstinence, are defined as follows:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation; may be oral, intravaginal or transdermal method;
- Progestogen-only hormonal contraception associated with the inhibition of ovulation; may be oral, injectable, implantable method;
- An intrauterine device;
- Intrauterine hormone-releasing system;
- Bilateral tubal occlusion;
- Vasectomized partner of a female subject (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study subject and that the vasectomized partner has received medical assessment of surgical success); *or*
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug, starting prior to first dose of study drug, for the duration of study drug, and for at least 60 days after the last dose of study drug. Total sexual abstinence should only be used as a contraceptive method if it is in line with a

subject's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal methods, are not acceptable methods of contraception.

Barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception. If used, this method must be utilized in combination with another acceptable method listed above.

6.9.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening (see Exclusion Criteria; Section 3.2) and Treatment Period of this trial, with exception of the treatment of AEs occurring during the study:

[redacted]

6.10 Blinding and Procedures for Unblinding the Study

This is an open-label study, and there are no procedures for blinding and unblinding.

7 ADVERSE EVENTS AND REPORTING REQUIREMENTS

7.1 Assessment of Safety

All subjects who receive treatment with AFM13 will be considered evaluable for safety. All AEs and SAEs will be collected from the time the subject gives informed consent up to and including [redacted]. There will be a baseline medical condition review taken at Screening. AEs, other than the primary disease under evaluation, that worsen in severity or frequency from this baseline assessment during the study, should be recorded and reported as AEs.

In addition, as part of the documentation of an AE in the electronic documentation system, sites will be asked to identify whether the event is related to an infusion-related reaction.

If the Investigator detects an SAE in a study subject after the end of the period of observation and considers the event possibly related to prior study drug or procedures, they should contact the Sponsor to determine how this event should be documented and reported.

7.2 Adverse Event Definition

An AE is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to AFM13.

During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs. AEs include:

- Worsening (change in nature, severity, or frequency) of conditions present at the start of the study;
- Intercurrent illness;
- Drug interactions;
- Experiences related or possibly related to concomitant medications;
- Clinically significant abnormal laboratory values or shifts from baseline; and
- Clinically significant abnormalities in physical examination, vital signs, weight or ECG.

Symptoms and signs of exacerbation or worsening of the subject's primary disease will not be captured as AEs. Progression of the disease under study will not be captured as an AE unless it is considered to be drug-related by the Investigator.

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the period of observation and did not worsen during study. In the latter case, the condition should be reported as medical history.

7.3 Importance of Adverse Event Reporting

Timely and complete reporting of safety information is very important to assist in the identification of any untoward medical occurrence, thereby ensuring:

- the safety of study subjects;
- a greater understanding of the overall safety profile of the investigational drug;
- recognition of any dose-related investigational drug toxicity;
- appropriate modification of study protocols;
- improvements in study design or procedures as required; and
- adherence to required ethical and regulatory requirements for clinical trial conduct.

7.4 Evaluating Adverse Events

Following the subject's written consent to participate in the study, all AEs should be collected. All identified AEs must be recorded and described on the appropriate AE page of the eCRF, except for those events occurring prior to the first dose of study drug, which should be recorded on the Medical History eCRF page. Where known, the diagnosis of the underlying illness or disorder should be recorded, rather than listing individual symptoms.

The following information should be captured for all AEs: date of onset and resolution, severity of the event (see definitions in Section 7.5), assessment whether the event was serious or non-serious, Investigator's opinion of the relationship to AFM13 (see definitions in Section 7.8) treatment required for the AE, action taken with AFM13 study drug and information regarding resolution/outcome.

7.5 Severity

All AEs (including SAEs) are to be accurately recorded on the AE page of the subject's eCRF. Each event will be graded for severity using the classifications of NCI CTCAE v5.0 (or higher) [redacted] For events not addressed in the NCI CTCAE v5.0 classifications, the following grading will apply:

- **Mild (Grade 1)** - Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)** - Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living.
- **Severe (Grade 3)** - Severe or medically significant but not immediately life -threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activity of daily living.
- **Life-threatening (Grade 4)** - Life-threatening consequences; urgent intervention indicated.
- **Fatal (Grade 5)** - Related to AE.

7.6 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose causes or qualifies as the following:

- Results in death.
- Is life-threatening:
  - "Life-threatening" means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization:
  - This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the SAE or that they occurred as a consequence of the event.
  - Visits to a hospital by ambulance or to the emergency room without admission will not be regarded as hospitalization unless the event fulfills any other of the serious criteria.

  Note: Preventive hospitalization due to current COVID-19 pandemic (eg, to minimize exposure to COVID-19) will not be categorized as SAE.
- Results in persistent or significant disability or incapacity:
  - "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect.
- Is an important medical event:
  - Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the event is otherwise explained, or the subject is lost to follow-up or withdraws consent.

7.7 Other Important Events for Immediate Reporting

AEs meeting the below criteria, although not categorized as 'Serious' per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements and the study needs:

- A new cancer (that is not a condition of the study);
- A reported pregnancy or lactation after receipt of study drug and for ≤60 days from last dose;

- An overdose (defined as any dose of AFM13 which more than the assigned dose for that subject is).
- Any confirmed or suspected COVID-19 infection (eg, in case the subject cannot be tested due to lock-down) should be reported as Important Medical Event, regardless of the hospitalization status or severity of the event; as this is an adverse event that may jeopardize the subject safety or may require intervention to prevent a severe, life threatening or fatal outcome. Note: Continuation in the study should be assessed by the Investigator and according to the protocol criteria for study termination. Dose delay vs. study termination should be driven by the overall health status of the subject, and the safety of the subject shall prevail at all times.

Such events must be reported within 24 hours to the Sponsor by means of an SAE form either by electronic report or paper.

7.7.1 Exposure During Pregnancy or Lactation

Although pregnancy and lactation are not considered AEs, it is the responsibility of Investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) or pregnancy in a subject's partner that occurs during the trial.

Pregnancies and lactations that occur in subjects after the ICF is signed but before starting study drug must be reported by the Investigator if they cause the subject to be excluded from the trial. Pregnancies and lactations that occur in a study subject or a pregnancy in a subject's partner from the time of first study drug through to 60 days following cessation of AFM13 study drug, must be reported by the Investigator. All reported pregnancies must be followed to the completion or termination of the pregnancy. If the pregnancy continues to term, the outcome ie, the health of the infant, will be requested by the Sponsor.

Such events must be reported within 24 hours to the Sponsor via email, fax, or telephone. The reporting procedures can be found in the SAE completion guidelines located in the Study Operations Manual (or equivalent).

7.7.2 Misuse and Overdose

Study drug misuse or overdose should be reported in the same format and within the same timelines as an SAE, even if they may not result in an adverse outcome. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

For the purpose of this protocol, an overdose is any dose of AFM13 which is more than the assigned dose level for that subject.

If the pharmacy discovers that an overdose has or may have been administered, they should contact the Investigator and Sponsor (or their delegate) immediately.

7.7.3 Investigational Product Complaints

Pharmaceutical technical complaints associated with the investigational product must be reported to the Sponsor immediately, following the guidance specified in the Pharmacy Manual. The same reporting timelines as for SAEs will apply.

7.8 Relationship

All AEs (including SAEs) will be assessed for the relationship of the AE to the study drug using the following definitions:

- **Not/unlikely related** - The AE is not related if exposure to the investigational product has not occurred, *OR* the occurrence of the AE is not reasonably related in time, *OR* the AE is considered unlikely to be related to use of the investigational product because there are no facts (evidence) or arguments to suggest a causal relationship *AND* there is a possible alternative explanation.
- **Possibly related** - The administration of the investigational product and AE are considered reasonably related in time *AND* the AE could be explained by causes other than exposure to the investigational product.
- **Probably related** - Exposure to the investigational product and AE are reasonably related in time *AND* the investigational product is more likely than other causes to be responsible for the AE *OR* is the most likely cause of the AE.
- **Definitely related** - There is a reasonable temporal sequence between exposure to the investigational product and the AE, *OR* the event follows a known or expected response pattern to the investigational product AND is confirmed by improvement on stopping the dosage of the investigational product. It may also be confirmed by reappearance upon repeated exposure where this is medically and ethically acceptable.

Please also refer to supporting information provided in [redacted] The relationship of the study drug to an AE will be determined by the Investigator and subsequently reviewed by the Sponsor.

For reporting and data analysis purposes, AEs reported with a causality assessment of "Definitely", "Probably", and "Possibly" are to be considered as "having a reasonable causal relationship" to study drug. In case of disagreement between the Investigator and the Sponsor, the more conservative assessment will determine the reportability of the case.

7.9 Unexpected Adverse Events

The Sponsor will assess all SAEs whether they are expected or unexpected. An unexpected AE is any adverse drug event, the outcome, specificity, or severity of which is not consistent with those noted in the current IB section Reference Safety Information.

7.10 Reporting Serious Adverse Events

Adverse Events classified as serious require expeditious handling and reporting to the assigned Drug Safety contact to comply with regulatory requirements.

Any SAE that occurs while a subject is on study ie, occurs within 30 days of the last study drug administration, regardless of any opinion as to the relationship of the SAE to the study drug,

must be notified to spm[2] immediately by completing and sending the Serious Adverse Event Report Form via eCRF completion (or email, as required) within 24 hours of becoming aware of the event (Table 5). Any SAE which occurs later than 30 days after the last study drug administration, that the Investigator considers to be related to study drug, must be reported in the same fashion.

Table 5: Contact Information for SAE Reporting

Drug Safety Contract Research Organization:	[redacted]
SAE E-mail Contact:	[redacted]

Abbreviations: SAE = serious adverse event

7.11 Reporting of Serious Adverse Events to Regulatory Authorities

In accordance with the US Code of Federal Regulations, Title 21 CFR Part 312.32, the European Directive 2001/20/EC, and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the Sponsor must submit written documentation in the form of an Investigational New Drug (IND) Safety Report or suspected unexpected serious adverse reaction (SUSAR) reports, respectively. The Sponsor should submit to the regulatory authority all safety updates and periodic reports, as required by applicable regulatory requirements. IND Safety Reports/SUSARs are required to be reported within 7 calendar days for life-threatening events and those resulting in death or 15 calendar days for all others. These timeframes begin with the first notification of the IND Safety Reports/SUSARs to the Sponsor or their delegate from the Investigator.

The Sponsor (or their delegate) will determine whether expedited reporting is necessary for SAEs depending on the assessment of seriousness, expectedness and relationship. In case of disagreement between the Investigator and the Sponsor regarding causal relationship, the more conservative assessment will determine the reportability of the case.

The Investigator must ensure they are aware and comply with any additional local reporting requirements. For all SAEs that are related and unexpected, the Sponsor (or their delegate) will assign a case number to be used in all future correspondence regarding the event and can provide a MedWatch or Council for International Organizations of Medical Sciences (CIOMS) form describing the event, for the Investigators to report to their Institutional Review Board (IRB)/Ethics Committee (EC) or other committee. Other SAEs (eg, expected or unrelated SAEs) should be reported per the relevant institution's procedures.

Where required, submission of Safety Updates by the Investigator to Competent Authorities should be handled according to local regulations. Otherwise, periodic safety reports to the regulatory agencies will be handled by the Sponsor (or their delegate). These safety updates will also include SAEs that do not require expedited reporting to the authorities.

Periodically (at least annually), the IB will be updated to include new and relevant safety information. Until such time that an AE becomes identified in the IB, it should be considered unexpected.

7.12 Follow Up Information on an SAE

Collection of complete information concerning SAEs is extremely important. Thus, follow-up information that becomes available as the SAE evolves, as well as supporting documentation (eg, hospital discharge summaries and autopsy reports), should be collected subsequently, if not available at the time of the initial report, and immediately sent using the same procedure as the initial SAE report. The original SAE form must be kept on file at the study site. The Sponsor (or their delegate) will also review SAE reports for missing information and send queries to the site for resolution as appropriate.

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out by the Investigator (or designee). An SAE is followed until it is considered resolved, returns to baseline, is chronically ongoing, stabilized or is otherwise explained by the Investigator.

8 STATISTICAL METHODS AND DATA ANALYSIS

Detailed statistical analysis information will be provided separately in the Statistical Analysis Plan (SAP) which will be finalized and signed before the database is locked. The SAP will detail all data handling rules, including the management of missing values and the handling of data for withdrawn subjects. The SAP will also outline protocol deviation criteria. Any deviations to the planned analyses specified or populations defined within the SAP will be justified in writing and presented within the final clinical study report (CSR).

