Official Title of Study:

An Exploratory Phase 1/2 Trial to Evaluate the Safety and Efficacy of JCAR017 Combinations in Subjects with Relapsed/Refractory B-Cell Malignancies (Platform)

Protocol: JCAR017-BCM-002

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AN EXPLORATORY PHASE 1/2 TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF JCAR017 COMBINATIONS IN SUBJECTS WITH RELAPSED/REFRACTORY B-CELL MALIGNANCIES (PLATFORM)

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PLATFORM

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(See appended electronic signature page)
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH), Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SUMMARY

Study Title

An exploratory Phase 1/2 trial to evaluate the safety and efficacy of JCAR017 combinations in subjects with relapsed/refractory B-cell malignancies (PLATFORM)

Indication

Relapsed/refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL) in subjects ≥ 18 years.

Objectives

Primary Objective:

Dose finding (Phase 1):

To evaluate the safety and to define the recommended Phase 2 dose and schedule (RP2D) of JCAR017 combinations in adult subjects with R/R aggressive B-cell NHL

Dose expansion (Phase 2):

To evaluate the efficacy of JCAR017 combinations in adult subjects with R/R aggressive B-cell NHL defined as complete response rate (CRR)

Secondary Objectives:

Dose finding (Phase 1):

- To assess the efficacy of JCAR017 combinations

Dose expansion (Phase 2):

- To assess the safety and other efficacy parameters of JCAR017 combinations
- To characterize changes in health-related quality of life (HRQoL) outcome measures for subjects treated with JCAR017 combinations

Phase 1/2:

- To characterize the pharmacokinetic (PK) profiles of JCAR017
- To characterize the PK profiles of the respective combination agents

Study Design

This is a global, open-label, multi-arm, parallel multi-cohort, multi-center, Phase 1/2 study to determine the safety, tolerability, PK, efficacy and HRQoL of JCAR017 in combination with various agents. This protocol is intended to evaluate various drug combinations with JCAR017, as separate arms, over the life of the protocol, using the same objectives. Each combination will be evaluated separately (ie, the intention is not to compare between combinations) for the purposes of the objectives, trial design, and statistical analysis. The following combinations will be tested:

- Arm A: JCAR017 in combination with durvalumab
- Arm B: JCAR017 in combination with avadomide (CC-122)

- Arm C: JCAR017 in combination with CC-220 (iberdomide)
- Arm D: JCAR017 in combination with ibrutinib
- Arm E: JCAR017 in combination with relatlimab and/or nivolumab
- Arm F: JCAR017 in combination with CC-99282

Additional arms will be added by way of amendment once combination agents have been selected.

The study will consist of 2 parts: dose finding (Phase 1) and dose expansion (Phase 2). Dose expansion may occur in one or more arms.

During the Phase 1 part, different arms may be opened to test JCAR017 in combination with combination agent(s). Within each arm, different doses and schedules of JCAR017 and the combination agent(s) may be tested in several cohorts (referring to the setting of the combination, eg, post-expansion, post-infusion, or pre-infusion) and subcohorts (referring to the specific dose schedule) per arm. During the Phase 2 part of the study, the expansion of any dose level and schedule (or subcohort) for any arm that has been shown to be safe may occur.

- **Arm A** will test JCAR017 in combination with durvalumab in adult subjects with R/R aggressive B-cell NHL. JCAR017 will be administered at a dose of 50 x 10^6 CAR+T cells (dose level 1 [DL1]) and 100 x 10^6 CAR+T cells (DL2) based on preliminary results from Study 017001 (NCT02631044). The combination agent will be administered at different doses and/ or schedules.
- **Arm B** will test JCAR017 in combination with CC-122 in adult subjects with R/R aggressive B-cell NHL. JCAR017 will be administered at a dose of 100 x 10^6 CAR+T cells (DL2) based on results from Study 017001. The combination agent will be administered at different doses.
- **Arm C** will test JCAR017 in combination with CC-220 (iberdomide) in adult subjects with R/R aggressive B-cell NHL. JCAR017 will be administered at a dose of 100 x 10^6 CAR+T cells (DL2) based on results from Study 017001. The combination agent will be administered at different doses and/or schedules.
- **Arm D** will test JCAR017 in combination with ibrutinib in adult subjects with R/R aggressive B-cell NHL. JCAR017 will be administered at a dose of 100 x 10^6 CAR+T cells (DL2) based on results from Study 017001. The combination agent may be administered at different doses and/or schedules.
- **Arm E** will test JCAR017 in combination with relatlimab and/or nivolumab in adult subjects with R/R aggressive B-cell NHL. JCAR017 will be administered at a dose of 100 x 10^6 CAR+T cells (DL2) based on results from Study 017001. The combination agent may be administered at different doses and/or schedules.
- **Arm F** will test JCAR017 in combination with CC-99282 in adult subjects with R/R aggressive B-cell NHL. JCAR017 will be administered at a dose of 100 x 10^6 CAR+T cells (DL2) based on results from Study 017001. The combination agent may be administered at different doses and/or schedules.

Other combination arms may be opened at a later stage. Please refer to Section 3.1.

During the dose and schedule finding part (Phase 1), a safety review committee (SRC) whose members include the medical monitor(s), drug safety physician, statistician, and a subset of investigators will recommend the Phase 2 dose and schedule (defined as RP2D) for each arm based on an integrated assessment of the safety, PK and pharmacodynamic (Pd) data, and preliminary efficacy information. The Bayesian Optimal Interval Design (BOIN) will be used for dose escalation/de-escalation decisions during the Phase 1 part of the study. The SRC may override the BOIN algorithm for safety concerns.

Enrollment will be staggered in Phase 1 in all arms, and a maximum of 9 dose-limiting toxicity (DLT) evaluable subjects will be evaluated in each subcohort. The first 6 subjects within a subcohort will enter the DLT period a minimum of 1 week apart or longer as specified for any individual Arm to allow appropriate safety monitoring. Dose-limiting toxicities will be assessed during the respective DLT period (see Section 9.3.1).

A dose expansion cohort (Phase 2) may be opened at a dose level and schedule in any arm that has been shown to be safe with at least 6 DLT evaluable subjects through the DLT period. Enrollment will stop when approximately 35 subjects are evaluable for response at Month 3 at the dose and schedule chosen as an RP2D. All patients in Phase 2 will be followed for safety as outlined in Table 31. No more than one subject per week will be treated until 6 subjects have been treated with the combination agent, to allow appropriate safety monitoring. After 6 subjects have been treated at the RP2D in the expansion cohort, further enrollment rules will be determined by the Sponsor considering the recommendation of the SRC.

All subjects from Phase 1 and Phase 2 will be followed for 24 months following JCAR017 infusion for disease status, treatment related adverse events, and until last subject last visit for survival.

Long term safety and efficacy follow-up of subjects exposed to gene therapy medicinal products that utilize integrating vectors is required as per health authority regulatory guidelines to assess the risk of delayed adverse events, monitor for multicompetent retrovirus or lentivirus and to monitor for vector persistence. Therefore, all subjects who received JCAR017 infusion under this current protocol will be asked to roll-over upon either premature discontinuation from or completion of this study and participate in a separate long-term follow-up (LTFU) protocol for up to 15 years after their JCAR017 infusion. The study will be conducted in compliance with International Council for Harmonisation (ICH) and Good Clinical Practices (GCPs) and FDA Guidance for Industry (Food and Drug Administration, 2020).

Study Population

Adult subjects (≥ 18 years) with histologically confirmed aggressive B-cell NHL (defined as diffuse large B-cell lymphoma [DLBCL] not otherwise specified [NOS] including transformed indolent NHL; follicular lymphoma Grade 3B, T cell/histiocyte-rich large B-cell lymphoma, Epstein-Barr virus [EBV] positive DLBCL NOS, primary mediastinal [thymic] large B-cell lymphoma, or high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology [double/triple-hit lymphoma (DHL/THL)] according to "The 2016 revision of the World Health Organization [WHO] classification of lymphoid neoplasms"); who must have relapsed or be refractory to at least 2 prior lines of systemic therapy for the disease under study. Previous therapy must have included a CD20-targeted agent and an anthracycline.

Length of Study

The enrollment rate is expected to be up to 4 subjects per month per arm for Phase 1 and up to 8 subjects per month per arm for Phase 2. The length of the enrollment period depends on the final number of subjects enrolled in Phase 1 and the number of arms explored and further evaluated in Phase 2. For each study Arm and assuming a maximum of 77 subjects in total for Phase 1 and Phase 2, with up to 4 subcohorts the enrollment period is expected to take at least 9 months for Phase 1 and at least 7 months for Phase 2. The follow-up period for each subject is approximately 24 months after the infusion of JCAR017. Thus, the total duration for an arm of the study is expected to be approximately 60 months.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date when the last subject enters the LTFU study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol, whichever is the later date.

Study Treatments

Subjects will receive treatment with JCAR017 (lisocabtagene maraleucel; liso-cel) and combination agent(s) at different doses and schedules. Subjects will be assigned to an arm and a subcohort by the Sponsor based on the subject's eligibility and slot availability. Subjects assigned to Arm A will receive JCAR017 in combination with durvalumab. Subjects assigned to Arm B will receive JCAR017 in combination with CC-122. Subjects assigned to Arm C will receive JCAR017 in combination with CC-220. Subjects assigned to Arm D will receive JCAR017 in combination with ibrutinib. Subjects assigned to Arm E will receive JCAR017 in combination with nivolumab with or without relatlimab. Subjects assigned to Arm F will receive JCAR017 in combination with CC-99282. Subjects who do not receive the combination treatment for any cause (eg, toxicity to the first therapy) will be replaced.

Overview of Key Efficacy Assessments

Positron emission tomography (PET)- computed tomography (CT)/ magnetic resonance imaging (MRI) assessment of response will be performed at baseline and approximately 1, 3, 6, 9, 12, 18, and 24 months following the JCAR017 infusion. Response and response-based endpoints will be assessed through local review for Phase 1 and for Phase 2 using the Lugano Classification. Treatment decisions will be based on investigator assessed response, and scans will be collected centrally to allow for a potential central review.

Overview of Key Safety Assessments

Safety will be monitored by physical examination, laboratory evaluation, neurologic examination, as well as by collecting adverse events (AEs).

Phase 1: DLTs will be assessed during the respective DLT period.

The following events will be considered DLTs:

- Death not related to progression
- Grade 4 neurotoxicity
- Grade 3 neurotoxicity of greater than 7 days' duration

- Grade 3 neurotoxicity that does not revert to baseline within 28 days of the start date of the Grade 3 event
- Grade 3 seizures that do not resolve to grade ≤ 2 within 3 days
- Grade 4 cytokine release syndrome (CRS)
- Grade 3 CRS that does not resolve to Grade ≤ 2 within 7 days
- Febrile neutropenia (defined by temperature ≥ 38.3°C and ANC < 0.5 x 10^9 /L) that does not resolve within 72 hours
- Any increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 × upper-limit of normal (ULN) and concurrent increase in total bilirubin > 3 × ULN that is unrelated to CRS and has no other probable reason to explain the combination of increases
- Any cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic Grade 3 or 4 event not pre-existing or not due to the underlying malignancy
- Any Grade 3 or 4 event deemed unexpected by the Investigator and considered a DLT upon evaluation by the SRC
- Any dose modification of the combination agent required based on a related AE or treatment interruption greater than 2 weeks

For Arm A, the following additional combination treatment-related events will be considered DLTs (if occurring after start of durvalumab):

- Grade ≥ 3 non-infectious colitis or non-infectious pneumonitis
- Grade ≥ 3 immune-related adverse event (irAE) or other Grade ≥ 3 autoimmune toxicity (excluding B-cell aplasia)

For Arm B, the following additional combination treatment-related events will be considered DLTs (if occurring after start of CC-122):

- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting > 24h

For Arm C, the following additional combination treatment-related events will be considered DLTs (if occurring after start of CC-220)

- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

For Arm D, the following additional combination treatment-related events will be considered DLTs (if occurring after start of combination therapy):

- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

For Arm E, the following additional combination treatment-related events will be considered DLTs (if occurring after start of combination therapy):

- Grade ≥ 3 non-infectious colitis or non-infectious pneumonitis
- Grade ≥ 3 immune-related adverse event (irAE) or other Grade ≥ 3 autoimmune toxicity (excluding B-cell aplasia)
- Grade 2 immune related-eye pain or reduction in visual acuity that requires systemic treatment
- Grade 2 eye pain or reduction in visual acuity that does not respond to topical therapy and that does not improve to Grade 1 within 2 weeks of initiation of topical therapy
- Grade 4 anemia
- Grade 3 hemolysis
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

For Arm F, the following additional combination treatment-related events will be considered DLTs (if occurring after start of combination therapy):

- Grade 4 anemia
- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

Statistical Methods

Phase 1:

Escalation or de-escalation will be based on the BOIN algorithm. With the target DLT rate of 0.30, the BOIN escalation boundary is λe=0.236 and the de-escalation boundary is λd=0.358. The BOIN dosing decision table is provided in Table 9.

Enrollment into Phase 1 of the study will be staggered such that in each arm, the first 6 subjects within a subcohort will enter the DLT period at intervals of at least 1 week. No more than 6 subjects can be in the DLT period simultaneously across subcohorts of a given arm that has not yet been shown to be safe. For a dose level to be shown to be safe, at least 6 DLT evaluable subjects must have completed the DLT period and it is estimated to be safe per the BOIN algorithm. Enrollment to the next dose level will be prioritized if open for enrollment.

Within each arm, a sample size of at least 6 DLT evaluable subjects per subcohort is planned with no more than 9 DLT evaluable subjects treated in a subcohort. The final number of subjects needed in Phase 1 in a given arm will depend on the number of DLTs observed within each subcohort. Non-DLT evaluable subjects will be replaced. With an expected rate of non-DLT evaluable subjects of around 30%, up to about 24 subjects may be enrolled in Phase 1 into arms A, B and F, up to about 48 subjects may need to be enrolled in Phase 1 in Arms C and E, and up to 12 subjects in Phase 1 in Arm D.

Subjects must have elevated disease burden at screening (sum of product of perpendicular diameters (SPD) of index lesions ≥ 25 cm^2 by CT scan). Arms A and B are not subject to this

requirement. Up to 15% of subjects per subcohort (ie, 1 in Phase 1 and 4 in an expansion cohort) may have Richter's transformation (transformed CLL) without elevated tumor burden.

Phase 2:

Within a study arm, the subcohort shown to be safe (RP2D) in Phase 1 may be expanded. The decision to expand a particular subcohort will be made by the Sponsor upon recommendation by the SRC after review of all available data. Enrollment will stop when a total of approximately 35 subjects are evaluable for safety and response at the dose and schedule chosen as a RP2D (eg, 9 in Phase 1 and 26 in Phase 2 – to achieve a total of approximately 35). No more than one subject per week will be treated until 6 subjects have been treated with the combination agent, to allow appropriate safety monitoring. After 6 subjects have been treated at the RP2D in the expansion cohort, further enrollment rules will be determined by the Sponsor considering the recommendation of the SRC.

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1. INTRODUCTION

1.1. Disease Background

1.1.1. Non-Hodgkin Lymphoma

Non-Hodgkin lymphomas (NHLs) comprise a heterogeneous group of malignancies. Within Europe, the incidence of NHL is approximately 49,533 with a mortality of 20,347 (Ferlay, 2015). In the United States (US), it is estimated that approximately 72,580 new cases of NHL will be diagnosed and approximately 20,150 subjects will die of their disease in 2016 (Siegel, 2016). Non-Hodgkin lymphomas are classified according to the current World Health Organization (WHO) classification (Swerdlow, 2016) into immature lymphoid neoplasms, mature B-cell neoplasms, T cell and natural killer (NK)-cell neoplasms, and post-transplant lymphoproliferative disorders. Mature B-cell lymphomas are further classified into indolent lymphomas (eg, multiple myeloma (MM), chronic lymphocytic leukemia [CLL]) and aggressive lymphomas (eg, diffuse large B-cell lymphoma [DLBCL]).

DLBCL is the most frequent lymphoma subtype, representing approximately 30% of all NHL. DLBCL can develop de novo or secondary to transformation of an indolent NHL. Estimated incidence in the European Union (EU) is 3 to 4/100,000/year, increasing with age from 0.3/100,000/year (35 to 39 years) to 26.6/100,000/year (80 to 84 years) (Tilly, 2012). About 10,000 deaths per year are due to DLBCL in the US (National Cancer Institute [NCI]). Most subjects with localized DLBCL can be cured with conventional combination immuno-chemo- or combined-modality therapy (Tilly, 2015). For subjects with advanced-stage disease, the majority of subjects can be cured with doxorubicin-based combination chemotherapy and rituximab (eg, R-CHOP). Prognosis depends on individual risk factors. The International Prognostic Index (IPI) for aggressive NHL includes five significant risk factors prognostic of overall survival (OS): Subject age, serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, and extranodal involvement. Subjects with ≥ 2 risk factors after age-adjustment have a poor prognosis with a 5-year OS-rate of 21% to 46%. Age- and stage-adjusted modifications are used for younger subjects with localized disease (Moller, 2003).

Despite overall improvement in outcomes of DLBCL, approximately one-third of subjects will develop relapsed/refractory (R/R) disease that remains a major cause of mortality. Refractory disease is defined as a $< 50\%$ decrease in lesion size or the appearance of new lesions. Relapsed disease reflects the (re)appearance of lesions after attainment of a partial or complete response (PR or CR) (Cheson, 2007). Relapsed/refractory subjects have a poor prognosis, particularly those who do not respond to second line chemotherapy with a median OS of 4.4 months (Van Den Neste, 2016).

Diffuse large B-cell lymphoma is a heterogeneous disease with several histological and molecular subtypes. The largest subgroup is DLBCL not otherwise specified (NOS). Molecular profiling by gene expression profiling (GEP) based on biologic similarity to normal stages of B-cell development (cell of origin [COO]) helped to further divide DLBCL into germinal center-like (GCB), activated B-cell-like (ABC) tumors, and primary mediastinal large B-cell lymphoma (PMBCL), a distinct clinical entity (Lenz, 2008). Immunohistochemistry (IHC) algorithms are

clinically used to identify the COO and helped to identify ABC DLBCL as a high-risk subtype less likely to respond to standard immune-chemotherapy.

Within the GCB group a specific high-risk group is defined by concurrent chromosomal rearrangements of c-MYC and the anti-apoptotic oncogene BCL2 or BCL6, referred to as double-hit lymphomas (DHL). In addition, in some cases there is a concurrent rearrangement of c-MYC and both antiapoptotic oncogenes BCL2 and BCL6, which are referred to as triple-hit lymphoma. DHL represents approximately 5% of de novo cases of DLBCL with very poor OS of ≤12 months when treated with R-CHOP (Camicia, 2015). Newer data suggest negative prognostic impact of P53 mutations or deletions in DLBCL (Schiefer, 2015).

Despite follicular lymphoma (FL) being an indolent lymphoma type, Grade 3B FL is regarded as aggressive lymphoma. Clinical behavior is very similar to DLBCL and FL frequently undergoes histological transformation into DLBCL. Consequently, current guidelines recommend to treat FL Grade 3B according to the DLBCL treatment algorithm (NCCN, 2016; Dreyling, 2014). These subjects are generally treated with an anthracycline-based chemotherapy combined with rituximab (eg, R-CHOP) and have a similar prognosis to that of de novo DLBCL.

1.1.2. CD19 as a Therapeutic Target

CD19 is a 95-kDa glycoprotein present on B-cells from early development until differentiation into plasma cells (Stamenkovic, 1988). It is a member of the immunoglobulin superfamily and a component of a B-cell surface signal transduction complex that positively regulates signal transduction through the B-cell receptor (Stamenkovic, 1988; Brentjens, 2011).

CD19 is an attractive therapeutic target because it is expressed by most B-cell malignancies, including B-cell NHL (Li, 1993; Li, 1996; Davila, 2012). Importantly, the CD19 antigen is not expressed on hematopoietic stem cells or on any normal tissue apart from those of the B-cell lineage.

1.1.3. CD19–Targeted Chimeric Antigen Receptors

CD19-specific chimeric antigen receptors (CARs) are single chain variable fragments (scFv) fused to a transmembrane domain and cytoplasmic signaling domains. Expression of the CD19-CAR in autologous T cells is achieved by ex vivo transduction using a recombinant retroviral or lentiviral vector. The CAR is expressed on the T cell surface and redirects the transfected T cells to CD19-expressing lymphoma cells, leading to CD19-specific tumor cell recognition, lysis, cytokine secretion and T cell proliferation (Sadelain, 2013). In clinical studies, CD19-targeted CARs have demonstrated encouraging activity in adult and pediatric subjects with R/R B-cell acute lymphoblastic leukemia (ALL) and B-cell NHL (Maude, 2018; Park, 2018; Gardner, 2017; Turtle, 2016; Schuster, 2017; Neelapu, 2017).

1.2. Compound Background

1.2.1. JCAR017 Investigational Drug Product

The JCAR017 (lisocabtagene maraleucel; liso-cel) investigational drug product is a novel, CD19-targeted, genetically modified, autologous, defined composition, T cell immunotherapy. JCAR017 is manufactured from autologous peripheral blood mononuclear cells (PBMCs) that are obtained via standard leukapheresis collection procedures. The PBMCs undergo sequential

positive selection for CD8+ and CD4+ T cells where the CD4 and CD8 purified T cell populations derived from the same starting material (leukapheresis) are separated, subsequently cryopreserved, transduced with CAR and expanded through parallel processing in order to ensure the final product is infused to the subjects in a defined cell composition. The CD19-specific CAR consists of an scFv binding domain derived from a murine CD19-specific monoclonal antibody (mAb; FMC63) and the 4-1BB and CD3ζ signaling domains. The truncated human epidermal growth factor receptor (EGFRt) protein is co-expressed with the CD19-specific CAR as a cell surface protein for analytical detection of transduced T cells. The JCAR017 drug product is provided as two individually formulated CD8+CAR+ and CD4+ CAR+ T cell suspensions in media containing dimethyl sulfoxide (DMSO) that are thawed and administered separately by intravenous (IV) infusion.

Please refer to the JCAR017 Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, clinical studies, and adverse event (AE) profile of the investigational product (IP).

1.2.2. Durvalumab (MEDI4736)

Durvalumab (MEDI4736, Durva) is a human immunoglobulin G (IgG)1 kappa monoclonal antibody (mAb) directed against human programmed cell death ligand 1 (PD-L1) protein. Durvalumab is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to programmed cell death 1 (PD-1) protein and cluster of differentiation (CD)80. The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent T cell-mediated cytotoxicity (ADCC) (Oganesyan, 2008; Ibrahim, 2015).

On 01 May 1, 2017, the US Food and Drug Administration (FDA) granted accelerated approval to durvalumab (IMFINZI™) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Refer to the durvalumab IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the IP.

1.2.3. CC-122 (Avadomide)

CC-122 is a nonphthalimide analog of thalidomide that retains binding affinity to a protein called cereblon (CRBN) (encoded by the CRBN gene), a member of the Cullin 4-ring ligase complex. In T cells, CC-122 binds to cereblon and promotes targeted degradation of the protein Aiolos, a transcriptional repressor of T cell activation. It is in part via the degradation of Aiolos that CC-122 exerts its T cell activation function.CC-122 has multiple activities, which include: immune modulation of several immune cell subsets such as monocytes, T cells, B-cells, and natural killer (NK) cells; antiproliferative activity in multiple tumor types including DLBCL, mantle cell lymphoma (MCL), FL, CLL, and MM represented by multiple cell lines; antigrowth activity in human cancer cells (HCC); and antiangiogenic activity as demonstrated by inhibition of endothelial cell sprout formation, growth factor induced endothelial cell migration and

invasion, and hypoxia-inducible factor (HIF)-1α protein expression in vitro. The antitumor activity of CC-122 was demonstrated in xenograft models of human myeloma, glioblastoma, and human lymphoma. The pharmacodynamic biomarker Aiolos is a protein that is degraded by CC-122 and can be measured in the peripheral blood in subjects administered CC-122. A dose-dependent trend in Aiolos inhibition, T cell activation, and B cell reduction was observed starting at the 0.5 mg dose cohort. Furthermore, a median decrease of 47% Aiolos protein levels was observed within 5 hours of dosing in NHL subjects as was a significant increase in IL-2 secretion (median increase of 6-fold in MM subjects and 4.4-fold in NHL subjects), suggesting increased T cell activation (Carpio, 2015; Hagner, 2015).

[redacted]

1.2.4. CC-220 (Iberdomide)

CC-220 is a novel cereblon (CRBN) E3 ligase modulatory compound (CELMoD) that is structurally similar to CC-122 and is being investigated in relapsed/refractory multiple myeloma (R/R MM) and systemic lupus erythematosus (SLE). CC-220 modulates CRBN, which induces ubiquitination of the transcription factors Aiolos and Ikaros, increasing their proteasome-dependent degradation and augmenting T cell function. CC-220 binds more potently to CRBN, is more efficient at degrading Aiolos and Ikaros than lenalidomide and pomalidomide, and has potent direct anti-proliferative effects on lymphoma cells.

[redacted]

1.2.5. Ibrutinib

Ibrutinib is an oral irreversible inhibitor of Bruton's tyrosine kinase (BTK) that is approved in the US as first-line therapy for patients with CLL, small lymphocytic lymphoma, and Waldenstrom's macroglobulinemia, and second-line treatment of marginal zone lymphoma and chronic graft versus host disease. Ibrutinib has shown beneficial activity in patients with the activated B cell–like subtype of DLBCL, with best responses evidenced in patients with chronic active B-cell receptor signaling (Wilson, 2015). Bruton's tyrosine kinase is a signaling molecule of the B-cell receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Non-clinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

There is a growing body of evidence that ibrutinib has a number of immunomodulatory effects on the T cell arm of the immune system. Improved T cell function and reduced T regulatory cells have been observed in both preclinical models and clinical trials. Although the underlying mechanism for these immunomodulatory effects is both multifactorial and complex, it has been postulated that off-BTK engagement of cysteine moieties in a variety of Tec kinase family members contributes to this potential.

Refer to the current ibrutinib package insert (Imbruvica US PI) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the IP.

1.2.6. Relatlimab

Relatlimab (BMS-986016) is a fully human lymphocyte activation gene 3 (LAG-3) specific antibody that was isolated following immunization of transgenic mice expressing human immunoglobulin (Ig) genes. Relatlimab binds to LAG-3 receptors expressed on T-cells with high affinity and prevents binding of this receptor to cells bearing its ligands, major histocompatibility complex (MHC) Class II (Andrews, 2017) and fibrinogen-like protein 1 (FGL-1) (Wang, 2019). Relatlimab binding inhibits the negative regulatory function of LAG-3 mediated through its interaction with ligands in vitro. By blocking the inhibitory LAG-3 signaling pathway, relatlimab enhances the anti-tumor immune response and, thus, has the potential to inhibit the growth of multiple malignancies when administered alone or in combination with other therapeutic immuno-oncology (IO) agents.

Refer to the current Relatlimab IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, and clinical safety profile of relatlimab.

1.2.7. Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. Nivolumab (OPDIVO™) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014). Dual checkpoint inhibition with relatlimab and nivolumab results in enhanced T-cell effector function that is greater than the effects of either antibody alone in murine syngeneic tumor models.

Refer to the current nivolumab IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, and clinical safety profile of nivolumab.

1.2.8. CC-99282

CC-99282 is a an oral cereblon-modulating agent (CELMoD) that is initially being developed for the treatment of patients with R/R NHL and CLL. Cereblon functions as a substrate receptor for a CRL4 ubiquitin E3 ligase (Ito, 2010; Lopez-Girona, 2012; Chamberlain, 2014) and the binding of cereblon modulating compounds induces the recruitment, ubiquitination, and destruction of key target substrates (eg, Ikaros family zinc finger proteins 1 and 3 [IKZF1 and IKZF3, aka Ikaros and Aiolos]) to mediate cellular effects (Gandhi, 2014; Krönke, 2014; Lu, 2014; An, 2017).

CC-99282 is structurally distinct from other CELMoDs in this class (eg, lenalidomide, CC-122 and CC-220), has increased potency, a distinct PK profile with longer half-life [redacted]) based on preliminary clinical data. [redacted]

CC-99282 elicits its pleiotropic effects in a cereblon ubiquitin ligase-dependent fashion through increased proteasome-dependent degradation of substrates including Ikaros and Aiolos. CC-99282 has exhibited single-agent antiproliferative effects with preclinical data showing potent cell-autonomous induction of apoptosis in DLBCL cell lines as well as potent immunomodulation of normal lymphocytes, including enhanced T cell function. The mechanism of activation is presumed to be through CRBN-mediated degradation of Aiolos and Ikaros, which act as repressors of the expression and secretion of IL-2, a marker of T cell activation.

[redacted]

1.3. Rationale

1.3.1. Study Rationale and Purpose

The purpose of this Phase 1/2 study is to evaluate the safety, tolerability, pharmacokinetics (PK), and efficacy of JCAR017 combinations with checkpoint inhibitors or with other therapies in adult subjects with R/R aggressive B-cell NHL [defined as DLBCL not otherwise specified (NOS) including transformed indolent NHL; follicular lymphoma (FL) Grade 3B, T cell/histiocyte-rich large B-cell lymphoma, Epstein-Barr virus (EBV) positive DLBCL NOS, primary mediastinal (thymic) large B-cell lymphoma (PMBCL), and high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology ("double/triple-hit lymphoma") according to "The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms" (Swerdlow, 2016)].

In clinical studies, CD19-targeted CARs have demonstrated encouraging activity in adult and pediatric subjects with R/R ALL and B-cell NHL. Emerging data indicates that in vivo expansion of CD19-targeted CAR T cells strongly correlates with antitumor response (Gardner, 2017; Kochenderfer, 2015; Schuster, 2017).

JCAR017, given as a dose after lymphodepleting (LD) chemotherapy, has been evaluated in the Study 017001, a trial in adult subjects with B-cell NHL. Study 017001 has shown that dose levels 1 and 2 (50×10^6 CAR+ T cells, and 100×10^6 CAR+ T cells, respectively) given as a dose after lymphodepletion are safe and have shown preliminary efficacy. The lymphodepletion regimen used was cyclophosphamide (300 mg/m^2/day x 3 days) combined with fludarabine (30 mg/m^2/day x 3 days) (flu/cy) (Abramson, 2017).

Although CAR T cell persistence can be detected in many subjects with lymphoma, fewer CRs have been observed in subjects with NHL compared to subjects with ALL. More specifically,

while higher overall response rates of up to 80 % (CR rate 47% to 60%) have been reported after CAR T cell infusion, responses in some are transient and subjects have been shown to relapse in the presence of persistent CAR T cells (Neelapu, 2017; Abramson, 2017). Another study reported a long term CR rate of 40% (Schuster, 2017).

Possible explanations for this are (Tran, 2017):

- Immunological exhaustion of circulating T cells and/or changes in T lymphocyte populations.
- An effect of the tumor microenvironment, eg, CAR T cells are suppressed by the lymphoma microenvironment and lose their antitumor activity before they are able to eliminate all lymphoma cells.

Accordingly, combination of JCAR017 with immune system modifiers such as checkpoint inhibitors or immunomodulatory compounds could restore the T cell function, reduce the immunosuppressive tumor microenvironment, and improve the response and durability of the response to JCAR017. In order to enhance the antitumor activity of JCAR017, this trial will test if the combination of JCAR017 with immunomodulatory agents is safe and improves the CRR and the durability of responses.

1.3.2. Rationale for the Study Design

To test the above assumptions, this trial uses a multi-arm, parallel cohort design to test various combinations of JCAR017 with different combination agents. Each combination will be tested in a dedicated study arm. Each study arm may test three general sequences of treatment in separate cohorts (see Figure 1):

- A post-expansion cohort will assess the safety and feasibility of boosting the JCAR017 efficacy after peak expansion of JCAR017, ie, after the first efficacy assessment around Day 29 post-JCAR017 infusion.
- A post-infusion cohort will assess the safety and feasibility of administering combination agents closer to peak expansion of JCAR017 (ie, within the first 2 weeks) with the intent to increase T cell health, modulate the tumor microenvironment and optimize T cell subpopulations following JCAR017 infusion and prior to peak expansion of JCAR017.
- A pre-infusion cohort will test the safety and feasibility of initiating treatment with a combination agent prior to JCAR017 infusion. This may increase the health of T cells in the primary leukapheresis starting material and translate into a healthier JCAR017 T cell product and potentially modulate the tumor microenvironment to make the tumor more susceptible to the JCAR017. Continuing the combination post infusion may potentially improve the pharmacodynamics of JCAR017 cells, ultimately improving efficacy and safety of JCAR017.

Additional cohorts may be added with the aim to combine approaches to maximize the efficacy of JCAR017 pending safety and preliminary efficacy results to further optimize JCAR017 efficacy.

This modular trial design allows parallel testing of different doses and schedules of novel combinations to improve clinical efficacy of JCAR017.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

1.3.3.1. JCAR017 Dose Rationale

JCAR017 has been generally tolerated at doses from 0.5 x 10^6 to 1 x 10^6 CAR+ T cells/kg in pediatric subjects with ALL conditioned with flu/cy. The maximum tolerated dose (MTD) was exceeded in this study in subjects treated after flu/cy LD chemotherapy: at 5 x 10^6 CAR+ T cells/kg in pediatric subjects with ALL (PLAT-02 study). Antitumor activity has been observed at all doses of JCAR017 tested.

The JCAR017 starting dose for Arm A is a dose of 50 x 10^6 CAR+ T cells (dose level 1 [DL1]), which converts in CAR+ T cells per kg to the middle of the dose ranges tolerated with JCAR017: 50 x 10^6 CAR+ T cells is equivalent to 0.5 x 10^6 CAR+ T cells/kg for a 100 kg adult and equivalent to 1 x 10^6 CAR+ T cells/kg for a 50 kg adult.

Dose level 2 (DL2) (100 x 10^6 CAR+ T cells) was also identified in Study 017001 to be safe and will be tested in this trial in Cohort 1B in Arm A and used as starting dose level for subsequent arms.

This trial will employ LD chemotherapy prior to the JCAR017 infusion with flu/cy (see Section 7.2.1 for dose details).

1.3.4. Rationale for Choice of Combination Compounds

As a monotherapy, CD19-targeted CAR T cells have been tested in adult subjects with aggressive B-cell NHL with a high overall response rate (ORR), but a lower than desirable rate of durable CR. Checkpoint proteins, inhibitory microenvironment factors and T cell intrinsic factors may decrease the function of the modified T cells in subjects with aggressive B-cell NHL, thereby limiting CAR T cell-mediated antitumor activity. Compounds that either disrupt inhibitory microenvironment factors or enhance the intrinsic biological activity of the JCAR017 cells offer an opportunity to enhance the potency and persistent efficacy of JCAR017 while maintaining acceptable safety and tolerability.

1.3.4.1. Rationale for JCAR017 in Combination with PD-1 or PD-L1 Blockade

CD8+ cytotoxic T cells recognition of target antigen presented on tumor cells involves formation of the immune synapse that induces activation and initiates tumor-cell killing after. Subsequent to activation, T cells express PD-1 on their surface and secrete interferons that in turn induce expression of checkpoint inhibitors such as PD-L1 and PD-L2 (Garcia Diaz, 2017) on tumor cells and bystander cells (Hoekstra, 2020). Binding of PD-L1 and/or PD-L2 on tumor cells (including lymphoma) and the tumor microenvironment to PD-1 on T cells (including CAR T cells) results in inhibitory checkpoint signaling that decreases cytotoxicity and leads to T cell exhaustion (Andorsky, 2011). High levels of PD-L1 promote T cell exhaustion, and PD-L1 blockade reinvigorates T cell function.

Expression of PD-1 / PD-L1 axis has been detected in various lymphomas. It is well established that tumor-infiltrating lymphocytes (TILs) express PD-1, [redacted]

[redacted]

Antibodies disrupting immune checkpoints have produced tumor regression in multiple cancers. PD-1 blocking antibodies inhibit the interaction of PD-L1 and PD-L2 with PD-1, whereas anti-PD-L1 antibodies inhibit the interaction between PD-L1 and PD-1 only, resulting in enhanced T cell activity, increased cytokine production, and tumor cell directed cytotoxicity.

Monoclonal blocking antibodies to PD-1 or PD-L1 have been shown to be safe and effective in subjects with various cancers, and may be useful in reversing the PD-L1 mediated immunosuppression in subjects treated with CAR T cells. Blockade of the PD-1/PD-L1 axis has been explored in NHL (Lesokhin, 2016). Results of a Phase 1 study of the PD-1 antagonist mAb nivolumab in NHL showed that PD-1 inhibition had an acceptable safety profile at similar dose levels (1 and 3 mg/kg) used for the treatment of solid tumors. Among 31 treated subjects with B-cell NHL, 71% experienced drug-related AEs, including two subjects (7%) with serious adverse events (SAEs) of pneumonitis. The clinical study included 11 subjects with DLBCL, and evidence of clinical activity was observed. Two subjects achieved a CR and two additional subjects achieved a PR. Median progression-free survival (PFS) was 6 weeks (range 6 to 29) for the cohort of subjects with DLBCL. Studies evaluating the activity of durvalumab in B-cell malignancies are currently ongoing (Siddiqi, 2019). See the durvalumab IB for details.

[redacted] to prolong CAR T cell effector function upon encounter with this immunosuppressive signal.

Durvalumab is a human IgG1κ mAb that binds to PD-L1 and inhibits the binding of PD-L1 to PD-1. In vitro studies have shown that durvalumab antagonizes the inhibitory effects of PD-L1 on primary human T cells, resulting in their enhanced proliferation and production of IFN-γ in response to T cell receptor stimulation. [redacted]

Nivolumab is a human IgG4 monoclonal antibody that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and programmed death-ligand 2 (PD-L2) (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response.

Preliminary results from a clinical trial investigating another CD19-directed CAR T cell product CTL019 (Schuster, 2017) in DLBCL identified high PD-L1 expression in lymphoma before CAR T cell infusion as one possible mechanism of resistance. Treatment of a subject not responding to CAR T cell therapy with a PD-1 blocking antibody resulted in a clinically significant antitumor response and expansion of CAR T cells (Chong, 2017). Phase 1 studies using antibodies against PD-1 or PD-L1 in combination with CD19-directed CAR T therapies, including JCAR017, have demonstrated acceptable safety profiles and indicate potentially beneficial effect on CAR T pharmacokinetics, indicating that further evaluation of this approach is warranted (Siddiqi 2019, Tholouli 2020).

1.3.4.2. Rationale for JCAR017 in Combination With CC-122

The molecular target for lenalidomide and CC-122 has been identified as the protein Cereblon (CRBN), a substrate receptor of the Cullin 4 RING E3 ubiquitin ligase complex. Binding of lenalidomide and CC-122 to a hydrophobic tri-tryptophan pocket within CRBN promotes the recruitment, ubiquitination, and subsequent proteasomal degradation of several protein substrates (Fischer, 2014; Chamberlain, 2014). Two of these substrates are the transcription factors Aiolos (IKZF3) and Ikaros (IKZF1) (Gandhi, 2014; Lu, 2014; Krönke, 2014). Lenalidomide and CC-122 mediated degradation of Aiolos and Ikaros in DLBCL cell lines results in de-repression of transcriptional start sites within the promoters of interferon stimulated genes (ISG), such as interferon regulated factor 7 (IRF7) (Hagner, 2015). Faster kinetics and greater depth of Aiolos and Ikaros degradation by CC-122 compared to lenalidomide resulted in decreased proliferation and increased apoptosis in cell lines representing both molecular subtypes of DLBCL, ABC-subtype and GCB-subtype, in contrast to lenalidomide, which predominantly has activity in ABC subtype DLBCL cell lines. Based on those results, a cell-of-origin independent antilymphoma activity of CC-122, in contrast to the ABC-subtype selective activity of lenalidomide, was postulated.

In early clinical studies of CC-122 as a single agent and in combination with Rituximab, encouraging signals of efficacy in relapsed and refractory DLBCL were shown broadly across cell of origin by gene expression profiling (GEP). Furthermore, analysis of paired tumor biopsies from DLBCL subjects collected prior to and approximately 2 weeks post administration of CC-122 demonstrated decreased intra-tumoral levels of Aiolos and upregulation of IRF7 in on-treatment biopsies, thereby confirming the mechanism of action identified in *in vitro* experiments (Hagner, 2015).

In addition to the cell autonomous activity of CC-122 against malignant B-cells, CC-122 exerts co-stimulatory effects on immune cells such T and NK-cells. The mechanism of activation was also determined to be through CRBN mediated degradation of Aiolos and Ikaros, negative

regulators of activation molecules and cytokines such as interleukin-2 (IL-2) expression (Gandhi, 2014; Krönke, 2014). In concordance with more potent Aiolos degradation, CC-122 demonstrated more potent T cell activation in vitro compared to lenalidomide. Additional *in vitro* experiments revealed CC-122 activated NK-cells as measured by flow cytometric analysis of cell surface markers and increased cytokine expression, as well as repair of dysfunctional cytolytic immune synapse formation (Apollonio, 2015). In DLBCL subjects, *ex vivo* assays indicate activation of T cells as measured by interferon gamma (IFN-γ) and IL-2 expression after a single dose of CC-122 from 0.5 mg up to the recommended phase 2 dose (RP2D) of 3 mg. In addition, within 2 weeks of CC-122 treatment, an increase in activated and central memory CD4+ and CD8+ T cell phenotypes was observed in peripheral blood in conjunction with a concomitant decrease in naïve CD4+ and CD8+ T cells. Preliminary clinical data suggest that lymphoma subjects with greater increases in cytotoxic activated T cells on CC-122 treatment have longer PFS (Hagner, 2015). Furthermore, a gene expression classifier that identifies DLBCL tumors with an immune infiltration at baseline enriches subjects with higher response rates and prolonged PFS in early clinical trials of CC-122 (Carpio, 2017).

CAR T cells have shown very high activity in subjects with ALL, and aggressive NHL. Nevertheless, some subjects do not respond or lose their response after CAR T cell therapy. Recent data suggest that one contributing factor for loss of response could be proliferative exhaustion and/or senescence of infused CAR T cells (Schuster, 2017; Neelapu, 2017; Abramson, 2017), either as a physiological "stress reaction" or due to the immunosuppressive tumor microenvironment (TME). [redacted]

1.3.4.3. Rationale for JCAR017 in Combination With CC-220

In vitro studies of JCAR017 and CC-122 revealed that CELMoD treatment targeting degradation of Ikaros and Aiolos protein in T cells both delayed onset of JCAR017 exhaustion during chronic stimulation and rescued cells from a hypofunctional exhausted state (Jessup, 2019). [redacted]

1.3.4.4. Rationale for JCAR017 in Combination With Ibrutinib

During the pathogenesis of NHL and CLL, lymph node tumor microenvironments with immunosuppressive features emerge through malignant B-cell and stromal-cell interactions, thus limiting antitumor immune surveillance (Moreira, 2013; Scott, 2014; Fraietta, 2016). Chronic lymphocytic leukemia results in dysfunctional circulating T cells that are prognostic of disease progression (Bonyhadi, 2005; Palmer, 2008; D'Arena, 2011). The immunosuppression associated with these diseases highlights potential adverse functional effects on adoptive T cell therapeutics as well as an opportunity to overcome these barriers through combinatorial strategies.

Notably, it was demonstrated that patients with CLL treated with the targeted inhibitor ibrutinib exhibited restored T cell function relative to untreated patients (Fraietta, 2016).

The microenvironment of lymph nodes and bone marrow can also provide stromal support for survival of malignant B-cells (Scott, 2014). Recent reports demonstrate a higher degree of clinical efficacy of CAR T cell therapies in acute B-cell leukemia compared with CLL, DLBCL, and other B-cell malignancies with significant lymphadenopathy (Turtle, 2016). More effective CAR T cell encounters might occur during periods of BTK inhibitor–induced lymphocytosis, either due to enhanced activation of CAR T cell responsiveness or increased sensitivity of the malignant B-cells outside the protective microenvironment. A reduction in tumor burden and disruption of the tumor microenvironment are likely to delay the onset of CAR T cell exhaustion and dysfunction. Indeed, ibrutinib improved tumor clearance when combined with CAR T cells in several murine tumor models (Ruella, 2016; Fraietta, 2016).

Ibrutinib influences the activity of kinases that could affect CAR T cell performance (Davids, 2014). In a small cohort of patients with CLL treated with ibrutinib, markers of exhaustion and tumor-mediated immunosuppression were reduced, and ibrutinib treatment was associated with increased effector-memory CD4 and CD8 T cells in some patients (Long, 2017). Treatment with ibrutinib has also been shown to reduce immunosuppressive cell populations in patients, which is another factor that may influence T cell functionality (Honda, 2012; Long, 2015; Sagiv-Barfi, 2015; Gunderson, 2016; Stiff, 2016; Ruella, 2016). Ibrutinib restores T cell functionality in CLL patients, enhances CAR T cell production, and potentially improves clinical efficacy (Fraietta, 2016; Ramsay, 2008). Of note, several recent published clinical studies, in which ibrutinib was administered in combination with anti-CD19 CAR T cells was well tolerated showing high response rates in R/R CLL and reduced incidence of severe cytokine release syndrome (CRS) (Gauthier, 2018; Gill, 2018).

A series of studies were conducted to test the in vitro and in vivo effects on JCAR017 when combined with ibrutinib (Qin, 2016). JCAR017 cells manufactured from DLBCL patients demonstrated increased cytolytic function in the presence of ibrutinib after serial stimulation and increased the percentage of JCAR017 Th1 cells and memory-like T cells. Furthermore, ibrutinib enhanced in vivo efficacy of JCAR017 cells in CD19+ tumor model. Taken together, this data indicates that ibrutinib has the potential to enhance intrinsic JCAR017 function in vivo in addition to direct tumor and anti-suppressive TME effects that may enable superior CAR T cell performance.

Combination strategies that improve CAR T cell potency, limit tumor environment–mediated immune dysfunction, and directly reduce tumor burden may increase the potential for durable clinical benefit of CAR T cell therapy. Ibrutinib has off target activity outside of BTK that is likely to influence T cell activation response (Byrd, 2016). Therefore, internal studies were performed to assess the treatment effects of ibrutinib on the intrinsic in vitro and in vivo functionality of JCAR017 cells (Qin, 2016, Qin, 2019). In prolonged stimulation assays, the presence of ibrutinib improved CAR T cell effector function. RNA-Seq analysis and surface marker profiling of these CAR T cells treated with ibrutinib revealed gene-expression changes consistent with skewing toward a memory-like, type 1 T-helper, BTK phenotype. Ibrutinib improved CD19+ tumor clearance and prolonged survival of tumor-bearing mice when used in combination with CAR T cells. Combining JCAR017 with ibrutinib is an attractive approach that may potentiate the promising clinical responses already achieved in CD19+ B-cell malignancies.

1.3.4.5. Rationale for JCAR017 in Combination with Relatlimab and Nivolumab

As described in Section 1.3.4.1 above, blockade of PD-1 with nivolumab may improve the anti-tumor activity of JCAR017. Addition of LAG-3 blockade to PD-1 blockade in combination with JCAR017 may further improve the anti-tumor activity in aggressive NHL by blocking inhibitory signals and preventing or restoring T cells from exhaustion.

LAG-3 (CD223) is a checkpoint receptor expressed on several immune cell types including activated CD4+ and CD8+ T cells, memory T cells, T_{reg} cells, and natural killer cells (Andrews, 2017). Activation of the LAG-3 pathway occurs when LAG-3 interacts with its ligands, such as MHC Class II or other emerging ligands (eg, FGL1), which triggers inhibitory activity that reduces the function of effector T cells (Andrews, 2017; Wang, 2019).

LAG-3 is often expressed on chronically exhausted T-cells and is frequently co-expressed with PD-1 on tolerized tumor infiltrating lymphocytes (TILs) across many tumor types (Chauvin, 2015, Speiser, 2014, Sharma, 2017). A similar pattern is seen in CAR T therapy where chronic exposure to antigen causes T cell dysfunction and upregulation of PD-1 and LAG3 exhaustion markers. [redacted]

Increased expression of LAG-3 on TILs, especially in the context of PD-1 expression, further promotes T cell exhaustion, leading to an impaired ability to attack tumor cells and an increased potential for tumor growth (Andrews, 2017, Woo, 2012). Preclinical studies indicate that inhibition of the LAG-3 pathway may restore effector function of exhausted T cells, promoting proinflammatory cytokine signaling, and ultimately, an anti-tumor response. The combination of

LAG-3 and PD-1 inhibition demonstrated enhanced anti-tumor activity by targeting independent pathways with distinct functions (Andrews, 2017).

Relatlimab is a blocking antibody specific to the LAG-3 receptor. Relatlimab is being investigated in different indications and lines of therapies in combination with nivolumab. Nivolumab and relatlimab have been shown to have encouraging clinical activity as combination therapy, with few overlapping toxicities. In the CA224020 Phase 1/2a study, the combination of nivolumab and relatlimab demonstrated tolerability, and preliminary clinical activity in advanced melanoma subjects that had been previously treated with anti-PD-1/PD-L1 therapy (Ascierto, 2017).

Clinical efficacy of relatlimab as monotherapy and in combination with nivolumab has been studied in CA224020 and CA224022 at different doses and schedules. As monotherapy, relatlimab demonstrated activity in hematologic malignancies in the Phase 1/2a study CA224022. Objective responses were observed in subjects with relapsed or refractory marginal zone lymphoma, Hodgkin lymphoma, and mantle cell lymphoma.

The Phase 1/2a study CA224020 is investigating the safety, tolerability, and effectiveness of relatlimab, with and without nivolumab, to treat various solid tumors (Ascierto, 2017a). Initial results show encouraging clinical activity when relatlimab is combined with nivolumab in the treatment of subjects with solid tumors. The combination dose of relatlimab 80 mg Q2W + nivolumab 240 mg Q2W induced responses in previously heavily treated advanced solid tumors and effected responses in tumors that had demonstrated resistance to nivolumab therapy. As of the cutoff date of 11Mar2020 for Part C of CA224020, objective responses were achieved with relatlimab plus nivolumab combination therapy in subjects with treatment naïve advanced melanoma, bladder cancer, NSCLC, renal cell carcinoma, gastric cancer, HCC, and squamous cell carcinoma of the head and neck (SCCHN).

Blockade of the PD-1/PD-L1 axis in combination with CD19 CAR T therapies has not been reported to result in additional toxicity either within the current study or other clinical trials (Osborne, 2020; Jacobson, 2020; Siddiqi, 2019).

Refer to the relatlimab and nivolumab IBs for further information.

1.3.4.6. Rationale for JCAR017 in Combination With CC-99282

CELMoDs have shown encouraging anti-tumor activity and treatment effect as monotherapy as well as in combination with an anti-CD20 monoclonal antibody at different doses and schedules across a range of NHL subtypes. In both clinical and preclinical settings, CELMoDs have been shown to induce and restore T cell functionality and inhibit T cell exhaustion through Cereblon-mediated degradation of Ikaros and Aiolos. The immunomodulation and anti-tumor effects of Ikaros and Aiolos degradation have been shown to be dose dependent. The differential dose and schedule requirements for optimal cytotoxicity versus T cell stimulation will be discussed in detail below.

Similar to *in vitro* studies of CC-122 and CC-220 with JCAR017 described above (Jessup, 2019), CC-99282 targets the degradation of Ikaros and Aiolos proteins in T cells. [redacted]

[redacted]

A major side effect of anti-tumor agents targeting Ikaros and Aiolos degradation is the development of neutropenia secondary to neutrophil maturation arrest. Neutropenia develops as a consequence of the depletion of Ikaros, a critical transcriptional factor controlling hematopoiesis. As has been shown with preclinical and clinical data from CC-122 and CC-220 investigational studies, neutropenia is due to late-stage maturation arrest of neutrophil progenitors (Carpio, 2015).

[redacted]

[redacted]

1.3.5.1. JCAR017 Pharmacokinetics, Immunogenicity, and Cytokine Secretion

The magnitude of CAR T cell expansion and persistence is a predictive biomarker that correlates with response. Upon infusion, CAR T cells can expand > 1,000-fold followed by a contraction phase and a persistence phase (Davila, 2014; Grupp, 2013; Kalos, 2011; Kochenderfer, 2010; Porter, 2011). In the Study 017001 (NCT02631044), a higher level of CD8+ JCAR017 were observed in responding subjects with durable response at Month 3, although persistence was not statistically different at 3 and 6 Months between those with durable response and relapse (Heipel, 2017).

[redacted]

One mechanism of the loss of CAR T cell persistence is the generation of humoral and/or cellular responses to chimeric antigen receptor (Lamers, 2011; Till, 2008; Kershaw, 2006). The development of immunogenicity to JCAR017 T cells and the association with the loss of JCAR017 persistence will be determined in this study.

[redacted]

Cytokine-associated toxicity such as cytokine release syndrome (CRS) and neurotoxicity (NT) have been observed with CAR T cell therapies (Bonifant, 2016; Turtle, 2016a; Davila, 2014). While some degree of correlation may exist between the development of CRS and efficacy, the severity of CRS has not been shown to be predictive of response, but rather associated with disease burden, in both B-ALL and B-NHL (Maude, 2018; Davila, 2014; Siddiqi, 2017). Understanding the basis of NT is still evolving thus identifying baseline factor(s) associated with risk of developing NT will be critical to manage and prevent severe NT (Hay, 2017; Gust, 2017). Initial findings from Study 017001 show that in addition to higher disease burden, higher baseline levels of inflammatory cytokines appear to be associated with higher incidence of CRS and NT and higher CAR T cell and cytokine peak levels (Heipel, 2017). Of the 59 subjects evaluable for safety, 32% developed CRS (2% Grade 4) and 20% developed NT (15% Grade 3 to 4). [redacted]

1.3.5.2. Circulating JCAR017 and Endogenous T Cell Phenotype

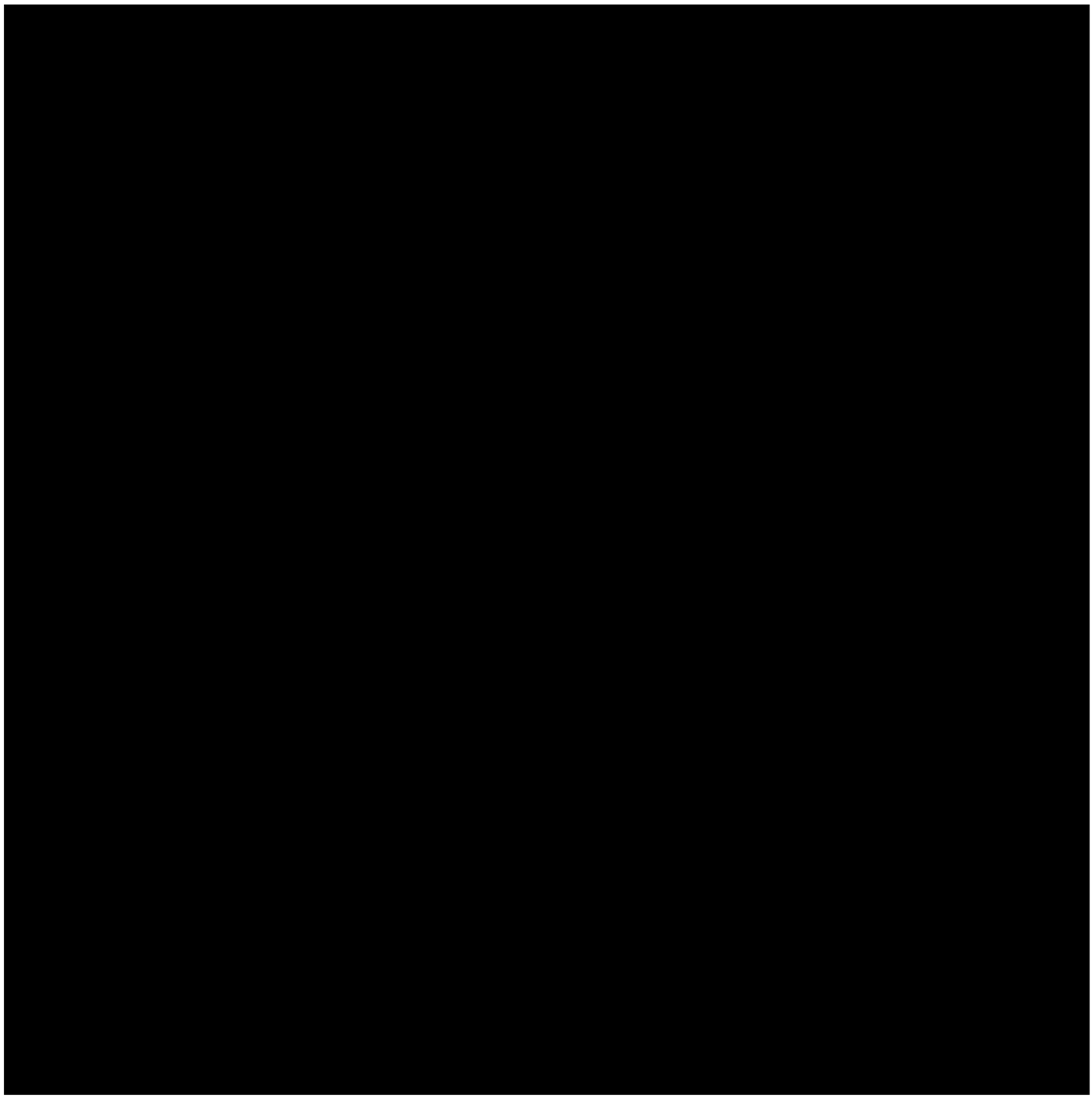
In addition to measuring the proliferation of CAR T cells, the differentiation and phenotype of JCAR017 and endogenous T cells will be monitored in peripheral blood. It has been demonstrated that the memory phenotype of CAR T cells both in the drug product and in vivo correlated with sustained remission and tumor control (Fraietta, 2018; Fraietta, 2018a; Barrett 2014). [redacted]

Cereblon E3 ligase modulation drugs, such as CC-122, CC-220 and CC-99282, not only enhance cytotoxic and memory T cell activation and proliferation, but also lead to increase regulatory T cell (T_{reg}) proliferation (Kneppers, 2011; Raja, 2014; Balaian, 2016; Jessup, 2019; Amatangelo, 2018; Schafer, 2018). Therefore, in parallel, circulating and tumor infiltrating immune cells such as T_{reg} that may abrogate the function and the activation state of JCAR017 T cells will be also monitored.

Ibrutinib can modulate BTK and phosphoinositide phospholipase C-γ (pPLCγ) signaling, as well as affect the memory/naïve distribution of T cells in CLL patients (Long, 2017; Sahaf 2018). Therefore the effect of ibrutinib on JCAR017 CAR T cell phenotype was investigated in vitro following activation by CD19+ tumor cells. Following stimulation, ibrutinib was not observed to have significant effects on CD25, CD38, CD39, or CD95, nor were there effects on central (TCM) or effector (TEM) memory subsets as assessed by the expression of CCR7 and CD45RA (Qin, 2016). However, ibrutinib subtly decreased the percentage of CAR T cells expressing CD69, CD107a, and PD-1 from some donors. Although dramatic changes in immune cell subsets were not observed by flow cytometry with ibrutinib and JCAR017 combination therapy,

molecular signature of ibrutinib-treated cells suggests the emergence of a Th1 memory-like T cell phenotype (Qin, 2016). This may be due to changes in the ratio of activation of interleukin-2-inducible T cell kinase (ITK) and PLCγ2 downstream of the T cell receptor (TCR).

[redacted]



[redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Note: "Combination agent" refers to the specific agent being tested in combination with JCAR017 within each arm.

Primary Objectives
The primary objectives of the study are: Dose finding (Phase 1): • To evaluate the safety and to define the recommended Phase 2 dose and schedule (RP2D) of JCAR017 combinations in adult subjects with relapsed/refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL) Dose expansion (Phase 2): • To evaluate the efficacy of JCAR017 combinations in adult subjects with R/R aggressive B-cell NHL defined as complete response rate (CRR)
Secondary Objectives
The secondary objectives are: Dose finding (Phase 1): • To assess the efficacy of JCAR017 combinations Dose expansion (Phase 2): • To assess the safety and other efficacy parameters of JCAR017 combinations • To characterize changes in health-related quality of life (HRQoL) outcome measures for subjects treated with JCAR017 combinations Phase 1/2: • To characterize the pharmacokinetic (PK) profiles of JCAR017 • To characterize the PK profile of the respective combination agents

Table 1: Study Objectives (Continued)

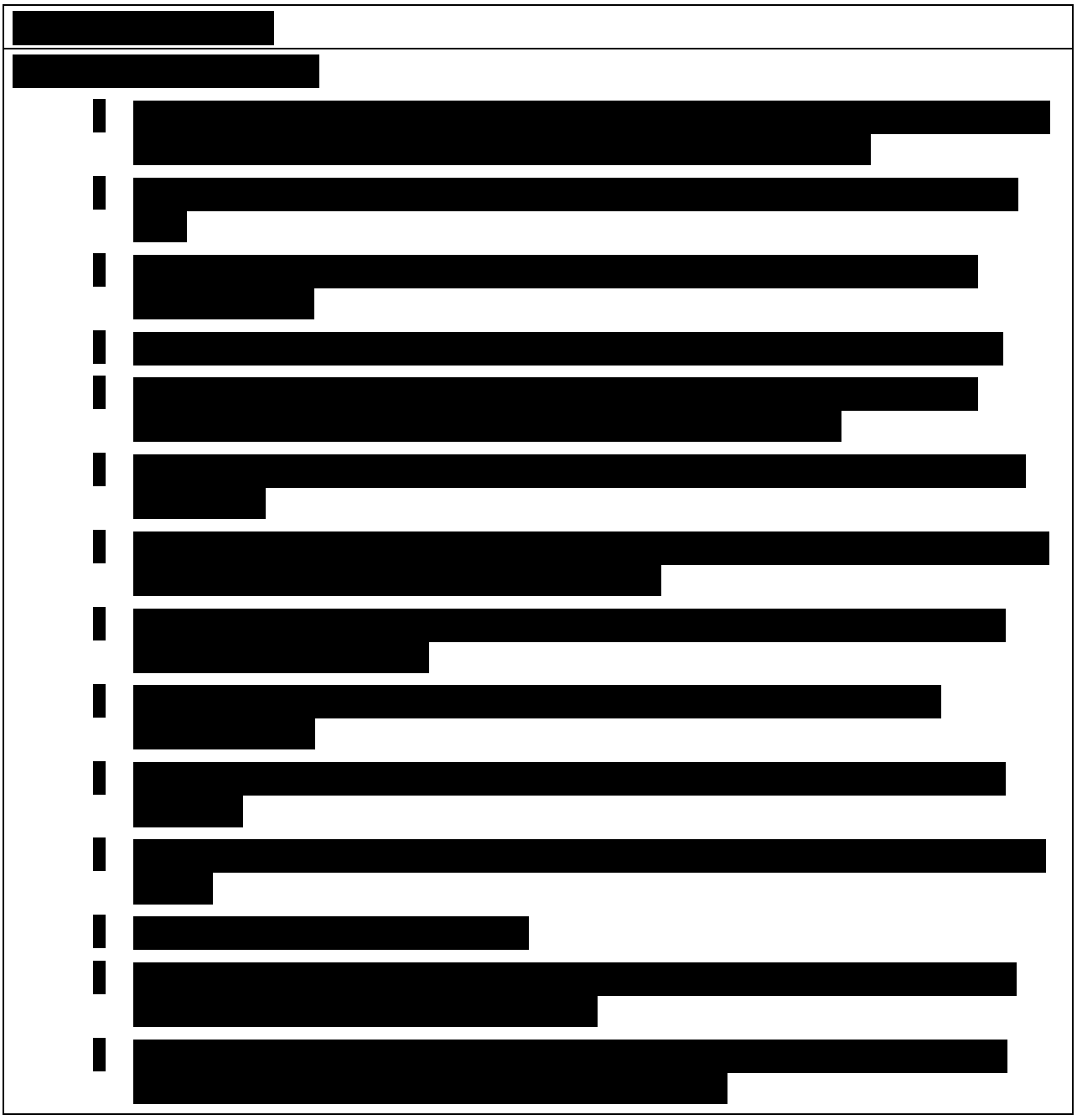


Table 2: Study Endpoints

Endpoint	Name	Description	Timeframe
Primary: Dose finding (Phase 1)	Dose-limiting toxicity (DLT) rates	Percentage of subjects having a DLT	From first dose of the combination agent until 1 month (28 days) after JCAR017 infusion (pre-JCAR017 cohort) or from JCAR017 infusion until 1 month (28 days) after the first dose of combination agent (post-JCAR017 cohort)
Primary: Dose expansion (Phase 2)	Complete response rate (CRR)	Percentage of subjects achieving a complete response (CR) according to the Lugano Classification (Cheson, 2014) by local review	At 3 months post-JCAR017 infusion and subsequently at 6 months post-JCAR017 infusion
Secondary: Dose finding (Phase 1)	Complete response rate (CRR)	Percentage of subjects achieving a complete response (CR) according to the Lugano Classification (Cheson, 2014) by local review	At 3 months post-JCAR017 infusion and subsequently at 6 months post-JCAR017 infusion
Secondary: Dose expansion (Phase 2)	Health-related quality of life (HRQoL)	HRQoL parameters assessed by European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire (EORTC-QLQ-C30) or European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L)	Up to 24 months post-JCAR017 infusion
Secondary (Phase 1/2)	Safety	Type, frequency, and severity of adverse events (AEs) and laboratory abnormalities	Up to 3 months after the dose of JCAR017 or after the last dose of the combination agent, whichever occurs last
	Efficacy: Progression-free survival (PFS)	Time from start of JCAR017, to progressive disease (PD) or death from any cause	Up to 24 months post-JCAR017 infusion
Secondary (Phase 1/2)	Efficacy: Overall survival (OS)	Time from start of JCAR017 to time of death from any cause	Up to last subject last visit
	Efficacy: Overall response rate (ORR)	Percentage of subjects achieving an objective response of partial response (PR) or better according to the Lugano Classification (Cheson, 2014)	At 1, 3, 6, 9, 12, 18 and 24 months post-JCAR017 infusion

Endpoint	Name	Description	Timeframe
	Efficacy: Duration of response (DOR)	Time from first response to disease progression or death from any cause	Up to 24 months post-JCAR017 infusion

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	Efficacy: Event-free survival (EFS)	Time from start of JCAR017 to death from any cause, disease progression, or starting a new anti-lymphoma therapy, whichever occurs first	Up to 24 months post-JCAR017 infusion
Secondary and Exploratory (Phase 1/2)	Pharmacokinetic (PK)	Maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the curve (AUC), and other relevant PK parameters of JCAR017 and the combination agent	Up to 24 months post-JCAR017 infusion
[redacted]			

Endpoint	Name	Description	Timeframe
	[redacted]	[redacted]	[redacted]

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description	Timeframe
	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]

3. OVERALL STUDY DESIGN

3.1. Study Design

This study is intended to evaluate various drug combinations with JCAR017, as separate arms, over the life of the protocol, using the same objectives. Each combination will be evaluated separately (ie, the intention is not to compare between combinations) for the purposes of the objectives, trial design and statistical analysis. The following combinations will be tested:

- Arm A: JCAR017 in combination with durvalumab
- Arm B: JCAR017 in combination with CC-122
- Arm C: JCAR017 in combination with CC-220
- Arm D: JCAR017 in combination with ibrutinib
- Arm E: JCAR017 in combination with relatlimab and/or nivolumab
- Arm F: JCAR017 in combination with CC-99282

Additional arms will be added by way of amendment once combination agents have been selected. Within each arm, cohorts and subcohorts will test different doses and schedules of the combination agent(s).

The study will consist of 2 parts: dose finding (Phase 1) and dose expansion (Phase 2).

3.1.1. Phase 1

The study started with one combination arm, Arm A. Arm B was added by protocol amendment 2 (28 Feb 2018) and Arms C and D added by protocol amendment 4 (29 Oct 2020). Arms E and F are added by protocol amendment 6. Other combination arms may be opened at a later stage via a protocol amendment.

Within each combination arm, up to 3 cohorts plus various subcohorts (eg, additional dose levels and schedules) may be tested (Figure 1). Subcohorts may test several dose levels of JCAR017 and the combination agent(s) and the optimal time to start the combination agent(s). Details on individual subcohorts will be provided in the respective study arm description.

The post-expansion cohort will assess the safety and feasibility of boosting the JCAR017 efficacy with combination agent(s) after peak expansion of JCAR017, ie, after the first efficacy assessment around Day 29 post-JCAR017 infusion.

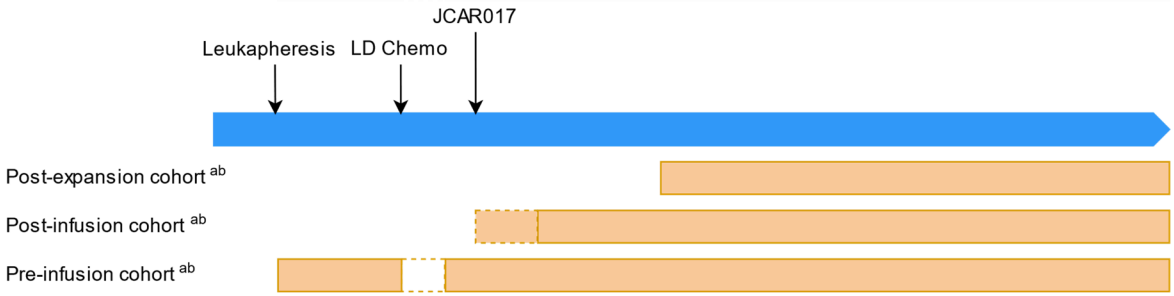
The post-infusion cohort will assess the safety and feasibility of administering combination agents closer to peak expansion of JCAR017 with the intent to increase T cell health, modulate the tumor microenvironment and optimize T cell subpopulations following JCAR017 infusion and prior to peak expansion of JCAR017 (ie, within the first 2 weeks).

The pre-infusion cohort will test the safety and feasibility of initiating treatment with a combination agent prior to JCAR017 infusion. This may increase the health of T cells in the primary leukapheresis starting material and translate into a healthier JCAR017 T cell product and potentially modulate the tumor microenvironment to make the tumor more susceptible to the JCAR017. Continuing the combination post infusion may potentially improve the

pharmacodynamics of JCAR017 cells, ultimately improving efficacy and safety of the infused JCAR017.

Additional cohorts may be added with the aim to combine approaches to maximize the efficacy of JCAR017.

Figure 1: High Level Study Design



■ = combination agent; LD = lymphodepleting.
[a] One study arm will test a given combination of JCAR017 with an agent. The timing of the combination relative to JCAR017 infusion may be tested in one or more cohorts.
[b] Subcohorts may evaluate different dose levels or schedules of JCAR017 or combination agent within a cohort.

The Bayesian Optimal Interval Design (BOIN) (Liu, 2015; Yuan, 2016) will be used for dose escalation/de-escalation decision during Phase 1.

Subjects must have elevated disease burden at screening (sum of product of perpendicular diameters (SPD) of up to 6 index lesions ≥ 25 cm^2 by CT scan). Arms A and B are not subject to this requirement. Up to 15% of subjects per subcohort (ie, 1 in Phase 1 and 4 in an expansion cohort) may have Richter's transformation (transformed chronic lymphocytic leukemia/CLL) without elevated tumor burden.

Enrollment will be staggered such that the first 6 subjects within a subcohort will enter the dose-limiting toxicity (DLT) period a minimum of 1 week apart (or longer as specified in the relevant arm) to allow appropriate safety monitoring. Dose-limiting toxicities will be assessed during the DLT period defined per arm (see Section 9.3.1). A RP2D will be established based on the tolerability and preliminary efficacy in the DLT evaluable subjects treated in the respective subcohort. The final number of subjects will depend on the number of dose levels and schedules tested and the number of DLTs observed within each subcohort. Non-DLT evaluable subjects will be replaced.

A safety review committee (SRC) whose members include the medical monitor(s), drug safety physician, statistician, and a subset of investigators will determine a RP2D for each combination treatment arm based on an integrated assessment of the safety, PK, Pd data, and preliminary efficacy information. The SRC may override the BOIN algorithm for safety concerns.

As a general rule, in post-JCAR017 cohorts JCAR017-related severe toxicities must have resolved before the combination agent is started. Detailed rules are described in the individual study arms.

Within an arm and cohort, a dose level or schedule (subcohort) shown to be safe in Phase 1 may be expanded in Phase 2. The decision to expand a particular subcohort will be made by the Sponsor upon recommendation by the SRC after review of all available data. Enrollment will stop when approximately 35 subjects are evaluable for safety and response at the dose and

schedule chosen as a RP2D (ie, 9 in Phase 1 and 26 in Phase 2). After 6 subjects have been treated at the RP2D in the expansion cohort further enrollment rules will be determined by the Sponsor considering the recommendation of the SRC.

3.1.2. All Phases

All subjects from both phases and all cohorts will be followed for AEs (including new malignancies) and concomitant medications/ procedures for at least 3 months after JCAR017 infusion. Safety follow-up for a given combination agent will be detailed in the respective study arm description and may increase the safety follow-up period.

All subjects from Phase 1 and Phase 2 will be followed for 24 months following JCAR017 infusion for disease status, treatment related AEs, and until the last subject last visit for survival. Post-study follow-up for survival, relapse, long-term toxicity (including new malignancies), and viral vector safety will continue under a separate long-term follow-up (LTFU) protocol for up to 15 years after the JCAR017 dose as per health authority regulatory guidelines.

The study will be conducted in compliance with the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

3.1.3. Study Arm A (JCAR017 in Combination with Durvalumab)

Arm A will evaluate the safety and efficacy of JCAR017 in combination with durvalumab. Subjects from both phases and all cohorts who reach a PR 3 months after JCAR017 infusion may continue durvalumab until progression for a maximum total duration of 12 months. Agreement must be obtained from the Sponsor.

3.1.3.1. Durvalumab Dose Rationale

The dose levels and treatment schedules for durvalumab are based on a safe dose established in Study CD-ON-MEDI4736-1108, a Phase 1/2a study to evaluate the safety, tolerability, and PK of durvalumab in subjects with advanced solid tumors and on population PK analyses. Population PK analysis indicated only a minor impact of body weight on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body weight-based (10 mg/kg every 2 weeks [Q2W]) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations using the population PK model. A fixed dose of 750 mg and 1500 mg was selected to approximate 10 mg/kg and 20 mg/kg, respectively (based on median body weight of approximately 75 kg). A total of 1000 subjects were simulated using a body weight distribution of 40 to 120 kg. Simulation results demonstrated that body weight-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with the fixed dosing regimen. Based on these results the dose of 1500 mg every 4 weeks (Q4W) is now being explored as a dose that provides continuous plasma concentration of antibody above the threshold needed for in vitro activity. The dose of 1500 mg Q4W is the RP2D across the durvalumab clinical program (for ongoing or planned studies in both solid tumors and hematologic malignancies). Over 1000 subjects with solid tumors and myelodysplastic syndrome were treated at a dose schedule equivalent to 1500 mg Q4W (ie, 10 mg/kg Q2W or 20 mg/kg Q4W which show similar exposure levels based on the area under the curves steady state), and available safety data support this as an appropriate dose for durvalumab

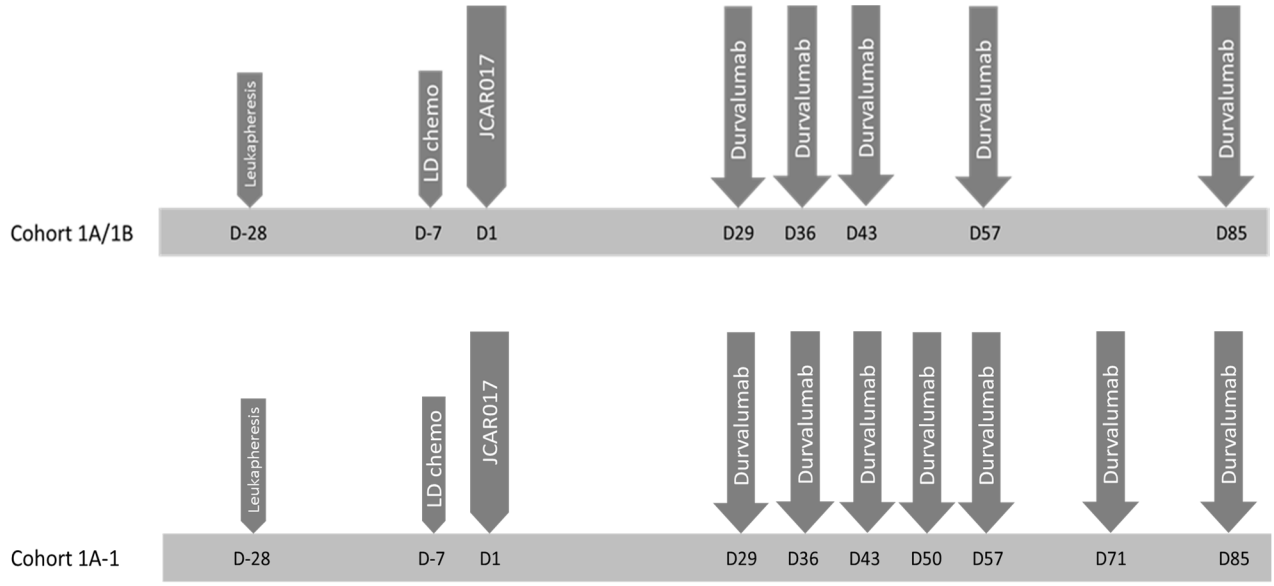
in this study. Extrapolation from the PK simulations defined a dose of 375 mg every week (Q1W) as expected to be equivalent to a dose of 5 mg/kg Q1W, which is believed to be comparable to a dose of 10 mg/kg Q2W and 20 mg/kg Q4W. Please refer to the durvalumab IB for further information.

Arm A Cohort 1 (post-JCAR017) will evaluate the safety and efficacy of starting durvalumab approximately Day 29 after infusion of JCAR017. Durvalumab will be administered at a dose of 375 mg Q1W for 2 weeks, then one dose of 750 mg Q2W, followed by 1500 mg Q4W. This dosing approach is based on PK simulations which show similar biological PD-L1 occupancy but shorter half-life at lower doses. See below Figure 2 and Table 3 for arm and cohort details and dose schedule. Please refer to for dose escalation/ de-escalation rules.

- Cohort 1A will use JCAR017 DL1 (50 x 10^6 CAR+ T cells)
- Cohort 1B will use JCAR017 DL2 (100 x 10^6 CAR+ T cells)
- Cohort 1A-1 will use JCAR017 DL1 (50 x 10^6 CAR+ T cells) and lower doses of durvalumab
- Cohort 1A-2 will use JCAR017 DL1 (50 x 10^6 CAR + T cells) and delayed doses of durvalumab

All subjects will be followed for AEs and concomitant medications/procedures for 3 months after the JCAR017 infusion and 3 months after the last dose of durvalumab, whichever occurs later. After this period, all subjects will be followed until 24 months after JCAR017 infusion for treatment related AEs and concomitant medications/procedures.

Figure 2: Arm A Overview



Abbreviations: D = day; LD chemo = lymphodepleting chemotherapy.

Table 3: Arm A Dosing Schedule

Cohort	JCAR017 Dose	Durvalumab Dose	Durvalumab Schedule[a]
1A	50 x 10^6 CAR+T cells (Dose level 1)	375 mg	Days 29 and 36 post-JCAR017 infusion
		750 mg	Day 43 post-JCAR017 infusion
		1500 mg	Days 57 and 85 post-JCAR017 infusion
1B	100 x 10^6 CAR+T cells (Dose level 2)	375 mg	Days 29 and 36 post-JCAR017 infusion
		750 mg	Day 43 post-JCAR017 infusion
		1500 mg	Days 57 and 85 post-JCAR017 infusion
1A-1	50 x 10^6 CAR+T cells (Dose level 1)	225 mg	Days 29 and 36 post-JCAR017 infusion
		375 mg	Days 43 and 50 post-JCAR017 infusion
		750 mg	Days 57 and 71 post-JCAR017 infusion
		1500 mg	Day 85 post-JCAR017 infusion
1A-2	50 x 10^6 CAR+T cells (Dose level 1)	375 mg	Days 43 and 50 post-JCAR017 infusion
		750 mg	Days 57 and 71 post-JCAR017 infusion
		1500 mg	Day 85 post-JCAR017 infusion

[a] Start date of durvalumab can be within 7 days of planned Day 29. In case of an earlier or later start (eg, Day 22), the next dosing dates should be rescheduled accordingly: in case durvalumab is started on Day 22 (375 mg), next dose (375 mg) would be 7 days after (Day 29), next dose (750 mg) would be 7 days later (Day 36), next dose (1500 mg) would be 2 weeks later (Day 50) and the last planned dose would be 4 weeks later (Day 78).

In case treatment with durvalumab is continued beyond Day 85 (see Section 3.1.3 for conditions and Section 6.3.1.1 for safety follow-up details), the subsequent doses should be given every 4 weeks at 1500 mg for a maximum total duration of 12 months.

3.1.4. Study Arm B (JCAR017 in Combination with CC-122)

Arm B will evaluate the safety and efficacy of JCAR017 in combination with CC-122.

Subjects who reach a PR or SD 6 months (Day 180) after JCAR017 infusion may continue CC-122 until progression or for up to Month 24, whatever is earlier. Agreement must be obtained from the Sponsor.

3.1.4.1. CC-122 Dose Rationale

CC-122 has shown preclinical activity and promising early clinical activity in R/R DLBCL. Dose levels selected for evaluation in Phase 1 target efficacious doses of CC-122 evaluated in the R/R setting. In addition, a candidate patient selection gene expression-based signature was associated with improved response rates in the selected population with R/R DLBCL. Preclinical data indicated that CC-122 is about 10 times more potent than lenalidomide in terms of immunomodulatory activities in T cells and NK cells (Gandhi, 2012) and is 5 to 10 times more potent in terms of anti-proliferative activity in a panel of human CLL cells (Hagner, 2014).

