Official Title:	A Randomized, Double Blind, Phase 3 Study of Platinum-Based Chemotherapy With or Without INCMGA00012 in First-Line Metastatic Squamous and Nonsquamous Non–Small Cell Lung Cancer (POD1UM-304)
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Statistical Analysis Plan

INCMGA 0012-304

A Randomized, Double-Blind, Phase 3 Study of Platinum-Based Chemotherapy With or Without INCMGA00012 in First-Line Metastatic Squamous and Nonsquamous Non–Small Cell Lung Cancer (POD1UM-304)

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Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803** **United States**
Protocol Version:	**Protocol Amendment 3 dated 18 OCT 2022**
CRF Approval Date:	**05 AUG 2022**
SAP Version:	**Amendment 1**
SAP Author:	[redacted], **Biostatistics**
Date of Plan:	**02 FEB 2023**

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Term
[redacted]	[redacted]
AE	adverse event
AESI	adverse events of special interest
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification (Code) (or Anatomic Therapeutic Chemical [ATC] Classification)
AUC	area under the curve
AUC_{0-t}	area under the plasma or serum concentration-time curve from time = 0 to the last measurable concentration at time = t
BICR	blinded independent central review
BMI	body mass index
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BSA	body surface area
CAS	crossover analysis set
CI	confidence interval
C_{max}	maximum observed plasma or serum concentration
C_{min}	minimum observed plasma or serum concentration over the dose interval
COVID-19	coronavirus disease 2019
CR	complete response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
[redacted]	[redacted]

Abbreviation	Term
[redacted]	[redacted]
FAS	full analysis set
FDA	Food and Drug Administration (US)
HR	hazard ratio
ICF	informed consent form
irAE	immune-related adverse event
IRR	infusion-related reaction
ITT	intent-to-treat
IV	intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	not evaluable
NSCLC	non–small cell lung cancer
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-L1	programmed death-ligand 1
PFS	progression-free survival
[redacted]	[redacted]
PK	pharmacokinetic(s)
PPS	per protocol set
PR	partial response
[redacted]	[redacted]
PT	preferred term
Q3W	every 3 weeks
QTcF	QT interval corrected by Fridericia
QTcB	QT interval corrected by Bazett
RECIST	Response Evaluation Criteria In Solid Tumors
ROS1	receptor tyrosine kinase (encoded by the gene ROS1)
SAP	Statistical Analysis Plan
SD	stable disease
SoA	schedule of activities
SOC	system organ class
TEAE	treatment-emergent adverse event
t_{max}	time to maximum concentration

Abbreviation	Term
TPS	tumor proportion score
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

This is a global, randomized, double-blind, study of IV INCMGA00012 or placebo combined with platinum-based chemotherapy in participants with metastatic nonsquamous or squamous NSCLC who have not previously received systemic therapy for advanced disease. The study originally planned to enroll approximately 530 participants in a 2:1 randomization between INCMGA00012 and placebo; however, enrollment will be increased to around 600 participants due to potential early censoring of participants from Ukraine. After Protocol Amendment 3, the planned dual primary endpoints of PFS and OS are modified to single primary endpoint OS, followed by secondary endpoint PFS with gatekeeping procedure on type I error spending. Full list of secondary [redacted] are in Section 2.2. INCMGA00012 or placebo will be administered for approximately 2 years (35 cycles) along with a standard of care chemotherapy regimen. Eligible participants assigned to placebo and chemotherapy will have the option of receiving open-label monotherapy INCMGA00012 in the crossover period following BICR documentation of progressive disease.

The purpose of this SAP is to provide details of the statistical analyses that have been outlined in the INCMGA 0012-304 Protocol. The scope of this plan includes the interim and final analyses that are planned and will be executed by the Department of Biostatistics or designee. If the study claims success at the interim analysis, the study may be unblinded per DMC recommendation, and a full CSR may be written to support registration activity on a need basis. The study will be followed in open-label fashion after the interim analysis in that case. The analyses of PK, [redacted] and pharmacodynamics will be executed by the Department of Clinical Pharmacokinetics and the Department of Translational Sciences, respectively.

The SAP has been developed in accordance with international recommendations for adapting clinical trials to unprecedented challenges caused by COVID-19 (EMA 2022, FDA 2020). Incyte believes these are equally relevant to the disruptions in study conduct that have been occurring in Ukraine since FEB 2022.

2. STUDY INFORMATION, OBJECTIVES, AND ENDPOINTS

2.1. Protocol and Case Report Form Version

This SAP is based on Study INCMGA 0012-304 Protocol Amendment 3 dated 18 OCT 2022 and CRFs approved 05 AUG 2022. Unless superseded by an amendment, this SAP will be effective for all subsequent Protocol amendments and eCRF versions.

2.2. Study Objectives and Endpoints

Table 1 presents the objectives and endpoints.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the OS of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	OS, defined as the time from randomization until death due to any cause.
Secondary	
To compare the PFS of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	PFS, defined as the time from randomization until disease progression by RECIST v1.1 as determined by BICR or death due to any cause.
To compare the ORR of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	ORR, defined as the proportion of participants who have a confirmed CR or PR per RECIST v1.1 based on BICR.
To compare the DOR of the combinations of INCMGA00012 and chemotherapy versus placebo and chemotherapy.	DOR, defined as the time from the earliest date of documented response until earliest date of disease progression or death from any cause, whichever comes first, per RECIST v1.1 based on BICR.
To evaluate the safety and tolerability of the combination of INCMGA00012 and chemotherapy and the combination of placebo and chemotherapy.	Number of participants experiencing AEs and number of participants discontinuing study drug due to AEs.
To evaluate the PK of INCMGA00012 375 mg Q3W when administered with chemotherapy.	Population PK parameters (including C_{max}, AUC) will be summarized.
[redacted]	

Table 1: Objectives and Endpoints (Continued)

Objectives	Endpoints
[redacted]	

3. STUDY DESIGN

3.1. Overall Study Design

This is a multiregional, randomized, double-blind, study of IV INCMGA00012 or placebo combined with platinum-based chemotherapy in participants with metastatic squamous or nonsquamous NSCLC who have not previously received systemic therapy for advanced disease and who do not have sensitizing driver mutations or gene rearrangement of EGFR, ALK, BRAF, or ROS1. Participants will be enrolled from sites in US, Latin America, Asia, Europe, Ukraine, Russia, and South Africa where access to an approved PD-L1 inhibitor is limited by regulatory approval status or reimbursement considerations. In Protocol Amendment 3, the study was modified to have OS as the primary endpoint, followed by PFS as determined by BICR as the secondary endpoint. Approximately 600 participants with NCSLC will be 2:1 randomized to receive either INCMGA00012 or placebo along with the standard of care platinum-based chemotherapy regimens. The enrollment of participants with squamous histology will be limited to < 40% of the total study population to mimic the expected frequency distribution of the disease (see Section 3.4). INCMGA00012 or placebo will be administered for approximately 2 years (35 cycles) along with a standard of care chemotherapy regimen. Randomization will be stratified as presented in Table 2. The enrollment of low PD-L1 expression (ie, TPS < 1%) will be capped at approximately 30%, again in keeping with expected population frequencies.

Table 2: Stratification Factors

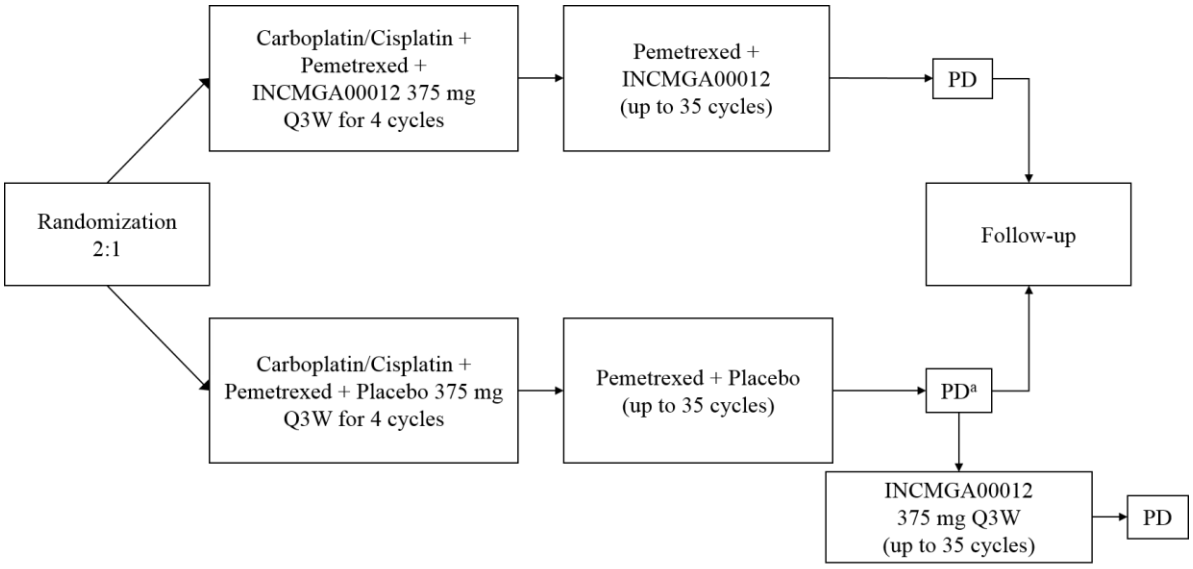
Stratification Factor	Stratum
PD-L1 TPS	< 1%, ≥ 1% to 49%, ≥ 50%
Geographic region	East Asia vs non–East Asia
Predominant tumor histology	squamous versus nonsquamous

