TRIAL STATISTICAL ANALYSIS PLAN

c36236762-02

BI Trial No.:	1402-0012
Title:	A phase II randomized, double-blinded, placebo-controlled parallel group trial to examine the efficacy and safety of 4 oral doses of BI 1358894 once daily over 12-week treatment period in patients with borderline personality disorder (BPD) Clinical Trial Protocol (c29157684-03), including Global Protocol Amendment 1 (08DEC2020), Global Protocol Amendment 2 (28JUN2021), Global Protocol Amendment 3 (27APR2022)
Investigational Product(s):	BI 1358894
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	26 January 2023 Final
Version:	2

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criterion
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AS	Adherent set
ATC	Anatomical, Therapeutic, Chemical
BI	Boehringer Ingelheim
CGI-S	Clinical Global Impression – Severity
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CT	Concomitant Therapy
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DBLM	Database Lock Meeting
DV	Protocol Deviations
ECMA	Ecological Momentary Assessment
ECG	Electrocardiogram
EDMS	Electronic Document Management System
EOT	End of Treatment
EQ-5D-5L	Euro Quality of Life-5 Dimensions-5 Levels
FAS	Full Analysis Set
fMRI	Functional magnetic resonance imaging
FU	Follow-up
ICH	International Conference on Harmonisation
IDEA	International Document Management & Electronic Archiving
IPD	Important Protocol Deviation
IVRS	Integrated Voice Response System

Term	Definition / description
LLT	Lowest Level Term
MAR	Missing at Random
MCPMod	Multiple Comparison Procedures and Modelling
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effects Model Repeated Measures
MQRM	Medical Quality Review Meeting
MRI	Magnetic Resonance Imaging
OAA	Overall AiCure Adherence
PGI-I	Patient Global Impression – Improvement
PK	Pharmacokinetics
PKS	PK parameter analysis set
PPS	Per Protocol Set
PT	Preferred Term
PD	Pharmacodynamics
QD	Quaque Die (once a day)
RDC	Remote Data Capture
REP	Residual Effect Period
RPM	Report Planning Meeting
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOC	System Organ Class
SS	Screened Set
STD	Standard Deviation
TMF	Trial Master File
TOM	Trial Oversight Meeting
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UDAEC	User-defined AE categories
ULN	Upper Limit of Normal
VAS	Visual Analog Scale

Term	Definition / description
WHO	World Health Organisation

3. INTRODUCTION

As per International Conference on Harmonisation (ICH) E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the CTP, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

R Version 3.3.2 with "DoseFinding" package (2) will be used for analyses based on Multiple Comparison Procedures and Modelling (MCPMod) and SAS® Version 9.4 will be used for all other analyses.

The main analyses of this TSAP will be conducted under the estimand concept. To quote ICH E9 R1, "An estimand is a precise description of the treatment effect reflecting the clinical question posed by a given clinical trial objective. It summarizes at a population level what the outcomes would be in the same patients under different treatment conditions being compared." So, an estimand is a way for the clinical trial protocol to address how intercurrent events will be handled. And according to ICH E9 R1, intercurrent events are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Or in other words, intercurrent events are occurrences after randomization that involve a change in treatment regimen.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In this TSAP the following are the changes to the statistical methods described in the CTP (including amendments).

- MCPMod analyses will be used to examine the relationship between change from baseline in ZAN-BPD score at Week 10 and BI 1358894 plasma concentration and will be reported in a separate analysis plan.

Also, EcMA endpoints were revised due to further consultation with EcMA expert [redacted] The wording was changed from:

- "Namely, the results of these assessments will be evaluated in an exploratory approach: a) Affective instability, b) Negative valence, c) Anxiety.",

to the below:

- There are a total of eight possible models, of which four are on psychological momentary states, namely, the effect of treatment on: (1) momentary negative affect, (2) momentary positive affect, (3) momentary anxiety and (4) momentary valence. The other half of the models are on psychological instabilities, they are, the effect of treatment on: (5) instability of negative affect, (6) instability of positive affect, (7) instability of anxiety and (8) instability of valence.

The above changes in analyses are not of a primary or secondary endpoint, therefore modifications do not warrant a CTP-amendment and can be done in this TSAP.

In addition, sensitivity analyses on PGI-S, CGI-S and PGI-Impact will not be performed due to the low rate of telemedicine assessments for the PGI-S, CGI-S and PGI-Impact.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT

Change from baseline in ZAN-BPD total score at Week 10 is the primary efficacy endpoint. See CTP Section 5.1 for details.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

There is no key secondary endpoint in this trial.

5.2.2 Secondary endpoint(s)

The secondary efficacy endpoints are:

- Response defined as ≥30% ZAN-BPD reduction from baseline at Week 10.
- Change from baseline in DERS-16 total score at Week 10.
- Change from baseline in STAI-S total score at Week 10.
- Change from baseline in PHQ-9 total score at Week 10.
- Change from baseline in CGI-S at Week 10.
- Change from baseline in PGI-S at Week 10.

5.3 FURTHER ENDPOINT(S)

[redacted]

- Percentage of patients with (S)AEs (including clinically relevant abnormalities of physical examination, vital signs, ECG test and laboratory tests)

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For details on the treatment regimen, assignment of treatment groups, and the selection of doses, refer to Section 4 of the CTP. Below in Table 6.1:1 are the descriptions of the short and long names of the treatments. Next, are the definitions of the study phases for the analysis periods (Table 6.1:2).

Table 6.1: 1 Treatment descriptions

Long Name	**Short Name**
Placebo	Placebo
BI 1358894 5 mg qd	BI 5 mg
BI 1358894 25 mg qd	BI 25 mg
BI 1358894 75 mg qd	BI 75 mg
BI 1358894 125 mg qd	BI 125 mg

Table 6.1: 2 Study analysis phases*

Study analysis phase	Description	Start Date (included)	End Date (included)
Screening phase	Screening (prior to treatment)	Date of informed consent	Date of first treatment administration minus 1 day
Treatment phase and residual effects period	On-treatment period	Date of first treatment administration	Date of last treatment administration + REP
Follow-up phase	Off-treatment period	Date of last treatment administration + REP +1 day	Date of last CTP visit

* The defined treatment periods are the same for all treatment groups.
REP is the residual effect period which is defined as 28 days after the last dose of trial treatment for safety, and 7 days after last dose for efficacy
Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the database (i.e., randomized patients). Consistency check listings (i.e., identification of violations of time windows) and a list of CTP deviations will be provided to be discussed at the Report planning meeting (RPM)/Database lock meeting (DBLM)/Medical Quality Review Meeting (MQRM). At these meetings, it will be decided whether a discrepant data value can

be used in analyses and/or whether it must be queried in the clinical database. Each CTP deviation must be assessed to determine whether it is an important Protocol Deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the current BI reference document "Identify and Manage Important Protocol Deviations (iPD)" (3).