The clinical database lock will occur after all data are reconciled (ie, "cleaned") for all subjects who receive at least one dose of AFM13. A single CSR will be generated for this study.

An addendum (or addenda) to the CSR will be generated as required to report any data obtained during the Follow-up Assessments.

Where appropriate, tables, listings and figures will be reported by Cohort. Data may be combined and/or summarized by cohort, dose (if different from cohort) and time point.

8.1 Analysis Sets

The study will have three separate cohorts: first cohort (Cohort A) with R/R PTCL subjects with CD30 ≥10%, second cohort (Cohort B) with R/R PTCL subjects with CD30 ≥1% to <10%, and the third cohort (Cohort C) with R/R TMF subjects with CD30 ≥1%. All three cohorts will be analyzed independently as described below.

The **full analysis set** (FAS) following the intent to treat (ITT) principle will consist of all subjects who received at least one dose of AFM13. The FAS will be the primary population for all efficacy related endpoints and the primary objective; a sensitivity analysis for all subjects who received at least one dose of AFM13 and had at least one post-baseline efficacy assessment will be conducted to support the results of the primary analysis.

The **safety set** will consist of all subjects who received at least one dose of AFM13 and had at least one post-baseline safety assessment (where the statement that a subject had no AE on the AE eCRF constitutes a safety assessment). The safety set will be the primary population for all safety related endpoints.

The **per protocol set** (PPS) will consist of all subjects in FAS who did not have any major protocol deviations. The primary analysis will be repeated to support the results of the primary analysis on the FAS.

The **pharmacokinetic set** (PK) set consists of all subjects who have at least received one dose of study drug and have at least one post dose PK measurement.

Additional sensitivity analyses might be needed due to the COVID-19 pandemic and those will be defined in the SAP, if deemed necessary.

Subjects who were screened and have signed the ICF but did not receive any treatment will be listed including reason for screen failure and any SAE (this will be recorded in the medical

history). These subjects will not be part of any summary table except for summarizing disposition.

8.1.1 Missing Data and Discontinuation

As this is a non-randomized study design, no imputation of missing values will be done for any analysis except for partial/missing AE dates and concomitant medication dates. Reasons for discontinuation of the study and the study drug will be listed and summarized.

Subjects with missing post-baseline response will be classified as non-responders; however, due to the COVID-19 pandemic additional analyses might be needed and will be specified in the SAP (see Section 2.1).

8.2 Demographic, Medical History, Prior Medication and Other Baseline Characteristics

Demographic characteristics, prior anti-cancer therapies and surgeries, medical history, prior medication and other baseline data will be listed and summarized using descriptive statistics for continuation data and contingency tables for categorical data. Prior medication/Prior anti-cancer therapies will be coded by WHO Anatomical, Therapeutic, and Chemical (ATC) terms. Medical history will be coded utilizing corresponding Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) and PTs.

8.3 Study Drug

The number of doses of AFM13 administered over the entire study period will be listed and summarized using descriptive statistics. The time on study drug until last treatment received will be listed and presented by descriptive statistics.

8.4 Concomitant Medication

Concomitant medication and significant non-drug therapies after the start of study drug will be listed and summarized by WHO ATC terms in contingency tables.

8.5 Primary Analysis

8.5.1 Overall Response Rate

Overall response by PET-CT as defined by achieving CR and/or PR assessed by an Independent Review Committee (IRC) utilizing the modified Lugano Classification Revised Staging System for malignant lymphoma (Cheson, 2014) for Cohorts A and B (PTCL) and the Olsen Criteria (Olsen, 2011) for Cohort C (TMF). Subjects with missing post-baseline response will be classified as non-responders in the FAS. Results will be presented by percentage rates and 95% CIs. In addition, CR and PR will be presented separately. For all response assessments, swimmer plots will be presented. All response assessments will be listed.

Cohorts A and Cohort C will be analyzed separately and independent from each other at the final analysis. Cohort A may be opened after the interim analysis for all PTCL subjects with CD30 ≥1%, if Cohort B showed the required ORR (see Section 8.8.1). The final analysis for

Cohort A will be conducted once all subjects have completed at least two post-baseline disease assessments (ie, ~ 16 weeks post-baseline assessment) to be categorized under the response endpoint or have withdrawn from study drug.

8.6 Secondary Analysis

8.6.1 Efficacy Analyses

Efficacy analyses will be performed based on IRC assessment and Investigator assessment of disease response.

8.6.1.1 Investigator-assessed ORR

The primary analysis will be repeated using the local Investigator-assessed ORR.

8.6.1.2 Duration of Response

The DOR defined as time from first assessment of PR or CR to the first assessment of progressive disease will be summarized by descriptive statistics including median DOR and respective 95% CIs and Kaplan-Meier estimates. DOR will also be listed.

Subjects who started a new anti-lymphoma therapy prior to a documented progressive disease (PD) will be censored at the last disease assessment prior to initiation of new anti-lymphoma therapy. Detailed censoring rules will be described in the SAP.

8.6.2 Safety Analysis

8.6.2.1 Adverse Events

Adverse events, related AEs, SAEs and related SAEs, AEs with NCI CTCAE Grades ≥3, related AEs of NCI CTCAE Grades ≥3, AEs leading to premature discontinuation, interruptions or discontinuation of study drug or dose modification will be analyzed descriptively utilizing corresponding MedDRA SOCs and PTs. NCI CTCAE toxicity grades will be utilized for classifying severity.

8.6.2.2 Safety Laboratory

Safety laboratory results will be graded by NCI CTCAE version v5.0 (or higher). If no grading exists values will be classified into low/normal/high based on laboratory normal ranges. Each parameter will be presented by descriptive statistics at each visit including change from baseline (Screening). Shift tables for CTCAE grades and normal ranges will be presented. All laboratory values will be listed. A separate listing for abnormal lab values (≥Grade 3, and low/high values) will be presented.

8.6.2.3 Vital Signs

Vital signs will be summarized by descriptive statistics at each visit including change from baseline will be presented and a listing will be provided.

8.6.3 Pharmacokinetic Analysis

The analysis plan for PK assessment for AFM13 in the study will be described in the pharmacokinetic analysis plan. [redacted]

Table 6: Pharmacokinetic Parameters

Parameter	Definition
C_{max}	The maximum concentration.
t_{max}	The time to reach maximum concentration.
AUC_{0-t}	The area under the concentration versus time curve from time zero to the sampling time at the last quantifiable concentration (C_t) at t_{last} (the time of the last quantifiable concentration) calculated by the linear up, log down rule.
λ_z	The apparent terminal elimination rate constant, estimated using the negative slope of the least square regression analysis of the natural log concentration versus time data for the terminal linear portion of the curve.
$t_{1/2}$	The terminal half-life, calculated from Ln 2 / λ_z.
$AUC_{0-\infty}$	The area under the concentration versus time curve from time zero to infinity as the sum of the 2 areas: AUC_{0-t} and AUC_{extrap}, where AUC_{extrap} is calculated as C_t/λ_z.
CL	The clearance calculated as: Dose/$AUC_{0-\infty}$.
V_{ss}	The apparent volume of distribution at steady state calculated as: Dose/AUC × (AUMC/$UC_{0-\infty}$ - $t_{1/2}$).

8.6.4 Immunogenicity Analysis

Immunogenicity parameters will be summarized by descriptive statistics and listed.

8.6.5 Quality of Life

The change in EQ-5D total score, EQ-5D pain score and in Skindex 29 from baseline will be analyzed over time. The score will be summarized by descriptive statistics and listed.

8.7 Exploratory Analyses

[redacted]

[redacted]

8.8 Sample Size Calculation

8.8.1 Estimated Sample Size

[redacted]

8.9 Interim Analysis

An interim analysis will be performed for Cohort A and Cohort B independently, with all subjects enrolled at, or prior to the cut-off date defined as the completion of the 20th subject for each cohort. Each interim analysis will be conducted once this number of subjects have completed at least one post-baseline disease assessment to be categorized under the response endpoint or have withdrawn from the trial medication. The results from this interim analysis will be non-binding as its main purpose is the evaluation of the comparability of Cohorts A and B, and in such a case they are comparable, they may be combined into one cohort. If the cohorts are considered to be not comparable, enrollment into Cohort B will be stopped.

8.10 Subgroup Analyses

9 QUALITY ASSURANCE

9.1 Data Recording, Monitoring of the Study and Regulatory Compliance

The project manager, or their designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, and fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit, the eCRF and other pertinent study materials will be reviewed with the Investigator's research staff. During the course of the study, the CRA will make regular site visits in order to review protocol compliance, examine CRFs and individual subject's medical records and assure that the study is being conducted according to pertinent regulatory requirements. Sites should ensure that source documentation is available to enable verification of all eCRF data entries. The review of medical records will be done in a manner to assure that subject confidentiality is maintained.

All eCRF data will be collected using an eCRF within a fully validated and CFR 21 Part 11-compliant electronic data capture system. All data will be entered into the eCRF by the site staff. These data will then be source-data verified and reviewed by the CRAs before data cleaning by Data Management is performed. All queries will be raised and resolved within the electronic data capture system. During entry, programmatic checking of the data will be performed and once saved into the database, more complex programmatic checks will also be performed. During the conduct of the study, all system users will have real-time access to the data. The level of access to the data and study privileges will be determined by their user role.

After all queries have been resolved, the SAP approved and signed, and any summary/analysis populations approved, the database will be locked, and the data released for summary and analysis. All summary and analysis of the data will be performed using appropriate version of SAS® and WinNonLin Pro, or equivalent.

9.2 Study Monitoring

CRAs will be responsible for the monitoring of the study. The CRA will review the progress of the study on a regular basis to ensure adequate and accurate data collections. Monitoring site visits to review the eCRF, subject case notes, administrative documentation, including the Investigator Site File, and frequent telephone/e-mail communications with site will be performed throughout the study.

At each study monitoring visit, the Investigator will make available all records pertaining to the study. To allow sufficient time to assemble documentation for the CRA, monitoring visits will be confirmed in advance of planned visits.

The process for study monitoring and source data verification requirements for the study will be specified in the Monitoring Plan (or equivalent).

9.3 Clinical Study Audit

The Sponsor, Sponsor representative, or external regulatory agency may at any time during or after completion of the study conduct a Good Clinical Practice (GCP) audit. Prior notice will be given to each site selected for audit in advance of a planned audit.

9.4 Clinical Study Report

The results of the study will be presented in an integrated CSR according to ICH guidelines.

9.5 Data Availability

The Investigator is required to maintain copies of all essential study documentation, including the Site Study File, all eCRF data (including the full audit trail and all data queries), signed ICFs and records for the receipt and disposition of study drug.

During the study, the Investigator must make study data accessible to the CRA, the Sponsor (or a third-party auditor assigned by the Sponsor), and relevant IRB/EC and regulatory agencies. A file (or appropriate records) for each subject must be maintained that includes the signed ICF and all source documentation related to that subject. The Investigator must ensure the availability of source documents from which the information in the eCRF was derived.

Please refer to Section 12.2 for details of required record retention for the study.

9.6 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 (or accepted equivalent) and a financial disclosure statement. All Sub-investigators will be required to provide a current curriculum vitae and a financial disclosure statement.

9.7 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor. Any such changes which may affect a subject's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/EC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (eg, change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/EC by the Principal Investigator.

10 ETHICAL CONSIDERATIONS

The Investigator will obtain written informed consent from each subject, or their authorized representative, participating in the study. The form must be signed, witnessed and dated. The ICF will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the ICH Guideline for GCP, and the terms of the Declaration of Helsinki. Copies of the signed document should be given to the subject and filed in the Investigator's Study File, as well as the subject's medical record if in conformance with the institution's Standard Operating Procedures.

The final study protocol and subject ICF will be approved by the appropriate IRB/EC for each investigational site. Approval will be received in writing before initiation of the study.

Changes to the protocol during the trial will be documented as amendments. Depending on the contents of the amendment and local legal requirements, the amendment will be submitted for approval to the relevant IRB/EC and to the relevant competent authorities prior to implementation. Exceptions are cases of changes made to protect subject safety, which will be implemented immediately.

If an amendment substantially alters the trial design, increases the potential risk to the subjects, affects the treatment of the subject, or might otherwise influence the willingness of the subject to participate in the trial, then the ICF must be revised and submitted to the relevant IRB/EC and, where necessary, to the relevant competent authorities, for review and approval. When a subject is currently undergoing trial procedures and is affected by the amendment, then the subject must be asked to consent again using the new ICF.