Participants with nonsquamous NCSLC will be randomized to receive INCMGA00012/placebo with pemetrexed plus cisplatin or carboplatin for 4 cycles, followed by INCMGA00012/placebo plus pemetrexed until progression. Participants with squamous NCSLC will be randomized to receive INCMGA00012/placebo with carboplatin plus paclitaxel or nab-paclitaxel followed by

INCMGA00012/placebo monotherapy until progression. Participants randomized to placebo and chemotherapy who have verification of progressive disease by BICR and qualified for the crossover period will have the option to receive INCMGA00012 monotherapy for up to approximately 2 years. Figure 1 presents the study design schema for nonsquamous NCSLC and squamous NCSLC participants.

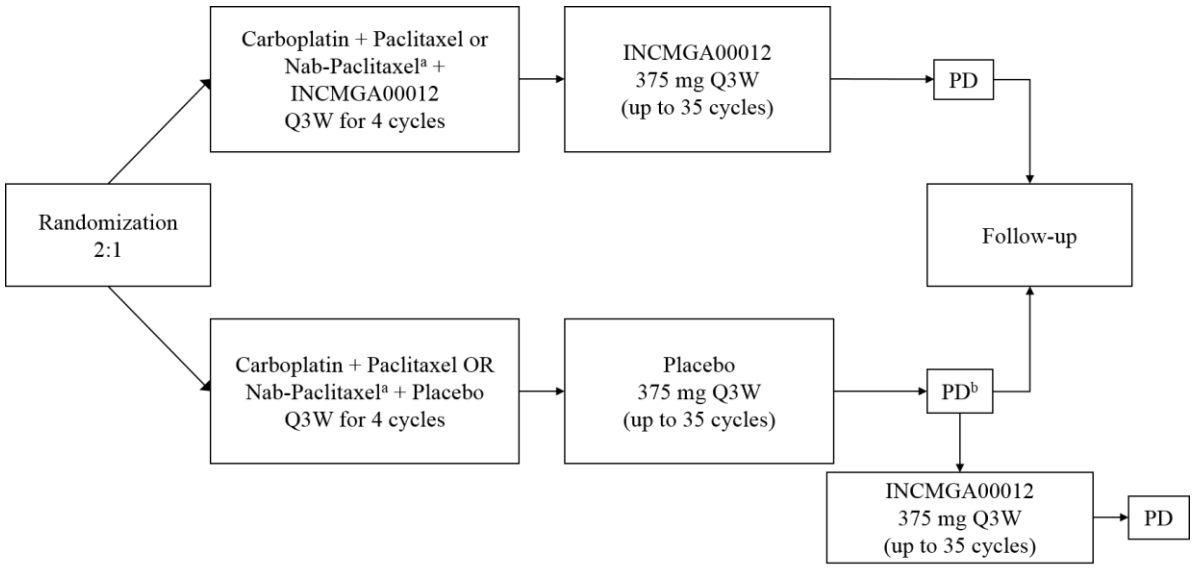
Figure 1: Study Design Schema

For nonsquamous NSCLC participants



[a] Optional crossover for qualified participants.

For squamous NSCLC participants



[a] Nab-paclitaxel is administered on Days 1, 8, and 15 of each Q3W cycle.
[b] Optional crossover for qualified participants.

3.1.1. Study Duration

The study begins when the first participant signs the ICF. The end of the study is defined as the date of the last visit (last scheduled procedure shown in the SoA) of the last participant in the study globally or as the date the last participant withdraws from the study or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

A participant is considered to have completed the study if he/she has completed treatment and survival follow-up periods of the study.

3.1.2. Response Assessment

Objective assessment of disease status will be evaluated according to RECIST v1.1 (Eisenhauer et al 2009) by BICR and the investigator. On-study treatment tumor assessments are scheduled every 6 weeks (± 7 days) for the first 24 weeks, then every 9 weeks (± 7 days) for the next 27 weeks, and subsequently every 12 weeks (± 14 days) until PD is verified by BICR (unless site investigator elects to continue treatment and follow iRECIST), the start of new anticancer therapy, withdrawal of consent, or death, whichever occurs first.

3.2. Randomization

Approximately 600 participants with metastatic NSCLC will be randomized 2:1 to receive either INCMGA00012 or placebo along with the standard of care platinum-based chemotherapy regimens. Randomization will be stratified by PD-L1 TPS (ie, < 1%, ≥ 1% to 49%, ≥ 50%), site geographic region (ie, East Asia vs non–East Asia), and predominant tumor histology (ie, squamous vs nonsquamous).

3.5. Schedule of Assessments

Refer to the Protocol Amendment 3 dated 18 OCT 2022 for a full description of all study procedures and assessment schedules for this study.

4. DATA HANDLING DEFINITIONS AND CONVENTIONS

4.1. Scheduled Study Evaluations and Study Periods

4.1.1. Study Drug, Study Treatment, and Treatment Groups

This is a randomized, double-blind study with optional crossover period for randomized placebo-treated participants. INCMGA00012 or placebo are the study drug in this study. INCMGA00012, placebo, and each chemotherapy regimen including pemetrexed, cisplatin, or carboplatin for nonsquamous NCSLC, and carboplatin and paclitaxel or nab-paclitaxel for squamous NCSLC are all considered as study treatments in this study.

There are 2 treatment groups during randomized period, and they are defined as below:

- Group A: INCMGA00012 + Chemotherapy
- Group B: Placebo + Chemotherapy

The treatment group during crossover period is defined as:

- Group C: INCMGA00012 monotherapy

Within each treatment group, there are 2 histologies, nonsquamous and squamous NSCLC with different chemotherapy selections. The analysis results will be presented by treatment groups and histologies.

4.1.2. Study Period

The statistical analysis is presented in 3 study periods in this study. The randomized period starts with randomization until the end of treatment period for each participant in Group A as defined in Section 4.1.8, or until date of first dose of crossover treatment for each participant in Group B. The crossover period is only applicable for Group B participants who crossed over to open-label monotherapy INCMGA00012, if eligible as per Protocol Section 6.7, and starts on date of first dose of crossover treatment. The overall period is the same as the randomized period for participants without crossover treatment, and covers from the first date of randomized period until the last date of crossover period for participants with crossover.

4.1.3. Day 1

Day 1 of safety endpoints for the randomized period is the date that the first dose of any component of study treatment is administered to the participants. Day 1 of other endpoints for the randomized period is the date of randomization. Day 1 for the crossover period is the date of the first dose of crossover treatment. Day 1 for the overall period is defined the same way as the randomized period.

4.1.4. Study Day

Study day will be separately defined for randomized, crossover, and overall periods following the same definition, but referring to different Day 1 associated to each period/endpoint, ie, Day 1 of safety endpoints during the randomized period/overall period, Day 1 of nonsafety endpoints during the randomized period/overall period, and Day 1 of the crossover period. If a visit/reporting date is on or after Day 1, then the study day at the visit/reporting date will be calculated as:

Day # = (Visit/Reporting Date – Day 1 date + 1).

If the visit/reporting date is before Day 1, then the study day at the visit/reporting date will be calculated as:

Day # = (Visit/Reporting Date – Day 1 date).

A study day of –1 indicates 1 day before Day 1.

4.1.5. Baseline Value

Baseline is the last nonmissing assessments obtained prior to or on Day 1 for each period and endpoint. Baseline of safety endpoints for randomized/overall period is the last nonmissing assessment obtained before the first administration of study treatment, ie, Day 1 of safety endpoint. Baseline of other endpoints for randomized/overall period is the last nonmissing assessment obtained prior to or on randomization date, ie, Day 1 of nonsafety endpoints. In randomized/overall period, if baseline is missing based on randomization date (Day 1 of nonsafety endpoints), the last assessment prior to first dose date (Day 1 of safety endpoint) may be used as baseline. Baseline for crossover period is the last nonmissing assessment obtained before the first administration of crossover treatment, ie, Day 1 of crossover period.

When scheduled assessments and unscheduled assessments occur on the same day and time of the assessment or time of first dose is not available, use the following conventions to determine baseline:

- If both a scheduled and an unscheduled visit are available on the day of the first dose and the time is missing, use the scheduled assessment as baseline.
- If all scheduled assessments are missing on the day of the first dose and an unscheduled assessment is available, use the unscheduled assessment as baseline.