Generally, a protocol deviation is considered as an iPD if it affects the rights or safety of the study subjects, or if it can potentially influence the primary outcome measurement(s) in a non-negligible way. If any iPDs are identified, they are to be summarized into categories and will be captured in the RPM/DBLM/MQRM minutes via an accompanying DV domain specifications Excel spreadsheet (4). If the data presents additional iPDs (e.g., based on monitor visits to the sites), then the DV domain specifications will be supplemented accordingly at TOMs or RPMs or through team review of the manual PD log.

The decision whether a patient will be excluded from the analysis will be made at the final RPM prior to Database Lock (DBL). The documentation of the iPD categories and how to handle iPDs in the analysis are listed in the DV domain specifications and stored within the Trial Master File (TMF) in Electronic Document Management System (EDMS). iPDs will be summarized and listed for the treated set.

6.3 SUBJECT SETS ANALYSED

The following analysis sets are defined for this trial:

- Screened Set (SS): consists of all subjects who signed informed consent.
- Treated Set (TS): consists of all subjects that have been randomized and that received at least one administration of study drug. The TS will be the main analysis set for the evaluation of safety. Subjects are analysed according to the actual received treatment.
- Full analysis set (FAS): consists of all subjects in TS that have a baseline and at least one evaluable post-baseline measurement for the primary endpoint. This is the main analysis set for the evaluation of efficacy data.
- Per protocol set (PPS): This is a subset of FAS, for subjects with adequate protocol compliance. It consists of all subjects in FAS without any important protocol deviations that impact efficacy assessments.
- Adherent set (AS): consists of all subjects in FAS that are at least 60% overall AiCure adherent to study medication. See Section 7.3.2 for further information.
- [redacted]

Table 6.3: 1 Subjects' sets analyzed

	Subject set					
Class of endpoint	TS	SS	FAS	PPS	[redacted]	AS
Primary and secondary endpoints, compliance			X	X*		
Further endpoints (except PK)			X			
Disposition		X				
[redacted]					[redacted]	
Safety variables and iPDs	X					
Demographics, baseline variables, exposure			X	(X)		
Primary endpoint adjusted for overall study AiCure adherence						X

* If the percentage of subjects in FAS with iPD that lead to the exclusion from the PPS is > 10%, then sensitivity analysis of the primary and secondary efficacy endpoints using PPS may be conducted.

(X) An additional PPS presentation of the demographic/baseline endpoints may be provided in the End of Text (EoT) section, if there are a non-negligible number of subjects that were treated, but without any post randomization data for the primary endpoint.

[redacted]

[redacted]

6.5 POOLING OF CENTERS

All subjects from all centers will be pooled for the statistical analysis of efficacy. The effect of region on the primary and selected secondary efficacy endpoints will also be investigated as described in Section 6.4. Therefore, this section is not applicable because center/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing data are not explicitly imputed and remain missing for all main analyses. All but one of the CTP-defined primary and secondary efficacy endpoints are continuous. Therefore, for these efficacy endpoints which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will ensure that missing data are handled implicitly via a missing at random assumption (MAR) by the statistical model. For the binary efficacy endpoint of ZAN-BPD response, missing data will not be imputed.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (5). Missing data and outliers of PK data are handled according to (6).

6.7 BASELINE, TIME WINDOWS, AND CALCULATED VISITS

Baseline is defined as the last observation at, or prior to Visit 2. Hence, if a subject is randomized at Visit 2, but does not start trial medication until a future visit (e.g., Visit 4), then his/her baseline is the latest assessment performed at Visit 2. However, for laboratory safety measurements, the last value prior to the first drug administration will be considered as the baseline value.

Planned and actual test days are included in the analysis data sets and are calculated relative to the beginning of treatment as indicated in Table 6.7: 1 below.

For efficacy measurements, only one observation per time window will be selected for statistical analysis –the first one in the corresponding time window. If there are two observations which have the same difference in days to the planned day, or if there are two observations on the same day, the first value will be selected. If an observation is available on the last day of treatment, this observation will be preferably selected over any later observation that is still within the time window. Assignment of efficacy observations to visits based on time windows will be based on the non-imputed (observed) data. Repeated and unscheduled efficacy measurements will be assigned to the nominal visits according to the time windows described in Table 6.7: 1.

For safety measurements, data collected at all visits will be used. For repeated and unscheduled safety measurements for the same visit on treatment, the worst of these will be selected for analysis. In the case for which there is no standard reference direction for the safety parameter, the average of all values for the same visit will be used for analysis.

Table 6.7: 1 Planned and actual study days

Visit	Relative to treatment start	
	Planned test day	Actual test day
2	1	Day 1
3	8	Day 2 – Day 12
4	15	Day 13 – Day 19
4A	22	Day 20 – Day 26
5	29	Day 27 – Day 33
5A	36	Day 34 – Day 40
6	43	Day 41 – Day 47
6A	50	Day 48 – Day 54
7	57	Day 55 – Day 61
7A	64	Day 62 – Day 68
8	71	Day 69 – Day 75
8A	78	Day 76 – Day 82
9 / EOT	85 (for completed subjects)	Day 83 – treatment stop date (stopdt) + 7 days
eEOT	N/A (for early discontinued subjects)	Date of the last administration of trial medication + 7 days (for early discontinued subjects). The number of days will be assigned to the visit. Thus, if days to eEOT is 56, it will be mapped to Visit 7. For those that early discontinue treatment but continue with the collection of efficacy data, those data points will be mapped to the later Visits as per the above Visit window. Hence, if this same subject collects ZAN-BPD at Day 74, it will be mapped to Visit 8.
FUP1	stopdt + 8 days	(stopdt + 8 days) to (stopdt + 11 days)
FUP2	stopdt + 14 days	(stopdt + 12 days) to (stopdt + 25 days)
End of Trial	stopdt + 28 days	(stopdt + 26 days) to stopdt + 30 days

- Days are counted relative to the day of randomization, which is defined as Day 1.
- stopdt stands for treatment stop date.