10.1 Ethical Conduct of the Study

The study will be conducted in accordance with ICH GCP, the Declaration of Helsinki, the European Union Clinical Trials Directive 2001/20/EC, the GCP Directive 2005/28/EC, the requirements of local IRB/EC, and the US Code of Federal Regulations, Title 21 CFR Part 50.

10.2 Informed Consent

The principles of informed consent in the Declaration of Helsinki and GCP guidelines will be implemented before any protocol-specific procedures or interventions are carried out.

All subjects will be informed that participation is voluntary and that they can cease participation at any time without necessarily giving a reason and without any penalty or loss of benefits to which they are entitled.

With the help of the ICF, the subject will be informed about the AFM13 study drug and anticipated effects and the reason, design and implication of the trial. The subject must give consent to participate prior to enrolment in the trial. This consent must be given in writing. The Investigator who conducts the informed consent discussion must also sign. The Investigator may delegate this responsibility to a suitably qualified member of the study team (eg, Sub-Investigator) if permitted by local regulations. This delegation of responsibility must be recorded in the Study File. By giving signed consent, the subject will confirm that his or her

participation is voluntary and that he or she will follow the instructions of the Investigator and answer the questions asked. Signatures must be personally dated.

The signed and dated consent form will be kept by the Investigator. Prior to participation in the trial, the subject should receive a copy of the signed and dated written ICF.

The ICF must include all elements required by law, local regulations, GCP and ICH guidelines including consent to allow the Sponsor, Sponsor representative, or external regulatory auditor to review the subject's medical records. This gives permission to examine, analyze, verify and reproduce any records and reports that are important to the evaluation of the trial.

Any party with direct access must take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of the subjects' identities and Sponsor's proprietary information. It is the CRA's responsibility to verify that each subject has consented, in writing, to direct access.

10.3 Patient Participation Card

A study participation card will be provided to subjects where required by local regulations or IRB/EC. The card will indicate that he or she is participating in a clinical trial and give the name and contact details of the Sponsor and the Investigator/study site. The subject will be asked to retain this card while participating in the trial and show it to any other medical practitioners consulted during this time. Subjects will be advised to contact the Investigator/study site if there are any questions. A sample patient participation card is shown below.

Figure 3: Sample Patient Participation Card

Dear Patient, ***Please inform any physician you visit during the course of the study that you are participating in a clinical trial by presenting this contact card.*** ***Please carry this card with you at all times until the end of the study.*** **Patient Name:**..... is participating in an open-label trial and is receiving an investigational product, AFM13, a novel, tetravalent bispecific chimeric (anti-human CD30 x anti-human CD16A) recombinant antibody construct (ROCK®). Patient Contact Card Version X/date		**Clinical Trial Contact Card** **Study AFM13-202:** A Phase II Open-label Multicenter Study to Assess the Efficacy and Safety of AFM13 in Patients with Relapsed or Refractory CD30-positive Peripheral T-cell Lymphoma or Transformed Mycosis Fungoides **In the case that additional medications must be prescribed, you need more information about the clinical trial, or the patient's condition has worsened, please contact the treating study physician:** Name: ..... Phone: ..... Address: ……..

10.4 Insurance

Appropriate insurance for this trial will be arranged by Affimed (or their delegate), as Sponsor of the clinical trial, in accordance with the regulatory requirements of the countries involved. A copy of the country-specific insurance certificate will be held in the Trial Master File and in the Investigator Site File.

10.5 Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the IRB/EC and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/EC in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/EC will be kept informed by the Investigator, contract research organization or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected adverse events.

10.6 Subject Privacy

The Investigator must ensure that subject privacy is maintained. On the eCRF or other documents submitted to the Sponsor, subjects will be identified by a subject number only. Clinical study documents that are not submitted to the Sponsor (eg, signed ICF) should be kept in a confidential file by the Principal Investigator.

In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or their designee personnel access to all pertinent medical records to verify the data gathered on the CRFs and to audit the data collection process. Regulatory agencies such as the FDA may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the subject as outlined in the subject consent form.

11 DATA CONFIDENTIALITY AND PUBLICATION POLICY

The original CRFs and all data generated during the clinical study are the property of the Sponsor. In addition, all information regarding AFM13 and the Sponsor's operations (eg, patent applications, formulas, manufacturing processes, basic scientific data or formulation information) supplied by the Sponsor to the Investigator and not previously published is considered confidential. This confidential information remains the sole property of the Sponsor and shall not be disclosed to others without the written consent of the Sponsor. The Investigator agrees to use this information only to perform this study and will not use it for other purposes, including publications and presentations, without the Sponsor's written consent.

The first publication of the study results shall be made by the Sponsor. Any proposed publication or presentation (including a manuscript, abstract or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review prior to submission. Publication of the results will not include confidential information, including inventions, non-public intellectual property rights and know how, without the permission of the Sponsor. The full terms of confidentiality, intellectual property and publication policy are described in the current Clinical Trial Agreement between the Sponsor and the site.

The Sponsor may announce quality assured summary data to comply with Financial Regulatory Authorities, while ensuring, so far as possible, that such announcements will not compromise the Investigators ability to publish the data in appropriate scientific forums.

12 DATA HANDLING AND RECORD KEEPING

12.1 Recording of Data

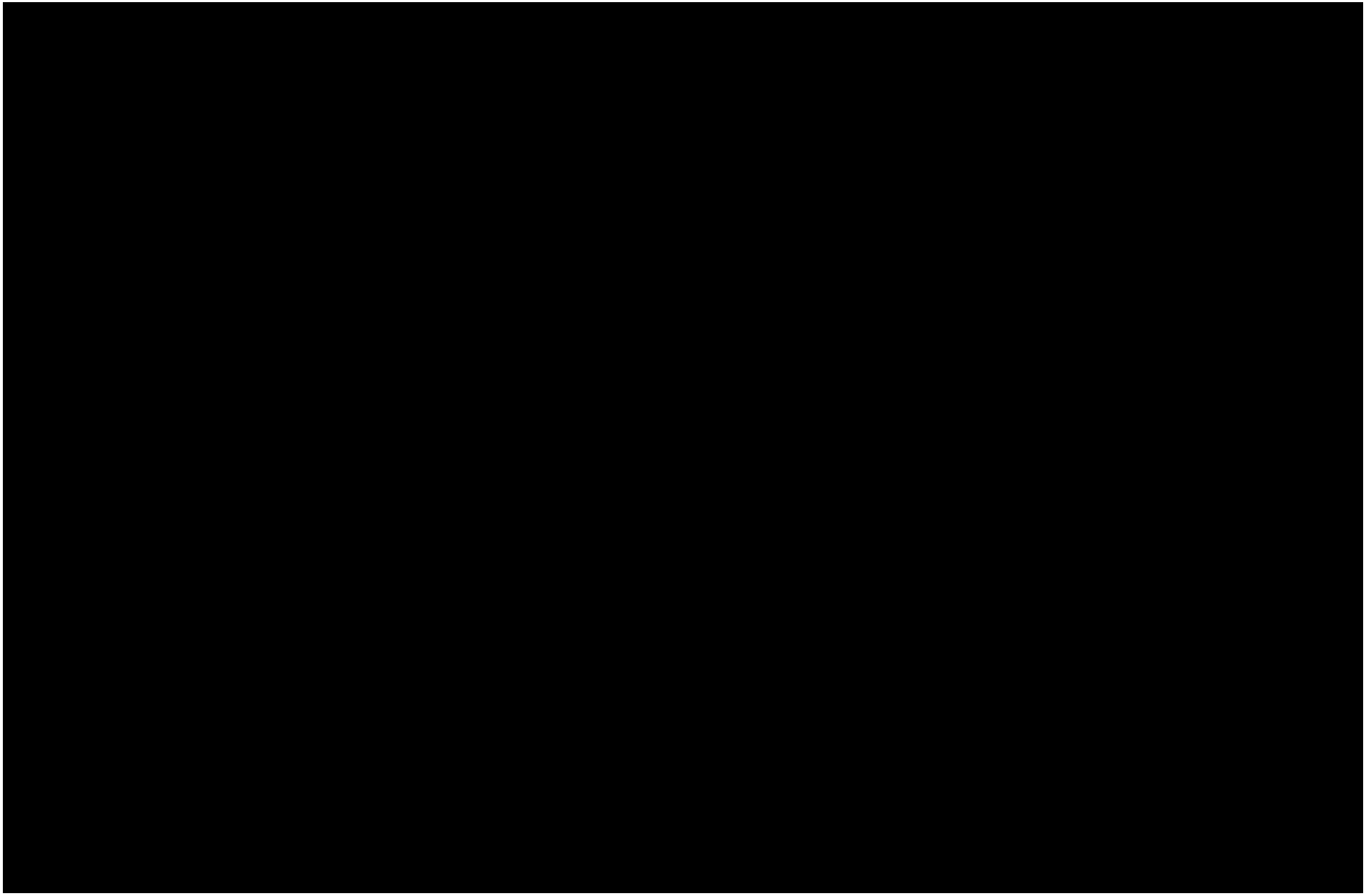
The Investigator will be responsible for the recording of all data on the CRFs provided, as certified by the Investigator's signature and date on the designated pages. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRFs.

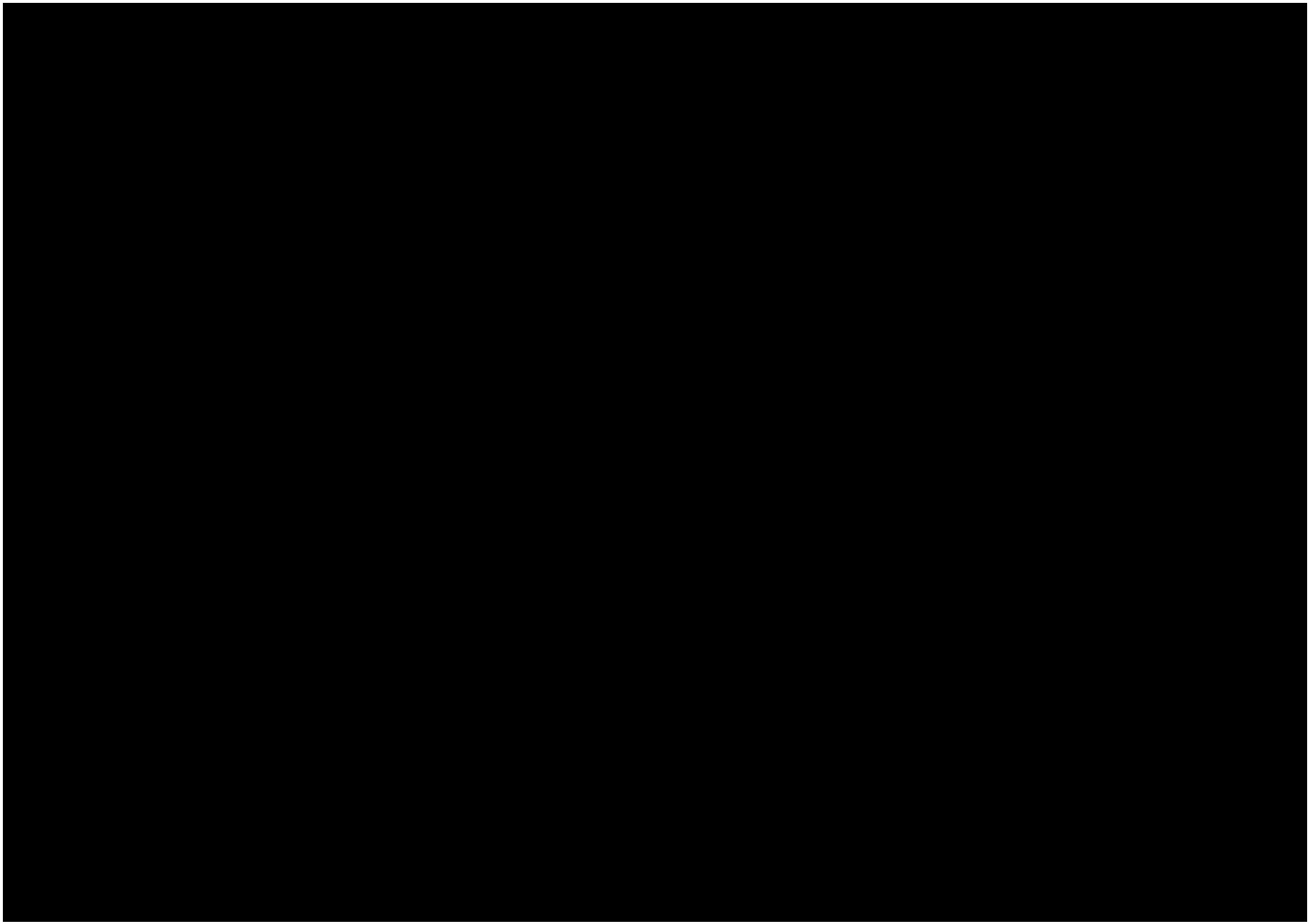
The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data. To facilitate photocopying, entries must be recorded legibly in black ink only. Erroneous entries will be crossed out with a single line, so as to remain legible. The correct value will be entered above the error and then initialed and dated by the person authorized to make the correction.