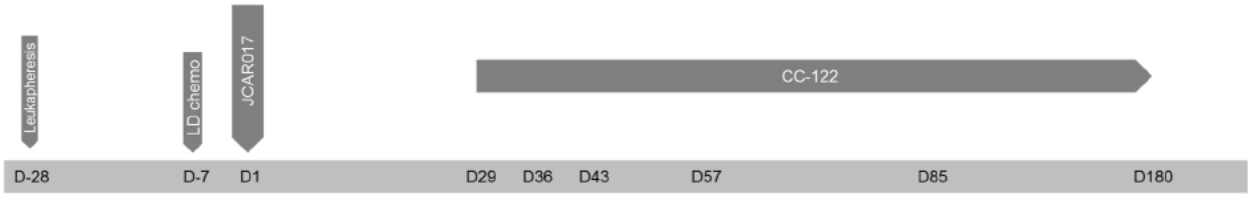
[redacted]

- All Cohorts will use JCAR017 DL 2 (100×10^6 CAR+ T cells)

[redacted]

Subjects will receive CC-122 continuously on 5 of 7 days until Day 180 (Month 6). All subjects will be followed for AEs and concomitant medications/procedures for 3 months after the JCAR017 infusion and 28 days after the last dose of CC-122, whichever occurs later. After this period, all subjects will be followed until 24 months after JCAR017 infusion for treatment related AEs and concomitant medications/procedures.

Figure 3: Arm B Overview



Abbreviations: D = day; LD chemo = lymphodepleting chemotherapy.

Table 4: Arm B Dosing Schedule

Cohort	JCAR017 Dose	[redacted]	CC-122 Schedule[a]
1A	100 x 10^6 CAR+T cells (Dose level 2)	[redacted]	Days 29 - 180 on 5 out of 7 days post-JCAR017 infusion
1B	100 x 10^6 CAR+T cells (Dose level 2)	[redacted]	Days 29 - 180 on 5 out of 7 days post-JCAR017 infusion
1A-1	100 x 10^6 CAR+T cells (Dose level 2)	[redacted]	Days 29 - 180 on 5 out of 7 days post-JCAR017 infusion

[redacted]

In case treatment with CC-122 is continued beyond Day 180 (see Section 3.1.4 for conditions and Section 6.3.1.2 for safety follow-up details), dosing should continue with a 5/7 day-schedule until progression or until Month 24 whichever is earlier.

3.1.5. Study Arm C (JCAR017 in Combination With CC-220)

Arm C will evaluate the safety and efficacy of JCAR017 in combination with CC-220.

3.1.5.1. CC-220 Dose Rationale

[redacted] See Section 10.6.5 for information on the risks associated with treatment using CC-220.

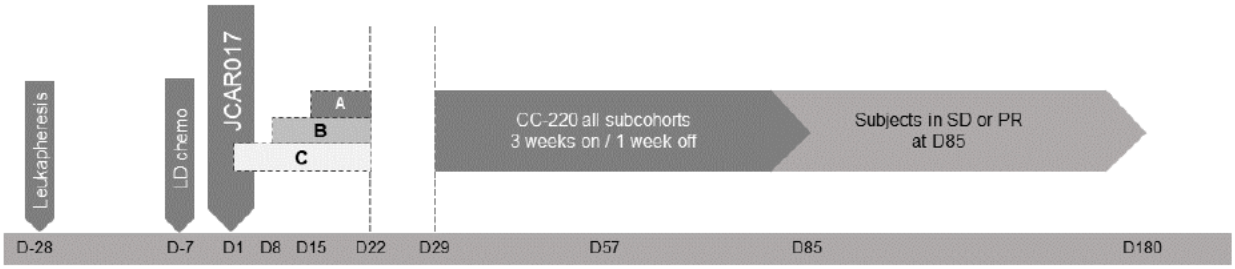
The CC-220 dose schedules selected for this study are based on data from [redacted]

[redacted]

Dosing will be started initially on Day 15, immediately after the predicted peak expansion of JCAR017 on Day 11; if safety data is acceptable and depending on the expansion profile of JCAR017 subsequent subcohorts may be explored with the intent to move towards concomitant administration.

The following terminology will be used to identify Arm C subcohorts: A, B and C represent the relative start date of CC-220 (A: Day 15, B: Day 8, C: Day 1), + and – represent dose escalation (+) or dose de-escalation (-) cohorts (see Figure 4).

Figure 4: Arm C Overview



Abbreviations: D = day; LD chemo = lymphodepleting chemotherapy; SD = stable disease; PR = partial response. Within schedules A, B and C, different doses (dose escalation or de-escalation) may be tested.

See Table 5 for arm and cohort details and dose schedule. Please refer Table 9 for dose escalation/ de-escalation rules.

- All Arm C Subcohorts will use JCAR017 DL 2 (100 x 10^6 CAR+ T cells)
  - [redacted]
- Subjects on Arm C will receive CC-220 for an initial period after JCAR017 infusion; the duration will depend on the specific treated subcohort. The start of CC-220 will be initially on Day 15 but may be advanced to Day 8 or Day 1:

- Subcohorts A, A+1 and A-1: CC-220 will be administered from Day 15 to Day 21
- Subcohorts B, B+1 and B-1: CC-220 will be administered from Day 8 to Day 21
- Subcohorts C, C+1 and C-1: CC-220 will be administered from Day 1 to Day 21

Subjects in all subcohorts must interrupt CC-220 dosing between Day 22 and Day 28 inclusive.

Subjects in all subcohorts will resume CC-220 on Day 29 until Day 85 (Month 3); subjects will take CC-220 on a schedule of 3 consecutive weeks out of 4.

All subjects will be followed for AEs and concomitant medications/procedures for 3 months after the JCAR017 infusion and 28 days after the last dose of CC-220, whichever occurs later. After this period, all subjects will be followed for 24 months after JCAR017 infusion for treatment related AEs and concomitant medications/procedures.

Subjects who reach a PR or SD at Day 85 (Month 3) after JCAR017 infusion may continue CC-220 until progression or for up to Month 12, whichever is earlier. Agreement must be obtained from the Sponsor.

Table 5: Arm C Dosing Schedule

Cohort	Sub-cohort	JCAR017 Dose	[redacted]	CC-220 Schedule
Cohort 1 Post-infusion	A	100 x 10^6 CAR+T cells	[redacted]	Days 15-21 and 29-85 post-JCAR017 infusion
	B			Days 8-21 and 29-85 post-JCAR017 infusion
	C			Days 1-21 and 29-85 post-JCAR017 infusion
	A+1	100 x 10^6 CAR+T cells	[redacted]	Days 15-21 and 29-85 post-JCAR017 infusion
	B+1			Days 8-21 and 29-85 post-JCAR017 infusion
	C+1			Days 1-21 and 29-85 post-JCAR017 infusion
	A-1	100 x 10^6 CAR+T cells	[redacted]	Days 15-21 and 29-85 post-JCAR017 infusion
	B-1			Days 8-21 and 29-85 post-JCAR017 infusion
	C-1			Days 1-21 and 29-85 post-JCAR017 infusion
[redacted]				

3.1.6. Study Arm D (JCAR017 in Combination With Ibrutinib)

Arm D will evaluate the safety and efficacy of JCAR017 in combination with ibrutinib.

3.1.6.1. Ibrutinib - Dose Rationale

Recent preclinical studies showed the ability of ibrutinib to restore CLL patient T cell functionality, enhance CAR T cell production and potentially improve clinical efficacy (Qin, 2016). [redacted]

In patients with recurrent B-cell lymphoma > 90% occupancy of the BTK active site in peripheral blood mononuclear cells was observed up to 24 hours after ibrutinib doses of ≥ 2.5 mg/kg/day (≥ 175 mg/day for average weight of 70 kg). Ibrutinib exposure increases with doses up to 840 mg (1.5 times the maximum approved recommended dosage) in patients with B-cell malignancies. Based on data from the preclinical studies described above along with the PK information reported in chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) clinical trials, a dose of 420 mg/day was selected for this combination arm. This is the dose currently approved by the FDA and other health authorities for treatment of CLL/SLL.

The safety and efficacy of JCAR017 in combination with ibrutinib will be evaluated in a pre-infusion cohort. See below Figure 5 and Table 6 for arm and cohort detail and dose schedule. See Section 10.6.6 for information on the risks associated with ibrutinib treatment.

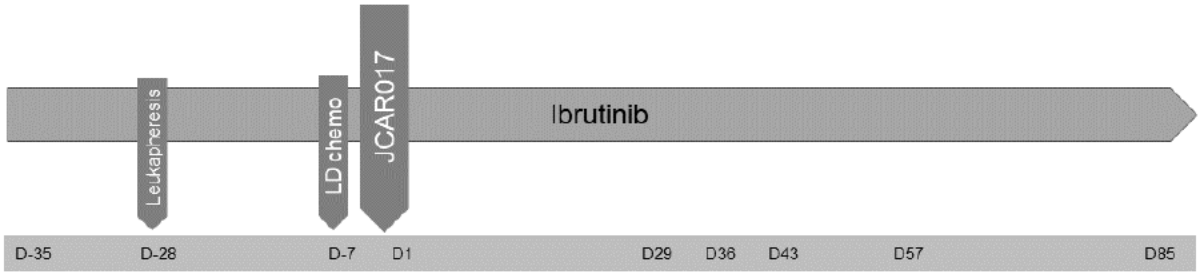
- Subcohort A will use JCAR017 DL2 (100 x 10^6 CAR+ T cells) in combination with a dose of 420 mg ibrutinib (daily) starting on or prior to Day -35

Subjects will receive ibrutinib daily starting at least 5 days prior to leukapheresis (on or prior to Day -35) until 1 day prior to the initiation of LD chemotherapy and restarting the day after LD chemotherapy. In case bridging therapy is needed for disease control, ibrutinib may be continued (or may be briefly discontinued and restarted) depending on the chemotherapy regimen used. Please refer to ibrutinib PI for a comprehensive list of tested chemotherapy regimens. In clinical trials ibrutinib was shown to be safe in combinations with R-CHOP, R-bendamustine, and lenalidomide (Younes, 2018; Kedmi, 2018; Nastoupil, 2018).

Subjects will receive ibrutinib until Day 85 (Month 3).

All subjects will be followed for AEs and concomitant medications/procedures for 3 months after the JCAR017 infusion and 28 days after the last dose of ibrutinib, whichever occurs later. After this period, all subjects will be followed for 24 months after JCAR017 infusion for treatment related AEs and concomitant medications/procedures.

Figure 5: Arm D Overview



Abbreviations: D = day; LD chemo = lymphodepleting chemotherapy.

Table 6: Arm D Dosing Schedule

Cohort	Subcohort	JCAR017 Dose	Ibrutinib Dose	Ibrutinib Schedule
Cohort 1 Pre-infusion	A	100 x 10^6 CAR+T cells	420 mg	Days -35[a] to 85 post-JCAR017 infusion
In case of severe CRS or NT ibrutinib must be paused until resolution.				

[a] Subjects will receive ibrutinib daily starting at least 5 days prior to leukapheresis (by Day -35) until the initiation of LD chemotherapy (unless continued bridging therapy is needed for disease control), through Day 85 (Month 3).

3.1.7. Study Arm E (JCAR017 in Combination With Relatlimab and/or Nivolumab)

Arm E will evaluate the safety and efficacy of JCAR017 in combination with nivolumab with or without relatlimab.

3.1.7.1. Nivolumab and Relatlimab Dose Rationale

The nivolumab doses of 240 mg Q2W or 480 mg Q4W were selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, NSCLC, and RCC) where body weight normalized dosing (mg/kg) was used.

Nivolumab PK has been extensively studied in multiple tumor types, including melanoma, NSCLC, RCC, cHL, SCCHN, CRC and urothelial carcinoma and has been safely administered at doses up to 10 mg/kg Q2W. Nivolumab monotherapy was originally approved as a body-weight based dose of 3 mg/kg Q2W, and was updated to 240 mg Q2W or 480 mg Q4W in multiple indications. Nivolumab 360 mg Q3W is also under evaluation in monotherapy and in combination therapy studies. Less frequent 360 mg Q3W and 480 mg Q4W dosing regimens can reduce the burden to patients of frequent, lengthy IV treatments and allow combination of nivolumab with other agents using alternative dosing regimens.

[redacted] This assessment is based on a comprehensive characterization of nivolumab PK, safety, efficacy, and exposure-response relationships across indications. [redacted] no clinically meaningful differences in PK across ethnicities and tumor types were observed. Using the PPK model, the exposures following administration of several dosing regimens of nivolumab administered as a

flat dose were simulated, [redacted]. The simulated average serum concentration at steady state [Cavgss] following administration [redacted] are predicted to be similar to those following administration of [redacted] administered to patients over a wide body weight range (34-180 kg) across tumor types.

Extensive exposure-response analyses of multiple PK measures (maximum serum concentration at Day 1, average serum concentration at Day 28 [$C_{avg}28$], and trough serum concentration at Day 28) and efficacy and safety endpoints indicated that the efficacy of the [redacted]. In E-R efficacy analyses for OS and ORR conducted in melanoma, RCC, and NSCLC using $C_{avg}28$ as the exposure measure, probabilities of achieving a response and survival probabilities at 1 year and 2 years for [redacted]. In exposure-response safety analyses, it was demonstrated that the exposure margins for safety are maintained following [redacted], and the predicted risks of discontinuations due to AEs or death, AE Grade 3+, and immune-mediated AEs (IMAEs) Grade 2+ are similar following [redacted] across tumor types. In addition, nivolumab exposures with [redacted] across tumor types are maintained well below the corresponding exposures observed with the well tolerated 1[redacted]

The relatlimab doses of [redacted] were selected to be evaluated in co-administration with nivolumab [redacted] in this study. The selected dose of relatlimab is based on the consideration that maximal target engagement will provide meaningful clinical activity. The pharmacokinetics (PK) and safety profile of relatlimab co-administered with nivolumab is not expected to be different than that of sequential administration of each drug implemented previously in other clinical trials. Please also refer to the details on the safety of relatlimab and nivolumab co administration in Section 10.6.7.

Relatlimab doses were selected after consideration of several factors including relatlimab PK, pharmacodynamics (Pd), benefit/risk assessment of relatlimab, nivolumab and liso-cel coadministration, and extensive nivolumab monotherapy clinical experience.

The relatlimab PK and Pd were characterized over a wide range of doses from [redacted]. Relatlimab AUC(tau) increased proportionally over a dose range of [redacted]. The different administration methods for combination therapy, including single-agent vial (SAV) sequential, SAV co-administration, and fixed dose combination [redacted] were found to have no significant effect on PK when compared to monotherapy.

[redacted]

[redacted]

From Study Day 57 subjects receiving relatlimab and/or nivolumab at a Q2W frequency switch to relatlimab and/or nivolumab Q4W which provides a more convenient dosing regimen for subjects. Based on PK modeling and simulations, [redacted]

Additional details on posologies and risk-benefit for both relatlimab and nivolumab can be found in the respective Investigator's Brochures. Please also refer to the current Investigator's Brochure and/or Pharmacy Manual for further details regarding storage, preparation, and administration of relatlimab or nivolumab.

3.1.7.2. Relatlimab and Nivolumab Dose Schedule

The doses and schedules of relatlimab and nivolumab are based on doses established in Studies CA224020 and CA224022 in advanced solid tumors and B-cell malignancies. Due to the temporal proximity of the planned start of combination agents to JCAR017 infusion, initial subcohorts will evaluate the combination therapy using a Q2W dose frequency for nivolumab or relatlimab up to Day 57. If safety data permits, subsequent subcohorts will use Q4W dose frequency throughout.

NOTE: to fit to the JCAR017 visit schedule, the dose frequency referred to as Q2W below will be given on Day 8, 22, 36, 57 and 85, or 15, 29, 43, 57 and 85; the Q4W frequency will be given on Day 8, 36, 57, 85, or Day 15, 57 and 85.

- All Arm E Subcohorts will use JCAR017 DL 2 (100 x 10^6 CAR+ T cells)
  - [redacted]

- [redacted]
- [redacted]

There will be no intra-subject dose escalations or reductions of relatlimab or nivolumab allowed.

Doses of study drug(s) may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

For relatlimab / nivolumab doses scheduled up to and including Day 22, a delay of more than 4 days requires that dose to be skipped.

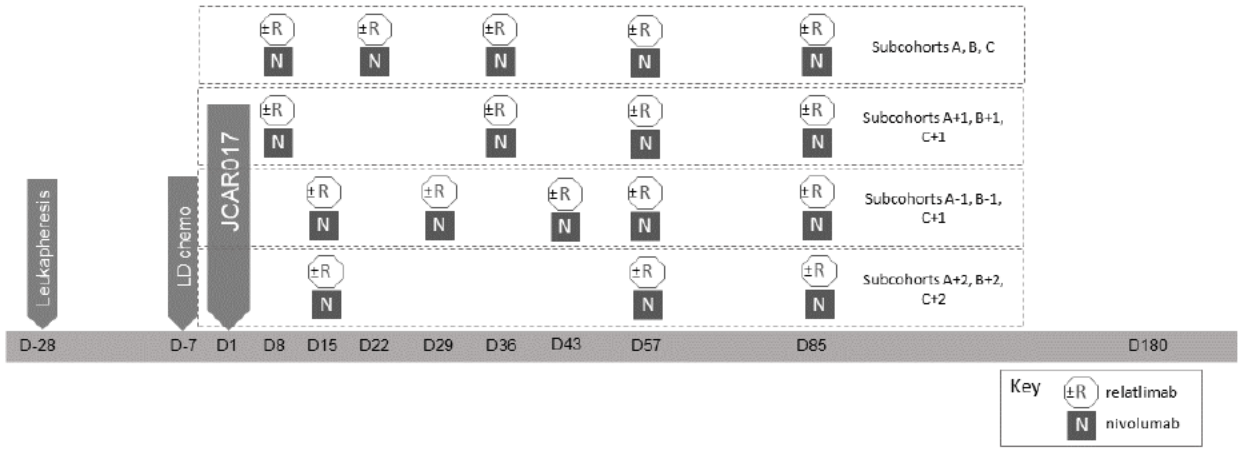
From Day 29 to Day 43, a delay to a dose of more than 7 days requires that dose to be skipped. Subjects may be dosed no less than 10 days from the previous dose.

For doses planned on Day 57 or 85, a delay to a dose of more than 15 days requires that dose to be skipped. Subjects may be dosed no less than 15 days from the previous dose.

A delay in dose administration will not affect the following scheduled administration visits per protocol. See Section 3.1.9.5 for information on how to proceed with a subject with a delay to start of relatlimab / nivolumab.

All subjects will be followed for AEs and concomitant medications/procedures for 3 months after the JCAR017 infusion and 100 days after the last dose of relatlimab or nivolumab, whichever occurs later. After this period, all subjects will be followed for 24 months after JCAR017 infusion for treatment-related AEs and concomitant medications/procedures.

Figure 6: Arm E Overview



Abbreviations: D = day; LD chemo = lymphodepleting chemotherapy

Table 7: Arm E Dosing Schedule

Cohort	Sub-cohort	JCAR017 Dose
Cohort 1 Post-infusion	A	100 x 10^6 CAR+T cells
	B	
	C	
	A+1	100 x 10^6 CAR+T cells
	B+1	
	C+1	
	A-1	100 x 10^6 CAR+T cells
	B-1	
	C-1	
	A+2	100 x 10^6 CAR+T cells
	B+2	
	C+2	

[redacted]

3.1.8. Study Arm F (JCAR017 in Combination With CC-99282)

Arm F will evaluate the safety and efficacy of JCAR017 in combination with CC-99282.

3.1.8.1. CC-99282 Dose Rationale

The CC-99282 [redacted] was selected based on emerging clinical data from the CC-99282-NHL-001 trial, and preclinical modeling of CC-99282 and JCAR017 combination assays.

CC-99282 is a novel therapeutic agent. [redacted]

The CC-99282 starting dose in the initial Subcohort A will be administered at [redacted] beginning on Day 8 post JCAR017 infusion, and will be given weekly through Day 85 post JCAR017 infusion.

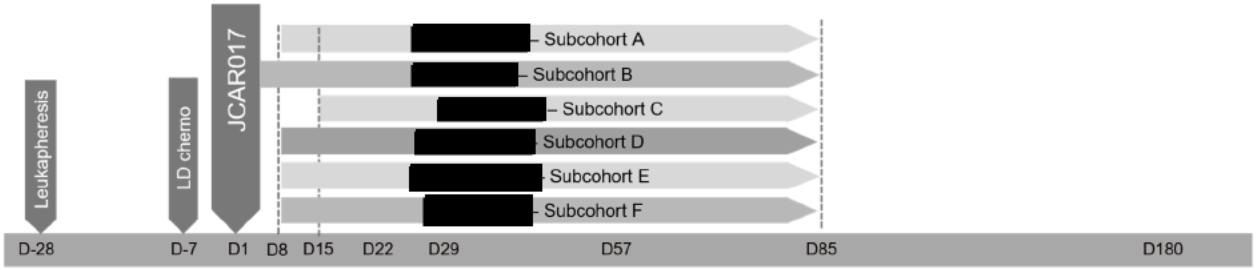
If the [redacted] dose is deemed to be safe and tolerable, subsequent subcohorts evaluating alternative doses and schedules maybe selected based on translational data. The dose may be

increased to [redacted]

See Figure 7 for additional dosing and schedule details and refer to Table 8 below for Dosing Schedule and Arm F Overview.

Overall, CC-99282 exhibits an acceptable safety profile in preclinical and in early clinical testing. Additional details on risk-benefit for CC-99282 can be found in the Investigator's Brochure. Please also refer to the current Investigator's Brochure and/or Pharmacy Manual for further details regarding storage, handling, and administration of CC-99282.

Figure 7: Arm F Overview



Abbreviations: D = day; LD chemo = lymphodepleting chemotherapy.

See Table 8 for arm and cohort details and dose schedule. Please refer to Table 9 for dose escalation/ de-escalation rules.

- All Arm F Subcohorts will use JCAR017 DL 2 (100 x 10^6 CAR+ T cells)
  - [redacted]

Table 8: Arm F Dosing Schedule

Cohort	Sub-cohort	JCAR017 Dose	[redacted]	CC-99282 Dosing Schedule
Cohort 1 Post-Infusion	A	100 x 10^6 CAR+ T cells	[redacted]	Starting on Day 8, Q7D
	B	100 x 10^6 CAR+T cells	[redacted]	Starting on Day 1, Q7D
	C	100 x 10^6 CAR+ T cells	[redacted]	Starting on Day 15, Q7D
	D	100 x 10^6 CAR+ T cells	[redacted]	Starting on Day 8, Q7D
	E	100 x 10^6 CAR+ T cells	[redacted]	Starting on Day 8 Q14D
	F	100 x 10^6 CAR+ T cells	[redacted]	Starting on Day 8 Q7D

[redacted]

All subjects will be followed for AEs and concomitant medications/procedures for 3 months after JCAR017 infusion and 28 days after the last dose of CC-99282, whichever occurs later. After this period, all subjects will be followed for 24 months after JCAR017 infusion for treatment related AEs and concomitant medications/procedures.

3.1.9. Dose and Cohort Decision Rules

3.1.9.1. Arm A

Subjects in Cohort 1A will receive JCAR017 at DL1. If no severe toxicities occur, durvalumab will be started around Day 29 (± 7 days). If toxicities to JCAR017 develop, durvalumab will not be started until AEs have resolved to baseline. Delay of the first infusion of durvalumab of more than 7 days (ie, Day 36) necessitates discussion with the Sponsor prior to durvalumab administration. Delay of subsequent durvalumab doses also needs discussion with the Sponsor. Subjects who do not receive durvalumab within 7 days of their scheduled start will not be evaluable for DLT and will be replaced. In subjects experiencing a DLT after durvalumab infusion, the durvalumab will be discontinued, and no additional doses of durvalumab will be given.

According to the BOIN algorithm, escalation to Cohort 1B (JCAR017 DL2) or de-escalation to Cohort 1A-1 or 1A-2 (JCAR017 DL1 with reduced durvalumab dose and/or modified schedule of administration of durvalumab) may occur (see Table 9). In case of de-escalation, it is anticipated that only one cohort will be opened and the decision will be taken based on the results from Cohort 1A by the Sponsor considering the SRC recommendation.

3.1.9.2. Arm B

Subjects in Cohort 1A will receive JCAR017 at DL2. If no severe toxicities occur, CC-122 will be started around Day 29 (± 7 days). Subjects with Grade 4 neutropenia, Grade 3 neutropenia associated with fever, or Grade 4 thrombocytopenia at D29 will not be allowed to start CC-122 unless recovered to Grade < 3 without fever. If other toxicities to JCAR017 develop, CC-122 will not be started until AEs have resolved to baseline. Delay of first dose of CC-122 of more than 7 days (ie, Day 36) necessitates discussion with the Sponsor. Delay of subsequent CC-122 doses also needs discussion with the Sponsor. Subjects who do not receive CC-122 within 7 days of their scheduled start will not be evaluable for DLT and will be replaced. In subjects

experiencing a DLT after CC-122 administration, the CC-122 will be paused and may be resumed after dose adjustment (see Table 27).

According to the BOIN algorithm, escalation to Cohort 1B (CC-122 dose of 3 mg) or de-escalation to Cohort 1A-1 (CC-122 dose of 1 mg) may occur (see Table 9). The decision will be taken based on the results from Cohort 1A by the Sponsor considering the SRC recommendation. The lower dose of 1 mg may be explored if recommended by the SRC.

3.1.9.3. Arm C

Subjects in Arm C will receive JCAR017 at DL2.

In the initial subcohort 1A if no severe toxicities to JCAR017 occur, CC-220 will be started around Day 15 (+ 3 days). Delay of first dose of CC-220 of more than 3 days (eg, Day 19 for subcohort 1A) necessitates discussion with the Sponsor. Delay of subsequent CC-220 doses also needs discussion with the Sponsor. Subjects who do not receive CC-220 within 3 days of their scheduled start will not be evaluable for DLT and will be replaced. In subjects experiencing a DLT after CC-220 administration, CC-220 will be paused and may be resumed after dose adjustment (see Appendix S). In case of severe CRS or NT, CC-220 must be paused until resolution.

At Day 29 subjects with Grade 4 neutropenia, Grade 3 neutropenia associated with fever, or Grade 4 thrombocytopenia at the scheduled start of CC-220 will not restart until recovered to Grade < 3 without fever. If other toxicities to JCAR017 develop, CC-220 will not be started until AEs have resolved to baseline. The same rules apply for all other subcohorts.

Based on the results of the combination including safety and laboratory data, and according to the BOIN algorithm (see Table 9), escalated or de-escalated starting doses of CC-220 and an earlier start of combination therapy may be evaluated. The starting CC-220 dose may be escalated to 0.6 mg or de-escalated to 0.3 mg and the start of CC-220 may be advanced to Day 8 (+ 3 days) or Day 1 (+ 3 days). The decision on which subsequent subcohort will be selected will be taken by the Sponsor considering the SRC recommendation from the previous subcohort.

3.1.9.4. Arm D

Subjects in Arm D will receive JCAR017 at DL2.

For subjects in the single subcohort 1A, ibrutinib will start at least 5 days prior to leukapheresis and continue until the day before LD chemotherapy and restarted the day after LD chemotherapy is completed. Delay of more than 7 days to restarting necessitates discussion with the Sponsor. Delays of subsequent ibrutinib doses require discussion with the Sponsor. In case of severe CRS or NT, ibrutinib must be paused until resolution.

In subjects experiencing a DLT after ibrutinib administration post-JCAR017, ibrutinib will be paused and may be resumed after dose adjustment (see Appendix T).

No additional subcohorts with alternative schedules, dose escalation or dose de-escalation are planned in Arm D.

3.1.9.5. Arm E

Subjects in Arm E will receive JCAR017 at DL2.

In the initial cohort 1A, if no severe toxicities to JCAR017 (ie, Grade ≥ 3 CRS or NT) occur, checkpoint inhibitor therapy with relatlimab and/or nivolumab (CPI) will be started around Day 8 (+ 4 days). If severe toxicities to JCAR017 develop, CPI will not be started until they have resolved to Grade ≤ 2. Delay of the first infusion of CPI of more than 4 days (ie, Day 12 for the initial subcohort) necessitates discussion with the Sponsor prior to administration. Delay of subsequent CPI doses also needs discussion with the Sponsor. Subjects who do not receive CPI within 4 days of their scheduled start will not be evaluable for DLT and will be replaced. In subjects experiencing a DLT after CPI infusion, continuation of combination therapy after resolution of symptoms depends on the nature and severity of the adverse event (see Appendix C for details).

In Phase 1 the first 3 subjects in each Arm E subcohort will enter the dose-limiting toxicity (DLT) period a minimum of 2 weeks apart; the next 3 subjects in the subcohort will enter the dose-limiting toxicity (DLT) period a minimum of 1 week apart. The first 6 subjects treated on the arm will be followed for safety to 90 days post JCAR017 before any decision on expansion is taken.

In Phase 1, subjects with a planned combination therapy start on Day 8 who do not receive CPI within 4 days of their scheduled start will instead be treated on the schedule for Day 15 start (eg, a subcohort 1A patient would be treated per the 1A-1 schedule). Similarly, for planned start on Day 15, if unable to start by Day 19, initiate CPI on Day 22 and continue on Day 36, Day 57 and Day 85. These subjects will not be evaluable for DLT in the new subcohort and will be replaced.

In Phase 2, subjects in subcohorts A+1, B+1 and C+1 (scheduled to start on Day 8 on a Q4W dose schedule) who cannot receive CPI within 4 days of their scheduled start will receive a Q2W dose on Day 15, or if still unable to start, Day 22. Subjects in subcohorts A+2, B+2 and C+2 (scheduled to start on Day 15 on a Q4W dose schedule) who cannot receive CPI within 4 days of their scheduled start will receive a Q2W dose on Day 22 or Day 29. If this occurs, sensitivity analyses will be performed to detect the impact on study results.

Based on the results of the combination including safety and laboratory data, and according to the BOIN algorithm (see Table 9), subcohorts with escalated doses of relatlimab or no relatlimab, or a later start of combination therapy may be evaluated. The decision on which subsequent subcohort will be selected will be taken by the Sponsor considering the SRC recommendation from the previous subcohort.

Dose delay criteria apply for all drug-related adverse events regardless of whether the event is attributed to nivolumab or relatlimab or both. Delay administration of both relatlimab (if scheduled) and nivolumab if the subject experiences severe toxicity to JCAR017 or if any of the delay criteria in Appendix C are met. Delay both relatlimab (if scheduled) and nivolumab dosing for any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

For subjects who require delay of CPI, re-evaluate weekly, or more frequently, if clinically indicated and resume dosing when criteria to resume treatment are met (see Section 3.1.7). Continue tumor assessments per protocol even if dosing is delayed. Continue periodic study visits to assess safety and laboratory studies every week or more frequently if clinically indicated during such dosing delays.

Subjects may resume treatment with study drug if they have completed AE management (eg, corticosteroid taper) or are on ≤ 20 mg prednisone or equivalent, and meet the requirements per Appendix C, and the delay to therapy is within the boundaries specified in Section 3.1.7.

CPI treatment must be permanently discontinued per criteria in Appendix C, Appendix D or Appendix E.

Discontinue relatlimab and nivolumab for any AE, laboratory abnormality, or intercurrent illness which in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued CPI dosing. Any event that leads to delay in CPI dosing lasting longer than 6 weeks requires discontinuation.

3.1.9.6. Arm F

Subjects in Arm F will receive JCAR017 at DL2

In the initial cohort 1A, if no severe toxicities to JCAR017 occur, CC-99282 will be started on Day 8 (+ 3 days). Delay of CC-99282 of more than 3 days (eg, after Day 11 for cohort 1A) necessitates discussion with the Sponsor. Delay of subsequent CC-99282 doses also requires discussion with the Sponsor. Subjects who do not receive CC-99282 within 3 days of their scheduled start will not be evaluable for DLT and will be replaced. In subjects experiencing a DLT after CC-99282 administration, CC-99282 will be paused and may be resumed after dose adjustment (Appendix U). In cases of Grade ≥ 3 CRS or NT, CC-99282 must be paused until resolution to Grade ≤ 2.

Subjects with Grade ≥ 3 CRS or NT at the scheduled start of CC-99282 will be delayed until recovered to Grade ≤ 2. Subjects with uncontrolled infection will also not start CC-99282. If other toxicities to JCAR017 develop, CC-99282 will not be started until they have resolved to Grade ≤ 2. The same rules apply for all other sub-cohorts. Administration of growth factor is allowed (see Section 8.1.2).

Based on the results of the combination including safety and laboratory data, and according to the BOIN algorithm (see Table 9), escalated or de-escalated starting doses of CC-99282 and an earlier start of combination therapy may be evaluated. The starting dose of CC-99282 may be escalated to 0.4 mg or de-escalated to 0.2 mg and the start of CC-99282 may be advanced to Day 1 (+3 days) or adjusted to Day 15 (+3 days). The decision on which subsequent sub-cohort will be selected will be taken by the Sponsor considering the SRC recommendation from the previous subcohort.

3.1.9.7. Dose Escalation and De-Escalation Rules

In Phase 1, decisions to move between dose levels (subcohorts) will be based on the BOIN algorithm in Table 9.

Expansion of a subcohort to Phase 2 evaluation requires a minimum of 6 subjects to have been evaluated for DLT at that dose level. Escalation between Phase 1 subcohorts requires a minimum of 3 subjects to have been evaluated for DLT at that dose level. De-escalation may be done with any number of prior subjects at that dose level.

Table 9: Dose Escalation and De-Escalation Rules Based on BOIN Algorithm

Action	The Number of Subjects Treated at the Current Dose Level								
	1	2	3	4	5	6	7	8	9
Target DLT rate = 0.3, λ_e=0.236, λ_d=0.358									
Escalate if number of subjects with DLT is ≤	0	0	0	0	1	1	1	1	2
De-escalate if number of subjects with DLT is ≥	1	1	2	2	2	3	3	3	4
Eliminate if number of subjects with DLT is ≥	NA	NA	3	3	4	4	5	5	5

Abbreviations: BOIN = Bayesian optimal interval; DLT = dose-limiting toxicity.

3.2. Stopping Rules

Adverse events and serious adverse events (SAEs) are expected to occur frequently in this study based on the subject population being accrued and on the nature of the advanced hematologic malignancy under study. Regular systematic review of SAEs will serve as the basis for pausing or prematurely stopping the study. Unexpected SAEs that are related to JCAR017 or the combination agent will be the primary criteria for pausing or stopping the study. Review of these SAEs, and any decision to pause enrollment or terminate the study, will be determined by the data safety monitoring board (DSMB), the Sponsor, and the medical monitor(s). Decisions to pause enrollment or terminate the study will be communicated promptly to Investigators, to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), Institutional Biosafety Committees (IBCs) (if applicable), and to the appropriate regulatory authorities.

3.2.1. Criteria for Pausing or Stopping the Study

1. The following SAEs occurring within 1 month (28 days) of the JCAR017 infusion or the start of the combination agent whichever occurs last, will be a criterion for pausing or stopping the study or arm if not related to disease progression considering SRC/ DSMB recommendation:
    - Life-threatening (Grade 4) toxicity attributable to protocol therapy that is unexpected, unmanageable (ie, does not resolve to Grade 3 or lower within 7 days), and unrelated to chemotherapy
    - Life threatening (Grade 4) toxicity to vital organs in 2 or more subjects
    - Death
2. If any of the following occur, the study or a specific arm will be terminated:

- Any subject develops uncontrolled JCAR017 proliferation that is unresponsive to treatment
- Any subject develops detectable replication-competent lentivirus (RCL) during the study
- The Sponsor, IRB/ IEC, or DSMB decides that subject safety may be compromised by continuing the study
- The Sponsor decides to discontinue the development of JCAR017 and/or the combination agent in this indication or the development of JCAR017 and/or the combination agent for all indications

Medical monitor(s) will review the events in item 1 and 2 closely, and if any unusual signal is detected or a study treatment-related death occurs, the DSMB will be informed immediately.

3.3. Safety Monitoring Boundaries

During the Phase 2 portion of the study, besides items 1 and 2 in Section 3.2.1, Bayesian framework safety monitoring boundaries (Thall, 1994; Yao, 2013) will be used to help detect safety signals that may occur during the course of the study. The boundaries are based on the cumulative number of subjects who have received at least one dose of JCAR017 or one dose of the combination agent and who experienced either at least one event of the following grades within 1 month (28 days) of JCAR017 infusion or start of combination agent whichever occurs last:

- A Grade 3 treatment-emergent adverse events of special interest (AESIs) that is unmanageable or fails to resolve to Grade 2 or better after 21 days
- A Grade 4 treatment-emergent AESI that is unmanageable or fails to resolve to Grade 3 or better after 7 days

Adverse events of special interest (AESI) may include but are not limited to:

- Infusion related reaction
- Cytokine release syndrome (CRS)
- Neurological toxicity (NT)
- Macrophage activation syndrome (MAS)
- Tumor lysis syndrome (TLS)
- Prolonged cytopenia
- Hypogammaglobulinemia
- Infections Grade ≥ 3
- Autoimmune disorders
- Secondary malignancy

Whenever the safety boundaries are crossed, enrollment will be paused and an ad hoc DSMB meeting will be held to review the data. The data to be reviewed by the DSMB are specified in

the DSMB charter and DSMB report template. The DSMB may override the safety stopping boundaries to recommend study continuation based on clinical and overall risk benefit considerations. Details regarding the Bayesian framework and the safety monitoring boundaries will be included in the statistical analysis plan.

The other safety monitoring activity includes periodic DSMB meetings as specified in the DSMB charter.

3.4. Study Duration for Subjects

The duration of participation for subjects who complete the study will be approximately 26 months. All subjects who receive JCAR017 will be eligible and asked to enroll into a separate LTFU protocol after completion of this study.

3.5. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date when the last subject enters the LTFU study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Approximately 55 subjects with R/R aggressive B-cell NHL in each arm will be enrolled worldwide to reach up to 18 DLT evaluable subjects in Phase 1 and if the expansion phase is opened at least 26 safety and efficacy evaluable subjects in Phase 2, in each arm. In study arms where Phase 1 subcohorts may evaluate both different combination doses and different treatment schedules the number of subjects treated may be higher (eg, a minimum of 6 and up to 36 evaluable subjects for Arm C).

4.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF).
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
4. Subject must have histologically confirmed at last relapse aggressive B-cell NHL according to the 2016 revision of the WHO classification of lymphoid neoplasms (Swerdlow, 2016) defined as:
   a. DLBCL NOS including transformed indolent NHL
   b. Follicular lymphoma Grade 3B
   c. T cell/histiocyte-rich large B-cell lymphoma
   d. EBV positive DLBCL, NOS
   e. Primary mediastinal (thymic) large B-cell lymphoma
   f. High grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology (double/triple-hit lymphoma)

   Note: If archival material is not available from latest relapse, a new tumor biopsy is required.
5. Subject´s disease must have relapsed or be refractory to at least 2 prior lines of systemic therapy. Previous therapy must have included a CD20-targeted agent and an anthracycline.

   Note: For subjects with transformed disease, the subject should have had at least 2 lines of systemic therapy for his/her transformed disease (ie, the DLBCL) to be eligible. Lines of therapy do not include those given for a previously indolent condition (eg, follicular lymphoma, CLL). Subjects do not have to have received anthracycline for their DLBCL if received for indolent disease.
6. Subject must have:
   a. Positron emission tomography (PET)-positive (Deauville score 4 or 5) and computed tomography (CT) measurable disease as per Lugano Classification (Cheson, 2014)

b. Sum of product of perpendicular diameters (SPD) of up to 6 index lesions ≥ 25 cm^2 by CT scan (not applicable to Arm A or B or subjects with Richter's transformation)

7. ECOG performance status ≤ 1 at screening.
8. Adequate organ function, defined as:

- Adequate bone marrow function to receive lymphodepleting chemotherapy defined as: absolute neutrophil count (ANC) ≥ 1.0 x 10^9 cells/L and platelets ≥ 50 x 10^9 cells/L
- Creatinine clearance ≥ 60 mL/min (estimated creatinine clearance by Cockcroft Gault see Appendix I for calculation)
- Serum alanine transaminase (ALT) ≤ 3.0 x ULN. In the case of documented liver involvement by lymphoma, ALT must be ≤ 5.0 x ULN
- Serum total bilirubin ≤ 2.0 mg/dL (34 µmol/L). In the case of Gilbert's syndrome, or documented liver or pancreatic involvement by lymphoma, serum total bilirubin must be ≤ 3.0 mg/dL (51 µmol/L)
- Adequate pulmonary function, defined as ≤ Grade 1 dyspnea according to Common Terminology Criteria for Adverse Events (CTCAE version 4.03) and oxygen saturation (SaO_2) ≥ 92% on room air
- Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) ≥ 40% as assessed by echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) performed within 4 weeks of leukapheresis
- Troponin-T or I (TnT or TnI) value < ULN (Arms B and E) or brain natriuretic peptide (BNP) ≤ 300 pg/ml (Arm B). Note: Subjects with baseline troponin-T or I > ULN or BNP > 100 pg/mL are eligible but should have cardiologist evaluation prior to enrollment in the trial for baseline assessment and optimization of cardioprotective therapy after discussion with the sponsor's medical monitor

Note: If troponin-T cannot be performed locally, troponin-I may be used instead. If BNP cannot be performed locally, NT pro-BNP may be used instead.

9. Subjects must agree to not donate blood, organs, sperm or semen, and egg cells for usage in other individuals while receiving the combination agent and for at least 12 months following lymphodepleting chemotherapy, or 5 months after the last dose of nivolumab or relatlimab, whichever is later. There is insufficient exposure data to provide any recommendation concerning the duration of refraining from tissue donation following treatment with JCAR017. Therefore, subjects treated with JCAR017 should not donate blood, organs, tissues or cells for transplantation.
10. Females of childbearing potential (FCBP) must:

a. Have 2 or 3 negative pregnancy tests as verified by the Investigator (one negative serum beta-human chorionic gonadotropin [ß-hCG] pregnancy test result at screening, one prior to Day 1 combination for subjects receiving the combination agent pre-JCAR017 infusion and one within 7 days prior to the first dose of lymphodepleting chemotherapy). She must agree to ongoing pregnancy testing during the course of the

study, and after end of study treatment, and for Arms B, C and F as specified in the CC-122, CC-220 or CC-99282 Pregnancy Prevention and Risk Management Plan (PPRMP) (see Appendix N, Appendix O, Appendix Q). This applies even if the subject practices true abstinence* from heterosexual contact.

b. Either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption. Contraception methods must include 1 highly effective and 1 additional effective (barrier) method of contraception, from screening until at least 12 months after lymphodepleting chemotherapy or 3 months after the last dose of durvalumab (Arm A), or 28 days after the last dose of CC-122 (Arm B), CC-220 (Arm C) or CC-99282 (Arm F) as specified in the CC-122, CC-220 and CC-99282 PPRMP (see Appendix N, Appendix O, Appendix Q), or 28 days after the last dose of ibrutinib (Arm D), or 24 weeks after the last dose of nivolumab or relatlimab and as described in Appendix P (Arm E), whichever is later. There is insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.
c. Agree to abstain from breastfeeding during study participation and for at least 1 year after lymphodepleting chemotherapy or 3 months after the last dose of durvalumab (Arm A) or 28 days after the last dose of CC-122 (Arm B), CC-220 (Arm C), ibrutinib (Arm D), or CC-99282 (Arm F). There is insufficient exposure data to provide any recommendation concerning the duration of abstaining from breastfeeding following treatment with JCAR017. Any decision regarding breastfeeding after JCAR017 infusion should be discussed with the treating physician.
d. Agree to ongoing pregnancy testing during the course of the study as outlined in the CC-122 PPRMP (Arm B) CC-220 PPRMP (Arm C) or CC-99282 PPRMP (Arm F).

Note: Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The following are examples of highly effective and additional effective methods of contraception:

Highly effective methods of contraception:

- Intrauterine device (IUD)
- Hormonal (birth control pill, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods of contraception:

- Male condom
- Diaphragm
- Cervical cap

11. Male subjects must:

    - Practice true abstinence* (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for 12 months after lymphodepleting chemotherapy or for at least 3 months (33 weeks for Arm E) after the last dose of the combination agent even if he has undergone a successful vasectomy, whichever occurs last.

    There is insufficient exposure data to provide any recommendation concerning the duration of contraception following treatment with JCAR017. Any decision regarding contraception after JCAR017 infusion should be discussed with the treating physician.

    * True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. In contrast, periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment:

1. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study based on investigator´s judgment.
2. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study based on investigator´s judgment.
3. Subject has any condition that confounds the ability to interpret data from the study based on investigator´s judgment.
4. Subjects with prior history of malignancies, other than aggressive R/R NHL, unless the subject has been free of the disease for ≥ 2 years with the exception of the following non-invasive malignancies:
    - Basal cell carcinoma of the skin
    - Squamous cell carcinoma of the skin
    - Carcinoma in situ of the cervix
    - Carcinoma in situ of the breast
    - Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or curatively treated prostate cancer
    - Other completely resected stage 1 solid tumor with low risk for recurrence
5. Prior treatment with any gene therapy product, including gene therapy with a non-integrating vector.
6. Prior treatment with any adoptive T cell therapy; prior hematopoietic stem cell transplant (HSCT) is allowed.

7. Prior allogeneic HSCT (Arm E); allogeneic HSCT within 90 days of leukapheresis (all other Arms).
8. Prior treatment with the combination agent from the assigned arm:
    a. Anti PD-1 or PD-L1 (Arms A and E)
    b. CC-122 (Arm B)
    c. CC-220 (Arm C)
    d. Prior treatment with ibrutinib is not exclusionary for subjects on any study arm
    e. Anti LAG-3 targeted agent (Arm E)
    f. CC-99282 (Arm F)
9. Removed
10. Presence of acute or chronic graft-versus-host disease (GVHD).
11. History of or active hepatitis B or hepatitis C or human immunodeficiency virus (HIV) infection.
12. Uncontrolled bacterial, viral or fungal infection at the time of leukapheresis, lymphodepleting chemotherapy or JCAR017 infusion.
13. Any history of myocarditis (Arm E); history any one of the following cardiovascular conditions within the past 6 months of signing the ICF: Class III or IV heart failure as defined by the New York Heart Association (NYHA), cardiac angioplasty or stenting, myocardial infarction, unstable angina, or other clinically significant cardiac disease (all Arms)
14. History or presence of clinically relevant central nervous system (CNS) pathology such as epilepsy, seizure, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis.
15. Subjects with active CNS or cerebrospinal fluid (CSF) involvement by malignancy.
16. Pregnant or nursing (lactating) women.
17. Subjects with active autoimmune disorders/processes or active neurological or inflammatory disorders, including pneumonitis.
18. Treatment with alemtuzumab within 6 months of leukapheresis, or treatment with fludarabine or cladribine within 3 months of leukapheresis.
19. Use of the following (see Section 8.2 for full details):
    - Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent) within 7 days of leukapheresis or 72 hours prior to JCAR017 administration. Physiologic replacement, topical, inhaled, and intranasal steroids are permitted
    - Chemotherapy given after leukapheresis to maintain disease control must be stopped ≥ 7 days prior to lymphodepleting chemotherapy
    - Cytotoxic chemotherapeutic agents that are not considered lymphotoxic (see below) within 1 week of leukapheresis. Oral chemotherapeutic agents are allowed if at least 3 half-lives have elapsed prior to leukapheresis

- Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine) within 2 weeks of leukapheresis
- Experimental agents within 4 weeks of leukapheresis unless no response or disease progression is documented on the experimental therapy and at least 3 half-lives have elapsed prior to leukapheresis
- GVHD therapies within 4 weeks of leukapheresis and JCAR017 administration (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-tumor necrosis factor (anti-tumor necrosis factor [TNF]), anti-IL6, or anti-IL6R)
- Donor lymphocyte infusions (DLI) within 6 weeks of JCAR017 administration
- Radiation within 6 weeks of leukapheresis. Subjects must have progressive disease in irradiated lesions or have additional non-irradiated, Positron emission tomography (PET)-positive lesions to be eligible. Radiation to a single lesion, if additional non-irradiated PET-positive lesions are present, is allowed up to 2 weeks prior to leukapheresis
- Live attenuated vaccines within 90 days prior to leukapheresis

20. For subjects to receive oral combination therapy (Arms B, C, D or F): History of a gastrointestinal (GI) condition or procedure that in the opinion of the investigator may affect oral drug absorption.
21. Progressive tumor invasion of venous or arterial vessels.
22. Deep venous thrombosis (DVT)/pulmonary embolism (PE) not managed on a stable regimen of anticoagulation.

5. TABLES OF EVENTS

5.1. Arm A

Table 10: Table of Events, Arm A Cohort 1

Please refer to the specified protocol section for further details on each procedure.

	Protocol Section	Pre-Treatment Period			Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lymphodepletion evaluation	Lymphodepletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to-5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22[b]**	**29[b]**	**36[b], 43, 57**	**85[c]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Procedures																						
Obtain consent	6.1.1	x[d]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[e]	-	x	x	-	-	-	x	-	x	x	x	x[f]	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.4.1	x[g]	-	x	-	x	x	x	x	x	x	x	x	x	x[f]	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-

Table 10: Table of Events, Arm A Cohort 1 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period											Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lymphodepletion evaluation	Lymphodepletion (start)											Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to-5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22[b]**	**29[b]**	**36[b], 43, 57**	**85[c]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
MMSE	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	-	-	-	-	-	-
Vital signs	6.4.2	x	x[e]	x	x	x	x	x	x	x	x	x	x	x[h]	x[f,h]	x[h]	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x[f]	-	-	-	-	-	-	-
12-lead ECG	6.4.9	x	-	x[i]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	6.4.8	x[j]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	6.1	x	-	-	x[k]	-	-	-	-	-	-	-	-	-	-	x	x	-	-	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[l]	-	-	-	if clinically indicated																-
Creatinine clearance	6.1	x	-	-	x[k]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	x[e]	x	x	x	x	x	x	x	x	x	x	x	x[f]	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x[f]	-	-	-	-	-	-	-
Chemistry	6.4.12	x	x[e]	x	x	x	x	x	x	x	x	x	x	x	x[f]	x	x	x	x	x	x	-

Table 10: Table of Events, Arm A Cohort 1 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period											Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lymphodepletion evaluation	Lymphodepletion (start)											Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to-5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22[b]**	**29[b]**	**36[b], 43, 57**	**85[c]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x[m]	x[m]	x[m]	x[m]	x[m]	x[m]	-
Thyroid function tests	6.4.12	x	-	-	-	x	-	-	-	-	-	x	-	x	x	x	x	x	x	x	x	-
HLA typing (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Donor chimerism (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 10: Table of Events, Arm A Cohort 1 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period											Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lymphodepletion evaluation	Lymphodepletion (start)											Follow-up period[a]					
Study Day	N/A	-42 to -28	-42 to -28	-14 to-7	-10 to-5	1	2	3	4	8	11	15	22[b]	29[b]	36[b], 43, 57	85[c]	180	270	365	545	730 EOS	q3m
Study Month														1		3	6	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7	±2	±7	±14	±14	±30	±30	±30	±30
Durvalumab administration (Arm A)																						
Cohort 1	3.1.3 7.2.4	-												x see Table 3 for dosing schedule details			-					
PET-CT/ MRI	6.5	x	-	x[i]	-	-	-	-	-	-	-	-	-	x	-	x	x[n]	x[n]	x[n]	x[n]	x[n]	-
BMB/BMA	6.1	x[o]	-	-	-	-	-	-	-	-	-	-	-	x[p]	if clinically indicated							-
Tumor biopsy	6.1	x[q]	-	x[i,q]	-	-	-	-	-	-	-	-	-	x[q]	at progression[q,r]							-
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to protocol mandated procedures			All AEs, con meds and con procedures[t]												AEs related to JCAR017 and /or combination agents, associated con meds and con procedures						-
EORTC-QLQ-C30	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	x D57	x	x	x	x	x	x	-
EQ-5D-5L	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	x D57	x	x	x	x	x	x	-
[redacted]																						
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

Table 10: Table of Events, Arm A Cohort 1 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period											Post-Treatment Period					Survi-val fol-low-up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion evaluation	Lymho-depletion (start)											Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to-5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22[b]**	**29[b]**	**36[b], 43, 57**	**85[c]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**

[redacted]

Table 10: Table of Events, Arm A Cohort 1 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period											Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lymphodepletion evaluation	Lymphodepletion (start)											Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to-5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22[b]**	**29[b]**	**36[b], 43, 57**	**85[c]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**

[redacted]

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; BNP = brain natriuretic peptide; [redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; diff = differential; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; FU = follow-up; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; I/E = inclusion and exclusion; IPI = international prognostic index; IVIG = intravenous immunoglobulins; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated

acquisition scan; N/A = not applicable; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PET = positron emission tomography; [redacted]

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.

[b] In case the first dose of the combination agent is not given on Day 29 but within the allowed time window, the next dose/visit dates should be rescheduled accordingly considering the same interval as in the original schedule: for example in case the combination agent is started on Day 22, the next dose/visit date would be 7 days after (Day 29), and subsequent dose/visit dates would be scheduled: 7 days later (Day 36), 2 weeks later (Day 50) and 4 weeks later (Day 78). (see Section 6.2.5, Section 6.2.6, and Section 6.2.8).

[c] In case treatment with combination agent in Arm A is continued beyond Day 85, please refer to Section 6.3.1.1.

[d] To be obtained any time before any study related procedure

[e] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.

[f] Assessments are to be done on Days 50 and 71 for subjects in Cohort 1A-1.

[g] Including GVHD assessment

[h] Subjects will have their blood pressure, pulse, and body temperature measured before, during, and after the durvalumab infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (within an hour prior to start of durvalumab administration);
- At 30 minutes during the infusion (± 5 minutes);
- At the end of the infusion (at 60 minutes ± 5 minutes);
- In the 2- hour observation period post-infusion: every 30 minutes after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion) (± 5 minutes).

If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.

[i] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 7 to 14 days prior to start).

[j] MUGA/ECHO allowed within 4 weeks of leukapheresis.

[k] Only on first day and prior to LD chemotherapy.

[l] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.

[m] Not required if B-cell recovery documented without recent administration of IVIG.

[n] PET/CT mandatory until Day 85 but afterwards, once PET is negative only CT is required.

[o] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available

[p] Only for subjects with bone marrow involvement at Screening.

[q] Mandatory at Screening (except if adequate archival sample is available refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects for whom not enough adequate material from archived or Screening sample is available for analysis and for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual), at Day 29 (prior to start of combination agent) for subjects not in CR, and at time of progression if clinically feasible.

[r] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed.

[s] Only for subjects receiving durvalumab after Day 85 (see Section 7.2.4 for conditions).

[t] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy

[u] [redacted]

[v] [redacted]

Table 11: Table of Events, Arm A Cohort 1A-2

	Protocol Section	Pre-Treatment Period			Treatment Period												Post-Treatment Period					Sur-vival fol-low-up
		Screening	Leuk-apheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22, 36**	**29**	**43, 50, 57, 71**	**85[b]**	**180**	**270**	**365**	**545**	**730 (EOS)**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 7**	**± 2**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**	**± 30**	**± 30**
Procedures																						
Obtain consent	6.1.1	x[c]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[d]	-	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.4.1	x[e]	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
MMSE	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	-	-	-	-	-	-
Vital signs	6.4.2	x	x[d]	x	x	x	x	x	x	x	x	x	x	x	x[f]	x[f]	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
12-lead ECG	6.4.9	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 11: Table of Events, Arm A Cohort 1A-2 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period												Post-Treatment Period					Sur-vival fol-low-up
		Screening	Leuk-apheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22, 36**	**29**	**43, 50, 57, 71**	**85[b]**	**180**	**270**	**365**	**545**	**730 (EOS)**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 7**	**± 2**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**	**± 30**	**± 30**
MUGA/ECHO	6.4.8	x[g]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	6.1	x	-	-	x[h]	-	-	-	-	-	-	-	-	-	-	x	x	-	-	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[i]	-	-	-	if clinically indicated																-
Creatinine clearance	6.1	x	-	-	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	x[d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Chemistry	6.4.12	x	x[d]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x[j]	x[j]	x[j]	x[j]	x[j]	x[j]	-
Thyroid function tests	6.4.12	x	-	-	-	x	-	-	-	-	-	-	-	-	x	x	x	x	x	x	x	-
HLA typing (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 11: Table of Events, Arm A Cohort 1A-2 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period												Post-Treatment Period					Sur-vival fol-low-up
		Screening	Leuk-apheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22, 36**	**29**	**43, 50, 57, 71**	**85[b]**	**180**	**270**	**365**	**545**	**730 (EOS)**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 7**	**± 2**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**	**± 30**	**± 30**
Donor chimerism (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2.1	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Durvalumab administration (Arm A)																						
Cohort 1A-2	6.2.6 7.1.2	-													x see Table 3 for dosing schedule details	-						
AEs/Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to protocol mandated procedures			All AEs, con meds and con procedures[t]												AEs related to JCAR017 and /or combination agents, associated con meds and con procedures					-
PET-CT/ MRI	6.5	x	-	x[k]	-	-	-	-	-	-	-	-	-	x	-	x	x[l]	x[l]	x[l]	x[l]	x[l]	-
BMB/BMA	6.1	x[m]	-	-	-	-	-	-	-	-	-	-	-	x[n]	if clinically indicated							-
Tumor biopsy	6.1	x[o]	-	x[k,o]	-	-	-	-	-	-	-	-	-	x[o]	at progression[o, p]							-
EORTC-QLQ-C30	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	x D57	x	x	x	x	x	x	-
EQ-5D-5L	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	x D57	x	x	x	x	x	x	-

Table 11: Table of Events, Arm A Cohort 1A-2 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period											Post-Treatment Period					Survival follow-up
		Screening	Leuk-apheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)											Follow-up period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to-7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22, 36**	**29**	**43, 50, 57, 71**	**85[b]**	**180**	**270**	**365**	**545**	**730 (EOS)**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**± 1**	**± 1**	**± 2**	**± 2**	**± 7**	**± 2**	**± 7**	**± 14**	**± 14**	**± 30**	**± 30**	**± 30**	**± 30**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

[redacted]

Table 11: Table of Events, Arm A Cohort 1A-2 (Continued)

	Protocol Section	Pre-Treatment Period			Treatment Period											Post-Treatment Period					Sur-vival fol-low-up
		Screening	Leuk-apheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)											Follow-up period[a]					
Study Day	N/A	-42 to -28	-42 to -28	-14 to-7	-10 to -5	1	2	3	4	8	11	15	22, 36	29	43, 50, 57, 71	85[b]	180	270	365	545	730 (EOS)	q3m
Study Month														1		3	6	9	12	18	24	
Visit Window (days)									+1	± 1	± 1	± 2	± 2	± 7	± 2	± 7	± 14	± 14	± 30	± 30	± 30	± 30

[redacted]

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count[redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; diff = differential; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; HLA = human leukocyte antigen; HSCT = stem cell transplant; I/E = inclusion and exclusion; IPI = international prognostic index; IVIG = intravenous immunoglobulins; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan; N/A = not

applicable; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PET = positron emission tomography; [redacted]

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.
[b] In case treatment with combination agent in Arm A is continued beyond Day 85 please refer to Section 6.3.1.1.
[c] To be obtained any time before any study related procedure
[d] Assessments should be done prior to leukapheresis, except for vital signs which are to be done prior to and after leukapheresis.
[e] Including GVHD assessment.
[f] Subjects will have their blood pressure, pulse, and body temperature measured before, during, and after the durvalumab infusion at the following times (based on a 60-minute infusion):
- At the beginning of the infusion (within an hour prior to start of durvalumab administration);
- At 30 minutes during the infusion (± 5 minutes);
- At the end of the infusion (at 60 minutes ± 5 minutes);
- In the 2- hour observation period post-infusion: every 30 minutes after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion) (± 5 minutes).

If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.

[g] MUGA/ECHO allowed within 4 weeks of leukapheresis.
[h] Only on first day and prior to LD chemotherapy.
[i] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.
[j] Not required if B-cell recovery documented without recent administration of IVIG.
[k] For subjects who receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the LD chemotherapy (recommended within 7 to 14 days prior to start).
[l] PET/CT mandatory until Day 85 but afterwards, once PET is negative only CT is required.
[m] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[n] Only for subjects with bone marrow involvement at Screening.
[o] Mandatory at Screening (except if adequate archival sample is available refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects for whom not enough adequate material from archived or Screening sample is available for analysis and for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual), at Day 29 (prior to start of combination agent) for subjects not in CR, and at time of progression if clinically feasible.
[p] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed.
[redacted].
[r] Additional assessments to be done at time of suspicion of CRS (ie, at time of high fever onset, 24 hours after fever onset and 48 hours after fever onset).
[redacted]
[t] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy.

5.2. Arm B

Table 12: Table of Events, Arm B Cohort 1

	Protocol Section	Pre-treatment Period			Treatment Period																	Post-Treatment Period						Sur-vival Fol-low-Up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)																	Follow-Up Period[a]						
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22[b]**	**29[b]**	**30, 31, 32, 39**	**36[b], 43, 57**	**50, 64, 71, 78**	**85**	**113**	**141, 169**	**180[c]**	**208**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**				**3**	**4**	**5**	**6**	**7**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**		**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Procedures																											
Obtain consent	6.1.1	x[d]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[e]	-	x	x	-	-	-	x	-	x	x	x	-	x	x	x	x	x D141	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	x	-	x	-	-	-	-	-	-	-	x	-	x D57	-	x	x	x D141	x	x	-	-	-	-	-
Physical examination	6.4.1	x[f]	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x D141	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	x	-	-	-	-	-	-	-	-	-

Table 12: Table of Events, Arm B Cohort 1 (Continued)

	Protocol Section	Pre-treatment Period			Treatment Period																	Post-Treatment Period					Sur-vival Fol-low-Up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)																	Follow-Up Period[a]					
Study Day	N/A	-42 to -28	-42 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22[b]	29[b]	30, 31, 32, 39	36[b], 43, 57	50, 64, 71, 78	85	113	141, 169	180[c]	208	270	365	545	730 EOS	q3m
Study Month														1				3	4	5	6	7	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7		±2	±2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30
MMSE	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x D32	x	-	x	-	-	-	-	-	-	-	-	-
Vital signs	6.4.2	x	x[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-
12-lead ECG	6.4.9	x	-	x[g]	-	-	-	-	-	-	-	-	-	x	If clinically indicated												-
MUGA/ECHO	6.4.8	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	If clinically indicated												-
Troponin-T and BNP	6.1	x	-	-	-	-	-	-	-	-	-	-	-	x	If clinically indicated												-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pregnancy testing	6.1	x	-	-	x[i]	-	-	-	-	-	-	-	x[j]	x[j]	-	x	x D50	x	x	x	-	x[k, l]	-	-	-	-	-
Pregnancy prevention counselling	6.1	x	-	-	-	-	-	-	-	-	-	-	-	x	-	x D43, D57	-	x	x	x	-	x[k, l]	-	-	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[m]	-	-	-	if clinically indicated																					-
Creatinine clearance	6.1	x	-	-	x[i]	-	-	-	-	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 12: Table of Events, Arm B Cohort 1 (Continued)

	Protocol Section	Pre-treatment Period			Treatment Period																	Post-Treatment Period					Sur-vival Fol-low-Up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)																	Follow-Up Period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22[b]**	**29[b]**	**30, 31, 32, 39**	**36[b], 43, 57**	**50, 64, 71, 78**	**85**	**113**	**141, 169**	**180[c]**	**208**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**				**3**	**4**	**5**	**6**	**7**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**		**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Hematology	6.4.12	x	x[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-
Chemistry	6.4.12	x	x[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	-	x D57	-	x[n]	-	-	x[n]	-	x[n]	x[n]	x[n]	x[n]	-
HLA typing (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Donor chimerism (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 12: Table of Events, Arm B Cohort 1 (Continued)

	Protocol Section	Pre-treatment Period			Treatment Period																	Post-Treatment Period					Sur-vival Fol-low-Up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)																	Follow-Up Period[a]					
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22[b]**	**29[b]**	**30, 31, 32, 39**	**36[b], 43, 57**	**50, 64, 71, 78**	**85**	**113**	**141, 169**	**180[c]**	**208**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**				**3**	**4**	**5**	**6**	**7**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**		**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
CC-122 administration																											
Cohort 1	3.1.4 7.2.5	-												x see Table 4 for dosing schedule details Subjects to enter doses taken in diary								-					
VTE prophylaxis	10.6.4.6	-												x if needed								-					
PET-CT/ MRI	6.5	x	-	x[g]	-	-	-	-	-	-	-	-	-	x	-	-	-	x	-	-	x[o]	-	x[o]	x[o]	x[o]	x[o]	-
BMB/BMA	6.1	x[p]	-	-	-	-	-	-	-	-	-	-	-	x[q]	if clinically indicated												-
Tumor biopsy	6.1	x[r]	-	x[g r]	-	-	-	-	-	-	-	-	-	x[r]	at progression[r,s]												-
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to protocol mandated procedures			All AEs, con meds and con procedures[t]																	AEs related to JCAR017 and/or combination agents, associated con meds and con procedures					-
EORTC-QLQ-C30	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	-	x D57	-	x	-	-	x	-	x	x	x	x	-
EQ-5D-5L	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	-	x D57	-	x	-	-	x	-	x	x	x	x	-

Table 12: Table of Events, Arm B Cohort 1 (Continued)

	Protocol Section	Pre-treatment Period			Treatment Period																	Post-Treatment Period					Survival Follow-Up
		Screening	Leukapheresis	Pre-lymphodepletion Evaluation	LD chemo (start)																	Follow-Up Period[a]					
Study Day	N/A	-42 to -28	-42 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22[b]	29[b]	30, 31, 32, 39	36[b], 43, 57	50, 64, 71, 78	85	113	141, 169	180[c]	208	270	365	545	730 EOS	q3m
Study Month														1				3	4	5	6	7	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7		±2	±2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

[redacted]

Table 12: Table of Events, Arm B Cohort 1 (Continued)

	Protocol Section	Pre-treatment Period			Treatment Period																	Post-Treatment Period					Sur-vival Fol-low-Up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)																	Follow-Up Period[a]					
Study Day	N/A	-42 to -28	-42 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22[b]	29[b]	30, 31, 32, 39	36[b], 43, 57	50, 64, 71, 78	85	113	141, 169	180[c]	208	270	365	545	730 EOS	q3m
Study Month														1				3	4	5	6	7	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7		±2	±2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; BNP = brain natriuretic peptide; [redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; I/E = inclusion and exclusion; IPI = international prognostic index; IVIG = intravenous immunoglobulins; LD = lymphodepleting chemotherapy; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan;

N/A = not applicable; PBMC = peripheral blood mononuclear cells; PD = progressive disease; PET = positron emission tomography; [redacted] VTE = venous thromboembolism.

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.

[b] In case the first dose of the combination agent is not given on Day 29 but within the allowed time window, the next visit dates should be rescheduled considering the same interval as in the original schedule: for example, in case the combination agent is started on Day 22, the next visit date would be 1 day after (Day 23), and the next visit will be 1 day after (Day 24) and should be continued as such for the subsequent visits. (Section 6.2.5, Section 6.2.6 and Section 6.2.7)

[c] In case treatment with combination agent is continued beyond Day 180 please refer to Section 6.3.1.2.

[d] To be obtained any time before any study related procedure.

[e] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.

[f] Including GVHD assessment.

[g] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 7 to 14 days prior to start).

[h] MUGA/ECHO allowed within 4 weeks of leukapheresis.

[i] Only on first day and prior to LD chemotherapy.

[j] As per Pregnancy Prevention Risk Management Plan (PPRMP) in Appendix N, females of childbearing potential (FCBP) must have two negative pregnancy tests prior to starting CC-122 dosing. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed 10 to 14 days prior to start of CC-122. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 24 hours prior to first administration of CC-122. The results of both tests must be confirmed to be negative prior to dosing. For females with irregular menstrual cycles, refer to the PPRMP in Appendix N.

[k] To be performed monthly if CC-122 continued beyond Day 180.

[l] To be done 28 days after the last dose of CC-122.

[m] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.

[n] Not required if B-cell recovery documented without recent administration of IVIG.

[o] PET/CT mandatory until Day 85 but afterwards, once PET is negative only CT is required.

[p] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.

[q] Only for subjects with bone marrow involvement at Screening.

[r] Mandatory at Screening (except if adequate archival sample is available: refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects for whom not enough adequate material from archived or Screening sample is available for analysis and for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual), at Day 29 (prior to start of combination agent) for subjects not in CR, and at time of progression if clinically feasible.

[s] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed.

[t] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy.

[u] [redacted]

5.3. Arm C

Table 13: Table of Events, Arm C

Please refer to the specified protocol section for further details on each procedure.

	Protocol Section	Pre-JCAR017 period			JCAR017 treatment period											Post-Treatment Period						Survival Follow-up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)											Follow-Up Period[a]						
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to -7**	**-10 to -5**	**1[b]**	**2**	**3**	**4**	**8[b]**	**11**	**15[b]**	**22**	**29**	**36[c], 43[c], 57**	**85[d]**	**113[e]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**4**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±7**	**±7**	**±14**	**±30**	**±30**	**±30**	**±30**
Obtain consent	6.1.1	x[f]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	7.3	x	x	x	x	x	-	-	-	x B	-	x A	-	x	x D57	x	-	x	-	-	-	x	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[g]	-	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	x	-	x	-	-	-	-	-	-	-	x	x D57	x	x	-	-	-	-	-	-
Physical examination	6.4.1	x[h]	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-

Table 13: Table of Events, Arm C (Continued)

	Protocol Section	Pre-JCAR017 period			JCAR017 treatment period											Post-Treatment Period						Survival Follow-up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)	Follow-Up Period[a]																
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to -7**	**-10 to -5**	**1[b]**	**2**	**3**	**4**	**8[b]**	**11**	**15[b]**	**22**	**29**	**36[c], 43[c], 57**	**85[d]**	**113[e]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**4**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±7**	**±7**	**±14**	**±30**	**±30**	**±30**	**±30**
MMSE[i]	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	-	-	-	-	-	-	-
Vital signs	6.4.2	x	x[g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-	-
12-lead ECG	6.4.9	x	-	x[j]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	6.4.8	x[k]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pregnancy testing	6.1	x	-	-	x[l,m]	x B,C	x A	-	-	x[m] B,C	-	x[m]	x[m]	x[m]	x D36 (A,B), D43 (A), D57	x[n,o]	x[n,o]	x[o]	x[o]	x[o]	-	-	-
Pregnancy prevention counselling	6.1	x	-	-	x	x C	-	-	-	x B	-	x A	-	x	x D57	x[n,o]	x[n,o]	-	-	-	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[p]	-	-	-	if clinically indicated																	-
Creatinine clearance	6.1	x	-	-	x[l]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	x[g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-	-

Table 13: Table of Events, Arm C (Continued)

	Protocol Section	Pre-JCAR017 period			JCAR017 treatment period											Post-Treatment Period						Survival Follow-up
		Screening	Leukapheresis	Pre-lymphodepletion Evaluation	LD chemo (start)											Follow-Up Period[a]						
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to -7**	**-10 to -5**	**1[b]**	**2**	**3**	**4**	**8[b]**	**11**	**15[b]**	**22**	**29**	**36[c], 43[c], 57**	**85[d]**	**113[e]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**4**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±7**	**±7**	**±14**	**±30**	**±30**	**±30**	**±30**
Chemistry	6.4.12	x	x[g]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	x D57	x[q]	-	x[q]	x[q]	x[q]	x[q]	x[q]	-
HLA typing (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Donor chimerism (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CC-220 administration	3.1.5 7.2.6	-			see Table 5 for dosing schedule details Subjects to enter doses taken in diary												-						-

Table 13: Table of Events, Arm C (Continued)

	Protocol Section	Pre-JCAR017 period			JCAR017 treatment period											Post-Treatment Period						Survival Follow-up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)											Follow-Up Period[a]						
Study Day	N/A	-42 to -28	-42 to -28	-14 to -7	-10 to -5	1[b]	2	3	4	8[b]	11	15[b]	22	29	36[c], 43[c], 57	85[d]	113[e]	180	270	365	545	730 EOS	q3m
Study Month														1		3	4	6	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7	±2	±7	±7	±7	±14	±30	±30	±30	±30
Thromboembolic event prophylaxis	8.1.3	-				x C				x B, C		x					-						-
PET-CT/ MRI	6.5	x	-	x[j]	-	-	-	-	-	-	-	-	-	x	-	x	-	x[r]	x[r]	x[r]	x[r]	x[r]	-
BMB/BMA	6.1	x[s]	-	-	-	-	-	-	-	-	-	-	-	x[t]	if clinically indicated								-
Tumor biopsy	6.1	x[u]	-	x[j, u]	-	-	-	-	-	-	-	-	-	x	-	at progression[u,v]							-
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to protocol mandated procedures			All AEs, con meds and con procedures[w]												AEs related to JCAR017 and/or combination agents, associated con meds and con procedures						-
EORTC-QLQ-C30 (Phase 2)	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	x D57	x	-	x	x	x	x	x	-
EQ-5D-5L (Phase 2)	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	x D57	x	-	x	x	x	x	x	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease therapy since study treatment discontinuation	6.3.1	-	-	-	Anticancer treatment since JCAR017																		-
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

Table 13: Table of Events, Arm C (Continued)

	Protocol Section	Pre-JCAR017 period			JCAR017 treatment period											Post-Treatment Period						Survival Follow-up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)											Follow-Up Period[a]						
Study Day	N/A	-42 to -28	-42 to -28	-14 to -7	-10 to -5	1[b]	2	3	4	8[b]	11	15[b]	22	29	36[c], 43[c], 57	85[d]	113[e]	180	270	365	545	730 EOS	q3m
Study Month														1		3	4	6	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7	±2	±7	±7	±7	±14	±30	±30	±30	±30

[redacted]

Table 13: Table of Events, Arm C (Continued)

	Protocol Section	Pre-JCAR017 period			JCAR017 treatment period											Post-Treatment Period						Survival Follow-up
		Screen-ing	Leuka-pheresis	Pre-lympho-depletion Evaluation	LD chemo (start)	Follow-Up Period[a]																
Study Day	**N/A**	**-42 to -28**	**-42 to -28**	**-14 to -7**	**-10 to -5**	**1[b]**	**2**	**3**	**4**	**8[b]**	**11**	**15[b]**	**22**	**29**	**36[c], 43[c], 57**	**85[d]**	**113[e]**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**4**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±2**	**±7**	**±7**	**±7**	**±14**	**±30**	**±30**	**±30**	**±30**
[redacted]																							

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count; [redacted] CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; FCBP = female of childbearing potential; GVHD = graft versus host disease; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; I/E = inclusion and exclusion; IPI = international prognostic index; IRT = interactive response technology; IVIG = intravenous immunoglobulins; LD = lymphodepleting chemotherapy; MMSE =

Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan; N/A = not applicable; [redacted]; PD = progressive disease; PET = positron emission tomography; PPRMP = pregnancy prevention risk management plan; [redacted].

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.

[b] In case the first dose of the combination agent is not given on the expected date (eg, Day 15 for subcohort A) but within the allowed time window, the next visit dates should be rescheduled considering the same interval as in the original schedule.

[c] Day 36 to be performed for subcohorts A and B and Day 43 to be performed for subcohorts B and C.

[d] In case treatment with combination agent is continued beyond Day 85 please refer to Section 6.3.1.3 and Table 14.

[e] To be performed only if patient received last dose of CC-220 on Day 85

[f] To be obtained any time before any study related procedure.

[g] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.

[h] Including GVHD assessment.

[i] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix G) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

[j] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 14 days prior to start).

[k] MUGA/ECHO allowed within 4 weeks of leukapheresis.

[l] Only on first day and prior to LD chemotherapy.

[m] Per PPRMP in Appendix O, FCBP must have two negative pregnancy tests prior to starting CC-220 dosing. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed 10 to 14 days prior to start of CC-220. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 24 hours prior to first administration of CC-220. The results of both tests must be confirmed to be negative prior to dosing. For females with irregular menstrual cycles, refer to the PPRMP in Appendix O.

[n] FCBP must have monthly pregnancy tests if CC-220 continued beyond Day 85.

[o] FCBP must have pregnancy test 28 days after the last dose of CC-220. Additionally, FCBP must have pregnancy tests every 3 months until 1 year after JCAR017.

[p] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.

[q] Not required if B-cell recovery documented without recent administration of IVIG.

[r] PET/CT mandatory until Day 85 but afterwards, once PET is negative only CT is required.

[s] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.

[t] Only for subjects with bone marrow involvement at Screening.

[u] Mandatory at Screening (except if adequate archival sample is available: refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects for whom not enough adequate material from archived or Screening sample is available for analysis and for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual), at Day 29 for subjects not in CR, and at time of progression if clinically feasible.

[v] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed.

[w] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy.

[x] [redacted]

[z] Additional assessments to be done at time of suspicion of CRS (ie, at time of high fever onset, 24 hours after fever onset and 48 hours after fever onset).

5.3.1. Arm C – For Subjects Continuing CC-220 Beyond Day 85

Table 14: Table of Events, Arm C Subjects Continuing CC-220 Beyond Day 85

Study Day	**113**	**141**	**169**	**180[a]**	**197**	**225**	**253**	**270[a]**	**281**	**309**	**337[b]**
Visit Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
IRT registration	x	x	x	see footnote a	x	x	x	see footnote a	x	x	x
ECOG	x	x	x		x	x	x		x	x	x
Weight	x	x	x		x	x	x		x	x	x
Physical examination	x	x	x		x	x	x		x	x	x
Vital signs	x	x	x		x	x	x		x	x	x
Pregnancy testing	x	x	x		x	x	x		x	x	x
Pregnancy prevention counselling	x	x	x		x	x	x		x	x	x
Hematology	x	x	x		x	x	x		x	x	x
Chemistry	x	x	x		x	x	x		x	x	x
Inflammatory markers	x	x	x		x	x	x		x	x	x
Immunoglobulins	x	x	x		x	x	x		x	x	x
CC-220 administration	see Table 5 for dosing schedule details Subjects to enter doses taken in diary										
Thromboembolic event prophylaxis	x										
BMB/BMA	if clinically indicated										
Tumor biopsy	at progression[c]										
AEs/ Con meds/ Con procedures	all AEs, con meds and con procedures										
[redacted]	[redacted]										

[a] For the list of assessments to be performed refer to table of events for Arm C (Table 13).
[b] Refer to Table 13 for next visit (Day 365).
[c] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed.

5.4. Arm D

Table 15: Table of Events, Arm D

Please refer to the specified protocol section for further details on each procedure.

	Protocol Section	Pre-JCAR017 Period				JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening		Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**Min. 5D before apheresis**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month															**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)										**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Obtain consent	6.1.1	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	-	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	7.3	x	x	x	x	x	x	-	-	-	x	-	-	-	x	x	x	x	-	-	-	x	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	-	x[c]	-	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	-	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.4.1	x[d]	-	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
MMSE[e]	6.4.5	-	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	-	-	-	-	-	-
Vital signs	6.4.2	x	-	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-

Table 15: Table of Events, Arm D (Continued)

	Protocol Section	Pre-JCAR017 Period				JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening		Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**Min. 5D before apheresis**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month															**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)										**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Pulse oximetry	6.4.3	x	-	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
12-lead ECG	6.4.9	x	-	-	x[f]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	6.4.8	x[g]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	6.1	x	-	-	-	x[h]	-	-	-	-	-	-	-	-	-	-	x[h]	x[h]	x[h]	x[h]	-	-	-
Urinalysis	6.1	x	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[i]	-	-	-	-	if clinically indicated																-
Creatinine clearance	6.1	x	-	-	-	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	-	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	-	x	-	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Chemistry	6.4.12	x	-	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Inflammatory markers	6.4.12	x	-	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	-	x	x	x	x	x[j]	x[j]	x[j]	x[j]	x[j]	x[j]	-

Table 15: Table of Events, Arm D (Continued)

	Protocol Section	Pre-JCAR017 Period				JCAR017 Treatment Period												Post-Treatment Period					Survi-val follow-up
		Screening		Leuk apher esis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**Min. 5D before apheresis**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month															**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)										**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
HLA typing (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Donor chimerism (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukapheresis	6.1.2	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ibrutinib administration	3.1.6 7.2.7	-	see Table 6 for dosing schedule details Subjects to enter doses taken in diary															-					
PET-CT/ MRI	6.5	x	-	-	x[f]	-	-	-	-	-	-	-	-	-	x	-	x	x[k]	x[k]	x[k]	x[k]	x[k]	-
BMB/BMA	6.1	x[l]	-	-	-	-	-	-	-	-	-	-	-	-	x[m]	if clinically indicated							-
Tumor biopsy	6.1	x[n]	-	-	x[f,n]	-	-	-	-	-	-	-	-	-	x[n]	at progression[o]							-

Table 15: Table of Events, Arm D (Continued)

	Protocol Section	Pre-JCAR017 Period				JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening		Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	Min. 5D before apheresis	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	57	85	180	270	365	545	730 EOS	q3m
Study Month															1		3	6	9	12	18	24	
Visit Window (days)										+1	±1	±1	±2	±2	±7	±7	±7	±14	±14	±30	±30	±30	±30
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to combination agents and/or protocol mandated procedures	All AEs, con meds and con procedures[p]															AEs related to JCAR017 and /or combination agents, associated con meds and con procedures					-
EORTC-QLQ-C30 (Phase 2)	6.8	-	-	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x	-
EQ-5D-5L(Phase 2)	6.8	-	-	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Disease therapy since study treatment discontinuation	6.3.1	-	-	-	-	Anticancer treatment since JCAR017																	-
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

Table 15: Table of Events, Arm D (Continued)

	Protocol Section	Pre-JCAR017 Period				JCAR017 Treatment Period												Post-Treatment Period					Survi-val follow-up
		Screening		Leuk apher esis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	Min. 5D before apheresis	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	57	85	180	270	365	545	730 EOS	q3m
Study Month															1		3	6	9	12	18	24	
Visit Window (days)										+1	±1	±1	±2	±2	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Table 15: Table of Events, Arm D (Continued)

	Protocol Section	Pre-JCAR017 Period				JCAR017 Treatment Period											Post-Treatment Period					Survival follow-up
		Screening		Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)											Follow-up period[a]					
Study Day	N/A	-49 to -35	Min. 5D before apheresis	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	57	85	180	270	365	545	730 EOS	q3m
Study Month															1		3	6	9	12	18	24	
Visit Window (days)										+1	±1	±1	±2	±2	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count; [redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; diff = differential; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; GVHD = graft versus host disease; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; I/E = inclusion and exclusion; IPI = international prognostic index; IRT = interactive response technology; IVIG = intravenous immunoglobulins; LD = lymphodepleting; Min = minimum; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan; N/A = not applicable; [redacted]; PD = progressive disease; PET = positron emission tomography; [redacted]

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.
[b] To be obtained any time before any study related procedure
[c] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.
[d] Including GVHD assessment

[e] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix G) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.
[f] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 14 days prior to start).
[g] MUGA/ECHO allowed within 4 weeks of leukapheresis.
[h] On first day and prior to LD chemotherapy. Additionally, FCBP must have pregnancy tests every 3 months until 1 year after JCAR017.
[i] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.
[j] Not required if B-cell recovery documented without recent administration of IVIG.
[k] PET/CT mandatory until Day 85 but afterwards, once PET is negative only CT is required.
[l] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[m] Only for subjects with bone marrow involvement at Screening.
[n] Mandatory at Screening (except if adequate archival sample is available: refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual),at Day 29 for subjects not in CR, and at time of progression if clinically feasible.
[o] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed.
[p] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy
[q] [redacted].
[r] Additional assessments to be done at time of suspicion of CRS (ie, at time of high fever onset, 24 hours after fever onset and 48 hours after fever onset).