There is no visit window mapping for C-SSRS given that it is collected nearly every week throughout the study.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (7).

The individual values of all subjects will be listed, sorted by dose group, subject number and visit. AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in an Appendix of the CTR.

For End-Of-Text tables, the set of summary statistics is N / Mean / Standard Deviation (SD) / Min / Median/ Max. For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles are preferred to mean, standard deviation, minimum and maximum. In general, means, medians, and percentiles are presented to one more decimal place than the raw data and SDs are presented to two more decimal places than the raw data. Minima and Maxima are presented to the same number of decimal places as the raw data.

Disposition of the patient population participating in the trial will be analyzed by treatment and presented by the categories in the standard CRF groups and presented in the CTR as a frequency-distribution.

For categorical data, tabulations of frequencies will include all defined categories even if there is no count in a category. Tabulations of frequencies will display the number of observations in a category as well as the percentage (%) relative to the number of subjects in the respective treatment group. All patients in the respective patient set are used whether they have non-missing values or not, unless otherwise specified. Percentages will be rounded to one decimal place. The category missing will be displayed only if there are missing values.

If applicable, conversion from days to weeks, months and years will be as follows:

- weeks = days ÷ 7
- months = 12 × days ÷ 365.25
- years = days ÷ 365.25.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics and summary tables are planned for this section of the report. Data will be summarised by treatment group and a "total" column will be included in the summary table.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

Concomitant diseases (i.e., baseline conditions) will be coded similarly as AEs using the most recent version of MedDRA. A summary of concomitant diseases will be provided by

treatment group, System Organ Class (SOC) and Preferred Term (PT). Concomitant diseases which are present at start of the study will be descriptively summarized by treatment.
A medication/therapy will be considered concomitant to treatment if it (1) is ongoing at the start of randomized trial treatment or (2) starts within the on-treatment period (see Section 6.1 for a definition of study analysis phases). A medication/therapy will be considered as prior medication/therapy, if the end date of the medication/therapy is at any time prior to the start of randomized trial treatment.

Concomitant therapies (CTs) are coded according to WHO Drug Dictionary. CTs will be classified according to the Anatomical, Therapeutic, Chemical (ATC) classification system. The third ATC level will be used to categorize CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, subjects receiving CTs with more than one possible ATC level-three category will be counted more than once and footnote will clarify this possible multiple counting in tables. The most current MedDRA and WHO DD versions will be used.

7.3 TREATMENT COMPLIANCE

7.3.1 CRF Compliance

Only descriptive statistics are planned for this section of the report. Treatment compliance is calculated at Week 1, 2, 4, 6, 8, 10 and 12(EOT) based on the CTP's flow chart.

Treatment Compliance = (number of tablets taken during a period) / (number of tablets that should have been taken during a period) * 100.

The cumulative treatment compliance during the entire treatment period is derived using the following examples:

For completers: if a subject's observed treatment compliance rates are 80%, 81%, 82%, 83%, 84%, 85%, 86% at Weeks 1, 2, 4, 6, 8, 10 and 12, then the cumulative treatment compliance percent = (.80*1 + .81*1 + .82*2 + .83*2 + .84*2 + .85*2 + .86*2)/12*100 = 83.42%.

For early discontinued subject: if a subject's observed treatment compliance rates are 80% at Week 1, 81% at Week 2, 82% at Week 4, 50% at eEOT, then the cumulative treatment compliance rate = (0.80*1 + 0.81*1 + 0.82*2 + 0.5*((eEOT date – drug start date + 1)/7 – 4))/((eEOT date – drug start date + 1)/7) * 100% = 74.3% if the quantity (eEOT date – drug start date + 1) is assumed to be 36 days.

If at a particular visit a participant did not return the trial drug kits, then the compliance at that visit is zero.

Treatment compliance will be summarised overall and by visit for the treated set (FAS) using descriptive statistics (N, mean, SD, minimum, median, maximum). The number and percentage of patients with the following overall compliance categories will be presented

using descriptive statistics (N, mean, SD, minimum, median, maximum). The number and percentage of patients with the following overall compliance categories will be presented:

- "<80%",
- "80% to <100%",
- ">=100%",
- missing.

7.3.2 AiCure Adherence

First, we define overall AiCure Adherence (abbreviated as OAA), as the sum of all tablet adherence minus the total number of tablets flagged as red, orange, or yellow alerts, divided by a denominator of 4 times 84. Or, in other words:

- OAA = [[(Sum of all tablet adherence) – (total number of red, orange, and yellow alerts)]/ 4*84] *100,
    - 84 = Number of days on treatment, and 4 is the number of tablets per dose.

Tablet adherence is the successful administration of a pill as captured by AiCure video. *Red alerts* are tablet administrations for which the AiCure video captures the dosing process, but includes strong visual proof of deceptive behaviors, non-adherence, and/or overdose of study drug. Examples include removing study drug from the mouth, 'cheeking', spitting out the drug, or using non-IP to dose. Also, in cases for which more than one pill was ingested simultaneously, a red alert is flagged. For *orange alerts*, the video captures the dosing process, but contains suggested visual proof of potentially deceptive behavior, potential non-adherence, or shows potential overdose of study drug. And lastly, for *yellow alerts* the video is missing visual information necessary to confirm adherence.

Note that tablet adherence is the administration of a tablet by the following method: visually confirmed by the AiCure app.

For subjects that discontinue treatment early, 84, which is the number of days from randomization to the planned treatment end, will be replaced by the total number of days from randomization to the respective date of early treatment discontinuation.

As defined in Section 6.3, the Adherent set (AS) consists of all subjects in FAS that achieved an OAA of at least 60%. Within these subjects, flags (or classifications) will be built to denote increasing thresholds of adherence (≥60%, ≥75%, ≥90%). Hence, it may be of interest to evaluate the effect of varying levels of overall adherence on efficacy.