[redacted]

[redacted]

4.1.7. Cycle Length and Duration

Each cycle is 21 days (3 weeks) for participants in this study. Cycle 1 Day 1 is the day of first infusion of INCMGA00012 or placebo. Day 1 of subsequent cycles will correspond with the infusion date of INCMGA00012/placebo or chemotherapy as reported in the dataset. Scheduled visits after Cycle 1 Day 1 will have a ± 3-day window. Tumor assessments will have ± 7-day window up to 51 weeks and subsequently ± 14-day window until PD is verified by BICR.

[redacted]

4.2. Variable Definitions

The following variables will only be calculated if not reported on the eCRF.

4.2.1. Body Mass Index

Body mass index will be calculated as follows:

BMI (kg/m^2) = [weight (kg)] / [height (m)]^2.

4.2.2. Body Surface Area

Body surface area will be calculated based on the formula Mosteller (1987) as follows:

Body surface area (m2) = {[weight (kg) × height (cm)] / 3600}½.

Sites will also record the body surface area value as calculated per institutional standards.

4.2.3. Prior and Concomitant Medication

Prior medication is defined as any nonstudy medication started before the randomization date.

Concomitant medication is defined as any nonstudy medication that is started accordingly:

- Before the randomization date and is ongoing throughout the study or ends on/after the date of first study treatment administration.
- On/after the randomization date and is ongoing or ends during the course of study treatment administration.

A prior medication could also be classified as "both prior and concomitant medication" if the end date is on or after the randomization date. In the listing, it will be indicated whether a medication is prior-only, concomitant-only, or both prior and concomitant.

For the purposes of analysis, all medications will be considered concomitant medications unless the medications can unequivocally be defined as not concomitant, that is, if the start date and end date are all missing, then the medication is considered as concomitant medication.

5. STATISTICAL METHODOLOGY

5.1. General Methodology

Unless otherwise noted, SAS® software (SAS Institute Inc, Cary, NC; v9.4 or later) will be used for the generation of all tables, figures, and statistical analyses. Descriptive summaries for continuous variables will include, but not be limited to, the number of observations, mean, standard deviation, median, minimum, and maximum. Descriptive summaries for categorical variables will include the number and percentage of participants in each category.

Interim analysis is planned for OS endpoint and is discussed in detail in Section 10.

5.2. Analysis Populations

5.2.1. Full Analysis Set

The FAS comprises all participants to whom study treatment has been assigned by randomization. Participants will be analyzed according to ITT principle (ie, according to the treatment and strata they have been assigned to during the randomization procedure).

The FAS will be used for the summary of demographics, baseline characteristics, and participant disposition and for analyses of all efficacy data.

5.2.2. Per Protocol Set

The PPS comprises all participants in the FAS who are considered compliant with the Protocol. The final list to exclude participants from PPS will be finalized prior to DBL.

Sensitivity analysis of the OS may be performed using the PPS.

5.2.3. Safety Population

The safety population comprises all participants who received at least 1 dose of study treatment. Treatment groups for this population will be determined by the actual treatment that the participant received regardless of treatment assignment at randomization.

The actual treatment received corresponds to:

- The randomized treatment if the participant took at least 1 dose of that treatment.
- The first treatment received if the randomized treatment was never received.

All safety analyses will be conducted by safety population.

5.2.4. Pharmacokinetic Evaluable Population

The PK evaluable population will include all participants who received at least 1 dose of INCMGA00012 and have provided at least 1 postdose sample.

[redacted]

5.2.6. Crossover Analysis Set

The CAS will include all participants randomized to Group B, who receive at least 1 dose of placebo, who then crossover and receive at least 1 dose of INCMGA00012. The CAS will be used for all analyses during crossover period.

6. BASELINE, EXPOSURE, AND DISPOSITION VARIABLES AND ANALYSES

Appendix A provides a list of planned tables, figures, and listings.

6.1. Baseline and Demographics, Physical Characteristics, and Disease History

The FAS will be used for all baseline disease characteristics and demographic summaries and data listings. Tables will be summarized by treatment groups for randomized period, crossover period, and overall period. Within each treatment group, data will be presented by histology and group total.

6.1.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed in detail. The following demographics will be summarized: age, sex, race, ethnicity, body weight, height, BMI, BSA, geographic region. Qualitative data will be summarized by contingency tables while quantitative data will be summarized by treatment groups and histology in descriptive summary statistics.

Numbers of participants per site per country will be summarized.

6.1.2. Baseline Disease Characteristics and Disease History

According to data collected in the eCRF, time since initial diagnosis, time since metastatic/advanced diagnosis, staging at initial diagnosis and current diagnosis, disease histology, site of disease involvement, smoking status, liver and brain metastases. The corresponding [redacted] and PD-L1 expression by the central laboratory will also be summarized for all participants in FAS by treatment group and histology based on data availability.

6.1.3. Prior Therapy

The number and percentage of participants recording prior radiation, prior adjuvant chemotherapy, or prior surgery will be summarized in FAS by treatment group and histology if data permits. Detailed information on prior therapy, prior radiation, and prior surgery will be listed in separate listings.

6.1.4. Medical History

Medical history will be summarized for all participants in FAS by treatment group and histology. This summary will be presented by primary SOC and PT.

6.2. Protocol Deviations

Protocol deviations will be presented in the participant data listings and categorized based on clinical review. Protocol deviations will be summarized by treatment group and histology descriptively. Important protocol deviations leading to exclusion of PPS will be summarized. Deviations related to COVID-19 or war will be listed.

6.3. Exposure

For participants in the safety population, exposure to INCMGA00012 or placebo, and each of the chemotherapy regimen including pemetrexed, cisplatin, carboplatin or (nab-) paclitaxel during randomized period, and exposure to INCMGA00012 during crossover period, will be summarized by treatment group and histology descriptively as follows:

- **Total number of infusions of INCMGA00012/placebo:** Total number of infusions of INCMGA00012/placebo per participant.
- **Total number of infusions of chemotherapy:** Total number of infusions of carboplatin, cisplatin, pemetrexed, paclitaxel, or nab-placlitaxel per participant.
- **Total dose administered of INCMGA00012/placebo (mg):** Accumulated actual administered dose of INCMGA00012/placebo at each infusion.

  For each infusion:

  If the entire infusion administered, then the actual administered dose is 375 mg.

  If the infusion was not completely administered, then the actual administered dose is the planned dose × (the estimated volume delivered / prepared volume).
- **Total dose administered of chemotherapy (mg):** Accumulated actual administered dose of chemotherapy at each infusion.

  For each infusion:

  If the entire infusion was administered, then the actual administered dose is the administered dose.

  If the infusion was not completely administered, then the actual administered dose is the planned dose × (the estimated volume delivered / prepared volume).

- **Total dose prescribed of INCMGA00012/placebo (mg):** Accumulated prescribed dose of INCMGA00012/Placebo at each infusion.
- **Total dose prescribed of chemotherapy (mg):** Accumulated prescribed dose of chemotherapy at each infusion.
- **Average dose of INCMGA00012/placebo and chemotherapy (mg):** Total dose administered of INCMGA00012/placebo**,** chemotherapy (mg) / total number of infusions of INCMGA00012/placebo**,** chemotherapy.
- **Duration of treatment of INCMGA00012/placebo, chemotherapy (months):** (Date of last dose of INCMGA00012/placebo, chemotherapy – date of first dose of INCMGA00012/placebo, chemotherapy + 1)/30.4375.
- **Compliance of INCMGA00012/placebo and chemotherapy (%):** 100 × Total dose administered of INCMGA00012/placebo, chemotherapy / total dose prescribed of INCMGA00012/placebo, chemotherapy.

Infusion information collected in the eCRF will be listed. Dose delay and temporary infusion interruption of INCMGA00012 or placebo and chemotherapy may be summarized/listed by treatment group and histology as needed. In addition, chemotherapy dose may be summarized and plotted over time to monitor potential dose reduction.

6.4. Prior and Concomitant Medication and Post-Therapy

Prior and concomitant medications will be coded using the WHO Drug Dictionary and summarized by ATC drug class and WHO drug term. Results will be summarized as number and percentage of participants with prior and concomitant medications by ATC class and WHO drug term. For the summary of concomitant medication, only on-treatment medications will be included. Medications with missing start/end dates will be considered as concomitant medication in the summary. Drugs intended to manage irAEs as well as prophylaxis/premedication may be summarized separately. Herbal and other medications used during treatment may also be summarized. Procedures and nondrug therapies will also be summarized/listed per CRF. Post-treatment anticancer therapy will be summarized. Other medications will be provided in the listing.

7. EFFICACY

A list of planned tables, figures, and listings is provided in Appendix A.

7.1. General Considerations

Efficacy endpoints of this study include and PFS, ORR, DOR, DCR based on RECIST v1.1 as determined by BICR, and OS. Listings of response assessment at each visit will be provided. Summary statistics will be summarized by treatment group and histology, while statistical testing on PFS and OS will be a stratified long-rank test on-treatment group level, taking histology as a stratification factor.