5.5. Arm E

Table 16: Table of Events, Arm E Cohorts 1A, 1B, 1C

Please refer to the specified protocol section for further details on each procedure.

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)													Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**+4 -2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Procedures																							
Obtain consent	6.1.1	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	7.3	x	x	x	x	x	-	-	-	x	-	-	-	x	x	x	x	x	-	-	-	x	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[c]	-	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.4.1	x[d]	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-

Table 16: Table of Events, Arm E Cohorts 1A, 1B, 1C (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)													Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**+4 -2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
MMSE[e]	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	x	-	-	-	-	-	-
Vital signs[f]	6.4.2	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
12-lead ECG	6.4.9	x	-	x[g]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	6.4.8	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Troponin T or I	6.1	x	-	-	-	-	-	-	x	-	-	-	x	-	x	x	x	x	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	6.1	x	-	-	x[i]	-	-	-	-	x[i]	-	-	-	-	x	x	x[i]	x[i]	x[i]	x[i]	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[j]	-	-	-	if clinically indicated																	-
Creatinine clearance	6.1	x	-	-	x[i]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Chemistry	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-

Table 16: Table of Events, Arm E Cohorts 1A, 1B, 1C (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)	Follow-up period[a]																	
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**+4 -2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	x[k]	x[k]	x[k]	x[k]	x[k]	x[k]	-
Thyroid function tests	6.4.12	x	-	-	-	x	-	-	x	-	-	-	x	-	x	x	x	x	-	-	-	-	-
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nivolumab infusion	7.2.8	-	-	-	-	-	-	-	-	x	-	-	x	-	x	x	x	-	-	-	-	-	-
Relatlimab infusion[t]	7.2.8	-	-	-	-	-	-	-	-	x	-	-	x	-	x	x	x	-	-	-	-	-	-

Table 16: Table of Events, Arm E Cohorts 1A, 1B, 1C (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)													Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**+4 -2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
PET-CT/ MRI	6.5	x	-	x[g]	-	-	-	-	-	-	-	-	-	x	-	-	x	x[1]	x[1]	x[1]	x[1]	x[1]	-
BMB/BMA	6.1	x[m]	-	-	-	-	-	-	-	-	-	-	-	x[n]	if clinically indicated								-
Tumor biopsy	6.1	x[o]	-	x[g,o]	-	-	-	-	-	-	-	-	-	x[o]	at progression[p]								-
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to protocol mandated procedures			All AEs, con meds and con procedures[q]													AEs related to JCAR017 and /or combination agents, associated con meds and con procedures					-
EORTC-QLQ-C30 (Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	-
EQ-5D-5L(Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	-
[redacted]																							
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

Table 16: Table of Events, Arm E Cohorts 1A, 1B, 1C (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	36	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		2	3	6	9	12	18	24	
Visit Window (days)									+1	+4 -1	±1	±2	+4 -2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Table 16: Table of Events, Arm E Cohorts 1A, 1B, 1C (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	36	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		2	3	6	9	12	18	24	
Visit Window (days)									+1	+4 -1	±1	±2	+4 -2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Table 16: Table of Events, Arm E Cohorts 1A, 1B, 1C (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	36	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		2	3	6	9	12	18	24	
Visit Window (days)									+1	+4 -1	±1	±2	+4 -2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count; [redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; diff = differential; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; FCBP = female of childbearing potential; GVHD = graft versus host disease; I/E = inclusion and exclusion; IPI = international prognostic index; IRT = interactive response technology; IVIG = intravenous immunoglobulins; LD = lymphodepleting; Min = minimum; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan; N/A = not applicable; [redacted]; PD = progressive disease; PET = positron emission tomography; [redacted].

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.

[b] To be obtained any time before any study related procedure

[c] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.

[d] Including GVHD assessment

[e] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix G) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

[f] Vital sign monitoring for relatlimab and/or nivolumab infusions are to be performed as described in Section 7.2.8 .

[g] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 14 days prior to start).

[h] MUGA/ECHO allowed within 4 weeks of leukapheresis.

[i] On first day and prior to LD chemotherapy. Additionally, FCBP must have pregnancy tests within 24 hours of first dose of nivolumab or relatlimab and every 3 months until 1 year after JCAR017.

j CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.
k Not required if B-cell recovery documented without recent administration of IVIG.
l Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
m Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
n Only for subjects with bone marrow involvement at Screening.
o Mandatory at Screening (except if adequate archival sample is available: refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual),at Day 29 for subjects not in CR, and at time of progression if clinically feasible.
p If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed .
q For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy.
r [redacted]

Table 17: Table of Events, Arm E Cohorts 1A+1, 1B+1, 1C+1

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)													Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Procedures																							
Obtain consent	6.1.1	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	7.3	x	x	x	x	x	-	-	-	x	-	-	-	x	x	x	x	x	-	-	-	x	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[c]	-	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.4.1	x[d]	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-

Table 17: Table of Events, Arm E Cohorts 1A+1, 1B+1, 1C+1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)	Follow-up period[a]																	
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
MMSE[e]	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	x	-	-	-	-	-	-
Vital signs[f]	6.4.2	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
12-lead ECG	6.4.9	x	-	x[g]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	6.4.8	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Troponin T or I	6.1	x	-	-	-	-	-	-	x	-	-	-	-	-	x	x	x	x	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	6.1	x	-	-	x[i]	-	-	-	-	x[i]	-	-	-	-	x	x	x[i]	x[i]	x[i]	x[i]	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[j]	-	-	-	if clinically indicated																	-
Creatinine clearance	6.1	x	-	-	x[i]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Chemistry	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-

Table 17: Table of Events, Arm E Cohorts 1A+1, 1B+1, 1C+1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	x[k]	x[k]	x[k]	x[k]	x[k]	x[k]	-
Thyroid function tests	6.4.12	x	-	-	-	x	-	-	x	-	-	-	-	-	x	x	x	x	-	-	-	-	-
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nivolumab infusion	7.2.8	-	-	-	-	-	-	-	-	x	-	-	-	-	x	x	x	-	-	-	-	-	-
Relatlimab infusion[t]	7.2.8	-	-	-	-	-	-	-	-	x	-	-	-	-	x	x	x	-	-	-	-	-	-

Table 17: Table of Events, Arm E Cohorts 1A+1, 1B+1, 1C+1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)													Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
PET-CT/ MRI	6.5	x	-	x[g]	-	-	-	-	-	-	-	-	-	x	-	-	x	x[l]	x[l]	x[l]	x[l]	x[l]	-
BMB/BMA	6.1	x[m]	-	-	-	-	-	-	-	-	-	-	-	x[n]	if clinically indicated								-
Tumor biopsy	6.1	x[o]	-	x[g,o]	-	-	-	-	-	-	-	-	-	x[o]	at progression[p]								-
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to protocol mandated procedures			All AEs, con meds and con procedures[q]													AEs related to JCAR017 and /or combination agents, associated con meds and con procedures					-
EORTC-QLQ-C30 (Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	-
EQ-5D-5L(Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	-
[redacted]																							
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

Table 17: Table of Events, Arm E Cohorts 1A+1, 1B+1, 1C+1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**

[redacted]

Table 17: Table of Events, Arm E Cohorts 1A+1, 1B+1, 1C+1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	36	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		2	3	6	9	12	18	24	
Visit Window (days)									+1	+4 -1	±1	±2	±2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Table 17: Table of Events, Arm E Cohorts 1A+1, 1B+1, 1C+1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**36**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**

[redacted]

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count; [redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; diff = differential; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; FCBP = female of childbearing potential; GVHD = graft versus host disease; I/E = inclusion and exclusion; IPI = international prognostic index; IRT = interactive response technology; IVIG = intravenous immunoglobulins; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan; N/A = not applicable; [redacted]; PD = progressive disease; PET = positron emission tomography; [redacted]

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.
[b] To be obtained any time before any study related procedure
[c] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.
[d] Including GVHD assessment
[e] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix G) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.
[f] Vital sign monitoring for relatlimab and/or nivolumab infusions are to be performed as described in Section 7.2.8 .
[g] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 14 days prior to start).
[h] MUGA/ECHO allowed within 4 weeks of leukapheresis.
[i] On first day and prior to LD chemotherapy. Additionally, FCBP must have pregnancy tests within 24 hours of first dose of nivolumab or relatlimab and every 3 months until 1 year after JCAR017.

[j] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.
[k] Not required if B-cell recovery documented without recent administration of IVIG.
[l] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[m] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[n] Only for subjects with bone marrow involvement at Screening.
[o] Mandatory at Screening (except if adequate archival sample is available: refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual), at Day 29 for subjects not in CR, and at time of progression if clinically feasible.
[p] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed .
[q] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy.
[redacted]
[s] Additional assessments to be done at time of suspicion of CRS (ie, at time of high fever onset, 24 hours after fever onset and 48 hours after fever onset).
[t] There are no relatlimab infusions for cohorts 1C, 1C-1, 1C+1, 1C+2. Relatlimab PK samples are not required for these cohorts.

Table 18: Table of Events, Arm E Cohorts 1A-1, 1B-1, 1C-1

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)													Follow-up Period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**+4 -1**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Procedures																							
Obtain consent	6.1.1	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	7.3	x	x	x	x	x	-	-	-	x	-	-	-	x	x	x	x	x	-	-	-	x	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[c]	-	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.4.1	x[d]	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
MMSE[e]	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	x	-	-	-	-	-	-
Vital signs[f]	6.4.2	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-

Table 18: Table of Events, Arm E Cohorts 1A-1, 1B-1, 1C-1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)	Follow-up Period[a]																
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**+4 -1**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
12-lead ECG	6.4.9	x	-	x[g]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	6.4.8	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Troponin T or I	6.1	x	-	-	-	-	-	-	-	-	x	-	-	x	x	x	x	x	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	6.1	x	-	-	x[i]	-	-	-	-	-	-	x[h]	-	-	x	x	x[i]	x[i]	x[i]	x[i]	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[j]	-	-	-	if clinically indicated																	-
Creatinine clearance	6.1	x	-	-	x[i]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Chemistry	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	x[k]	x[k]	x[k]	x[k]	x[k]	x[k]	-
Thyroid function tests	6.4.12	x	-	-	-	x	-	-	-	-	x	-	-	x	x	x	x	x	-	-	-	-	-

Table 18: Table of Events, Arm E Cohorts 1A-1, 1B-1, 1C-1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up Period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**+4 -1**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nivolumab infusion	7.2.8	-	-	-	-	-	-	-	-	-	-	x	-	x	x	x	x	-	-	-	-	-	-
Relatlimab infusion[t]	7.2.8	-	-	-	-	-	-	-	-	-	-	x	-	x	x	x	x	-	-	-	-	-	-
PET-CT/ MRI	6.5	x	-	x[g]	-	-	-	-	-	-	-	-	-	x	-	-	x	x[l]	x[l]	x[l]	x[l]	x[l]	-
BMB/BMA	6.1	x[m]	-	-	-	-	-	-	-	-	-	-	-	x[n]	if clinically indicated								-
Tumor biopsy	6.1	x[o]	-	x[g,o]	-	-	-	-	-	-	-	-	-	x[o]	at progression[p]								-

Table 18: Table of Events, Arm E Cohorts 1A-1, 1B-1, 1C-1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up Period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**+4 -1**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to protocol mandated procedures			All AEs, con meds and con procedures[q]													AEs related to JCAR017 and /or combination agents, associated con meds and con procedures					-
EORTC-QLQ-C30 (Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	-
EQ-5D-5L(Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	-
[redacted]																							
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

[redacted]

Table 18: Table of Events, Arm E Cohorts 1A-1, 1B-1, 1C-1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up Period[a]					
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	43	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		2	3	6	9	12	18	24	
Visit Window (days)									+1	±1	±1	+4 -1	±2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Table 18: Table of Events, Arm E Cohorts 1A-1, 1B-1, 1C-1 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up Period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**+4 -1**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**

[redacted]

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count; [redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; diff = differential; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; FCBP = female of childbearing potential ; GVHD = graft versus host disease; I/E = inclusion and exclusion; IPI = international prognostic index; IRT = interactive response technology; IVIG = intravenous immunoglobulins; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging;

MUGA = multi-gated acquisition scan; N/A = not applicable; PD = progressive disease; PET = positron emission tomography;

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.
[b] To be obtained any time before any study related procedure
[c] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.
[d] Including GVHD assessment
[e] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix G) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.
[f] Vital sign monitoring for relatlimab and/or nivolumab infusions are to be performed as described in Section 7.2.8 .
[g] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 14 days prior to start).
[h] MUGA/ECHO allowed within 4 weeks of leukapheresis.
[i] On first day and prior to LD chemotherapy. Additionally, FCBP must have pregnancy tests within 24 hours of first dose of nivolumab or relatlimab and every 3 months until 1 year after JCAR017.
[j] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.
[k] Not required if B-cell recovery documented without recent administration of IVIG.
[l] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[m] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[n] Only for subjects with bone marrow involvement at Screening.
[o] Mandatory at Screening (except if adequate archival sample is available: refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual), at Day 29 for subjects not in CR, and at time of progression if clinically feasible.
[p] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed .
[q] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy.

Table 19: Table of Events, Arm E Cohorts 1A+2, 1B+2, 1C+2

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)													Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Procedure																							
Obtain consent	6.1.1	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	7.3	x	x	x	x	x	-	-	-	x	-	-	-	x	x	x	x	x	-	-	-	x	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[c]	-	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	x	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.4.1	x[d]	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
MMSE[e]	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	x	-	-	-	-	-	-
Vital signs[f]	6.4.2	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-

Table 19: Table of Events, Arm E Cohorts 1A+2, 1B+2, 1C+2 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period													Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)													Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
12-lead ECG	6.4.9	x	-	x[g]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	6.4.8	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Troponin T or I	6.1	x	-	-	-	-	-	-	-	-	x	-	-	x	x	x	x	x	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	6.1	x	-	-	x[i]	-	-	-	-	-	-	x[i]	-	-	x	x	x[i]	x[i]	x[i]	x[i]	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[j]	-	-	-	if clinically indicated																	-
Creatinine clearance	6.1	x	-	-	x[i]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
Chemistry	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x	x[k]	x[k]	x[k]	x[k]	x[k]	x[k]	-
Thyroid function tests	6.4.12	x	-	-	-	x	-	-	-	-	x	-	-	x	-	x	x	x	-	-	-	-	-

Table 19: Table of Events, Arm E Cohorts 1A+2, 1B+2, 1C+2 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nivolumab infusion	7.2.8	-	-	-	-	-	-	-	-	-	-	x	-	-	-	x	x	-	-	-	-	-	-
Relatlimab infusion[t]	7.2.8	-	-	-	-	-	-	-	-	-	-	x	-	-	-	x	x	-	-	-	-	-	-
PET-CT/ MRI	6.5	x	-	x[g]	-	-	-	-	-	-	-	-	-	x	-	-	x	x[l]	x[l]	x[l]	x[l]	x[l]	-
BMB/BMA	6.1	x[m]	-	-	-	-	-	-	-	-	-	-	-	x[n]	if clinically indicated								-
Tumor biopsy	6.1	x[o]	-	x[g,o]	-	-	-	-	-	-	-	-	-	x[o]	at progression[p]								-

Table 19: Table of Events, Arm E Cohorts 1A+2, 1B+2, 1C+2 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to protocol mandated procedures			All AEs, con meds and con procedures[q]													AEs related to JCAR017 and /or combination agents, associated con meds and con procedures					-
EORTC-QLQ-C30 (Phase 2)	6.8	-	-	x	-	x	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	-
EQ-5D-5L(Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	-	x	x	x	x	x	x	x	-
[redacted]																							
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x

[redacted]

Table 19: Table of Events, Arm E Cohorts 1A+2, 1B+2, 1C+2 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	43	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		2	3	6	9	12	18	24	
Visit Window (days)									+1	+4 -1	±1	±2	±2	±7	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Table 19: Table of Events, Arm E Cohorts 1A+2, 1B+2, 1C+2 (Continued)

	Protocol Section		Pre-JCAR017 Period		JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**43**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**2**	**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**+4 -1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**

[redacted]

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count; [redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; diff = differential; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; FCBP = female of childbearing potential ; GVHD = graft versus host disease; I/E = inclusion and exclusion; IPI = international prognostic index; IRT = interactive response technology; IVIG = intravenous immunoglobulins; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging;

MUGA = multi-gated acquisition scan; N/A = not applicable; [redacted]; PD = progressive disease; PET = positron emission tomography; [redacted]

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.
[b] To be obtained any time before any study related procedure
[c] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.
[d] Including GVHD assessment
[e] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix G) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.
[f] Vital sign monitoring for relatlimab and/or nivolumab infusions are to be performed as described in Section 7.2.8 .
[g] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 14 days prior to start).
[h] MUGA/ECHO allowed within 4 weeks of leukapheresis.
[i] On first day and prior to LD chemotherapy. Additionally, FCBP must have pregnancy tests within 24 hours of first dose of nivolumab or relatlimab and every 3 months until 1 year after JCAR017.
[j] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.
[k] Not required if B-cell recovery documented without recent administration of IVIG.
[l] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[m] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[n] Only for subjects with bone marrow involvement at Screening.
[o] Mandatory at Screening (except if adequate archival sample is available: refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual), at Day 29 for subjects not in CR, and at time of progression if clinically feasible.
[p] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed .
[q] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy.

[redacted]

5.6. Arm F

Table 20: Table of Events, Arm F

Please refer to the specified protocol section for further details on each procedure.

	Protocol Section	Pre-JCAR017 Period			JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Procedures																						
Obtain consent	6.1.1	x[b]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
I/E criteria	4.2, 4.3 6.1.2 6.2.1	x	x	x	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IRT registration	7.3	x	x	x	x	x	-	-	-	x	-	-	-	x	x	x	x	-	-	-	x	-
Medical history	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPI	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ECOG	6.4.7	x	x[c]	-	x	x	-	-	-	x	-	x	x	x	x	x	x	x	x	x	x	-
Height	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weight	6.4.4	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Physical examination	6.4.1	x[d]	-	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Routine neurologic examination	6.4.5	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
MMSE[e]	6.4.5	-	-	-	-	x	-	-	x	x	-	x	-	x	x	x	-	-	-	-	-	-

Table 20: Table of Events, Arm F (Continued)

	Protocol Section	Pre-JCAR017 Period			JCAR017 Treatment Period											Post-Treatment Period					Survi-val follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)	Follow-up period[a]																
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Vital signs	6.4.2	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Pulse oximetry	6.4.3	x	-	x	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-
12-lead ECG	6.4.9	x	-	x[f]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
MUGA/ECHO	6.4.8	x[g]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Viral serology	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Serum pregnancy	6.1	x[h]	-	-	x[h]	x[h]	-	-	-	x[h]	-	x[h]	-	x[h]	x[h]	x[h]	x[h]	x[h]	x[h]	-	-	-
Pregnancy Prevention Counselling	6.1	x	-	-	x	x	-	-	-	x	-	x	-	x	x	x	-	-	-	-	-	-
Urinalysis	6.1	x	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CSF assessment	6.4.6 6.7.2	x[i]	-	-	-	ici																-
Creatinine clearance	6.1	x	-	-	x[h]	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hematology	6.4.12	x	x[c]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	-
Coagulation	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-	-

Table 20: Table of Events, Arm F (Continued)

	Protocol Section	Pre-JCAR017 Period			JCAR017 Treatment Period											Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)											Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
Inflammatory markers	6.4.12	x	-	x	-	x	x	x	x	x	x	x	x	x	x	x	-	-	-	-	-	-
Immunoglobulins	6.4.12	x	-	-	-	-	-	-	-	-	-	x	x	x	x	x[j]	x[j]	x[j]	x[j]	x[j]	x[j]	-
HLA typing (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Donor chimerism (only for subjects with prior allogeneic HSCT)	6.1.1	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leukapheresis	6.1.2	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lymphodepleting chemotherapy	7.2.1	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
JCAR017 administration	7.2.2	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Table 20: Table of Events, Arm F (Continued)

	Protocol Section	Pre-JCAR017 Period			JCAR017 Treatment Period											Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)	Follow-up period[a]																
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		3	6	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7	±7	±7	±14	±14	±30	±30	±30	±30
CC-99282 administration	3.1.8	-	-	-	-	See Table 8 for dosing schedule details. Subjects to enter doses taken in diary											-	-	-	-	-	-
PET-CT/ MRI	6.5	x	-	x[f]	-	-	-	-	-	-	-	-	-	x	-	x	x[k]	x[k]	x[k]	x[k]	x[k]	-
VTE prophylaxis	10.6.4.6	-				x if needed											-					
BMB/BMA	6.1	x[l]	-	-	-	-	-	-	-	-	-	-	-	x[m]	if clinically indicated							
Tumor biopsy	6.1	x[n]	-	x[f,n]		-	-	-	-	-	-	-	-	x[n]	at progression[o]							
AEs/ Con meds/ Con procedures	8 10	AEs, con meds and con procedures related to combination agents and/or protocol mandated procedures				All AEs, con meds and con procedures[p]											AEs related to JCAR017 and /or combination agents, associated con meds and con procedures					
EORTC-QLQ-C30 (Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x	-
EQ-5D-5L(Phase 2)	6.8	x	-	x	-	x	-	-	-	-	-	-	-	x	x	x	x	x	x	x	x	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 20: Table of Events, Arm F (Continued)

	Protocol Section	Pre-JCAR017 Period			JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		3	6	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7	±7	±7	±14	±14	±30	±30	±30	±30
Disease therapy since study treatment discontinuation	6.3.1	-	-	-	-	Anticancer treatment since JCAR017																
Survival status	6.3.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x
[redacted]																						

Table 20: Table of Events, Arm F (Continued)

	Protocol Section	Pre-JCAR017 Period			JCAR017 Treatment Period												Post-Treatment Period					Survival follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)												Follow-up period[a]					
Study Day	N/A	-49 to -35	-49 to -28	-14 to -7	-10 to -5	1	2	3	4	8	11	15	22	29	57	85	180	270	365	545	730 EOS	q3m
Study Month														1		3	6	9	12	18	24	
Visit Window (days)									+1	±1	±1	±2	±2	±7	±7	±7	±14	±14	±30	±30	±30	±30

[redacted]

Table 20: Table of Events, Arm F (Continued)

	Protocol Section	Pre-JCAR017 Period			JCAR017 Treatment Period											Post-Treatment Period					Survi-val follow-up
		Screening	Leukapheresis	Pre-lympho-depletion evaluation	Lympho-depletion (start)											Follow-up period[a]					
Study Day	**N/A**	**-49 to -35**	**-49 to -28**	**-14 to -7**	**-10 to -5**	**1**	**2**	**3**	**4**	**8**	**11**	**15**	**22**	**29**	**57**	**85**	**180**	**270**	**365**	**545**	**730 EOS**	**q3m**
Study Month														**1**		**3**	**6**	**9**	**12**	**18**	**24**	
Visit Window (days)									**+1**	**±1**	**±1**	**±2**	**±2**	**±7**	**±7**	**±7**	**±14**	**±14**	**±30**	**±30**	**±30**	**±30**
[redacted]																						

Abbreviations: AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; CBC = complete blood count; [redacted]; CNS = central nervous system; Con = concomitant; Con meds = concomitant medications; CR = complete response; CRS = cytokine release syndrome; CSF = cerebrospinal fluid; CT = computed tomography; D = day; diff = differential; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life C30 questionnaire; EOS = end of study; EQ-5D-5L = European Quality of Life-5 Dimensions health state classifier to 5 Levels; FCBP = female of childbearing potential; GVHD = graft versus host disease; HLA = human leukocyte antigen; HSCT = hematopoietic stem cell transplant; I/E = inclusion and exclusion; IPI = international prognostic index; IRT = interactive response technology; IVIG = intravenous immunoglobulins; LD = lymphodepleting; MMSE = Mini Mental State Examination; MRI= magnetic resonance imaging; MUGA = multi-gated acquisition scan; N/A = not applicable; [redacted];

PD = progressive disease; PET = positron emission tomography; [redacted].

[a] Efficacy evaluations (CT, PET, CBC w/diff, BMA/BMB) not required after PD or subsequent anticancer treatment.
[b] To be obtained any time before any study related procedure
[c] Assessments should be done on the day but prior to the leukapheresis (or within 24 h prior), except for vital signs which are to be done also after leukapheresis.
[d] Including GVHD assessment.
[e] If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams (see Appendix G) until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.
[f] For subjects that receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, these assessments must be performed after completion of the treatment and as close as possible to the start of the lymphodepleting chemotherapy (recommended within 14 days prior to start).
[g] MUGA/ECHO allowed within 4 weeks of leukapheresis.
[h] On first day and prior to LD chemotherapy. Additionally, FCBP must have pregnancy tests every 3 months until 1 year after JCAR017. As per Pregnancy Prevention Risk Management Plan (PPRMP) in Appendix Q, females of childbearing potential (FCBP) must have two negative pregnancy tests prior to starting CC-99282 dosing. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed 10 to 14 days prior to start of CC-99282. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 24 hours prior to first administration of CC-99282. The results of both tests must be confirmed to be negative prior to dosing. For females with irregular menstrual cycles, refer to the PPRMP in Appendix Q. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed 28 days after last dose of CC-99282
[i] CSF assessment and CNS imaging to be performed in case of clinical suspicion of CNS involvement. Soluble factors may be measured in CSF at screening and whenever a CSF is performed.
[j] Not required if B-cell recovery documented without recent administration of IVIG.
[k] PET/CT mandatory until Day 85 but afterwards, once PET is negative only CT is required.
[l] Archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available.
[m] Only for subjects with bone marrow involvement at Screening.
[n] Mandatory at Screening (except if adequate archival sample is available: refer to Section 6.1), mandated at pre-lymphodepletion evaluation visit for subjects who received treatment for disease control (see JCAR017-BCM-002 laboratory manual),at Day 29 for subjects not in CR, and at time of progression if clinically feasible.
[o] If disease progression is assessed, please refer to Section 6.3.3 for the list of assessments to be performed.
[p] For subjects receiving LD chemotherapy but not JCAR017, all AEs and associated concomitant medications will be collected for 30 days following the last dose of LD chemotherapy

[redacted]

6. PROCEDURES

Any questions regarding the protocol should be directed to the Medical Monitor(s) or designee. Tables of Events are provided as indicated in Table 21.

Table 21: Links to Tables of Events

Arm and Cohort	Table of Events
Arm A Cohort 1	Table 10
Arm A Cohort 1A-2	Table 11
Arm B Cohort 1	Table 12
Arm C	Table 13
Arm C – subjects continuing CC-220 beyond Day 85	Table 14
Arm D	Table 15
Arm E Cohorts 1A, 1B, 1C	Table 16
Arm E Cohorts 1A+1, 1B+1, 1C+1	Table 17
Arm E Cohorts 1A-1, 1B-1, 1C-1	Table 18
Arm E Cohorts 1A+2, 1B+2, 1C+2	Table 19
Arm F	Table 20

6.1. Pre-Treatment Period

6.1.1. Screening (Approximately 1 to 2 Weeks Prior to Leukapheresis)

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations should be completed within approximately 1 to 2 weeks of leukapheresis unless noted otherwise below. For Arm D, screening evaluations are to be performed a maximum of 3 weeks prior to leukapheresis in order to allow exposure to ibrutinib for at least 5 days prior to leukapheresis.

Waivers to the protocol will not be granted during the conduct of this trial under any circumstances.

Safety laboratory analyses and all assessments will be performed locally. Screening laboratory values must demonstrate subject eligibility, but may be repeated within the screening window if necessary.

The following assessments are to be performed at screening as specified in the Table of Events (see Section 5), after informed consent has been obtained:

- Assess eligibility per inclusion/exclusion criteria. All inclusion/exclusion criteria must be met in order for subjects to enroll in the study

- Obtain medical history, including: disease diagnosis and history, HSCT history, chemotherapy, radiation and surgical history, and history of prior gene therapy. May include history of toxicities related to prior treatments and allergies
- Complete physical examination, including height, weight, vital signs (see Section 6.4.2), oxygen saturation via pulse oximetry and GVHD assessment (if applicable)
- Routine neurologic examination
- ECOG performance status assessment and International Prognostic Index (IPI) status
- MUGA scan or cardiac ECHO (performed within 4 weeks of leukapheresis) for LVEF
- 12-lead electrocardiogram (ECG)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Troponin-T or I (Arms B and E) and brain natriuretic peptide (BNP) (Arm B)

    Subjects who are found at Screening to have baseline troponin-T > ULN or BNP > 100 pg/mL must have baseline evaluation by a cardiologist during Screening to optimize cardioprotective therapy.
  - Hematology
  - Coagulation
  - Inflammatory markers
  - Thyroid function tests (Arms A and E)
  - Immunoglobulins
  - Viral serology

Note: Subjects with positive hepatitis B surface antibody (HBsAb) but with negative hepatitis B core antibody (HBcAb) and hepatitis B surface antigen (HBsAg) or subjects with HBsAg, HBcAb and HBsAg negative are eligible for the study.

  - Serum ß-HCG pregnancy test on women of child-bearing potential
  - Determination of creatinine clearance (by Cockcroft-Gault – see Appendix I)
- Pregnancy prevention counselling (Arms B, C and F)

[redacted]

[redacted]

- Urinalysis
- Lumbar puncture or Ommaya reservoir tap for CSF assessment if CNS involvement suspected
- Only for subjects with prior allogeneic HSCT:
  - HLA typing
  - Donor chimerism
- If radiographic scans performed since the last anticancer treatment are not available to confirm the presence of PET-positive lymphoma, the Investigator should confirm the presence of lymphoma by clinical assessment or by a new PET scan
- Collection of tissue from latest archived tumor biopsy (block or slides) for tumor evaluation. If archival sample is before most recent relapse or no or insufficient archival sample is available, a new tumor biopsy is required. In case sufficient tumor biopsy material is not obtained during screening for Arms A, B and C, tumor biopsy may be performed prior to LD chemotherapy.
- Bone marrow aspirate and biopsy (archival bone marrow biopsy is allowed if performed after last therapy and sufficient archival sample is available)
- Record AEs, associated concomitant medications and procedures related to protocol-mandated procedures. Any clinically significant conditions/events unrelated to study procedures should be reported as described in the CRF completion guidelines (CCGs).
- Administration of European Quality of Life-5 Dimensions health state classifier to 5 Levels (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer-Quality of Life C30 (EORTC-QLQ-C30) questionnaires (Phase 2 only)
- [redacted]

6.1.2. Leukapheresis (Approximately 4 Weeks Prior to JCAR017 Administration)

Following enrollment on the study, subjects on Arm D subcohort A will start ibrutinib a minimum of 5 days prior to leukapheresis (see Section 3.1.6).

Following enrollment on the study, a leukapheresis collection will be performed on each subject to obtain a sufficient quantity of peripheral blood mononuclear cells (PBMCs) for the production of the JCAR017 investigational product. Prior to leukapheresis, appropriate protocol mandated washout periods are to be followed (see Table 22).

Should a technical issue arise during the procedure or in the processing of the product such that it cannot be used for JCAR017 administration, the subject may have a second collection procedure performed. Subjects must continue to meet eligibility requirements for repeat leukapheresis.

The following assessments are to be performed within 24 hours before the leukapheresis:

- Inclusion/Exclusion criteria assessment: Subjects must be evaluated for adequate organ function (as defined in Section 4.2) and evidence of active infections prior to the leukapheresis being started. In case of suspected infection, subject should be treated and leukapheresis postponed until the active infection has resolved.
- ECOG performance status assessment
- Vital signs (pre and post leukapheresis)
- Collection of peripheral blood samples for clinical laboratory evaluations and leukapheresis preparation:
  - Chemistry
  - Hematology

[redacted]

- Record AEs, associated concomitant medications and procedures related to protocol-mandated procedures
- [redacted]

[redacted]

Table 22: Washout Periods Prior to Leukapheresis

Treatment	Washout
Systemic therapy	
Alemtuzumab	6 months
Fludarabine	3 months
Cladribine	3 months
Experimental agents	4 weeks/3 half-lives (whichever is greater)
Lymphotoxic chemotherapeutic agents (eg, cyclophosphamide, ifosfamide, bendamustine)	2 weeks
Therapeutic doses of corticosteroids (defined as > 20 mg/day prednisone or equivalent)	7 days
Cytotoxic chemotherapeutic agents not considered lymphotoxic	7 days

Table 22: Washout Periods Prior to Leukapheresis (Continued)

Treatment	Washout
Oral chemotherapeutic agents (eg, lenalidomide and ibrutinib)[a]	3 half-lives
Radiation therapy	
Radiation, multiple lesions	6 weeks
Radiation, single lesion, if additional non-irradiated PET-positive lesions are present	2 weeks

[a] Subjects on Arm D are expected to continue ibrutinib.

6.1.3. Pre-Lymphodepletion Evaluation

The following assessments are to be done as close as possible to the start of the lymphodepleting chemotherapy prior to any study treatment as specified in the Table of Events (see Table 21).

In addition, for subjects who receive chemotherapy for disease control (see Section 8.1.1) while JCAR017 is being manufactured, the assessments must be performed after completion of the chemotherapy:

- Assess/ confirm eligibility per inclusion/exclusion criteria:
  - PET positive disease
  - Adequate bone marrow function to receive LD chemotherapy as assessed by the investigator
  - Adequate organ function (as defined in Section 4.2)
  - No uncontrolled bacterial, viral or fungal infection

In case of suspected infection, subject should be treated and LD chemotherapy postponed until the active infection has resolved.

- Complete physical examination, including weight, and vital signs (see Section 6.4.2), oxygen saturation via pulse oximetry and GVHD assessment (if applicable).
- Routine neurologic examination
- 12-lead ECG
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
- [redacted]

- Computed tomography (CT)/ magnetic resonance imaging (MRI) of chest, neck, abdomen, and pelvis, and PET scan (recommended within 14 days of start of lymphodepleting chemotherapy and must be done within 6 weeks of the start of lymphodepleting chemotherapy).
- Collection of tissue for tumor evaluation for subjects for whom there was no screening biopsy performed, insufficient adequate biopsy material is available, or intervening treatment for disease control was received
- Record all AEs, associated concomitant medications and procedures related to protocol-mandated procedures
- Administration of EQ-5D-5L and EORTC-QLQ-C30 questionnaires (Phase 2,

6.2. Treatment Period

6.2.1. Lymphodepleting Chemotherapy

Subjects enrolled on Arm D should stop ibrutinib a minimum of 24 hours prior to the first dose of LD chemotherapy. Ibrutinib should be restarted the day after the last dose of LD chemotherapy. In addition, ibrutinib may be interrupted for invasive procedures per institutional standards.

Upon notification from the Sponsor that JCAR017 will be available, LD chemotherapy should be initiated so as to be completed 2 to 7 days prior to JCAR017 infusion. For details on LD chemotherapy refer to Section 7.2.1.

The following assessments are to be performed on each day before administration of lymphodepleting chemotherapy:

- Inclusion/Exclusion criteria assessment: Subjects must be evaluated for evidence of active infections prior to the LD chemotherapy to be started. In case of suspected infection, subject should be treated accordingly and LD chemotherapy postponed until the active infection has resolved. Subjects with rapid deterioration or rapid disease progression should not start LD chemotherapy. In the event that a subject experiences any of the above, the Sponsor must be contacted and discussion regarding delay of treatment must occur.
- Vital signs and pulse oximetry
- ECOG performance status assessment (only once within 24 hours prior to start of LD chemotherapy)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry

  - Hematology
  - Creatinine clearance (CrCl) (by Cockcroft-Gault) (only once within 24 hours prior to start of LD chemotherapy – see Appendix I). If CrCl is below the acceptable level, direct measurement of renal function may be performed (eg, by 24 hr urine collection).
  - Serum ß-hCG pregnancy test on women of child-bearing potential (only on first day, prior to start of LD chemotherapy)
- Pregnancy prevention counselling (Arm C and F)
- Record all AEs, concomitant medications and procedures
- [redacted]

Subjects on Arm D will restart ibrutinib on the day after the last dose of LD chemotherapy as described in Section 3.1.6.

6.2.2. Day 1 (JCAR017 Administration)

Subjects who do not have adequate social support (a full-time caregiver) outside of the hospital or do not have reliable transportation to the clinic for scheduled evaluations or emergencies post therapy should be considered for hospitalization for the first 14 days of treatment. Subjects with high tumor burden are at higher risk of developing CRS and NT.

Subjects on Arm C subcohorts C, C+1 and C-1 will start CC-220 on Day 1 approximately 2 hours after JCAR017 infusion and once the subject is clinically stable, as described in Section 3.1.5.

Subjects on Arm D will take ibrutinib on Day 1 approximately 2 hours after JCAR017 infusion and once the subject is clinically stable, as described in Section 3.1.6.

Subjects on Arm F subcohort B will start CC-99282 on Day 1 approximately 2 hours after JCAR017 infusion and once the subject is clinically stable, as described in Section 3.1.8. [redacted]

In case the first dose of the combination agent is not given on the expected date (Day 1 for Arm C subcohorts C, C+1, C-1 or Arm D) but within the allowed time window (see Sections 3.1.9.3 and 3.1.9.4), subsequent visit dates should be rescheduled considering the same interval as in the original schedule.

The following assessments are to be performed prior to the JCAR017 infusion and combination agent (if applicable):

- Inclusion/Exclusion criteria assessment: Subjects should not experience a significant worsening in clinical status compared to initial eligibility criteria and/or rapid disease progression that would, in the opinion of the treating physician, increase the risk of adverse events associated with JCAR017 infusion. Subjects who meet at least one of the following criteria on the day of scheduled JCAR017 infusion should have JCAR017 administration delayed:

- Suspected or active systemic infection
- Onset of fever ≥ 38°C/100.4°F, not related to underlying disease
- Presence of progressive radiographic abnormalities on chest x-ray, or requirement for supplemental oxygen to keep saturation greater than 91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New onset or worsening of other non-hematologic organ dysfunction ≥ Grade 3
- Taking any of the prohibited medications as described in Section 8.2

Subjects with active infection must have JCAR017 infusion postponed until the active infection has resolved (subjects with suspected/active infection must have negative culture for at least 24 hours on appropriate antibiotics or negative rapid viral panel). Subjects with organ toxicities may not receive JCAR017 until the organ toxicities have recovered to ≤ Grade 2. In case of delayed infusion, lymphodepleting chemotherapy may need to be repeated after discussion with the sponsor (see Section 7.2.1). In the event that a subject experiences any of the above, the Sponsor must be contacted and discussion regarding delay of treatment must occur.

- Physical examination
- Weight
- Vital signs including pulse oximetry (measured approximately every 15 minutes starting from 15 minutes prior to the first IV administration until one hour after the last IV administration, and hourly for the next 2 hours [see Section 6.4.2]. If the subject's vital signs are not stable 3 hours following the final IV administration, vital signs should be monitored as clinically indicated until stable).
- ECOG performance status assessment
- Routine neurologic examination
- Mini-Mental Status Exam (MMSE) (see Appendix G). If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE (see Section 6.4.5).
- Record all AEs, concomitant medications and procedures
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
  - Thyroid function tests (Arms A and E)

  - Pregnancy testing (Arm C subcohorts B, B+1, B-1, C, C+1, C-1 and Arm F)
- Pregnancy prevention counselling (Arm C subcohorts C, C+1, C-1 and Arm F)
- Thromboembolic event prophylaxis (Arm C subcohorts C, C+1, C-1 and Arm F if needed)
- Urinalysis
- [redacted]
- Administration of EQ-5D-5L and EORTC-QLQ-C30 questionnaires (Phase 2, [redacted]
- [redacted]
- [redacted]

JCAR017 infusion will be performed at the specified dose in Table 3 (2 to 7 days after completion of lymphodepleting chemotherapy).

6.2.3. Days 2, 3, and 4 (+ 1 day for Day 4)

The following assessments are to be performed:

- Vital signs and pulse oximetry
- Routine neurologic examination
- Physical examination
- MMSE (Day 4 only, see Appendix G and Section 6.4.5)
- Record all AEs, concomitant medications and procedures
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
  - Pregnancy testing (Arm C cohorts 1A, 1A+1, 1A-1 require one negative test 10-14 days prior to starting CC-220)

  - Thyroid function tests (Day 4, Arm E cohorts 1A, 1B, 1C, 1A+1, 1B+1 and 1C+1)
  - Troponin T or I (Day 4, Arm E cohorts 1A, 1B, 1C, A+1, B+1 and C+1)
- Thromboembolic event prophylaxis (Arm C subcohorts C, C+1, C-1 and Arm F if needed)
- [redacted]

6.2.4. Days 8 and 11 (± 1 day)

Subjects on Arm C subcohorts B, B+1 and B-1 will start CC-220 on Day 8 as described in Section 3.1.5. In case the first dose of the combination agent is not given on the expected date (eg, Day 8 for subcohort B) but within the allowed time window, subsequent visit dates should be rescheduled considering the same interval as in the original schedule.

Subjects on Arm E subcohorts A, B, C, A+1, B+1 and C+1 will start nivolumab ± relatlimab on Day 8 as described in Section 3.1.7.

Subjects on Arm F subcohorts A, D, E and F will start CC-99282 on Day 8 as described in Section 3.1.8. [redacted]

The following assessments are to be performed:

- Physical examination
- Vital signs and pulse oximetry
- ECOG performance status assessment (Day 8)
- Routine neurologic examination
- MMSE (Day 8 only, see Appendix G and Section 6.4.5)
- Record all AEs, concomitant medications and procedures
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation

  - Inflammatory markers
  - Pregnancy testing (Day 8 only, Arm C subcohorts B, B+1, B-1 and C, C+1, C-1, Arm E subcohorts A, B, C, A+1, B+1 and C+1, and Arm F)
  - Troponin T or I (Day 11 only, Arm E subcohorts A-1, B-1, C-1, A+2, B+2 and C+2)
  - Thyroid function test (Day 11 only: Arm E subcohorts A-1, B-1, C-1, A+2, B+2 and C+2)
- Pregnancy prevention counselling (Day 8 only, Arm C subcohorts B, B+1, B-1 and Arm F)
- Thromboembolic event prophylaxis (Arm C subcohorts B, B+1, B-1 and C, C+1, C-1 and Arm F if needed)
- [redacted]

6.2.5. Days 15 and 22 (± 2 days)

Subjects on Arm C subcohorts A, A+1 and A-1 will start CC-220 on Day 15 as described in Section 3.1.5. In case the first dose of the combination agent is not given on the expected date (eg, Day 15 for subcohort A) but within the allowed time window, subsequent visit dates should be rescheduled considering the same interval as in the original schedule.

Subjects on Arm E subcohorts A-1, B-1, C-1, A+2, B+2 and C+2 will start nivolumab ± relatlimab on Day 15 as described in Section 3.1.7.

Subjects on Arm F subcohort C will start CC-99282 on Day 15 as described in Section 3.1.8. [redacted].

Arms A and B: The following assessments are to be performed at Days 15 and 22 (in case the first dose of the combination agent is administered on Day 22 then see Day 29 section [Section 6.2.6] for the assessments to be performed). However, for subjects receiving the combination agent post-JCAR017, Day 22 assessments should be performed if combination agent is given on Day 29. In case combination agent is given earlier than Day 29 (within the allowed time window), Day 29 assessments must be performed prior to start of the combination agent (eg, if combination agent is started on Day 22, Day 29 assessments must be performed prior to the start of the combination agent). The next regular visit will be Day 29. At this visit, only assessments scheduled for Day 36 should be performed. After that, the next subsequent protocol visits are to be performed.

- Vital signs and pulse oximetry
- ECOG performance status assessment
- Physical examination
- Routine neurologic examination
- MMSE (Day 15 only, see Appendix G and Section 6.4.5)
- Record all AEs, concomitant medications and procedures
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
  - Thyroid function tests (Day 15: Arm A; Day 22: Arm E subcohorts A, B, C)
  - Troponin T or I (Day 22, Arm E subcohorts A, B, C)
  - Immunoglobulins
- Pregnancy testing (within 10 to 14 days prior to the start of CC-122) (Arm B) (Day 22)
- Pregnancy testing (Arm C and Arm F; Day 15 only Arm E subcohort A-1, B-1, C-1 and A+2, B+2, and C+2)
- Pregnancy prevention counselling (Day 15 only, Arm C subcohorts A, A+1, A-1, Arm E subcohorts A-1, B-1, C-1, A+2, B+2 and C+2, and Arm F)
- Thromboembolic event prophylaxis (Arm C and Arm F is needed)
- [redacted]

6.2.6. Day 29 (± 7 days)

Subjects who do not have adequate social support (a full-time caregiver) outside of the hospital or do not have reliable transportation to the clinic for scheduled evaluations or emergencies post

therapy should be considered for hospitalization for the first 14 days of treatment. Subjects with high tumor burden are at higher risk of developing CRS and NT.

The following assessments are to be performed at Day 29.

Arms A and B only:

The assessments described below are to be performed at the above mentioned dates for subjects receiving the combination agent post-JCAR017 considering that the combination agent is started on the scheduled day (Day 29). If the first dose of the combination agent is given earlier or later than scheduled (within the allowed window), the following assessments should be shifted by the same number of days. In case the first dose of the combination agent is not given on Day 29 but within the allowed time window, the next dose/visit dates should be rescheduled accordingly: in case the combination agent is started on Day 22, the next dose/visit date would be 7 days after (Day 29), and subsequent dose/visit dates would be scheduled: 7 days later (Day 36), 2 weeks later (Day 50) and 4 weeks later (Day 78). For subjects who have only received JCAR017 and will not receive the combination agent due to any reason, the next visit will be on Day 57.

The following assessments are to be performed prior to the dose of combination agent, if scheduled for that day:

- Physical examination
- Vital signs and pulse oximetry
- Weight (Arm B and Arm C)
- ECOG performance status assessment
- 12-lead electrocardiogram (ECG) (Arm B)
- Pregnancy testing (within 24 hours prior to the (re)start of CC-122 or CC-220) (Arms B, C and F)
- Routine neurologic examination
- Tumor biopsy (for subjects not in CR)
- Bone marrow biopsy and aspirate (only for subjects with bone marrow involvement at Screening)
- MMSE (see Appendix G and Section 6.4.5)
- Administration of EQ-5D-5L and EORTC-QLQ-C30 questionnaires (Phase 2, [redacted]
- [redacted]
- Record all AEs, concomitant medications and procedures
- Response evaluation by CT and PET scan
- Collection of peripheral blood samples for clinical laboratory evaluations:

  - Chemistry
  - Troponin-T and BNP (Arm B; Arm E subcohorts A-1, B-1, C-1, A+2, B+2 and C+2)
  - Hematology
  - Coagulation
  - Inflammatory markers
  - Thyroid function tests (Arm A, Arm E subcohorts A-1, B-1, C-1)
  - Immunoglobulins
  - Determination of creatinine clearance (by Cockcroft-Gault – see Appendix I) (Arm B)
- Pregnancy prevention counselling (Arm B, Arm C, Arm F)
- Thromboembolic event prophylaxis (Arm C); if needed (Arm B and Arm F)
- [redacted]

Combination agent will be started or restarted as per Table 3 for subjects in Arm A, Table 4 for subjects in Arm B, or Table 5 for Arm C.

6.2.7. Days 30, 31, 32 and 39 (Arm B)

The assessments described below are to be performed at the above mentioned dates for subjects receiving the combination agent post-JCAR017 considering that the combination agent is started on Day 29. In case the first dose of the combination agent is given earlier or later than Day 29 (within the allowed window), the following assessments should be performed before subsequent doses of the combination agent.

The following assessments are to be performed:

- Vital signs and pulse oximetry
- Routine neurologic examination
- Physical examination
- MMSE (Day 32 only, see Appendix G and Section 6.4.5)
- Record all AEs, concomitant medications and procedures

- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
- 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated
- [redacted]

6.2.8. Days 36, 43, and 57 (± 2 days)

Arm A and Arm B only: the assessments described below are to be performed at the above mentioned dates for subjects receiving the combination agent post-JCAR017 considering that the combination agent is started on Day 29 the first dose of the combination agent is given earlier or later than Day 29 (within the allowed window), the following assessments should be performed before subsequent doses of the combination agent.

For subjects who have only received JCAR017 and will not receive the combination agent due to any reason, the next visit will be on Day 85.

For subject in Arm A - Cohort 1A-1, some of the following assessments are also to be performed on Days 50 and 71 (see Table 10 for the details).

For subjects in Arm A - Cohort 1A-2, please refer to Table 11 for the details of the assessments to be performed at the above mentioned visits.

Arm C: Day 36 visit is to be performed for Arm C subcohorts A and B while Day 43 is to be performed for Arm C subcohorts B and C.

Arm D: only Day 57 visit is required.

Arm E: Day 36 visit is to be performed for subcohorts A, B, C, A+1, B+1, C+1; Day 43 visit performed for subcohorts A-1, B-1, C-1, A+2, B+2, C+2; Day 57 visit is performed for all subcohorts.

The following assessments are to be performed, prior to the dose of combination agent, if scheduled for that day:

- Physical examination
- Vital signs and pulse oximetry
- ECOG performance status assessment
- Weight (Arm B and Arm C) (Day 57)

- Routine neurologic examination
- Bone marrow biopsy and aspirate (if clinically indicated)
- MMSE (see Appendix G and Section 6.4.5)
- Administration of EQ-5D-5L and EORTC-QLQ-C30 questionnaires (Day 57) (Phase 2, [redacted]
- [redacted]
- [redacted]
- Record all AEs, concomitant medications and procedures
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Coagulation
  - Inflammatory markers
  - Thyroid function tests (Arm A; Day 36: Arm E subcohorts A, B, C, A+1, B+1, C+1; Day 43 Arm E subcohorts A-1, B-1, C-1; Day 57 Arm E all subcohorts)
  - Troponin T or I (Day 36: Arm E subcohorts A, B, C, A+1, B+1 and C+1; Day 43 Arm E subcohorts A-1, B-1, C-1, A+2, B+2, C+2; Day 57 Arm E all subcohorts)
  - Immunoglobulins (Day 57 for Arms B, C, D, E and F; Day 36: Arm E subcohorts A, B, C, A+1, B+1, C+1; Day 43 Arm E subcohorts A-1, B-1, C-1, A+2, B+2, C+2)
- Pregnancy testing (Arm B and Arm C; Day 36 Arm E subcohorts A, B, C, 1A+1, 1B+1, 1C+1; Day 43 Arm E subcohorts A-1, B-1, C-1, A+2, B+2, C+2; Day 57 Arm E all subcohorts and Arm F)
- Pregnancy prevention counselling (Day 43 Arm B) (Day 57 Arm B, Arm C and Arm F)
- Thromboembolic event prophylaxis (Arm C); if needed (Arm B and Arm F if needed)
- 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated (Arm B)
- [redacted]

6.2.9. Days 50, 64, 71 and 78 (± 2 days) (Arm B)

The assessments described below are to be performed at the above mentioned dates for subjects receiving the combination agent post-JCAR017 considering that the combination agent is started on the scheduled day (Day 29).

If the first dose of the combination agent is given earlier or later than scheduled (within the allowed window), the following assessments should be shifted by the same number of days.

For subjects who have only received JCAR017 and will not receive the combination agent due to any reason, the next visit will be on Day 85.

The following assessments are to be performed, prior to the dose of combination agent, if scheduled for that day:

- Physical examination
- Vital signs and pulse oximetry
- VTE prophylaxis if needed; 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated
- [redacted]
- Record all AEs, concomitant medications and procedures
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Inflammatory markers
- Pregnancy testing (Day 50)

6.2.10. Day 85 (± 7 days)

The assessments described below are to be performed at the above mentioned dates for subjects receiving the combination agent post-JCAR017 considering that the combination agent is started on the scheduled day (Day 29). If the first dose of the combination agent is given earlier or later than scheduled (within the allowed window), the following assessments should be shifted by the same number of days.

Arms A and C: If the combination agent is continued beyond Day 85, see Section 6.3.1.

For subjects who have only received JCAR017 and will not receive the combination agent due to any reason, the next visit will be on Day 180.

The following assessments are to be performed, prior to the dose of combination agent, if scheduled for that day:

- Physical examination
- Vital signs
- ECOG performance status assessment

- Weight (Arm B and Arm C)
- Routine neurologic examination
- Bone marrow biopsy and aspirate (if clinically indicated)
- MMSE (see Appendix G and Section 6.4.5)
- Administration of EQ-5D-5L and EORTC-QLQ-C30 questionnaires (Phase 2, [redacted]
- [redacted]
- [redacted]
- Record all AEs, concomitant medications and procedures
- PET scan (not required for subjects in CR, subjects who have progressed, or after institution of additional anticancer treatment. A PET scan should be performed to verify PD)
- CT/MRI scan (not required after PD or after institution of additional anticancer treatment)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Thyroid function tests (Arm A and Arm E)
  - Inflammatory markers
  - Immunoglobulins (Not required if B-cell recovery documented without recent administration of intravenous immunoglobulin [IVIG])
  - Serum ß-HCG pregnancy test on women of child-bearing potential
  - Troponin T or I (Arm E all subcohorts)
- Pregnancy prevention counselling (Arm B, Arm C and Arm F)
- Thromboembolic event prophylaxis (Arm C); if needed (Arm B)
- 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated (Arm B)
- [redacted]

[redacted]

6.2.11. Day 113 (± 7 days) (Arm B)

The following assessments are to be performed:

- Physical examination
- Vital signs
- Weight
- ECOG performance status assessment
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Inflammatory markers
- Bone marrow biopsy and aspirate (if clinically indicated)
- Pregnancy testing
- Pregnancy prevention counselling
- VTE prophylaxis if needed
- 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated
- [redacted]
- Record all AEs, concomitant medications and procedures

6.2.12. Days 141 and 169 (± 7 days) (Arm B)

The following assessments are to be performed:

- Physical examination (Day 141)
- Vital signs
- Weight (Day 141)
- ECOG performance status assessment (Day 141)
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Inflammatory markers
- Pregnancy testing
- Pregnancy prevention counselling
- VTE prophylaxis if needed;

- 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated
- [redacted]
- Record all AEs, concomitant medications and procedures

6.2.13. Day 180 (± 7 days) (Arm B)

Note: Arm A, C and D Day 180 visits are described in Section 6.3 since they occur after the end of treatment.

The following assessments are to be performed:

- Vital signs
- Weight
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Chemistry
  - Hematology
  - Inflammatory markers
- [redacted]
- VTE prophylaxis if needed
- 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated
- [redacted]
- Record all AEs, concomitant medications and procedures

6.3. Post-Treatment Period

6.3.1. Follow-up

All subjects who received any dose of JCAR017, including subjects who withdraw from treatment early and those with progressive disease, should complete the post-treatment follow-up visits at approximately Days 113 (Arm C only), 180 (except Arm B), 208 (Arm B), 270 (± 14 days), 365, 545, and 730 (± 30 days), Months 6 (except Arm B), 7 (Arm B), 9, 12, 18, and 24 or end of study [EOS]) after the JCAR017 infusion for disease status and survival. The following assessments will be performed in subjects who have not received subsequent anticancer treatment:

- Physical examination
- Vital signs
- Weight (Day 113 Arm C only, Day 208 Arm B only)
- ECOG performance status assessment
- PET scan (not required for subjects in CR, subjects who have progressed, or after institution of additional anticancer treatment. A PET scan should be performed to verify PD. Once a PET scan is negative, only a CT scan is required. Not required for Arm C Day 113)
- CT/MRI scan (not required after PD or after institution of additional anticancer treatment)
- Administration of EQ-5D-5L and EORTC-QLQ-C30 questionnaires (Phase 2, [redacted]; not required for Arm C at Day 113)
- [redacted]
- Record AEs related to JCAR017 and /or combination agents and associated concomitant medications and procedures
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology
  - Chemistry
  - Thyroid function tests (Arm A; Day 180 for Arm E)
  - Immunoglobulins (not required if B-cell recovery documented without recent administration of intravenous immunoglobulins [IVIG]; not required for Arm C Day 113)
  - Serum ß-HCG pregnancy test on all women of child-bearing potential (Day 180 – Except Arm B; Day 113 – Arm C; Day 208 – Arm B; Day 270 and 365 – Except arms A and B)
  - Troponin T or I (Day 180 only: Arm E all subcohorts)
- [redacted]

- [redacted]
- [redacted]
- Bone marrow biopsy and aspirate (if clinically indicated)
- 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated (Arm B)

The following assessments will be performed in subjects who have received subsequent anticancer treatment:

- Collection of anticancer treatment since the dose of JCAR017
- Physical examination at Day 365 and Day 730 (Month 12 and 24 visits)
- Immunoglobulins on Months 6 (Except Arm B), 9, 12, 18 and 24 (not required if B-cell recovery documented without recent administration of IVIG)
- [redacted]
- [redacted]
- Pregnancy test at Month 3, if applicable
- Record all AEs, concomitant medications and procedures from start of LD chemo or start of combination agent whichever occurs first until Day 85 (Month 3). After this time record only AEs, associated concomitant medications and procedures related to JCAR017 and/or lymphodepleting chemotherapy or combination agents, and concomitant medications at the time of those events, according to Section 10.1
- [redacted]

Note: Subjects who receive HSCT post-JCAR017 (but no other anticancer treatment) should continue to undergo scans, unless they have demonstrated PD prior to transplant. A PET scan should be performed to verify PD.

6.3.1.1. Specific Follow-up for Durvalumab After Day 85 in Arm A

In case treatment with durvalumab is continued beyond Day 85 (see Section 3.1.3 for conditions where this could occur), the following assessments are to be performed on the day of durvalumab infusion:

- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology
  - Chemistry
  - Thyroid functional tests

In addition, a serum ß-HCG pregnancy test on women of child-bearing potential should be performed 3 months after the last dose of durvalumab.

Record AEs, associated concomitant medications, and procedures as described in Section 10.1 and Section 8.

6.3.1.2. Specific Follow-up for CC-122 After Day 180 in Arm B

In case treatment with CC-122 is continued beyond Day 180 (see Section 3.1.4 for conditions where this could occur), the following assessments are to be performed:

Every 4 weeks:

- Weight
- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology
  - Chemistry
- Pregnancy testing
- 12-lead ECG, Troponin-T and BNP, MUGA/ECHO: if clinically indicated

In addition, a serum ß-HCG pregnancy test on women of child-bearing potential should be performed 28 days after the last dose of CC-122. Deep vein thrombosis prophylaxis should also be performed if needed.

Record all AEs, associated con meds and procedures from start of LD chemo or start of combination agent whichever occurs first until 3 months after JCAR017 or 28 days after last dose of CC-122, whichever occurs later. After this time, record only AEs related to JCAR017 and/or lymphodepleting chemotherapy or combination agents and associated concomitant medications/procedures.

6.3.1.3. Specific Follow-up for CC-220 After Day 85 in Arm C

In case treatment with CC-220 is continued beyond Day 85 (see Section 3.1.5 for conditions where this could occur), the following assessments are to be performed in addition to the follow-up schedule (see also Table 14).

After stopping CC-220, the subsequent 2 visits in Table 14 covering the below assessments must be performed before returning to the standard follow-up schedule in Section 6.3.1.

Every 4 weeks:

- ECOG
- Physical examination
- Vital signs
- Weight
- Pregnancy testing and prevention counselling

A serum ß-HCG pregnancy test on women of child-bearing potential should be performed 28 days after the last dose of CC-220.

- Collection of peripheral blood samples for clinical laboratory evaluations:
  - Hematology
  - Chemistry

  - Inflammatory markers
- CC-220 supply and recording in interactive response technology (IRT) system
- Bone marrow biopsy and aspirate (if clinically indicated)
- Tumor biopsy (at progression if clinically feasible)
- Record all AEs, associated con meds and procedures from start of LD chemo or start of combination agent whichever occurs first until 3 months after JCAR017 or 28 days after last dose of CC-220, whichever occurs later. After this time, record only AEs related to JCAR017 and/or lymphodepleting chemotherapy or combination agents and associated concomitant medications/procedures.
- [redacted]

For patients continuing CC-220 beyond Day 85 thromboembolic event prophylaxis should be continued (see Section 10.6.4.6).

6.3.2. Unscheduled Evaluations

If the Investigator feels that a subject needs to be evaluated at a time other than the protocol-specified visit, the subject may be asked to come in to the clinic for an unscheduled evaluation. The following assessments may be performed and recorded in the case report form (CRF), as appropriate:

- Physical examination
- Vital signs
- ECOG performance status assessment
- MMSE (see Appendix G and Section 6.4.5)
- Clinical laboratory evaluations
- PET scan
- CT/MRI scan
- Tumor biopsy (see the JCAR017-BCM-002 laboratory manual)
- Bone marrow aspirate and biopsy (see the JCAR017-BCM-002 laboratory manual)
- CSF assessment and brain imaging if clinical suspicion of CNS involvement (see the JCAR017-BCM-002 laboratory manual)

[redacted]

[redacted]

6.3.3. Assessments Upon Disease Progression

The following assessments will be performed as soon as possible after disease progression and should be documented as an unscheduled visit if outside of a regular visit window:

- Tumor biopsy, if clinically feasible (see the JCAR017-BCM-002 laboratory manual)
- Body fluids (eg, CSF, pleural effusion, ascites) as clinically indicated
- Administration of EQ-5D-5L and EORTC-QLQ-C30 questionnaires (Phase 2, [redacted]
- [redacted]

[redacted]

6.3.3.1. Assessments Upon Start of Subsequent Anticancer Treatment

If a subject starts a new anticancer treatment before reaching the follow-up period, the mandatory visits planned during the treatment period after Day 29 would be Day 57, Day 85 (regardless of treatment arm) and Day 180 (Arm B). During these visits, assessments described in Section 6.3.1 for subjects who have received subsequent anticancer treatment should be performed.

6.3.4. Assessments at Time of Death

In case an autopsy is performed, blood and tissue samples will be collected for central analysis of markers related to safety and efficacy of the CAR T cells.

6.3.5. Early Withdrawal

If a subject voluntarily withdraws prematurely from the study, a visit will be scheduled as soon as possible, and all of the assessments listed for the Day 730 (24 months [EOS]) visit will be performed.

6.3.6. New Malignancies Follow-up Period

New malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm and cohort the subject was in. This includes any new malignancies, regardless of causal relationship to IP(s), occurring throughout the subject's entire participation in the study. If a subject develops a new malignancy, the Sponsor will request a tumor sample (refer to JCAR017-BCM-002 laboratory manual) and blood samples (see also Section 6.4.10 and Section 6.4.11).

6.3.7. Survival Follow-up

All subjects, except screen failures, will be followed for survival every 3 months until last subject last visit. Additional survival follow-up information will be collected in the context of the LTFU protocol.

6.3.8. Long-Term Follow-up

Because this protocol involves gene transfer, long-term follow-up for lentiviral vector safety, disease status, and long-term survival will continue on this protocol until 24 months after last dose of JCAR017, regardless of disease status, and under a separate LTFU protocol thereafter for up to 15 years after the JCAR017 infusion as per health authority regulatory guidelines (Food and Drug Administration [FDA], 2006; FDA, 2018; European Medicines Agency [EMA], 2009).

All subjects who either complete the primary follow-up period specified in this protocol or who prematurely withdraw after JCAR017 infusion will be asked to enroll in the LTFU protocol at the EOS visit or at the time of withdrawal, respectively. A separate informed consent form will be provided for the LTFU protocol. Subjects who do not consent to participate in the LTFU protocol will be followed for survival through public record.

6.4. Safety Assessments

6.4.1. Physical Examination

A physical examination should include assessments of the following body parts/systems: abdomen, extremities, heart, lungs, and neurological. In addition, symptom-directed exams should be performed.

6.4.2. Vital Signs

Vital signs include temperature, respiratory rate, heart rate, blood pressure. On the day of JCAR017, durvalumab and relatlimab/nivolumab administration, special monitoring is to be performed, refer respectively to Section 7.2.2.4, Section 7.2.4.3 and Section 7.2.8 for details.

6.4.3. Pulse Oximetry

SaO_2 will be assessed by pulse oximetry as per the Tables of Events (See Table 21).

6.4.4. Height and Weight

Height in centimeters (cm) or inches (in) and body weight to the nearest kilogram (kg) or pound (lb) in indoor clothing, but without shoes will be measured according to the Tables of Events (See Table 21). For subjects receiving CC-122 or CC-220, weight is to be assessed every 4 weeks.

6.4.5. Routine Neurologic and Mini Mental State Examinations

A routine neurologic examination should include, at minimum, a physical exam to assess cranial nerves, motor and sensory skills, coordination and balance, and the Mini Mental State Examination (MMSE; see Appendix G). The MMSE may be administered by an appropriately trained provider (ie, physician, nurse); a neurologist is not required. Efforts should be made to have the same provider perform the MMSE on a given subject to maintain consistency of assessment. If subjects develop neurologic symptoms suspicious of and/or diagnosed as neurologic toxicity, subjects will have daily MMSE exams until resolution of symptoms, unless the subject is medically incapacitated and/or medically unable to complete the MMSE.

6.4.6. Cerebrospinal Fluid Assessment

Cerebrospinal fluid (CSF) assessment and CNS imaging should be performed if CNS involvement is suspected at screening or at any time during the study as clinically indicated (eg, if new CNS symptoms occur, or if clinical signs or suspicion of CNS lymphoma exist). CSF will be analyzed for cell count and differential cytology, and for the presence of JCAR017 (see the JCAR017-BCM-002 laboratory manual for instructions on sending a sample for JCAR017 testing). CSF cultures (bacterial, fungal, viral) should be performed as clinically indicated for suspicion of infection.

6.4.7. ECOG Performance Status

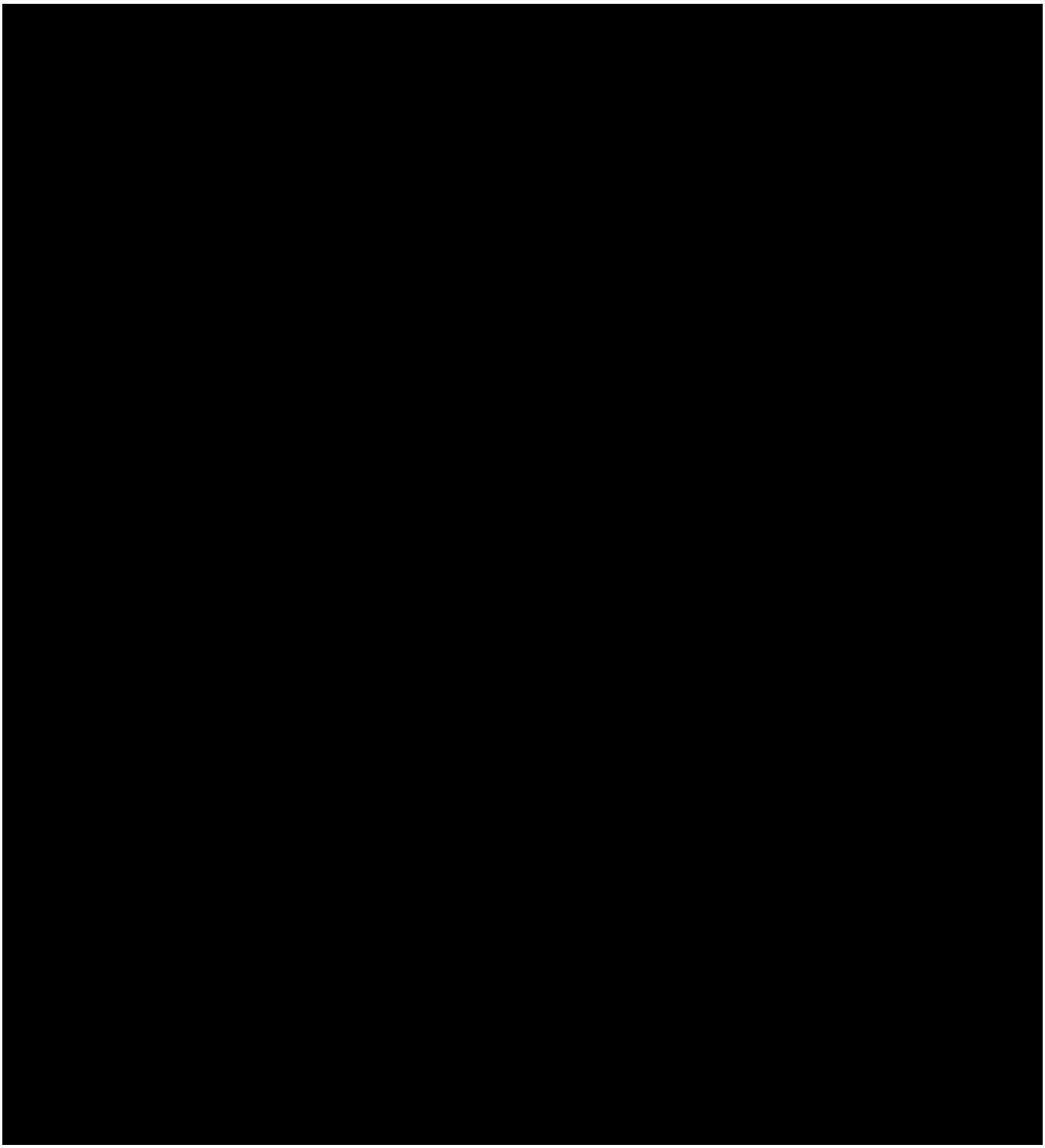
ECOG performance status (see Appendix B) will be used to evaluate subject eligibility at screening and will be assessed throughout the study at time points specified in the Tables of Events (See Table 21).

6.4.8. Multi-gated Acquisition Scan / Echocardiogram

An assessment of LVEF will be performed by ECHO or MUGA to assess the cardiac function of the subject and to confirm study eligibility.

6.4.9. Electrocardiogram

A standard 12-lead ECG should be obtained. ECG tracings should be labelled with the study number, subject number, date, and Investigator's signature, and kept in the source documents at the study site.



6.4.12. Clinical Laboratory Evaluations

Screening and other laboratory evaluations (see Appendix H) will be performed according to the Tables of Events (See Table 21). Additional assessments should be performed between scheduled study visits as clinically required in order to diagnose and monitor AEs/SAEs or expected events.

6.5. Efficacy Assessment

Efficacy response will be assessed according to the "Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification" (Cheson, 2014) based on radiographic tumor assessments. Subjects will have radiographic disease assessment by PET and/or CT or MRI scans (minimum of chest, neck, abdomen, and pelvis) at baseline and approximately 1, 3, 6, 9, 12, 18 and 24 months following treatment or until disease progression. Efficacy assessment will be performed by PET/CT until Month 3 and afterwards, once PET is negative, only CT is required. Starting from protocol Amendment 4 please refer to the Celgene Lugano Classification guidelines (Appendix F).

6.5.1. Potential Pseudoprogression

If a subject demonstrates early tumor progression (defined as occurring prior to/at 3 months after JCAR017 or start of combination agent, whichever occurs last), the investigator is responsible for evaluating whether the subject is experiencing a possible pseudoprogression (ie, tumor flare (see Section 10.6.4.3), which is local inflammatory reaction indicating early tumor response at sites of disease such as lymph nodes) which has been described in subjects treated with checkpoint inhibitors (Cheson, 2016).

6.6. Pharmacokinetics

6.6.1. Pharmacokinetics of JCAR017

Assessment of JCAR017 PK will be determined by qPCR to detect the JCAR017 transgene and/ or by flow cytometry to enumerate JCAR017 cells. Peripheral blood and CSF will be collected as indicated in the Tables of Events (See Table 21).

Detailed information regarding the collection, handling, and shipment of PK assessment samples is provided in the JCAR017-BCM-002 laboratory manual.

6.6.2. Pharmacokinetics of Durvalumab

PK sampling will be performed for all subjects taking JCAR017 in combination with durvalumab (Arm A). The sampling time points will be as follows:

- Post-expansion cohort: pre-infusion of durvalumab (-30 to -5 minutes prior to dose) and end of infusion (EOI [+ up to 5 mins]) on each infusion day of durvalumab (see Section 3.1.3 and Table 3).
- If treatment with durvalumab is continued beyond Day 85, PK sampling will be done pre-infusion of durvalumab (-30 to -5 minutes prior to dose) and EOI (+ up to 5 mins) on each infusion day of durvalumab.

6.6.3. Pharmacokinetics of CC-122

PK sampling will be performed for all subjects taking JCAR017 in combination with CC-122 (Arm B). The sampling time points will be as follows:

- Post-expansion cohort: pre-dose of CC-122 (-30 to -5 minutes prior to dose), 1.5 hours (± 10 min) and 3 hours post-dose (± 10 min) on Day 29 and Day 36 (see Section 3.1.4 and Table 4) and only pre-dose on Days 85 and 180.

6.6.4. Pharmacokinetics of CC-220

PK sampling will be performed for all subjects taking JCAR017 in combination with CC-220 (Arm C).

Pharmacokinetic blood samples will be collected in subjects pre-dose of CC-220 (22 to 26 hours after the preceding dose and prior to the next dose), 2 hours (± 10 min) and 4 hours post-dose (± 10 min) on Day 36 (see Section 3.1.5 and Table 5) and only pre-dose (or 22 to 26 hours after the preceding dose) on Days 22 and 85.

The sampling will allow evaluation of plasma CC-220, and as appropriate, the pharmacologically active metabolite, M12, in an exploratory manner.

6.6.5. Pharmacokinetics of Ibrutinib

PK sampling will be performed for all subjects taking JCAR017 in combination with ibrutinib (Arm D). The sampling time points will be as follows:

- Pre-dose of ibrutinib (-4 hours to -5 minutes prior to ibrutinib dose) on Days 1, 15, 29, and 85

6.6.6. Pharmacokinetics of Nivolumab and Relatlimab

PK sampling will be performed for all subjects in Arm E. The sampling time points will be as follows:

Table 23: Pharmacokinetic Sampling for Arm E

Cohort	Sub-cohort	Nivolumab ± Relatlimab Schedule	Study Day							
			8	15	22	29	36	43	57	85
Cohort 1 Post-infusion	A, B, C	Day 8, 22, 36, 57, 85	pre/post	-	pre	-	pre	-	pre/post	pre
	A+1, B+1, C+1	Day 8, 36, 57, 85	pre/post	-	x	-	pre	-	pre	pre
	A-1, B-1, C-1	Day 15, 29, 43, 57, 85	-	pre/post	-	pre	-	pre	pre/post	pre
	A+2, B+2, C+2	Day 15, 57, 85	-	pre/post	-	x	-	-	pre	pre

Study Day visit windows are given in Section 5.5.
For subjects receiving relatlimab in combination with nivolumab, post infusion samples for both nivolumab and relatlimab if given should be collected after the end of infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration, the collection of this sample should also be delayed accordingly. Post-infusion samples may not be collected from the same intravenous access as drug was administered; refer to the Laboratory Procedures Manual for additional restrictions.
Peripheral blood samples will also be taken pre-dose at the above timepoints for immunogenicity to nivolumab / relatlimab.

6.6.7. Pharmacokinetics of CC-99282

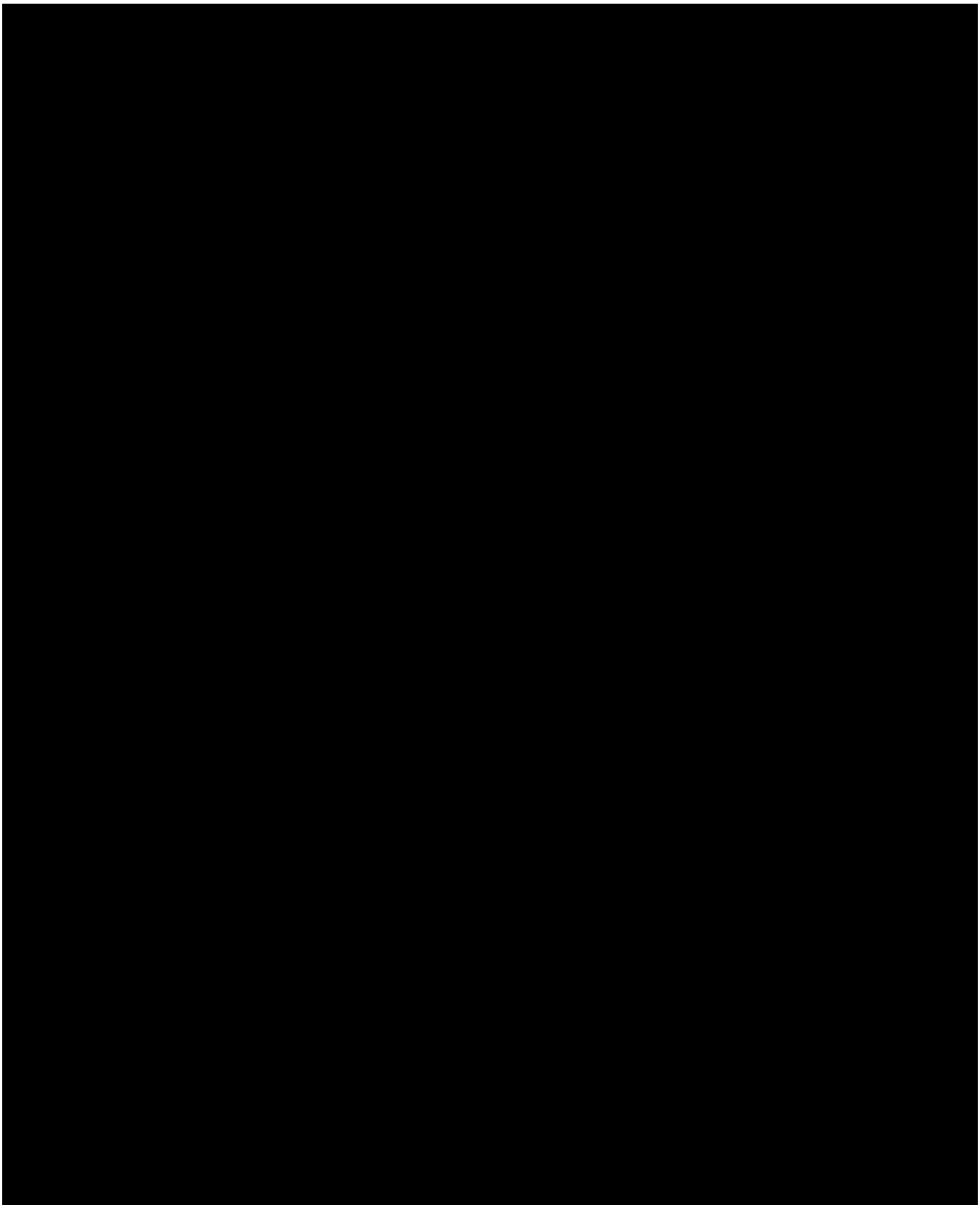
PK and PD sampling will be performed for all subjects taking JCAR017 in combination with CC-99282 (Arm F). The sampling timepoints will be as follows:

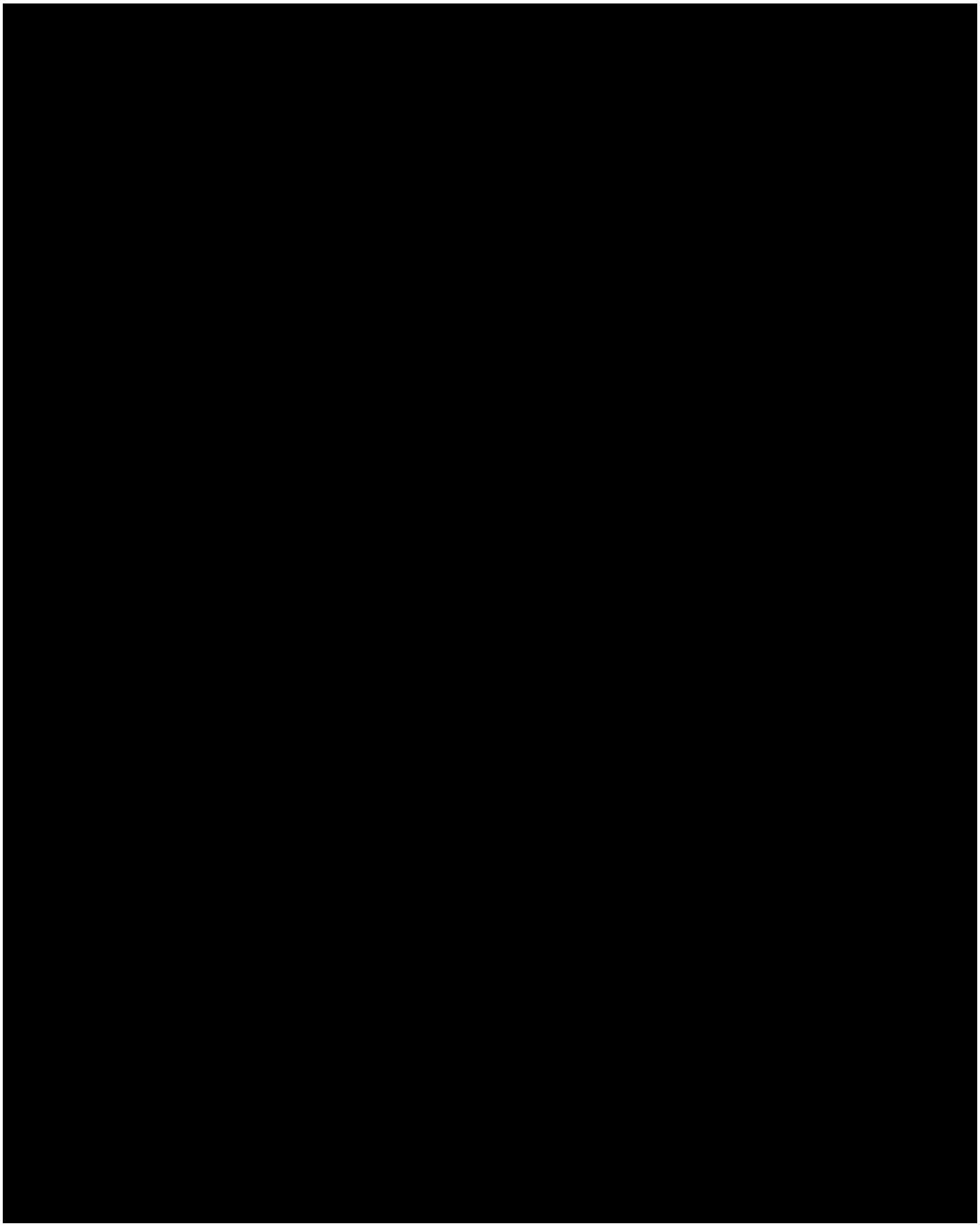
Table 24: Pharmacokinetic Sampling for Arm F

Cohort	Sub-cohort	CC-99282 Schedule	Study Day								
			1	2[b]	3[c]	8	9[b]	10[c]	15	22	29
Cohort 1 Post-Infusion	A	Day 8, Q7D	-	-	-	Pre-dose, 1, 2, 6 hr	x	x	x	-	-
	B	Day 1, Q7D	Pre-dose, 1, 2, 6 hr	x	x	x	-	-	-	-	-
	C[a]	Day 15, Q7D	-	-	-	-	-	-	Pre-dose, 1, 2, 6 hr	x	-
	D	Day 8, Q7D	-	-	-	Pre-dose, 1, 2, 6 hr	x	x	x	-	-
	E	Day 8 Q14D	-	-	-	Pre-dose, 1, 2, 6 hr	x	x	x	-	-
	F	Day 8 Q7D	-	-	-	Pre-dose, 1, 2, 6 hr	x	x	x	-	-

Abbreviations: hr = hour; Q7D = every 7 days
Study Day visit windows are given in Section 5.6.
[a] Subjects in subcohort C will be discharged at Day 15 and return to the clinic at Day 22.
[b] 24 hours after CC-99282 dose.
[c] 48 hours after CC-99282 dose.