An evaluation of the primary endpoint to varying levels of adherence to treatment may be of interest, please see Section 7.4.2.3 for further details.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

The primary endpoint is the change from baseline to Week 10 in ZAN-BPD total score. Baseline refers to the measurement recorded at randomization (Visit 2), if data at Visit 2 is missing, then data from Visit 1 will be considered baseline.
Despite the COVID-19 pandemic, the collection of complete data at all visits is our goal. Therefore, to avoid missing data due to a subject's potential inability to attend their in-person clinical visit, a virtual assessment via videoconferencing will be available to ascertain the ZAN-BPD. For the primary analysis of the primary endpoint, we assume no discernible difference between the in-person and virtual collection of the ZAN-BPD. Hence, all data while subjects are on treatment, whether in-person or virtual, will be used in the evaluation of the primary analysis of the primary endpoint.

The primary analysis of the primary endpoint will use a hypothetical estimand. The hypothetical approach focuses on the treatment effect assuming all subjects complied with the CTP and remained on the assigned trial medication, i.e., study drug is taken as directed. Hence, the hypothetical estimand evaluates the treatment effect if intercurrent events do not occur. Therefore, this analysis will include all data collected while on treatment which is defined as the time from the date of the first dose of trial medication until the date of the last dose of trial medication plus 7 days. Any data collected after a patient discontinues trial drug, regardless of reason, will be censored and will not be included in the primary analysis. Therefore, the primary analysis of the primary endpoint will be evaluated under the hypothetical estimand regardless of the potential influence of COVID-19.

The Multiple Comparison Procedures and Modelling (MCPMod) approach (8, 9) is implemented in two main stages: (1) **trial design stage**; (2) **trial analysis stage**. The procedures for the trial design stage, including the selection of candidate models covering a suitable range of dose-response shapes and sample size and power calculations are provided in the CTP Section 7.2.2 and 7.5. The procedures for the trial analysis stage are specified below. FAS is used for the primary analysis of the primary efficacy endpoint.

MMRM analysis
The change from baseline in ZAN-BPD at Week 10 for each dose group as well as the corresponding variance-covariance matrix are estimated by a mixed effects model repeated measure (MMRM) including the fixed categorical covariates of treatment, visit and the baseline ZAN-BPD total score strata indicator (≤18 vs. ≥19), the continuous fixed covariate of baseline ZAN-BPD total score, and treatment-by-visit interaction, as well as baseline-by-visit interaction. Patient is considered as random. The unstructured covariance matrix is used to estimate the within subject variability. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom. Analyses will be implemented using SAS 9.4 PROC MIXED.

More specifically, the change in ZAN-BPD from baseline (Visit 2), at Visits 3, 4, 5, 6, 7 and 8 (Weeks 1, 2, 4, 6, 8 and 10) will be evaluated using an MMRM accounting for the following sources of variation: 'treatment', 'visit', 'baseline ZAN-BPD strata indicator' (≤18 vs. ≥19),

'baseline ZAN-BPD' as a continuous covariate, and the 'treatment*visit' and 'baseline*visit' interaction as fixed effects, as well as the random 'subject' effect. The methods described in Section 10.1 will be utilized to resolve model non-convergence.

SAS code for MMRM:
The following SAS code will be used to calculate the MMRM.

```
PROC MIXED DATA=indata cl method=reml;
        CLASS visit trt stratum subject;'
        MODEL ept = stratum visit*trt base*visit / ddfm=kr s CL;
        REPEATED visit / subject= subject type=un r rcorr;
        LSMEANS visit*trt / pdiff=all om cl alpha=0.10 slice=visit;
RUN;
```

Results of the MMRM (N, mean, SE and 95% CI per dose group and timepoint) will be presented in tables and displayed graphically.

MCPMod Analysis
The adjusted mean estimates of the change from baseline at Week 10 for each dose and their estimated variance-covariance matrix from the MMRM model are used in the trial analysis stage. Then, the multiple pair-wise comparison procedure will be implemented using the optimal contrast tests which control the family-wise type I error rate at one-sided $\alpha = 0.10$.

For the MCPMod test, the optimal contrasts corresponding to the candidate models are calculated as in the trial design stage (using the R-function optContr using weights proportional to the sample size of each dose group) and are shown in Table 7.4.1: 1 below. These contrasts will be updated using the expected model means from the candidate set and the estimated variance-covariance matrix from the data. The final contrasts will be presented in the CTR.

Table 7.4.1:1 Optimal contrast coefficients

	Optimal Contrast Coefficients for Dose				
Model	**0**	**5mg**	**25mg**	**75mg**	**125mg**
Linear	-0.583	-0.209	-0.110	0.136	0.765
Emax1	-0.736	-0.175	0.064	0.243	0.604
Emax2	-0.862	0.052	0.177	0.206	0.425
Sigmax	-0.684	-0.250	0.032	0.276	0.627
Exponential	-0.479	-0.187	-0.161	-0.016	0.842

Proof of concept is established if at least one dose-response model is statistically significant, i.e., the null hypothesis of a flat dose-response curve is rejected indicating a benefit of one BI 1358894 dose over placebo.

Once the significance of a dose-response signal is established, the dose-response profile and the target dose can be estimated using the model averaging method.

The selected dose-response model(s) is re-fitted to the data without any parameter assumptions to generate a set of new estimates of the model parameters from the data. The final dose-response model is obtained via the weighted model averaging of the significant models (p-value<0.10) based on Akaike Information Criterion (AIC) (the smaller the AIC value the better the model fit). The weights for each significant model (M_k) are given by,

$$w(M_k) = \frac{exp(-0.5 * AIC(M_k))}{\sum_{i=1}^{K} exp(-0.5 * AIC(M_i))}$$

where AIC(M_k) is the AIC for model M_k.

The estimate of the target dose is the smallest dose producing an effect greater than or equal to the target effect size of 0.32 based on the final dose-response model (accounting for safety and other relevant information). Specifically, the target effect size considers the observed standard deviation (SD) and the adjusted mean treatment effect. Thus, if the observed SD is 9.5, then to achieve the target effect size of 0.32, the observed placebo-adjusted difference would need to be at least 3. Test statistics and p-values will also be displayed for different dose-response models. Figures and tables will be displayed for the MCPMod modelling.