7.2. Disposition of Participants

The number and percentage of participants who are randomized, treated, crossed-over, ongoing with treatment, who discontinue study treatment with a primary reason for discontinuation, who are on study, and who withdraw from the study with a primary reason for study withdrawal will be summarized for all participants in the FAS by treatment group and histology for randomized period and crossover period, respectively.

7.2.1. Response Criteria

Overall response will be categorized using RECIST v1.1 by BICR or the investigators. Participants will have their overall response evaluated as CR, PR, SD, PD, or NE for RECIST v1.1 at each postbaseline radiological assessment based on changes in target lesions, nontarget lesions, and appearance of new lesions.

7.2.2. Primary Analysis

The study has primary endpoint OS. Progression-free survival was considered as a secondary endpoint in Protocol Amendment 3. The overall Type I error 2.5% will be used for OS analysis.

7.2.2.1. Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death due to any cause.

The primary efficacy analysis is the comparison of median time of OS between the 2 treatment groups. The following statistical hypotheses will be tested to address the primary efficacy objective:

H_0: $OS_A \leq OS_B$ versus H_1: $OS_A > OS_B$

where OS_A and OS_B are the median time for Group A and Group B, respectively. Overall survival will be analyzed by a stratified log-rank test at an overall 1-sided 2.5% level of significance based on the data observed in the FAS population, according to the treatment group participants were randomized and the strata they were assigned at randomization. Kaplan-Meier curves, medians, and 95% CIs of the median OS will be presented for each treatment group.

The HR for OS will be calculated, along with its 95% CI, from a stratified Cox model using the same stratification factors as for the log-rank test with Efron's likelihood approximation to account for ties in event times.

7.2.2.2. Subgroup Analysis for Overall Survival

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the OS endpoint will be estimated and plotted within each category of the following classification variables:

- Age category (< 65 vs ≥ 65 years, < 75 vs ≥ 75 years, and < 85 vs ≥ 85 years)
- Sex (female, male)
- Race (White, Asian, vs other)
- Brain metastasis (presence vs absence)
- Smoking status (never vs former/current smoker)
- Investigator's choice of chemotherapy (for nonsquamous NSCLC vs squamous NSCLC)
- PD-L1 TPS (< 1%, ≥ 1% to 49%, ≥ 50%)
- Site geographic region (East Asia vs non-East Asia)
- Country enrollment (eg, China, Ukraine, and any countries with ≥ 100 participants randomized, vs all other countries combined)
- Predominant tumor histology (squamous vs nonsquamous)

Subgroup analyses will only be performed if at least 5 participants are present in each subgroup. Some grouping of classes will be considered if there are too few participants in some subgroups. Subgroup analysis may also be conducted on whether participants experienced COVID-19 or not.

Efficacy analyses in subgroups will generally be exploratory and are intended to explore the intrinsic consistency of any treatment effects found overall.

Subgroup analyses of the primary endpoint will be performed on the FAS by presenting the point estimates of HR of randomized treatment Group A versus Group B during randomization period under stratified Cox model in the subgroup with the 95% CIs. Summary tables and forest plots may be presented.

7.2.2.3. Sensitivity and Supportive Analyses for Overall Survival

In order to adjust for crossover effect in placebo arm, rank preserving structural failure time model and inverse probability of censoring weighting method may be used to analyze the OS endpoint as supportive analyses.

An unstratified log-rank test may be considered for OS as sensitivity analysis. As a sensitivity analysis to OS endpoint, COVID-19 deaths and deaths due to war could be considered as a competing risk to disease death. In addition, OS will be repeated in the following 2 populations:

1. Excluding all participants from Ukraine
2. Only including Ukraine participants from sites that are well-monitored (list will be provided prior to the DBL)

7.2.3. Secondary Analyses

7.2.3.1. Progression-Free Survival

Progression-free survival is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS will be assessed via BICR according to RECIST v1.1.

The primary analysis is the comparison of median time of PFS between the 2 treatment groups. The following statistical hypotheses will be tested to address the primary efficacy objective:

H_0: $PFS_A \leq PFS_B$ versus H_1: $PFS_A > PFS_B$

where PFS_A and PFS_B are the median time for Group A and Group B, respectively. If OS endpoint is tested as statistically significant, then PFS will be analyzed using a stratified log-rank test at an overall 1-sided 2.5% level of significance in the FAS population, according to the treatment group participants were randomized and the strata they were assigned during randomization. The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with 95% CIs will be presented by treatment groups and histology. A stratified Cox regression with Efron's method for tie-handling will be used to estimate the HR of PFS, along with 95% CIs using the same strata information assigned during randomization. The analysis of PFS will be conducted at the time of the OS interim analysis. The p-value will be a nominal p-value if OS is not statistically significant at the time of the IA.

If participants have no observed death or disease progression before data cutoff or new anticancer therapy, the participants will be treated as censored at their last adequate tumor assessment before data cutoff or new anticancer therapy according to Table 3, which is based on the FDA Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics (FDA 2015). Date of death will be determined using the Death Report, Survival Follow-Up, and Participant Status collected in the eCRFs.

Progression-free survival via investigator assessments will be analyzed by stratified log-rank test and stratified Cox regression model as supportive analysis.

As a sensitivity analysis, unstratified log-rank test may be considered for PFS. In addition, study discontinuation due to clinical progression, and death or documented progression by BICR after 2 missed scheduled tumor assessment may be considered as events for PFS in sensitivity analysis as illustrated in Table 4. Subgroup analysis may be conducted on PFS as well.

7.2.3.2. Objective Response Rate

Objective response rate is defined as the proportion of participants with best objective response of CR or PR according to RECIST v1.1 by BICR. Objective response rate will be calculated based on the FAS according to the ITT principle, presented by treatment group along with approximate 95% CI. The Cochran-Mantel-Haenszel chi-square test (stratum based on the baseline stratification factor) will be used to compare the 2 treatment groups with respect to the ORR at a 1-sided 2.5% level of significance if OS and PFS are both statistically significant. As a supportive analysis, ORR as assessed by the investigator will be calculated by treatment group and presented along with the approximate 95% CI.

7.2.3.3. Duration of Response

Duration of response is defined as the time from first CR or PR that is subsequently confirmed, to the time of first documented disease progression per RECIST v1.1 or death due to any cause. If a participant does not have an event, DOR is censored at the date of the last adequate tumor assessment before data cutoff or new anticancer therapy following the same algorithm as censoring of PFS (see Table 3). The Kaplan-Meier estimate of the distribution function will be constructed for DOR. The estimated median along with 95% CIs will be reported. Analysis of DOR will be according to RECIST v1.1 as determined by BICR in the FAS. Analysis of DOR according to investigator assessment may be provided.

8. SAFETY AND TOLERABILITY

All safety analyses during randomized period and overall period will be based on safety population. Some safety analysis will be done during the crossover treatment period based on CAS. All listings and tables will be presented by actual treatment received. Safety analysis will be conducted by treatment groups and by histology.

A list of planned tables, figures, and listings is provided in Appendix A.

8.1. General Considerations

The clinical safety data (eg, vital signs, ECGs, laboratory tests, and AEs) will be summarized with descriptive statistics (eg, mean, frequency) using safety population during randomized period and overall period, and using CAS during crossover period, respectively.

8.2. Adverse Events

8.2.1. Adverse Event Definitions

TEAE will be summarized by treatment groups and histology for randomized period, crossover period, as well as overall period. In randomized period and overall period, a TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of study treatment until end of randomized/overall period. Adverse events that occur after starting new anticancer therapy (including crossover treatment) will not be considered as TEAEs for randomized/overall period. AEs that occur after crossover treatment should still be considered as TEAE for overall period. For crossover period, a TEAE is any AE either reported for the first time or worsening of a pre-existing event after the first dose of crossover treatment until end of crossover period or prior to the start of a new anticancer therapy. Analysis of AEs (as discussed below) will be limited to TEAEs, but data listings will include all AEs regardless of their timing in relation to study treatment administration.

Adverse events will be tabulated by MedDRA PT and SOC. Severity of AEs will be graded using the NCI CTCAE v5.0. The CTCAE reporting guidelines and grading details are available on the Cancer Therapy Evaluation Program website. Exposure adjusted TEAEs may be summarized based on on-treatment duration of randomized period.

The subset of AEs considered by the investigator to be related to study treatment will be considered to be treatment-related AEs. If the investigator does not specify the relationship of the AE to study treatment, the AE will be considered to be treatment-related. The incidence of TEAEs and treatment-related AEs will be tabulated. In addition, serious TEAEs will also be tabulated.

Any missing onset date, causality, or severity must be queried for resolution. Unresolved missing causality and severity will be handled according to the following rules:

- An unresolved missing causality will be considered treatment-related.
- An unresolved missing severity will be identified as an unknown severity.

For purposes of analysis, all AEs will be considered TEAEs unless the AE can unequivocally be defined as not treatment-emergent.