[redacted]





6.8.1. EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire will be used as a measure of health-related quality of life. The QLQ-C30 is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, emotional, cognitive and social), three symptom scales (fatigue, nausea/vomiting, and pain), a global health status/health-related quality of life (HRQoL) scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items – no item occurs in more than one scale.

The QLQ-C30 employs a week recall period for all items and a 4-point scale for the functional and symptom scales/items with response categories "Not at all", "A little", "Quite a bit" and "Very much". The two items assessing global health status/ HRQoL utilize a 7-point scale ranging from 1("Very Poor") to 7 ("Excellent") (Aaronson, 1993). [redacted]

6.8.2. EQ-5D-5L

EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L consists of the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels (no problems, slight problems, moderate problems, severe problems, extreme problems)

In 2005, a Task Force was established within the EuroQol Group to investigate methods to improve the instrument's sensitivity and to reduce ceiling effects. After much discussion, the Task Force decided that there should be no change in the number of dimensions for a new version of EQ-5D.

However, previously published studies by EuroQol Group members showed that experimental 5-level versions of EQ-5D could significantly increase reliability and sensitivity (discriminatory power) while maintaining feasibility and potentially reducing ceiling effects.

The EQ-5D-5L still consists of 2 pages – the EQ-5D-5L descriptive system (page 2) and the EQ Visual Analogue Scale (page 3). The descriptive system comprises the same 5 dimensions as the EQ-5D-3L (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

However, each dimension now has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a cardinal score.

The EuroQol Group had received feedback over the years that respondents sometimes found it difficult to draw a line from the box to the scale. It was also cumbersome for administrators to record their scores. The EQ-5D-5L now asks respondents to simply 'mark an X on the scale to indicate how your health is TODAY' and then to 'write the number you marked on the scale in the box below'.

This should make the task easier for both respondents and users (Herdman, 2011; EuroQol, 1990). See Appendix K.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

7.1.1. JCAR017 (Lisocabtagene maraleucel; liso-cel)

See Section 1.2.1 for JCAR017 description.

See the JCAR017 Product Administration Manual for details of packaging and labeling, product request and shipment, product preparation and administration, and product disposal and destruction.

7.1.2. Durvalumab (Arm A)

See Section 1.2.2 for durvalumab description.

7.1.3. CC-122 (Arm B)

See Section 1.2.3 for CC-122 description.

7.1.4. CC-220 (Arm C)

See Section 1.2.4 for CC-220 description.

7.1.5. Ibrutinib (Arm D)

See Section 1.2.5 for ibrutinib description.

7.1.6. Relatlimab (Arm E)

See Section 1.2.6 for relatlimab description.

7.1.7. Nivolumab (Arm E)

See Section 1.2.7 for nivolumab description.

7.1.8. CC-99282 (Arm F)

See Section 1.2.8 for CC-99282 description.

7.2. Treatment Administration and Schedule

Subject eligibility criteria must be reconfirmed prior to starting lymphodepleting chemotherapy and subsequent treatment with JCAR017.

7.2.1. Lymphodepleting Chemotherapy

Lymphodepleting chemotherapy will be obtained locally according to local clinical study agreement and in accordance with local guidelines.

Subjects will be treated with fludarabine IV (30 mg/m^2/day for 3 days) plus cyclophosphamide IV (300 mg/m^2/day for 3 days) concurrently prior to treatment with JCAR017. Refer to the most recent package inserts for further details on administration of these agents.

LD chemotherapy should be initiated so as to be completed 2 to 7 days before JCAR017 administration. If side effects from the lymphodepleting chemotherapy occur, JCAR017 infusion may be delayed for up to 14 days after lymphodepleting chemotherapy upon discussion with the Sponsor. Delay of LD chemotherapy by more than 14 days requires discussion with the Sponsor; delay of LD doses or JCAR017 may require some screening procedures and/or LD chemotherapy to be repeated. Refer to Section 6.2.1 for the assessments that will be performed on each day of lymphodepleting chemotherapy.

LD chemotherapy must only be given if the subject has adequate performance and adequate bone marrow function to receive LD chemotherapy as assessed by the Investigator.

The recommended administration is as follows:

- The IV hydration is 1 L of balanced crystalloid (according to institutional guideline) given at 500 mL/hr starting 2 hours prior to cyclophosphamide
- Fludarabine 30 mg/m^2 IV over 30 minutes
  - If creatinine clearance 60 to 70 mL/min: Reduce dose by 20% each daily dose of fludarabine
  - If creatinine clearance < 60 mL/min: Withhold dose, subject no longer eligible

  Indirect calculation of creatinine clearance should be performed using the Cockcroft-Gault formula (Appendix I). Direct measurement of creatinine clearance is also acceptable.
- Cyclophosphamide 300 mg/m^2 IV over 60 minutes
- Additional 1 L of balanced crystalloid (according to institutional guidelines) given at 500 mL/hr

Antiemetic therapy may be given prior to LD chemotherapy per institutional practice. Mesna may be used for subjects with a history of hemorrhagic cystitis per institutional practice.

7.2.2. JCAR017 Treatment

7.2.2.1. JCAR017 Dose and Schedule

JCAR017 will be infused at a dose of JCAR017 positive transduced viable T cells (CAR+ T cells) at 2 dose levels depending on cohort assignment. JCAR017 will be given on Day 1 (2 to 7 days after completion of lymphodepleting chemotherapy).

- DL1 : 50 x 10^6 CAR+ T cells
- DL2 : 100 x 10^6 CAR+ T cells

7.2.2.2. JCAR017 Preparation and Cell Thawing

See the JCAR017-BCM-002 Product Administration Manual for details.

7.2.2.3. JCAR017 Premedication

Subjects should be pre-medicated with 500 to 650 mg acetaminophen oral (PO) and 25 to 50 mg diphenhydramine hydrochloride (PO or IV) 30 to 60 minutes prior to JCAR017 infusion. In case

the diphenhydramine is not available in a country, it is acceptable to use another H1 antihistamine.

These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Pre-medication with steroids should be avoided.

7.2.2.4. JCAR017 Administration

Each JCAR017 dose consists of CD4+ CAR+ T cells and CD8+ CAR+ T cells, administered separately via IV. The subject must be continuously monitored during each IV administration of JCAR017. Vital signs (temperature, respiratory rate, heart rate, blood pressure, and SaO_2 by pulse oximetry) will be measured approximately every 15 minutes starting from 15 minutes prior to the first IV administration until one hour after the last IV administration, and hourly for the next 2 hours. If the subject's vital signs are not stable 3 hours following the final IV administration, vital signs should be monitored as clinically indicated until stable.

See the JCAR017-BCM-002 Product Administration Manual for complete information.

7.2.4. Durvalumab Treatment

Durvalumab will be administered as an IV infusion at the assigned dose. In Arm A Cohort 1, continued dosing at an approximately Q4W interval may be allowed after Day 85. Maximal total duration of treatment with durvalumab will be 12 months (see Section 3.1.2).

Guidelines for management of durvalumab-related toxicities are presented in Appendix C, Appendix D and Appendix E. Any subject meeting any of the criteria for withholding therapy on the day of their scheduled durvalumab infusion will have the durvalumab infusion withheld until the abnormalities improve.

7.2.4.1. Durvalumab Drug Product

Durvalumab (MEDI4736) will be supplied by Celgene in single use vials in single count cartons and labeled appropriately as investigational material for this study. Each 10R vial will be supplied as a vialed liquid solution containing 500 mg (nominal) of durvalumab at a concentration of 50 mg/mL. Durvalumab should be stored in accordance with the product label.

- Sites will supply IV infusion bags with dilution solution and infusion lines with appropriate filters. IV infusion bags of normal saline (0.9% [w/v] sodium chloride or 5% [w/v] dextrose injection, 250 mL size). Saline or dextrose bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride. Infusion lines should contain a 0.2 to 0.22 µm in-line filter.

Since the compatibility of durvalumab with other IV medications and solutions than normal saline, is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.

For additional information on preparation and storage, please refer to the Pharmacy Manual.

7.2.4.2. Durvalumab Premedication

Subjects should be premedicated with 500 to 650 mg acetaminophen PO and 25 to 50 mg diphenhydramine hydrochloride (PO or IV) 30 to 60 minutes prior to durvalumab infusion.

These medications may be repeated every 6 hours as needed based on the Investigator's assessment of symptoms. Premedication with steroids should be avoided.

7.2.4.3. Durvalumab Preparation and Administration

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated investigational product (IP) manager using aseptic technique. Total time from needle puncture of the vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

Durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% [w/v] dextrose, with a final in-bag concentration ranging from 0.15 mg/mL to 20 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter.

The IV bag size should be selected such that a final durvalumab in-bag concentration of 0.15 mg/mL to 20 mg/mL is achieved. Infusions should be given over a period of 60 minutes.

Note: Special monitoring requirements are associated with each infusion of durvalumab:

- Subjects will have their temperature, blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):
  - At the beginning of the infusion (at 0 minutes)
  - At 30 minutes during the infusion (±5 minutes)
  - At the end of the infusion (at 60 minutes ±5 minutes)
  - In the 2-hour observation period post-infusion: every 30 minutes (±5 minutes) after the infusion (ie, 90, 120, 150, and 180 minutes from the start of the infusion)
- If the infusion takes longer than 60 minutes, then temperature, blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.

7.2.4.4. Durvalumab Dose Interruptions

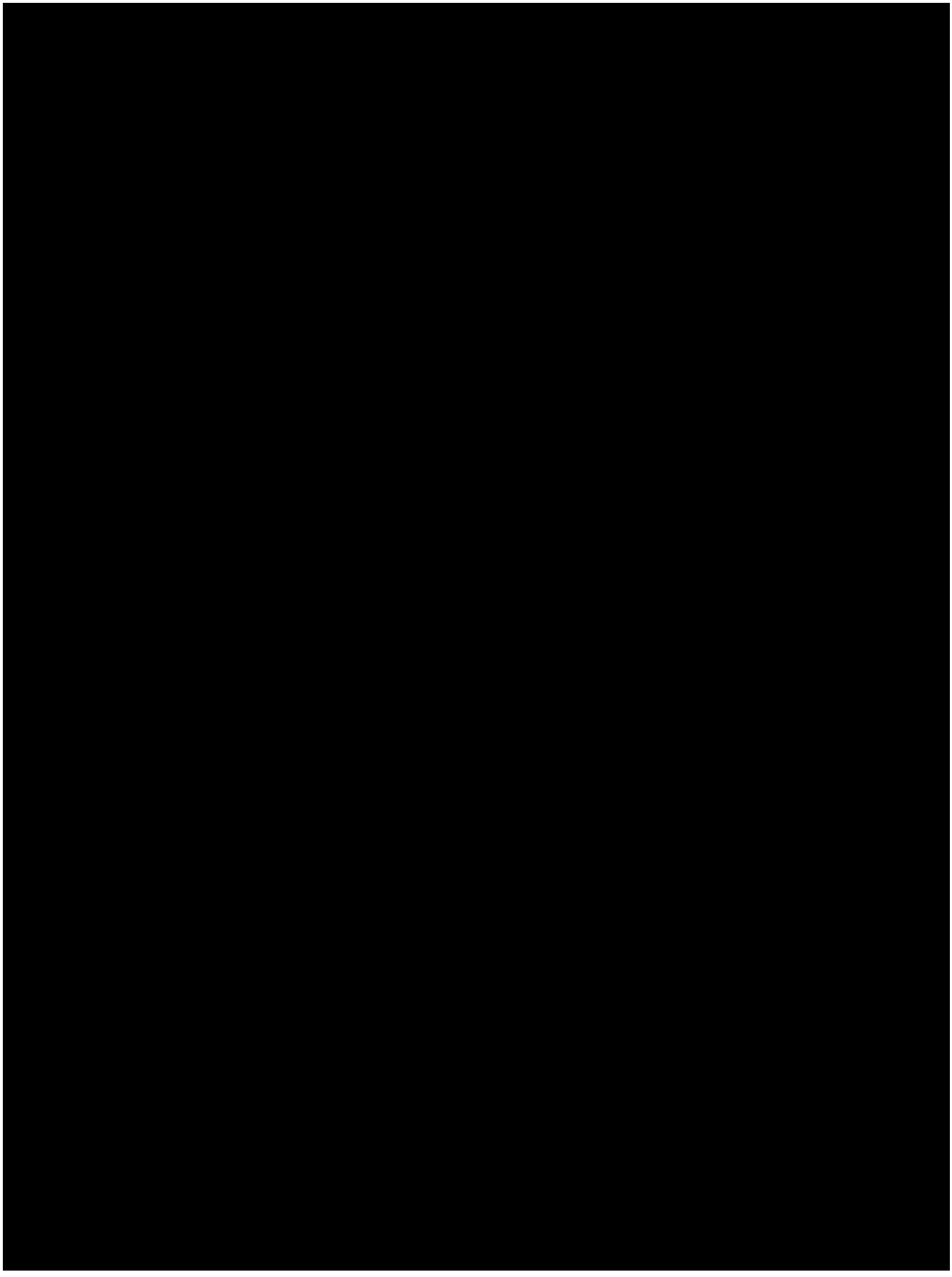
Dose interruptions are permitted for appropriate management of AEs. Treatment may be interrupted or discontinued or infusion rate may be changed at the discretion of the investigator for severe infusion or allergic reactions, or other toxicities.

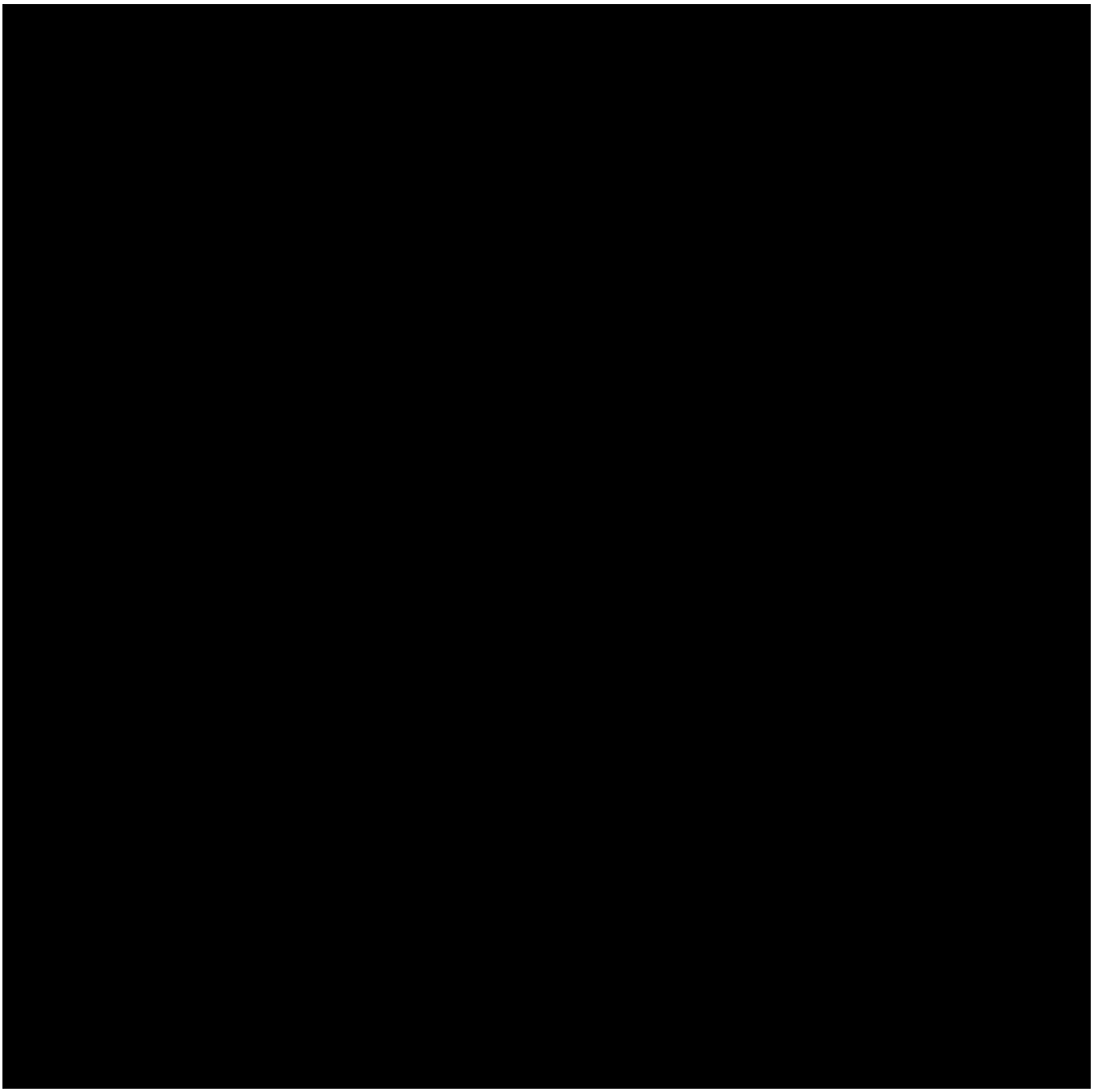
Dose modifications must be recorded in the Dose Administration CRF.

7.2.4.5. Durvalumab Dose Modification Guidelines

Subjects will be evaluated for AEs at each visit with the National Cancer Institute CTCAE version 4.03 used as a guide for the grading of severity, with the exception of tumor lysis syndrome (Cairo, 2004) in Appendix L.

Dose modifications guidelines for immune mediated reactions (Haanen, 2017), non-immune-mediated reactions and infusion-related reactions should be followed and are detailed respectively in Appendix C, Appendix D and Appendix E.





7.2.7. Ibrutinib Treatment

7.2.7.1. Ibrutinib Drug Product

For Phase 1 ibrutinib (IMBRUVICA®; 140-mg formulated capsules) will be sourced locally by the clinical site responsible for use in this trial and stored as directed per the package insert. Ibrutinib will be labeled by the clinical site as per local regulations.

For Phase 2 ibrutinib will be supplied or obtained according to local clinical study agreement and labeled in accordance with local regulations.

Please refer to local ibrutinib prescribing information for more details on known precautions, warnings, and adverse reactions (see current version of Prescribing Information).

7.2.7.2. Ibrutinib Administration

Subjects should be instructed to take ibrutinib orally with a glass of water at approximately the same time each day.

7.2.7.3. Ibrutinib Dose Modification

Ibrutinib dose may be modified in a stepwise manner for treatment-related toxicity according to the guidance provided in Table 29 or as determined by the Investigator in consultation with the Medical Monitor. Reintroduction of ibrutinib following interruption may be done in a stepwise manner back to the full intended dose. Dose modifications must be recorded in the Dose Administration CRF.

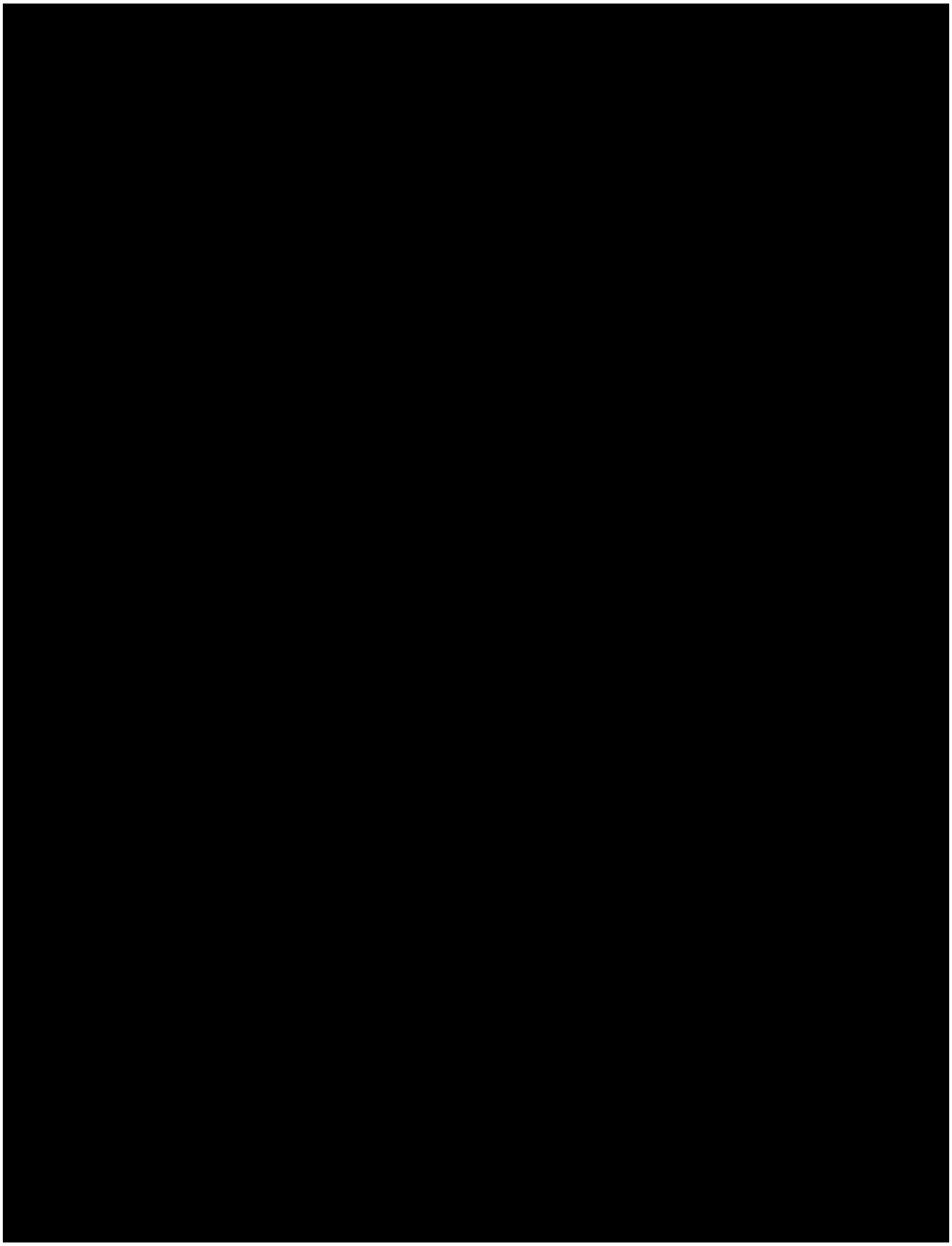
Table 29: Ibrutinib Dose Modification Levels

Starting Ibrutinib Dose	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction	4th Reduction
420 mg QD	Pause until recovery, restart 420 mg QD	Pause until recovery, reduce to 280 mg QD	Pause until recovery, reduce to 140 mg QD	Discontinue permanently

Abbreviations: QD = once a day.

Please refer to the ibrutinib PI for full details.

[redacted]



7.2.10. Definition of Dose-limiting Toxicity

Dose-limiting toxicities will be evaluated during the DLT evaluation period for the subjects in Phase 1. The severity grading of adverse events will be determined according to NCI CTCAE Version 4.03 or higher. CRS is graded as per Appendix M.

A DLT will be defined as below:

- Death not related to disease progression
- Grade 4 neurotoxicity
- Grade 3 neurotoxicity of greater than 7 days' duration
- Grade 3 neurotoxicity that does not revert to baseline within 28 days of the start date of the Grade 3 event

- Grade 3 seizures that do not resolve to Grade ≤ 2 within 3 days
- Grade 4 CRS
- Grade 3 CRS that does not resolve to Grade ≤ 2 within 7 days
- Febrile neutropenia (defined by temperature ≥ 38.3°C and ANC < 0.5 x 10^9 /L) that does not resolve within 72 hours
- Any increase in aspartate aminotransferase (AST) or ALT > 5 x ULN and concurrent increase in total bilirubin > 3 x ULN that is unrelated to CRS and has no other probable reason to explain the combination of increases
- Any cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic Grade 3 or 4 event not pre-existing or not due to the underlying malignancy
- Any other Grade 3 or 4 event deemed unexpected by the Investigator and considered a DLT upon evaluation by the SRC
- Any AE requiring dose modification of the combination agent required based on a related AE or any treatment interruption greater than 2 weeks

For Arm A, the following additional combination treatment-related events will be considered DLTs (if occurring after start of durvalumab):

- Grade ≥ 3 non-infectious colitis or non-infectious pneumonitis
- Grade ≥ 3 immune-related adverse event (irAE) or other Grade ≥ 3 autoimmune toxicity (excluding B-cell aplasia)

For Arm B, the following additional combination treatment-related events will be considered DLTs (if occurring after start of CC-122):

- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting > 24 hours

For Arm C, the following additional combination treatment-related events will be considered DLTs (if occurring after start of CC-220):

- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

For Arm D, the following additional combination treatment-related events will be considered DLTs (if occurring after start of combination therapy):

- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

For Arm E, the following additional combination treatment-related events will be considered DLTs (if occurring after start of combination therapy):

- Grade ≥ 3 non-infectious colitis or non-infectious pneumonitis

- Grade ≥ 3 immune-related adverse event (irAE) or other Grade ≥ 3 autoimmune toxicity (excluding B-cell aplasia)
- Grade 2 immune-related eye pain or reduction in visual acuity that requires systemic treatment
- Grade 2 eye pain or reduction in visual acuity that does not respond to topical therapy and that does not improve to Grade 1 within 2 weeks of initiation of topical therapy
- Grade 4 anemia
- Grade 3 hemolysis
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

For Arm F, the following additional combination treatment-related events will be considered DLTs (if occurring after start of combination therapy):

- Grade 4 anemia
- Grade 4 neutropenia lasting ≥ 7 days
- Grade 3 or 4 thrombocytopenia with clinically significant bleeding

Should a subject experience a suspected DLT, the treating investigator should contact the sponsor's medical monitor prior to declaring the event a DLT. All DLT cases will also be discussed with the SRC during regular calls with sites and their respective investigators aiming to review and share all safety related events including but not limited to DLTs.

Please see Section 10 for further details on AE reporting.

7.2.11. Overdose

Overdose, as defined for this protocol, refers to flu/cy (IV), durvalumab (IV), CC-122 (PO), CC-220 (PO), ibrutinib (PO), nivolumab (IV), relatlimab (IV), CC-99282 (PO) or JCAR017 (IV). On a per-dose basis, an overdose is defined as the following amount over the protocol-specified dose of these drug(s) assigned to a given subject, regardless of any associated AEs or sequelae:

- PO: any amount over the protocol-specified dose
- IV: 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate.

In the event of overdose the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the CRF. See Section 10 for the reporting of AEs associated with overdose.

7.3. Method of Treatment Assignment

Assignment of subjects to arm and subcohorts will be done by the Sponsor based on subject's eligibility and available slots.

A telephone- and web-based Integrated Response Technology (IRT) system will be used to register candidates as subjects in the trial. The IRT will also be used to schedule shipment of combination agent based on the cohort a subject is assigned to.

7.3.1. Packaging and Labeling

The identity of JCAR017 will be checked and verified at each critical step of cell processing as part of the chain of identity. [redacted] Additional information may be included on the label as applicable per local regulations.

7.3.2. Cell Product Supply and Storage

Detailed instructions on the storage, handling, and preparation of JCAR017 cell product will be provided in the JCAR017 Product Administration Manual.

7.4. Investigational Product Accountability and Disposal

7.4.1. Accountability Procedures

An inventory must be performed and a product receipt log filled out and signed by the person accepting the shipment of JCAR017 cell product, durvalumab, CC-122, CC-220, ibrutinib, nivolumab, relatlimab or CC-99282.

[redacted]

8. CONCOMITANT MEDICATIONS AND PROCEDURES

8.1. Permitted Concomitant Medications and Procedures

Medications will be recorded as shown in Table 30. Subjects should be discouraged from use of illicit drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

Table 30: Reporting Periods for Concomitant Medications

Arm	Start	End	Required Reporting
All	Informed Consent	Initiation of LD chemotherapy or first dose of combination agent, whichever occurs first	Medications taken by the subject at the time of an AE related to protocol-mandated procedures or for active medical history conditions[a]
A	Start of LD chemotherapy	90 days after last dose of LD chemotherapy, JCAR017 infusion, or durvalumab (whichever is later)	All medications
B	Start of LD chemotherapy	90 days after last dose of LD chemotherapy or JCAR017, or 28 days after last dose of CC-122 (whichever is later)	
C	Start of LD chemotherapy	90 days after last dose of LD chemotherapy or JCAR017, or 28 days after last dose of CC-220 (whichever is later)	
D	Start of ibrutinib	90 days after last dose of LD chemotherapy or JCAR017, or 28 days after last dose of ibrutinib (whichever is later)	
E	Start of LD chemotherapy	90 days after last dose of LD chemotherapy, JCAR017, nivolumab or relatlimab (whichever is later)	
F	Start of LD chemotherapy	90 days after last dose of LD chemotherapy or JCAR017, or 28 days after last dose of CC-99282 (whichever is later)	
All	End of previous period	End of study	Only medications ongoing at the time of AEs related to any study procedure or JCAR017 or combination agent will be collected

Abbreviations: AE = adverse event; CCGs = CRF compliance guidelines; CRF = Case report form; LD = lymphodepleting.
[a] Medications given, procedures and transfusions performed for a clinically significant condition unrelated to protocol-mandated procedures should be reported as described in the CCGs.

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects (refer to Section 8.1.1), including side effects from trial treatments or

disease progression. Supportive care, including, but not limited to antiemetic medications, may be administered at the discretion of the Investigator.

All concomitant treatments, including blood and blood products (see Section 8.1.2), used from 30 days prior to first dose of any IP must be reported on the CRF.

For information regarding other drugs that may interact with any IP and affect its metabolism, pharmacokinetics, or excretion, please see the IB and/or local package insert.

Vaccination with a killed vaccine is permitted at any time with consultation with the medical monitor.

Due to the large amount of data generated during hospitalizations, a targeted concomitant medication collection approach will be utilized for the CRF. Therefore, the following medications should NOT be entered on the CRF during inpatient and Intensive Care Unit (ICU) stays:

- IV fluids
- Heparin flushes
- Stool softeners
- Vitamins, minerals, health supplements
- Saline
- Lotions

8.1.1. Anticancer Treatments between Leukapheresis and Lymphodepleting Chemotherapy

If necessary, anticancer treatment is allowed for disease control while JCAR017 is being manufactured (ie, after leukapheresis and prior to lymphodepleting chemotherapy). Chemotherapy is allowed if completed at least 7 days prior to the start of lymphodepleting chemotherapy. If other agents are used, the washout periods noted in the exclusion criteria (see Section 4.3) must be met. The use of therapeutic agents with little/no evidence in the scientific literature for NHL should be discussed with Celgene. Local radiation is allowed to a single lesion or subset of lesions if other un-irradiated PET-positive lymphoma lesions are present. If anticancer treatment is necessary during this time, the pre-JCAR017 evaluation PET and CT/MRI assessments and other pre JCAR017 study procedures (see Section 6.1.3) must be performed after the anticancer treatment has been completed. The subject must continue to have PET-positive disease (except Arm D) and meet pre-JCAR017 eligibility criteria pertaining to adequate organ function, active infections, pregnancy, and washout of prior therapy before initiation of LD chemotherapy.

8.1.2. Growth Factors and Transfusions of Blood and Blood Products

Secondary neutropenia prophylaxis with granulocyte colony-stimulating factor (G-CSF) is recommended for subjects in Arms B, C and F. Secondary prophylaxis with G-CSF for subjects who experienced Grade 4 neutropenia or neutropenic fever from a prior cycle of CC-122 or CC-220 (for which primary prophylaxis was not received), or for subjects enrolled in Arm F who

experience Grade 4 neutropenia or neutropenic fever lasting 7 days should be initiated after discussion with the sponsor.

If G-CSF is given following lymphodepleting chemotherapy to support hematopoiesis it should be stopped at least 2 days before the start of combination therapy where this is dependent on ANC or platelet count.

Other growth factors (eg, erythropoietin) may be prescribed after leukapheresis or at any time during the treatment and follow-up periods at the Investigator's discretion once a subject has experienced cytopenic or myelosuppressive events. For all arms, growth factors or transfusions of blood or blood products cannot be administered during the Screening period to increase a subject's blood values in order to meet entry criteria (see Section 4).

8.1.3. Thromboembolic Event Prophylaxis

Subjects and investigators are advised to be observant for the signs and symptoms of thromboembolism. Subjects should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is recommended that the Investigator carefully assess an individual subject's underlying risk for thromboembolism and bleeding and consider prophylactic measures with anti-coagulation or anti-platelet agents as per institutional or clinical standards. Thromboembolic event prophylaxis is mandatory for subjects enrolled in Arm C.

8.2. Prohibited Concomitant Medications and Procedures

The following medications are considered exclusionary or should be used with caution during the study. The sponsor must be notified if a subject receives any of these during the study.

- Any investigational anticancer therapy
- Any concurrent chemotherapy, radiation therapy, immunotherapy, biologic or hormonal therapy for cancer treatment
- Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 20 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers

  Note: Use of immunosuppressive medications for the management of IP-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.
- Herbal and natural remedies are to be avoided
- Concurrent use of St John´s wort
- Live attenuated vaccines during the study through 30 days after the last dose of investigational product (100 days for subjects who have received nivolumab or relatlimab on Arm E)

The following medications are prohibited until lack of response, subsequent therapy for lymphoma, or 1 year following JCAR017 treatment, whichever comes first:

- Steroids: therapeutic doses (> 20 mg/day of prednisone or equivalent) unless used for treatment of CRS, NT or MAS/HLH. Therapeutic doses may be used in life-threatening situations and for other medical conditions when indicated, or after loss of detectable JCAR017 cells. Pre-treatment containing steroids may be given for necessary medications (eg, IVIG) after discussion with the Sponsor. Pre-medication with steroids for JCAR017 administration is not allowed. Physiologic replacement dosing of steroids is allowed. Topical steroids, inhaled steroids, and intrathecal steroids for CNS relapse prophylaxis are permitted.

The following medications are prohibited during the treatment and follow-up periods unless used as an anticancer agent after lack of adequate response to JCAR017 or progression of lymphoma:

- Donor lymphocyte infusion (DLI)
- GVHD therapies (eg, calcineurin inhibitors, methotrexate or other chemotherapeutics, mycophenolate, rapamycin, thalidomide, immunosuppressive antibodies such as anti-TNF, anti-IL6, or anti-IL6R)
- Anticancer agents, excluding lymphodepleting chemotherapy and agents used for treatment of uncontrolled JCAR017 proliferation or sCRS
- Cetuximab, or other anti- epidermal growth factor receptor (EGFR) treatments, unless intended for treatment of uncontrolled JCAR017 proliferation or sCRS
- Experimental agents
- Radiation, unless needed for local control of a single tumor lesion in the presence of other non-irradiated PET-positive lesions

8.2.1. Additional Concomitant Medication Guidance for Arm B

Based on in vitro studies, CYP3A4/5 and CYP1A2 appear to be the major isozymes involved in oxidative metabolism of CC-122, with very minor contributions by other CYP enzymes, including CYP2C8 and CYP2C19. Hence, caution should be used when co-administering CC-122 with drugs that are known strong inducers or inhibitors of CYP3A4/5 or CYP1A2, as these may affect the exposure to CC-122. The effects of these compounds on the exposure to CC-122 have not been evaluated in a clinical setting. Examples of these drugs include the following:

- CYP3A4/5 inhibitors: telithromycin, clarithromycin, atazanavir, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, and saquinavir.
- CYP3A4/5 inducers: rifampin, phenytoin and carbamazepine.
- CYP1A2 inhibitors: ciprofloxacin, enoxacin and fluvoxamine.

A comprehensive listing of drugs that are CYP3A4 inhibitors can be accessed online at the following address: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

8.2.2. Additional Concomitant Medication Guidance for Arm C

Medications that are strong inhibitors or inducers of CYP3A4/5 are prohibited. Of note, any antibiotics/antifungals listed as strong inhibitors or inducers of CYP3A4/5 should be avoided and replaced by alternate treatment. In general, azole antifungals such as itraconazole and the antibiotics clarithromycin and rifampin should be avoided. Also, grapefruit, St. John's Wort, and related products are prohibited while participating in this study. Please refer to Appendix V for a list of medications that are strong inhibitors or inducers of CYP3A4/5. Please note this list is not exhaustive. If there are any questions regarding whether a medication is a strong CYP3A4/5 inhibitor or inducer, please contact the Medical Monitor or designee.

8.2.3. Additional Concomitant Medication Guidance for Arm D

The coadministration of ibrutinib with a strong or moderate CYP3A inhibitor may increase ibrutinib plasma concentrations. Increased ibrutinib concentrations may increase the risk of drug-related toxicity. Dose modifications of ibrutinib are recommended when used concomitantly with posaconazole, voriconazole and moderate CYP3A inhibitors.

Concomitant use of other strong CYP3A inhibitors should be avoided. Hold ibrutinib if these inhibitors will be used short-term (such as anti-infectives for seven days or less).

Grapefruit and Seville oranges during ibrutinib treatment should be avoided, as these contain strong or moderate inhibitors of CYP3A.

The coadministration of ibrutinib with strong CYP3A inducers may decrease ibrutinib concentrations and therefore should be avoided. Please refer to Appendix V for a list of medications that are strong inhibitors or inducers of CYP3A4/5. Please note this list is not exhaustive. If there are any questions regarding whether a medication is a strong CYP3A4/5 inhibitor or inducer, please contact the Medical Monitor or designee.

Please refer to ibrutinib prescribing information for full details.

8.2.4. Additional Concomitant Medication Guidance for Arm F

It is recommended to initiate growth factor support for neutropenia of Grade 3 or higher while subjects are receiving combination therapy with CC-99282.

CC-99282 is a substrate of CYP3A4/5. Drugs that are strong inhibitors or inducers of CYP3A4/5 should be avoided. Examples of these drugs include, but are not limited to:

- CYP3A4/5 inhibitors: atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin.
- CYP3A4/5 inducers: carbamazepine, phenytoin, and rifampin.

If use of one of these drugs becomes necessary, the risks and benefits should be discussed with the Sponsor's study physician prior to its concomitant use with CC-99282.

Please refer to the CC-99282 IB for full details.

8.3. Required Concomitant Medications and Procedures

Lymphodepleting regimens accompany JCAR017 administration and utilize cyclophosphamide and fludarabine. Please refer to the currently approved cyclophosphamide and fludarabine phosphate package insert.

Premedication should be given prior to JCAR017 and durvalumab administration. Please refer respectively to Section 7.2.2.3 and Section 7.2.4.2 for the details.

Supportive care for the management of CRS is detailed in Appendix M. In some cases, tocilizumab, an anti-IL-6R-antibody, may be required to treat toxicities such as severe cytokine release syndrome. All JCAR017 global sites (eg, US, EU) must have at least 2 doses of tocilizumab available prior to infusion per a given subject. It is recommended to resupply in case tocilizumab is given Please refer to the currently approved Actemra®/ RoActemra® package insert. The preferred dose to intervene in subjects with CRS is 8 mg/kg.

In some cases, dexamethasone may also be given in combination with tocilizumab. The preferred dose for dexamethasone in subjects with CRS is between 10 to 20 mg (see Appendix M).

An additional anti-IL-6 antagonist, siltuximab, should also be considered in the event of sCRS. Please refer to the current approved package insert.

Thromboembolic event prophylaxis will be started on the day CC-220 is started for subjects in Arm C and continued until the end of CC-220 treatment.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This study is a Phase 1/2, multi-center, open-label study of the combination of JCAR017 and immunomodulatory agents in subjects with R/R aggressive B-cell NHL. Phase 1 is a dose and schedule finding phase and Phase 2 is an expansion phase in which additional subjects will be enrolled at the recommended Phase 2 dose and schedule established in Phase 1. Rules for enrollment prioritization between arms will be specified each time additional arms will be added.

The primary objective of Phase 1 is to assess the safety and to determine the RP2D of the JCAR017 combinations per arm using a BOIN design. The combination agents are as follows:

- Arm A: durvalumab
- Arm B: CC-122
- Arm C: CC-220 (iberdomide)
- Arm D: ibrutinib
- Arm E: nivolumab ± relatlimab
- Arm F: CC-99282

Within an arm, a dose expansion cohort (Phase 2) may be opened at any dose and schedule that has been shown to be safe with at least 6 DLT evaluable subjects through the DLT period. The primary objective of Phase 2 is to evaluate hierarchically the preliminary efficacy of JCAR017 first on CR rate (CRR) at 3 months and subsequently on CRR at 6 months when administered in combination with checkpoint inhibitors or immunomodulatory compounds.

The secondary objectives (Phase 1 and Phase 2 in each arm) are to further evaluate safety, other efficacy endpoints and to characterize the PKs of JCAR017 and the respective combination agent.

[redacted]

9.2. Study Population Definitions

For each arm in this study, the following analysis populations will be defined for the analysis and presentation of the data.

9.2.1. Screened Set

The Screened set will include all subjects who have signed informed consent.

9.2.2. Enrolled Set

The Enrolled set will include all subjects who have signed informed consent, who meet all eligibility criteria at screening and undergo leukapheresis (Arms A, B, C, E and F) or those who

have signed informed consent, meet all eligibility criteria at screening and either receive combination therapy or undergo leukapheresis (Arm D).

9.2.3. Leukapheresed Set

The Leukapheresed set will include all subjects who have undergone leukapheresis.

9.2.4. JCAR017 Treated Set

The JCAR017 Treated set will include all subjects who have received an infusion of conforming JCAR017 cell product.

9.2.5. Combination Treated Set

The Combination Treated set will include all subjects who have received an infusion of conforming JCAR017 cell product and at least one dose of the combination agent.

9.2.6. Safety Set

The Safety set will include all subjects who have received an infusion of conforming JCAR017 cell product or at least one dose of the combination agent.

9.2.7. DLT Evaluable Set

The DLT evaluable set includes all subjects who have either received an infusion of conforming JCAR017 cell product and at least one dose of the combination agent and have completed the DLT evaluation period (see Section 9.3.1), or who have received an infusion of conforming JCAR017 cell product and at least one dose of the combination agent and have experienced at least one DLT prior to completion of the DLT evaluation period.

9.2.8. Efficacy Evaluable Set

The Efficacy Evaluable set includes subjects in the Combination Treated set who have a baseline and at least one valid post-baseline tumor response assessment.

9.3. DLT Related Definitions

9.3.1. Definition of DLT Evaluation Period

Subjects enrolled in Phase 1 will be observed for DLTs as follows:

9.3.1.1. Arms A, B and C

Subjects will be observed for DLT from JCAR017 infusion until 28 days after the first dose of the combination agent.

9.3.1.2. Arm D

Subjects will be observed for DLT from the start of JCAR017 infusion until 28 days after JCAR017 infusion.

9.3.1.3. Arm E

Subjects will be observed for DLT from the start of JCAR017 infusion until 28 days after the first dose of the combination agent.

9.3.1.4. Arm F

Subjects will be observed for DLT from the start of JCAR017 infusion until 28 days after the first dose of the combination agent.

9.3.2. Definition of a Subject Evaluable for DLTs

Subjects enrolled in Phase 1 are considered evaluable for DLTs if they received an infusion of conforming JCAR017 cell product and at least one dose of the combination agent and complete the specified DLT evaluation period or if they have received an infusion of conforming JCAR017 cell product and at least one dose of the combination agent and experience a DLT during the DLT evaluation period. Subjects who are unable to start combination therapy within a given, subcohort-specific timeframe are not evaluable for DLT.

Non DLT evaluable subjects will be replaced with another subject at the same dose level. Additional subjects within any dose cohort may be enrolled at the discretion of the SRC.

9.4. Sample Size and Power Considerations

9.4.1. Phase 1

In each arm, dose escalation or de-escalation within any cohort will be based on the BOIN algorithm. With the target DLT rate of 0.30, the BOIN escalation boundary is $\lambda e=0.236$ and the de-escalation boundary is $\lambda d=0.358$. The BOIN dosing decision table is provided in Table 9.

The BOIN design is a Bayesian dose-finding method that optimizes subject ethics by minimizing the chance of exposing subjects to sub-therapeutic and overly toxic doses. The BOIN design yields an average performance comparable to that of the continual reassessment method (CRM) in terms of selecting the MTD, but has a lower risk of assigning subjects to sub-therapeutic or overly toxic doses (ie, better subject ethics).

In each arm, enrollment into Phase 1 will be staggered such that the first 6 subjects in each subcohort will enter the DLT period at intervals of at least 1 week. A longer interval may be specified for a specific arm (see Section 3.1.9). Until a subcohort has 6 subjects with complete DLT information and has been shown to be safe, no more than 6 subjects can be in the DLT period simultaneously across subcohorts of a given arm. Enrollment to the next dose level will be prioritized if open for enrollment.

In cohorts within each arm, a sample size of at least 6 DLT evaluable subjects per subcohort is planned with no more than 9 DLT evaluable subjects treated in a subcohort. The final number of subjects needed in Phase 1 in a given arm will depend on the number of DLTs observed within each subcohort. Non-DLT evaluable subjects will be replaced. With an expected rate of non-DLT evaluable subjects of around 30%, up to about 24 subjects may need to be enrolled in Phase 1 into Arms A, B and F, up to about 48 subjects may need to be enrolled in Phase 1 in Arms C and E and up to 12 subjects in Phase 1 in Arm D.

9.4.2. Phase 2

[redacted]

Given these

[redacted]

9.4.3. Total Sample Size

The total sample size will depend on whether subcohorts and arms are selected for evaluation, planned as up to 240 evaluable subjects across Arms A-F.

9.5. Background and Demographic Characteristics

Subject's age, height, weight, and continuous baseline variables will be summarized using descriptive statistics, while sex, race and other categorical variables will be provided using frequency tabulations for the Leukapheresed set, Enrolled set, JCAR017 Treated set and Combination Treated set for each cohort and arm. Medical history data will be summarized using frequency tabulations by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) for the Enrolled set, JCAR017 Treated set and Combination Treated set for each cohort and arm.

9.6. Subject Disposition

9.6.1. Phase 1

Summaries of subject disposition will be provided for each cohort and arm for the Screened set, Enrolled set, and JCAR017 Treated set. The number and percentage of subjects who are eligible

for study treatment but not able to successfully generate a JCAR017 cell product, along with the reason(s) for manufacturing failure, will be summarized per cohort and per arm. Summary of subjects enrolled by site will be provided. Summary of subjects with protocol deviations and violations will be provided per cohort and per arm.

9.6.2. Phase 2

Summaries of subject disposition will be provided by arm for the Screened set, Enrolled set and JCAR017 Treated set. The number and percentage of subjects who are eligible for study treatment but not able to successfully generate a JCAR017 cell product, along with the reason(s) for manufacturing failure, will be summarized per arm. Summary of subjects enrolled by site will be provided. Summary of subjects with protocol deviations and violations will be provided per arm.

9.7. Efficacy Analysis

For each arm, the primary efficacy analysis will be based on the Combination Treated set. JCAR017 Treated set, Efficacy Evaluable set and the Leukapheresed set will be used as supportive analysis when applicable.

For binary endpoints such as overall response rate (ORR), the frequency distribution (n, %) will be provided. The point estimate together with two-sided exact 95% confidence intervals (CI) will be provided.

For time-to-event endpoints such as duration of response (DOR), event-free survival (EFS), progression-free survival (PFS) and overall survival (OS), the Kaplan-Meier product limit method will be used to estimate the survivorship function. Event rates at specific time points will be estimated from the Kaplan-Meier curves. Medians together with two-sided 95% confidence intervals will be calculated.

9.7.1. Primary Efficacy Analysis (Phase 2)

The primary efficacy endpoints of Phase 2 are CRR at 3 months post-JCAR017 infusion and subsequently CRR at 6 months post-JCAR017 infusion. The CRR is defined as the proportion of subjects achieving a CR according to the Lugano Classification, prior to start of another non-study anticancer therapy.

For each arm, primary analysis of the proportion of subjects achieving a CR at 3 months and 6 months post-JCAR017 infusion will be done using an exact binomial test (0.05 two-sided significance level) and in a Bayesian framework. Subjects from Phase 1 under RP2D will be used during the analysis of the Phase 2 data as prior information during both interim monitoring and final analysis (prior for Phase 2 based on a combination of Jeffreys prior and CR numbers during Phase 1 in a beta binomial model).

Bayesian posterior and predictive probability of success will be used for the monitoring of efficacy on CRR at 3 months after JCAR017 infusion during the dose expansion phase. Phase 2 will be stopped for futility at interim monitoring if posterior predictive probability of success is smaller than 10% after 15 evaluable subjects.

9.7.2. Secondary Efficacy Analysis (Phase 1 and Phase 2)

Secondary efficacy endpoints and analyses:

- CRR for Phase 1 at 1, 3, 6, 9, 12, 18 and 24 months post-JCAR017 infusion and Phase 2 at 1, 3, 6, 9, 12, 18 and 24 months post-JCAR017 infusion. The CRR is defined as the proportion of subjects achieving a CR according to the Lugano Classification, prior to start of another non-study anticancer therapy. CRR will be analyzed in a similar fashion than primary efficacy endpoint. Subjects with unknown or missing response will be counted as non-responder in the analysis;
- ORR based on the best overall response for Phase 1 and Phase 2 at 1, 3, 6, 9, 12, 18 and 24 months post-JCAR017 infusion. The ORR is defined as the proportion of subjects achieving an objective response of partial response (PR) or better according to the Lugano Classification, prior to start of another non-study anticancer therapy. ORR will be analyzed in this same fashion as the primary efficacy endpoint. Subjects with unknown or missing response will be counted as non-responder in the analysis;
- PFS for Phase 1 and Phase 2, evaluated up to 24 months post-JCAR017 infusion. PFS is defined as time from JCAR017 infusion to disease progression or death from any cause. PFS will be summarized using Kaplan-Meier estimates.
- OS for Phase 1 and Phase 2, evaluated up to last subject last visit. OS is defined as the time from JCAR017 infusion to death. OS will be summarized using Kaplan-Meier estimates. Data from surviving subjects will be censored at the last time that the subject is known to be alive.
- DOR for Phase 1 and Phase 2, evaluated up to 24 months post-JCAR017 infusion (for responders only). DOR is defined as the time from first response to disease progression or death from any cause. DOR will be summarized using Kaplan-Meier estimates.
- EFS for Phase 1 and Phase 2, evaluated up to 24 months post-JCAR017 infusion. EFS is defined as time from JCAR017 infusion to disease progression, starting a new anti-lymphoma therapy, or death from any cause, whichever occurs first.
- Censoring rules for PFS, DOR and EFS will be described in the SAP.

9.8. Safety Analysis

Safety analysis including treatment-emergent adverse events (TEAEs) and laboratory findings will be based on both the JCAR017 Treated set and Combination Treated set. Data will be aggregated for all cohorts per arm as well as separately for each cohort per arm. Literature "book" values will be utilized for this study.

TEAEs ≥ Grade 3 in subjects infused with JCAR017 in a clinical trial setting include neurologic toxicities, such as encephalopathy, hypotension, cytokine release syndrome, febrile neutropenia, and hypoxia.

TEAEs ≥ Grade 3 in subjects treated with durvalumab in a clinical trial setting include irAEs, such as pneumonitis, hypersensitivity reactions, cytopenias, infections, venous thromboembolism and endocrine disorders.

The following safety assessments will also be performed:

- The timing and length of inpatient hospitalization
- Physical exam
- MMSE
- Laboratory evaluations to monitor closely for neurologic changes, CRS, and fever
- Expected cytopenias and potential infections attributable to the lymphodepleting chemotherapy

9.8.1. Phase 1 DLT

Dose-limiting toxicity will be listed by cohort and arm using the DLT Evaluable analysis set.

Safety analysis including TEAEs and laboratory findings will be based mainly on the JCAR017 Treated set and Combination Treated set per cohort and per arm.

9.8.2. Adverse Events

Adverse events will be coded using MedDRA system organ class (SOC) and preferred term (PT).

The severity of each adverse event will be graded by the Investigator using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher, unless otherwise specified in the protocol. If CTCAE criteria do not exist for a given event, the Investigator should use one of the following: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

Related AEs are those for which the Investigator selects "Related" to JCAR017 or any other combination drugs on the AE CRF. Relatedness will always default to the Investigator's choice, not that of the medical monitor. AEs suspected to be related to any study drug, will be tabulated as JCAR017 alone, JCAR017 in combination or combination drug alone.

Adverse events will be identified and captured as SAEs if they meet the definition for SAE.

A JCAR017 TEAE is defined as any AE that occurs or worsens after the JCAR017 infusion and up to 90 days after the JCAR017 infusion.

A combination TEAE is defined as any AE that occurs or worsens after the first JCAR017 infusion and up to 90 days after the dose of JCAR017 or 90 days after the last dose of durvalumab, 28 days after the last dose of CC-122, ibrutinib or CC-99282, or 90 days after the last dose of nivolumab or relatlimab, whichever occurs last.

All AEs will be listed. The focus of AE summarization will be on JCAR017 TEAEs with additional combination period (pre-JCAR017 and post-JCAR017).

Adverse event summaries will provide the number and percentage of subjects with TEAEs by SOC and PT, based on the JCAR017 Treated set and Combination Treated set as follows (a brief-high level summary will also be provided):

- All TEAEs;
- All TEAEs by severity grade;
- Grade $\geq$ 3 TEAEs;
- All treatment related AEs;
- Treatment related Grade $\geq$ 3 AEs;
- All SAEs;
- All treatment-related SAEs;
- All AEs leading to treatment discontinuation;
- All AEs leading to death;
- AEs leading to study discontinuation

Multiple occurrence of the same events will be counted only once per subject in each summary.

Adverse events will be summarized and listed first by SOC in descending order of incidence and then by PT (within each SOC), also in descending order of incidence. In summaries by severity grade, the most severe grade will be used for those AEs that occur more than once in an individual subject during the study.

In addition to the above summary tables, all TEAEs and SAEs will be summarized by SOC only and by PT only in order of descending incidence.

9.9. Laboratory Evaluations

The focus of the laboratory data summarization will be on the JCAR017 treatment-emergent and combination treatment-emergent laboratory abnormalities using the JCAR017 Treated set and Combination Treated set.

JCAR017 treatment-emergent laboratory abnormalities are defined as an abnormality that, compared to baseline, worsens by at least one grade after the JCAR017 infusion and up to 3 months after the JCAR017 infusion.

Combination treatment-emergent laboratory abnormalities are defined as an abnormality that, compared to baseline, worsens by at least one grade after the JCAR017 infusion or after the start of the combination, whichever occurs first and up to 3 months after the dose of JCAR017, 3 months after the last dose of the combination agent, whichever occurs last.

All laboratory data will be listed with a variable indicating whether the event is treatment-emergent.

9.9.1. Numeric Laboratory Results

Summaries of laboratory data will be based on observed data and will be reported using conventional units. Baseline, raw values, and changes from baseline will be summarized using descriptive statistics for each laboratory test specified in the study protocol.

9.9.2. Graded Laboratory Values

Applicable hematological and serum biochemistry laboratory data will be programmatically graded according to CTCAE (Version 4.03 or higher) severity grade: mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life threatening (Grade 4). Grade 0 includes all non-missing values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.

9.9.3. Summaries of Laboratory Abnormalities

All laboratory data will be listed. The focus of laboratory data summarization will be on JCAR017 treatment-emergent laboratory abnormalities. Summaries (number and percentage of subjects) of baseline, post-baseline at each visit, and worst post-baseline treatment-emergent laboratory abnormalities will be provided. Subjects will be categorized according to the most severe abnormality grade. All summaries of laboratory abnormalities will be based on the JCAR017 Treated set and Combination Treated set.

Shift tables will be presented by showing the change in CTCAE severity grade from baseline to each post-baseline visit and to the maximum post-baseline grade. For parameters for which a CTCAE severity scale does not exist, shift tables will be presented showing change in results from the baseline value (low, normal, and high) to each post-baseline visit and to the worst post-baseline value (low, normal, and high).

9.10. Interim Analysis

The interim safety and efficacy findings at the end of Phase 1 subcohorts, and the primary and updated analysis in Phase 2 may be submitted for public presentation. In general, each subcohort with different combination therapies in different subject populations will be analysed separately, but subcohorts may be pooled based on the need of analyses. In addition, interim data may also be pooled for aggregate safety and efficacy based on analyses performed for regulatory authorities (e.g. DSUR) or for presentation to the DSMB.

9.11. Other Topics

9.11.1. Safety Review Committee

During Phase 1, the SRC will be convened to recommend a Phase 2 dose and schedule for each combination treatment arm based on an integrated assessment of the safety, PK and Pd data, and preliminary efficacy information. The SRC may also override the BOIN algorithm for safety concerns.

During Phase 2, the SRC will be convened to evaluate the safety profile and tolerability.

This committee will be composed of the medical monitor, drug safety physician, and statistician as well as selected active Investigators to be identified at the start of the study. Operational details for the SRC will be detailed in a separate SRC charter.

9.11.2. Data Safety Monitoring Board

An independent DSMB will review cumulative study data over the course of the study to evaluate safety, protocol conduct, and scientific validity and integrity of the trial. The DSMB, composed of a statistician and selected physicians with experience in hematology/oncology and/or T cell therapy, will be assembled under a dedicated charter specifically developed for safety oversight of the study. DSMB members will not be actively involved in the study design, conduct, or subject accrual and must not have financial, proprietary, professional, or other interests that may affect impartial, independent decision making.

The DSMB will be convened prior to enrollment of the first subject on the protocol and will meet approximately quarterly throughout the trial and as needed to address any safety issues that may arise. Subject safety will be evaluated as specified in DSMB charter. The DSMB will provide advice to the Sponsor as outlined in the DSMB charter. The effectiveness of the risk mitigation plan will be reviewed by the DSMB at each meeting. Operational details for the DSMB will be detailed in the DSMB charter.

9.11.3. Pharmacokinetics

Maximum concentration, time to maximum concentration, area under the curve of JCAR017 will be calculated using noncompartmental methods. JCAR017 concentrations and PK parameters will be summarized descriptively. Persistence of JCAR017 will be summarized. In addition, concentrations of the respective combination agents will be summarized descriptively. Full details will be included in the SAP.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF (see Section 7.2.11 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for JCAR017, durvalumab, CC-122, CC-220, ibrutinib, nivolumab, relatlimab, CC-99282, or flu/cy overdose. Actual treatment should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

Adverse events must be recorded as shown in Table 31. If they meet the seriousness criteria, they will be reported to Drug Safety as provided in Section 10.5.

Table 31: Recording Periods for Adverse Events

Arm	Start	End	Required Recording
All	Signing of informed consent	Start of LD chemotherapy or investigational product, whichever is earlier (except Arm D which is until start of ibrutinib)	AEs related to any protocol-mandated procedure[a] Each AE with a change in toxicity grade will be recorded in the CRF as a separate AE record
A	Start of LD chemotherapy	90 days after JCAR017 infusion or last dose of durvalumab (whichever is later)	All AEs Each AE with a change in toxicity grade will be recorded in the CRF as a separate AE record
B	Start of LD chemotherapy	90 days after JCAR017 infusion or 28 days after last dose of CC-122 (whichever is later)	
C	Start of LD chemotherapy	90 days after JCAR017 infusion or 28 days after last dose of CC-220 (whichever is later)	
D	Start of ibrutinib	90 days after JCAR017 infusion or 28 days after last dose of ibrutinib (whichever is later)	
E	Start of LD chemotherapy	90 days after JCAR017 infusion or last dose of relatlimab or nivolumab (whichever is later)	
F	Start of LD chemotherapy	90 days after JCAR017 infusion or 28 days after last dose of CC-99282 (whichever is later)	
All	End of previous period	End of study	Only AEs related to any study procedure or JCAR017 or combination agent will be collected; changes in toxicity grade will be recorded as a single event with the highest toxicity grade experienced at any time during the event recorded

Abbreviations: AE = adverse event; CCGs = CRF compliance guidelines; CRF = Case report form; LD = lymphodepleting.
[a] Any clinically significant conditions/events unrelated to study procedures should be reported either in medical history or as an adverse event as described in the CCGs.

If a subject receives lymphodepleting therapy but not JCAR017, all AE/SAEs should be recorded/reported for 30 days following the last dose of lymphodepleting chemotherapy.

Serious adverse events made known to the Investigator at any time thereafter that are suspected of being related to IP will be recorded as well. Documentation must be supported by an entry in the subject's source document. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome. In addition to recording CRS as a diagnosis, the signs and symptoms of CRS will be recorded on a separate

CRF. Any medical condition already present prior to first LD chemotherapy should not be reported as an AE unless the medical condition is related to any study procedure and increases in severity. In this case, it should be reported as an AE and indicated as a worsening event.

Inpatient or ICU stays, while anticipated, are not scheduled protocol-defined visits. In addition, inpatient or ICU admissions can generate large amounts of clinical data (eg, multiple concomitant medications, frequent concomitant medication dose changes, laboratory values, and vital sign assessments). Therefore, targeted collection of data from inpatient or ICU stays, as well as a separate CRF for detailing specific adverse events of special interest (AESI; ie, signs and symptoms of CRS and neurotoxicity), will be utilized for the purpose of adequately describing the expected risks of JCAR017 and the recommendations for managing these risks.

AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs meeting the criteria described in Table 31 must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- routine treatment or monitoring of the studied indication not associated with any deterioration in condition.

- the administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- a procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- a procedure that is planned (ie, planned prior to start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

For both AEs and SAEs, the Investigator must assess the severity/ intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03 or higher); CRS is to be graded as per Appendix M.

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale or Version 3.0 of NCI CTCAE as in the case of TFR (refer to Table 41):

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the LD chemotherapy, JCAR017 or the combination agent and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	a causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	there is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

10.2.5. Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

Serious adverse events will be followed until they return to baseline, the event stabilizes or is no longer considered clinically significant by the Investigator; the subject dies or withdraws consent; or study closure.

10.3. Abnormal Laboratory Values

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies and suspected pregnancies (including elevated βhCG or positive pregnancy test) occurring at any time after receipt of lymphodepleting chemotherapy or infusion of JCAR017 in either a female subject of childbearing potential or a partner of childbearing potential of a male subject are immediately reportable events.

Additionally pregnancies and suspected pregnancies in either a female subject of childbearing potential or a partner of childbearing potential of a male subject that occur while the subject is receiving IP, or within 3 months of the last dose of durvalumab, or within 28 days after the last dose of CC-122, CC-220, ibrutinib or CC-99282, or 24 weeks after the last dose of nivolumab or relatlimab, are considered immediately reportable events. Investigational product is to be discontinued immediately.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

10.4.1. Females of Childbearing Potential

In case of pregnancies and suspected pregnancies in female subjects, the Investigator will follow the subject until completion of the pregnancy and afterwards up to 1 year of the newborn baby, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate

method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in-utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject taking IP becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. The pregnant partner will be asked for consent for follow-up by the Investigator until completion of the pregnancy and afterwards up to 1 year of the newborn baby.

10.5. Reporting of Serious Adverse Events

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. [redacted] This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IP) recorded in the CRF as described in Section 10.1.

The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to [redacted] as soon as these become available. [redacted]

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.5.2. Death Reports

Deaths due to progressive disease will not be reported as an SAE unless considered related to IP (if assessed as lack of efficacy by the investigator). Any sign, symptom, or manifestation of progressive disease that meet any of the seriousness criteria and result in death will be reported

as individual SAEs. Any other AEs leading to death should be reported as an SAE according to Table 31.

10.6. Potential Risks and Management of Treatment Toxicities

A summary of potential risks and management of treatment toxicity is provided below. See the respective IB (US PI for Arm D) for a complete discussion of potential risks associated with JCAR017 and combination agent.

10.6.1. Management of Toxicities Associated with JCAR017

Cytokine release syndrome (CRS) and neurologic toxicities (NT) are associated with CAR T cell therapies. Celgene has developed specific toxicity management guidelines (TMG) for CRS and NT associated with Celgene cellular products based on current clinical experience across the clinical development programs (Appendix M). These recommendations are based on the CRS revised grading system (Lee, 2014) and the Common Toxicity Criteria for Adverse Events (CTCAE) and need to be used for grading of CRS and NT to guide management in this trial.

If available and adopted as per site standard practice, CRS and NT grading according to the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading System (Lee, 2019) should also be recorded in the eCRF to inform future modifications of the management guidelines.

10.6.1.1. Cytokine Release Syndrome

Administration of JCAR017 is associated with cytokine release syndrome (CRS). Cytokine release syndrome is characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, and anorexia. Clinical symptoms and severity of CRS are highly variable (Lee, 2014), and management can be complicated by concurrent conditions. With JCAR017, CRS usually occurs within two weeks after infusion (Abramson, 2017).

- Fever, especially high fever ($\geq$ 38.5°C or $\geq$ 101.3°F), is a commonly-observed hallmark of CRS, and many features of CRS mimic infection. Hence, infection must be considered in all subjects presenting with CRS symptoms and appropriate cultures must be obtained and empiric antibiotic therapy initiated per institution standard of care.
- Less common symptoms associated with CRS include cardiac dysfunction, adult respiratory distress syndrome, renal and/or hepatic failure, coagulopathies, disseminated intravascular coagulation, and capillary leak syndrome.
- Neurologic toxicity has been observed concurrently with CRS.
- With CAR T cell products, CRS has been reported in a few cases to be associated with findings of macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH), and the physiology of the syndromes may overlap.

Please refer to Appendix M for detailed description of CRS, grading and treatment recommendations.

10.6.1.2. Fever

The possibility of CRS should be considered for all subjects with fever (≥ 38°C or ≥ 100.4°F) following JCAR017 treatment. Subjects should be monitored closely for hemodynamic instability and changing neurologic status. Febrile subjects, neutropenic or otherwise, should be evaluated promptly for infection and managed per institutional or standard clinical practice.

10.6.1.3. Cytopenias

Severe cytopenias, including anemia, leukopenia, neutropenia, and thrombocytopenia, can occur with both JCAR017 and lymphodepleting chemotherapy, and delayed recovery has been observed. Complete blood counts should be monitored after JCAR017 infusion until count recovery. Institutional guidelines should be followed in the event of Grade ≥ 3 cytopenias.

10.6.1.4. Infections

Life-threatening and fatal infections have been observed. Severe infections, may include bacterial, fungal (including *pneumocystis jirovecii*), and viral infections (eg, cytomegalovirus [CMV], hepatitis B virus [HBV], respiratory viruses and other viruses). A high index of suspicion is warranted in the event of prolonged or recurrent cytopenias, especially in conjunction with hypogammaglobulinemia, severe lymphopenia, and/or recent use of corticosteroids. Viral reactivation and other serious opportunistic infections should be considered in these settings, and prophylactic, pre-emptive, or symptomatic treatment with antimicrobial, antifungal, anti-pneumocystic, and/or antiviral therapies should be considered per local institutional guidelines.

10.6.1.5. Neurologic Toxicities

CAR T cell therapy is associated with unique neurologic toxicities. Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity. With JCAR017, to date, the start of neurologic symptoms has been noted between 3 to 23 days (median 10 days) (Abramson, 2017) after CAR T cell infusion and in severe cases may require admission to the intensive care unit (ICU) for frequent monitoring, respiratory support, or intubation for airway protection. The symptoms are variable generally occur as CRS is resolving or after CRS resolution.

Please refer to Appendix M for detailed description of neurologic toxicities, grading and treatment recommendations.

10.6.1.6. Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a serious disorder potentially associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages. MAS is typically characterized by high-grade, non-remitting fever, cytopenias, and hepatosplenomegaly. Laboratory abnormalities found in MAS include elevated inflammatory cytokine levels, serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and decreased circulating NK cells. Other findings include variable levels of transaminases, signs of acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. There are no definitive diagnostic criteria for MAS; it is typically diagnosed using published criteria for hemophagocytic lymphohistiocytosis (Schulert, 2015). While there is considerable overlap in

clinical manifestations and laboratory findings between MAS and CRS, other distinguishing MAS physical findings such as hepatosplenomegaly and lymphadenopathy are not common in adult subjects treated with activated T cell therapies.

Subjects treated with JCAR017 should be monitored for MAS, and cytokine-directed therapy should be considered as clinically indicated.

10.6.1.7. Infusion Reactions

Administration of JCAR017 may cause infusion reactions, such as fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea.

To minimize the risk of infusion reactions, all subjects should be pre-medicated with acetaminophen and diphenhydramine. Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and anti-emetics. Corticosteroids should be avoided because of the potential impact on efficacy of infused JCAR017 cells.

The following guidelines should be followed for infusion reactions:

- Grade 1: administer symptomatic treatment; continue JCAR017 administration of both CD8+ and CD4+ components at the same dose and rate
- Grade 2: stop administration of JCAR017; administer symptomatic treatment, and resume JCAR017 administration of both CD8+ and CD4+ components at a reduced rate of administration only after symptoms resolution
- Grade 3: stop administration of JCAR017, administer symptomatic treatment, and resume at a reduced rate of administration only after symptoms resolve. If Grade 3 reaction recurs, discontinue JCAR017 administration; no further CD8+ or CD4+ components of JCAR017 should be administered
- Grade 4: discontinue administration of JCAR017 and administer symptomatic treatment as necessary; no further no further CD8+ or CD4+ components of JCAR017 should be administered

10.6.1.8. Tumor Lysis Syndrome

Both lymphodepleting chemotherapy and JCAR017 may cause tumor lysis syndrome (TLS) in subjects with high disease burden. Subjects should be closely monitored for laboratory evidence of TLS (hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia) (see Appendix L), and subjects at high risk for developing TLS, such as those with high disease burden and high cell turnover, should receive prophylactic treatment including administration of allopurinol and hydration, per standard clinical practice.

10.6.1.9. B-cell Aplasia

B-cell aplasia is an expected potential off-tumor, on-target toxicity. Prolonged B-cell aplasia has been observed in other CD19-directed CAR T cell programs (Davila, 2013; Grupp, 2013). Serum immunoglobulin levels will be obtained from all subjects prior to and at various time points following JCAR017 treatment. Hypogammaglobulinemic subjects (serum immunoglobulin G (IgG) < 500 mg/dL) should be considered for intravenous immunoglobulin replacement therapy per institutional guidelines.

10.6.1.10. Graft-Versus-Host Disease

The likelihood of graft-versus-host disease (GVHD) occurring with CAR T cell therapy is low, but it remains a theoretical risk. Subjects who have undergone allo-HSCT and who have active, acute or chronic GVHD at screening are excluded from enrolling in this protocol. However, due to residual donor engraftment, some or all JCAR017 T cells may be of donor origin. Subjects who received a previous allo-HSCT will be assessed for donor chimerism at screening and will be monitored closely throughout the study for signs of GVHD.

10.6.2. Risks Associated with Lymphodepleting Chemotherapy

Subjects will receive fludarabine and cyclophosphamide prior to treatment with JCAR017 to facilitate lymphodepletion and CAR T cell engraftment. Refer to the package inserts or summary of product characteristics for specific details surrounding the risks of fludarabine and cyclophosphamide.

10.6.3. Risks Associated with Durvalumab

Based on the mechanism of action of durvalumab leading to T cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study for subjects treated in Arm A. Potential irAEs may be similar to those seen with the use of ipilimumab, nivolumab (BMS-936558), and BMS-936559 and may include immune-mediated enterocolitis, dermatitis, hepatitis, endocrinopathies, vasculitis, non-infectious meningitis and non-infectious encephalitis (Hodi, 2010; Brahmer, 2012; Topalian, 2013). Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or disease progression), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy.

In addition to the dose modifications shown in Appendix C, it is recommended that management of irAEs follow the guidelines outlined for ipilimumab (Weber, 2012). These guidelines recommend the following:

- Subjects should be evaluated to identify any alternative etiology
- In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related
- Symptomatic and topical therapy should be considered for low-grade events
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event
- More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab, mycophenolate, etc).

If the investigator has any question in regard to an AE being an irAE, the investigator should immediately contact the Sponsor's medical monitor.

Dose modifications (ie, dose interruption, dose hold, or infusion rate modification) of durvalumab may be required in the event of treatment related toxicity. See Appendix C, Appendix D and Appendix E for detailed instructions for durvalumab dose modifications and toxicity management.

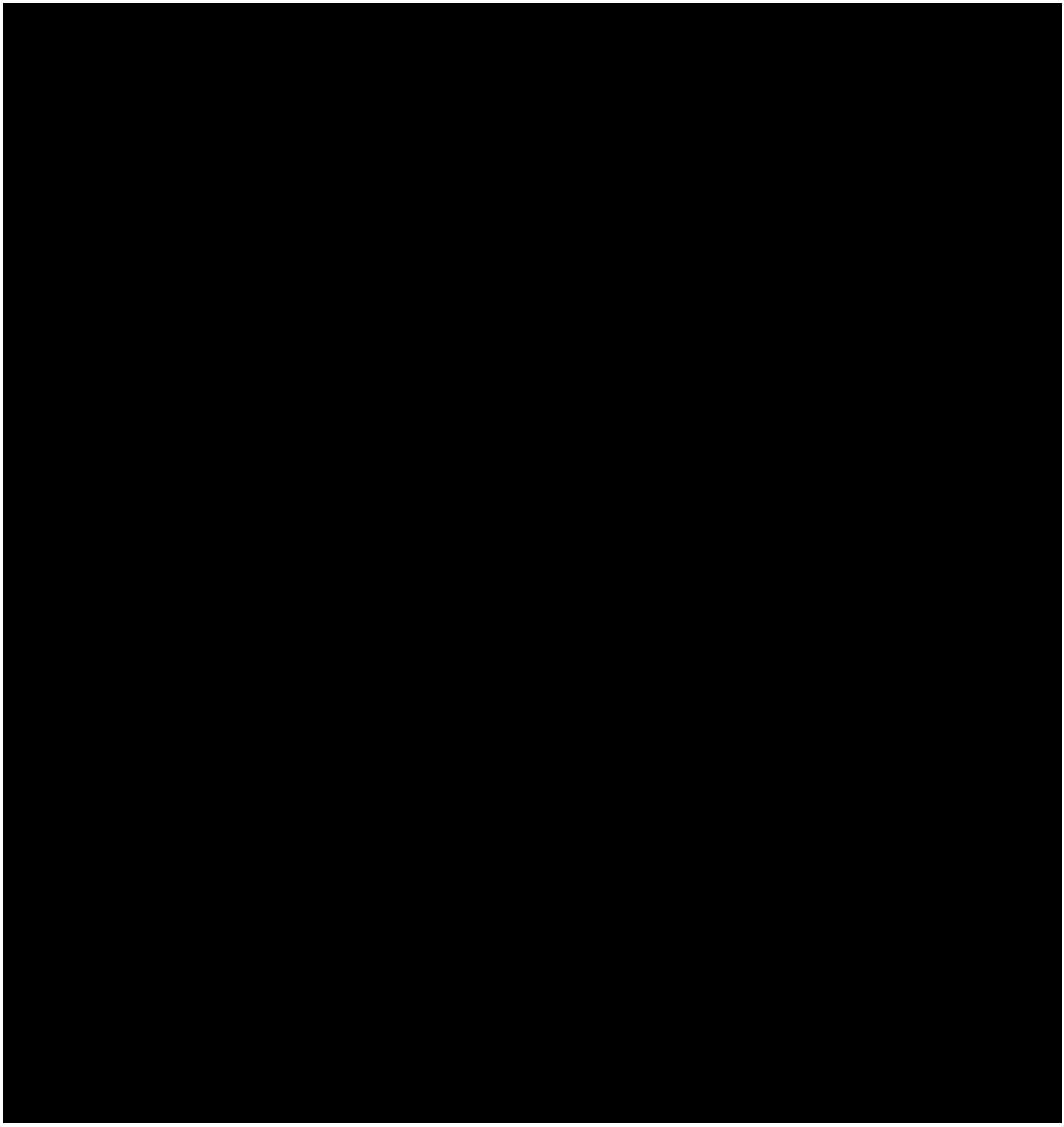
Administration of durvalumab may cause infusion reactions, such as fever, rigors, rash, urticaria, dyspnea, hypotension, and/or nausea.

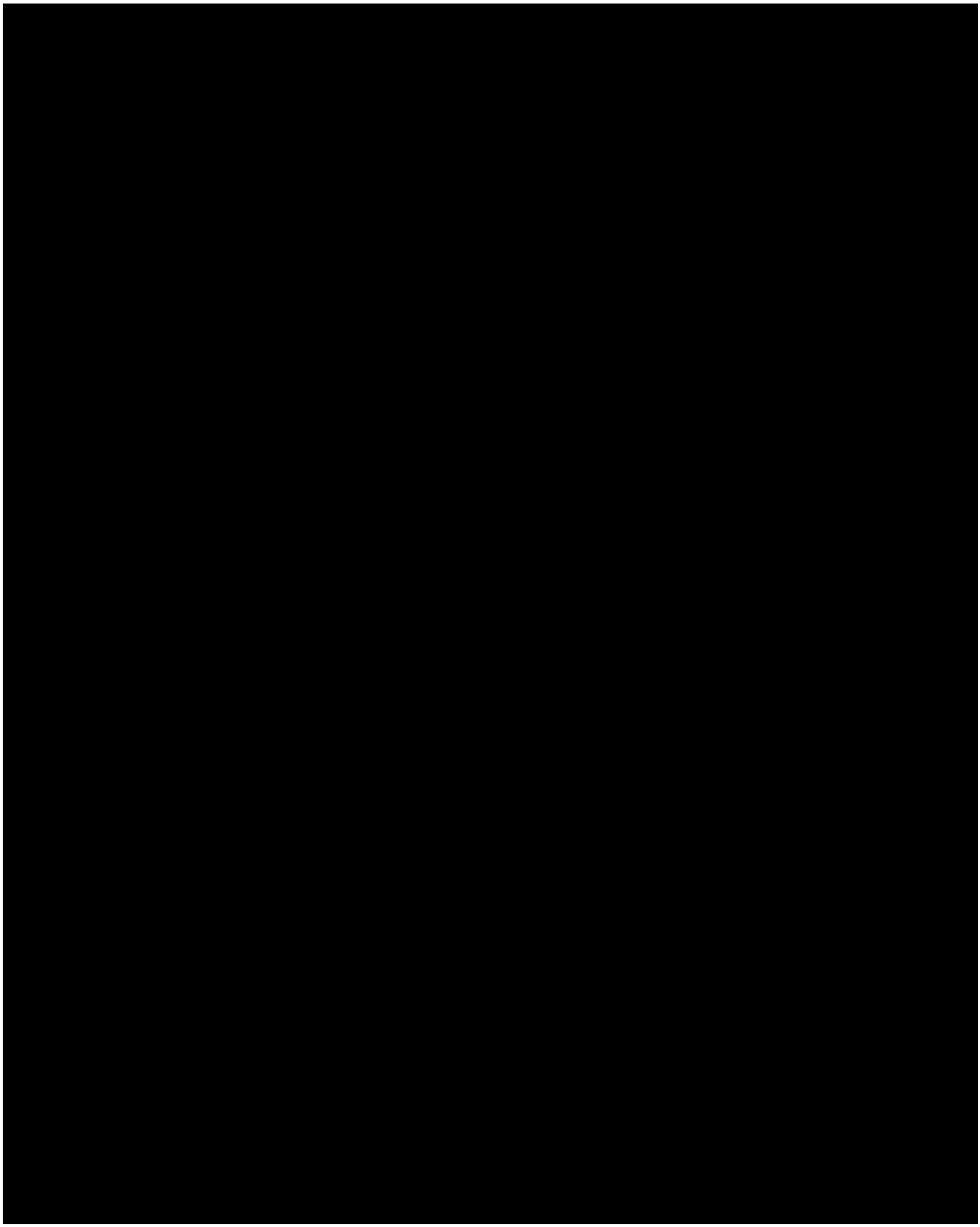
To minimize the risk of infusion reactions, all subjects should be pre-medicated with acetaminophen and diphenhydramine. Mild infusion reactions should be managed expectantly with antipyretics, antihistamines, and anti-emetics. Rigors may be treated with meperidine.