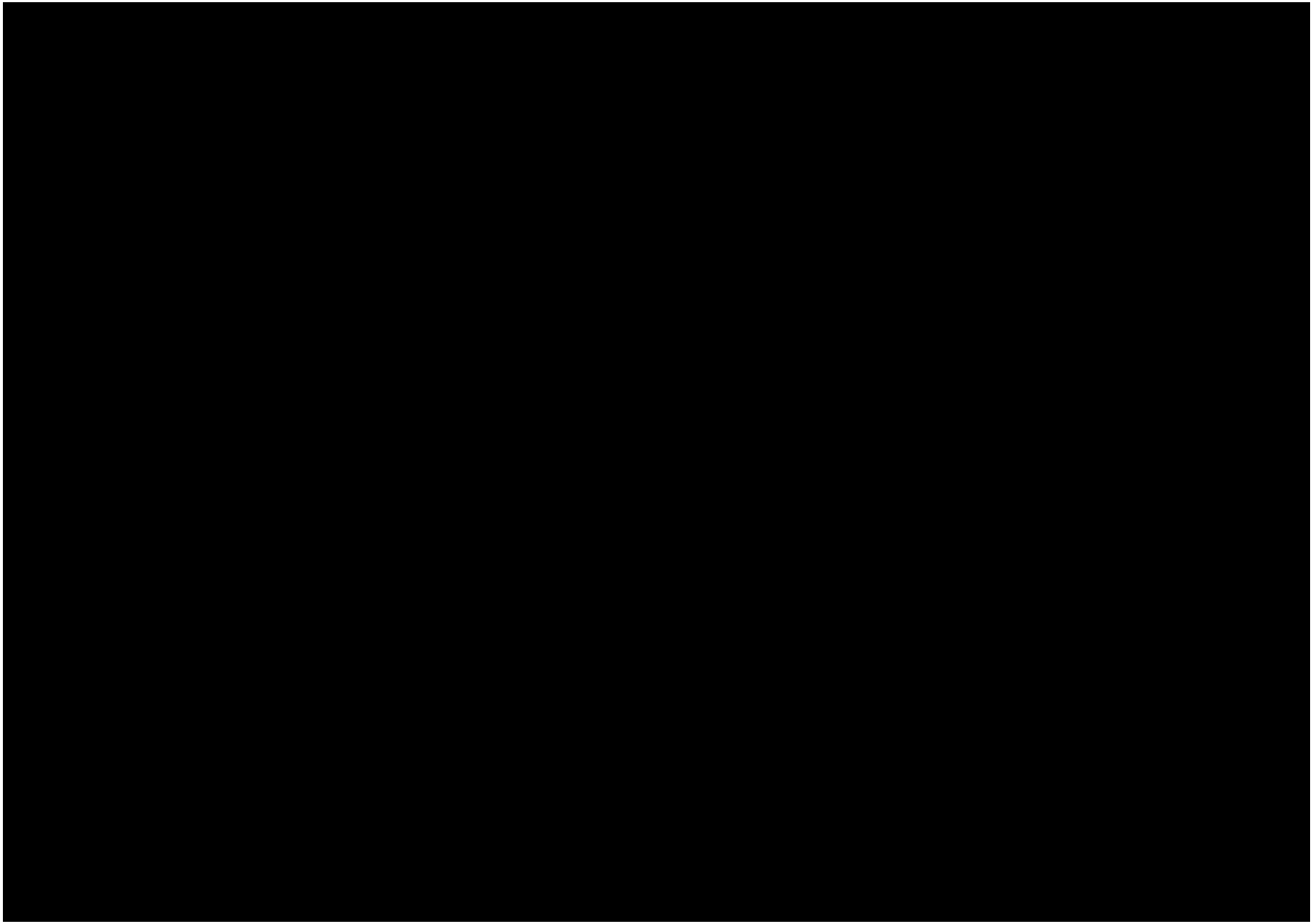
12.2 Study Record Retention

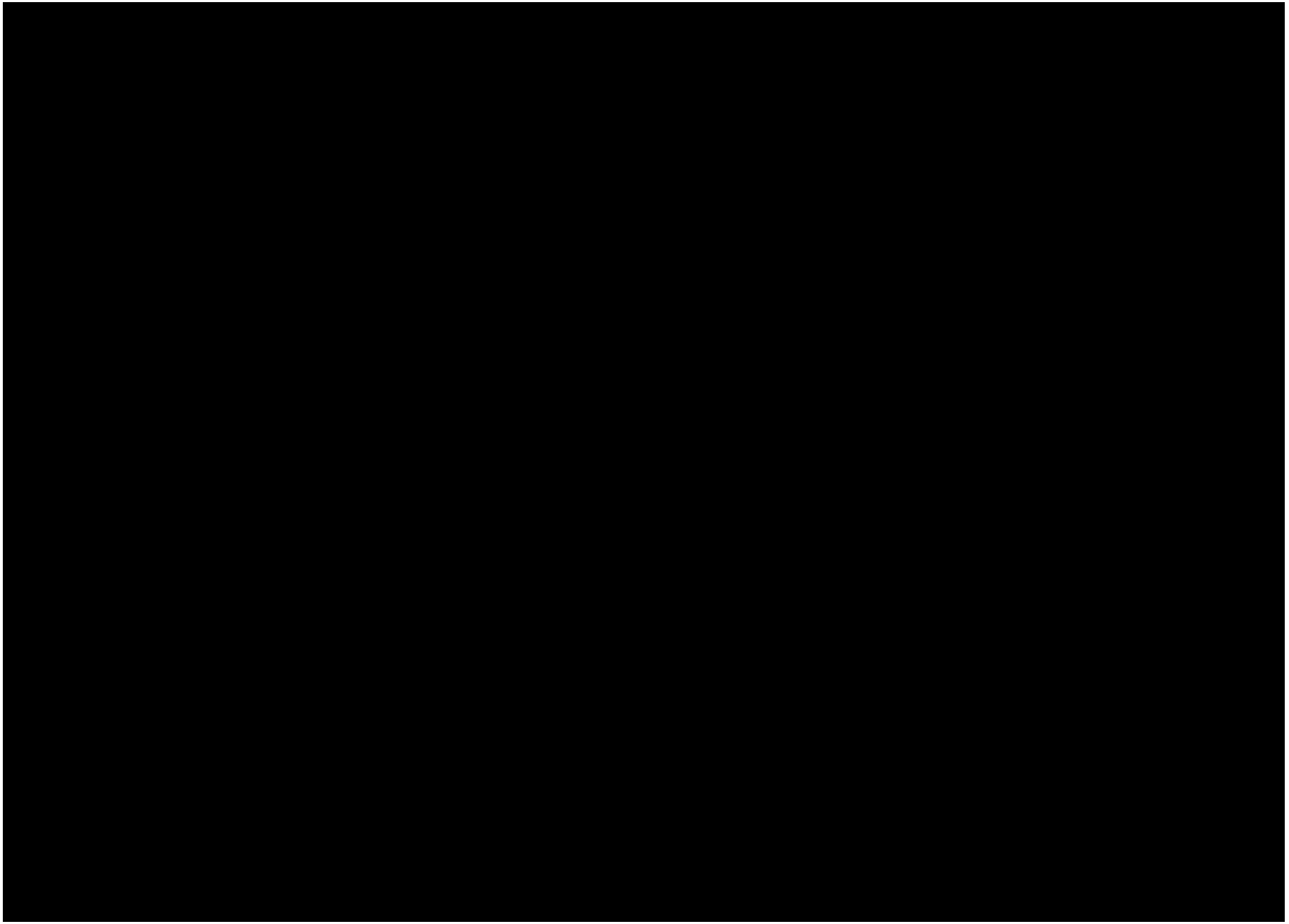
All clinical study documents must be retained by the Investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, US, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator must retain all clinical study documents until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, or by local regulations.

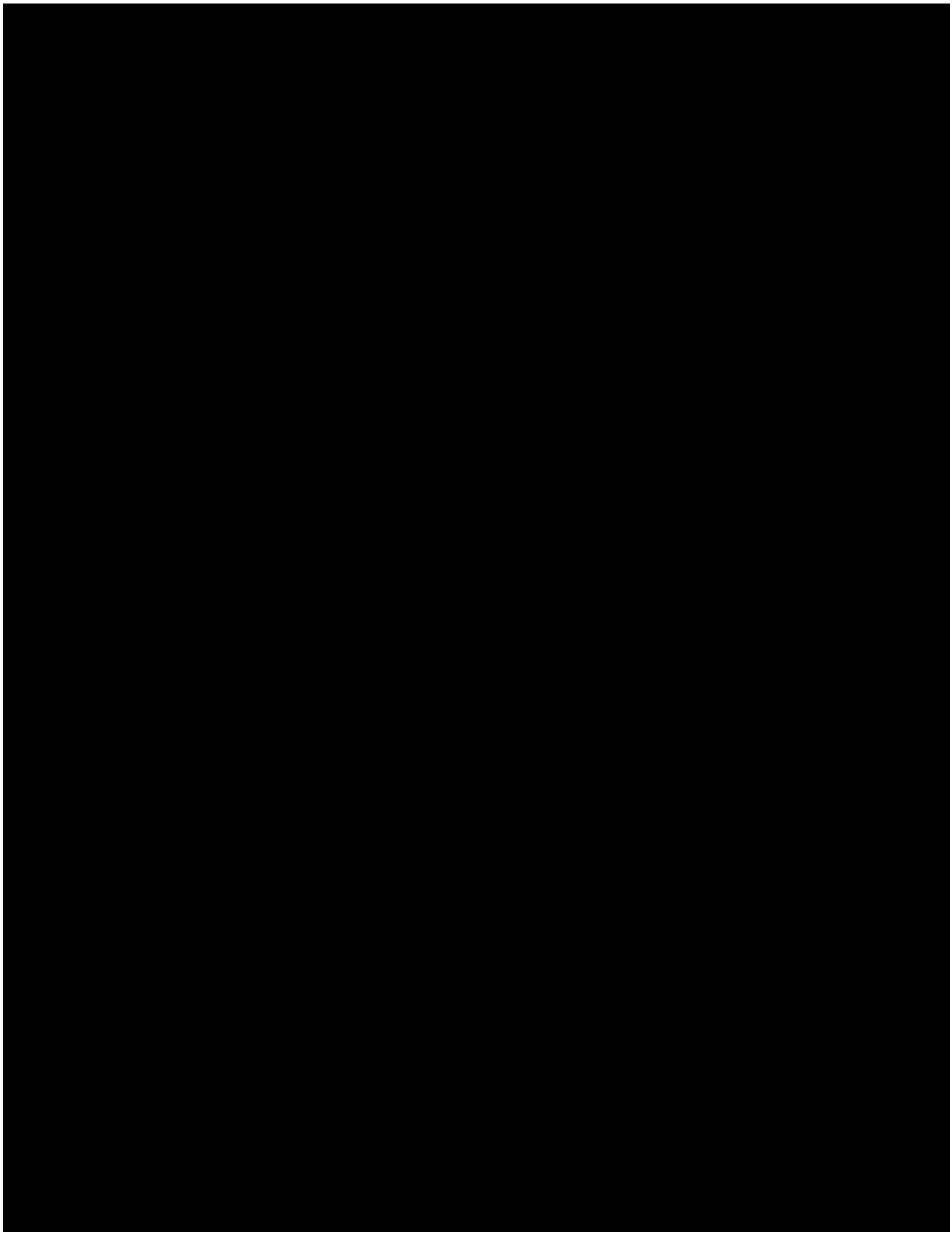
Subjects' medical files should be retained in accordance with applicable legislation and with the maximum period permitted by the hospital, institution or private practice.