8.2.2. Adverse Events of Special Interest

Immune-related AEs as well as infusion reaction will be considered as AESI in this study. Adverse events of special interest identified in the AE dataset will be summarized. Predefined PTs are grouped into AESI categories, and used to identify irAEs or infusion reaction without consideration of investigator's assessment of causality. Diagnosis of infusion reaction occurred anytime of the treatment period, or symptom of infusion reaction that occurred within 1 day of infusion, and resolved within 2 days from AE onset, are captured as infusion reactions.

Immune-related AE as well as infusion reaction will be separately summarized and combined together to capture AESI. An overall summary of AESI will include number (%) of participants reporting any AESIs, any serious AESIs, any ≥ Grade 3 AESIs, any treatment-related AESIs, any fatal AESIs, and any AESIs leading to INCMGA00012/placebo drug interruption in planned treatment/discontinuation and other categories as necessary.

8.2.3. Adverse Event Summaries

An overall summary of AEs during randomized period, crossover period, and overall period will include:

- Number (%) of participants reporting any TEAEs
- Number (%) of participants reporting any serious TEAEs
- Number (%) of participants reporting any Grade 3 or higher TEAEs
- Number (%) of participants reporting any TEAEs related to INCMGA00012/placebo
- Number (%) of participants reporting any TEAEs related to chemotherapy (not in crossover treatment period)
- Number (%) of participants reporting any TEAEs related to COVID-19
- Number (%) of participants who had any INCMGA00012/placebo treatment-related serious TEAEs
- Number (%) of participants who had any INCMGA00012/placebo treatment-related Grade 3 or higher TEAEs
- Number (%) of participants who temporarily interrupted INCMGA00012/placebo infusion because of TEAEs
- Number (%) of participants who delayed the next scheduled INCMGA00012/placebo infusion because of TEAEs
- Number (%) of participants who permanently discontinued INCMGA00012/placebo because of TEAEs
- Number (%) of participants who permanently discontinued chemotherapy because of TEAEs (not in crossover treatment period, and list each drug separately)
- Number (%) of participants who had a fatal TEAE

The following summaries will be produced by MedDRA terms (if 10 or fewer participants appear in a table, a listing may be appropriate):

- Overall summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of TEAEs by PT in decreasing order of frequency
- Summary of TEAEs by SOC, PT, and maximum severity
- Summary of Grade 3 or higher TEAEs by SOC and PT
- Summary of Grade 3 or higher TEAEs by PT in decreasing order of frequency
- Summary of INCMGA00012/placebo treatment-related TEAEs by SOC and PT
- Summary of chemotherapy treatment-related TEAEs by SOC and PT
- Summary of INCMGA00012/placebo treatment-related TEAEs by PT in decreasing order of frequency
- Summary of TEAEs related to COVID-19 by SOC and PT
- Summary of TEAEs related to COVID-19 by SOC, PT, and maximum severity
- Summary of serious TEAEs related to COVID-19 by SOC and PT
- Summary of TEAEs with a fatal outcome by SOC and PT
- Summary of TEAEs with a fatal outcome by PT in decreasing order of frequency
- Summary of serious TEAEs by SOC and PT
- Summary of INCMGA00012/placebo treatment-related serious TEAEs by SOC and PT
- Summary of serious TEAEs by PT in decreasing order of frequency
- Summary of TEAEs leading to next scheduled INCMGA00012/placebo dose delay by SOC and PT
- Summary of TEAEs leading to INCMGA00012/placebo infusion interruption by SOC and PT
- Summary of TEAEs leading to discontinuation of INCMGA00012/placebo by SOC and PT
- Summary of TEAEs leading to discontinuation of any chemotherapy by SOC and PT

The following summaries for AESIs will be included:

- Overall summary of immune-related TEAEs
- Overall summary of infusion reaction TEAEs
- Summary of TEAEs of special interest (IRR and irAE separately) by group term and PT

- Summary of TEAEs of special interest (IRR and irAE separately) by PT in decreasing order of frequency
- Summary of TEAEs of special interest (IRR and irAE separately) by group term, PT, and maximum severity
- Summary of TEAEs of special interest (IRR and irAE separately) with a fatal outcome by group term and PT
- Summary of TEAEs of special interest (IRR and irAE separately) leading to next scheduled INCMGA00012/placebo dose delay by group term and PT
- Summary of TEAEs of special interest (IRR and irAE separately) leading to INCMGA00012/placebo infusion interruption by group term and PT
- Summary of TEAEs of special interest (IRR and irAE separately) leading to INCMGA00012/placebo drug discontinuation by group term and PT
- Summary of Grade 3 or higher TEAEs of special interest (IRR and irAE separately) by group term and PT

8.3. Clinical Laboratory Tests

8.3.1. Laboratory Value Definitions

Laboratory values and change from baseline values will be summarized descriptively by treatment groups and histology, by visit during randomized and crossover periods, respectively. Baseline will be determined according to Section 4.1.5. If there are multiple values that meet the criteria for baseline, Table 5 may be referred as tiebreaker to delineate which value will be defined as baseline.

Table 5: Baseline Laboratory Identification

Priority	Laboratory Visit	Proximity to Visit Window	Tiebreaker
1	Scheduled	In-window	Use smallest laboratory sequence number
2	Unscheduled	In-window	
3	Scheduled	Out-of-window	

Laboratory test values outside the normal range will be assessed for severity based on CTCAE grade or similar criteria where clinical intervention is required for CTCAE grading. The incidence of abnormal laboratory values and shift tables relative to baseline will be tabulated.

8.3.2. Laboratory Value Summaries

All test results and associated normal ranges from laboratories will be reported in SI units. Any laboratory test results and associated normal ranges from local laboratories will be converted to SI units. For test results that will be summarized with available normal ranges, the number and percentage of participants with the laboratory values being low (but never high), normal, high (but never low), and both low and high will be calculated for each test. This shift summary may be produced for each test for the safety population during randomized period, and crossover

analysis set during crossover period, respectively. The denominator for the percentage calculation will use the number of participants in the baseline category (ie, low, high, normal, missing) as the denominator for the percentage in each of the categories during the treatment period. For numeric laboratory values, baseline value, postbaseline value, change from baseline, and percentage change from baseline will be summarized by visit.

Shift tables will be presented showing change in CTCAE grade from baseline to worst postbaseline grade during randomized and crossover periods, respectively. Separate summaries for abnormally high and abnormally low laboratory values will be provided when the laboratory parameter has both high and low grading criteria. The denominator for the percentage calculation will be the number of participants in the baseline category.

The following summaries will be produced for laboratory data (by laboratory parameter) reported during on-treatment period. All laboratory assessments will be listed, and those collected after on-treatment period will be flagged in the listings.

- Number and percentage of participants with worst postbaseline CTCAE grade (regardless of the baseline status) will be summarized. Each participant will be counted only for the worst grade observed after baseline.
- Shift tables using CTCAE grades comparing baseline with the worst postbaseline value will be produced for laboratory parameters with CTCAE grades.
- For laboratory parameters where CTCAE grades are not defined, shift tables to the worst postbaseline value will be produced using the low/normal/high classifications based on laboratory reference ranges.
- For laboratory parameters with any worsening postbaseline CTCAE grades than baseline, the worst postbaseline CTCAE grades will be summarized according to CTCAE severity grade levels.
- Number and percentage of participants meeting categorical liver function test criteria, including ALT, AST, and ALT or AST ($\geq 3 \times$, $5 \times$, $8 \times$, $10 \times$, $20 \times$ ULN); total bilirubin ($\geq 1 \times$, $2 \times$ ULN); ALP ($\geq 1.5 \times$, $2 \times$, $3 \times$, $5 \times$, $8 \times$, $10 \times$ ULN); combined categories of ALT/AST and total bilirubin (eg, ALT/AST $\geq 3 \times$ ULN and total bilirubin $\geq$ ULN); combined categories of ALT/AST total bilirubin; and ALP (ALT or AST $\geq 3 \times$ ULN, total bilirubin $\geq 2 \times$ ULN, and ALP $< 2 \times$ ULN at the same visit; potential drug induced liver injury). The worst values observed postbaseline for each participant will be used for each of the categories.

8.4. Vital Signs

Values at each scheduled visit, change, and percentage change from baseline for vital signs, including systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, body temperature, and weight will be summarized descriptively by treatment groups and histologies during randomized period and crossover period.

Criteria for clinically notable vital sign abnormalities are defined in Table 6. The abnormal values for participants exhibiting clinically notable vital sign abnormalities will be listed. Alert vital signs are defined as an absolute value outside the defined range and percentage change from

baseline greater than 25%. The abnormal values for participants exhibiting alert vital sign abnormalities will be listed.