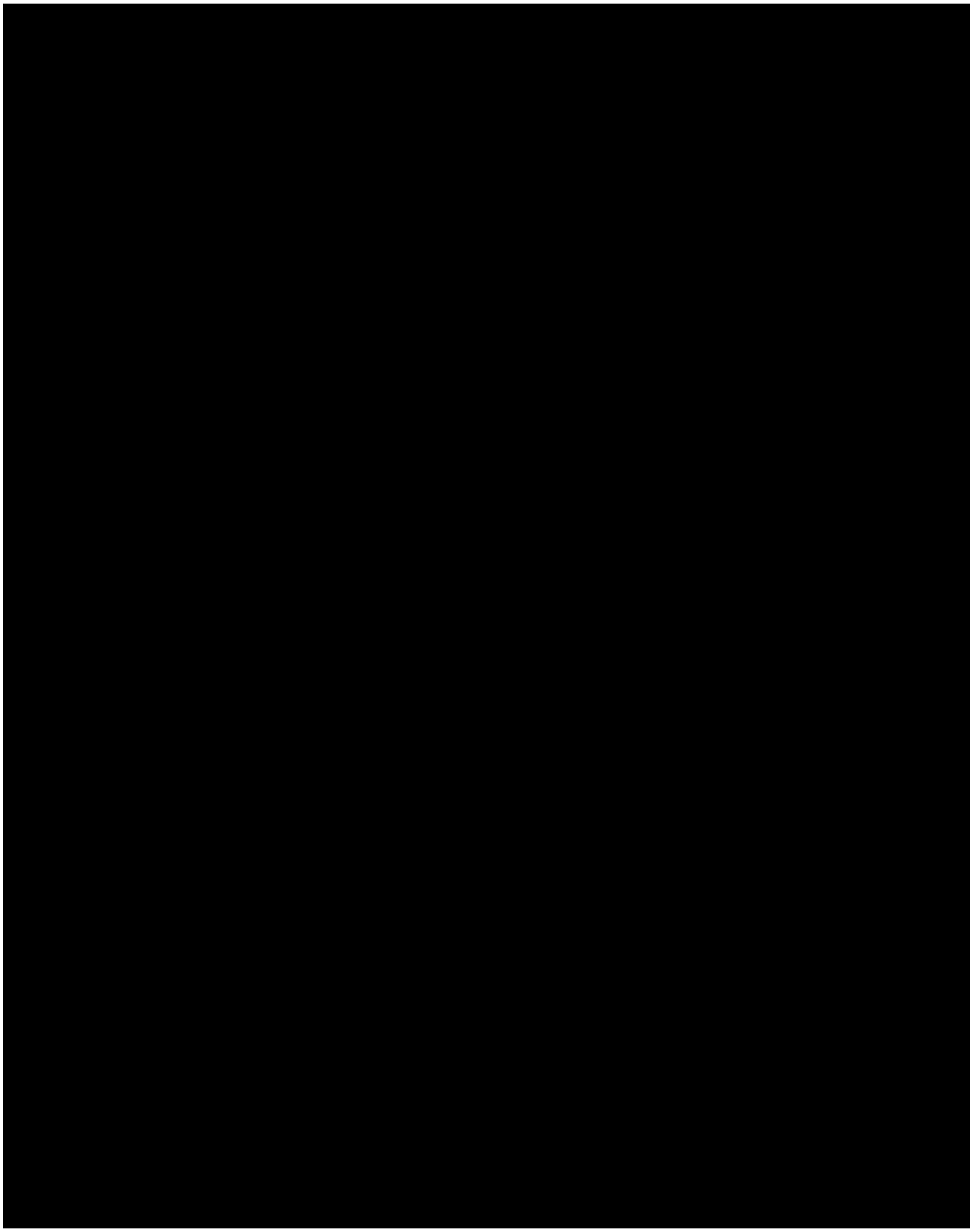
The following guidelines should be followed for infusion reactions:

- Grade 1: administer symptomatic treatment; continue durvalumab administration at the same dose and rate
- Grade 2: stop administration of durvalumab; administer symptomatic treatment, and resume durvalumab administration at a reduced rate of administration only after symptoms resolution

- Grade 3: stop administration of durvalumab, administer symptomatic treatment, and resume at a reduced rate of administration only after symptoms resolve. If Grade 3 reaction recurs, discontinue durvalumab administration
- Grade 4: discontinue administration of durvalumab and administer symptomatic treatment as necessary







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10.6.6. Risks Associated with Ibrutinib

10.6.6.1. Hemorrhage

Fatal bleeding events have occurred in subjects treated with ibrutinib. The mechanism for the bleeding events is not well understood. Ibrutinib may increase the risk of hemorrhage in subjects receiving antiplatelet or anticoagulant therapies and subjects should be monitored for signs of bleeding.

Consider the benefit-risk of withholding ibrutinib for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

10.6.6.2. Infections

Fatal and non-fatal infections (including bacterial, viral, or fungal) have occurred with ibrutinib therapy. Cases of progressive multifocal leukoencephalopathy (PML) and *pneumocystis jirovecii* pneumonia (PJP) have occurred in subjects treated with ibrutinib. Prophylaxis should be considered according to standard of care in subjects who are at increased risk for opportunistic infections. Subjects should be monitored and evaluated for fever and infections and treated appropriately.

10.6.6.3. Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia, thrombocytopenia, and anemia based on laboratory measurements occurred in subjects with B-cell malignancies treated with single agent ibrutinib. Subjects should be monitored monthly with complete blood counts.

10.6.6.4. Cardiac Arrhythmias

Fatal and serious cardiac arrhythmias (ventricular tachyarrhythmias, atrial fibrillation and atrial flutter) have occurred with ibrutinib therapy. These events have occurred particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmias.

Subjects should be periodically monitored clinically for cardiac arrhythmias. An ECG should be performed for subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest pain) or new onset dyspnea. Cardiac arrhythmias should be managed

appropriately, and if it persists, consider the risks and benefits of ibrutinib treatment and follow dose modification guidelines.

10.6.6.5. Hypertension

Hypertension has occurred in subjects treated with ibrutinib with a median time to onset of 4.6 months. Subjects should be monitored for new onset hypertension or hypertension that is not adequately controlled after starting ibrutinib. Existing anti-hypertensive medications should be adjusted and/or anti-hypertensive treatment initiated as appropriate.

10.6.6.6. Tumor Lysis Syndrome

Tumor lysis syndrome has been infrequently reported with ibrutinib therapy. Assess the baseline risk (eg, high tumor burden) and take appropriate precautions. Subjects should be monitored closely and treated as appropriate.

10.6.6.7. Embryo-Fetal Toxicity

Based on findings in animals, ibrutinib can cause fetal harm when administered to a pregnant woman. Administration of ibrutinib to pregnant rats and rabbits during the period of organogenesis caused embryo-fetal toxicity including malformations at exposures that were 2-20 times higher than those reported in subjects with hematologic malignancies. Women should avoid becoming pregnant while taking ibrutinib and for 1 month after stopping the treatment. If ibrutinib is used during pregnancy or if the subject becomes pregnant while taking ibrutinib, the subject should be apprised of the potential hazard to a fetus.

For a comprehensive list of risks of ibrutinib refer to the package insert.

[redacted]

10.6.7.2. Clinical Safety of Nivolumab Monotherapy

Overall, the safety profile of nivolumab monotherapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. There was no pattern in the incidence, severity, or causality of AEs with respect to nivolumab dose level.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the nivolumab IB.

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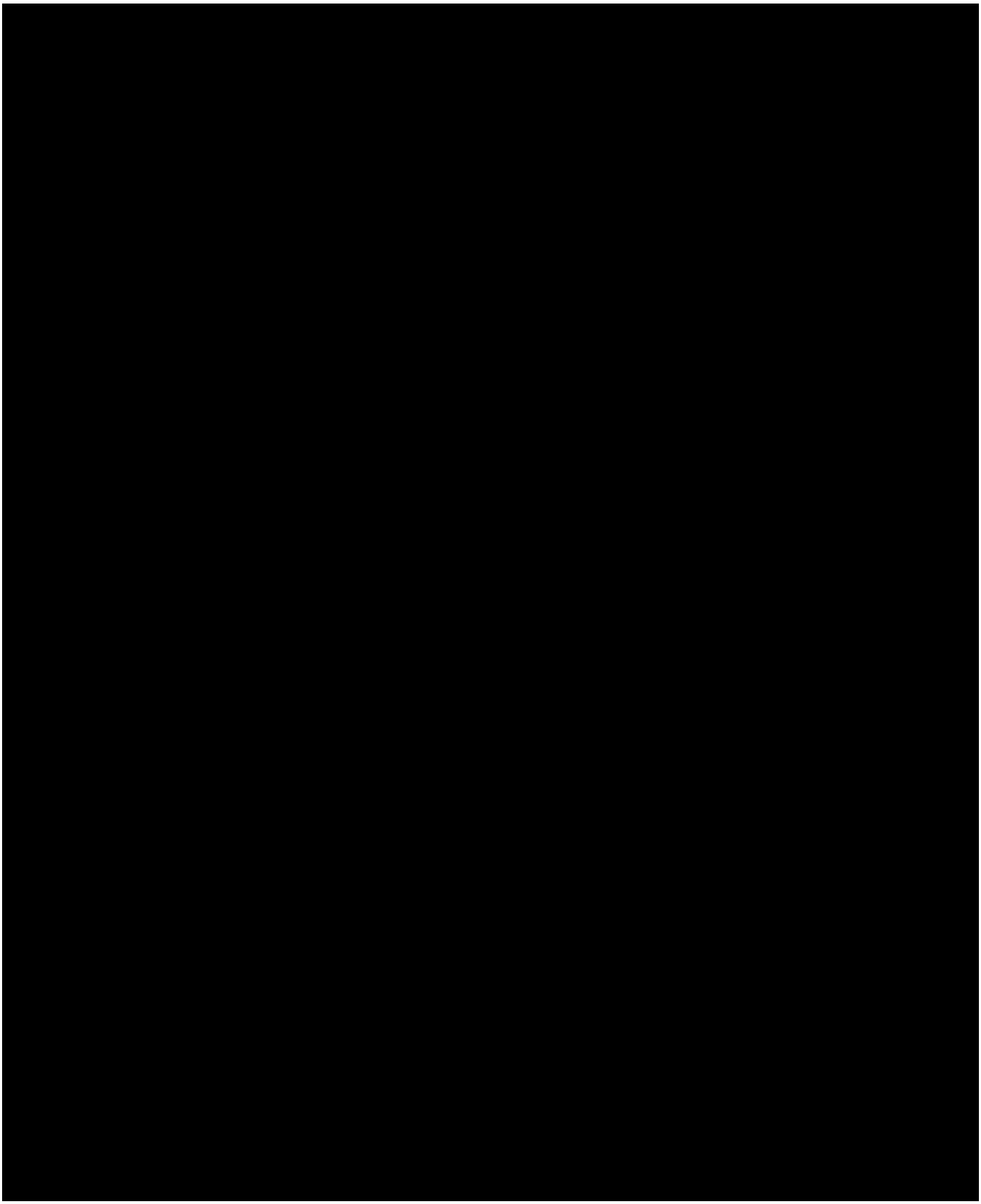
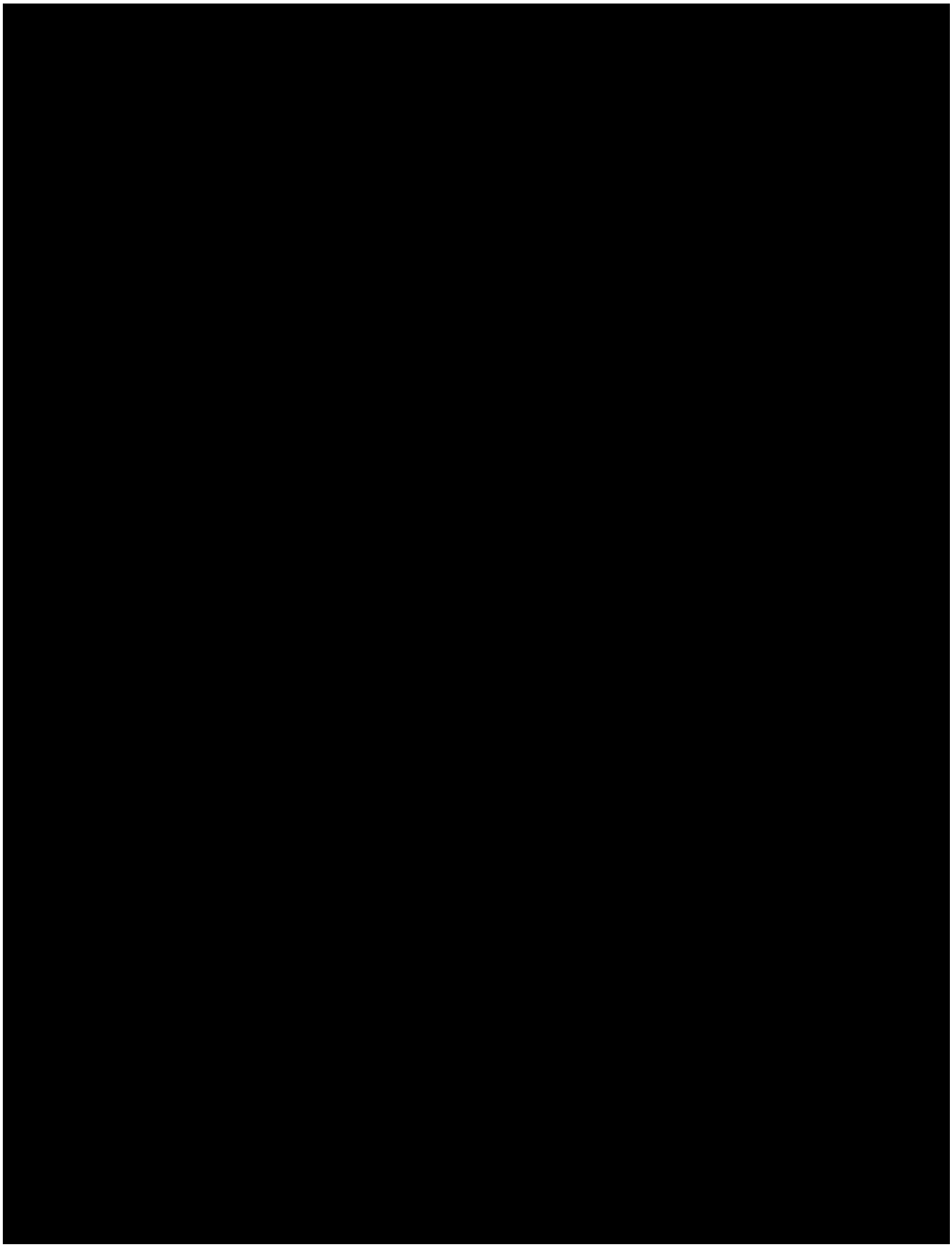
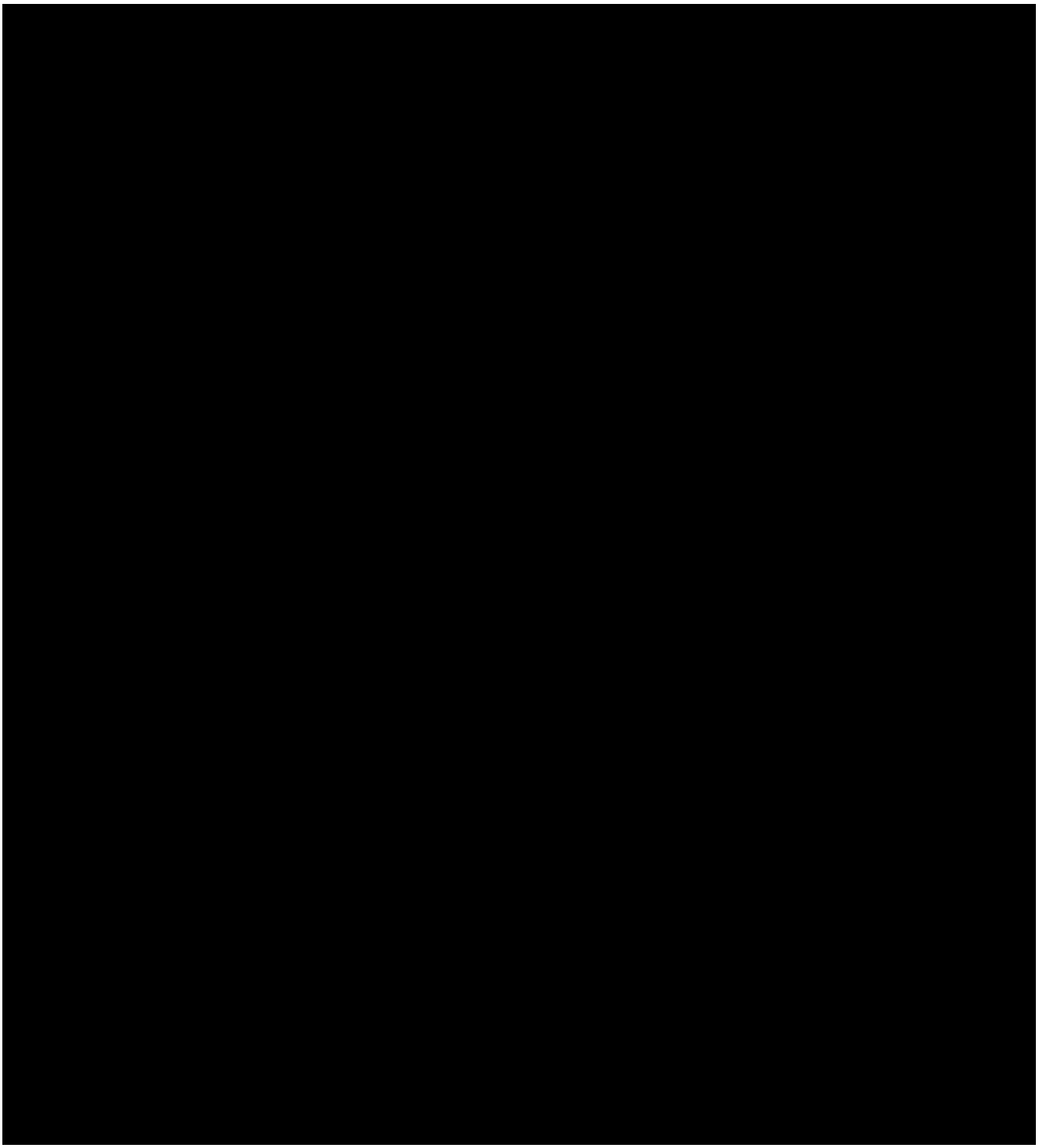




10.6.7.5. Complications of Allogeneic Hematopoietic Stem Cell Transplantation

Complications of allogeneic HSCT after treatment with PD-1/PD-L1 inhibitors including nivolumab, administered before allogeneic HSCT, may be associated with an increased risk of transplant-related complications, including GVHD. Fatal cases have been reported in clinical studies. Study subjects who receive allogeneic HSCT after relatlimab and/or nivolumab should be monitored closely for early evidence of transplant-related complications and prompt interventions should be implemented.



10.7. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to JCAR017, or to the combination agent based on the respective IBs for durvalumab, CC-122, CC-220, CC-99282, nivolumab, relatlimab, or PI for ibrutinib.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, suspected unexpected serious adverse reactions (SUSARs) in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Celgene and the IRB/EC (see Section 14.3 for record retention information).

[redacted]

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Manufacturing failure
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/contract research organization Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, IP will be identified on the package labeling.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Council for Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions, including obligations of confidentiality of Celgene information. The Investigator should maintain a list of Sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent form (ICF) and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original ICF signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the ICF must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the ICF. The revised ICF signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. Protocol Amendments

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the ICF should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc).

In addition, the Investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene standard operating procedures (SOPs). These data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. The Investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed ICFs for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

15.3. Product Quality Compliant

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. Product Quality Complaints may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subject. Examples of PQCs include (but are not limited to): mixed product,

mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [redacted]

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

17. REFERENCES

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18. APPENDICES

APPENDIX A. TABLE OF ABBREVIATIONS

Table 33: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ABC	Activated B-cell like
[redacted]	[redacted]
ADCC	Antibody dependent T cell mediated toxicity
ADL	Activity of daily life
AE	Adverse event
AED	Antiepileptic drug
AESI	Adverse event of special interest
ALL	Acute lymphoblastic leukemia
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
ATA	Anti-therapeutic antibody
[redacted]	[redacted]
β-hCG	Beta-human chorionic gonadotropin
BCR	B-cell receptor
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BNP	Brain natriuretic peptide
BOIN	Bayesian Optimal Interval Design
BTK	Bruton's tyrosine kinase
CAR	Chimeric antigen receptor
CBC	Complete blood count
CCGs	CRF completion guidelines
CD	Cluster of differentiation
CELMoD	Cereblon E3 ligase modulator
[redacted]	[redacted]
Chemo	Chemotherapy
cHL	Classical Hodgkin lymphoma
CHO	Chinese hamster ovary
CI	Confidence intervals

Abbreviation or Specialist Term	Explanation
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum concentration
CMV	Cytomegalovirus
CNS	Central nervous system
COO	Cell of origin
CR	Complete response
CRBN	Cereblon
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRF	Case report form
CRP	C-reactive protein
CRR	Complete response rate
CRS	Cytokine release syndrome
CSF	Cerebrospinal fluid
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
DHL	Double-hit lymphoma
DL	Dose level
DLBCL	Diffuse large B-cell lymphoma
DLI	Donor lymphocyte infusion
DLT	Dose-limiting toxicity
DMSO	Dimethyl sulfoxide
[redacted]	[redacted]
DOR	Duration of response
DSMB	Data safety monitoring board
DVT	Deep venous thrombosis
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or Specialist Term	Explanation
EEA	European Economic Area
EEG	Electroencephalogram
EFS	Event-free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EOI	End of infusion
EORTC -QLQ-C30	European Organisation for Research and Treatment of Cancer – Quality of Life C30 Questionnaire
EOS	End of study
EQ-5D-5L	European Quality of Life-5 Dimensions health state classifier to 5 Levels
EU	European Union
Fc	Fragment crystallizable
FCBP	Female of child bearing potential
FDA	Food and Drug Administration
FGL-1	Fibrinogen-like protein 1
FL	Follicular lymphoma
flu/ cy	Fludarabine/ cyclophosphamide
GCB	Germinal center-like
GCP	Good Clinical Practice
[redacted]	[redacted]
[redacted]	[redacted]
GI	Gastrointestinal
GM-CSF	Granulocyte-macrophage colony stimulating factor
GVHD	Graft versus host disease
HBcAB	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Human cancer cells
HIF	Hypoxia-inducible factor
HIV	Human immunodeficiency virus

Abbreviation or Specialist Term	Explanation
HLA	Human leukocyte antigen
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplant
IB	Investigator's brochure
IBC	Institutional biosafety committee
ICF	Informed consent form
ICH	International council for harmonisation
ICU	Intensive care unit
IEC	Independent ethics committee
IFN-γ	Interferon gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IKZF1	Ikaros family zinc finger proteins 1
IL	Interleukin
IND	Investigational New Drug
IO	Immuno-oncology
IP	Investigational product
IPI	International Prognostic Index
irAE	Immune-related adverse event
IRB	Institutional review board
IRT	Interactive response technology
ITK	IL-2 inducible T cell kinase
IUD	Intrauterine device
IV	Intravenous
IVIG	Intravenous immunoglobulins
LAG-3	Lymphocyte activation gene 3
LD	Lymphodepleting
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
mAb	Monoclonal antibody

Abbreviation or Specialist Term	Explanation
MAS	Macrophage activation syndrome
MCL	Mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MM	Multiple myeloma
[redacted]	[redacted]
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multi-gated acquisition scan
NaCl	Sodium chloride
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NOS	Not otherwise specified
NSAIDs	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung cancer
NT	Neurotoxicity
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
Pd	Pharmacodynamics
PD	Progressive disease
PD1	Programmed cell death 1
PD-L	Programmed cell death ligand
PE	Pulmonary embolism
PET	Positron emission tomography
PFS	Progression-free survival
PI	Package insert / Prescribing information
PK	Pharmacokinetics
PLCγ	Phosphoinositide phospholipase C-γ

Abbreviation or Specialist Term	Explanation
PMBCL	Primary mediastinal large B-cell lymphoma
PO	Per os (oral)
PPDP	Protocol product deviation plan
PPK	Population pharmacokinetics
PPRMP	Pregnancy prevention and risk management plan
PQC	Product quality complaint
PR	Partial response
PT	Preferred term
q3m	Every 3 months
Q2W	Every 2 weeks
Q4W	Every 4 weeks
QD	Every day
[redacted]	[redacted]
RCC	Renal cell carcinoma
R-CHOP	Rituximab- cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone
[redacted]	[redacted]
RP2D	Recommended Phase 2 dose and schedule
[redacted]	[redacted]
R/R	Relapsed or refractory
SAE	Serious adverse event
SaO_2	Oxygen saturation
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of the head and neck
scFv	Single chain variable fragment
sCRS	Severe cytokine release syndrome
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SLE	Systemic lupus erythematosus
SLL	Small lymphocytic lymphoma
SOC	System organ class

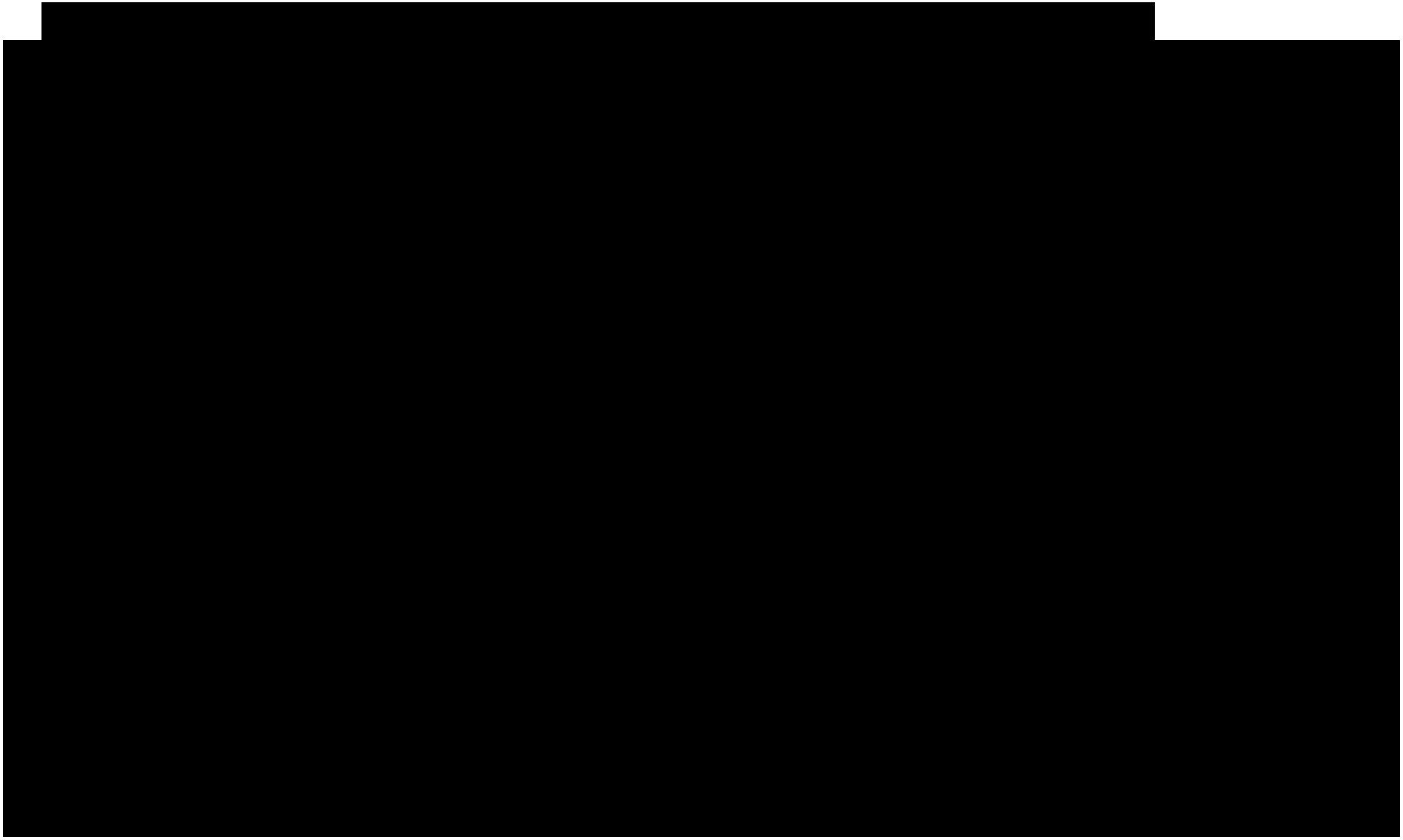
Abbreviation or Specialist Term	Explanation
SOP	Standard operating procedure
SPD	Sum of product of perpendicular diameters
SRC	Safety review committee
SUSAR	Suspected unexpected serious adverse reaction
TCR	T cell receptor
TEAE	Treatment-emergent adverse events
TFR	Tumor flare reaction
THL	Triple-hit lymphoma
TIL	Tumor-infiltrating lymphocytes
TLS	Tumor lysis syndrome
TNF	Tumor necrosis factor
TnI	Troponin I
TNM	Tumor, nodes, metastasis
TnT	Troponin T
Treg	Regulatory T cell
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
US/ USA	United States/ United States of America
VTE	Venous thromboembolism
WHO	World Health Organization

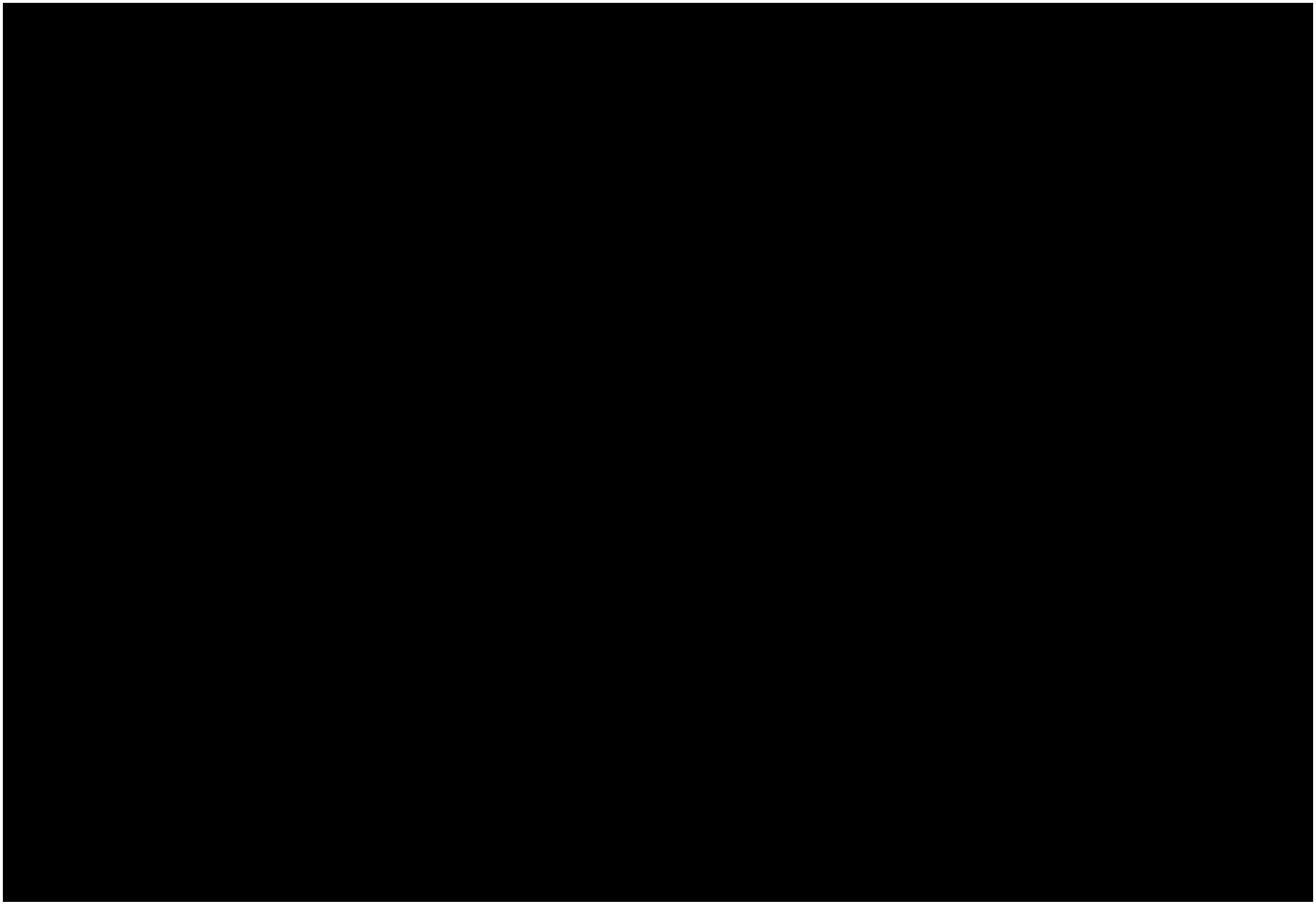
APPENDIX B. PERFORMANCE STATUS BY EASTERN COOPERATIVE ONCOLOGY GROUP SCALE

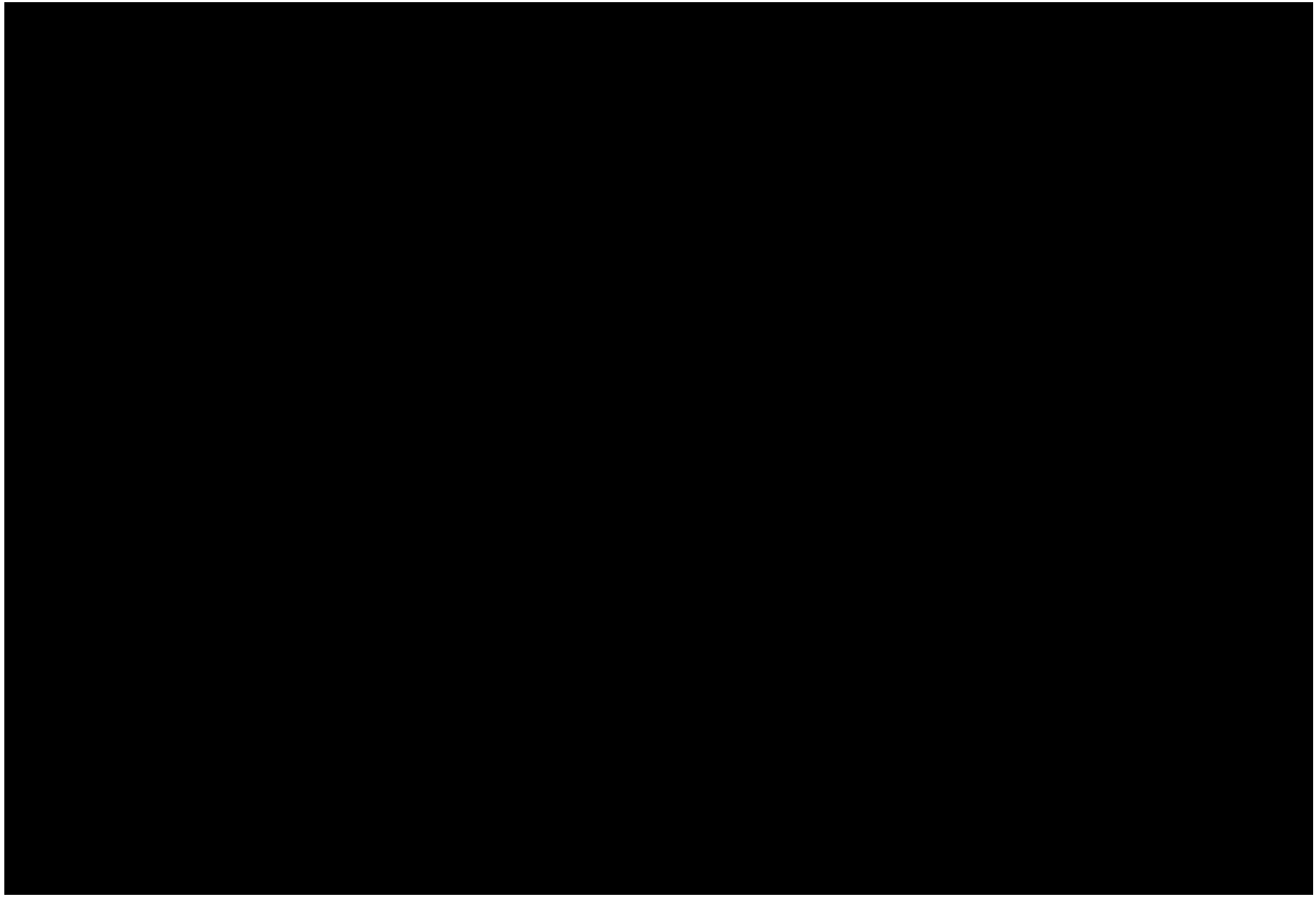
Table 34: Performance Status by Eastern Cooperative Oncology Group Scale

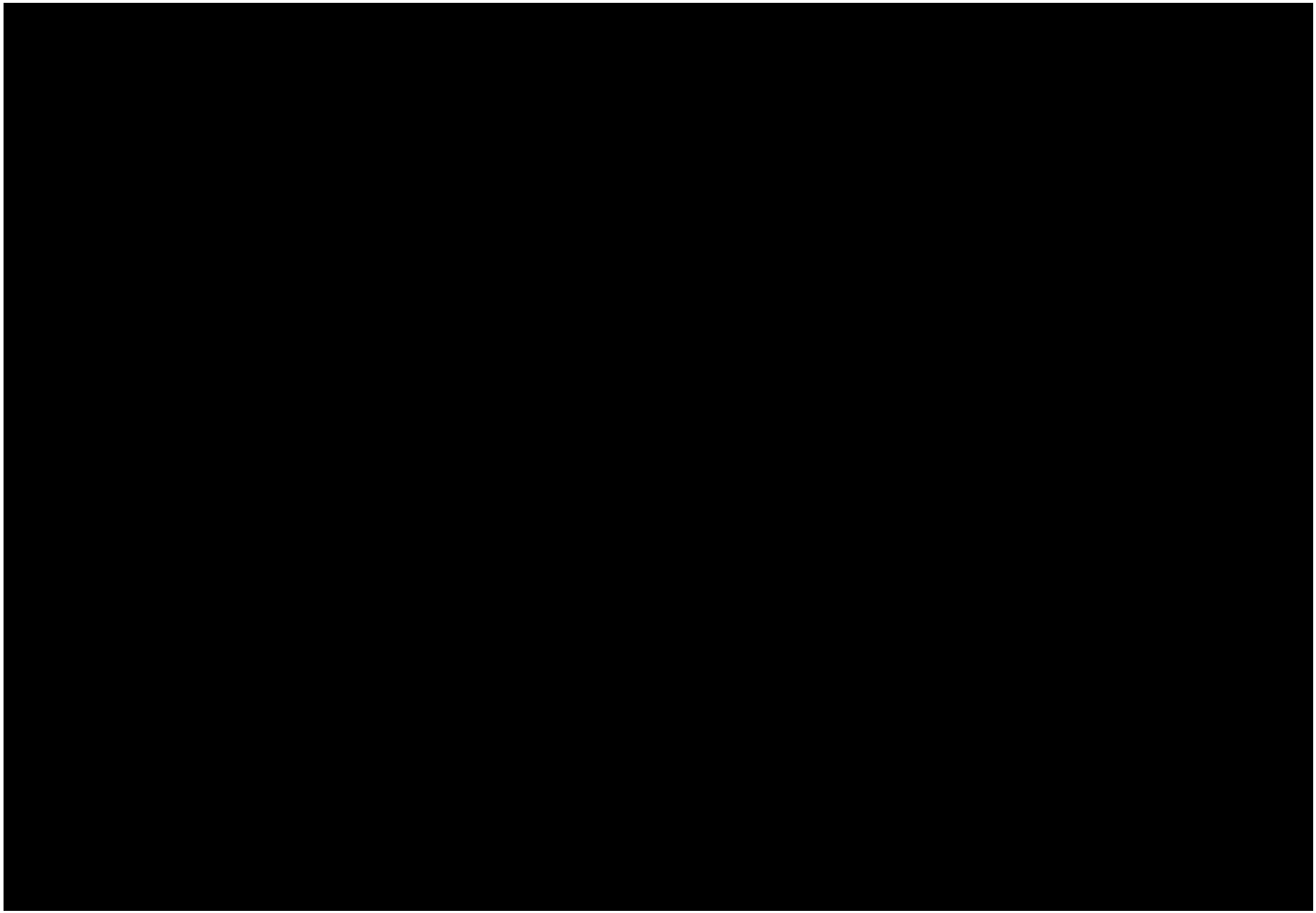
Score	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Oken, 1982.









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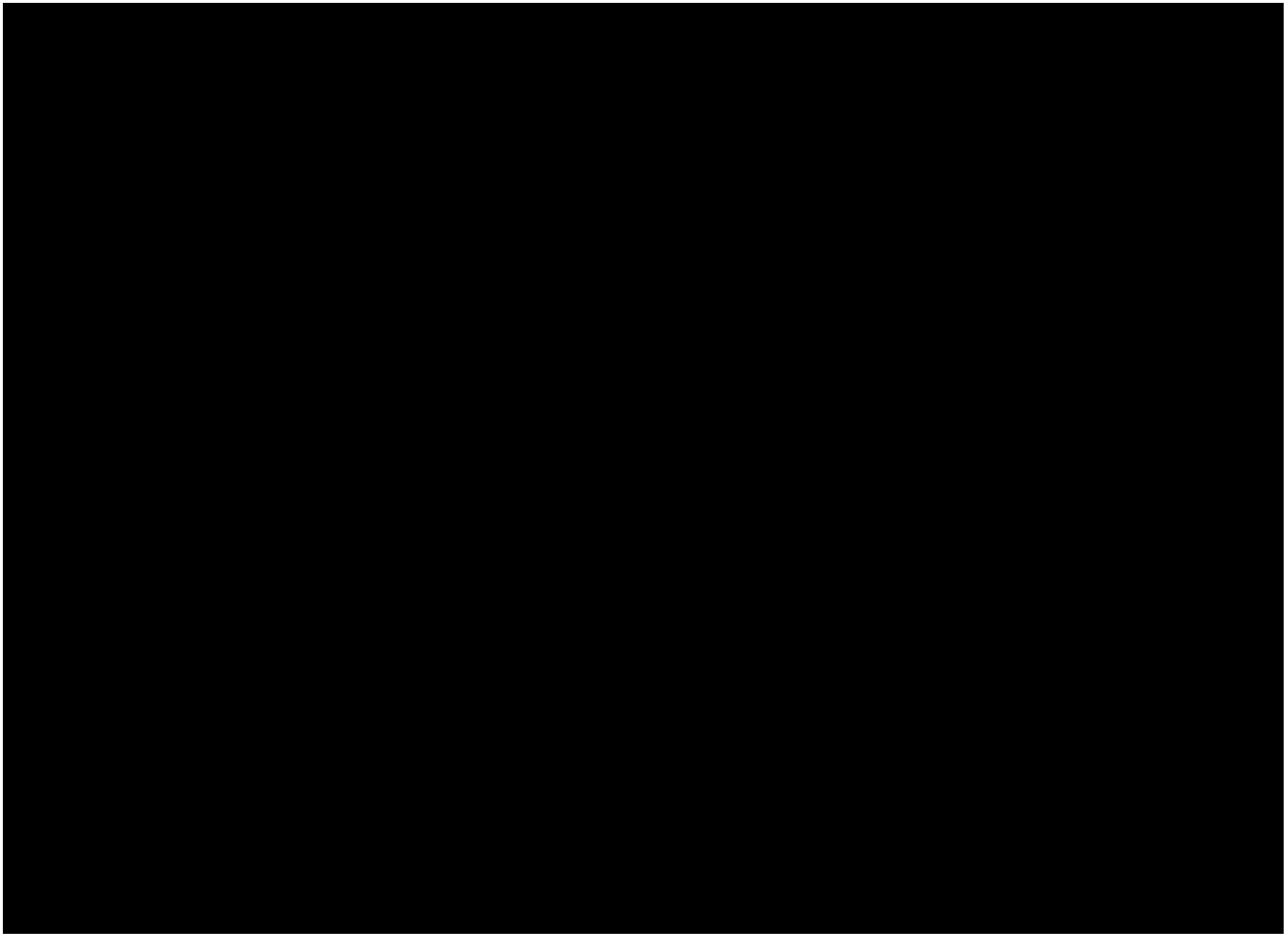

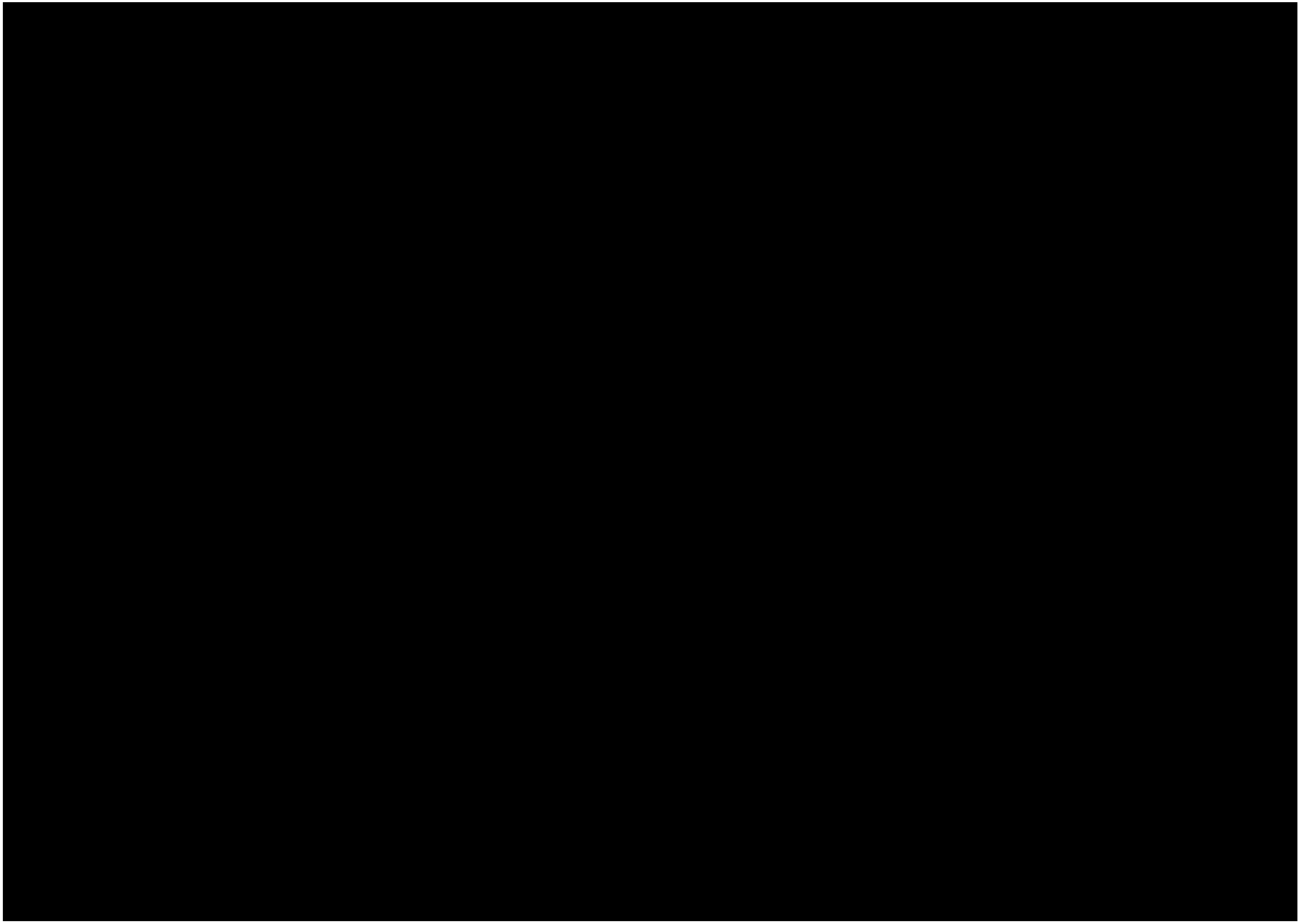

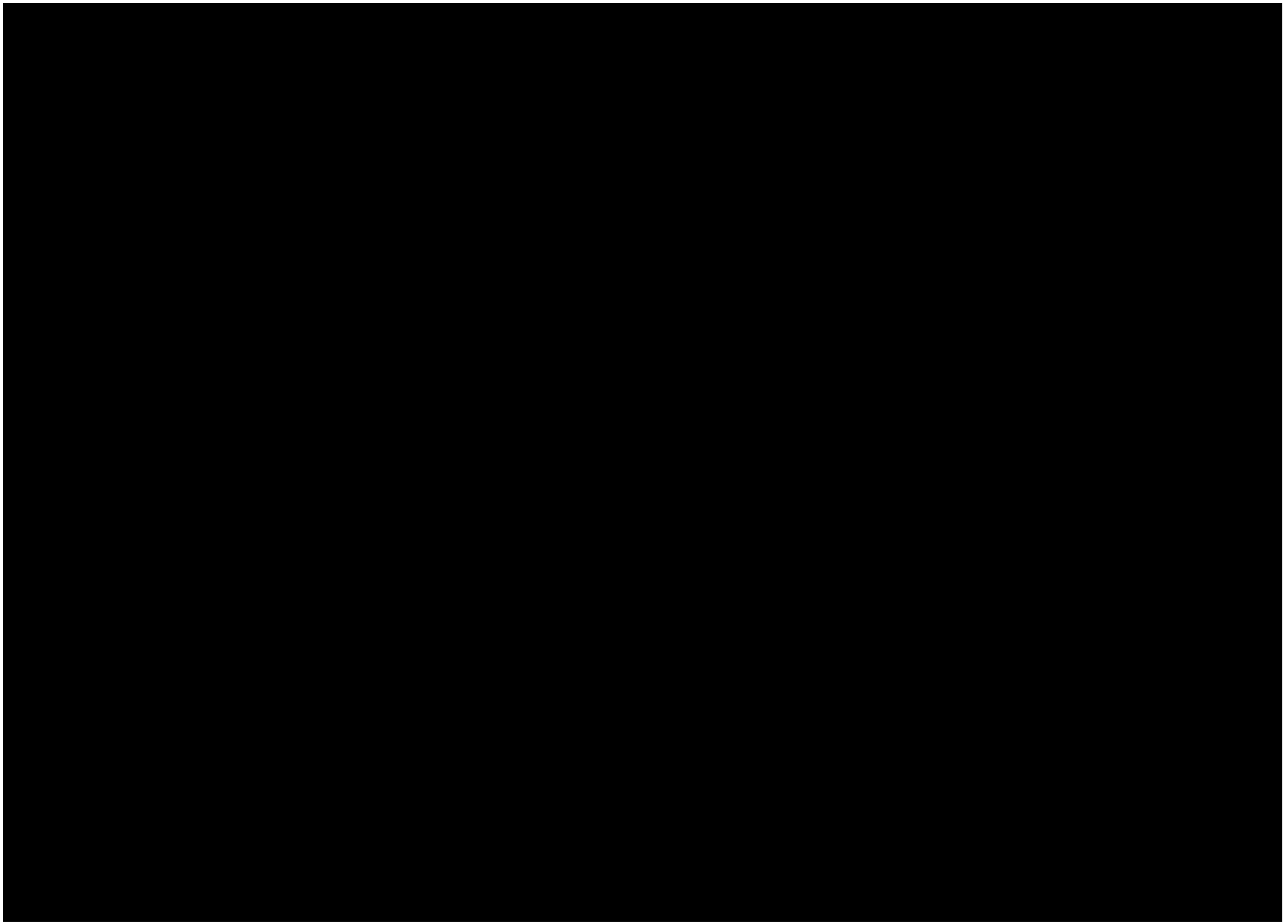

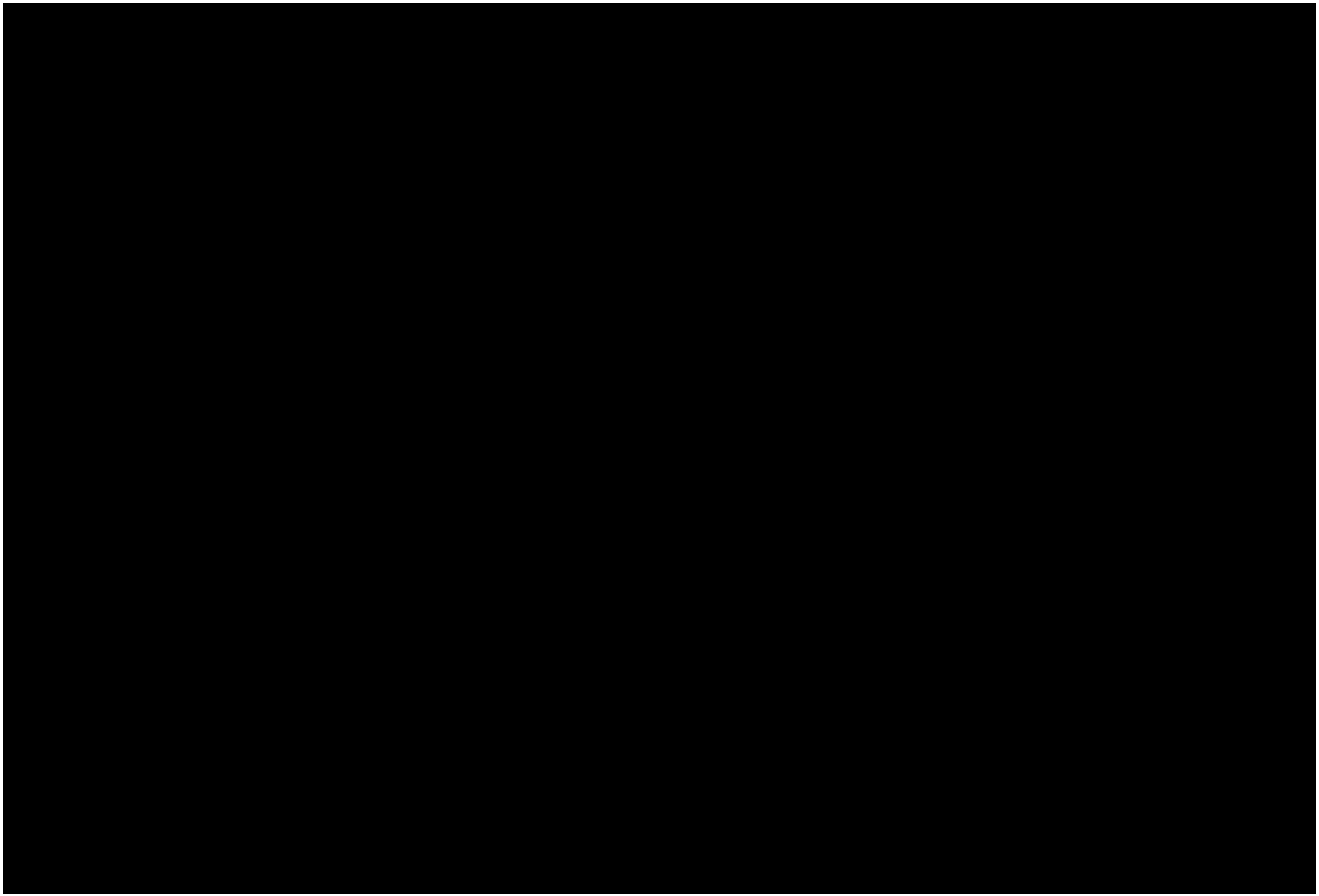

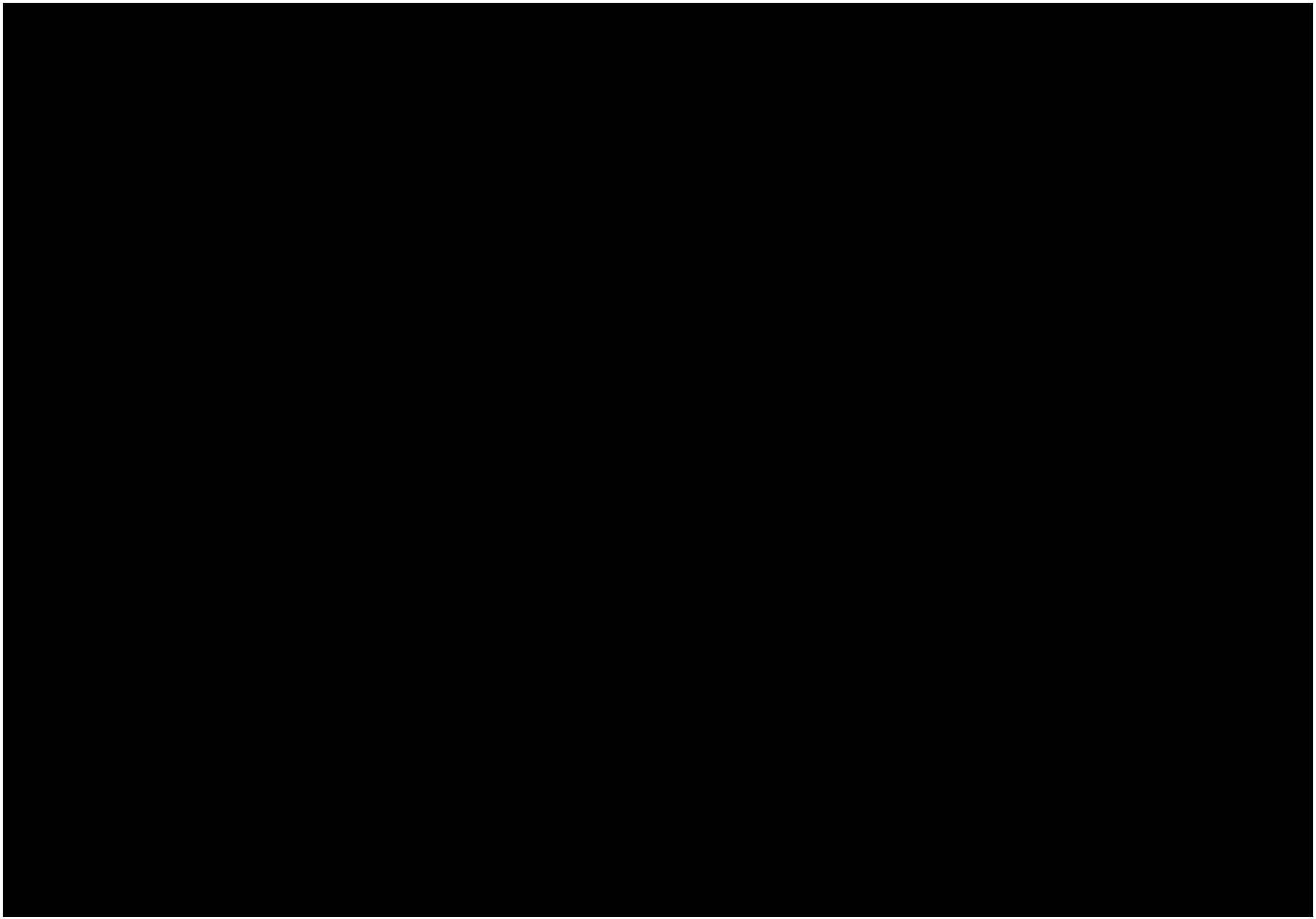

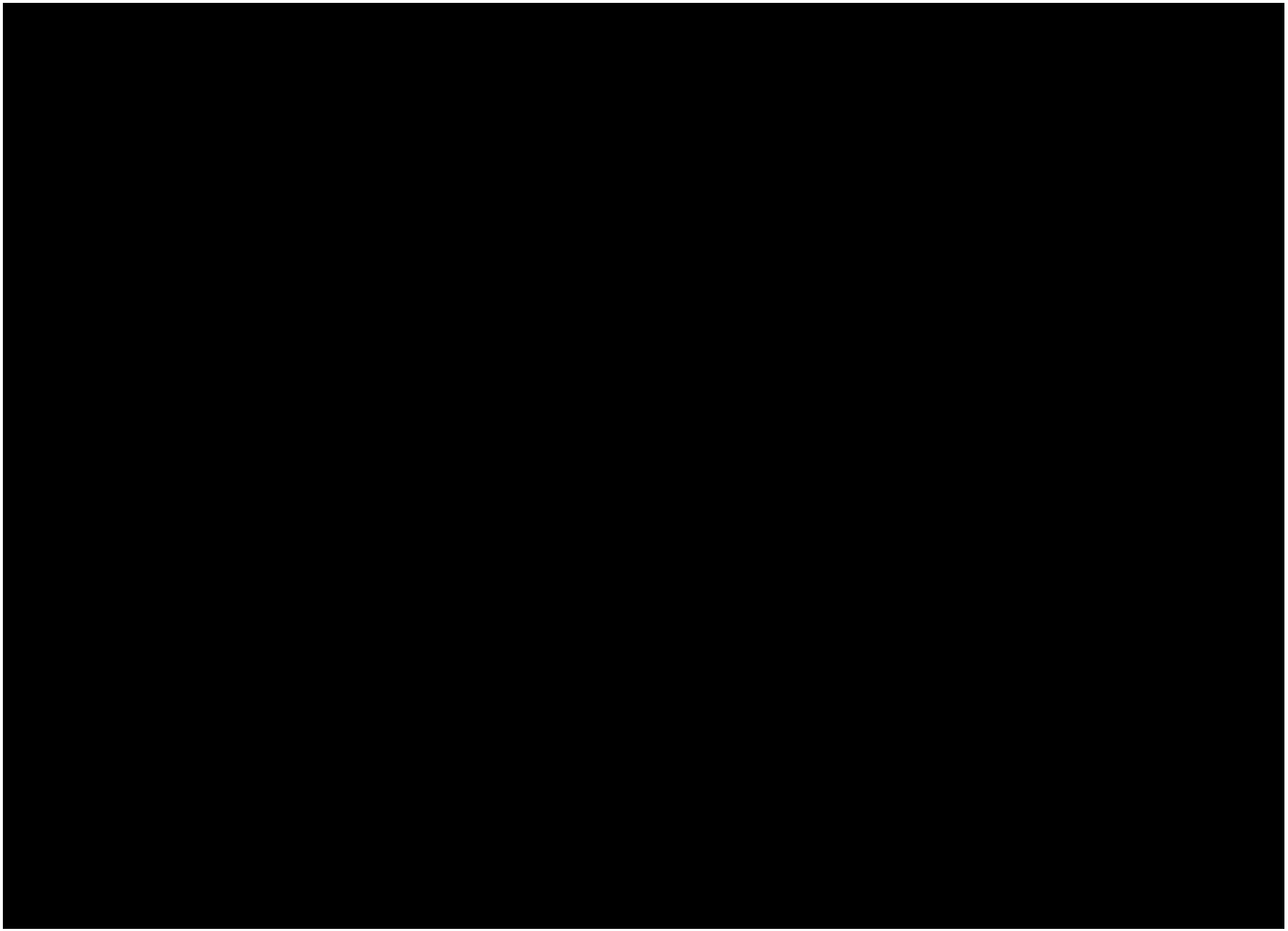

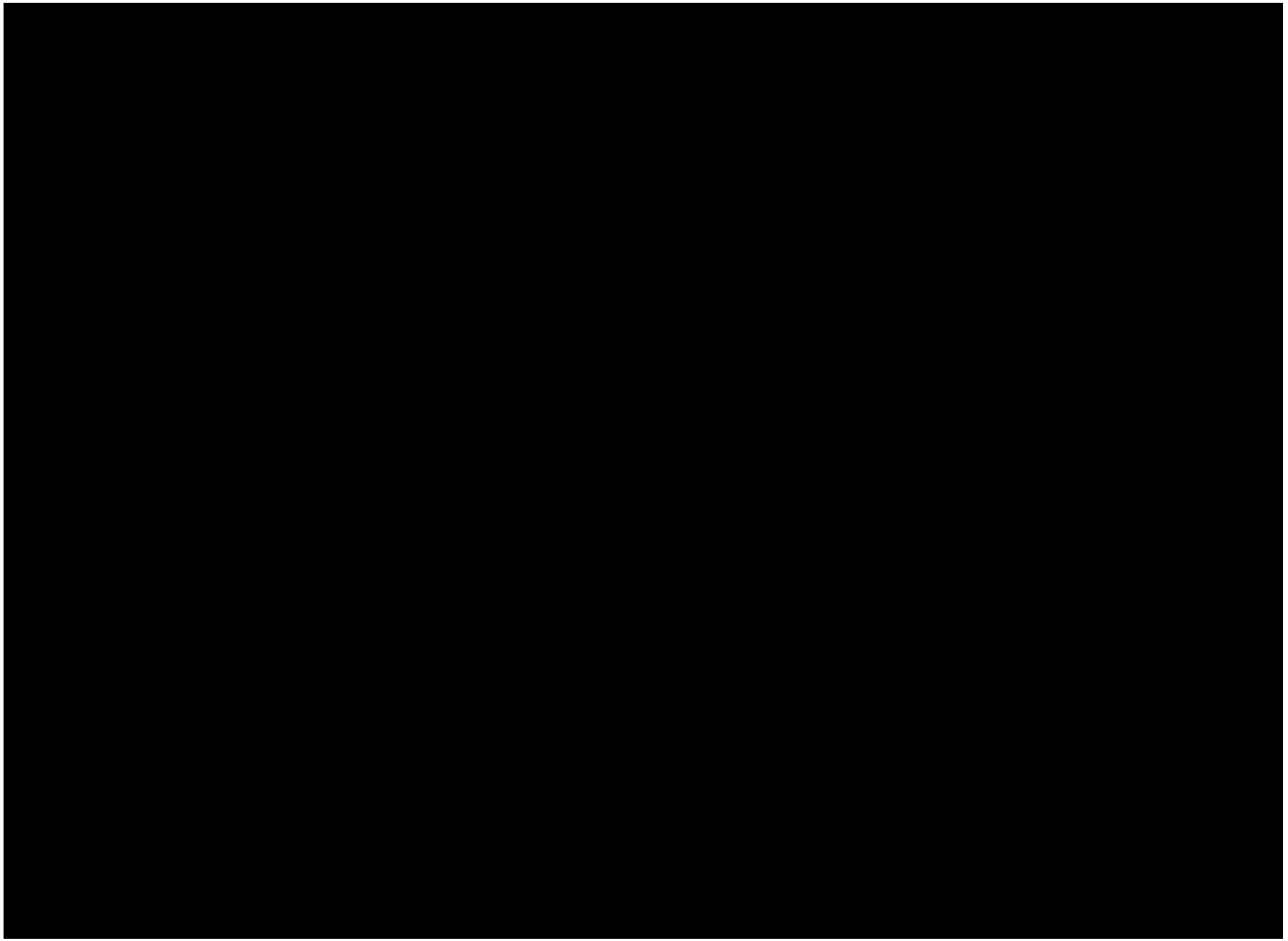

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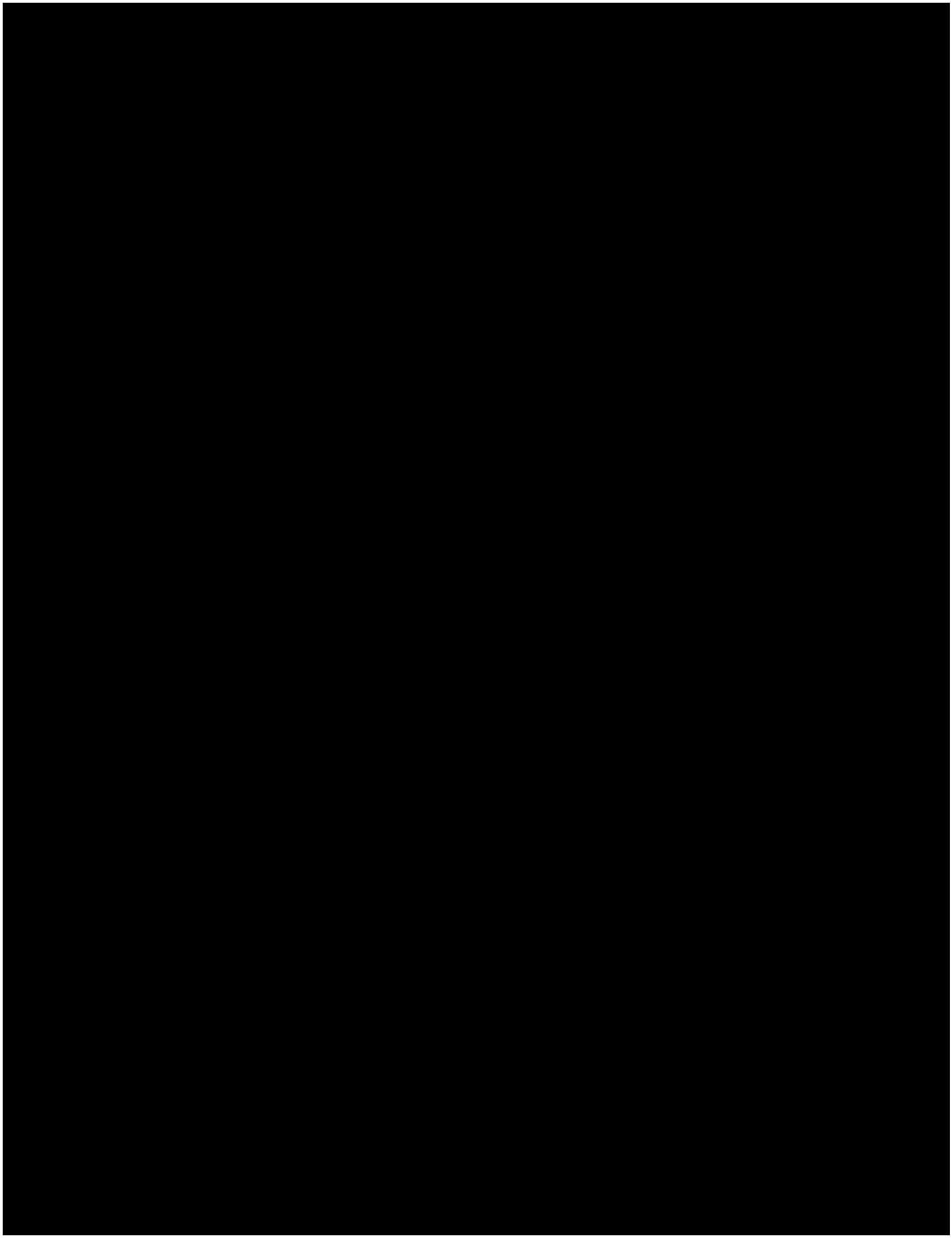
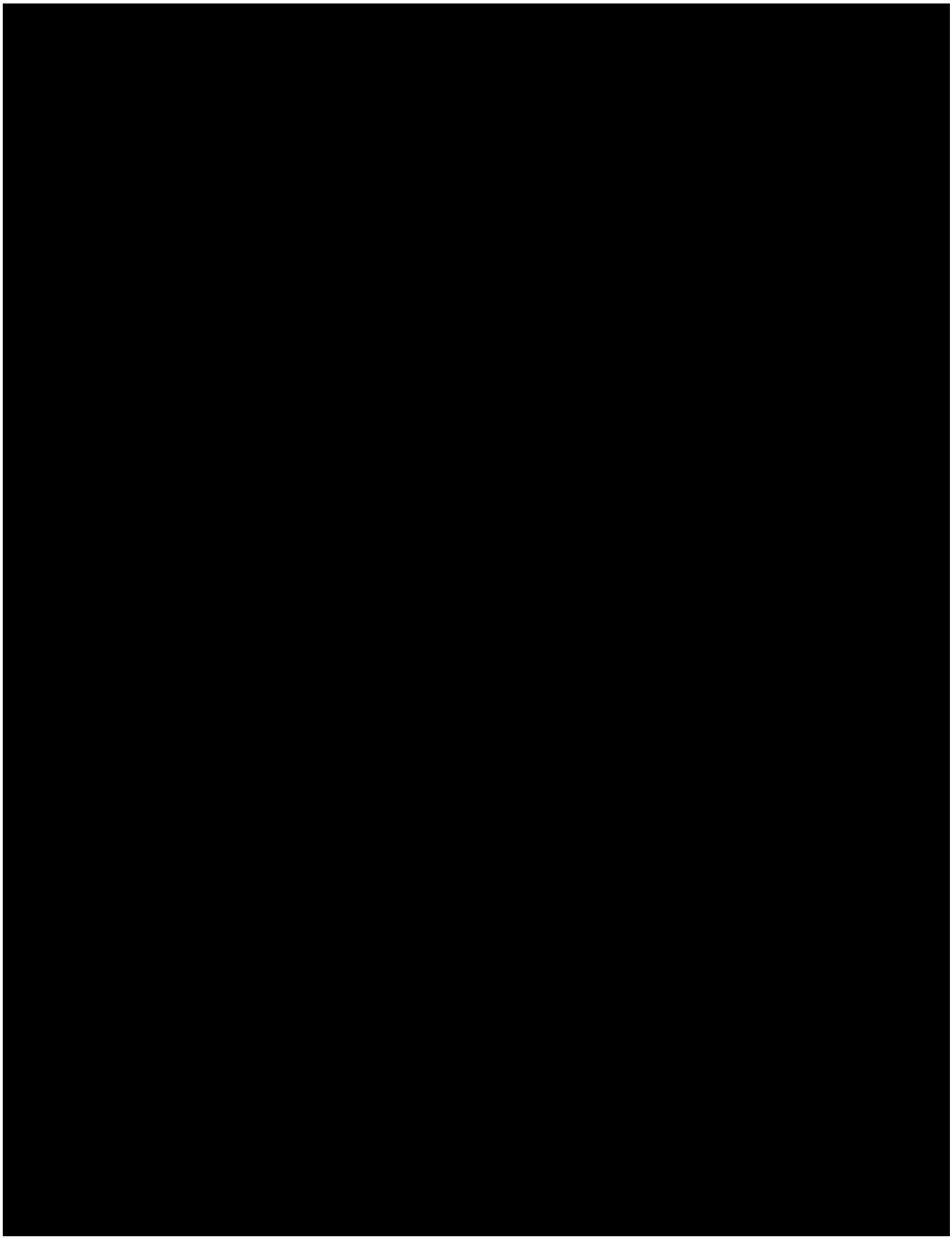
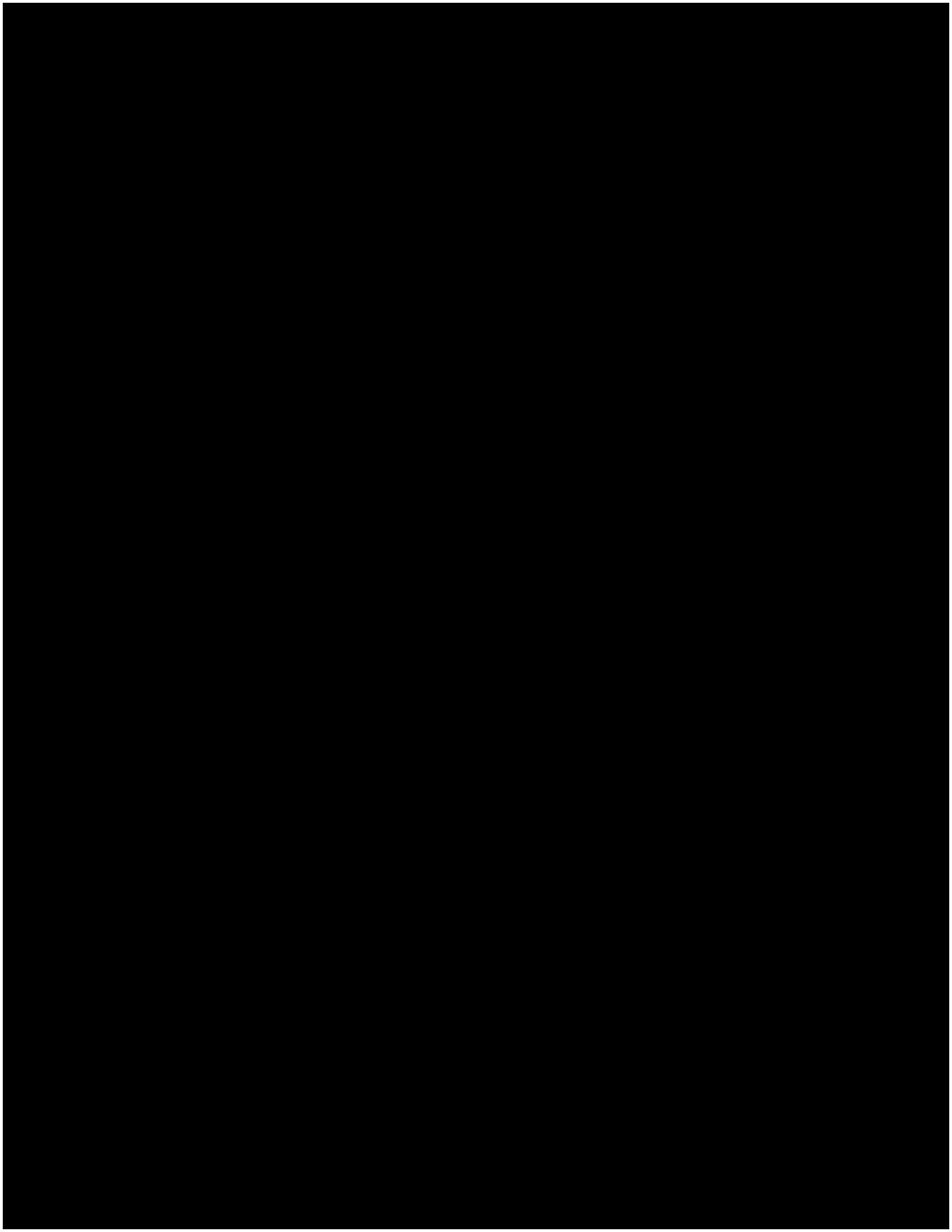
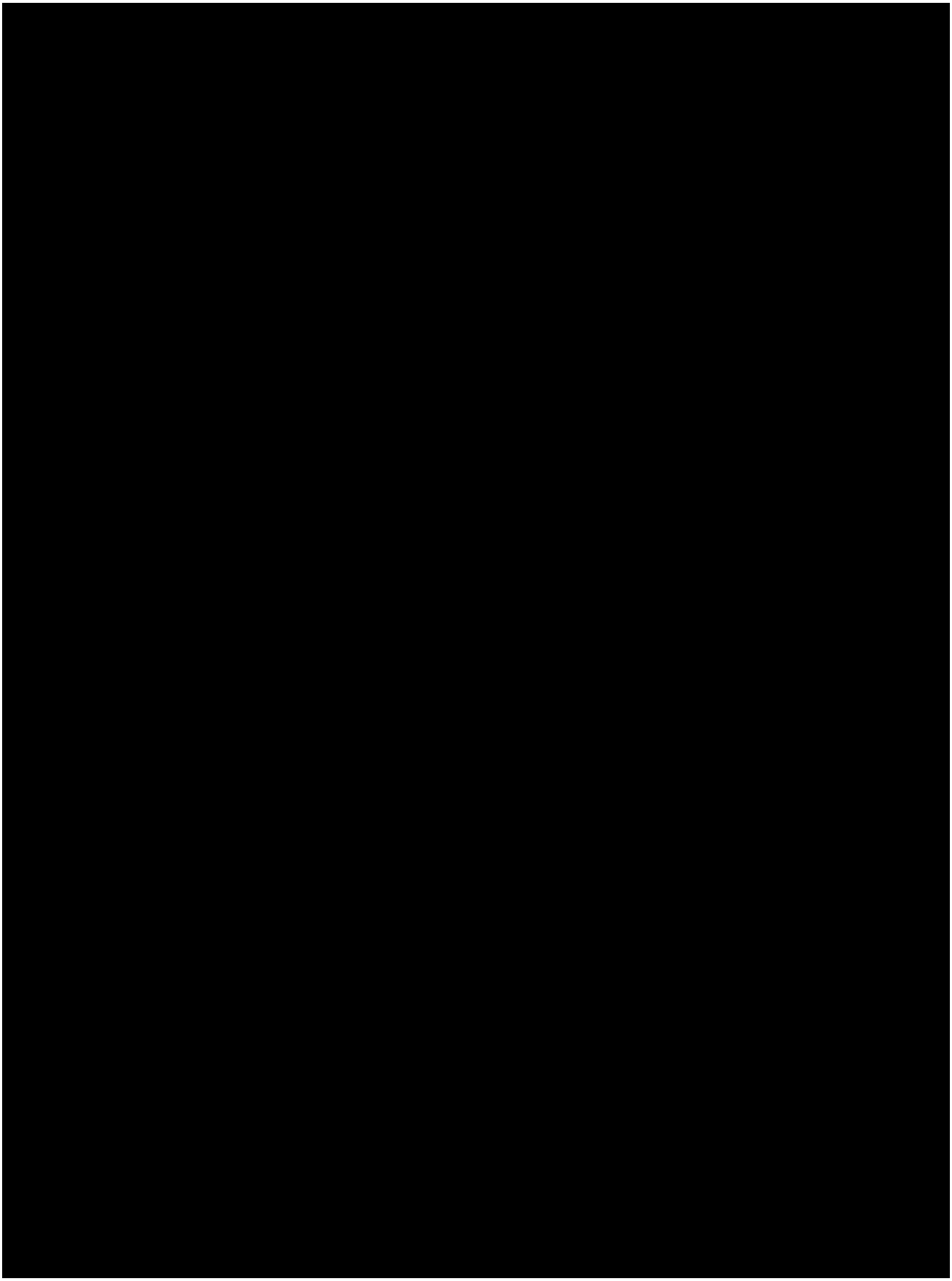
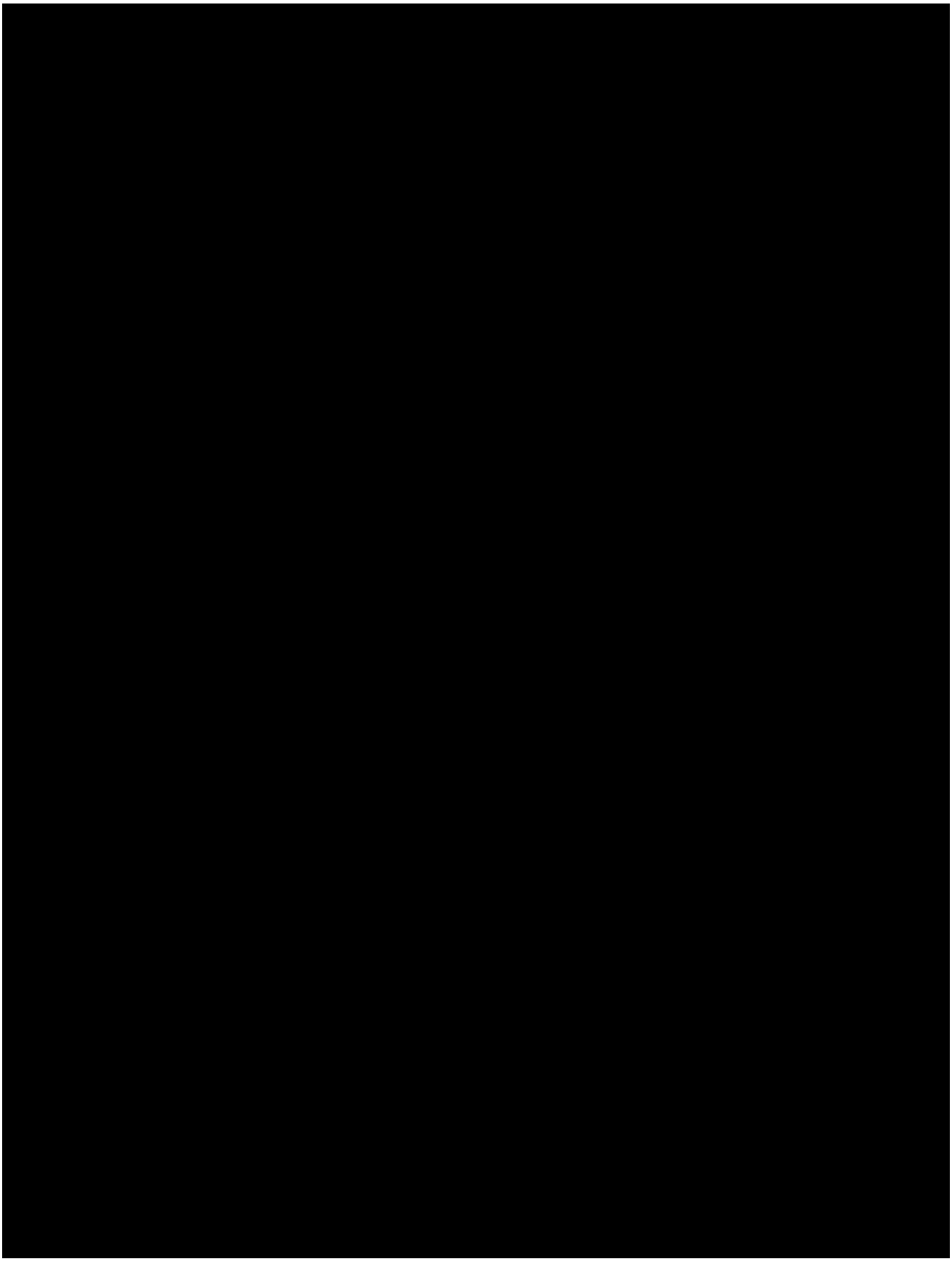
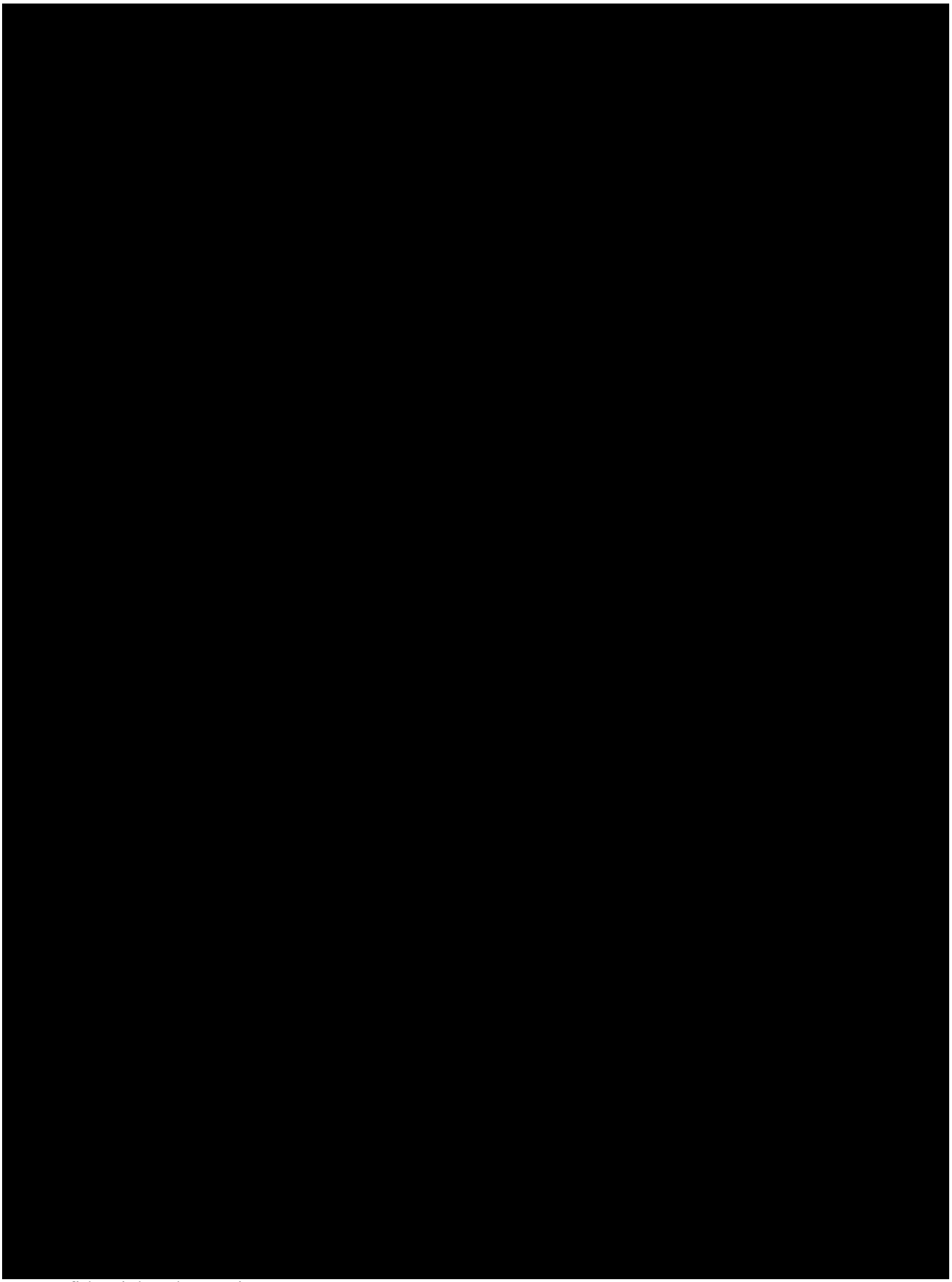