The following displays are planned:
- Table of the contrast coefficients per dose group and candidate model, together with the MCPMod test statistics and p-values for each model and the critical value
- For the average model, figure of the dose-response curve
- For all significant model shapes, figures of the dose-response curve plus 95% confidence band (of the predicted shape)

The MCPMod trial analysis will be implemented by calling an R function/package within SAS. *Please see Section 10.3 for R code to implement the MCPMod analysis*.

7.4.2 Sensitivity analysis, supplementary analysis, subgroup analysis, exploratory analysis of the primary endpoint(s)

7.4.2.1 Sensitivity analyses

To explore the robustness of inferences (results) from the main estimator to deviations from its underlying assumptions, several sensitivity analyses will be conducted targeting the same estimand, the hypothetical estimand. In the sensitivity analyses that follow, a certain aspect of the main analysis of the primary endpoint is altered to allow the possibility of identifying which assumptions, if any, are responsible for potential differences observed.

Exclude virtual collections of ZAN-BPD

The first sensitivity analyses to the primary analysis of the primary endpoint will assess the assumption of no discernible difference between the in-person and virtual collection of the ZAN-BPD. Unlike the primary analysis, this sensitivity analysis will assume a difference between the in-person and virtual data assessments and shall exclude all virtual collections of

the ZAN-BPD. This analysis of the primary endpoint will use the hypothetical estimand (the same estimand as that of the primary analysis). However, here we recognize the virtual collection as a deviation. This sensitivity analysis will follow the same analysis methodology (MCPMod/MMRM) as specified in the primary analysis, but with the exclusion of all virtual collections of the ZAN-BPD.

Dose response patterns
If considered necessary and for the purpose of further model refinement, the MCPMod analysis may be repeated on the primary endpoint but with an extended set of dose response patterns, including the original candidates.

Additional risk factors
Further sensitivity analyses to the primary analysis of the primary endpoint will be conducted with additional covariates of interest. The additional fixed categorical covariates of stable concomitant psychotherapy use (Yes, No) and Sex (Male, Female) will be included into the MMRM model.

PPS
Sensitivity analysis of the primary and secondary efficacy endpoints using the PPS may be conducted if more than 10% of patients in FAS have an iPD which lead to exclusion from the PPS.

7.4.2.2 Supplementary analyses to the primary endpoint

Supplementary analysis is a general description for analyses that are conducted in addition to the main and sensitivity analysis to provide additional insights into the understanding of the treatment effect. Supplementary analyses should generally be given lower priority than sensitivity analyses. Please see below Table 7.4.2.2:1 for an overview of the supportive sensitivity and supplementary analyses to the main analysis of the primary endpoint.

Table 7.4.2.2: 1 Overview of the main analysis of the primary endpoint and its sensitivity/supplementary analyses.

Primary Analysis	Sensitivity Analysis	Supplementary Analysis 1	Supplementary Analysis 2
Hypothetical estimand (main analysis)	Hypothetical estimand	Treatment policy (repeats primary analysis)	Treatment policy (repeats sensitivity analysis)

Does not recognize alternate collection of the ZAN-BPD. Assumes no discernible difference between in-person and virtual ZAN-BPD.	Recognizes alternate collection of the ZAN-BPD. Assumes a difference between the in-person and virtual assessment. Excludes virtual collections of ZAN-BPD.	Does not recognize alternate collection of the ZAN-BPD. Assumes no discernible difference between in-person and virtual data ZAN-BPD.	Recognizes alternate collection of the ZAN-BPD. Assumes a difference between the in-person and virtual assessment. Excludes virtual collections of ZAN-BPD.

Treatment policy estimand

1. Supplementary analysis 1 repeats *the primary analysis of the primary endpoint* but under the treatment policy estimand i.e., effectiveness/intention to treat. Under treatment policy, we assess the treatment effect irrespective of intercurrent events, hence all measurements are relevant. We maintain the assumption of no discernible difference between the in-person and virtual collection of the ZAN-BPD. The treatment policy estimand will use all available ZAN-BPD data including data collected after treatment discontinuation or other intercurrent events. If telemedicine assessments need to be implemented due to COVID-19 related factors, the treatment policy estimand will use all available data regardless of administration method (i.e., in-person, video, and audio). This supplementary analysis to the primary endpoint will follow the same analysis methodology (MCPMod/MMRM) as specified in the primary analysis.

2. Supplementary analysis 2 repeats the *sensitivity analysis of the primary endpoint* (exclude virtual collections of ZAN-BPD) but under the treatment policy estimand i.e., effectiveness/intention to treat. Here, and like the sensitivity analysis, we maintain the assumption of a discernible difference between the in-person and virtual collection of the ZAN-BPD and shall exclude all virtual collections of the ZAN-BPD. The treatment policy estimand will use all other available ZAN-BPD data including data collected after treatment discontinuation or other intercurrent events. This analysis to the primary endpoint will follow the same analysis methodology (MCPMod/MMRM) as specified in the primary analysis.

7.4.2.3 Subgroup analyses to the primary endpoint

The primary efficacy endpoint will be further analyzed for the AiCure adherent subgroup as defined in Section 6.3 and 6.4. This study is not adequately powered to confirm treatment differences in any subgroup analysis. Any subgroup analyses performed will be considered exploratory. This subgroup analysis will explore if the treatment effect differs in the AiCure adherent subgroup. The 3 subgroups are: (1) overall adherence >=60%, (2) overall adherence >=75%, and (3) overall adherence >=90%. The conduct of these analyses is subject to the available sample size of the subgroup and more categories could be defined. The same statistical approach and methods used for the primary analysis of the primary efficacy endpoint will be used.

Subgroup analysis by Region and Race
The least square mean estimates from the MMRM model (as done for the primary endpoint) on the change from baseline in ZAN-BPD at Week 10 for each dose group will be compared against several subgroups of interest, particularly regions and race. For the subgroups on regions please see Table 10.2:1. For the subgroups on race, they are: white and non-white. The analyses of the subgroups will follow the same methods as detailed for the primary analysis of the primary endpoint.