Table 6: Criteria for Clinically Notable Vital Sign Abnormalities

Parameter	High Threshold	Low Threshold
Systolic blood pressure	> 155 mmHg	< 85 mmHg
Diastolic blood pressure	> 100 mmHg	< 40 mmHg
Pulse	> 100 bpm	< 45 bpm
Respiratory rate	> 24 breaths/min	< 8 breaths/min
Temperature	> 38°C	< 35.5°C

8.5. Electrocardiograms

Twelve-lead ECGs such as heart rate, RR, PR, QRS, QT, and QTc intervals will be obtained for each participant during the study. Values at each scheduled visit, change, and percentage change from baseline will be summarized by treatment groups for each ECG parameter during randomized period and crossover period. Baseline will be determined as the last nonmissing ECG measurements taken on or before Day 1.

Criteria for clinically notable ECG abnormalities are defined in Table 7. Participants exhibiting clinically notable ECG abnormalities will be listed with study visit. Abnormal values for participants with alert ECG values, defined as both the absolute value and the percentage change from baseline being outside normal ranges, will be identified and listed.

Table 7: Criteria for Clinically Notable Electrocardiogram Abnormalities

Parameter	High Threshold	Low Threshold
QTc (QTcF/QTcB)	> 480 ms	< 295 ms
PR	> 220 ms	< 75 ms
QRS	> 120 ms	< 50 ms
QT	> 500 ms	< 300 ms
RR	> 1330 ms	< 600 ms
Heart rate	> 100 bpm	< 50 bpm

Twelve-lead ECGs will be obtained for each participant during the study. Electrocardiogram abnormalities, both at baseline and postbaseline visits, will be tabulated. Incidences of abnormalities will be listed with study visit and a description of the abnormality.

9. PHARMACOKINETIC AND TRANSLATIONAL ANALYSES

The analysis described in this section will be conducted by PK and translational group, and summarized in a separate report.

9.1. Pharmacokinetic Assessments

Serum concentrations of INCMGA00012 will be monitored using a quantitative sandwich ELISA method. Single and multiple dose PK parameters for INCMGA00012, C_{max}, t_{max}, C_{min}, and AUC_{0-t} will be derived from INCMGA00012 serum concentration versus time data. Population PK analyses may be conducted using data from this study alone or combined with data from other studies. Pharmacokinetic parameters will be summarized as a secondary endpoint of the study.

[redacted]

10. INTERIM ANALYSES

10.1. Interim Analysis of Overall Survival

An interim analysis for OS is planned when approximately 60% of the targeted OS events will have been documented. Under the assumption of 14-month median OS in the placebo plus chemotherapy arm, it is expected that treatment with INCMGA00012 plus chemotherapy will result in a 30% reduction in HR (corresponding to an increase in median OS from 14 months to 20 months under exponential model assumption). If the true HR is 0.7 (under alternative hypothesis), a total of 341 OS events will be required to have 87% power at a 1-sided overall 2.5% level of significance to reject the null hypothesis (HR = 1) using a log-rank test and a 2-look group sequential design with Lan-DeMets (O'Brien and Fleming 1979) alpha spending function to determine efficacy stopping boundary. Considering a recruitment period of 34 months at a uniform rate of 18 participants/month with a 6-month ramp-up period and 20-month minimum follow-up, approximately 530 participants will be randomized in 2:1 ratio. However, due to potential early censoring from Ukraine participants, a total of 600 participants will be enrolled to ensure enough number of events will be observed within reasonable follow-up time.

The primary intent of the interim analysis will be to unblind early for outstanding efficacy.

If the OS endpoint crossed the boundary to claim statistical significance at interim analysis, the trial will be unblinded and a full CSR may be written based on this data cut.

11. CHANGES AND MODIFICATIONS TO THE ANALYSIS PLAN

All versions of the SAP are listed in Table 9.

Table 9: Statistical Analysis Plan Versions

SAP Version	Date
Original	05 APR 2022
Amendment 1	02 FEB 2023

11.1. Changes to Protocol-Defined Analyses

The CAS population has been added to analyzed data from the crossover period.

11.2. Changes to the Statistical Analysis Plan

[redacted]

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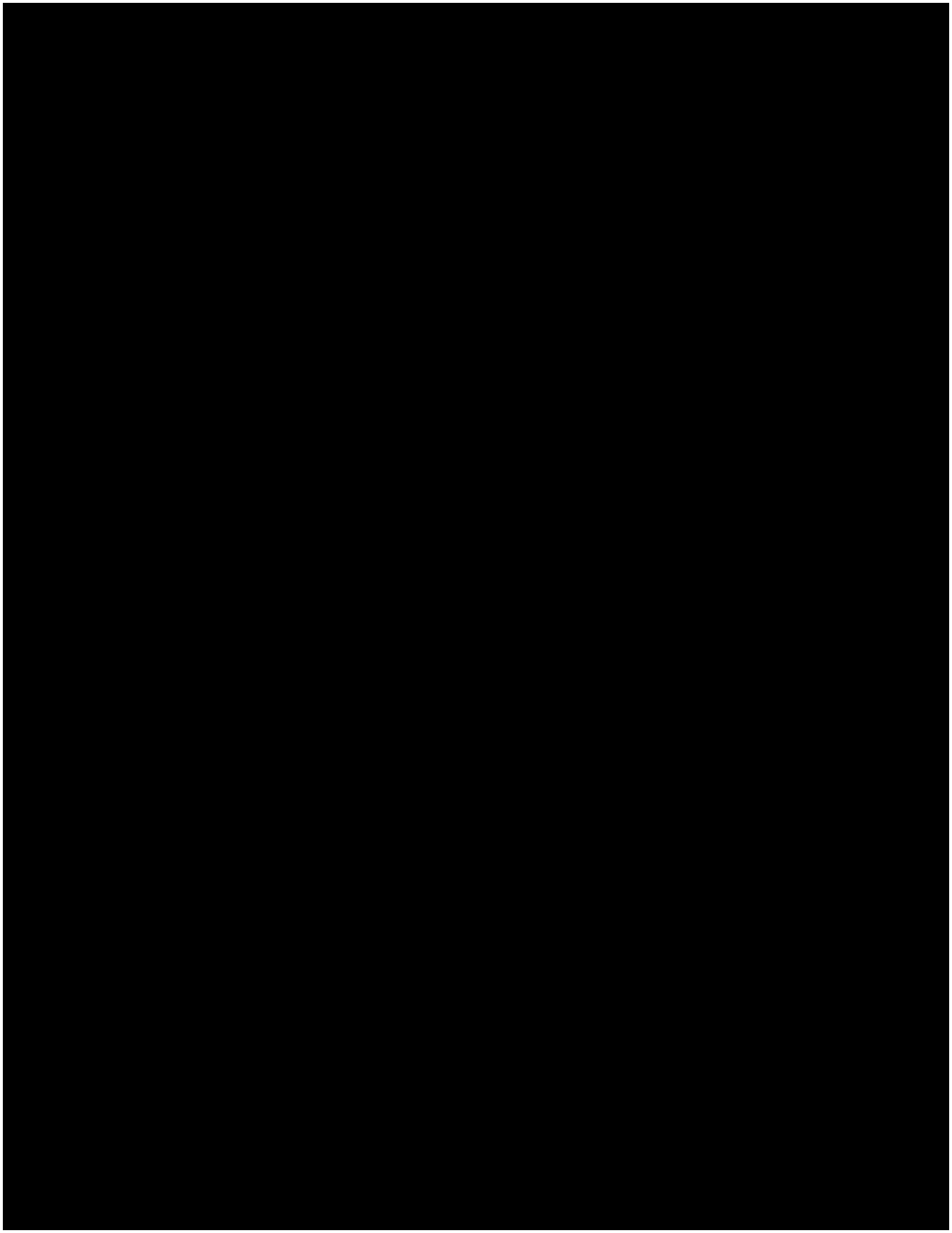