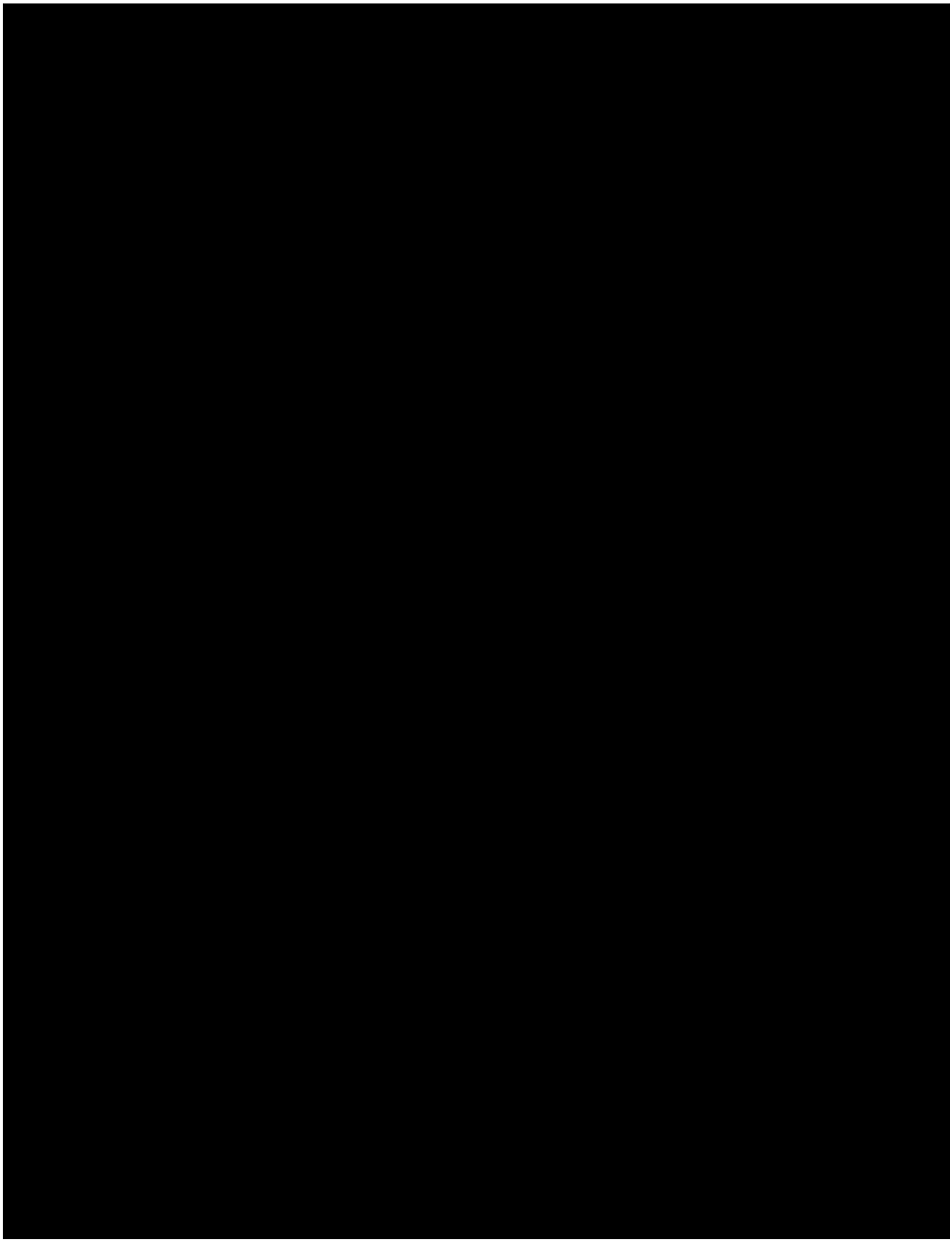


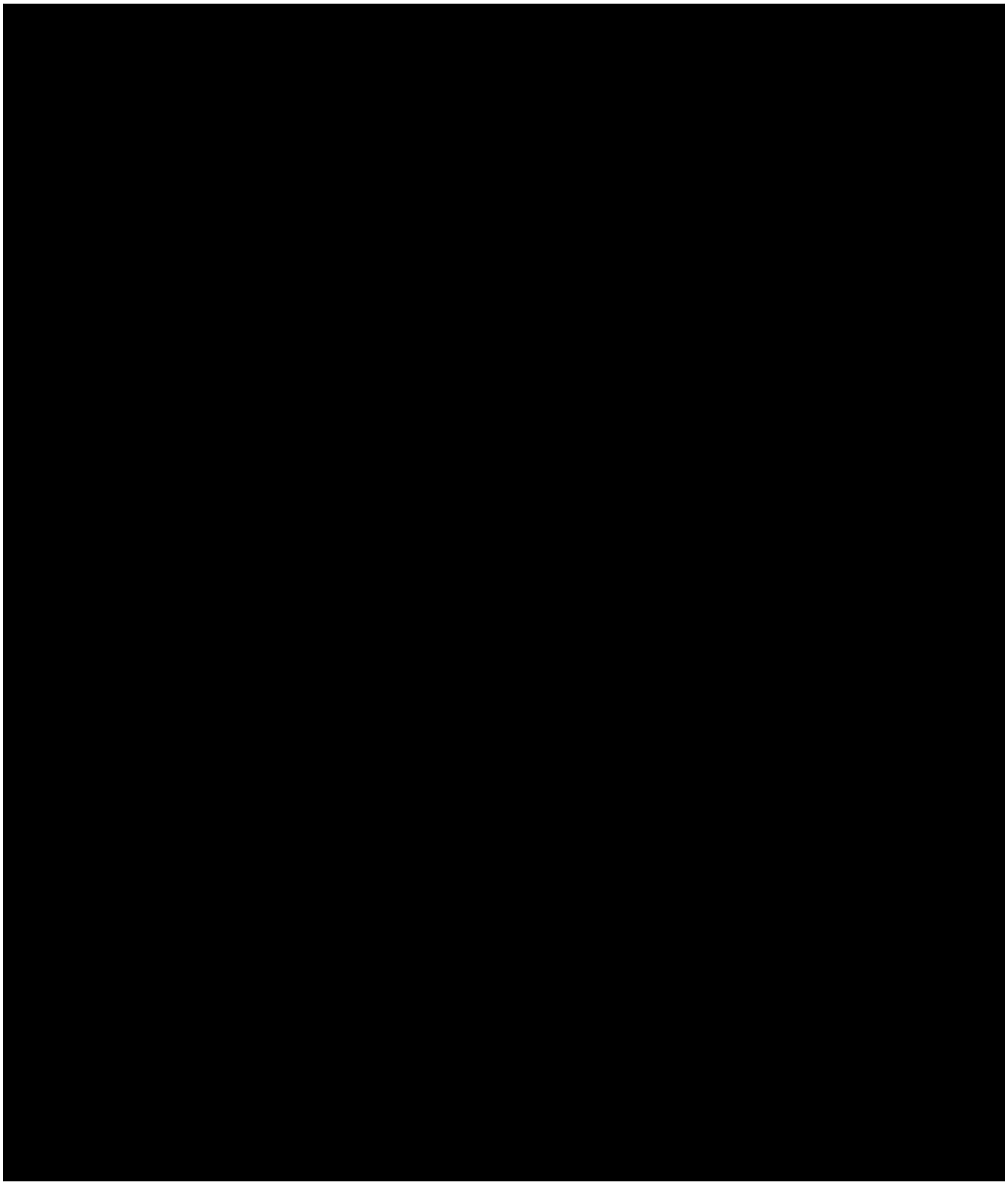


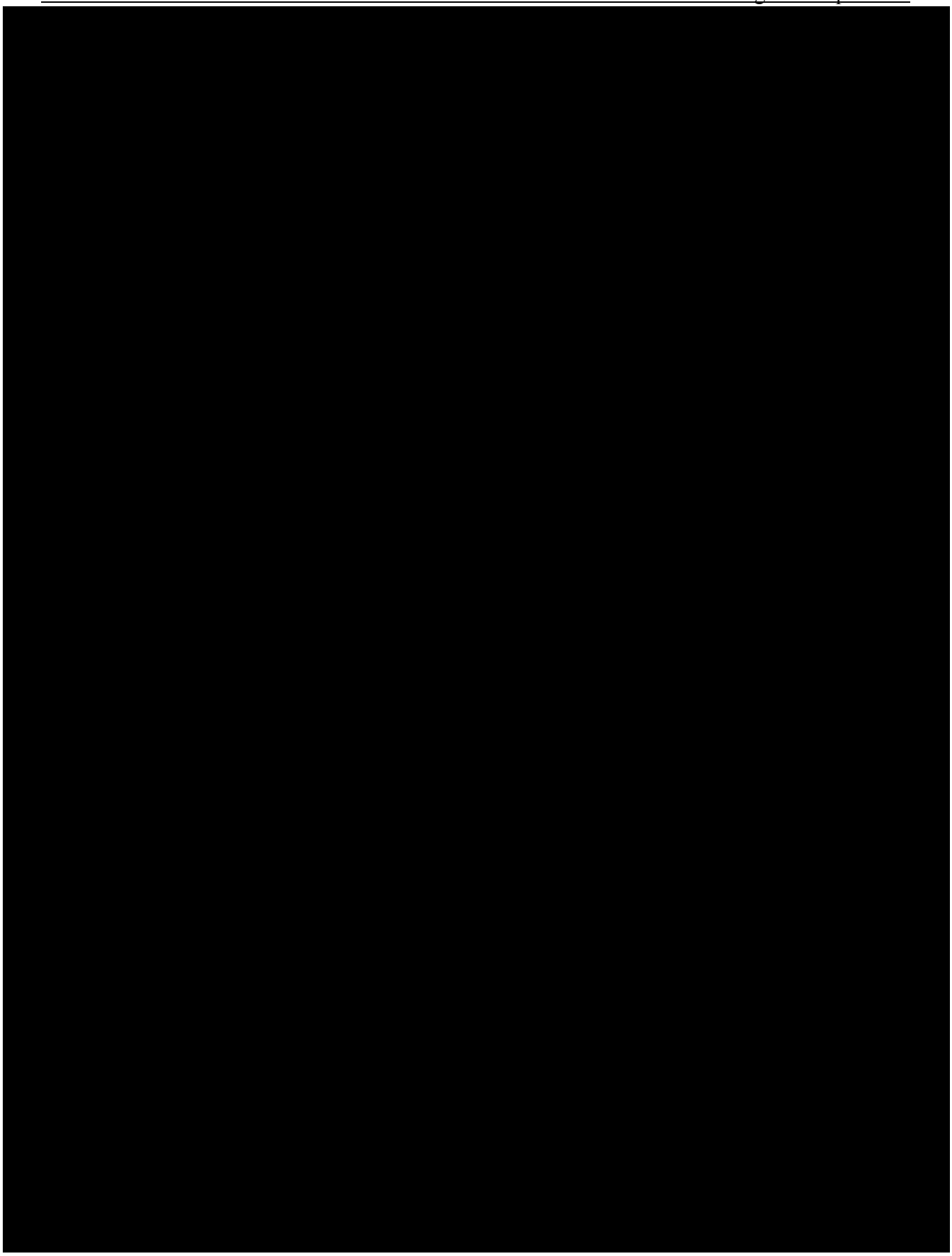


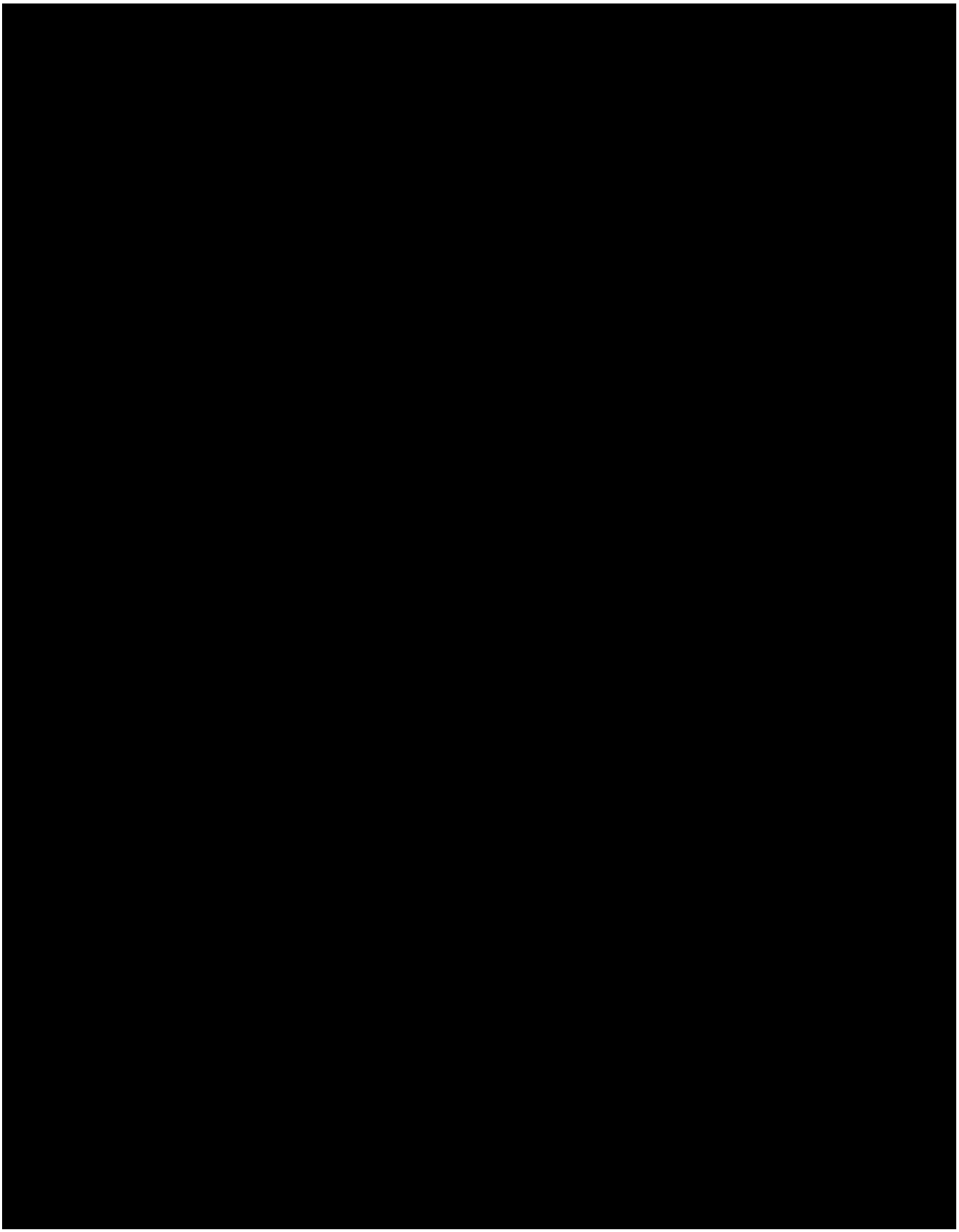


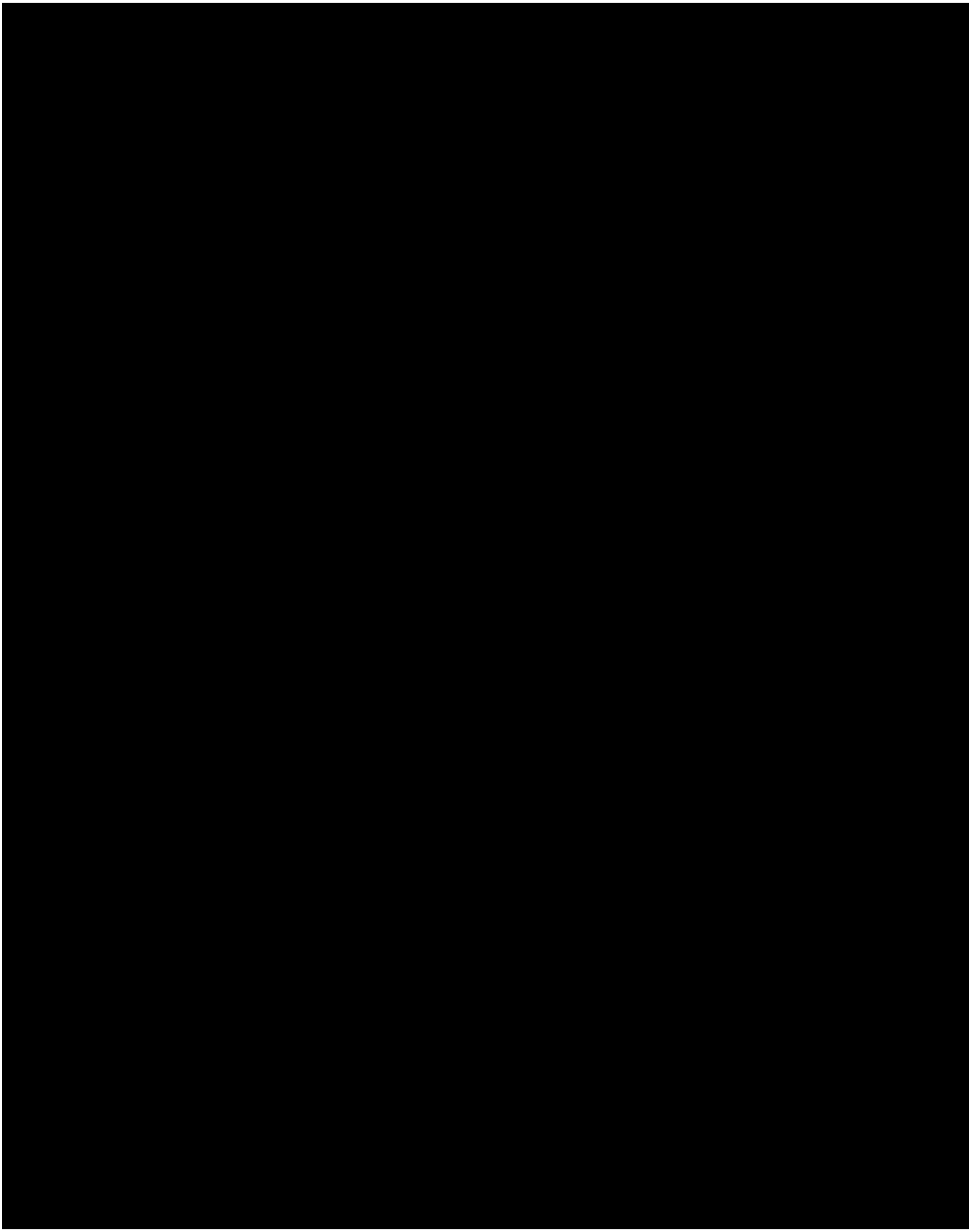


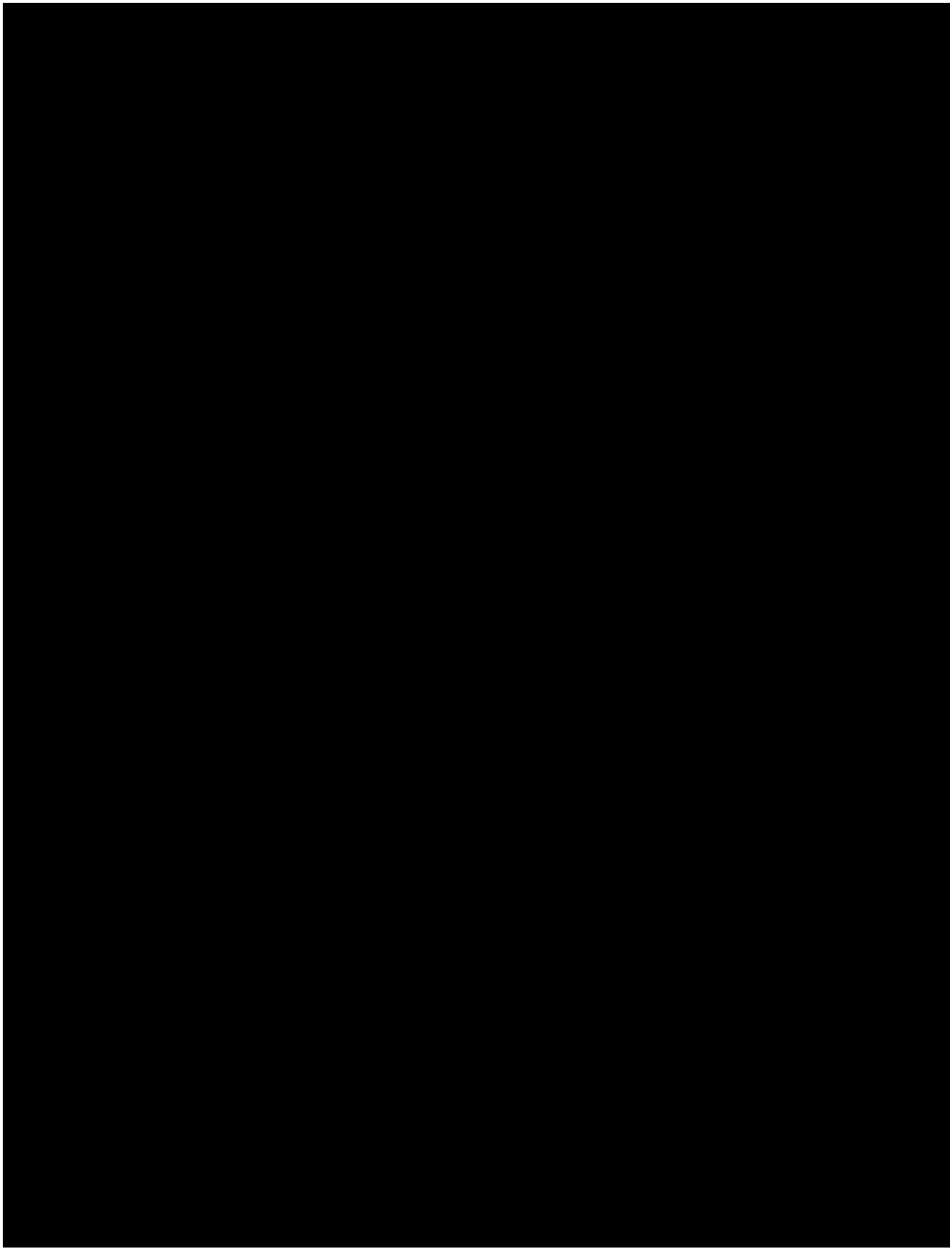


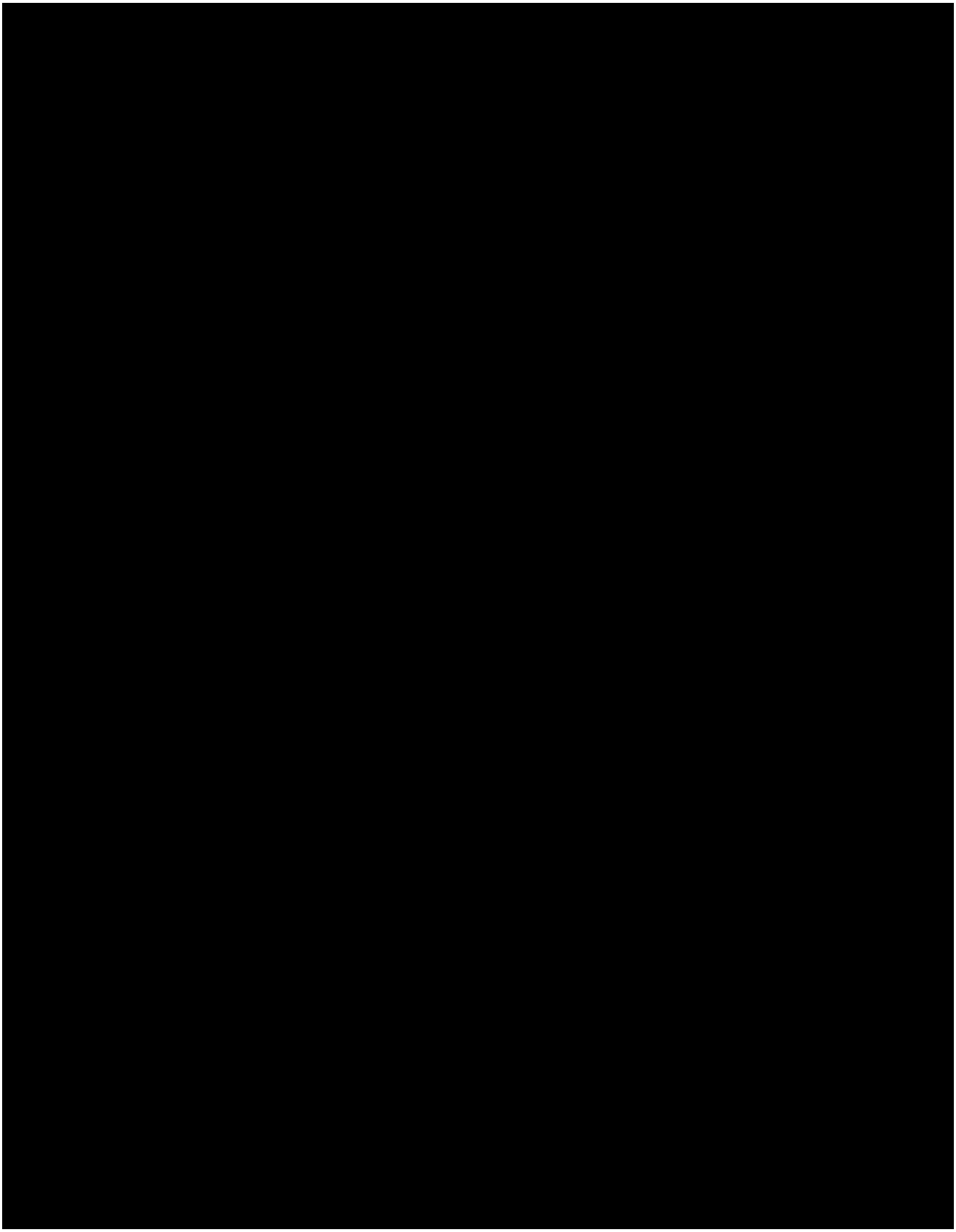


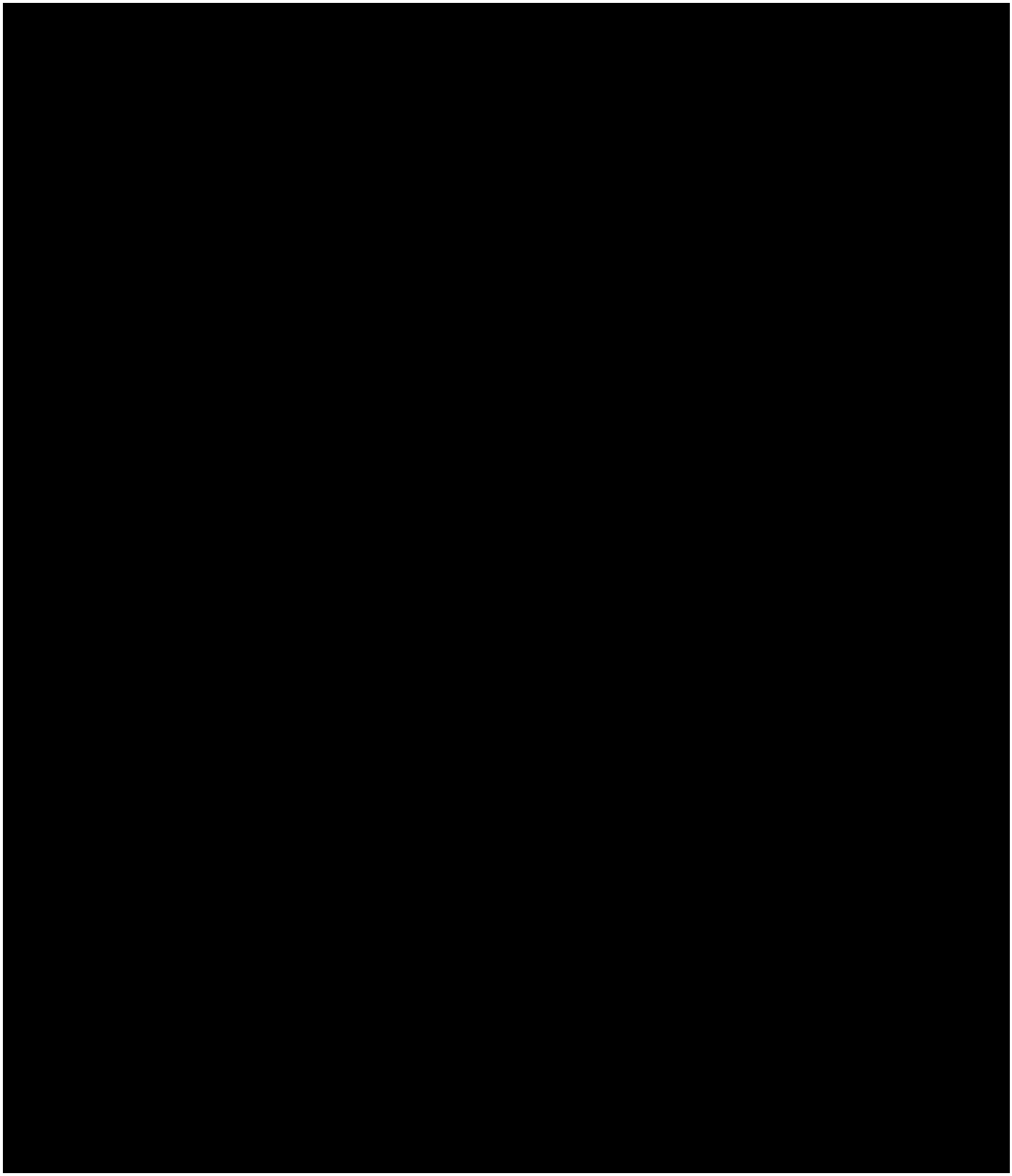


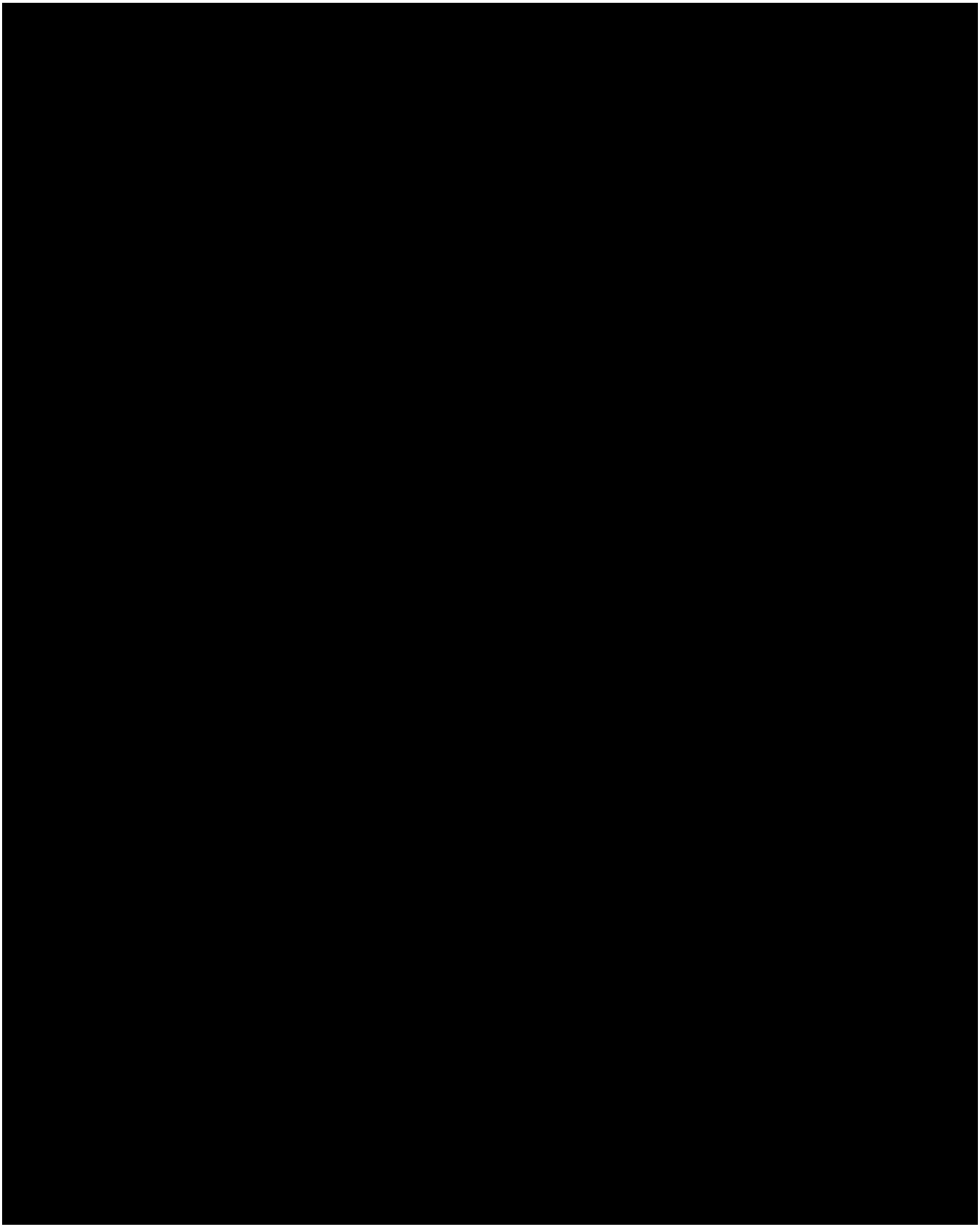


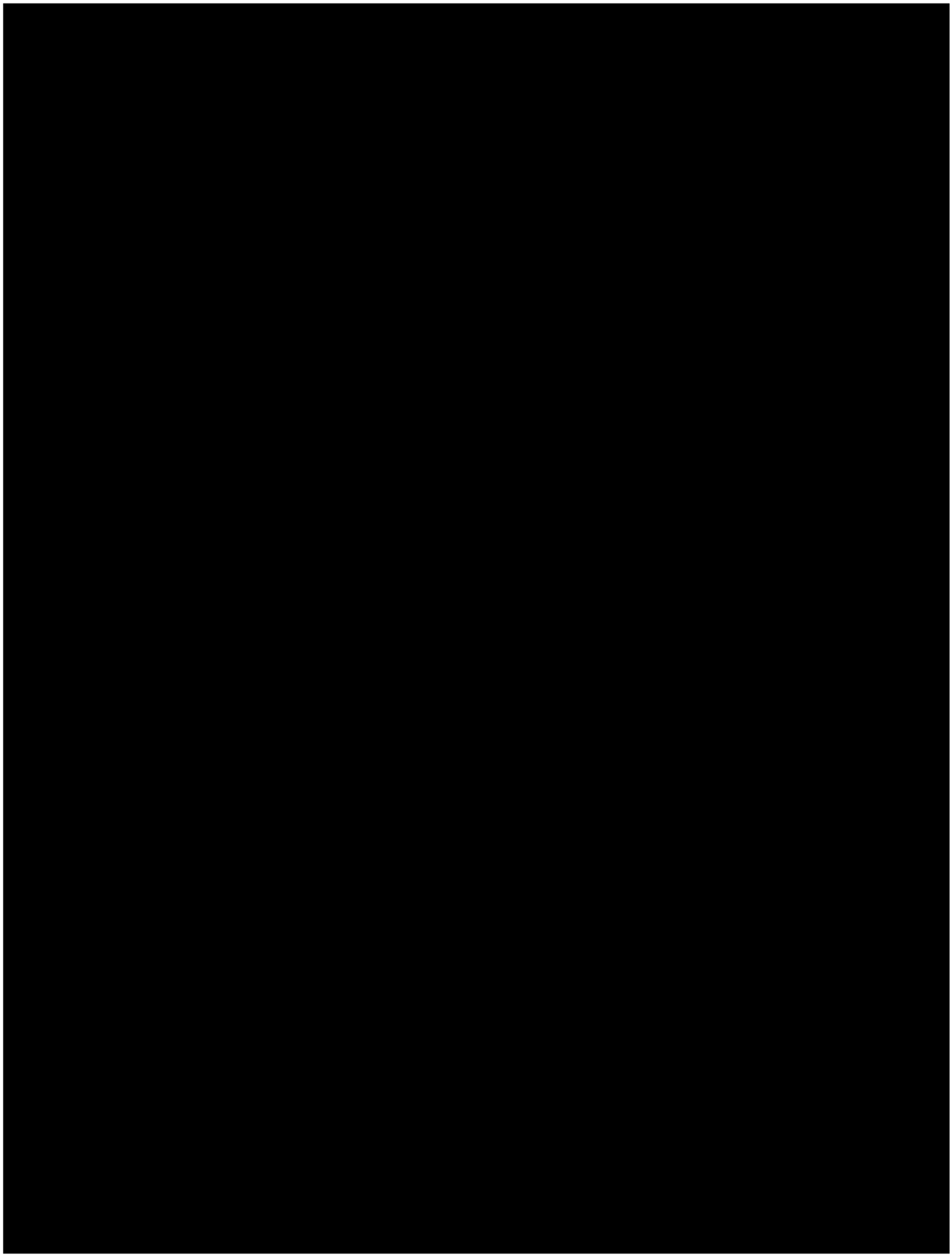


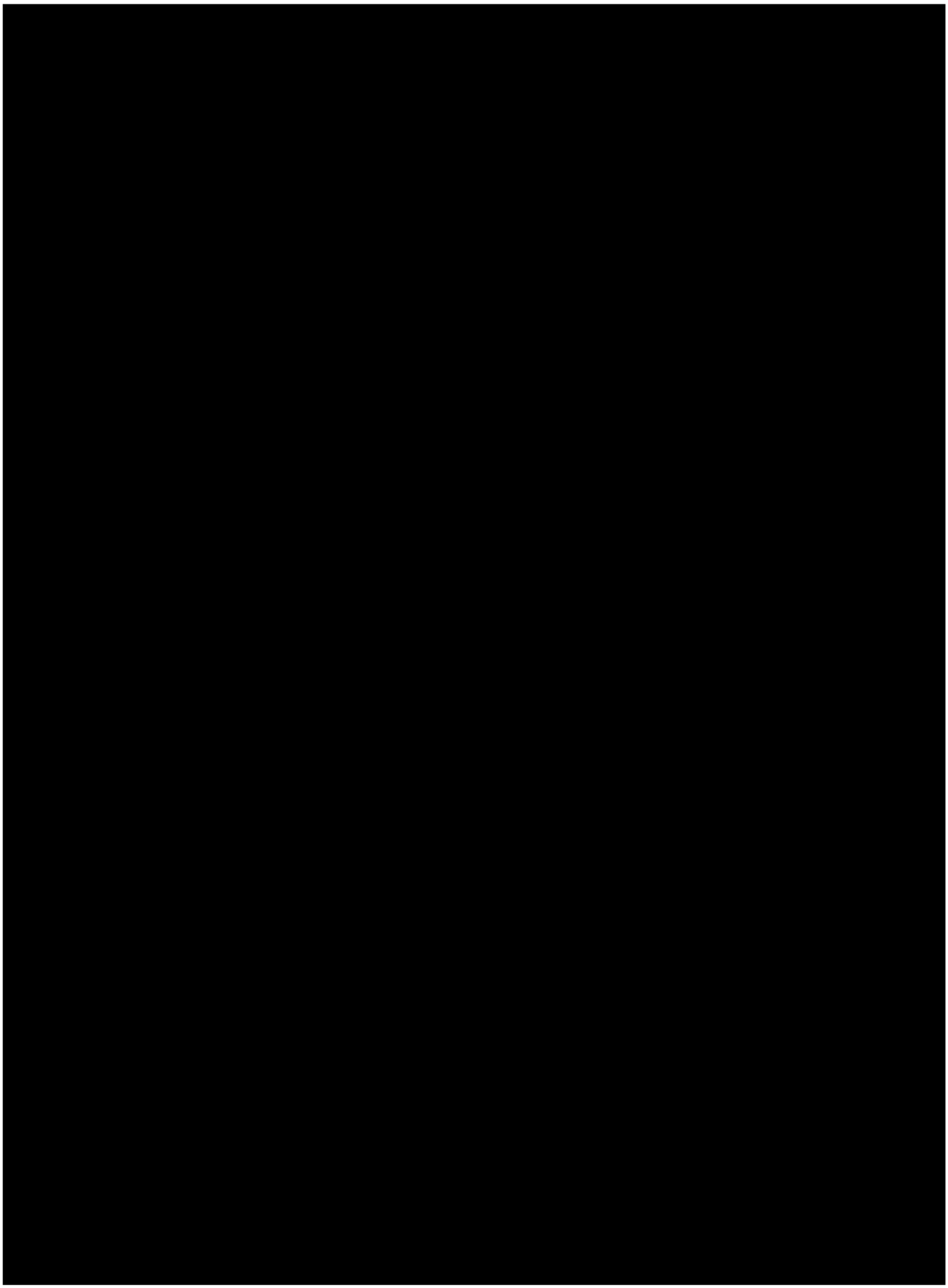












APPENDIX H. LOCAL CLINICAL LABORATORY EVALUATIONS

Table 35: Local Clinical Laboratory Evaluations

Laboratory Panel	Analytes
Chemistry	Glucose, BUN, creatinine, sodium, potassium, chloride, calcium, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, ALT (SGPT), AST (SGOT), magnesium, phosphate, bicarbonate, LDH, β2-microglobulin, uric acid, triglycerides, troponin-T[a] (or troponin-I if unavailable), BNP [a]
Hematology	CBC with differential
Coagulation	PT, aPTT, INR, fibrinogen, and D-dimer
Urinalysis	Appearance, pH, specific gravity, protein Glucose, ketones, RBCs, WBCs Casts, crystals, or other components
Pregnancy	ß-HCG (serum or urine[a])
Viral serology	HIV Hepatitis B (HBsAb, HBsAg, and HBcAb), Hepatitis C (Hep C Ab)
HLA typing	HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQB1
Inflammatory markers	CRP, ferritin
Thyroid function tests	TSH, fT4, fT3
Donor chimerism	% stem cell donor
Disease characterization	Histology, cell of origin, immunochemistry, cytogenetics, molecular sub-typing
Cerebrospinal fluid	RBCs, WBCs with differential, glucose, protein
Immunoglobulins	IgG, IgM, IgA

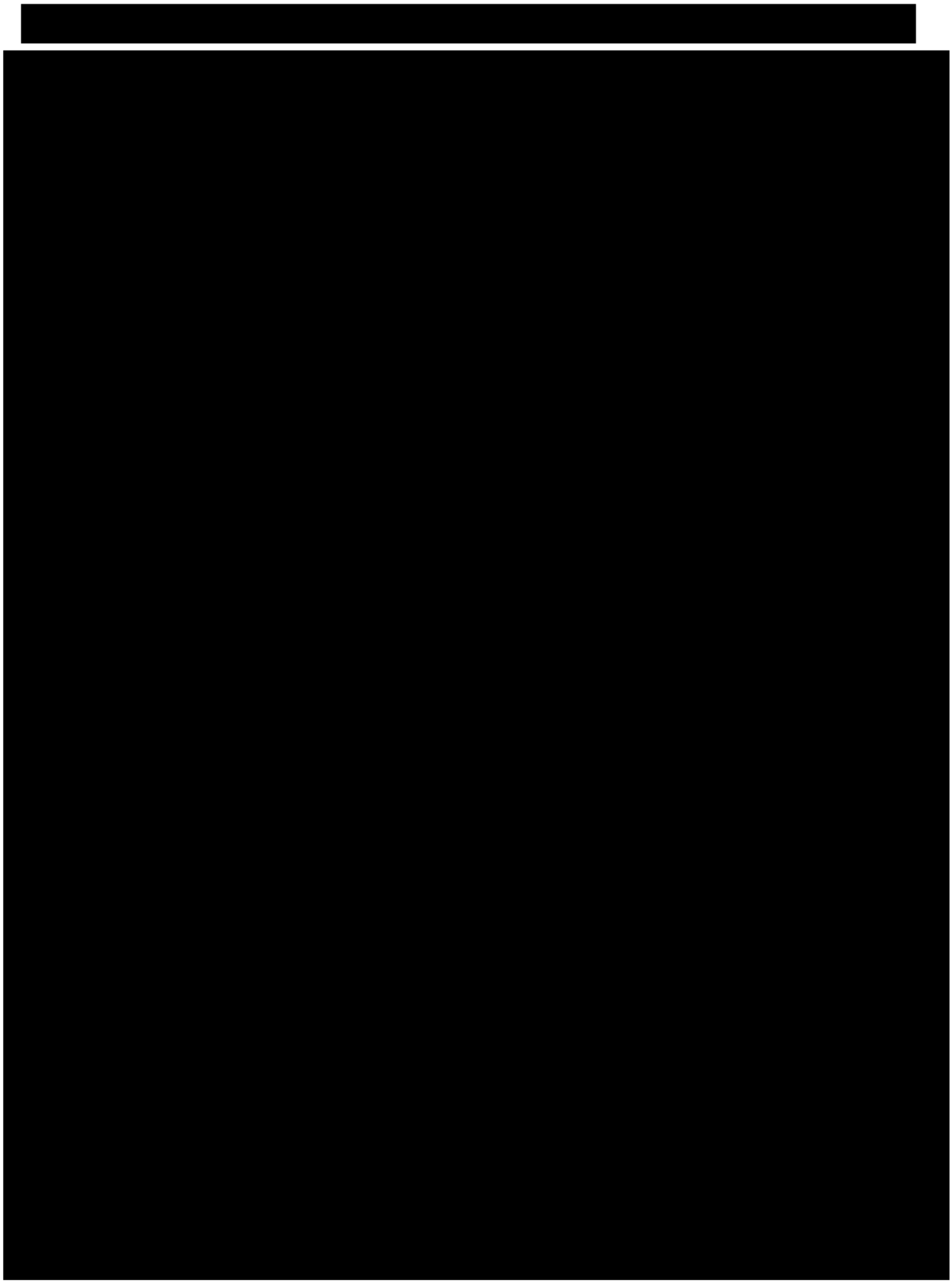
Abbreviations: ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CBC = complete blood count; CRP = C-reactive protein; FISH = fluorescence in situ hybridization; fT3= free triiodothyronine; fT4= free thyroxine; HIV= Human Immunodeficiency Virus; HLA = human leukocyte antigen; Ig = immunoglobulin; INR = international normalized ratio; LDH = lactate dehydrogenase; PT = prothrombin time; RBC = red blood cell; TSH = Thyroid stimulating hormone; WBC = white blood cell.

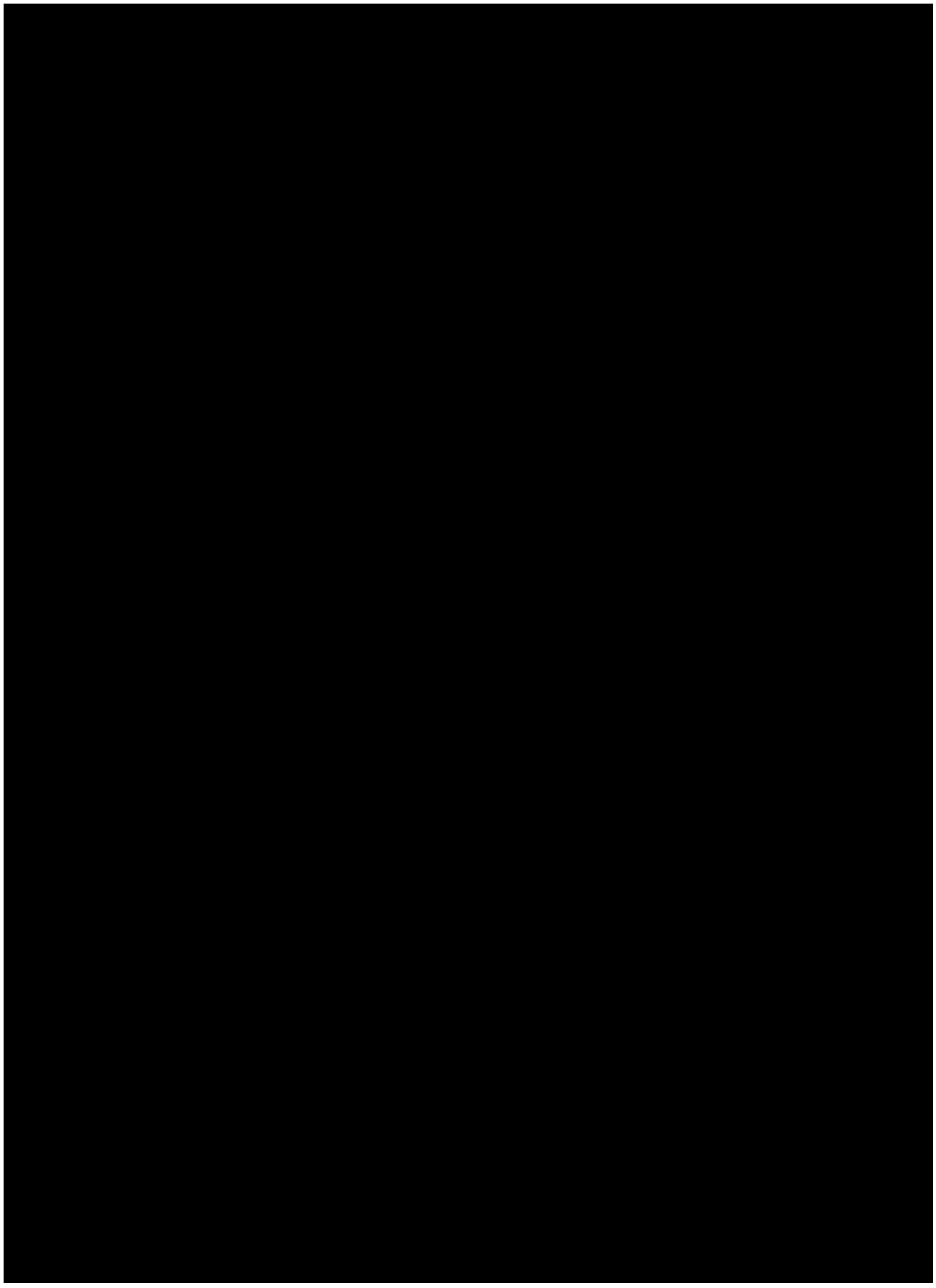
[a] Only to be performed at the timepoints as specified in the schedule of evaluations. See Section 4.2 for permitted substitutions.

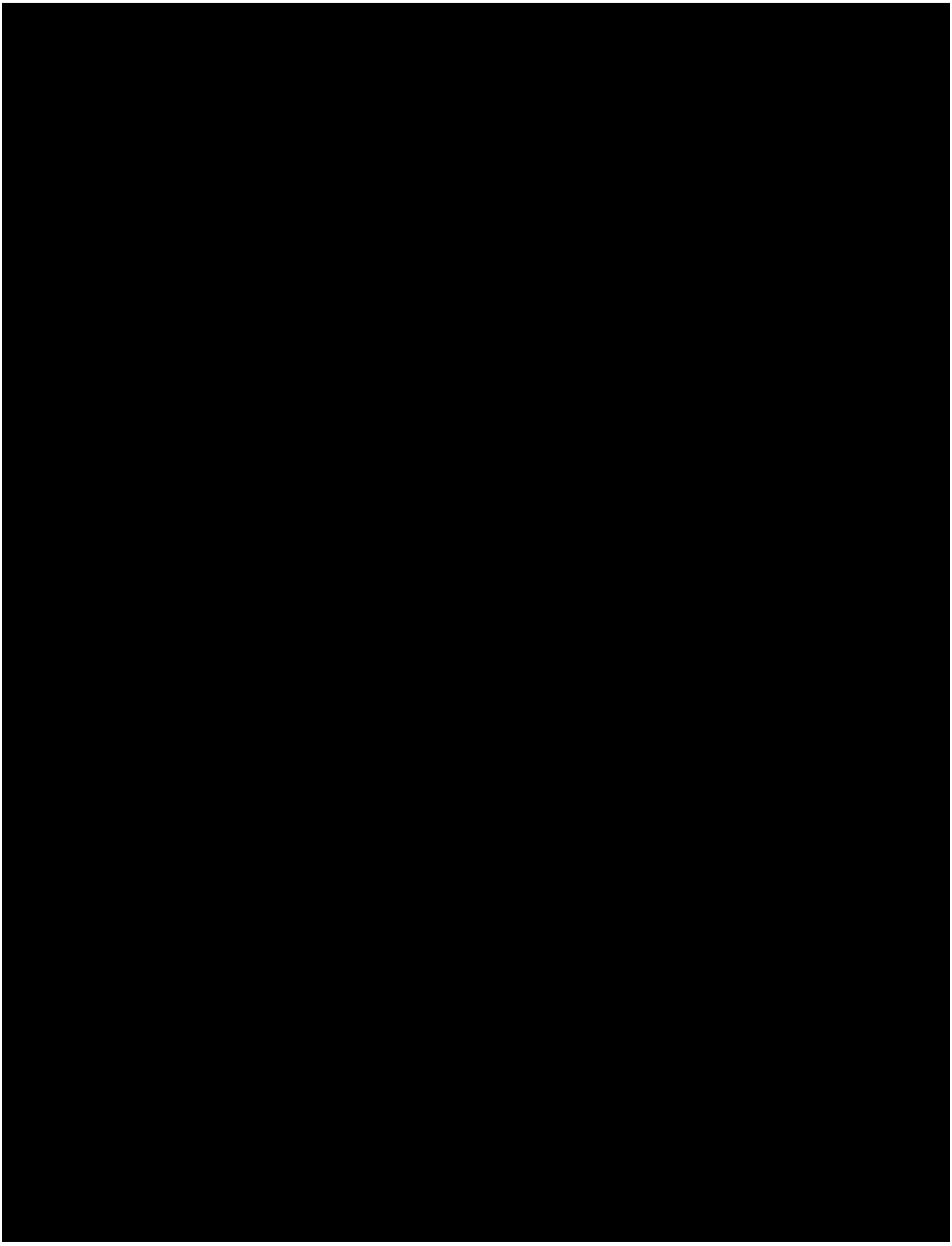
APPENDIX I. COCKCROFT-GAULT EQUATION FOR CALCULATING ESTIMATED CREATININE CLEARANCE

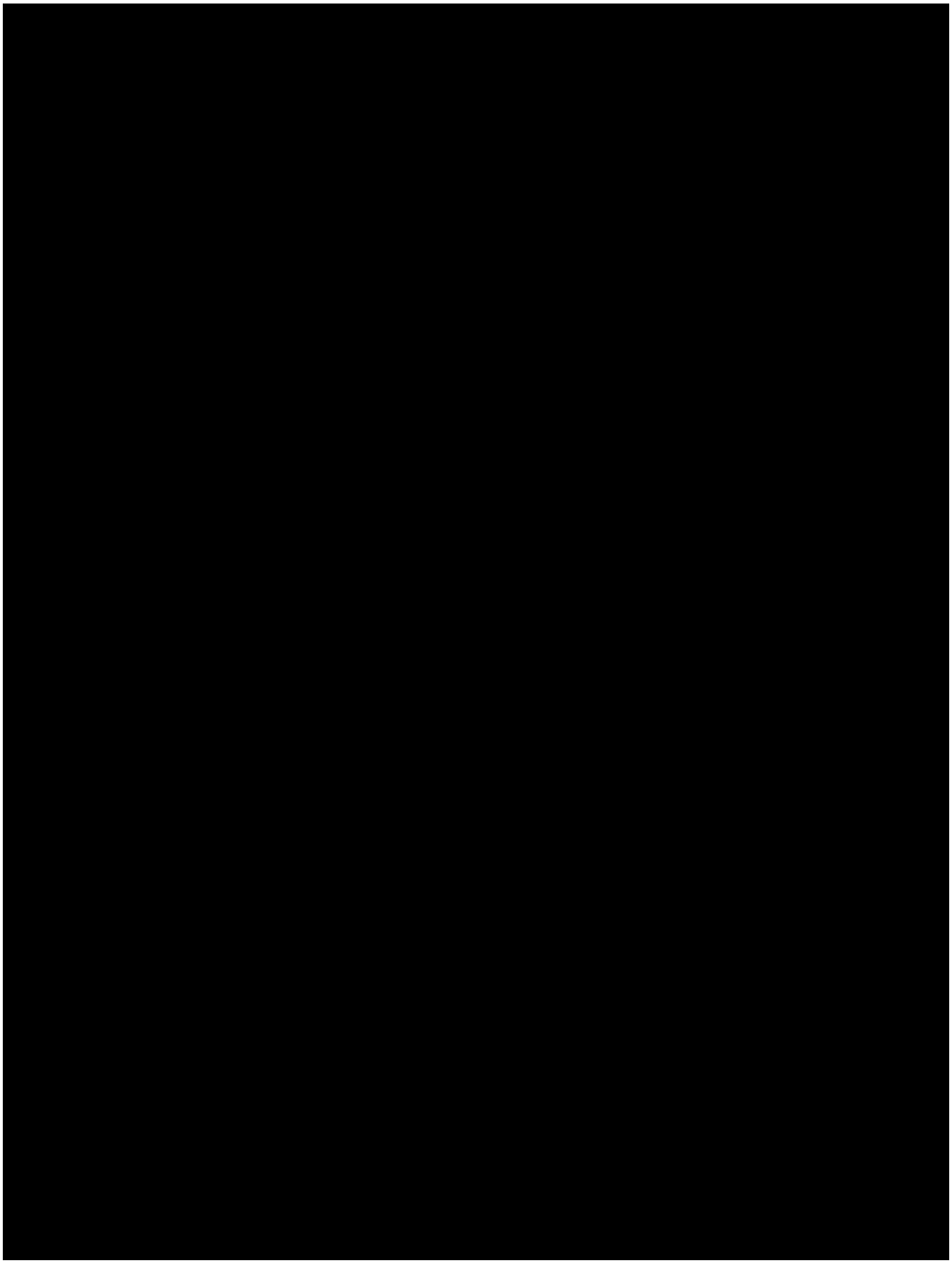
Table 36: Cockcroft-Gault Equation for Calculating Estimated Creatinine Clearance

Serum creatinine units	Gender	Estimated Creatinine Clearance (mL/min)
mg/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)}}{72 \times \text{subject serum creatinine (mg/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 0.85}{72 \times \text{subject serum creatinine (mg/dL)}}$
μM/dL	Male	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.23}{\text{Subject serum creatinine (μM/dL)}}$
	Female	$\frac{(140 - \text{subject age [years]}) \times \text{subject weight (kg)} \times 1.04}{\text{Subject serum creatinine (μM/dL)}}$









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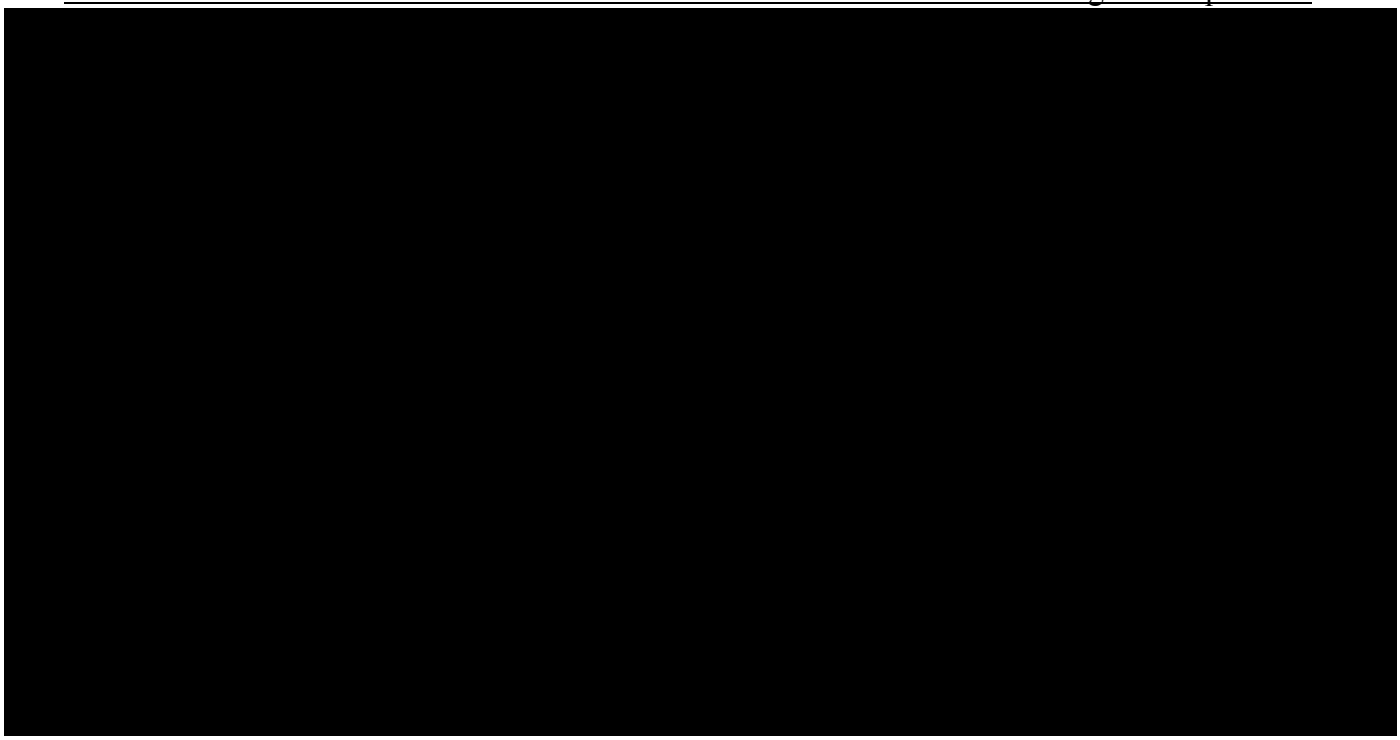

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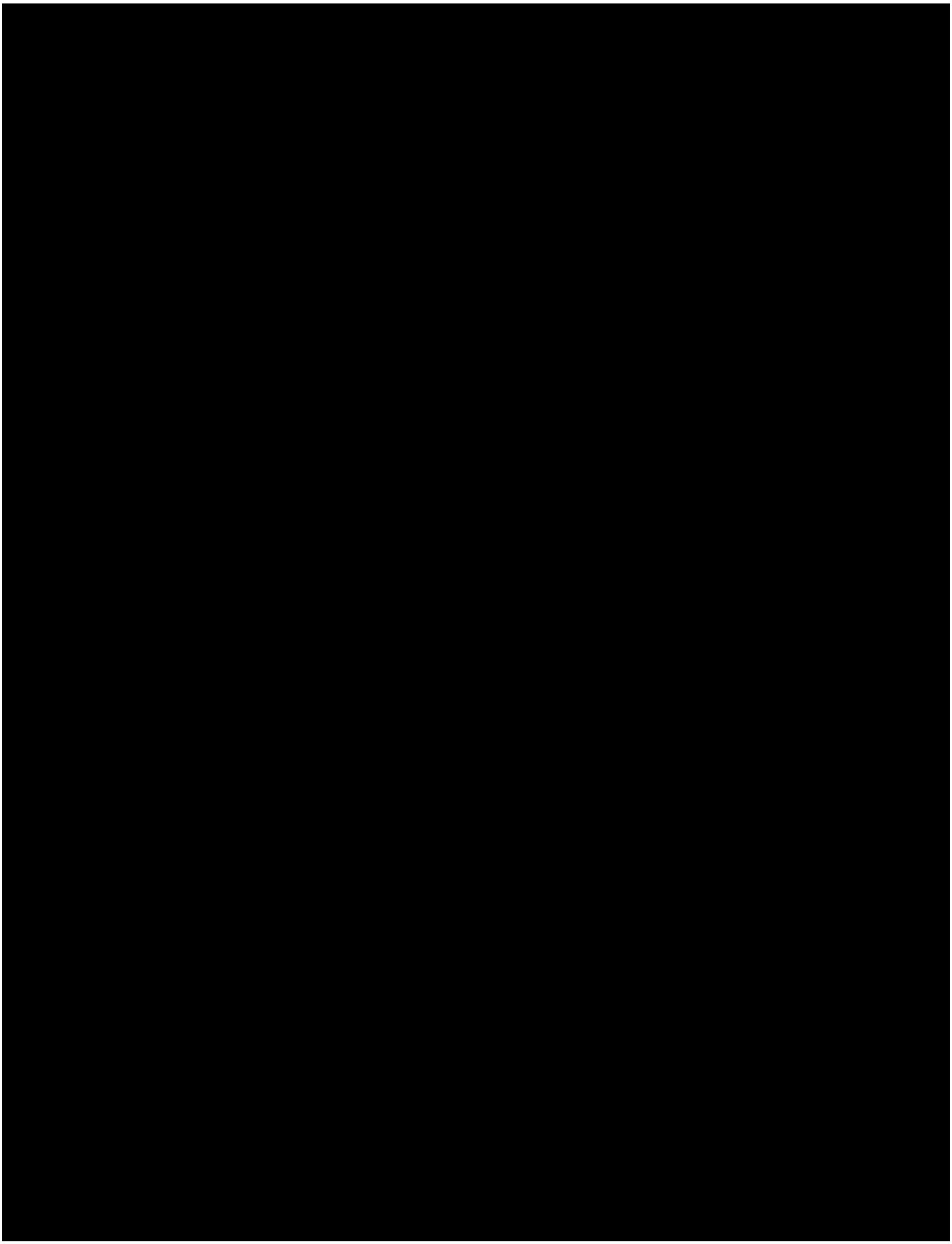