Subgroup analysis for Asian participants
The sample size of participants of Asian ethnicity at 4% is very limited and prohibitive to conducting meaningful statistical inference. However, there's regulatory interest in quantifying the effect of treatment on the subgroup of Asian participants. Thus, the analysis on change from baseline at Week 10 in ZAN-BPD total score will be evaluated descriptively (by (i) treatment, and by (ii) combined active treatment vs placebo) using standard aggregate measures such as unadjusted mean, median, and quartile ranges.

Furthermore, there is interests in evaluating the subgroup of East Asians which is defined as Japanese participants from sites in Japan. Given the low numbers of participants, descriptive statistics and patient listings will be created for the clinical trial report.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the CTP.

7.5.2 (Other) Secondary endpoint(s)

Logistic regression analysis
The binary secondary endpoint of ZAN-BPD response (defined as ≥30% ZAN-BPD reduction from baseline at Week 10) will be analyzed through a logistic regression model to obtain an estimate of the population odds ratio (OR) and associated confidence intervals between active arms and placebo. This logistic regression will be adjusted for fixed factors of treatment, baseline ZAN-BPD strata indicator (≤18 vs. ≥19), and the continuous covariate of baseline ZAN-BPD total score. The analysis will be performed on the FAS. Adjusted odds ratios

together with 95% confidence intervals will be used to quantify the effect of treatment, comparing all treatments to placebo.

The SAS code for the logistic regression model is as follows:

```
proc logistic data=indata;
  class trt stratum/ param=GLM; /* include (ref="placebo") for trt*/
  model resp = trt base stratum / link=LOGIT covb;
  lsmeans trt / cl;
run;
```

Adjusted odds ratio together with 95% confidence intervals, comparing all treatments to placebo, will be presented.

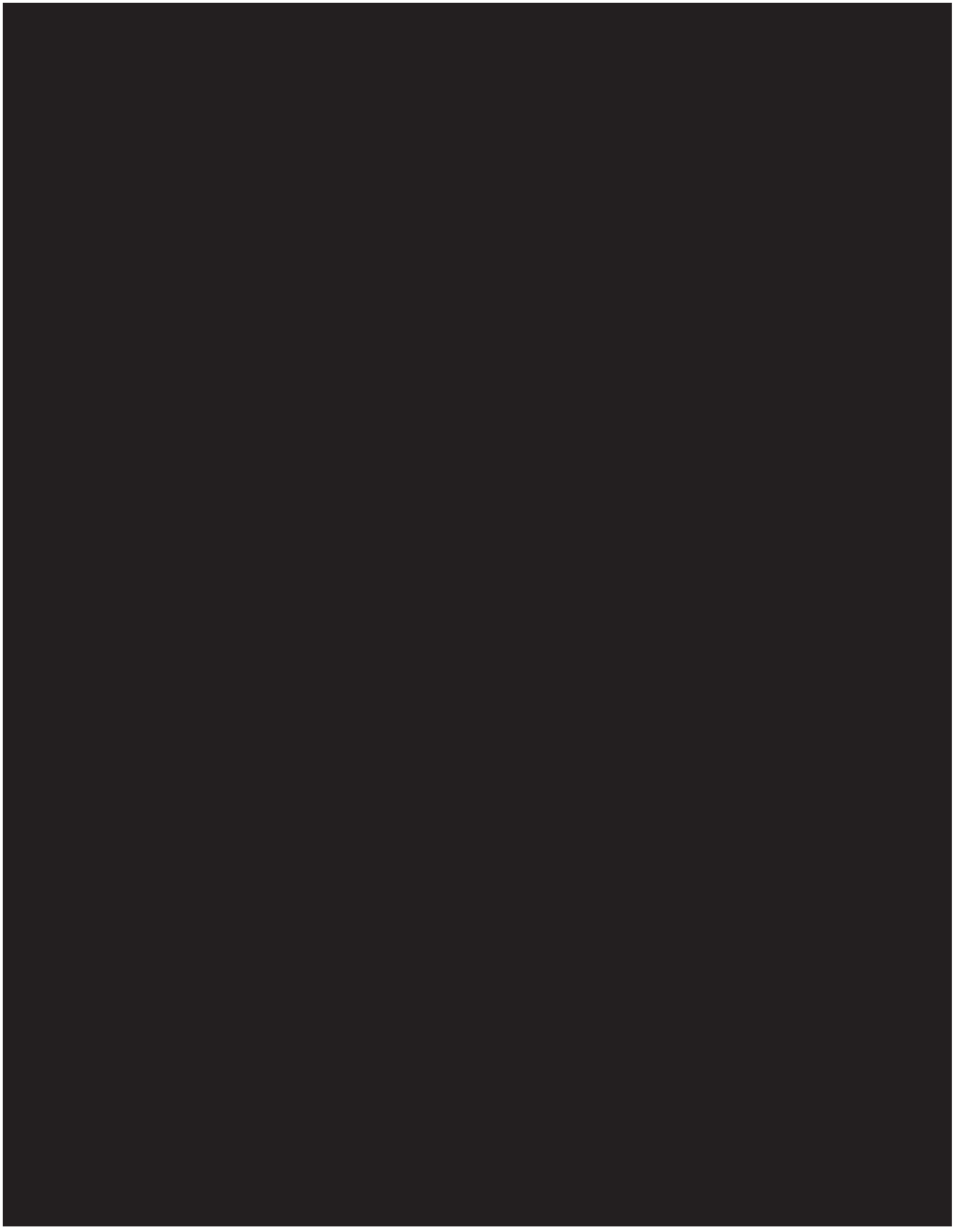
For *the rest of the secondary endpoints*: (i) change from baseline in DERS-16 total score at Week 10, (ii) change from baseline in STAI-S total score at Week 10, (iii) change from baseline in PHQ-9 total score at Week 10, (iv) change from baseline in CGI-S at Week 10, and (v) change from baseline in PGI-S at Week 10, an MMRM model like that described for the primary endpoint analysis will be used to obtain the adjusted change from baseline at Week 10 for each of the BI active arms versus placebo.