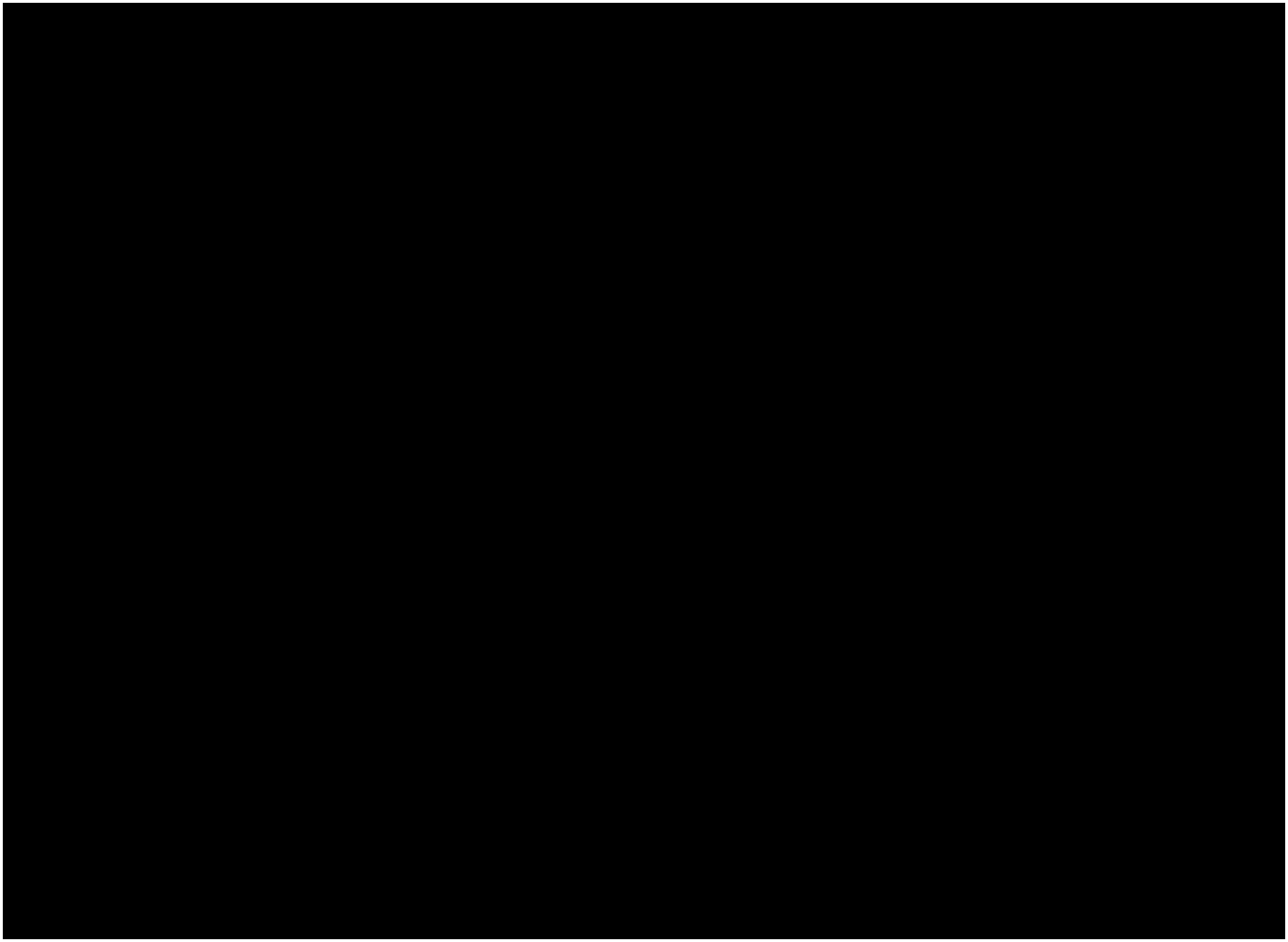


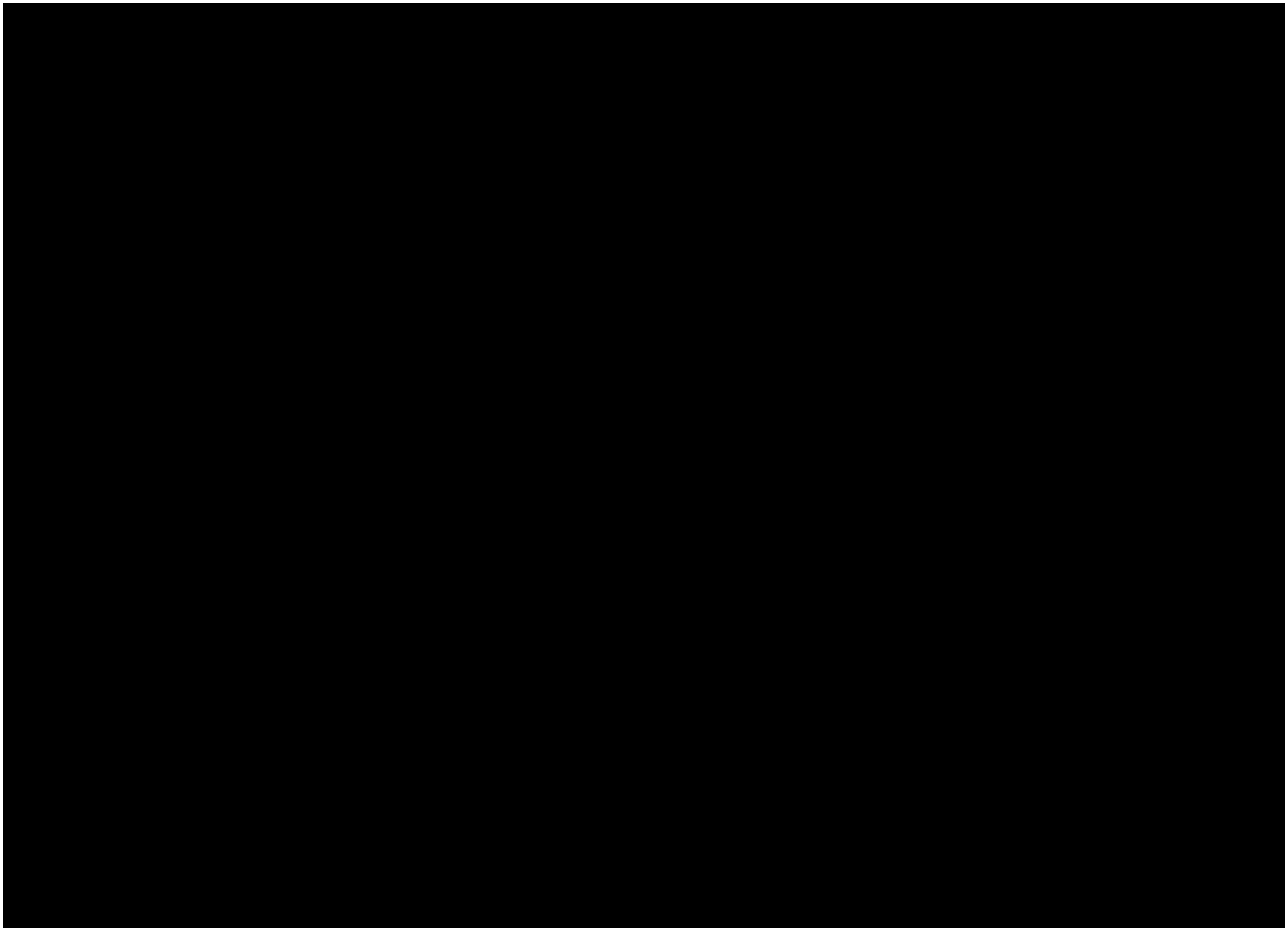


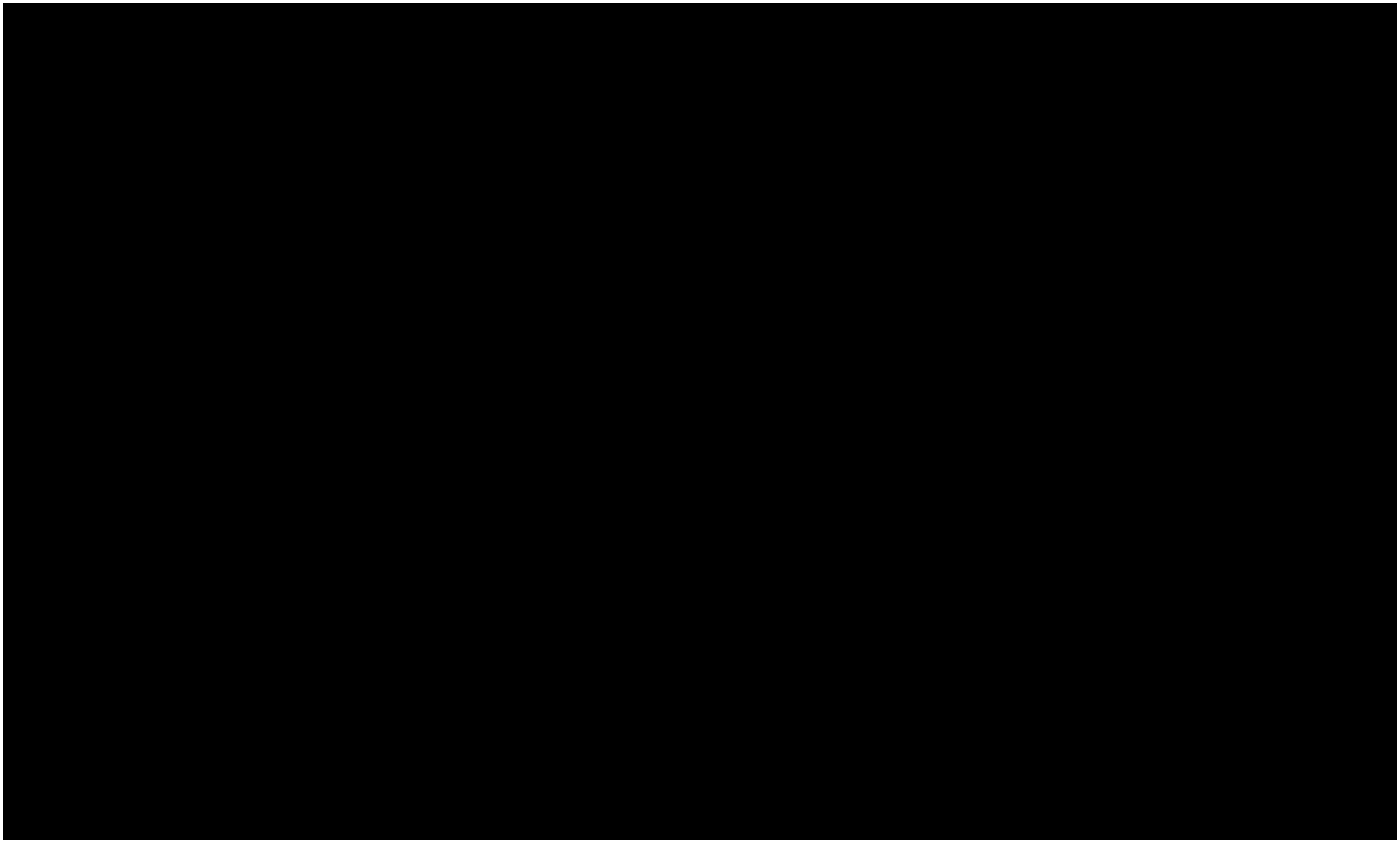


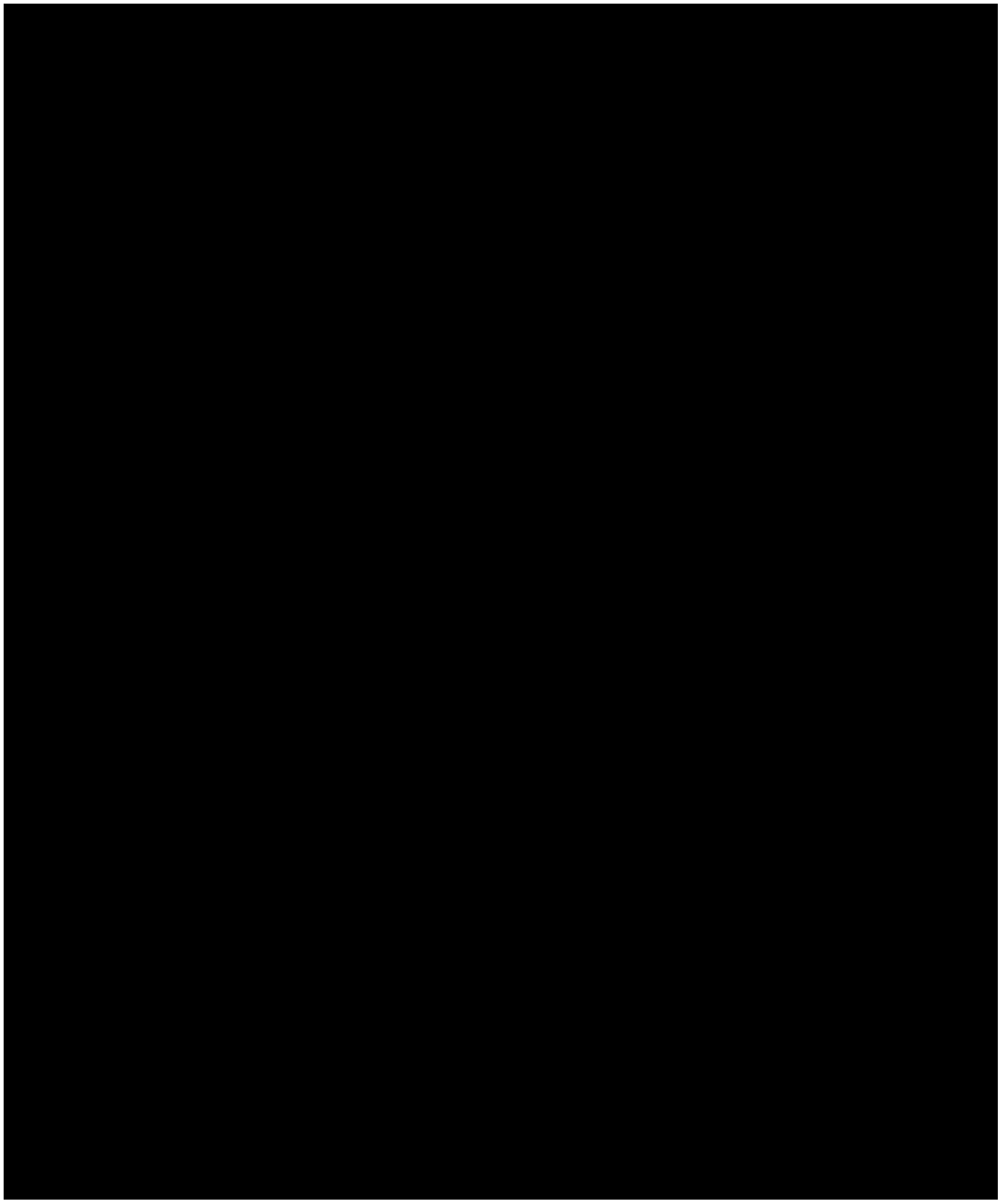