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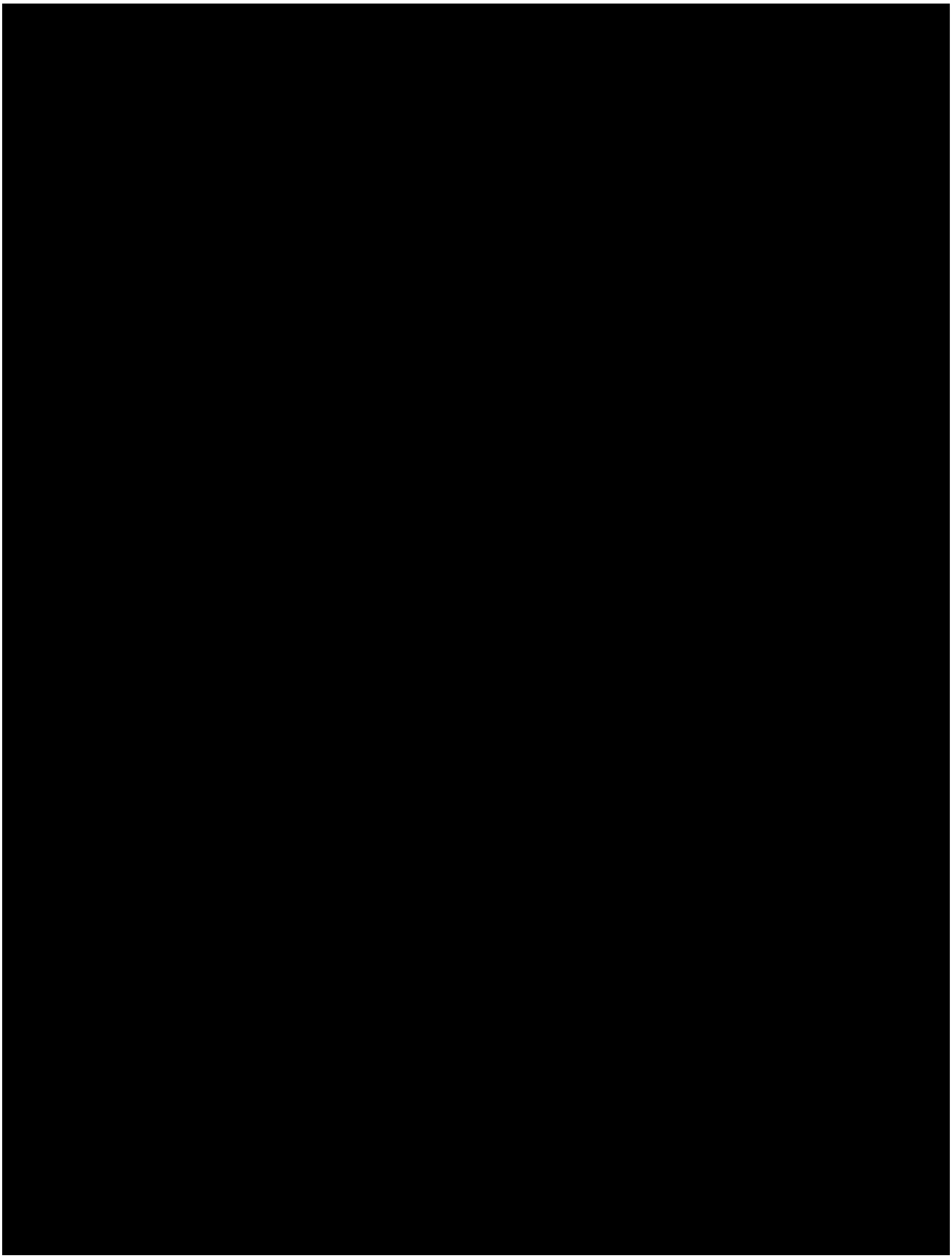