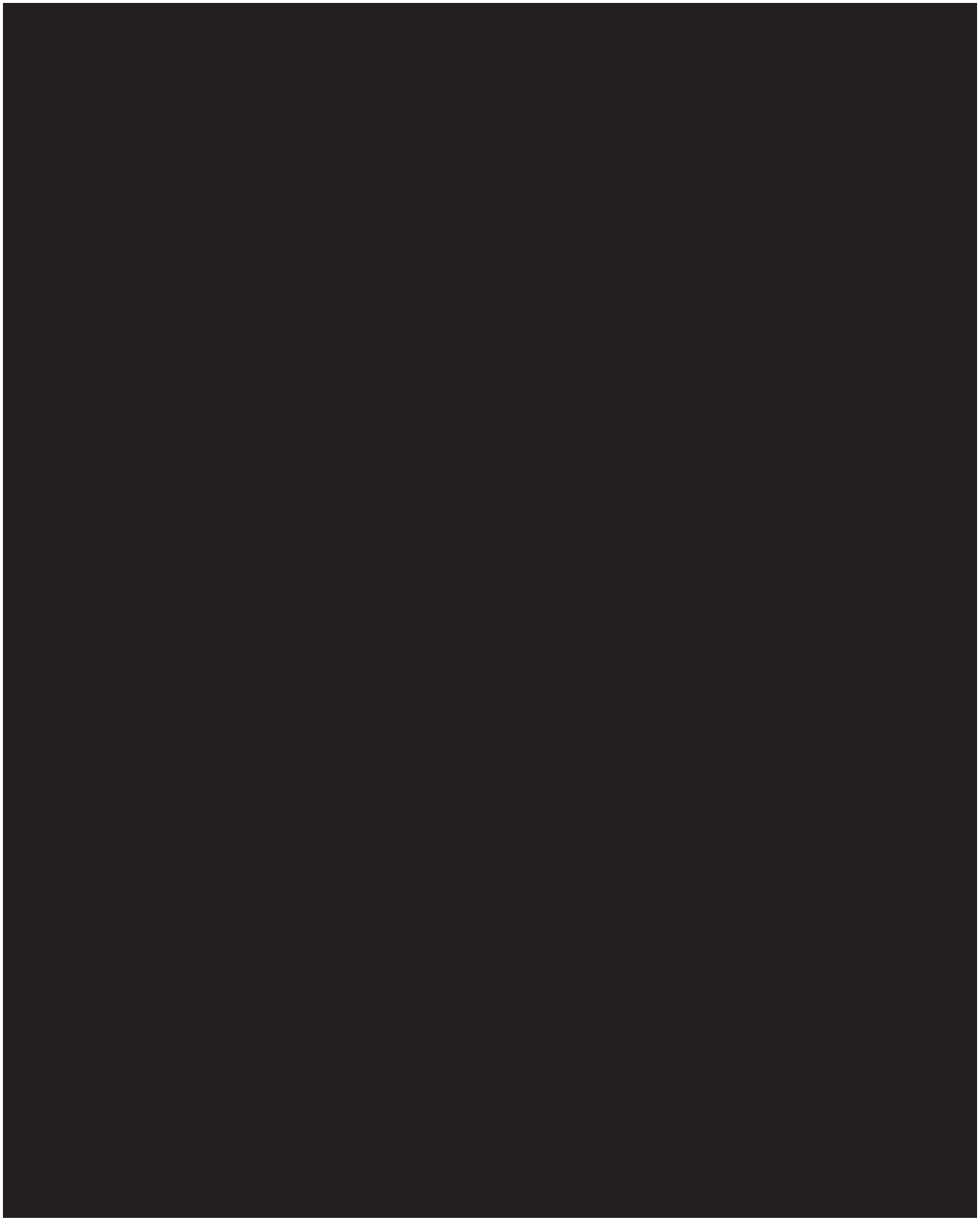
The analysis of standard PK parameters is performed according to (6).

7.5.3 Sensitivity analysis of ZAN-BPD response

Additional risk factors to ZAN-BPD response

The binary secondary endpoint of ZAN-BPD response (defined as ≥30% ZAN-BPD reduction from baseline at Week 10) will be analyzed through a logistic regression model as detailed in Section 7.5.2, but with the addition of further potential risk factors to the estimate of the population odds ratio (OR) and associated confidence intervals between active arms and placebo. The logistic regression model for ZAN-BPD response will be repeated (as given in Section 7.5.2) but with the addition of the covariates of stable concomitant psychotherapy (yes/no) and sex (male/female). The analysis will be performed on the FAS. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing all treatments to placebo. In case zero event is observed in any of the combination of treatment arm and strata, a penalized regression based on the Firth's bias reduction method (10, 11) will be used.





7.7 EXTENT OF EXPOSURE

Extent of exposure will be calculated as the difference between last intake of study drug and the first administration of the study drug plus one day. Descriptive statistics will be provided for number of days of exposure for each treatment arm. Also, cumulative exposure of number and percentage (N, %) of subjects will also be displayed as "< 1 week", "1 to < 2 weeks", "2 to <3 weeks", "3 to <4 weeks", "4 to <6 weeks", "6 to <8 weeks", "8 to <10 weeks", "10 to <12 weeks", "12 weeks", ">12 weeks", or "missing".

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set. AEs will be coded based on the most current version of MedDRA. Analysis will be performed as defined in Section 7.2.5 of the CTP.

7.8.1 Adverse Events

The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. The reporting and analyses of AEs will follow the BI guideline (12). AEs will be coded with the most current version of MedDRA.

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF will be collapsed into one AE event if all the following apply:

- All AE attributes are identical (LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, and outcome).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarisation of AE data, please refer to (5, 12).

The analysis of AEs will be based on the concept of treatment emergent adverse events, thus, all adverse events occurring between the date of the first administration of trial treatment through the date of the last administration of trial treatment + residual effect period will be assigned to the on-treatment period. Adverse events that occur before first drug intake will be assigned to 'screening', and adverse events that occur within 28 days after the residual effect period will be assigned to 'follow-up'. For details on the treatment definitions, see Section 6.1.

Adverse events of special interest (AESIs)

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
- an elevation of AST and / or ALT ≥ 3-fold ULN combined with an elevation of total
  - bilirubin ≥ 2-fold ULN measured in the same blood draw sample; and / or
- marked peak aminotransferase (ALT and / or AST) elevations ≥ 10-fold ULN.

Refer to CTP Section 5.2.6.1.4 for details.
Other significant AE (according to ICH E3)

According to ICH E3 (13), AEs classified as "other significant" needs to be reported and will include those non-serious and non-significant AEs with

1. action taken = 'discontinuation' or 'action taken = reduced'; or
2. marked hematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor / Investigator during medical quality review at TOM.