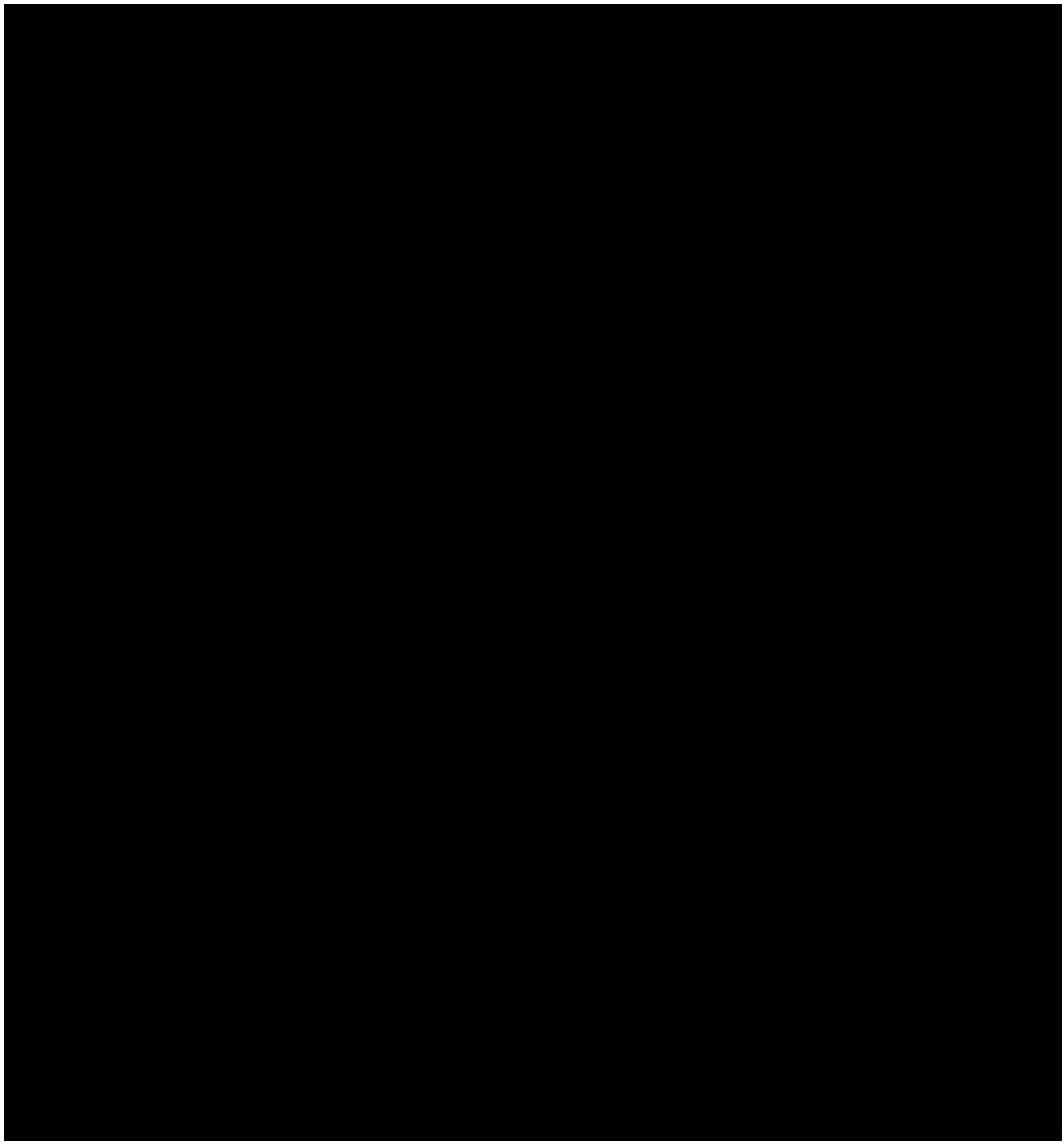


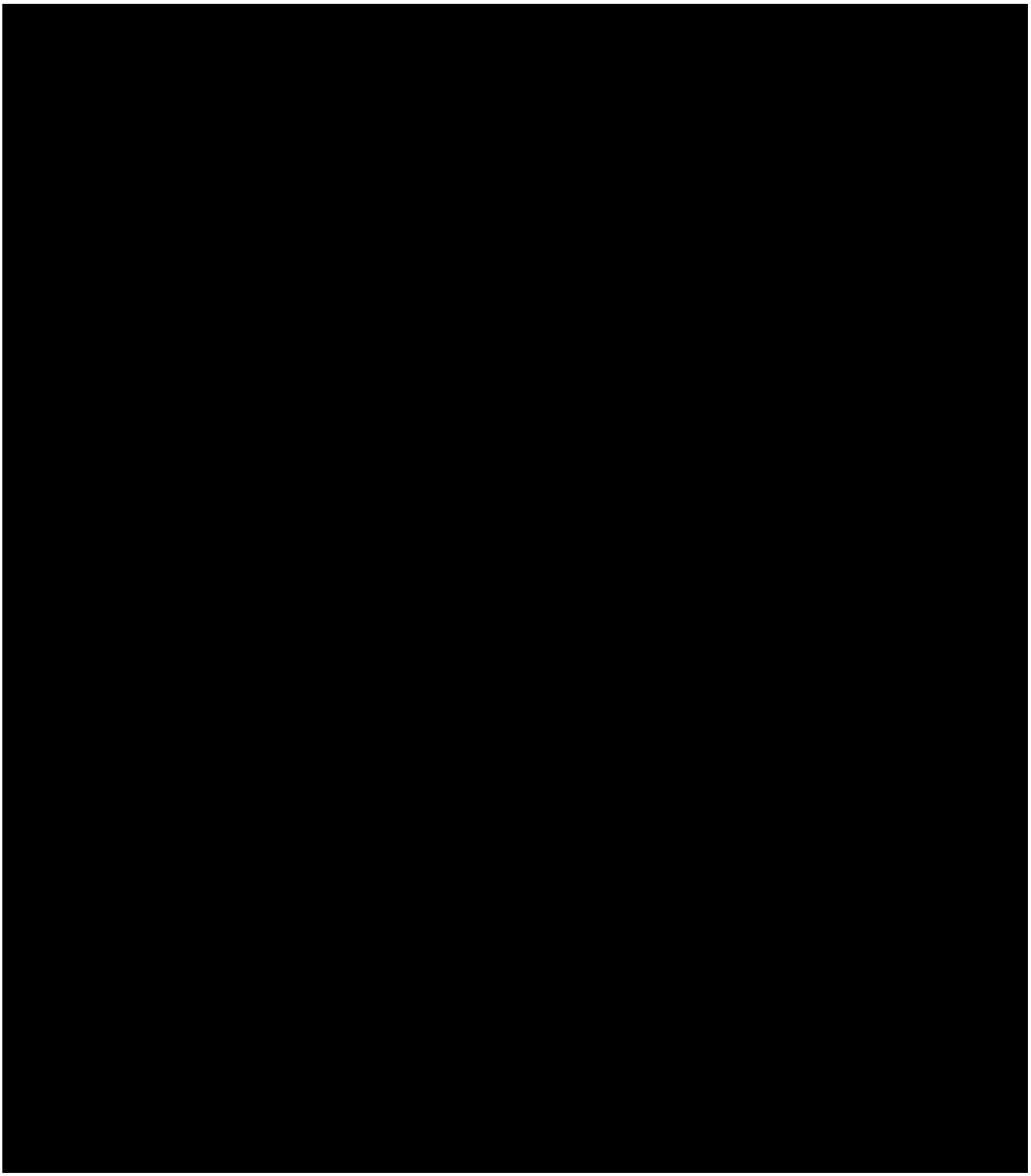


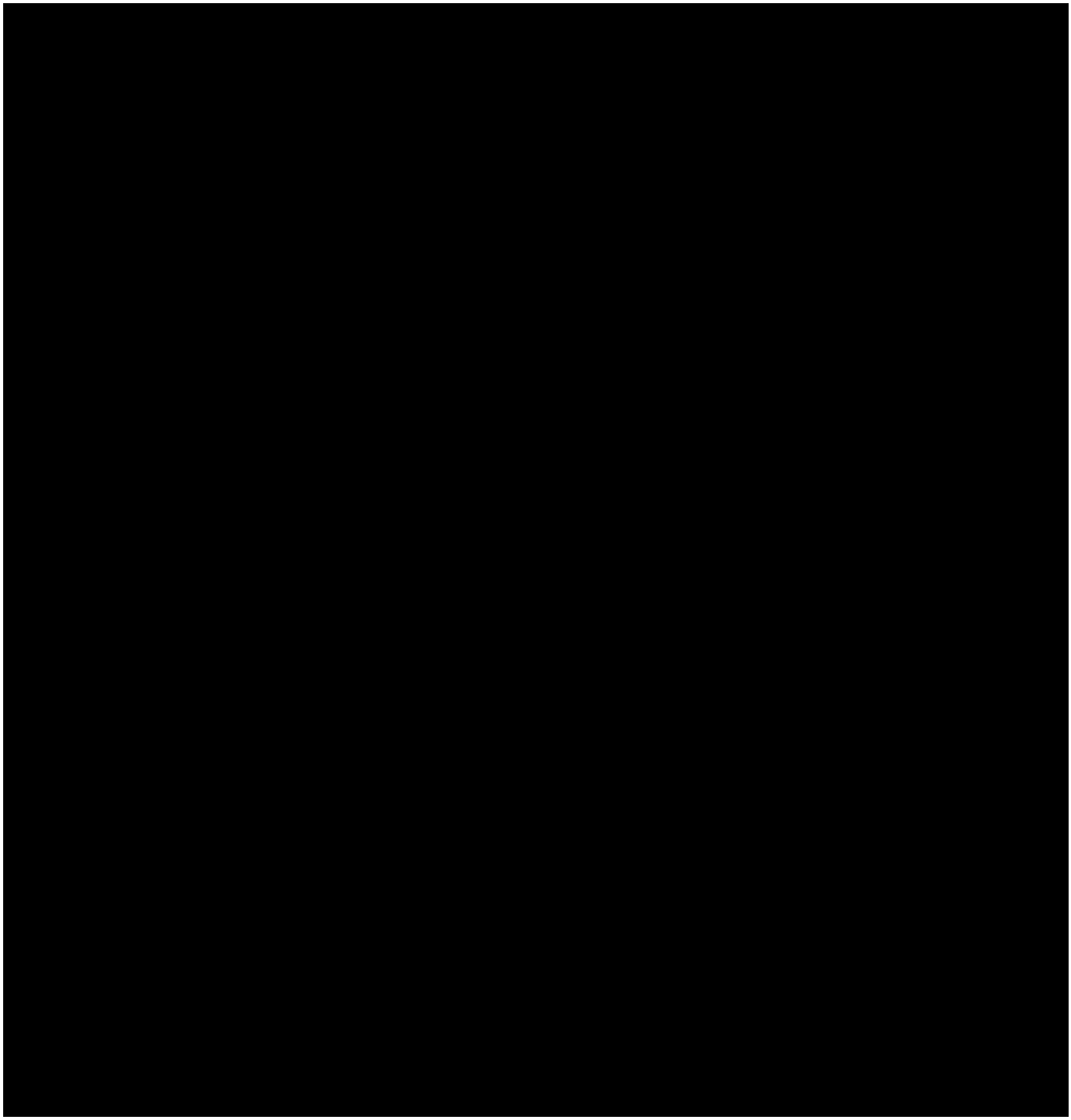