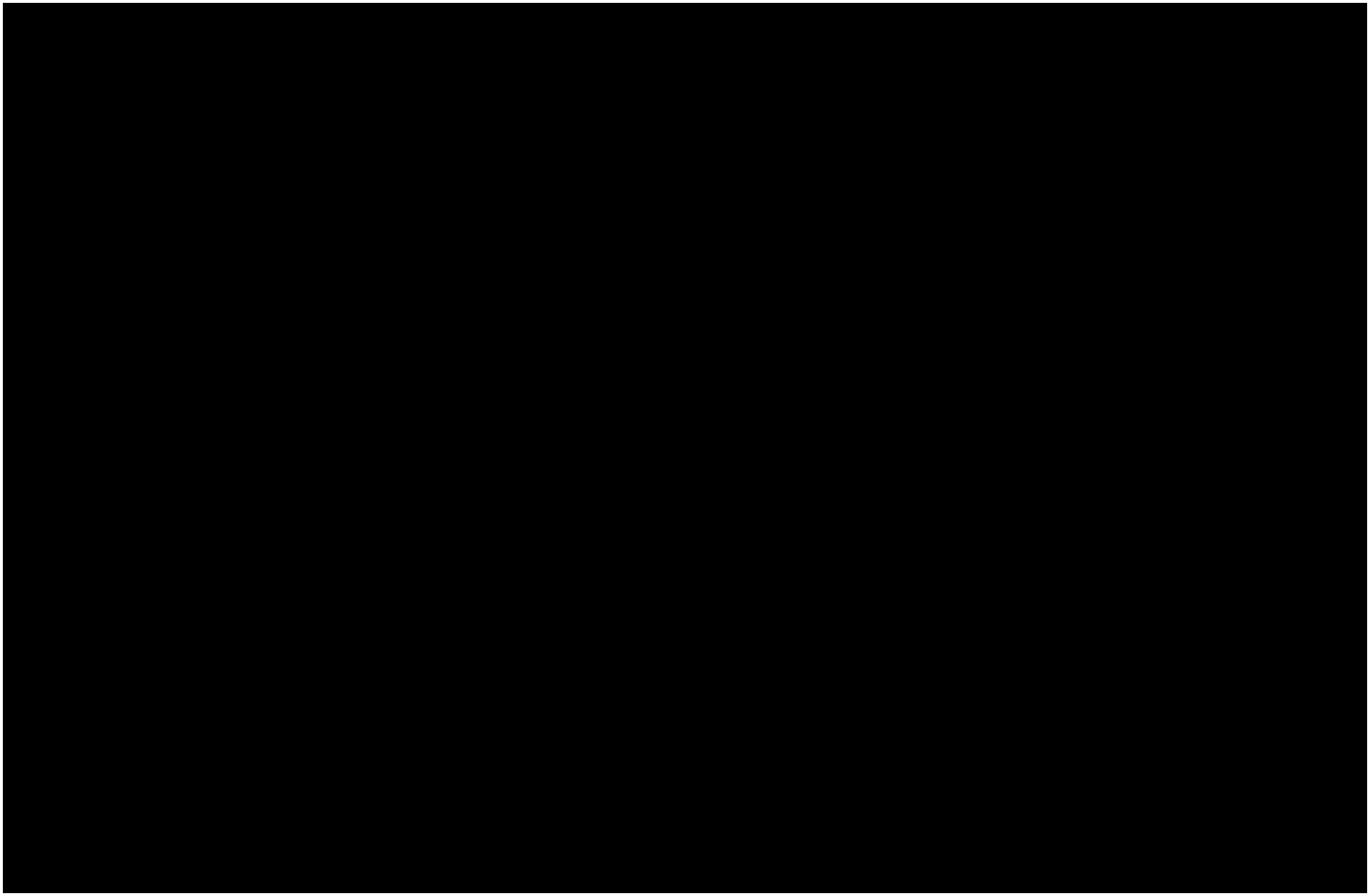

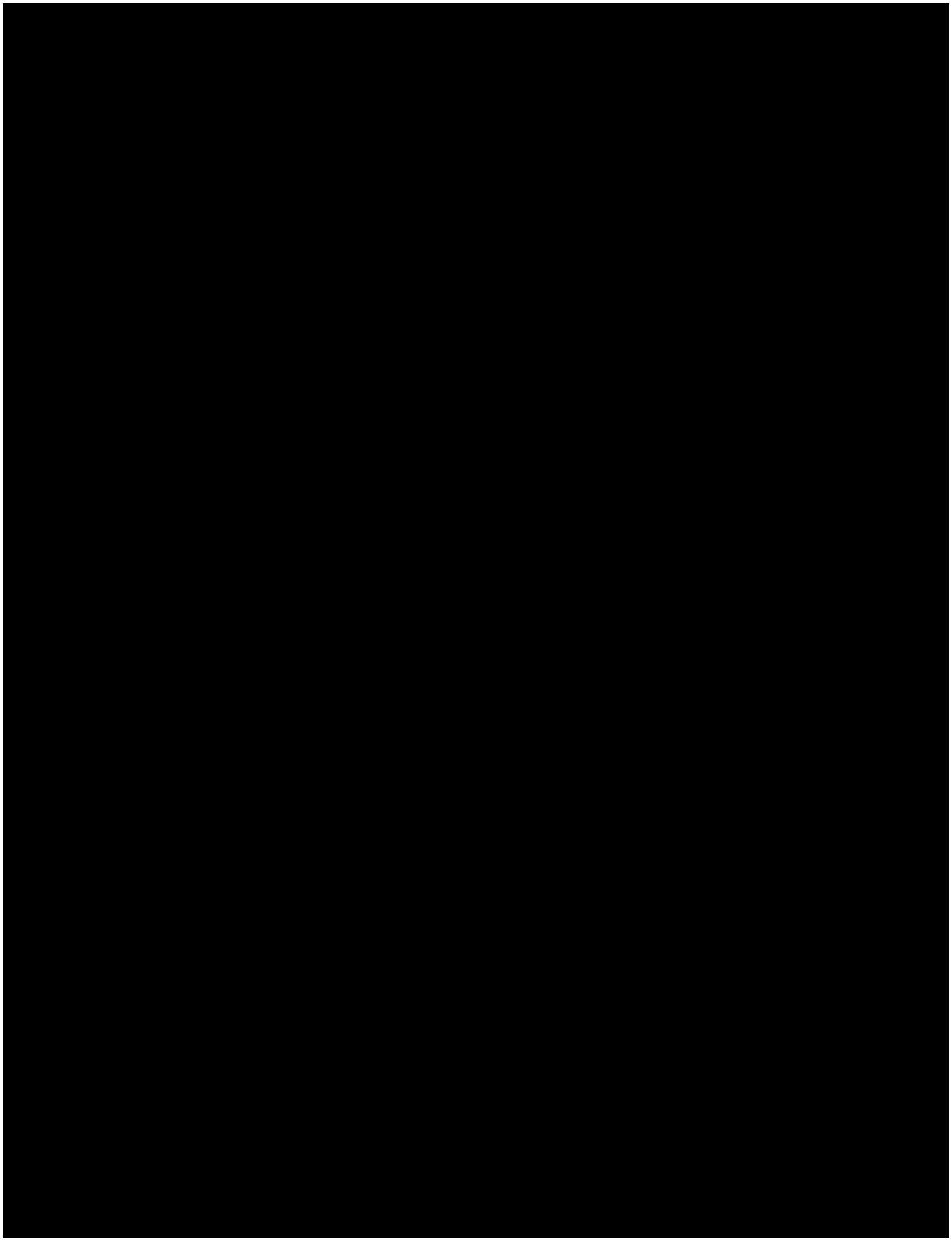

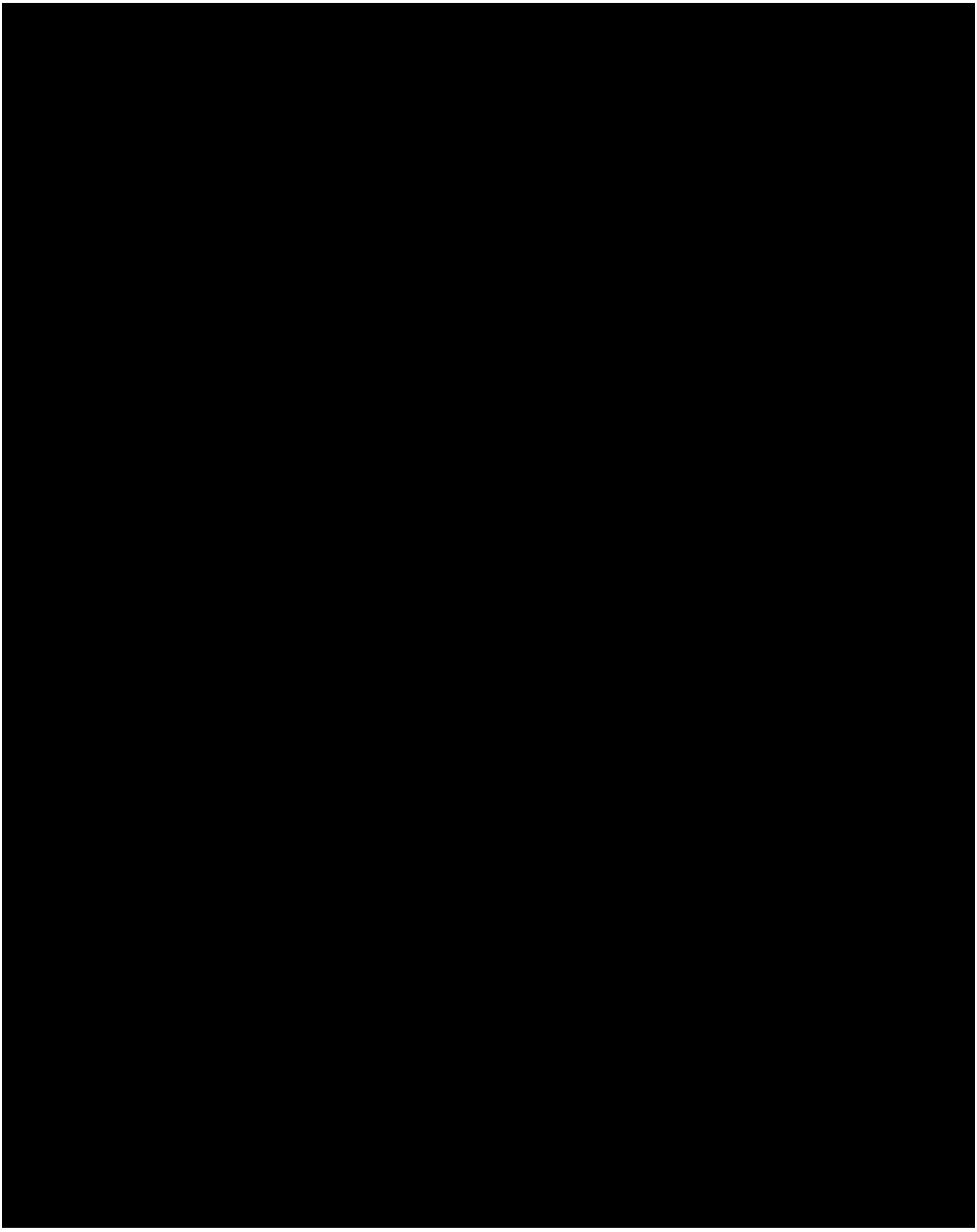

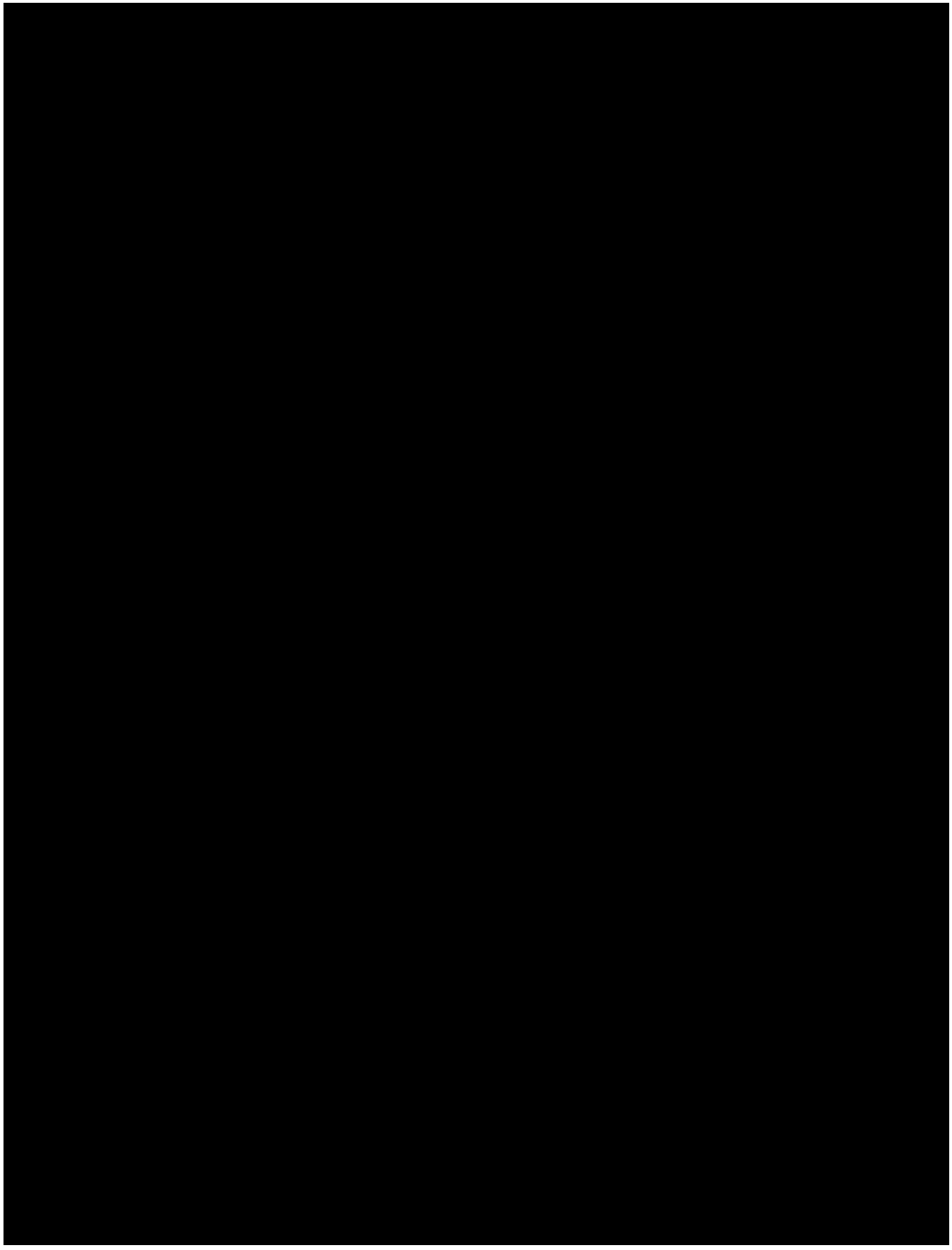

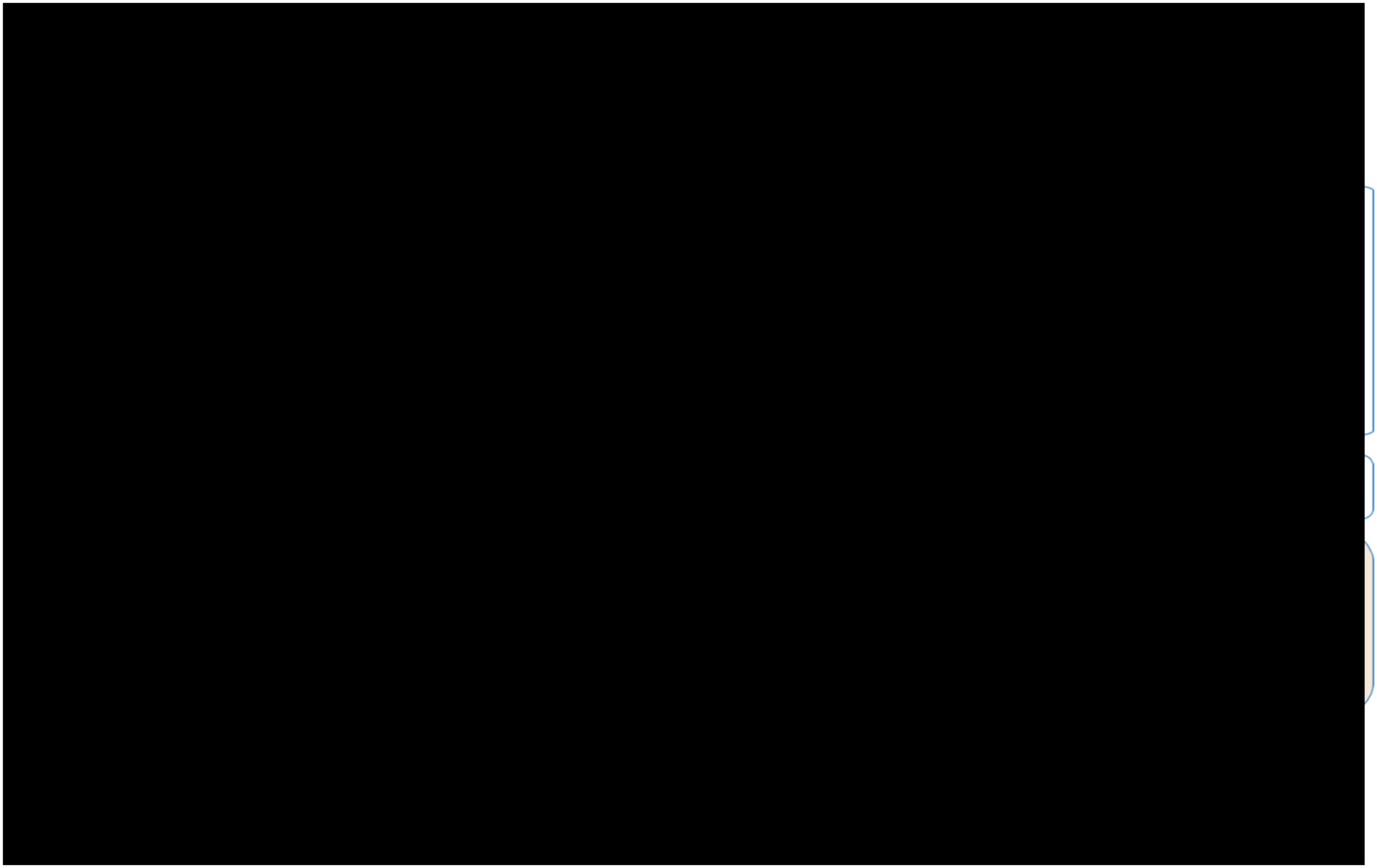

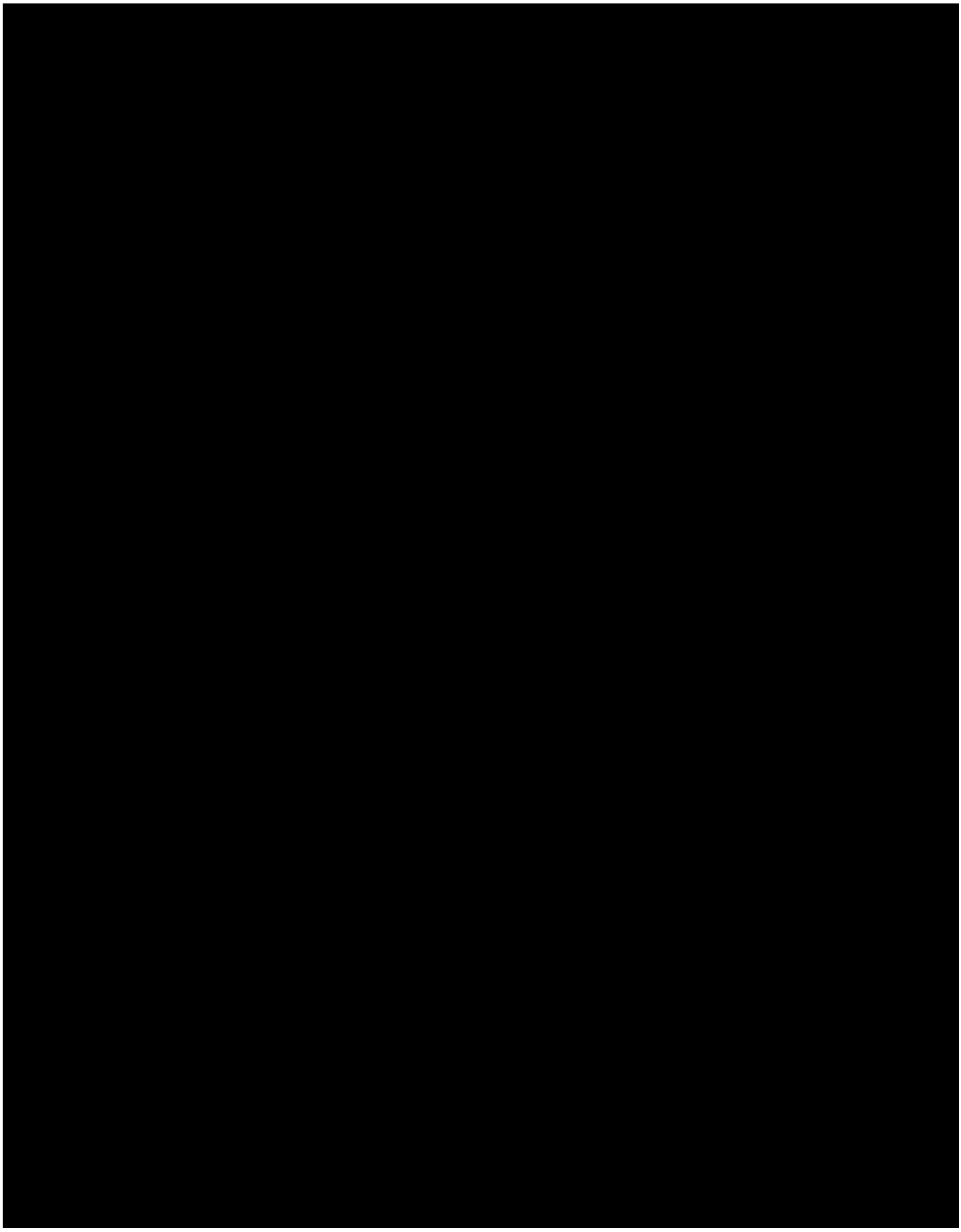

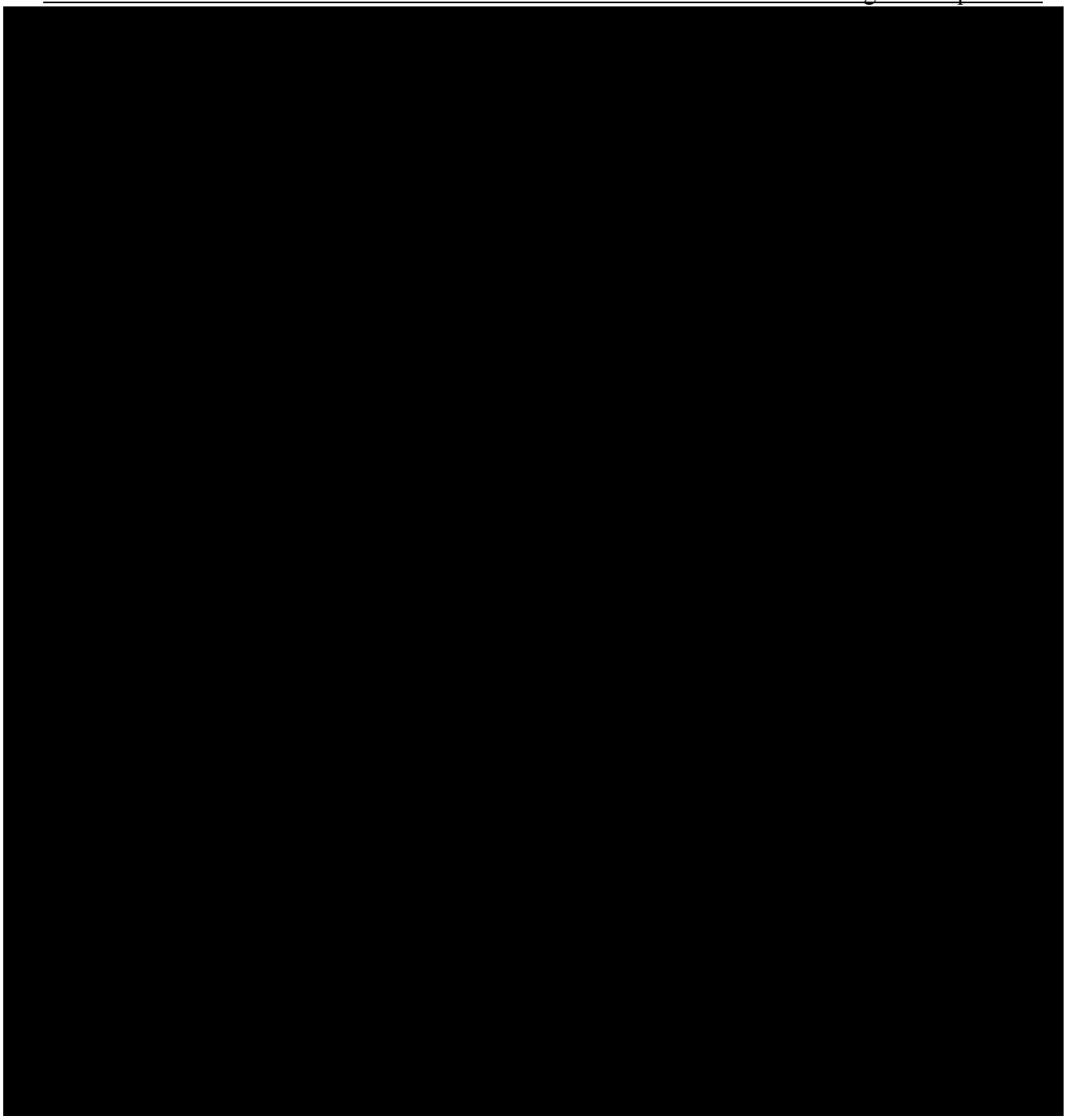

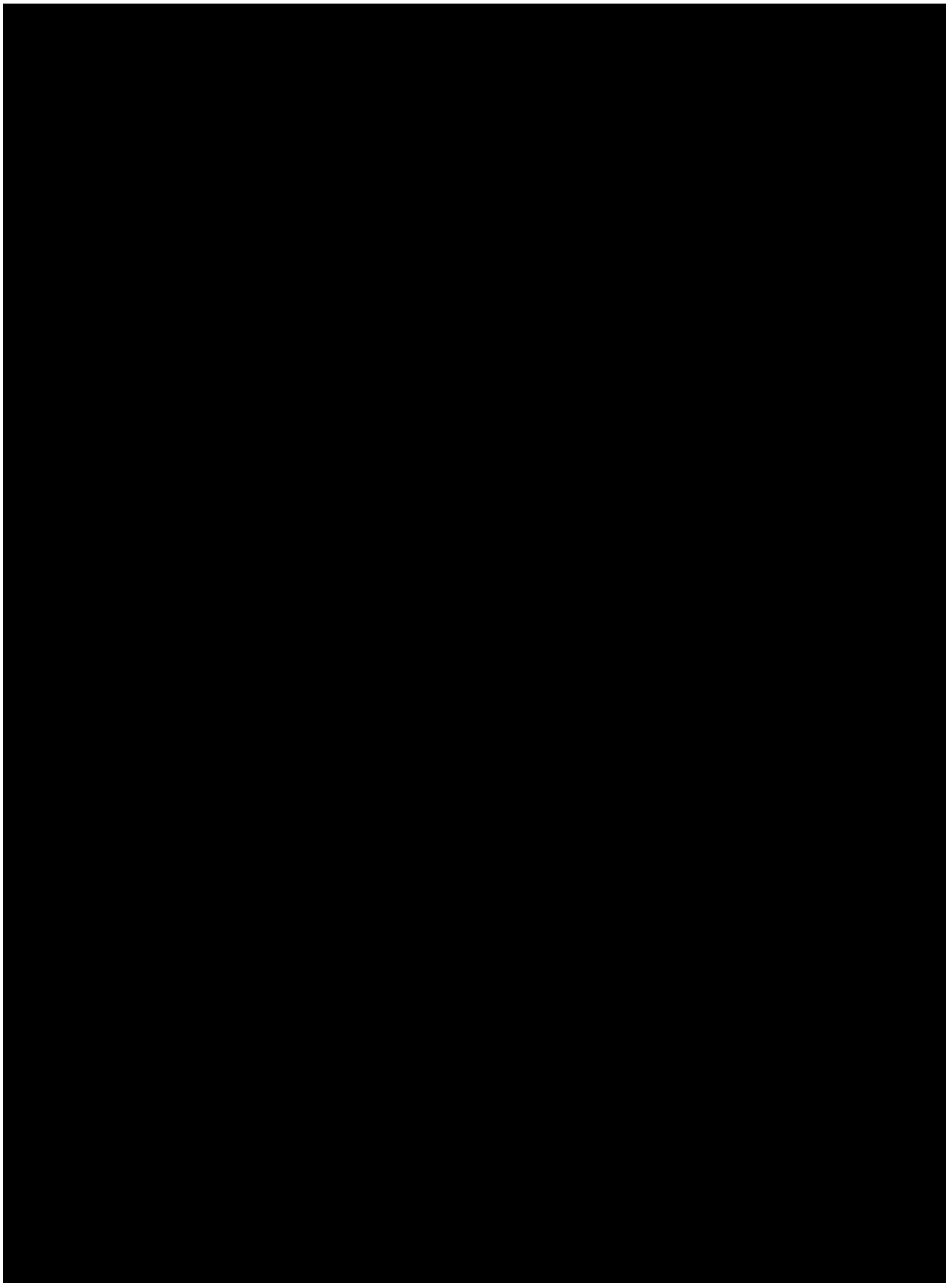

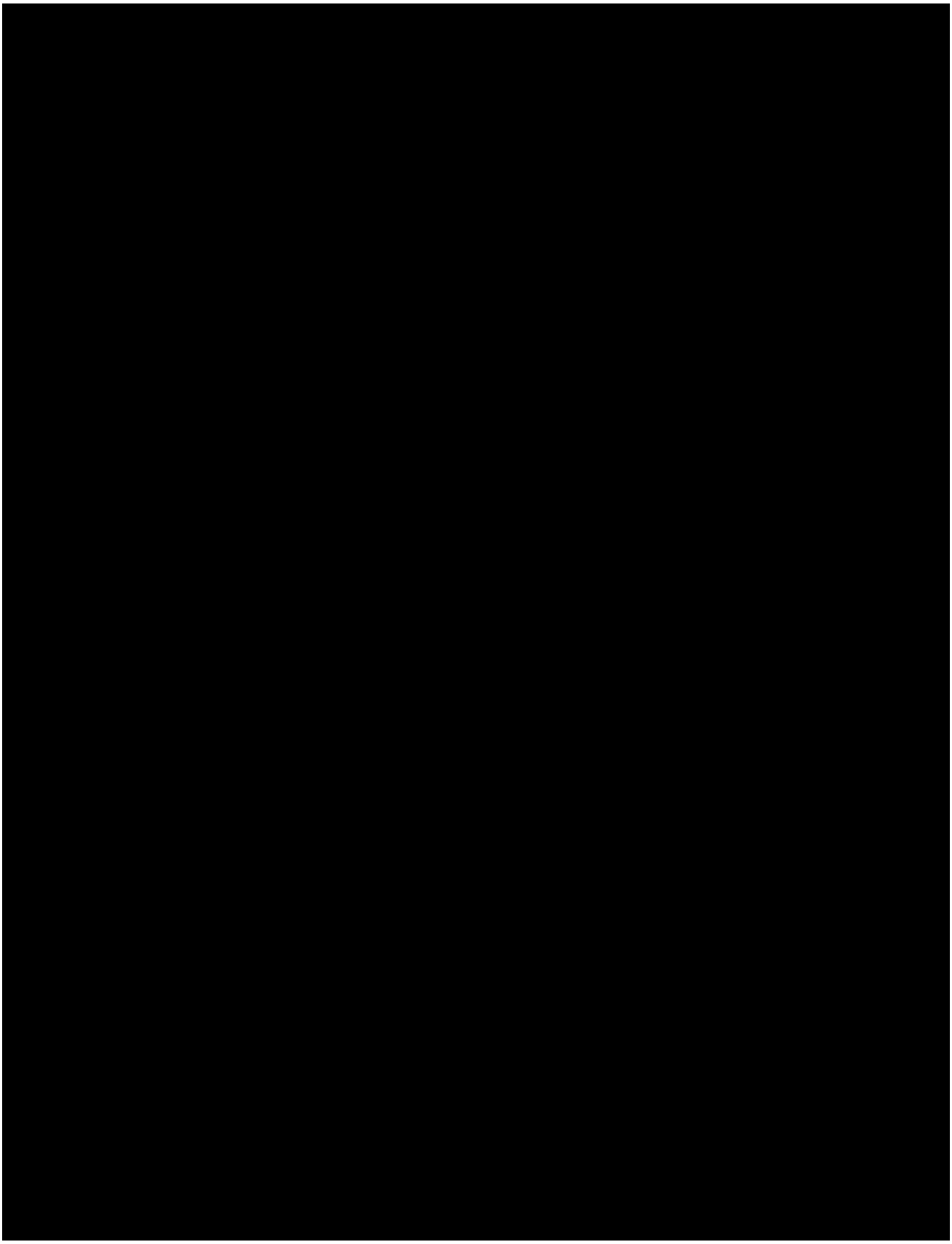

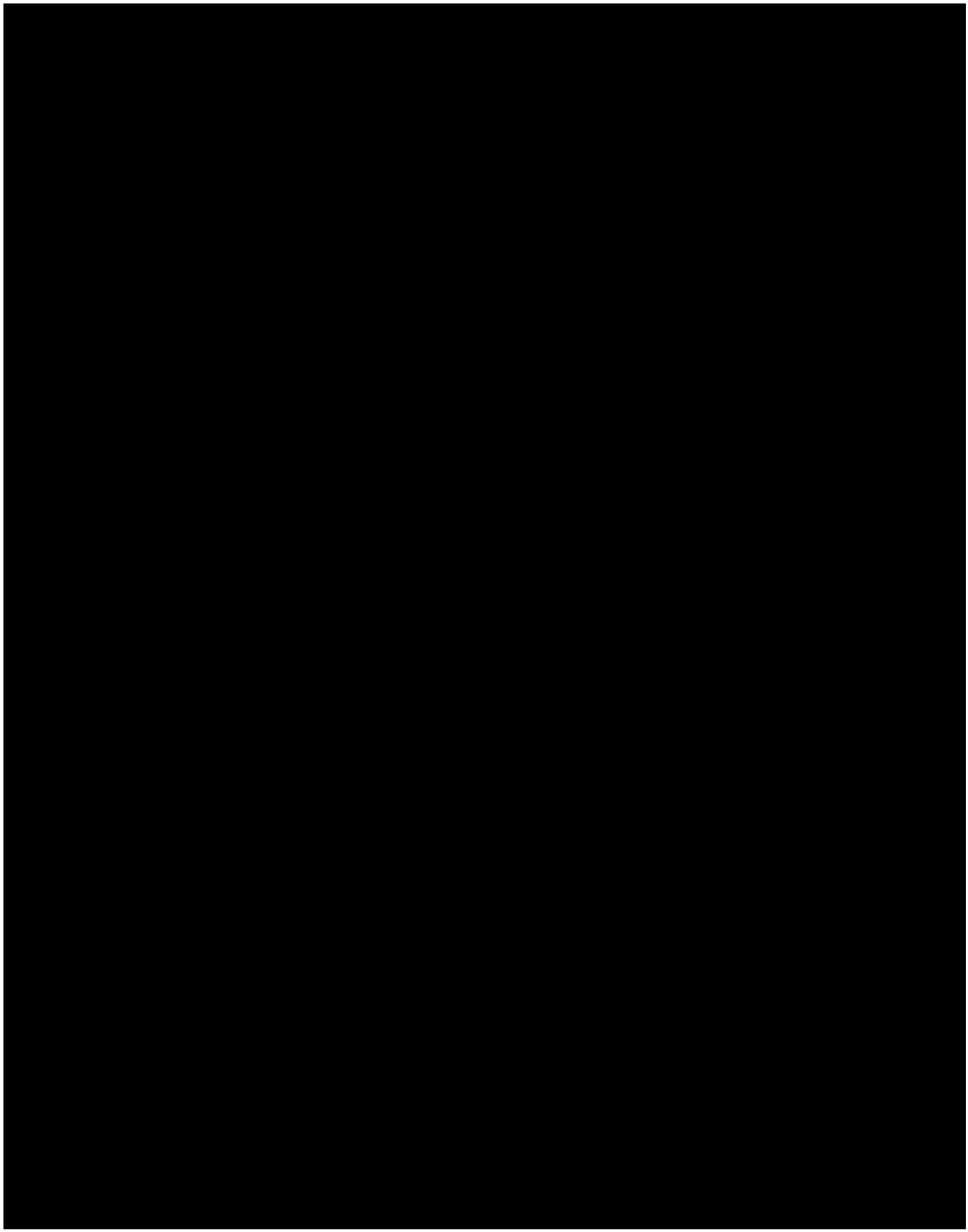

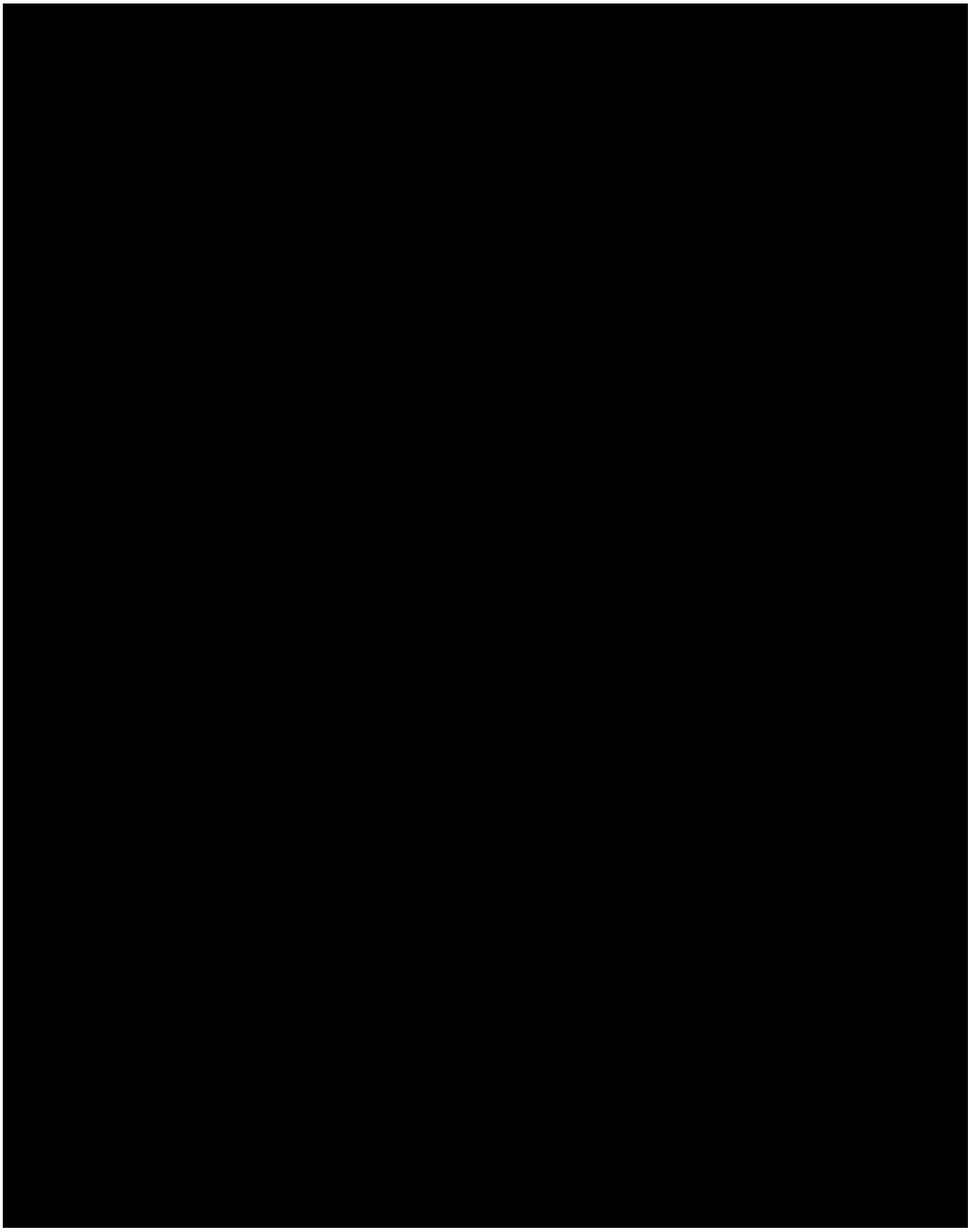

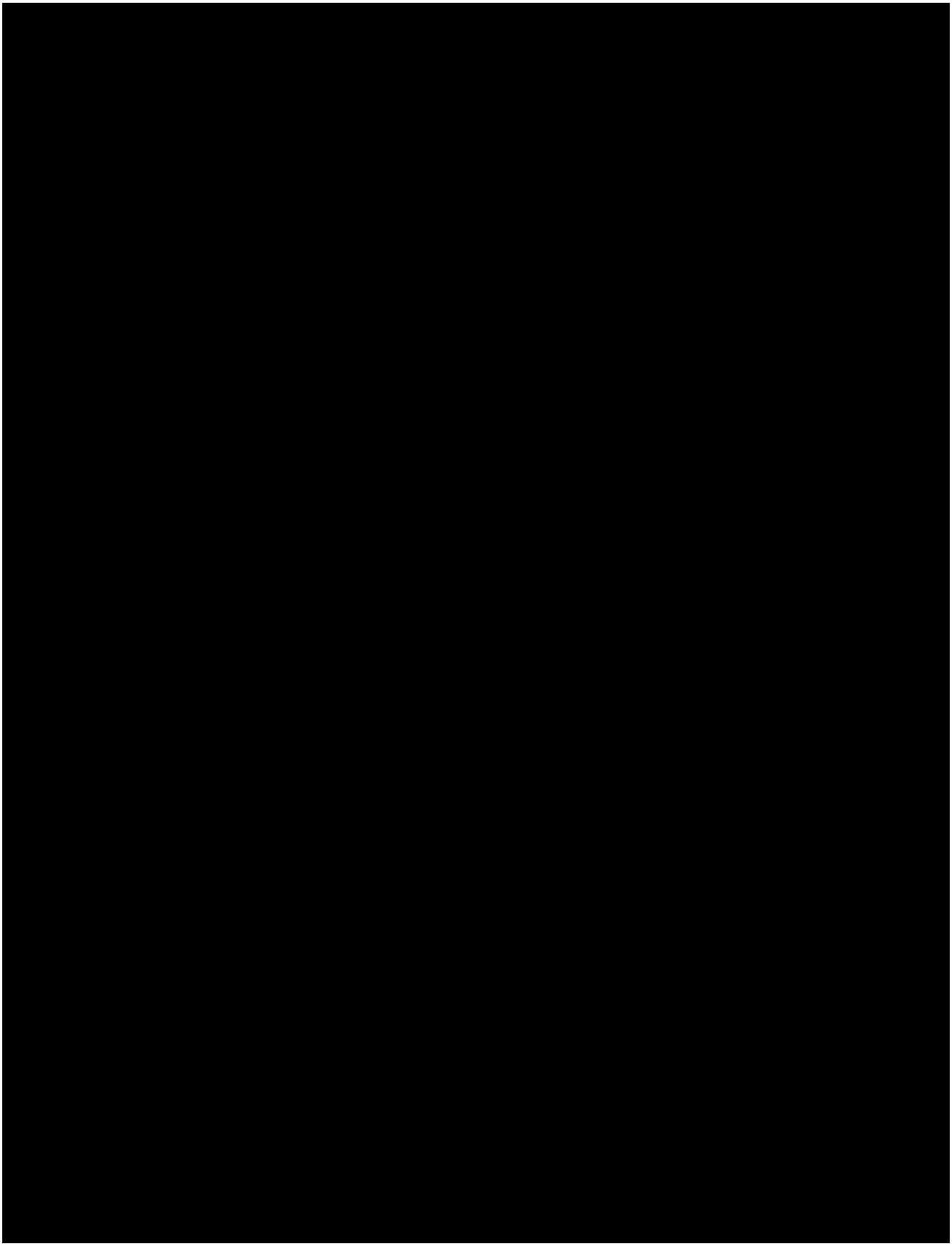

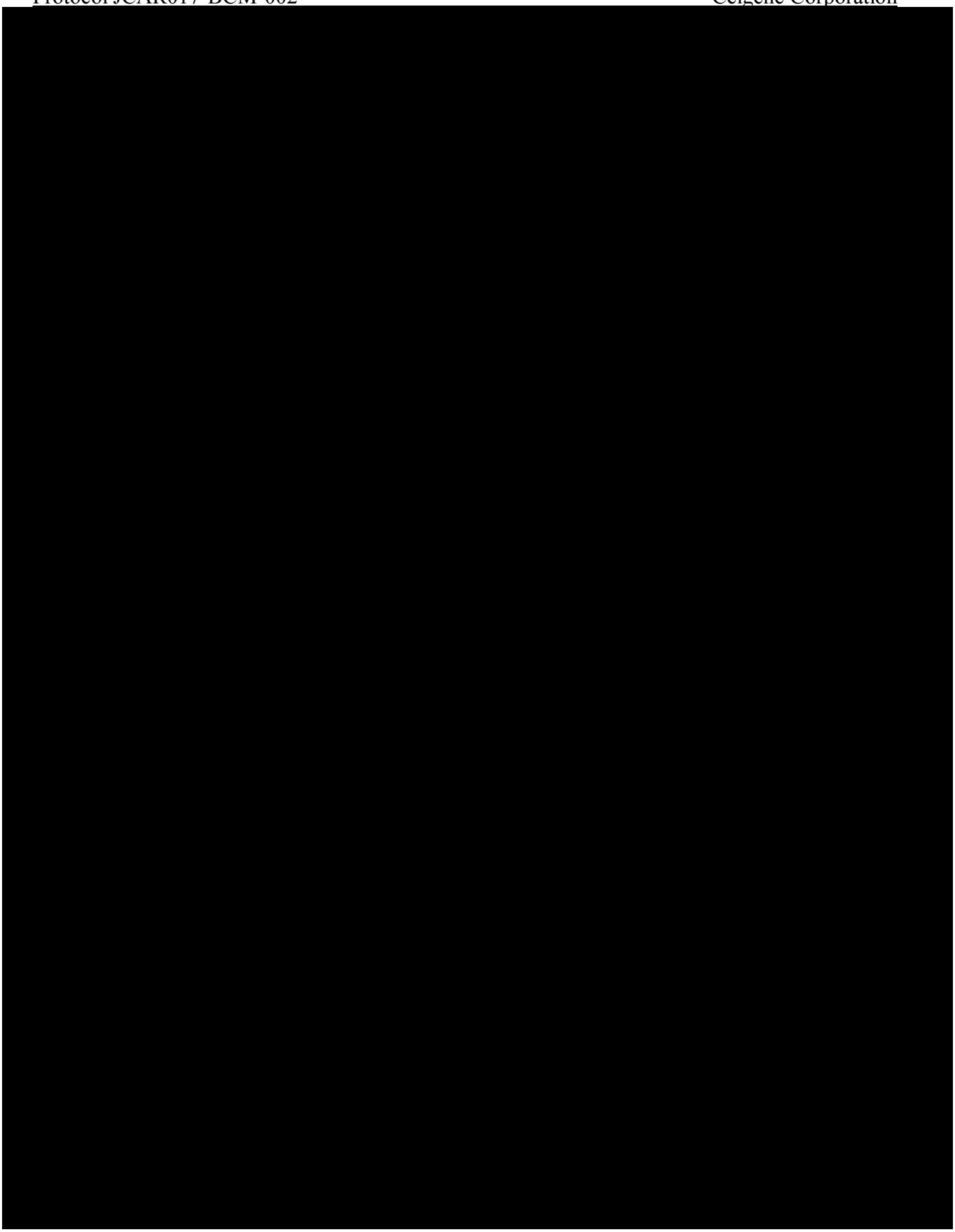

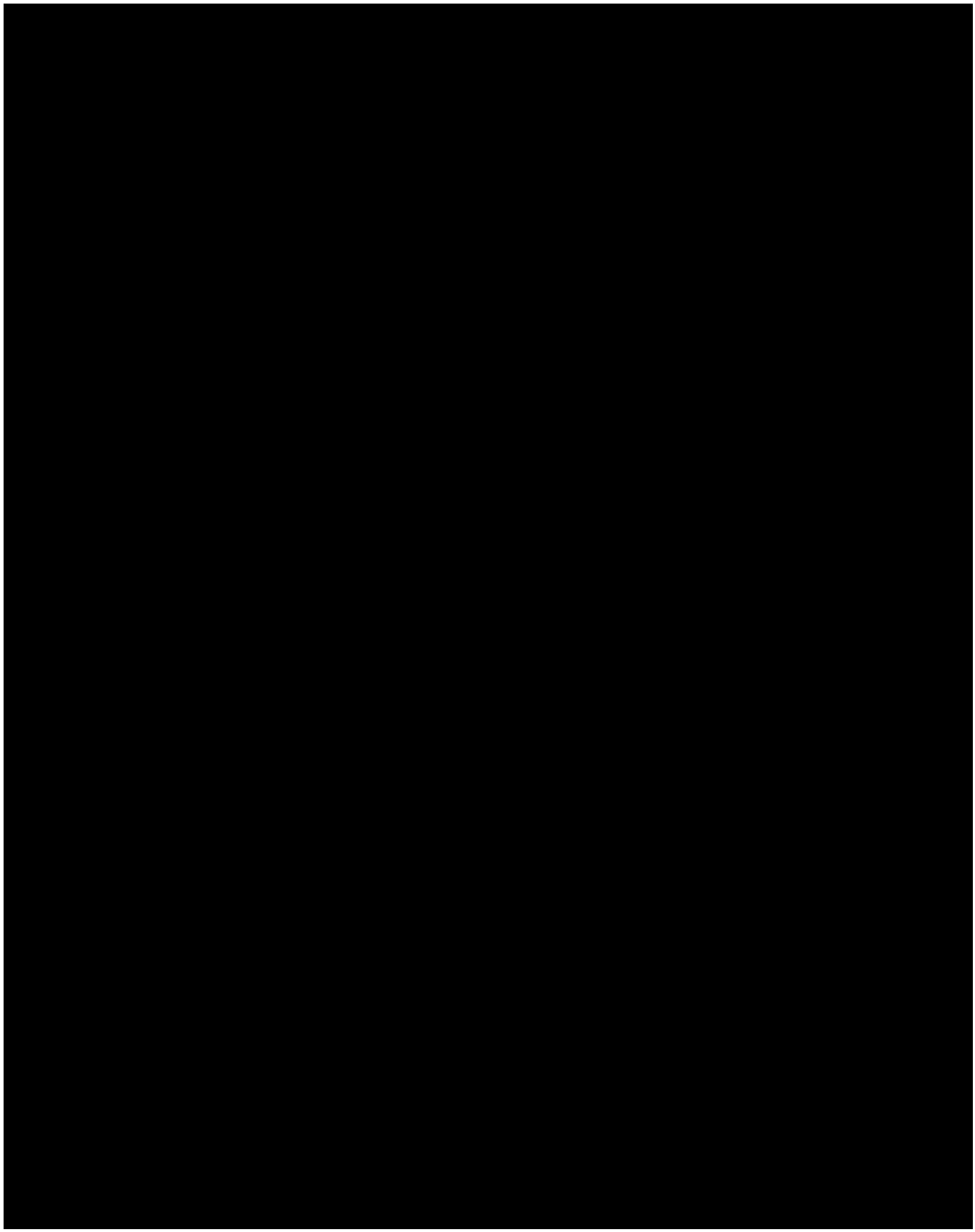

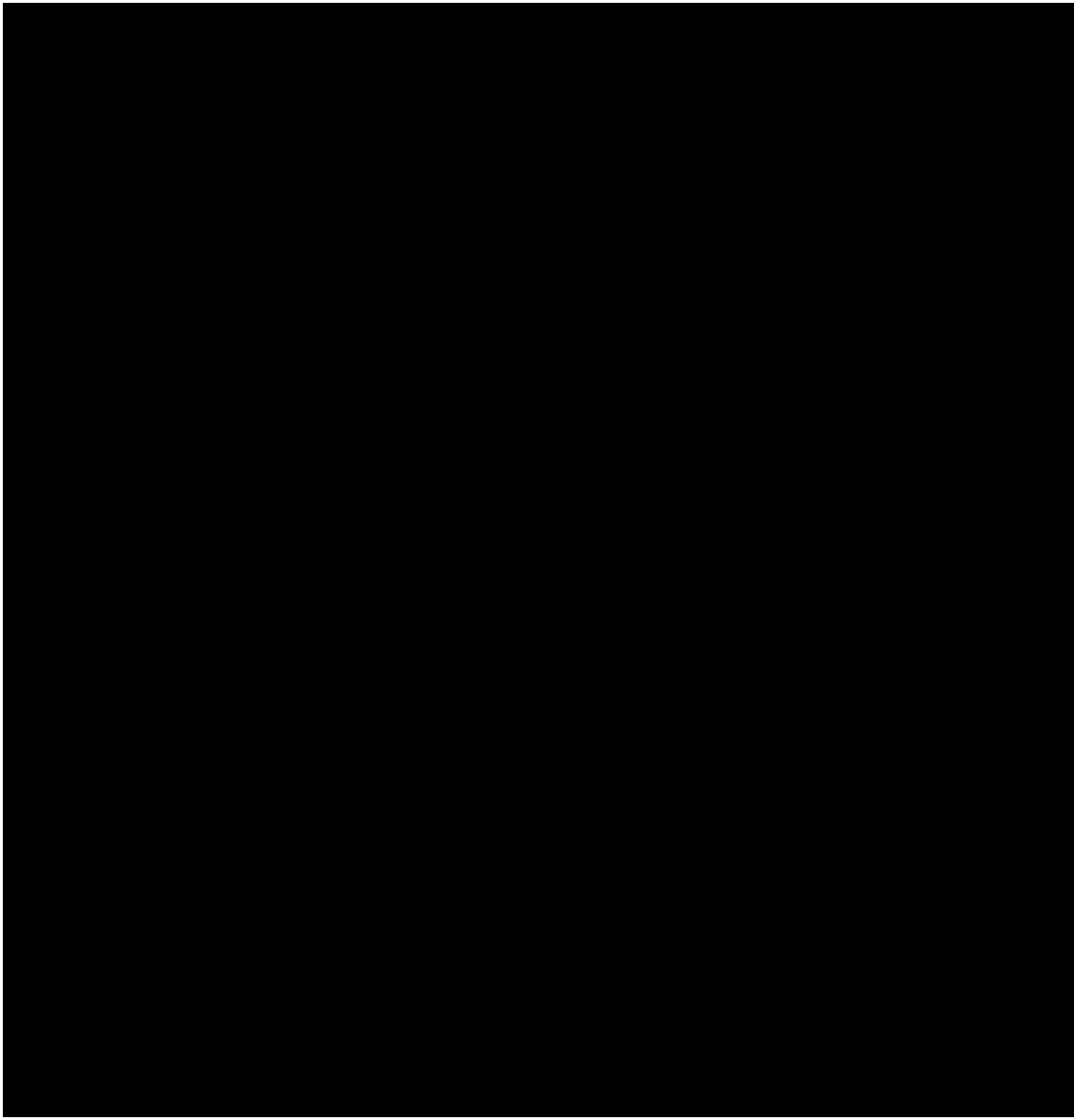

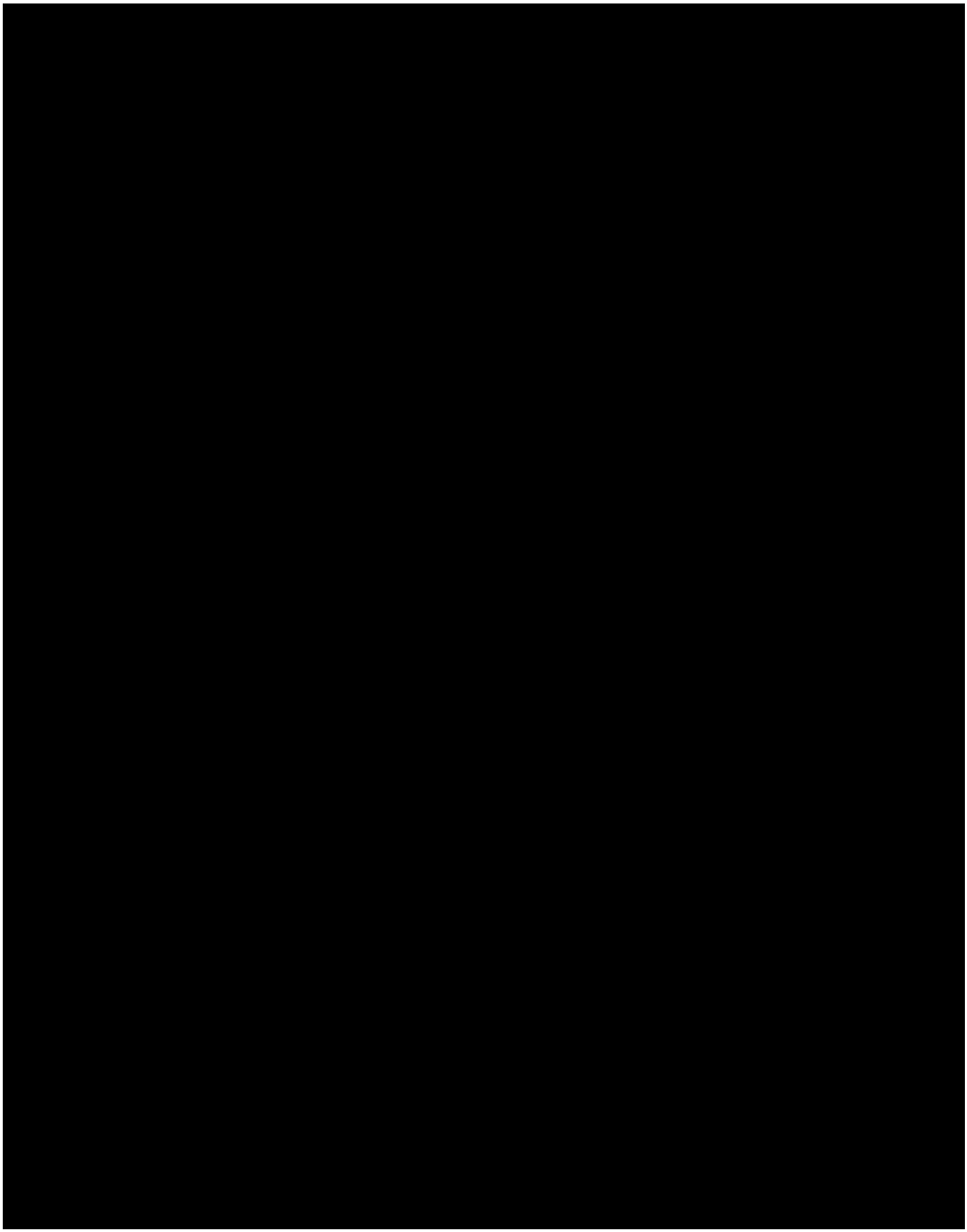

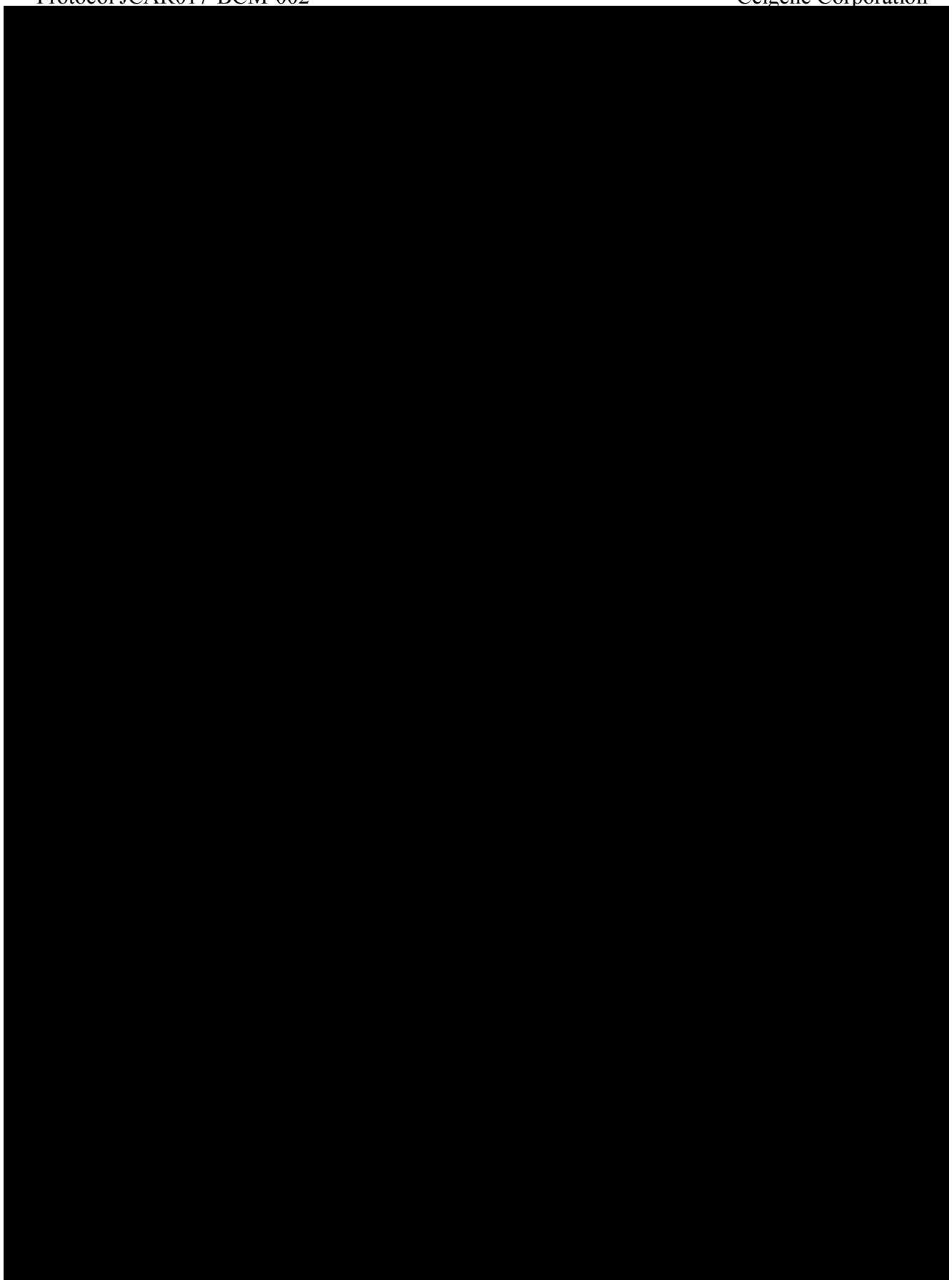

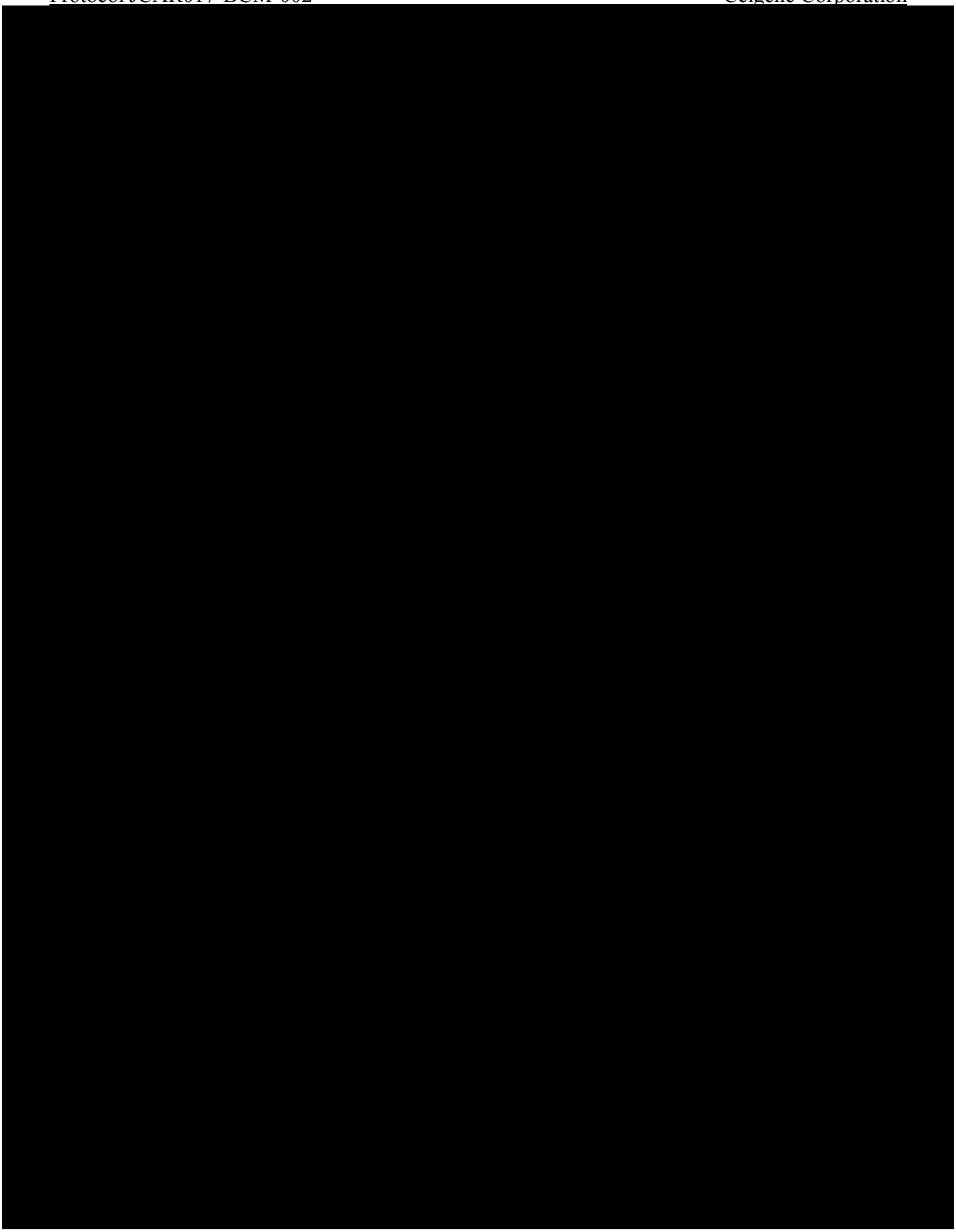

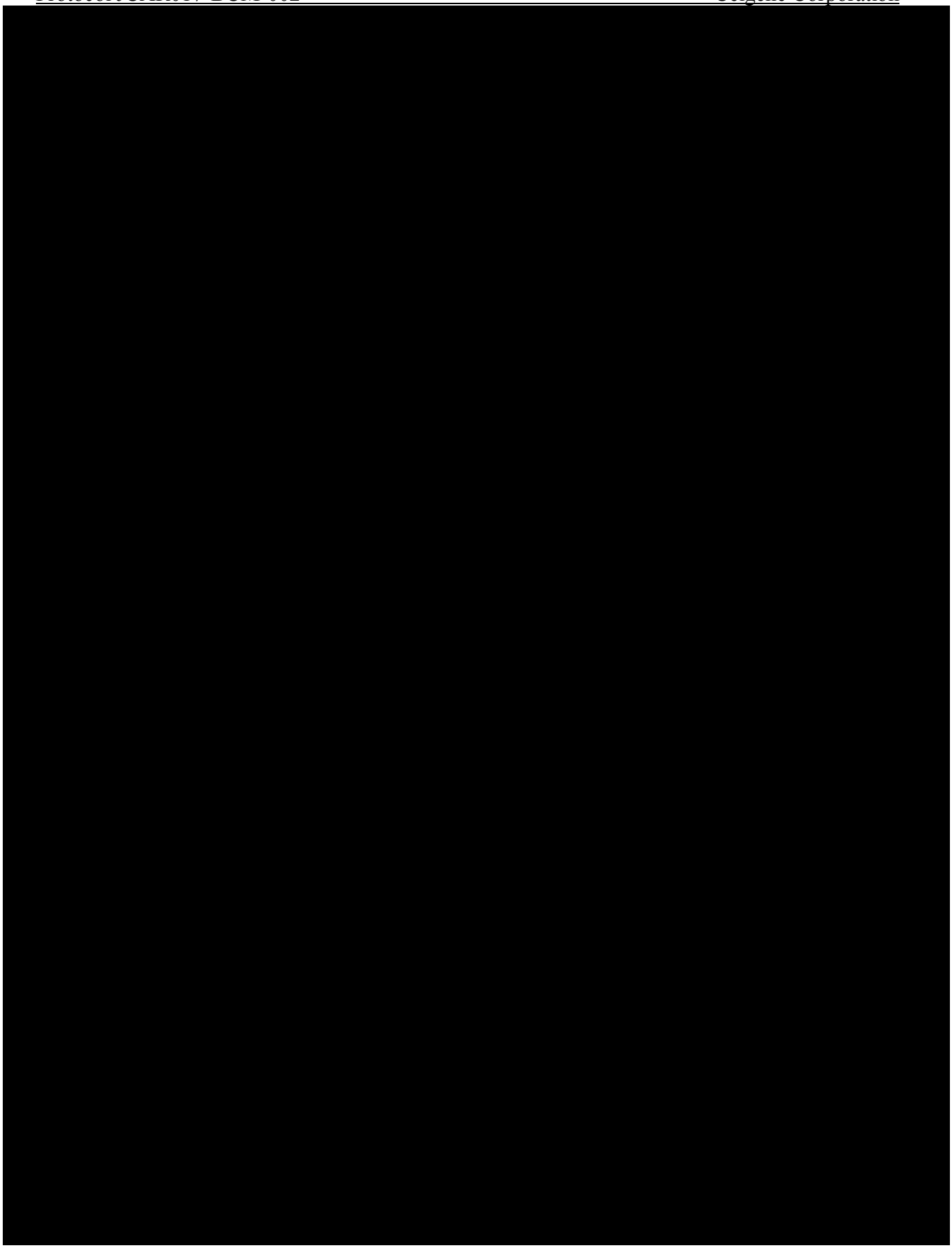

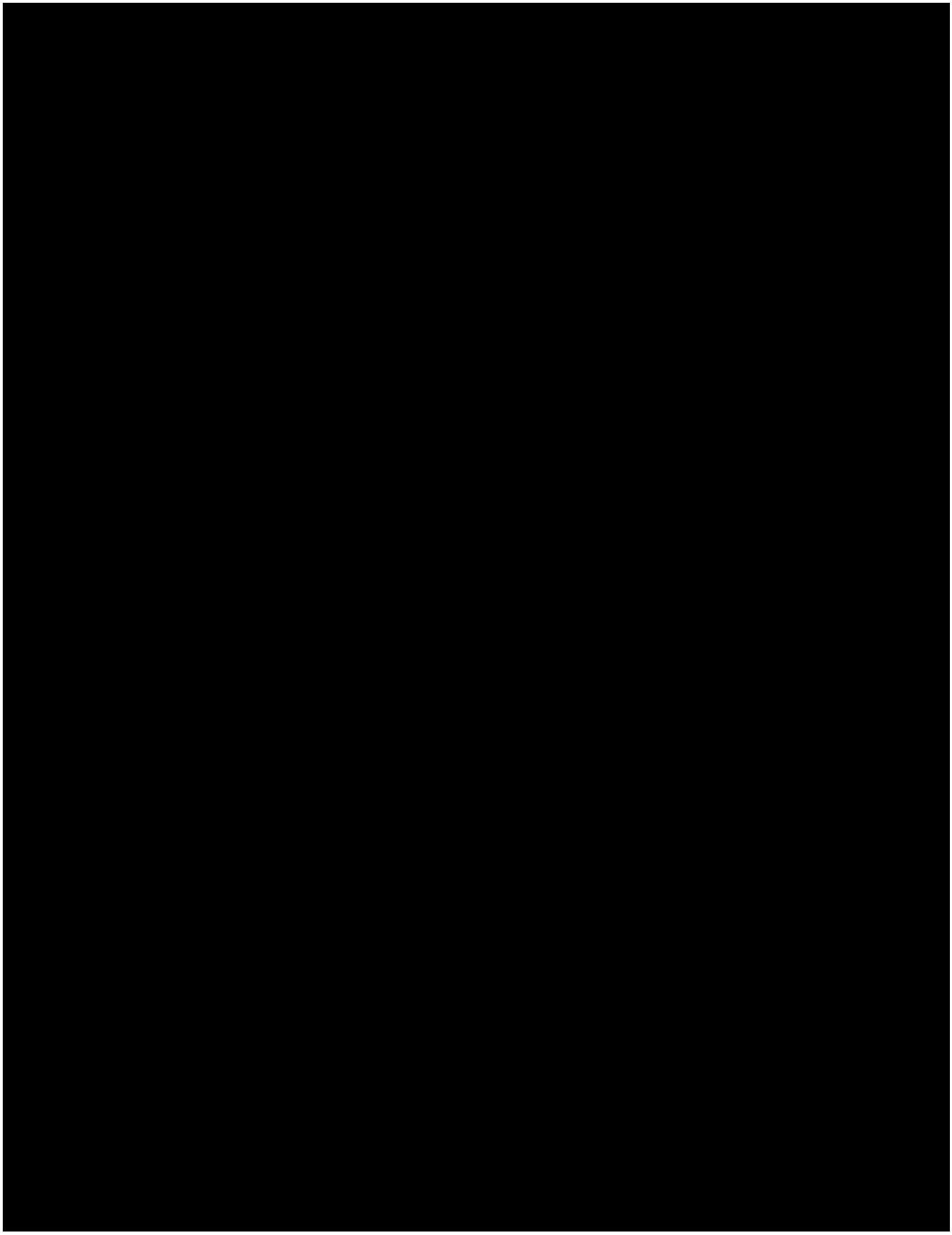

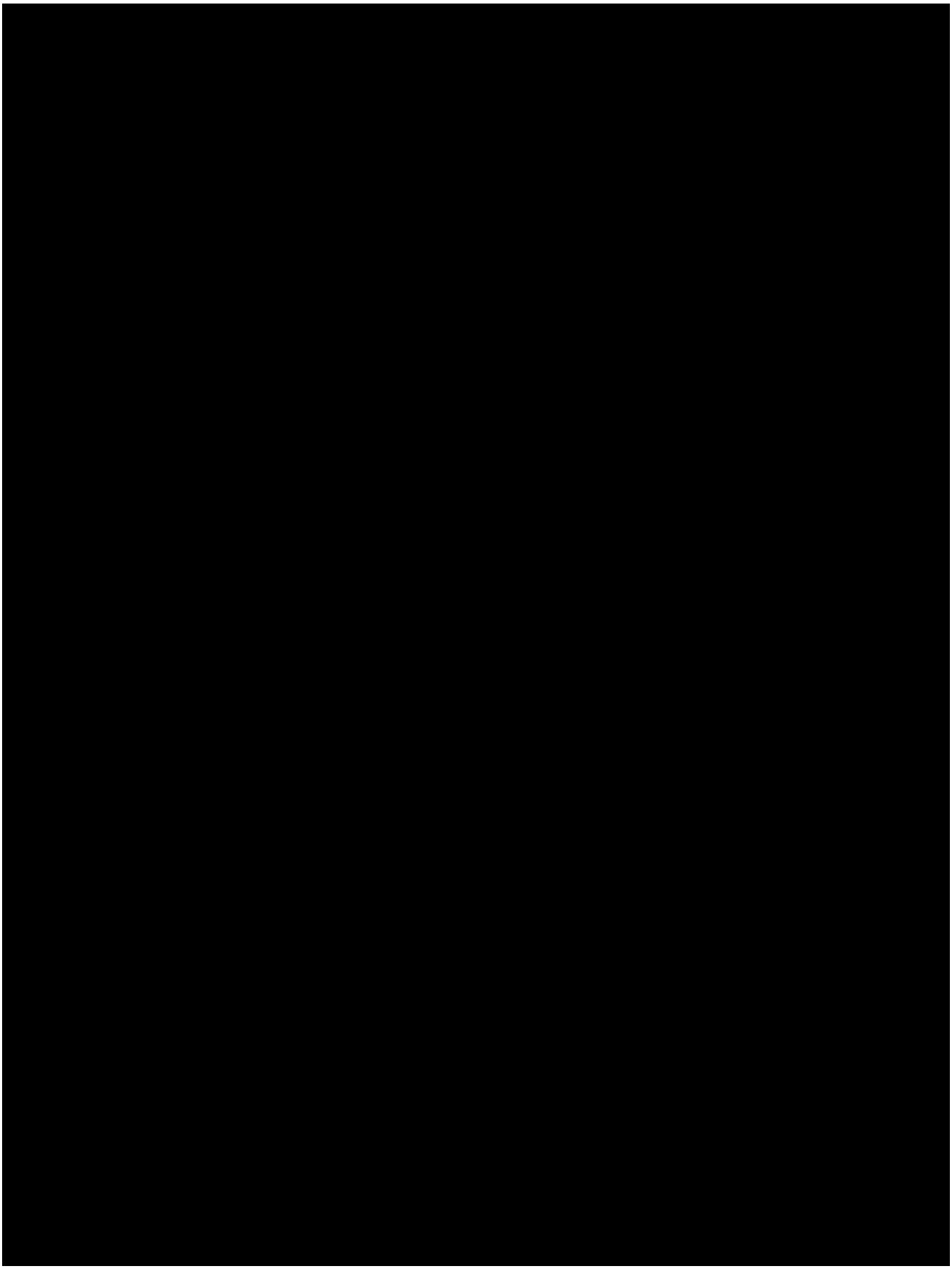

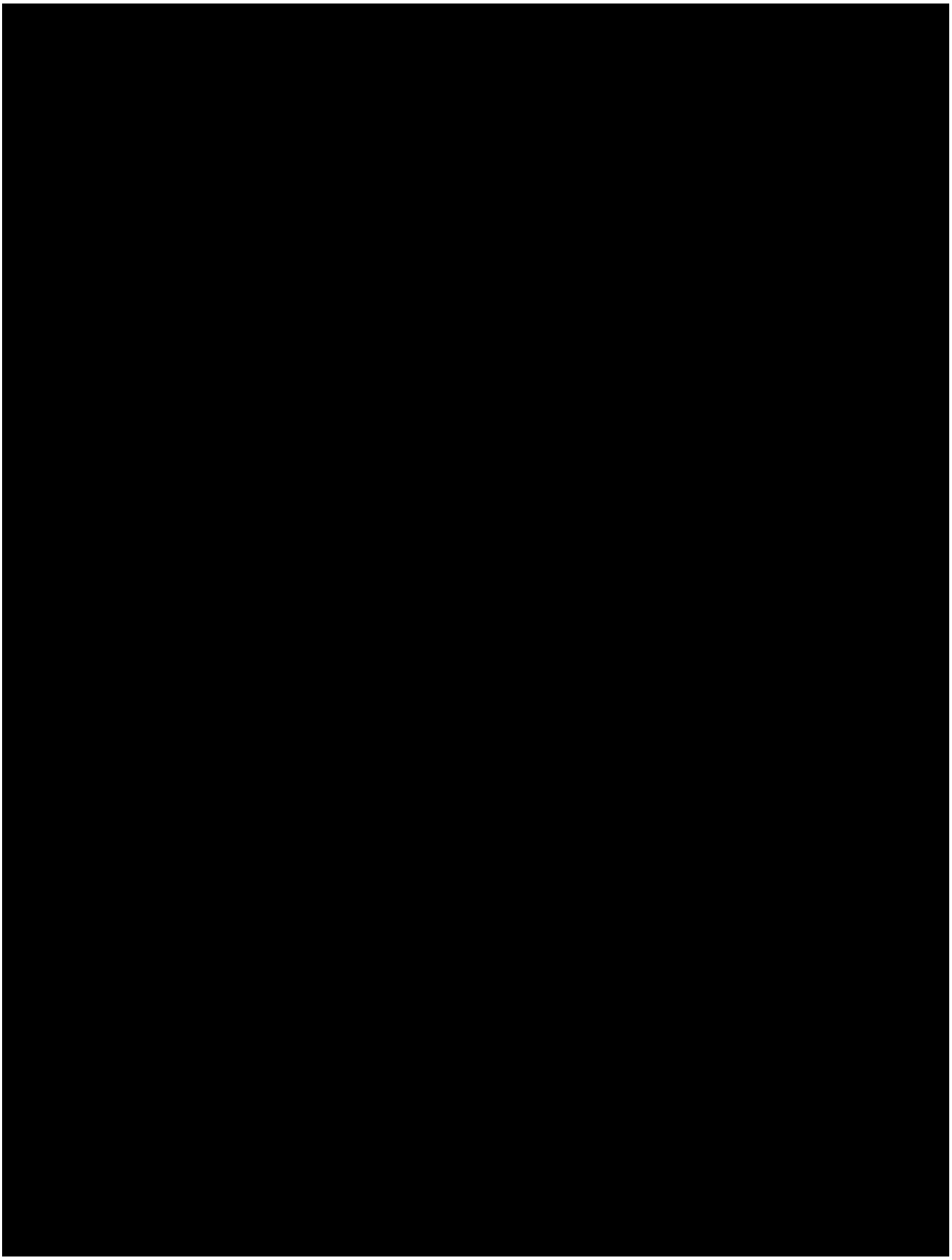

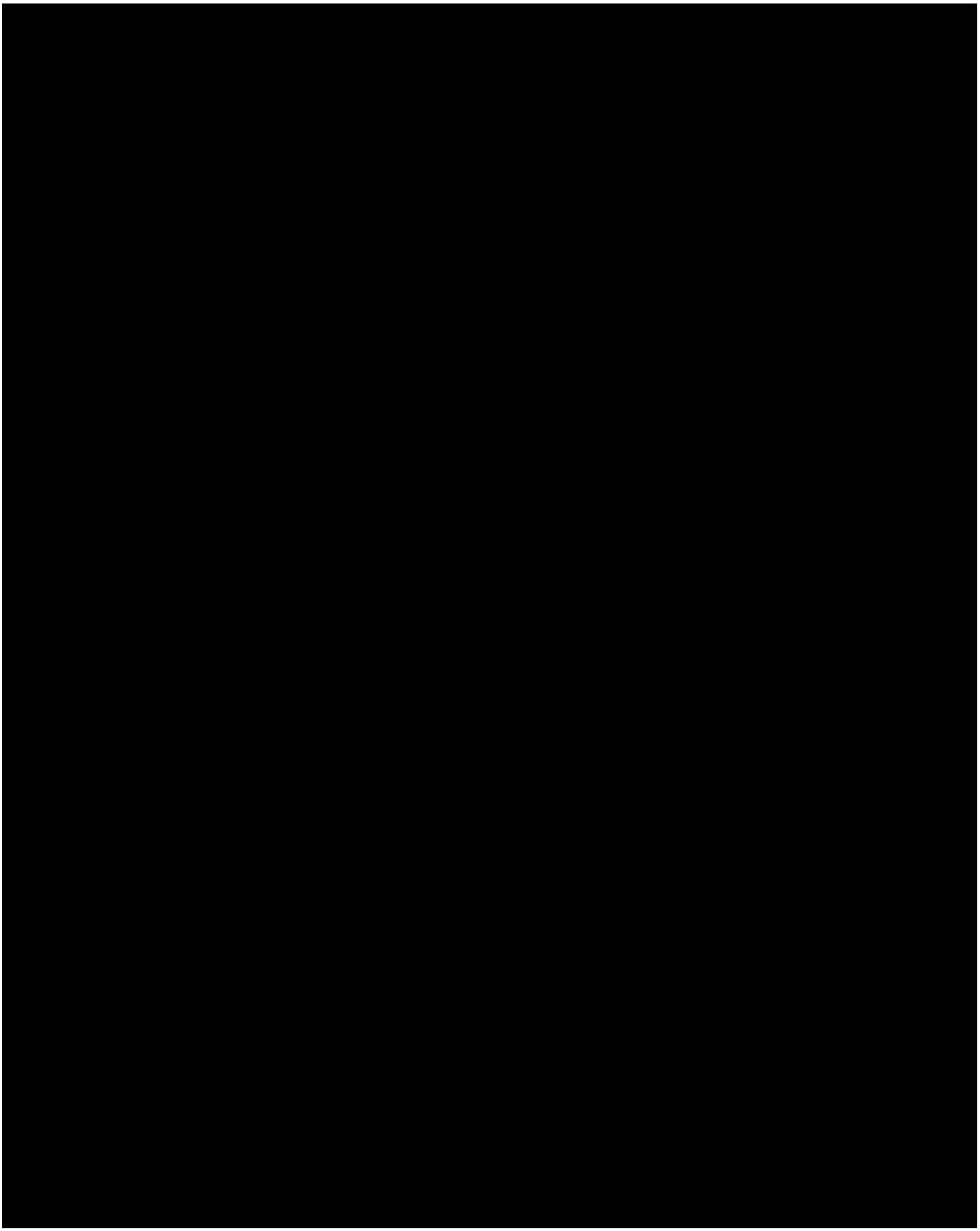

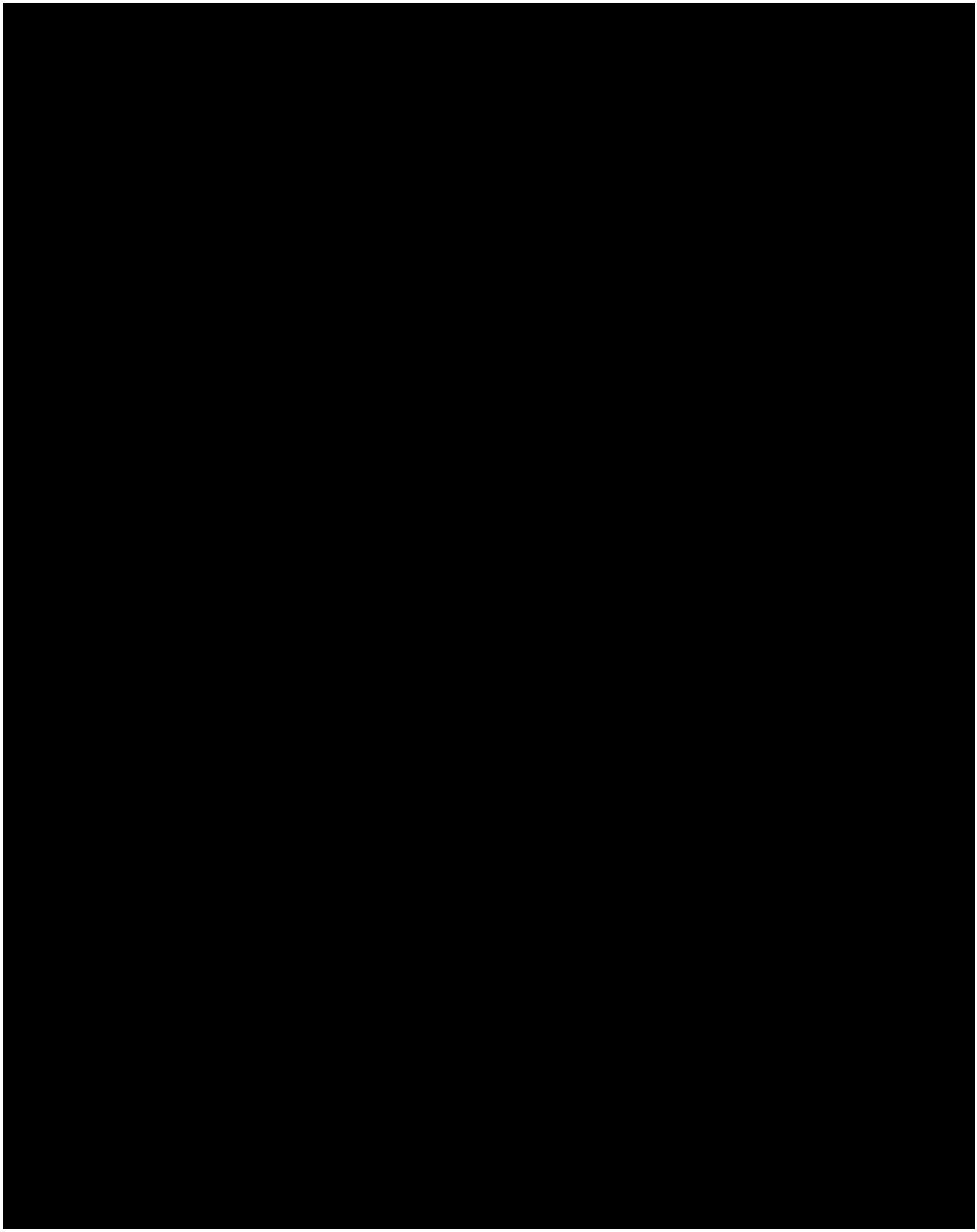

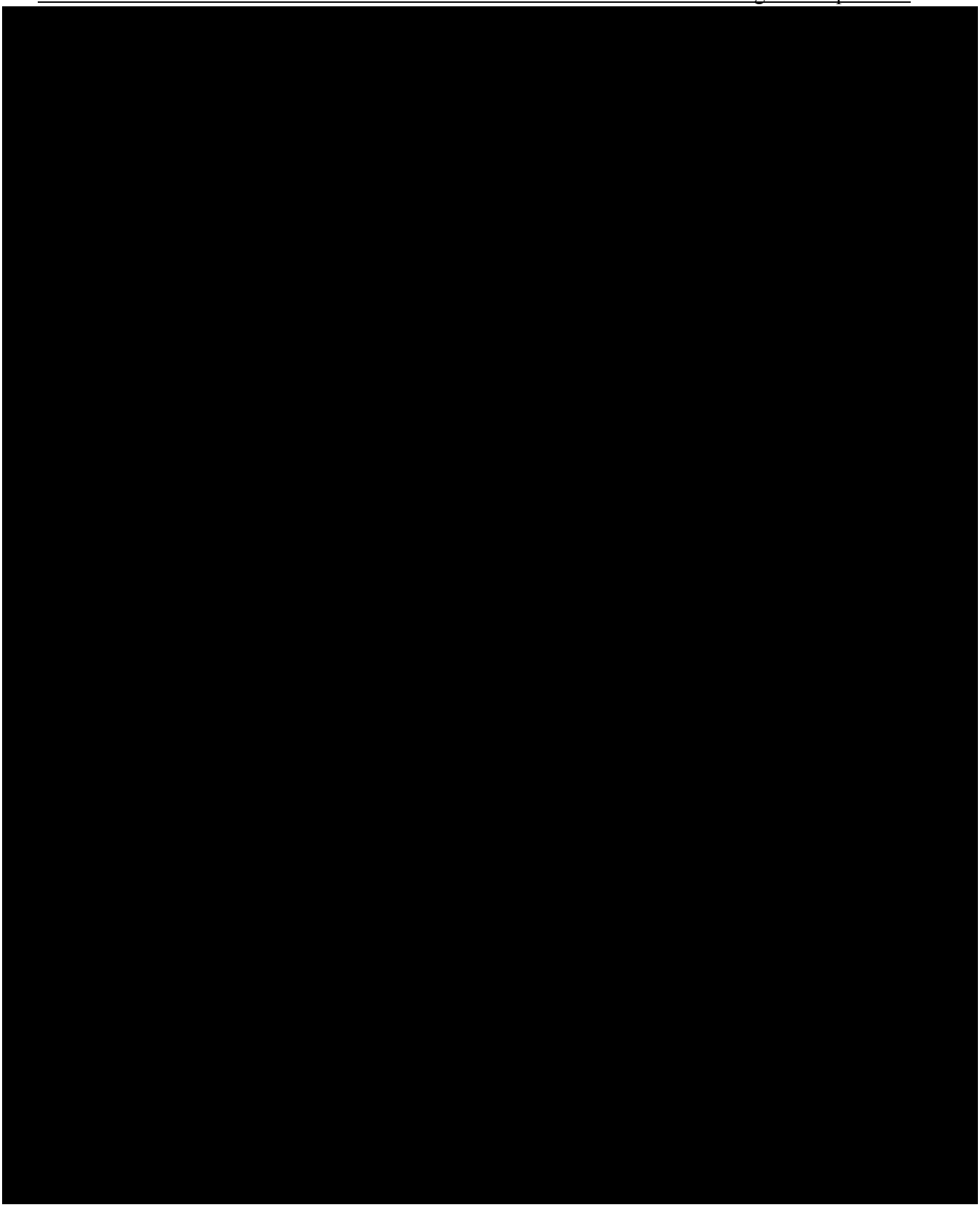

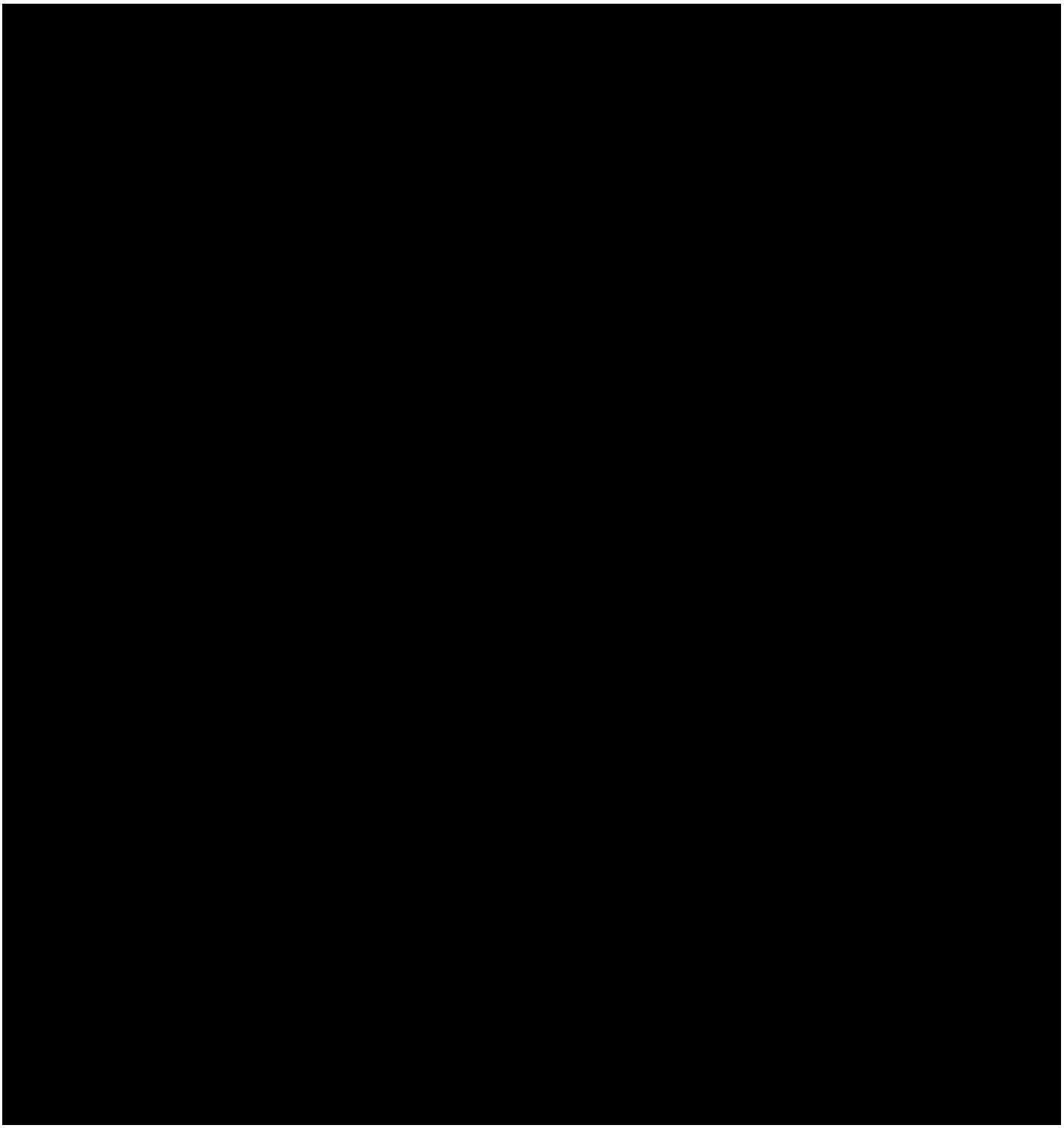

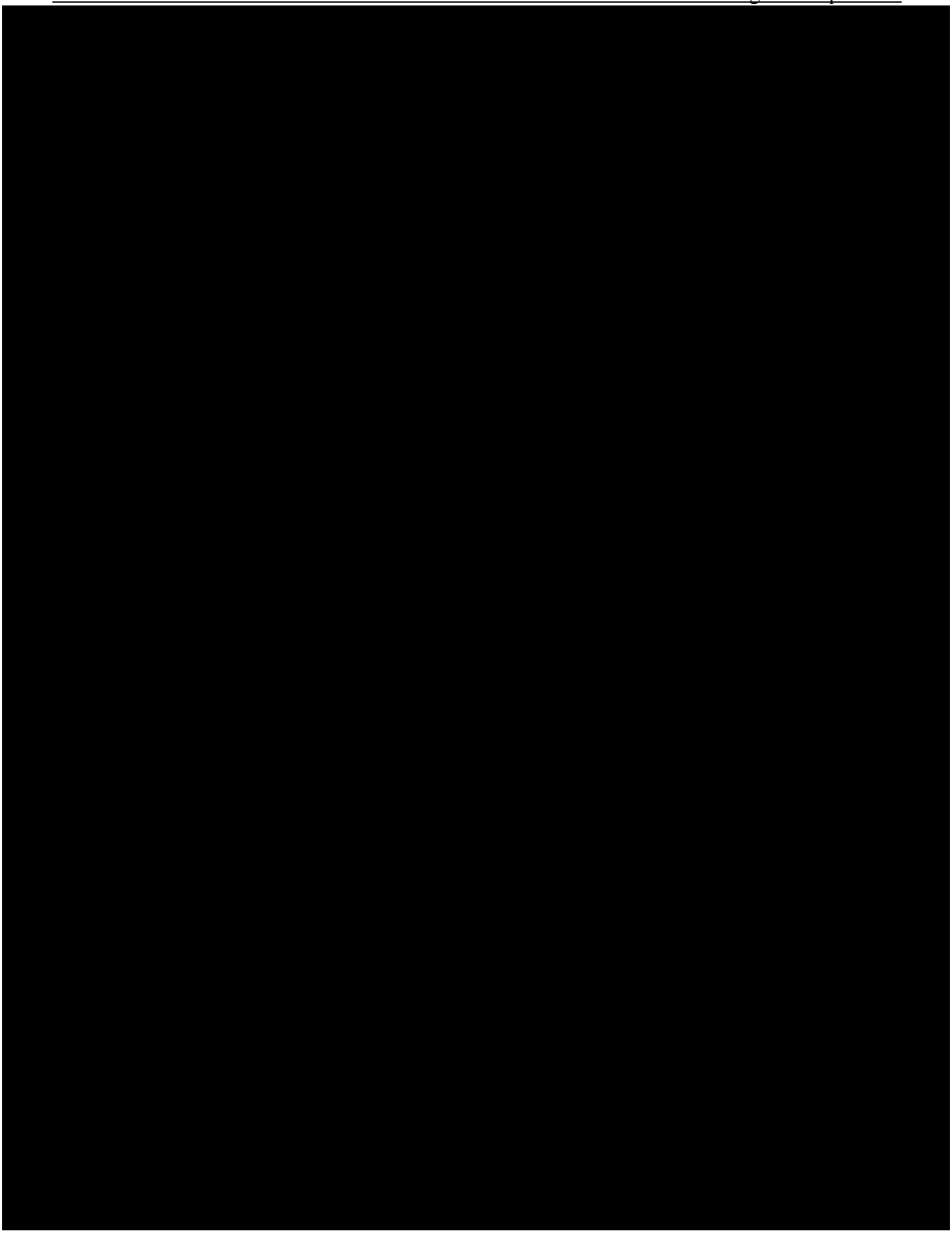

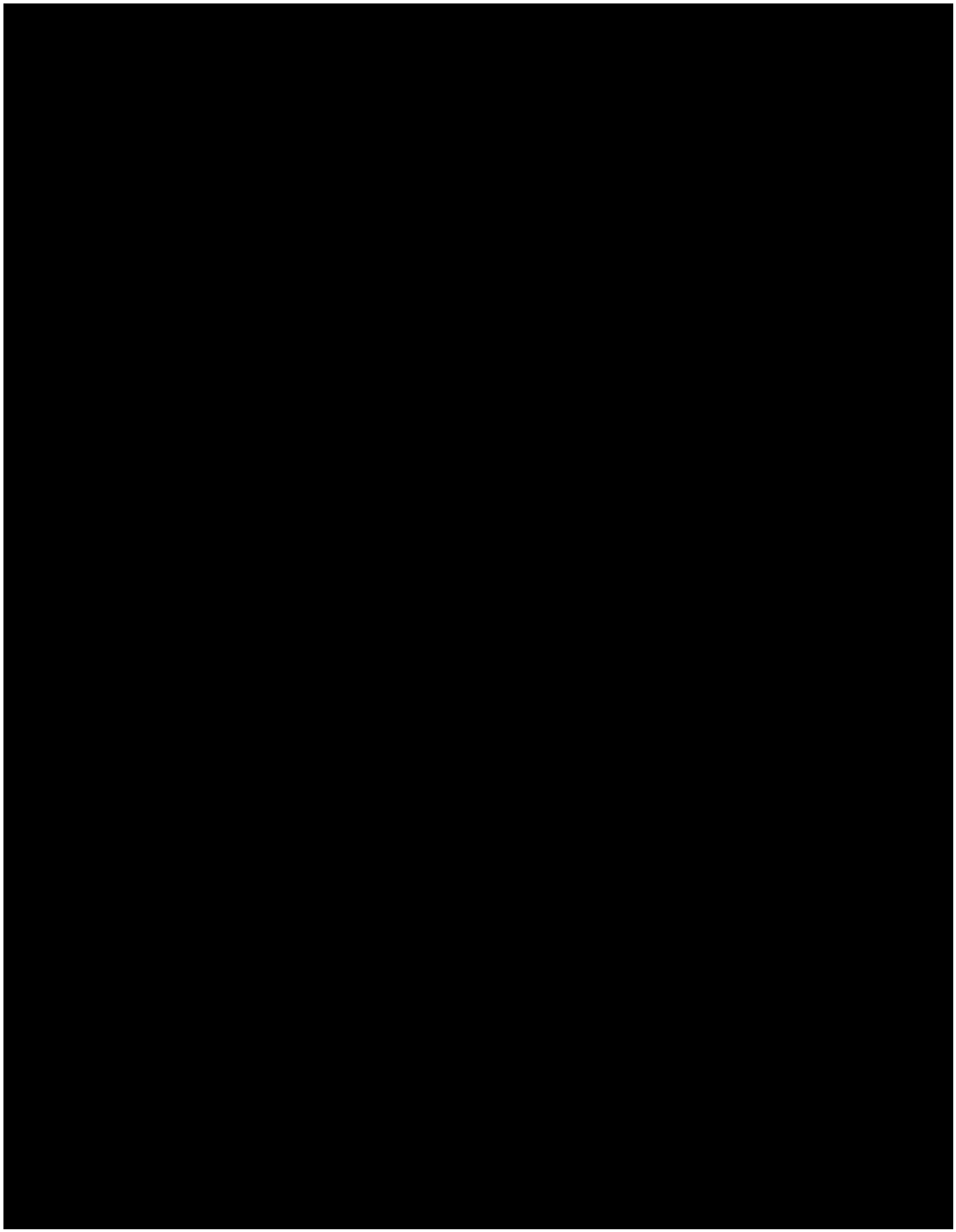

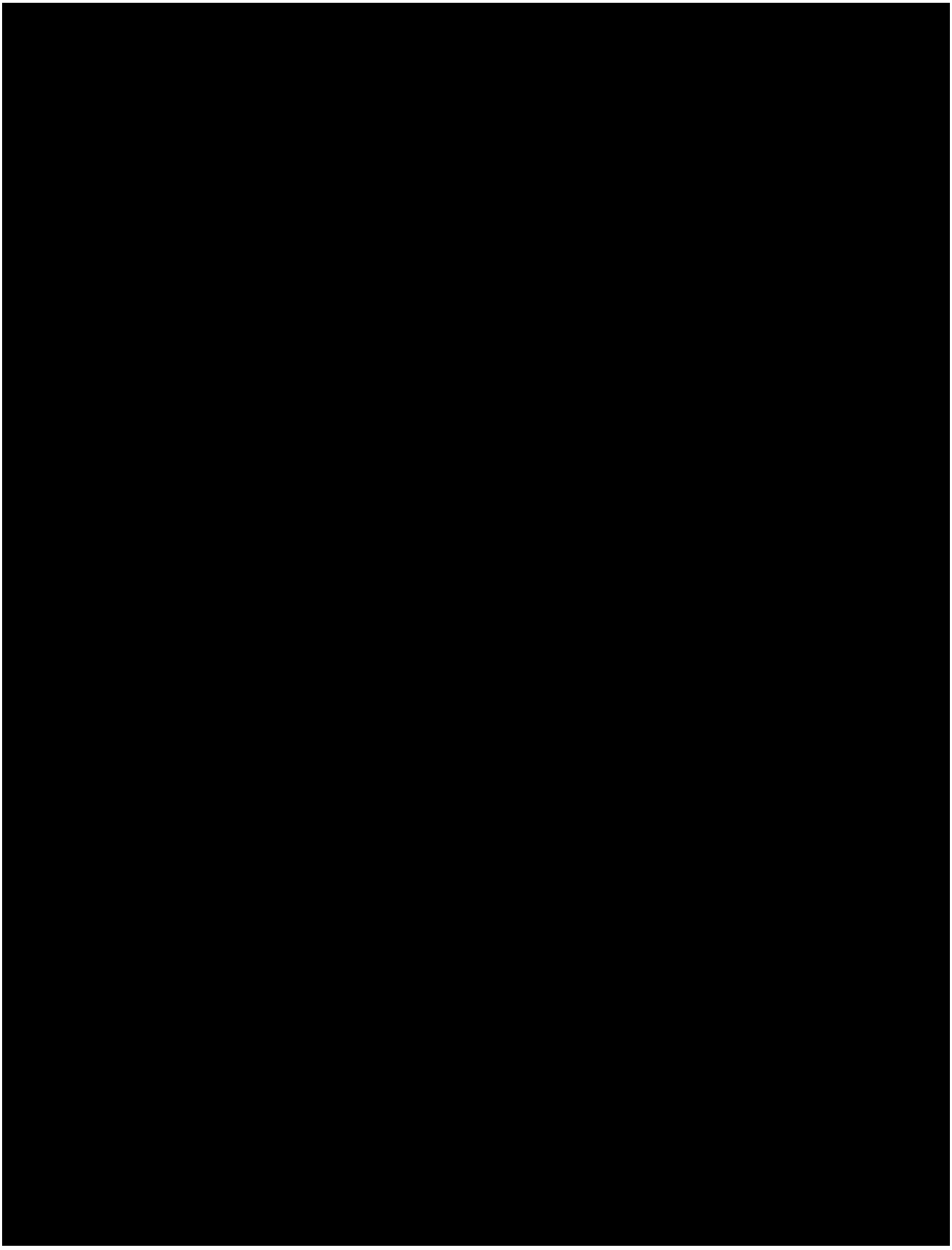

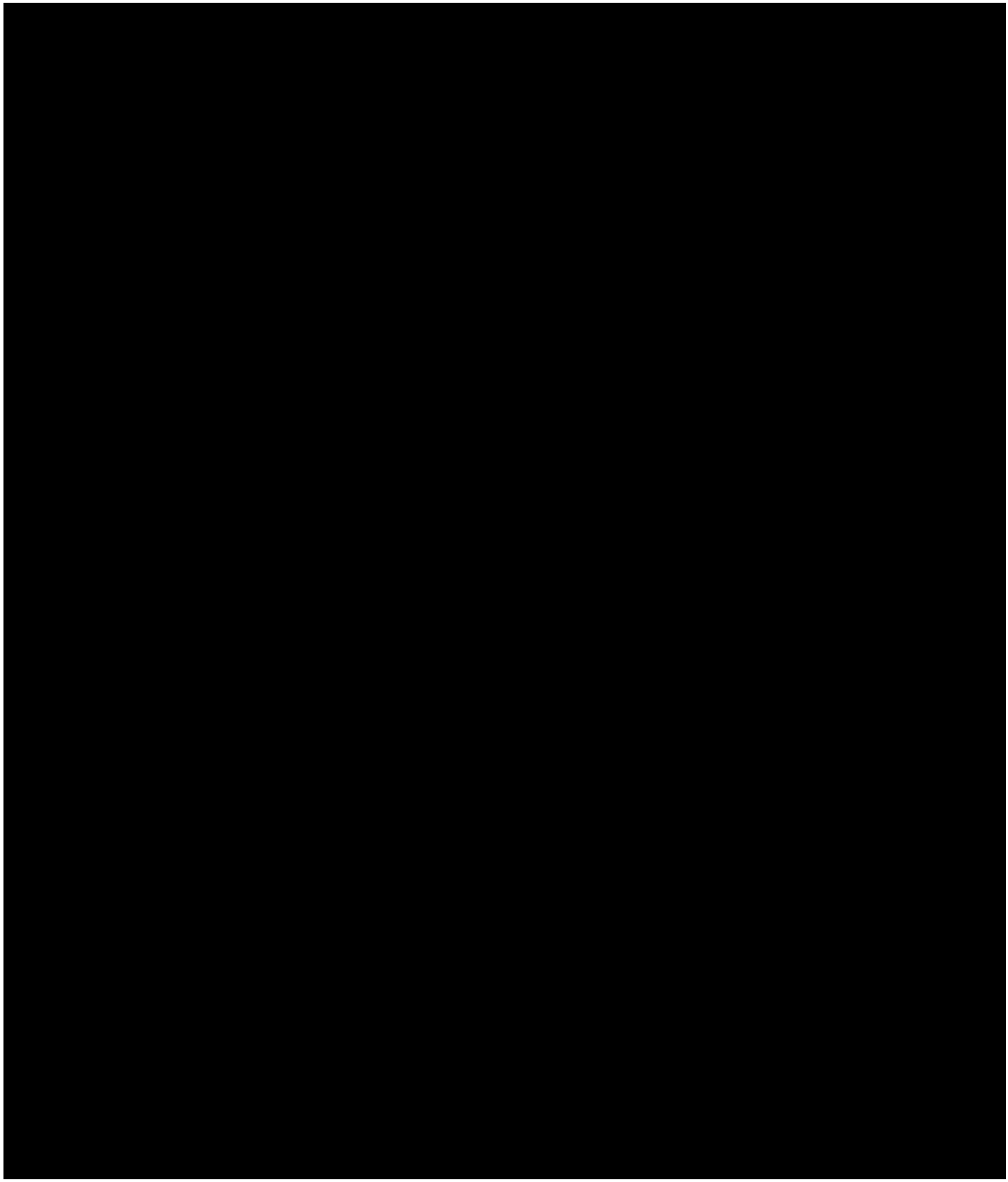

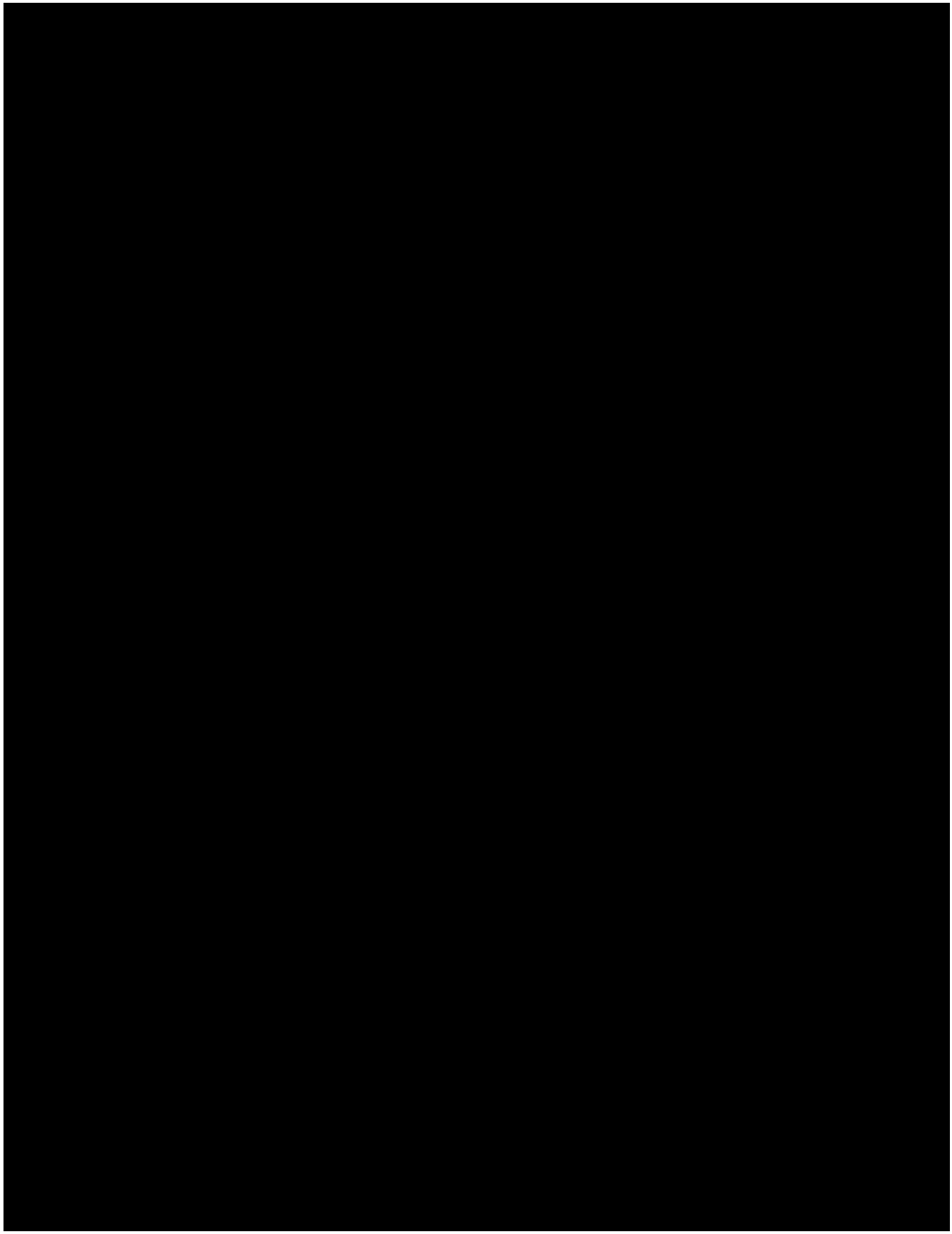

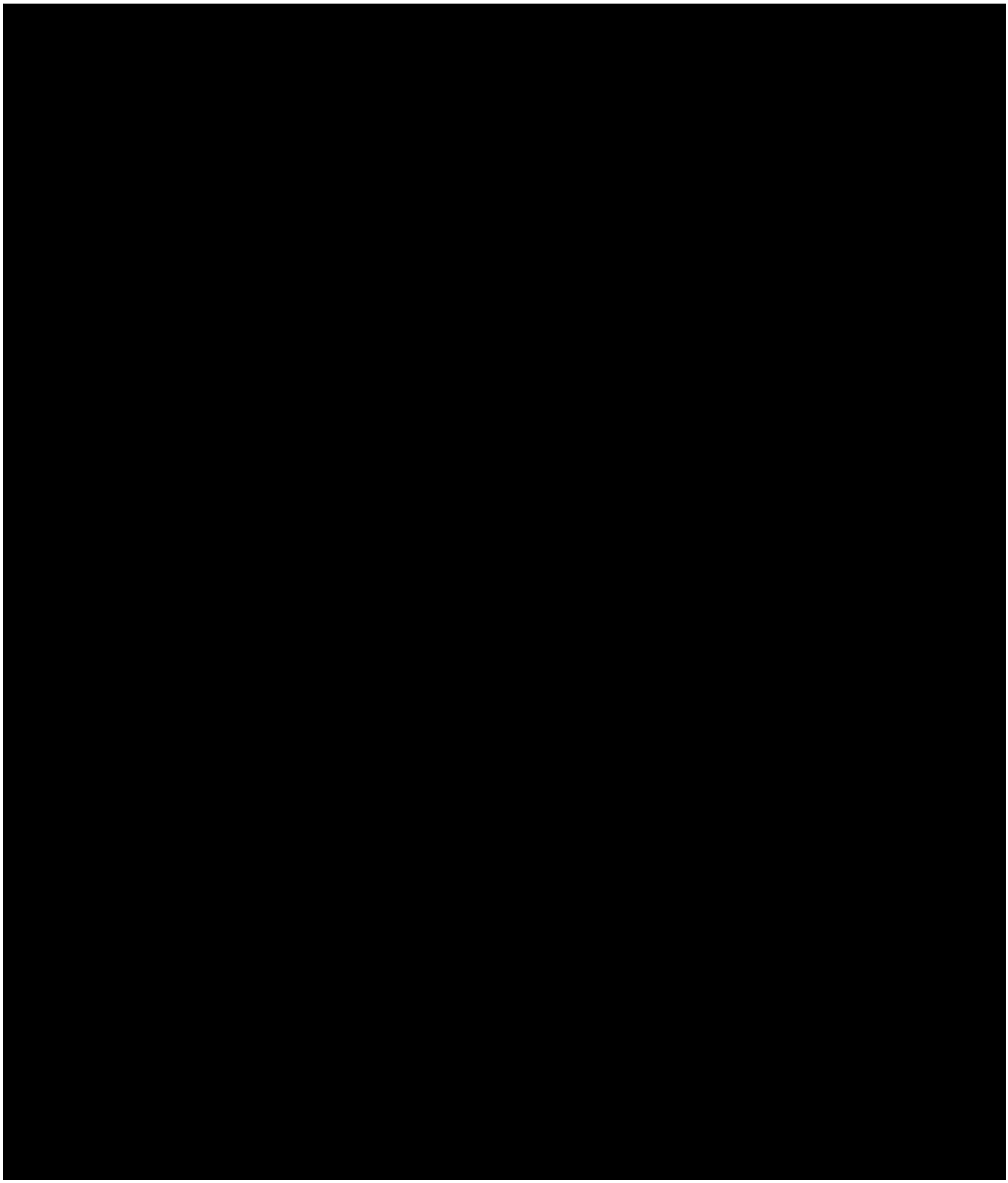

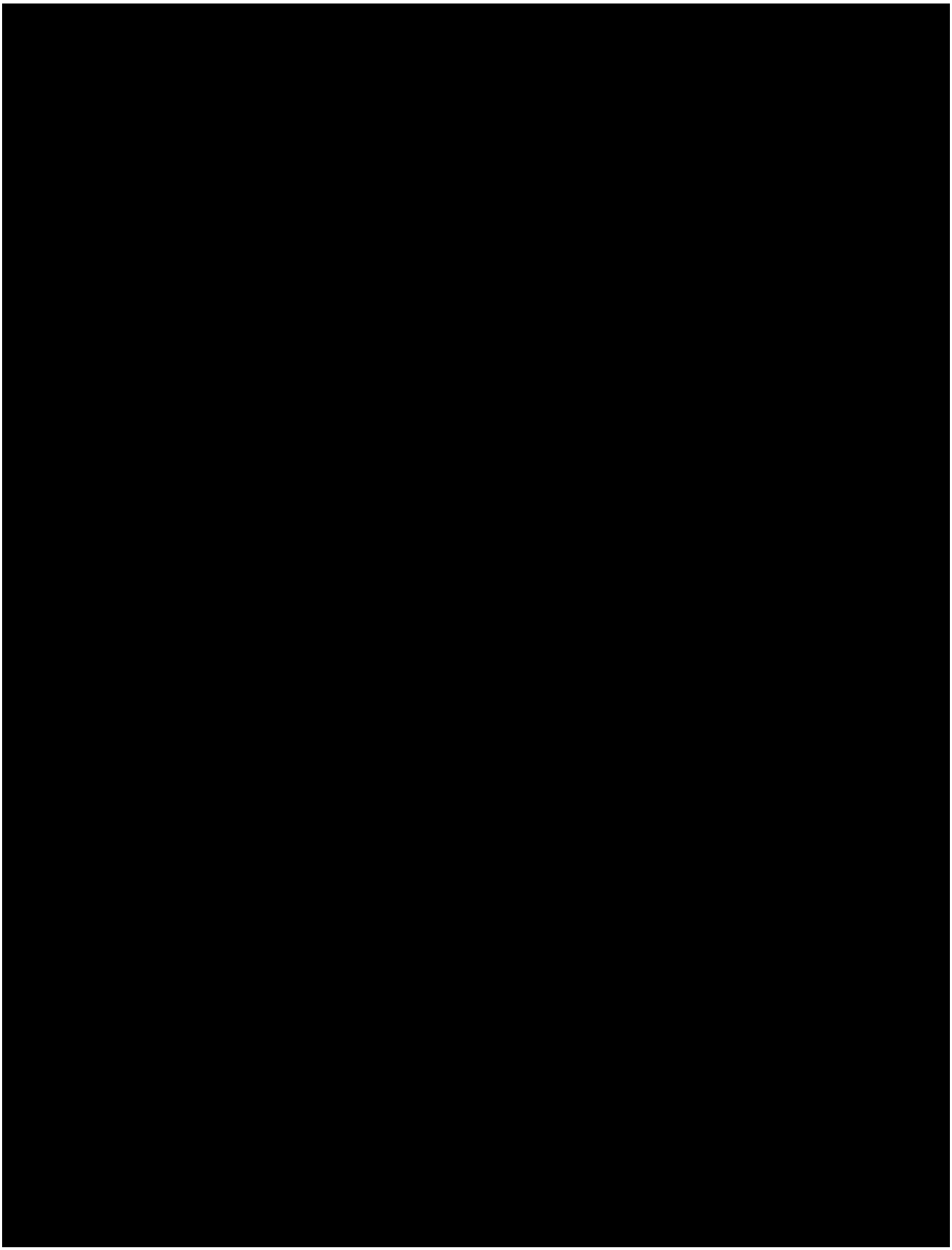

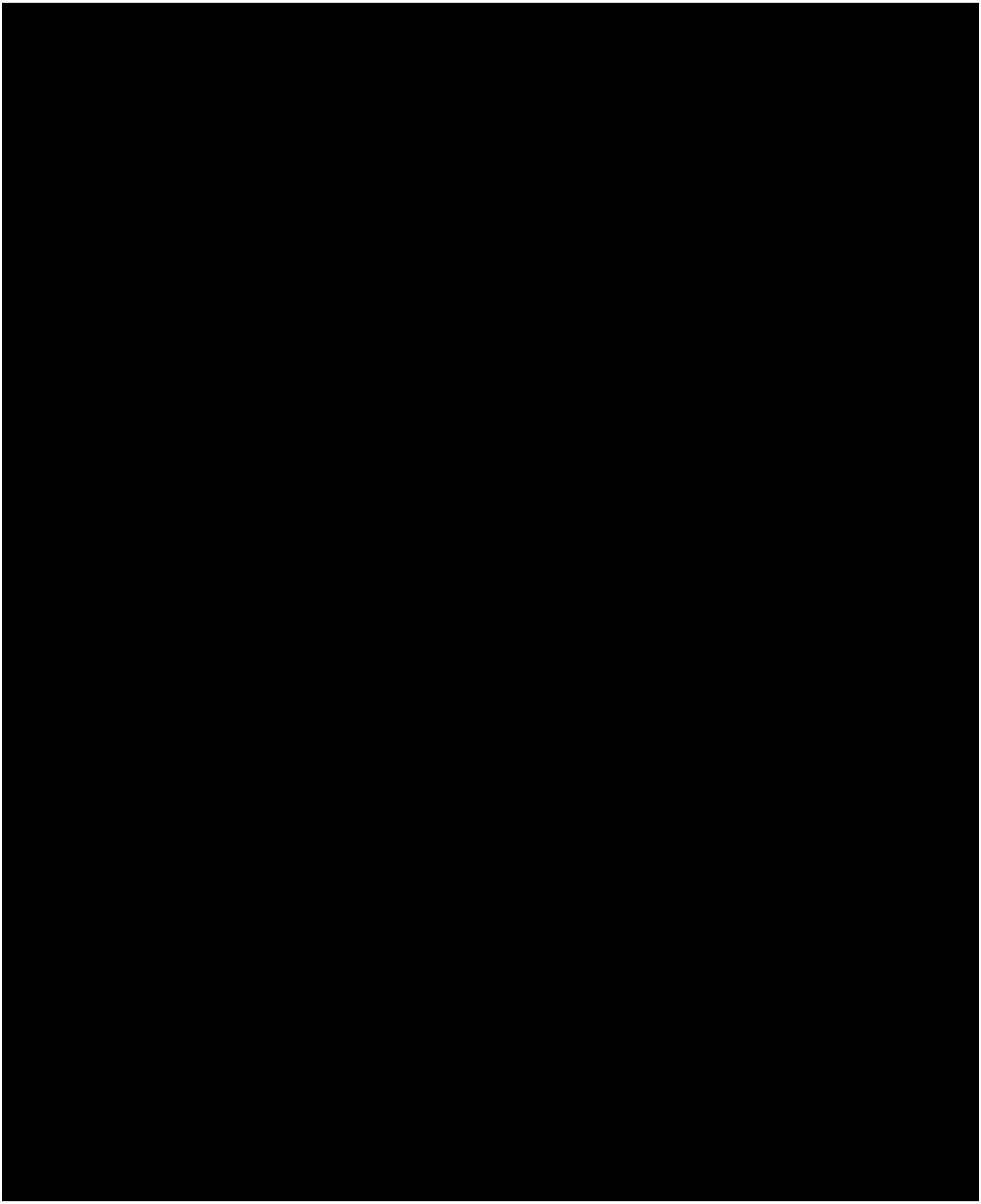

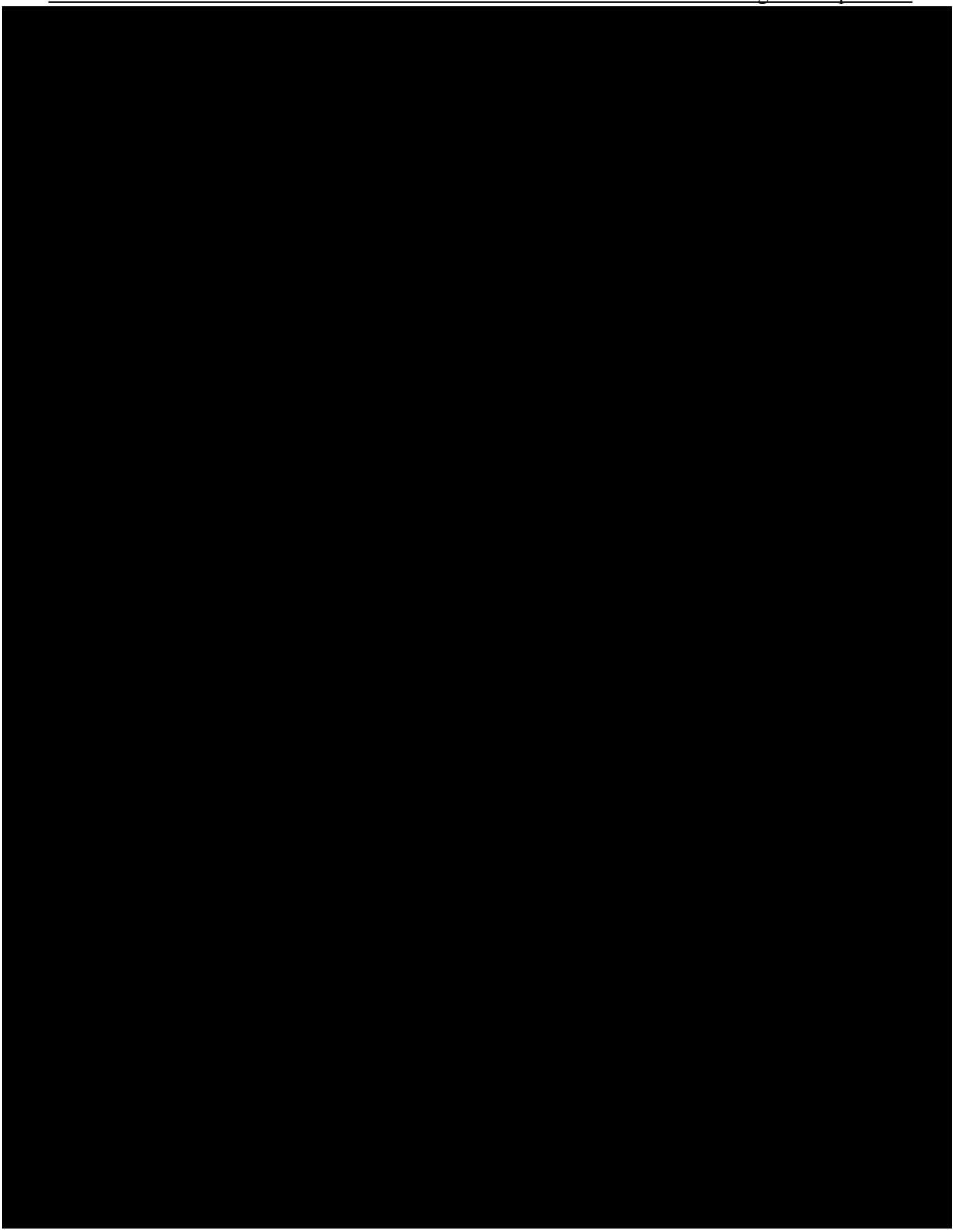

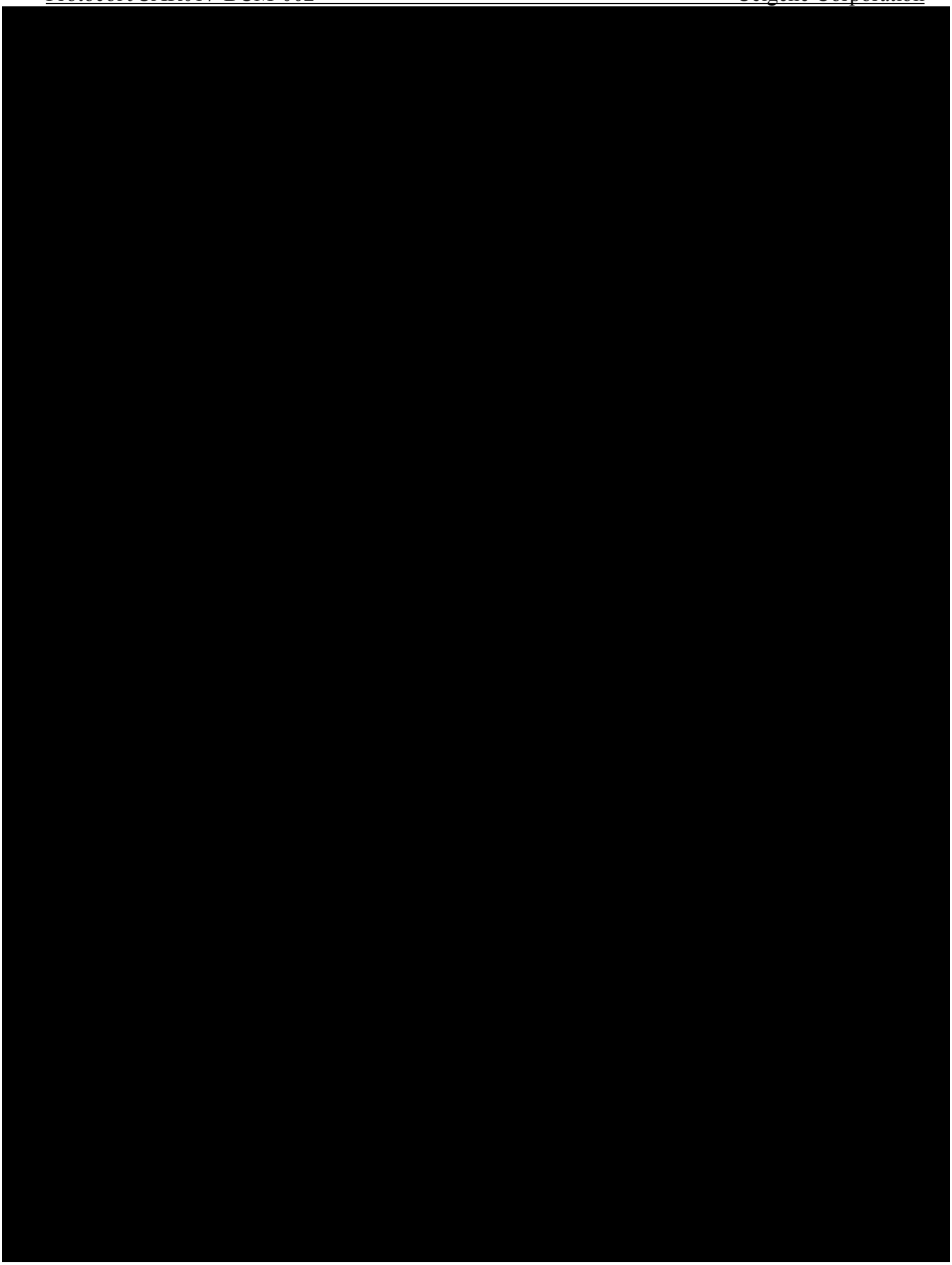

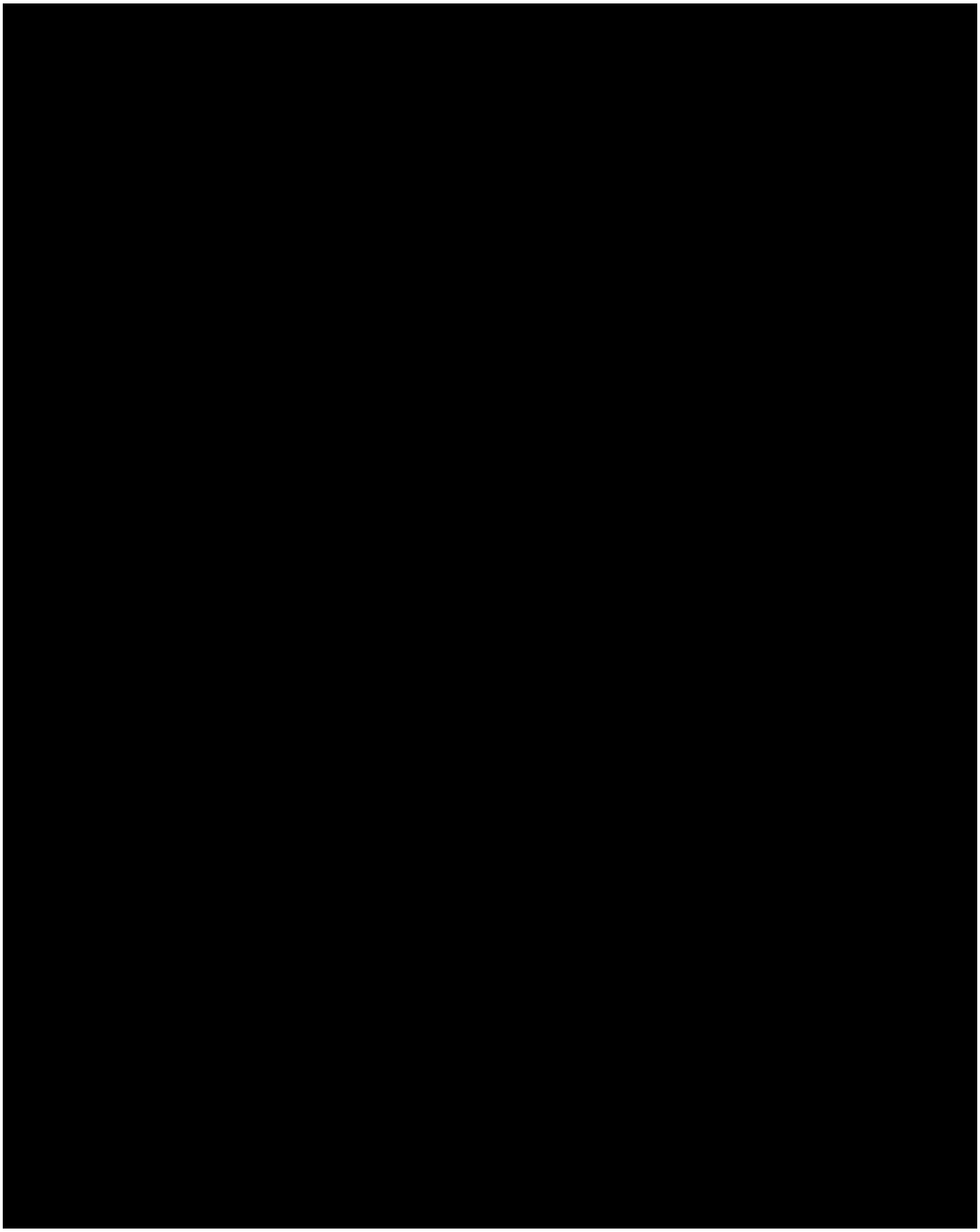

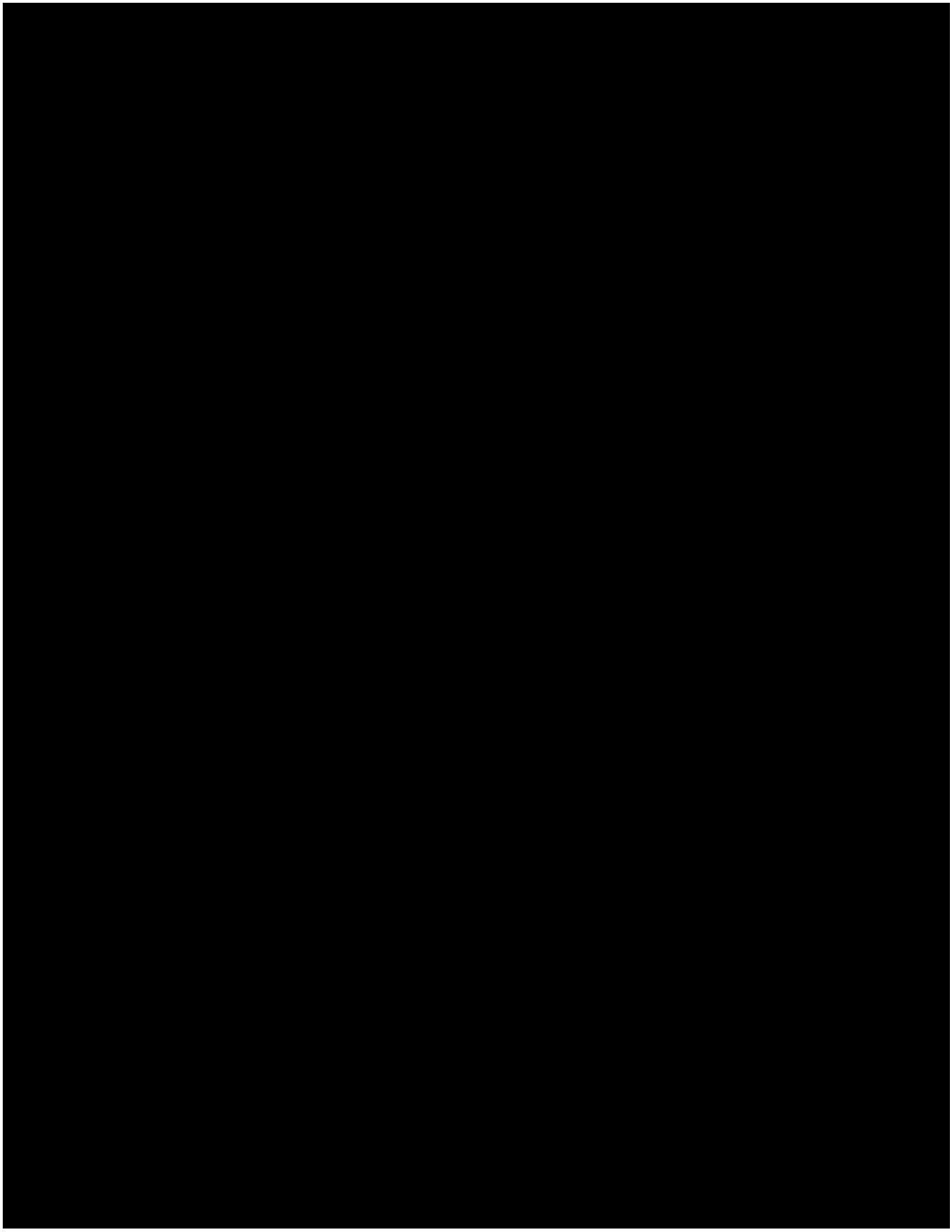

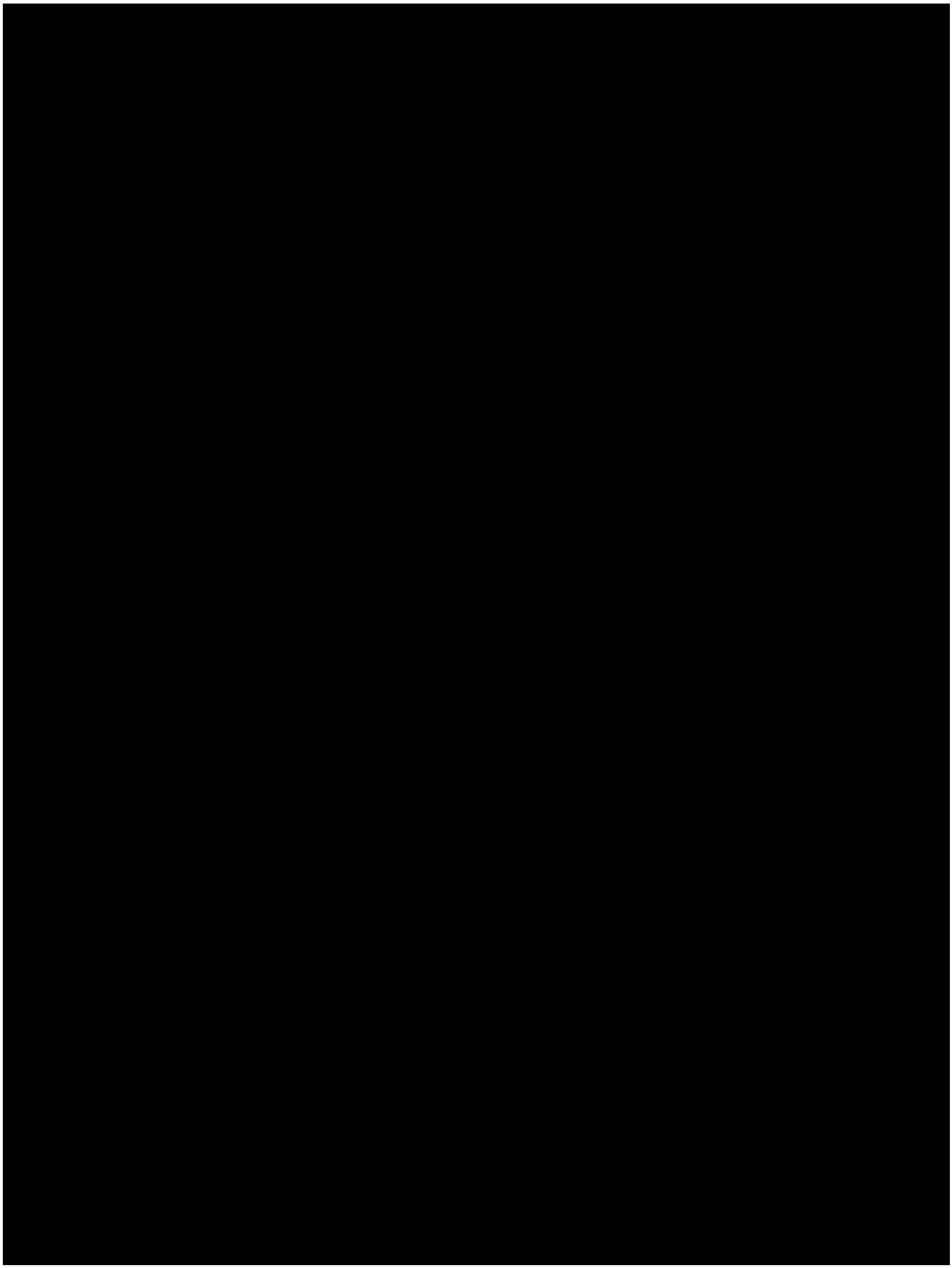

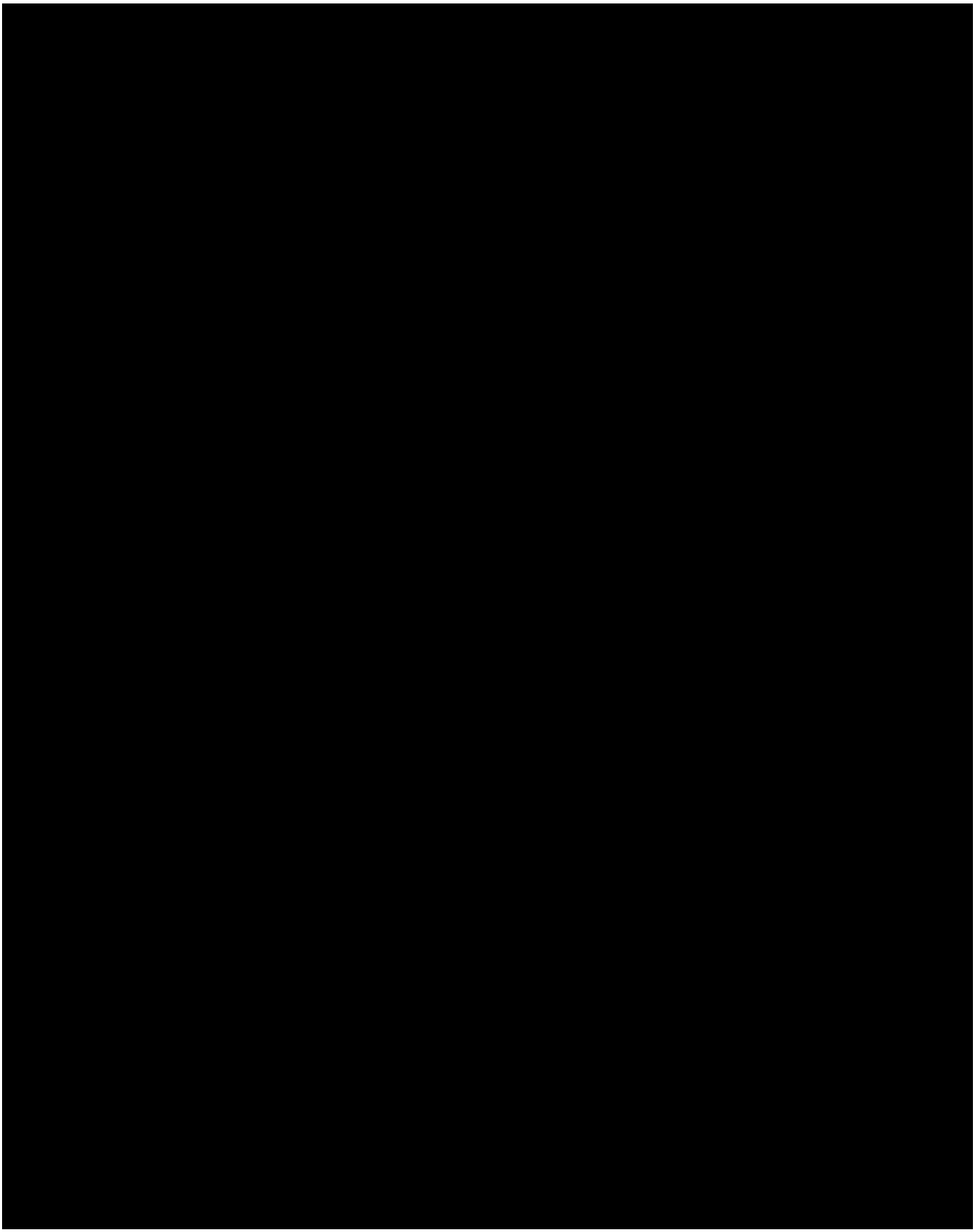