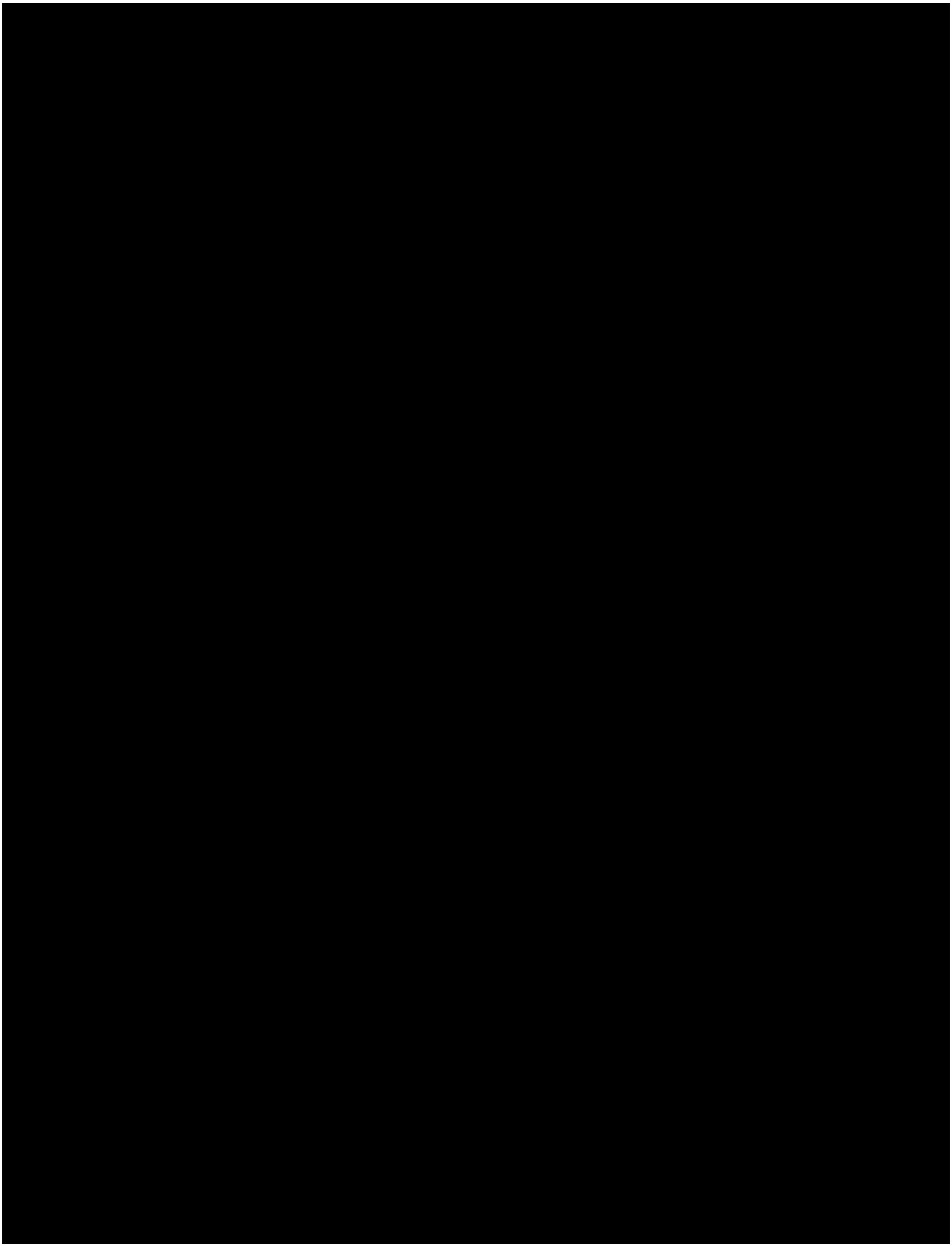

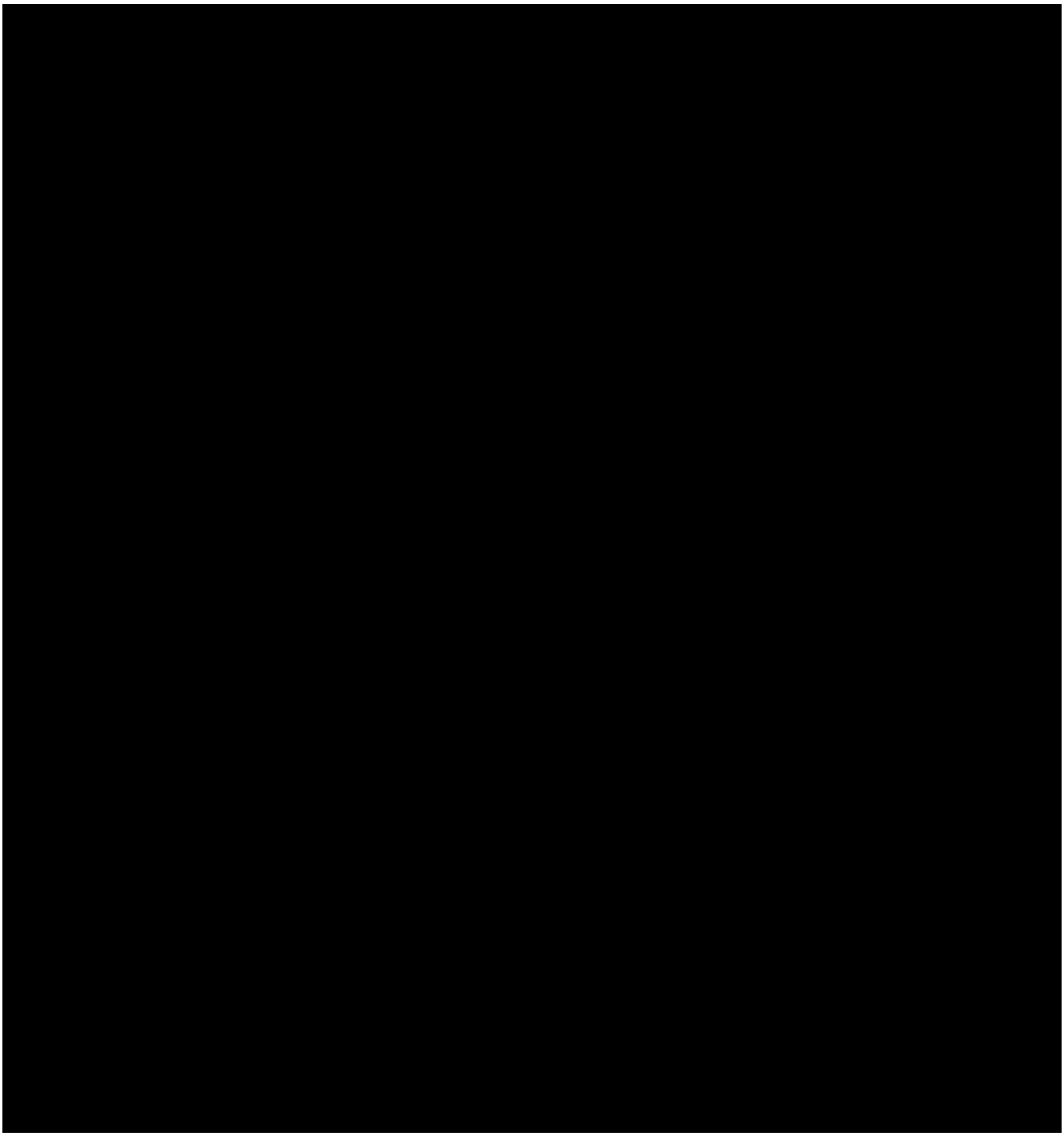

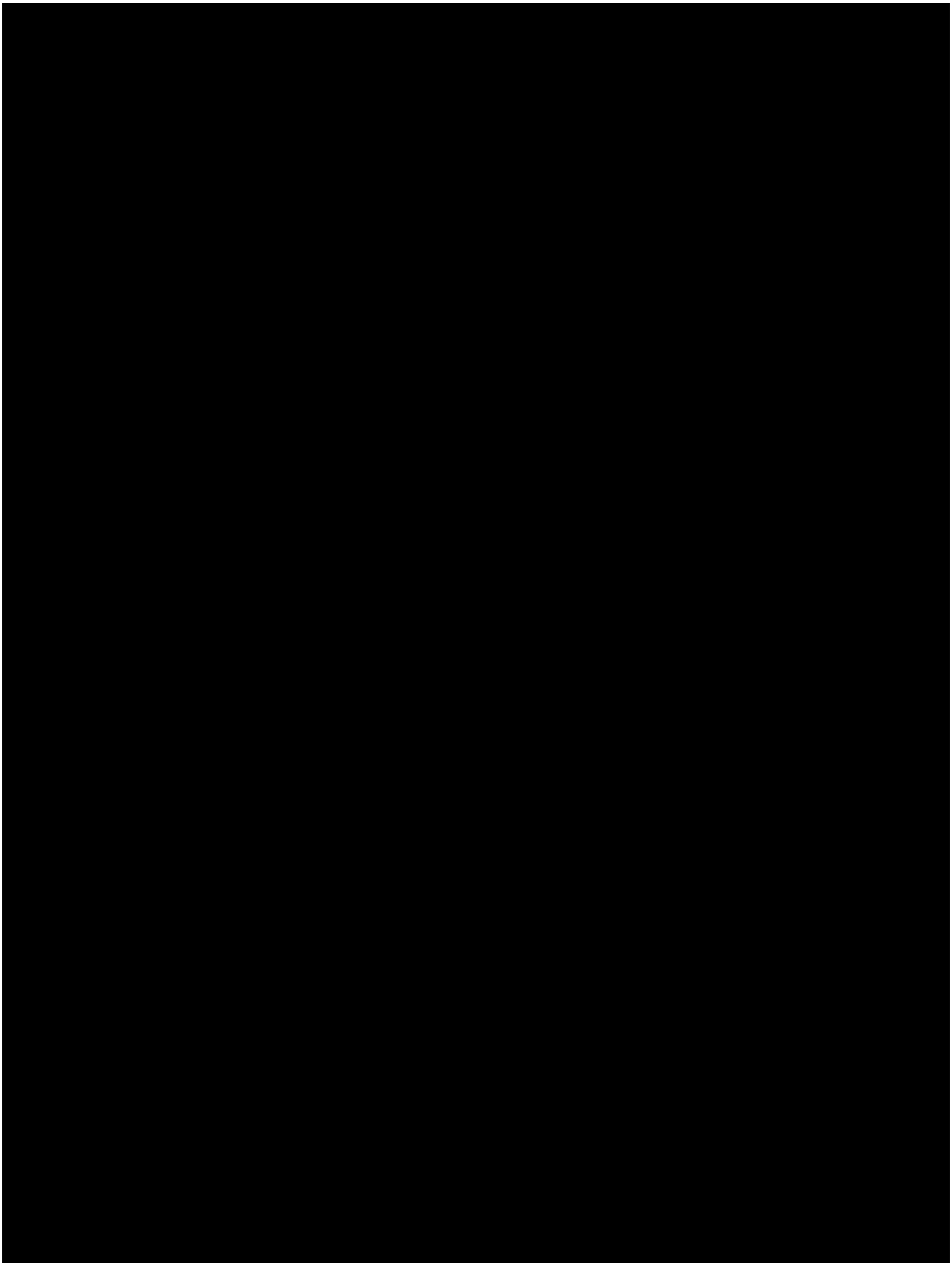

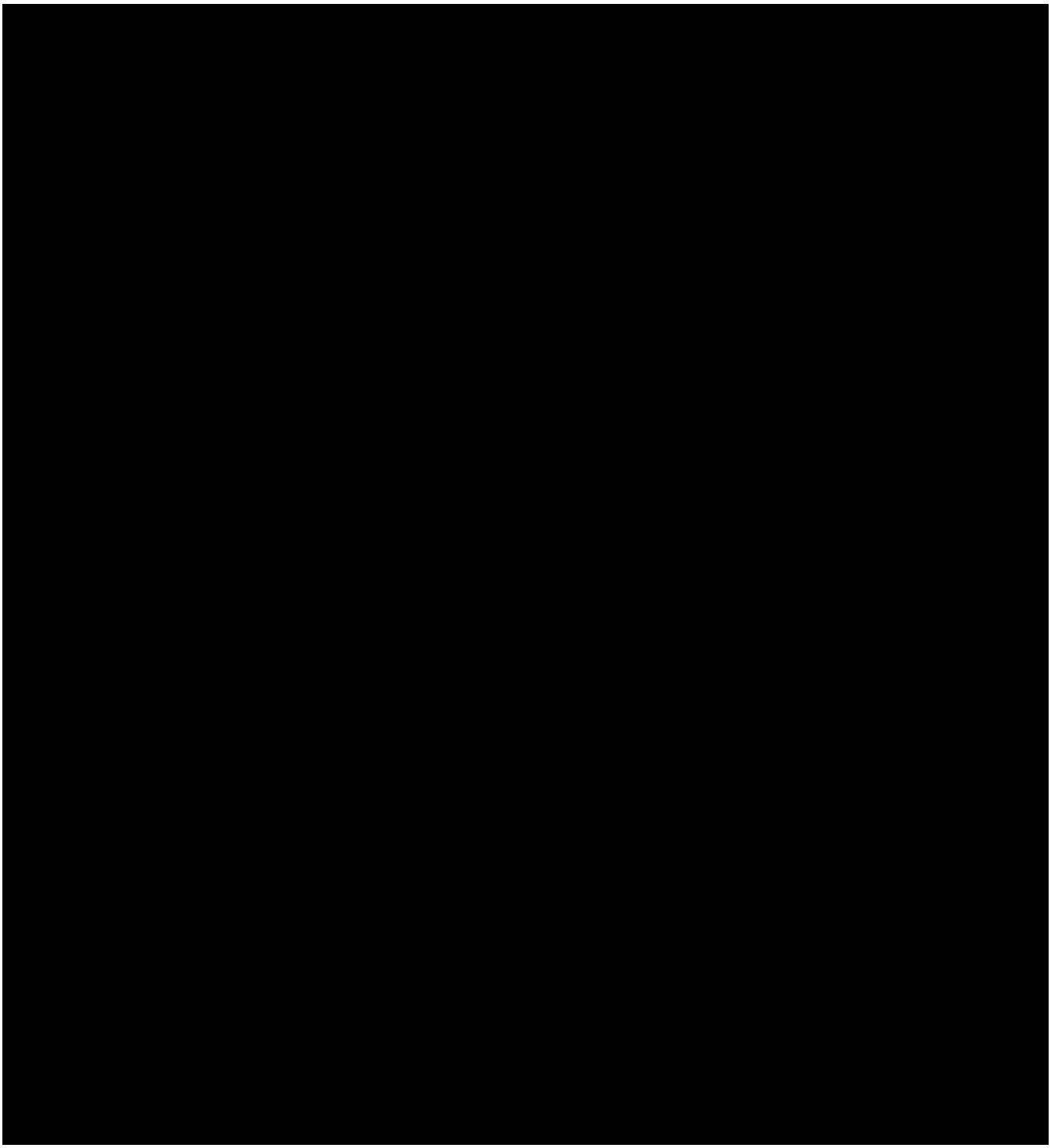

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