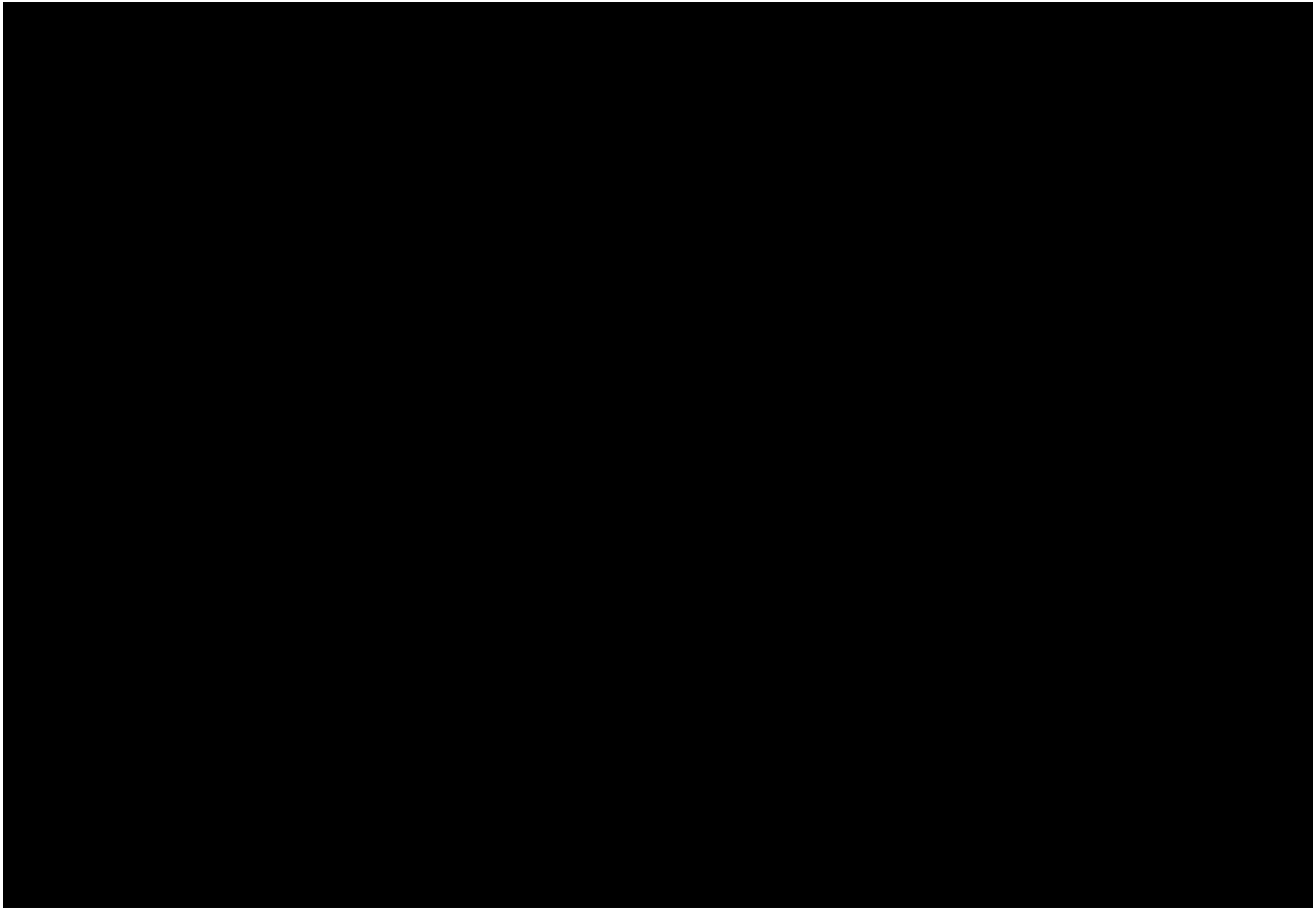


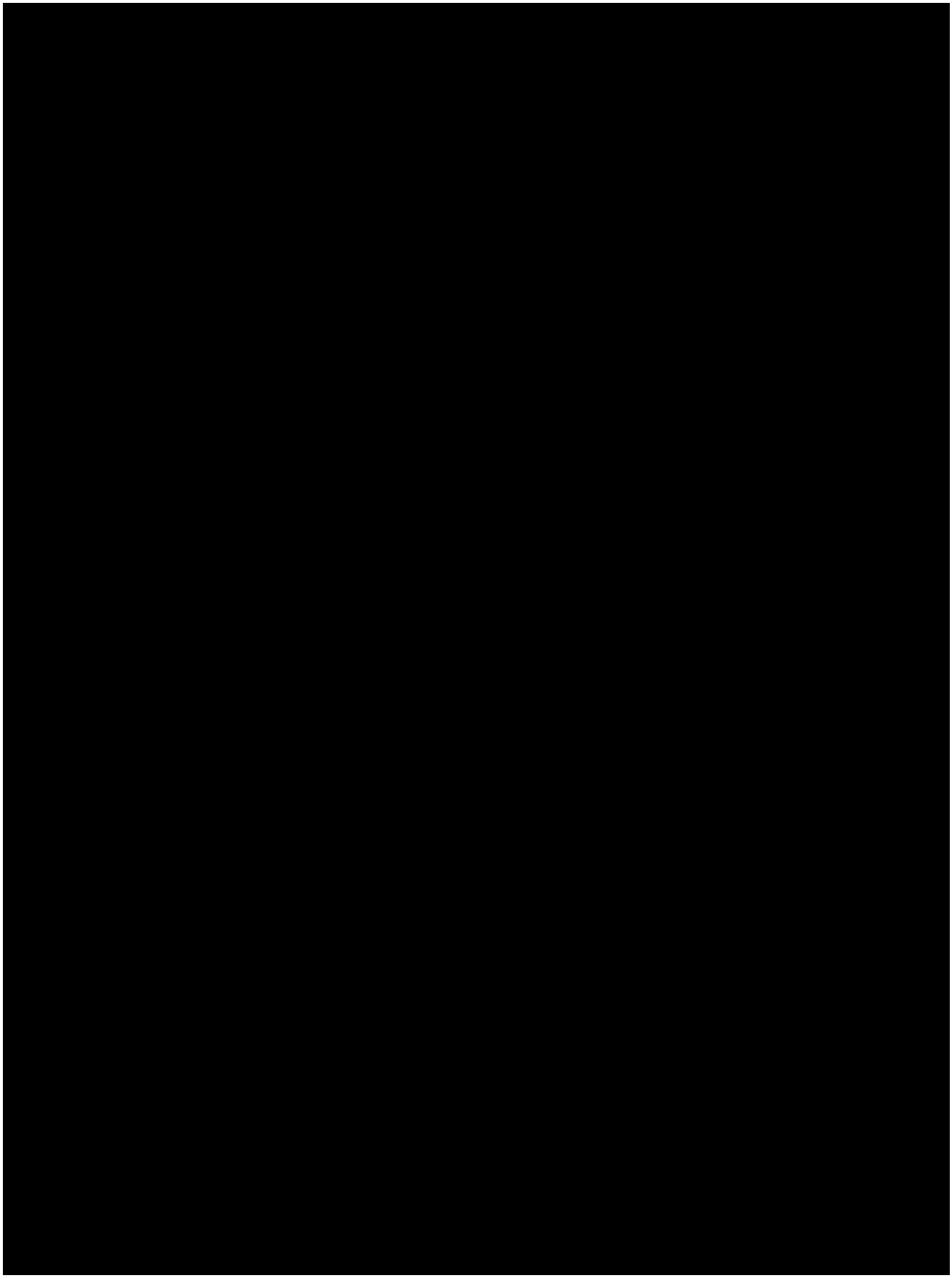


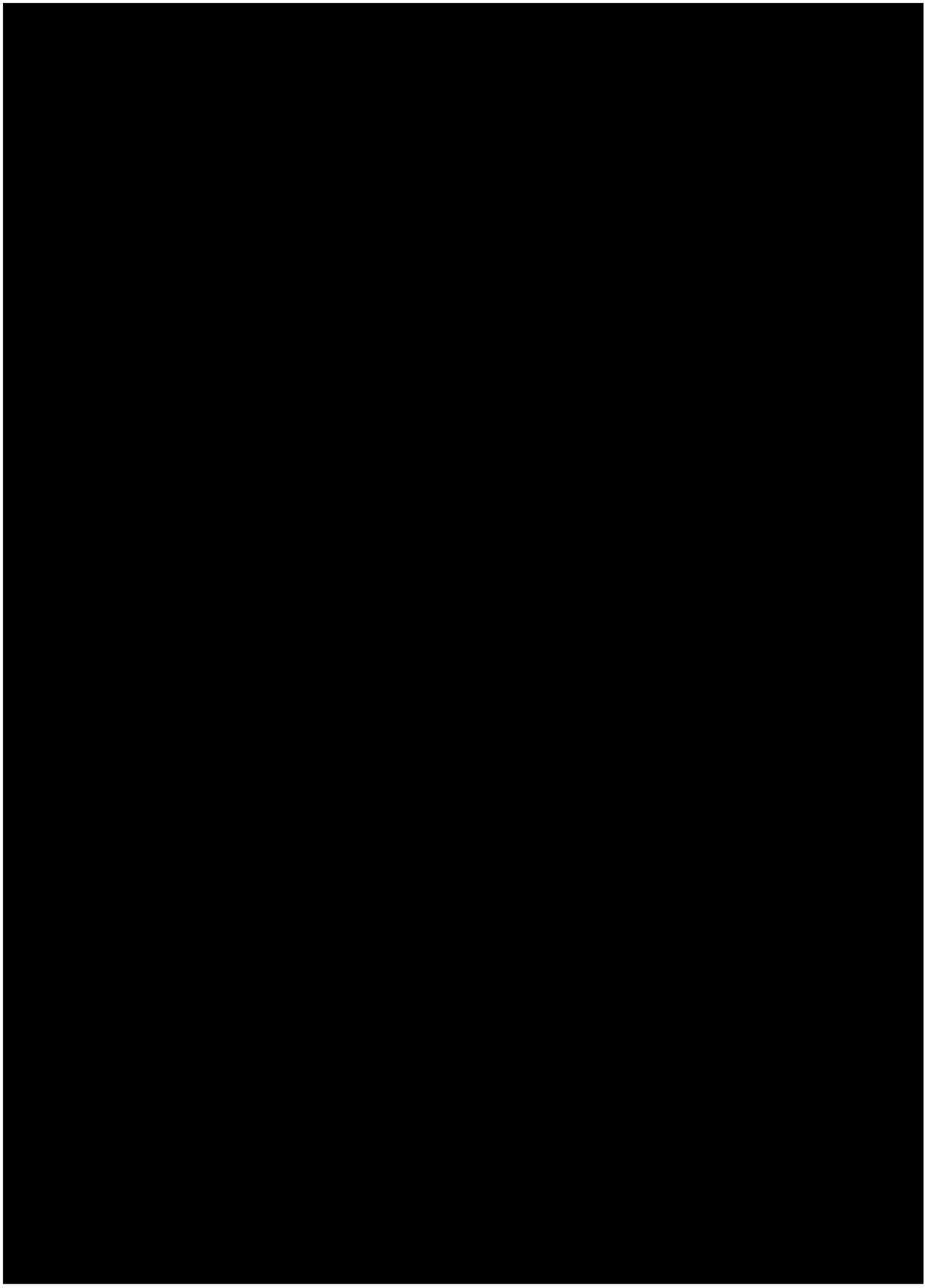


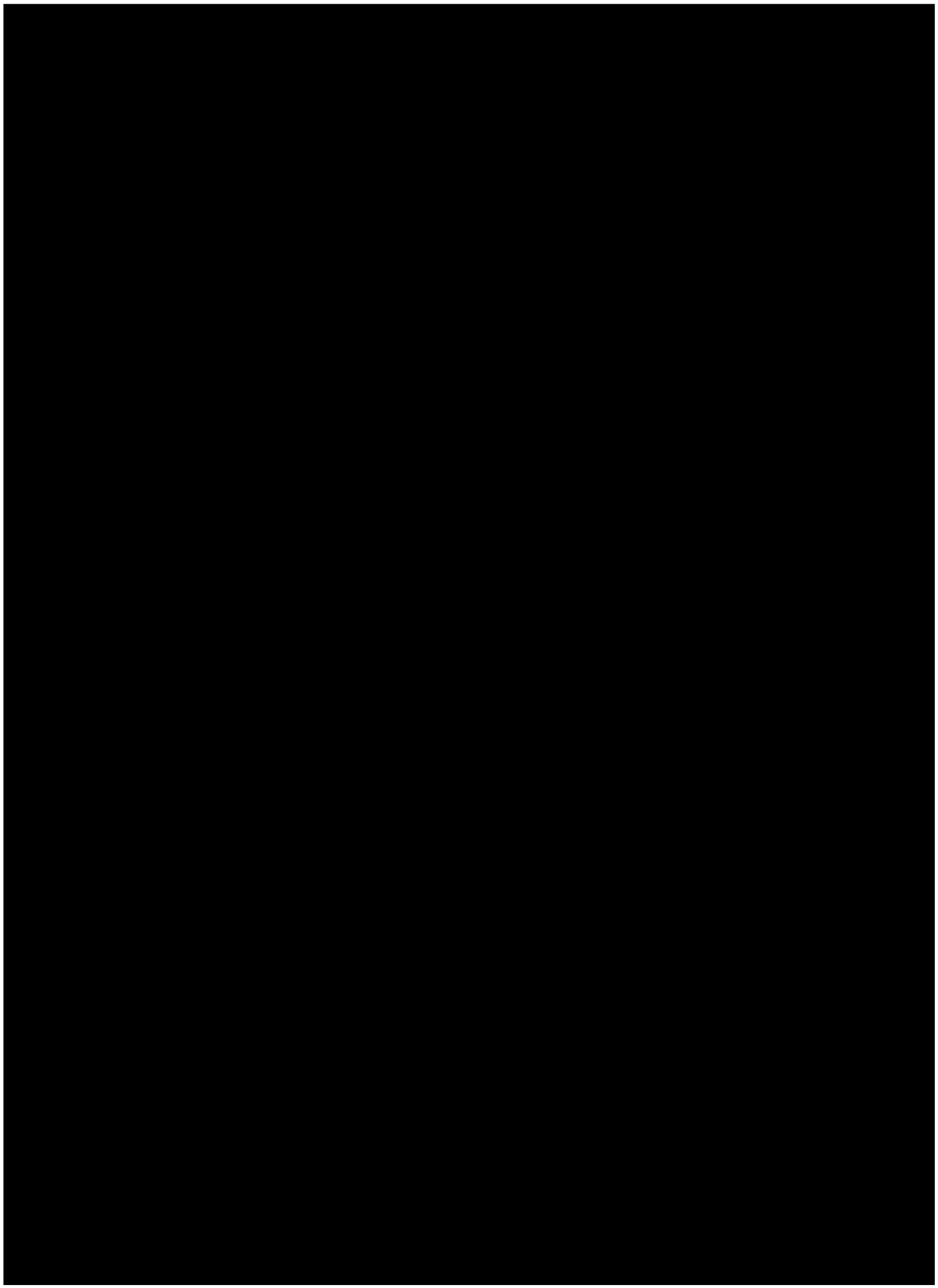