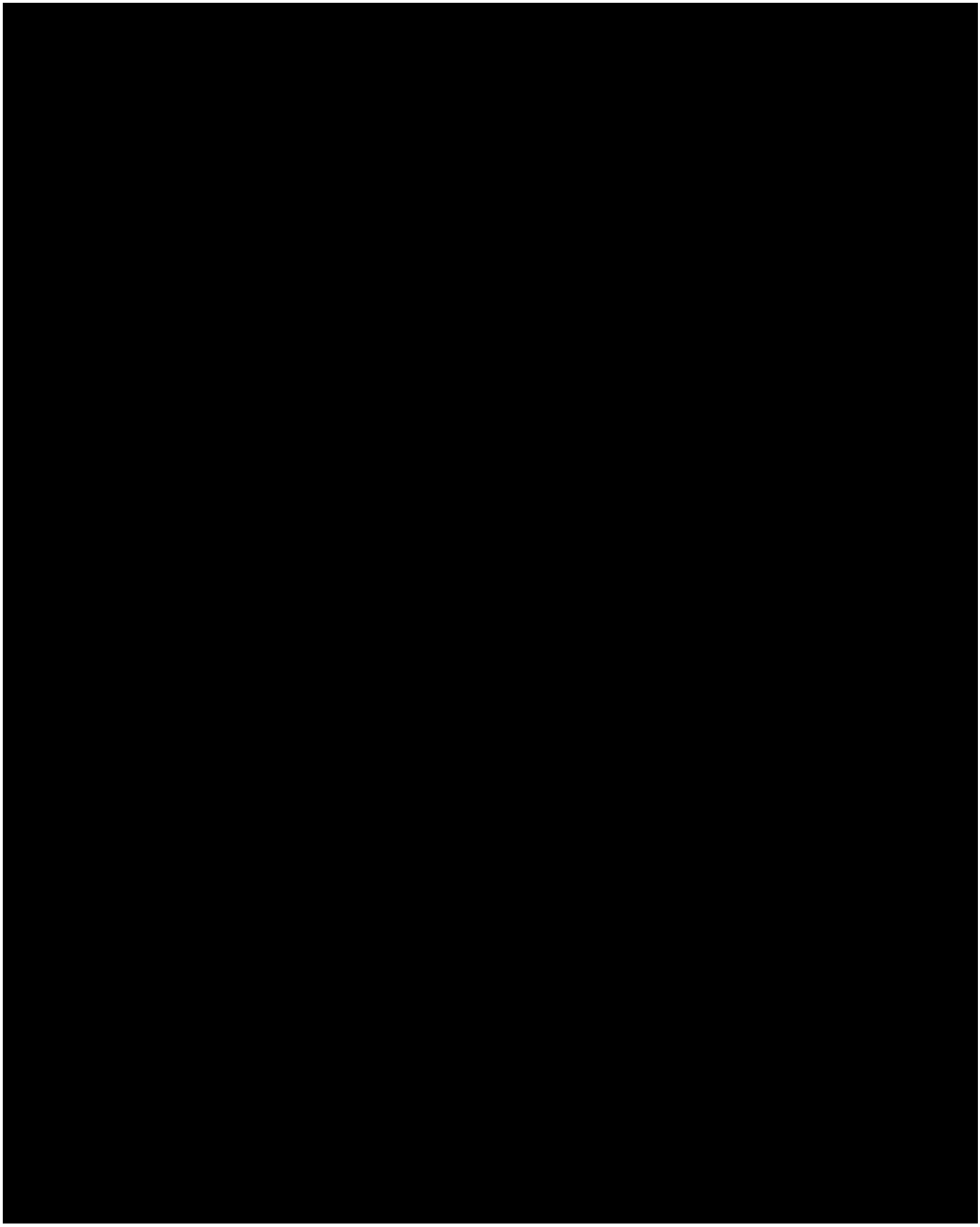

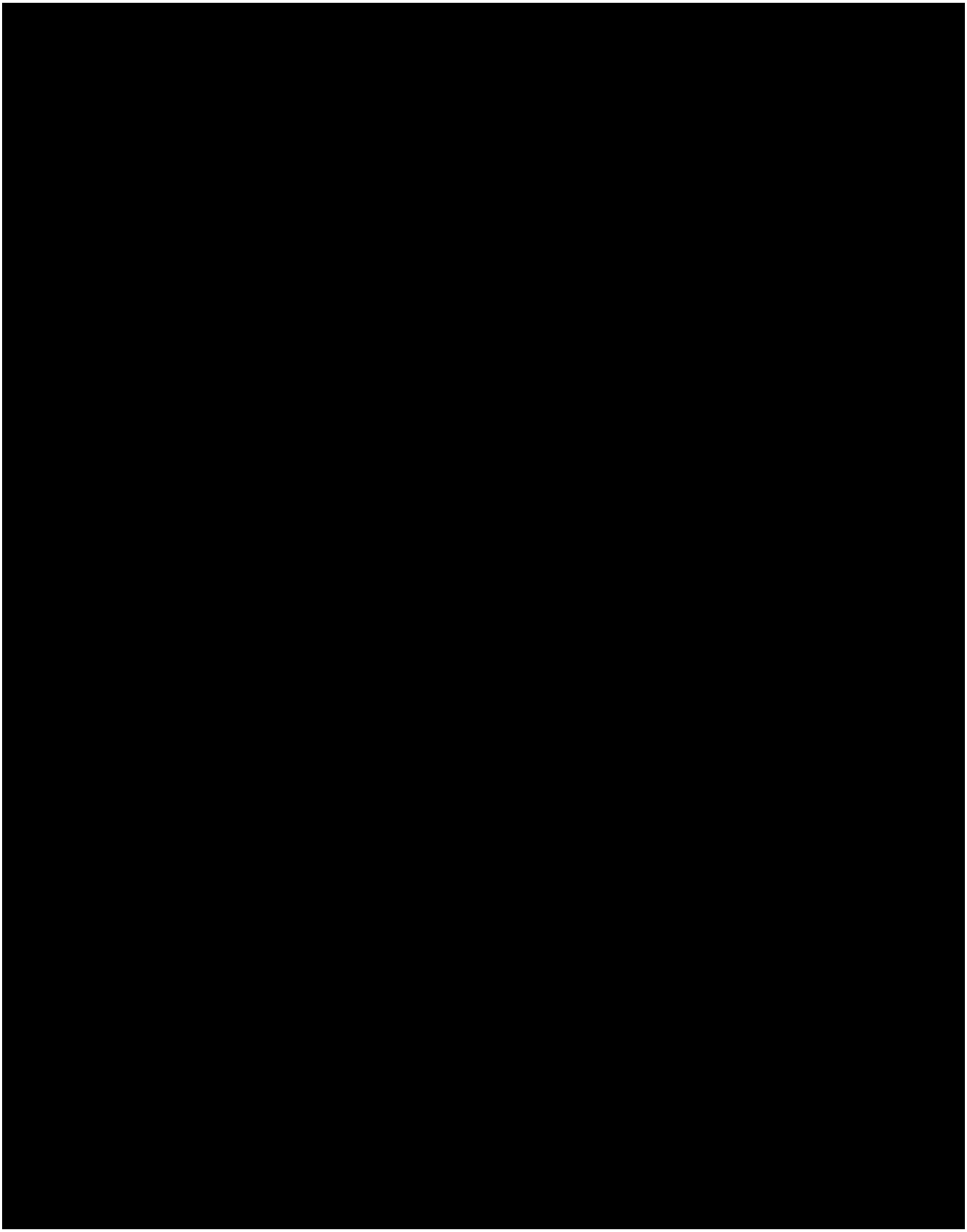

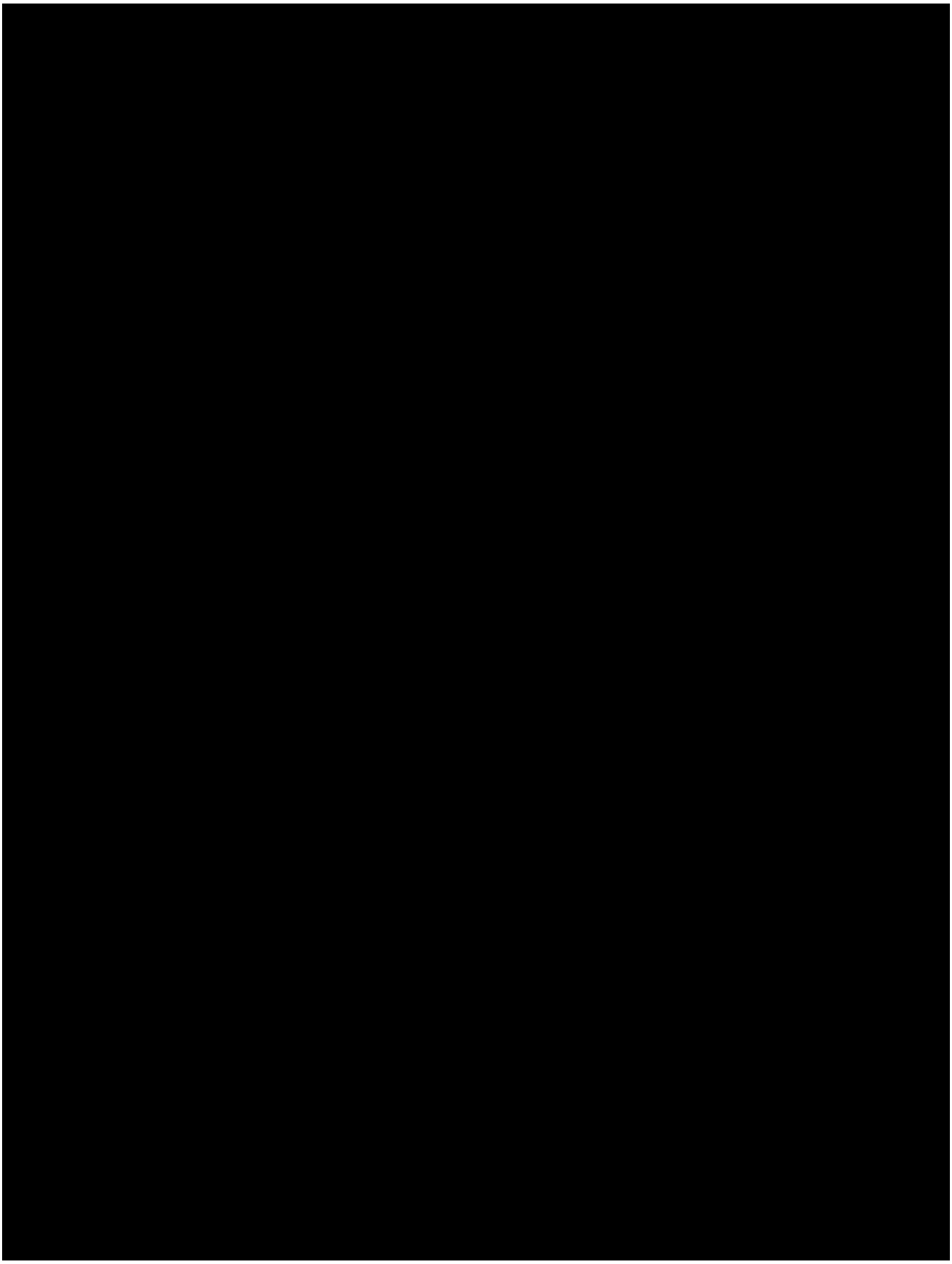

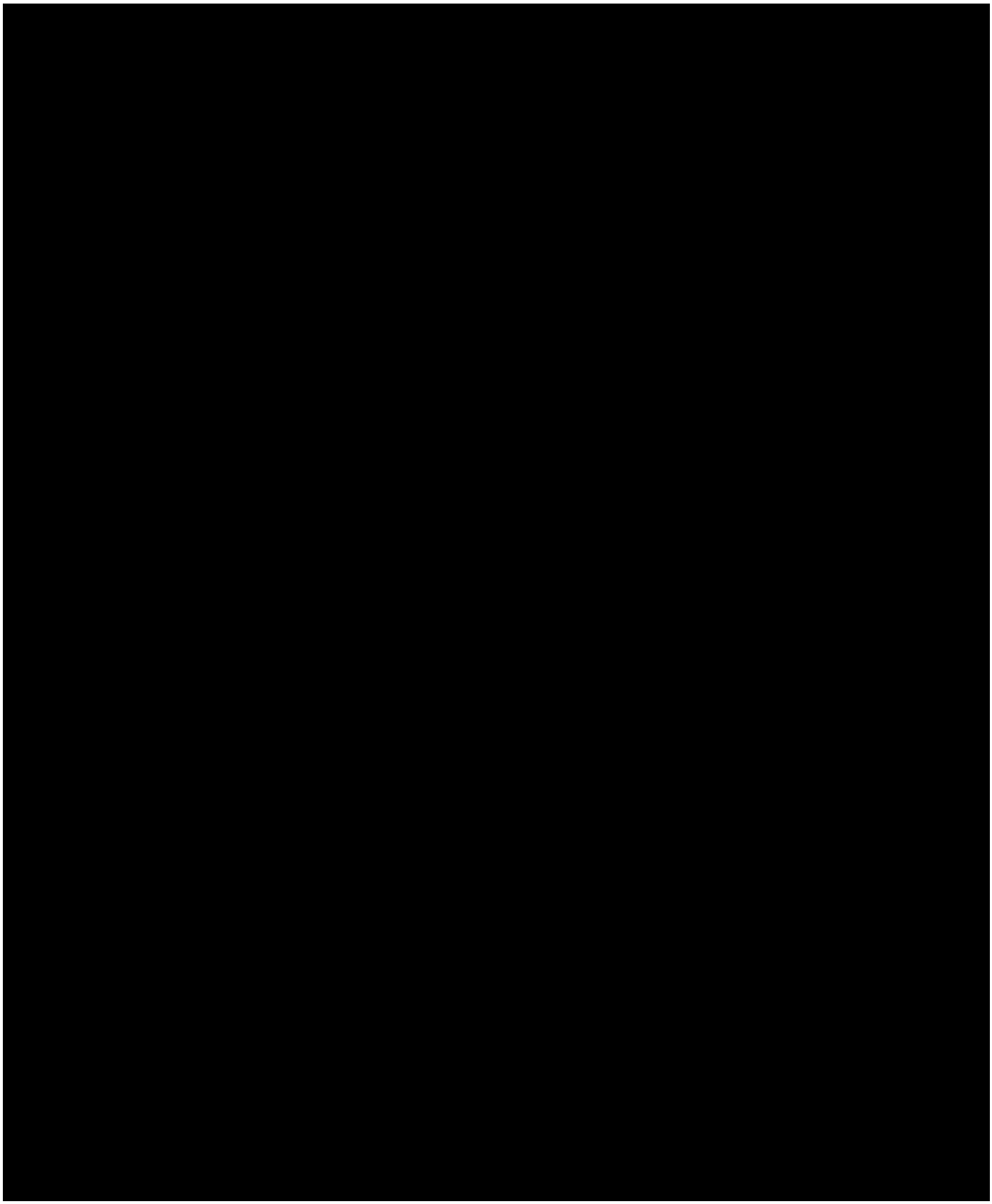

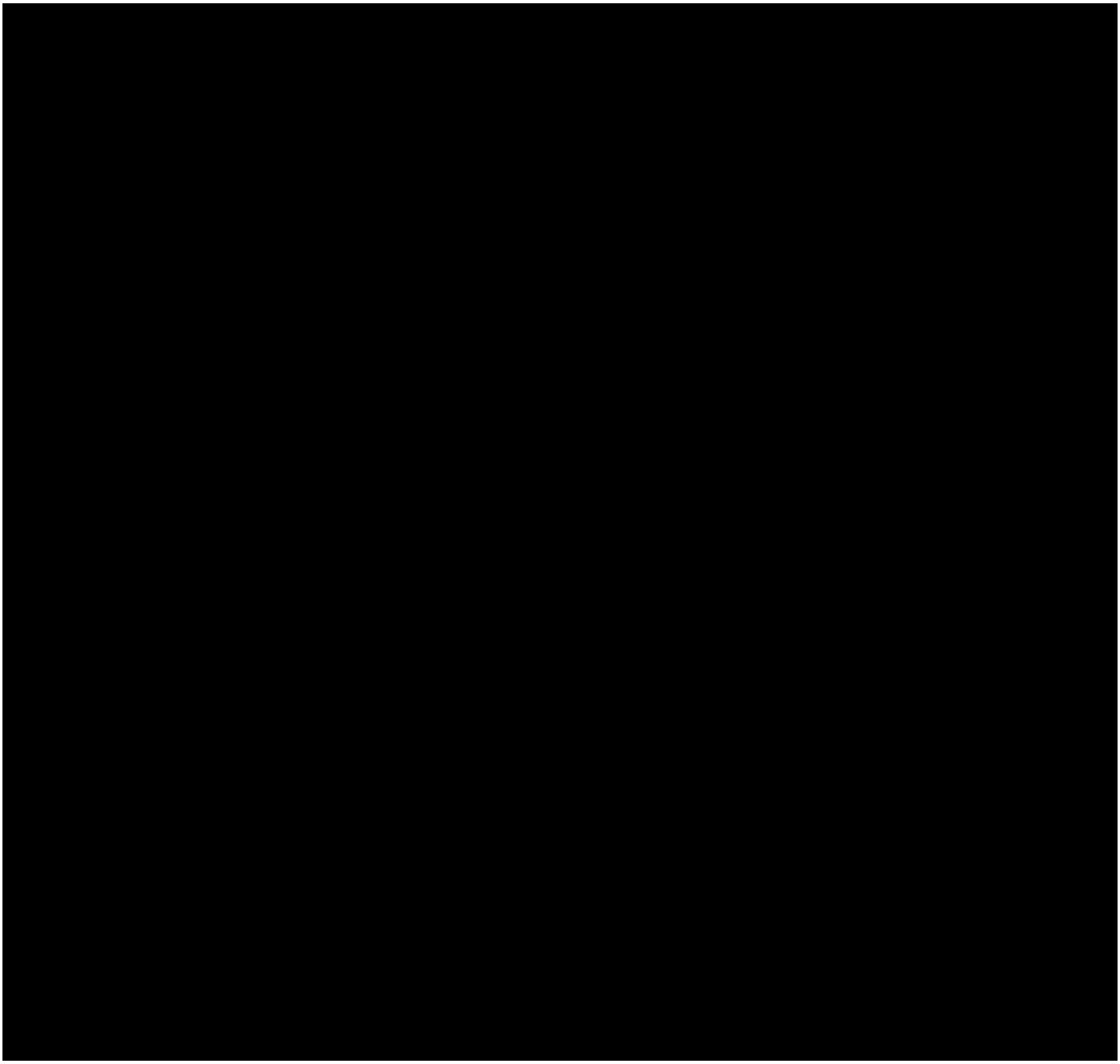

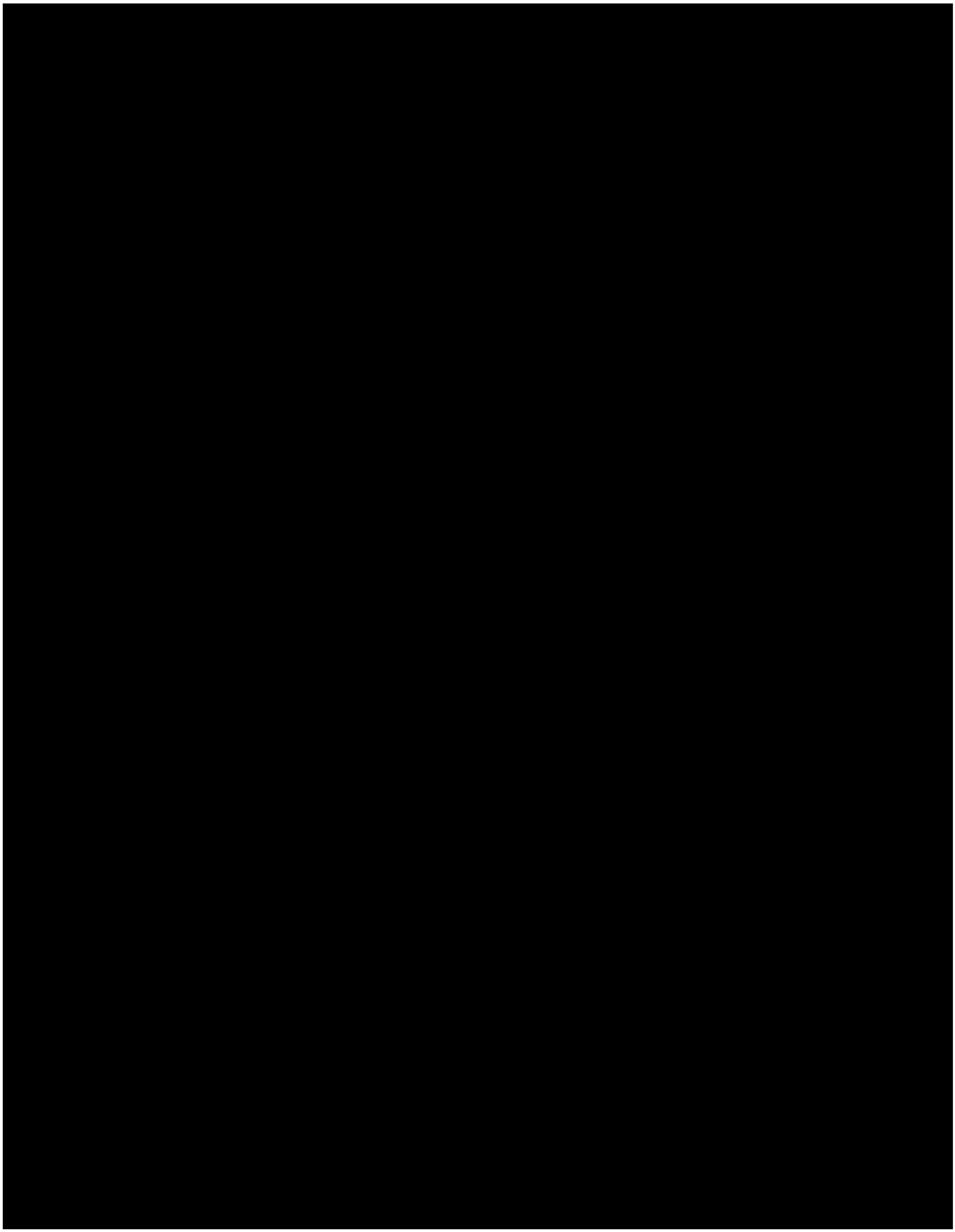

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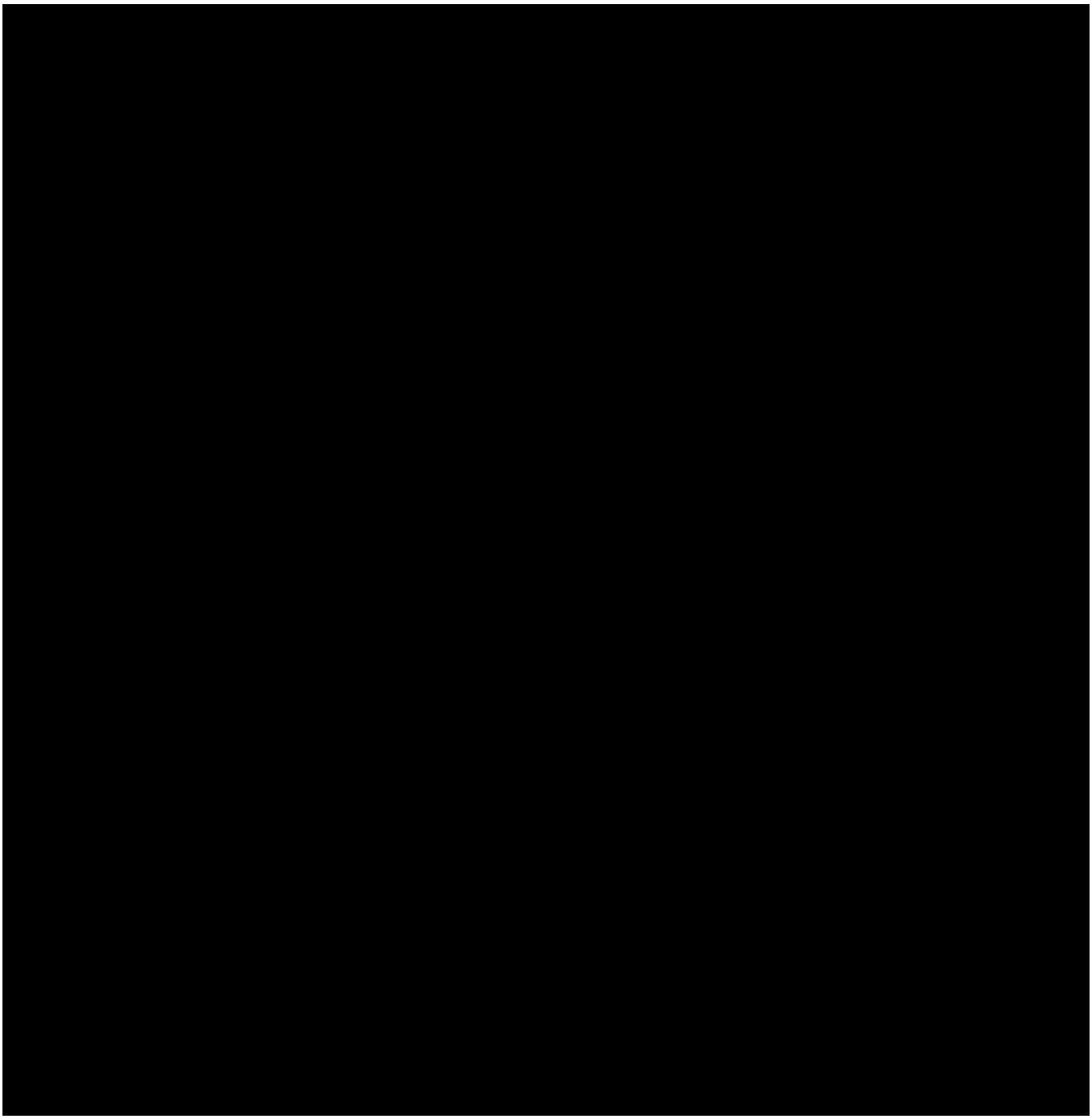

APPENDIX V. MEDICATIONS THAT ARE CYP3A4/5 STRONG INHIBITORS AND INDUCERS

A comprehensive listing of drugs that are CYP3A4 inhibitors can be accessed online at the following address: http://medicine.iupui.edu/clinpharm/ddis/table.aspx.

Table 48: Medications that are CYP3A4/5 Strong Inhibitors

Drug Class	Generic Name
Human Immunodeficiency Virus (HIV) Protease Inhibitor	Atazanavir
	Indinavir
	Darunavir
	Lopinavir
	Saquinavir
	Nelfinavir
	Ritonavir and ritonavir containing coformulations
Antihepaciviral (NS 3/4A) Protease Inhibitor	Boceprevir
	Telaprevir
	Ombitasvir-paritaprevir- ritonavir
	Ombitasvir-paritaprevir- ritonavir plus dasabuvir
CYP450 Inhibitor	Cobicistat and cobicistat containing coformulations
Azole Antifungal	Itraconazole
	Ketoconazole
	Posaconazole
	Voriconazole
Macrolide antibiotic	Telithromycin
	Clarithromycin
Antiprogestin	Mifepristone
Serotonin Reuptake Inhibitor	Nefazodone
Phosphatidylinositol 3-kinase inhibitor	Idelalisib

Table 49: Medications that are CYP3A4/5 Strong Inducers

Drug Class	Generic Name
Anticonvulsant	Carbamazepine
	Fosphenytoin
	Phenytoin
	Phenobarbital
	Primidone
Antineoplastic/Antiandrogen	Enzalutamide
	Apalutamide
Antineoplastic agent	Mitotane
Cystic fibrosis agent	Lumacaftor
Antitubercular	Rifampin (rifampicin)
Herbal	St. John's wort

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