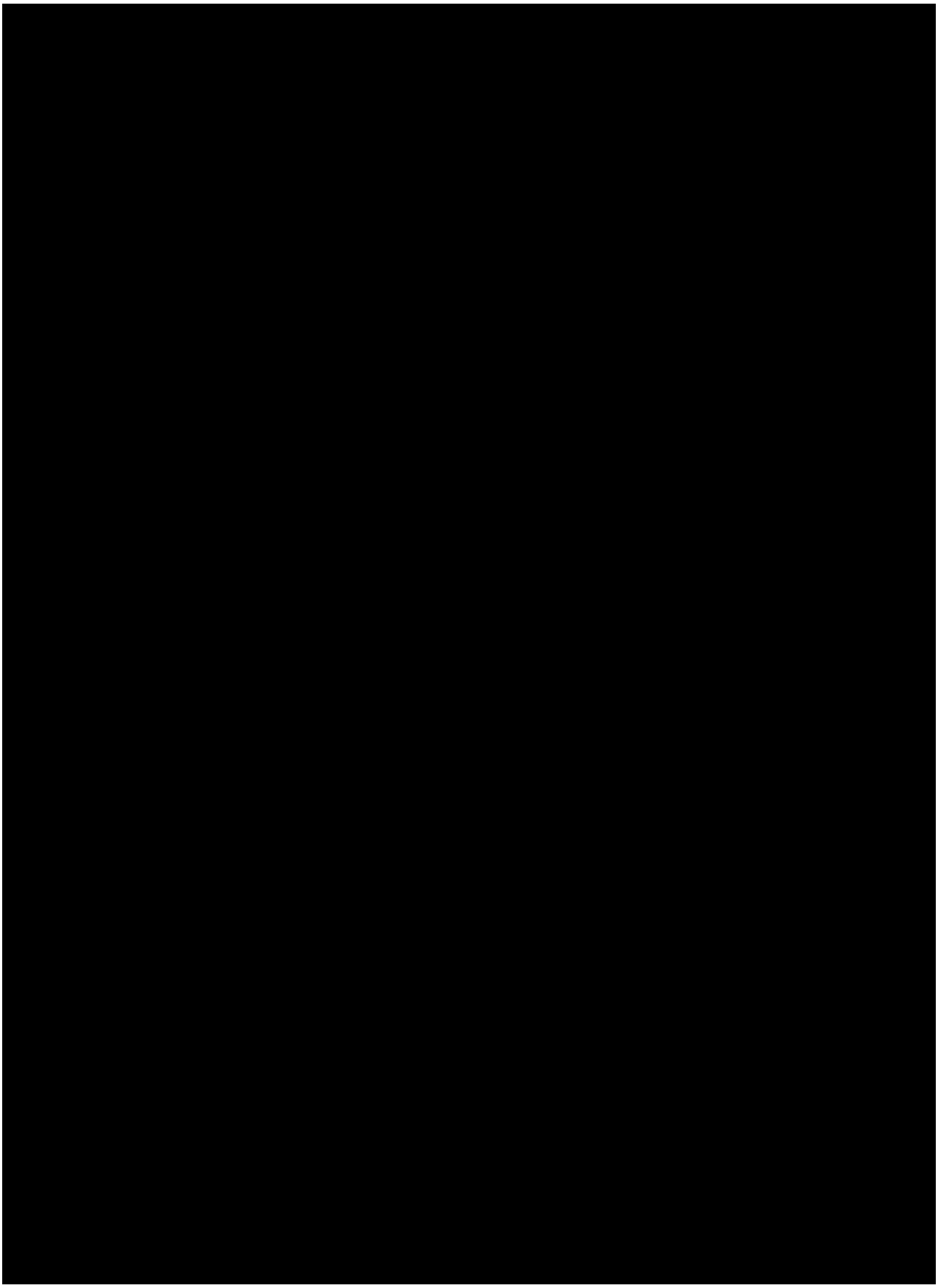


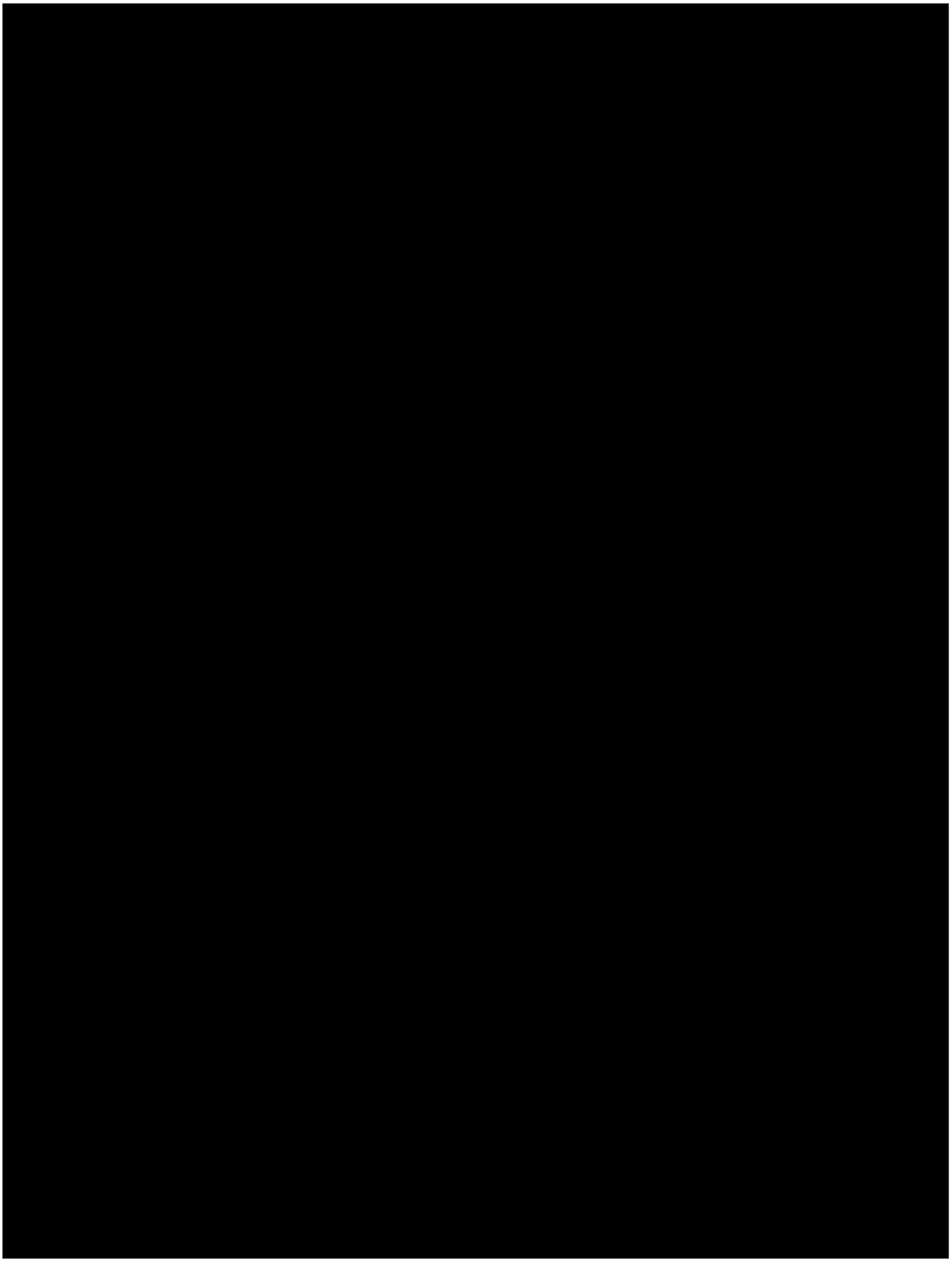












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