AE summaries
An overall summary of adverse events will be presented. The frequency of patients with adverse events will be summarized by treatment, primary system organ class (SOC) and preferred term (PT) according to MedDRA. The SOCs will be sorted by default alphabetically and PTs will be sorted by frequency within an SOC. Separate tables will be provided for patients with:

- drug-related AEs
- serious AEs
- serious related AEs
- AESIs
- other significant AEs (according to ICH E3)

- AEs leading to death
- AEs leading to discontinuation of trial medication
- AEs occurred with incidence in the preferred term >2%
- AEs occurred with incidence in the preferred term >5%
- AEs occurred during the follow-up period.

AEs suggestive of abuse potential

In support of an evaluation of human abuse potential, user-defined AE categories (UDAEC) are defined in Section 10.5. In addition, frequency of subjects with AEs suggestive of abuse potential will be summarized by treatment, UDAEC, and preferred term. A listing of the AEs and a listing of subjects with >100% compliance or unreturned medication kits will also be provided.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (14). Only patients with at least one available on-treatment value will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings. Study visits will be presented by the Visit labels in Table 6.7.1.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report. In case of multiple measurements including unscheduled visits, the value for the vital sign measurement will be the average of all the measurements for the corresponding visit.

7.8.4 ECG

12-lead ECG measurements will be assessed as described in the CTP Flow Chart. 12-lead ECG-findings before first intake of trial drug will be considered as baseline condition or as AEs (during the trial) if judged clinically relevant by the investigator and will be analysed as such. No separate listing or analysis of these ECG data will be prepared.

7.8.5 Others

7.8.5.1 EcMA

Ecological Momentary Assessment (EcMA)
Exploratory analyses of treatment effect onset will be conducted using Ecological Momentary Assessment data (refer to section 5.6.2 of CTP), comparing change from baseline to Week 10 regarding momentary affect and instability on: negative affect, positive affect, anxiety, and valence.

Negative affect is the arithmetic mean of the six PANAS negative scale items (upset, guilty, afraid, ashamed, scared, distressed). Positive affect is the arithmetic mean of the four PANAS positive scale items (active, enthusiastic, inspired, attentive). Anxiety is the arithmetic mean of the three PANAS-X FEAR negative scale items (afraid, frightened, and scared). And finally, valence = average [-1*Negative affect, Positive affect].

There are a total of eight possible models, of which four are on psychological momentary states, namely, the effect of treatment on:

- (1) momentary negative affect, (2) momentary positive affect, (3) momentary anxiety and (4) momentary valence.

The other half of the models are on psychological instabilities, they are, the effect of treatment on:

- (5) instability of negative affect, (6) instability of positive affect, (7) instability of anxiety and (8) instability of valence.

This EcMA is an intensive longitudinal assessment where extensive diary sampling is conducted. In this EcMA design, nesting comes from repeated measures over time, nested within subjects. Thus, the statistical method should account for statistical dependency that may result from nested (or clustered) data. Please see Section 10.4 for further details.

7.8.5.2 Analysis of COVID Impact

This section aims to characterize the impact of the SARS-CoV-2 infection/COVID-19 disease on subjects': (i) adherence to the protocol, (ii) adverse events and (iii) efficacy. Regarding the first point, a descriptive analysis of premature discontinuations of trial medication/study due to COVID-19 disruption will be presented. In addition, the frequency of subjects with protocol deviations associated with COVID-19 disruption will be tallied. And lastly, we will look at the proportion of subjects that completed/missed the ZAN-BPD assessment at each clinic visit.

Now, for the second point (from the paragraph above), we propose four tables and a listing to study the distribution of adverse events in subjects infected with SARS-CoV-2, namely:

- Adverse events overall summary on subjects with SARS-CoV-2 infection while on treatment with study drug
- Adverse events by treatment, primary system organ class and preferred term on subjects with SARS-CoV-2 infection while on treatment with study drug
- Adverse events leading to discontinuation by treatment, primary system organ class and preferred term on subjects with SARS-CoV-2 infection while on treatment with study drug
- Serious adverse events by treatment, primary system organ class and preferred term on subjects with SARS-CoV-2 infection while on treatment with study drug, and
- Subjects with COVID-19 related study disruption.

Lastly, is the impact of COVID-19 on efficacy. The collection of complete data at all visits is our goal, despite the COVID-19 pandemic. To avoid missing data due to a subject's potential

inability to attend their in-person clinical visit, we made provisions for a virtual assessment via videoconferencing to ascertain the ZAN-BPD. Please refer to Sections 7.4.2.1 and 7.4.2.2 where the Sensitivity Analysis, and the Supplementary Analysis 1 and Supplementary Analysis 2 are discussed in detail.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Standard approach: This approach is the default option for double-blind pivotal trials, or trials that potentially could be pivotal and do not require expedited reporting, or non-pivotal double-blind trials that choose not to use a fast-track approach.

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form.

The following plan for an End of Treatment database lock will be implemented if deemed necessary for decision making.

End of Treatment Lock (Interim Database Lock):

This section details the planned time point at which the database will be declared ready for the End of Treatment (interim database) lock. This interim database lock will consist of all data up through the End of Treatment (EoT), Week 12.

The treatment information will be released for this End of Treatment analyses, thus, given that the database will be unblinded with this lock, there is no need for specification in the logistics plan.

Once the last patient has completed their End-of-Treatment (EOT) visit and all corresponding data has been entered and cleaned to the level documented in the "Data Delivery Request" (DDR) form, the data will be declared ready to be unblinded via the "Data Ready to be Unblinded and/or Final Trial Closure Notification" (RUN) form. Then the treatment information will be released for analysis.

The data collection for the off-treatment residual effect period until the End-of-Study (EoS)/ Follow-Up visit will continue into the unblinded trial database. Once trial data collection has been completed and all data has been entered and cleaned as documented on the RUN form, a final data lock will be performed.

After the release of treatment information, it is expected that only trial data related to the off-treatment residual effect period will be entered and changed. Therefore, after the timepoint of release of treatment information, all changes affecting trial data up to the End-of-Treatment (EoT) visit will be documented and summarized in the CTR.

9. REFERENCES

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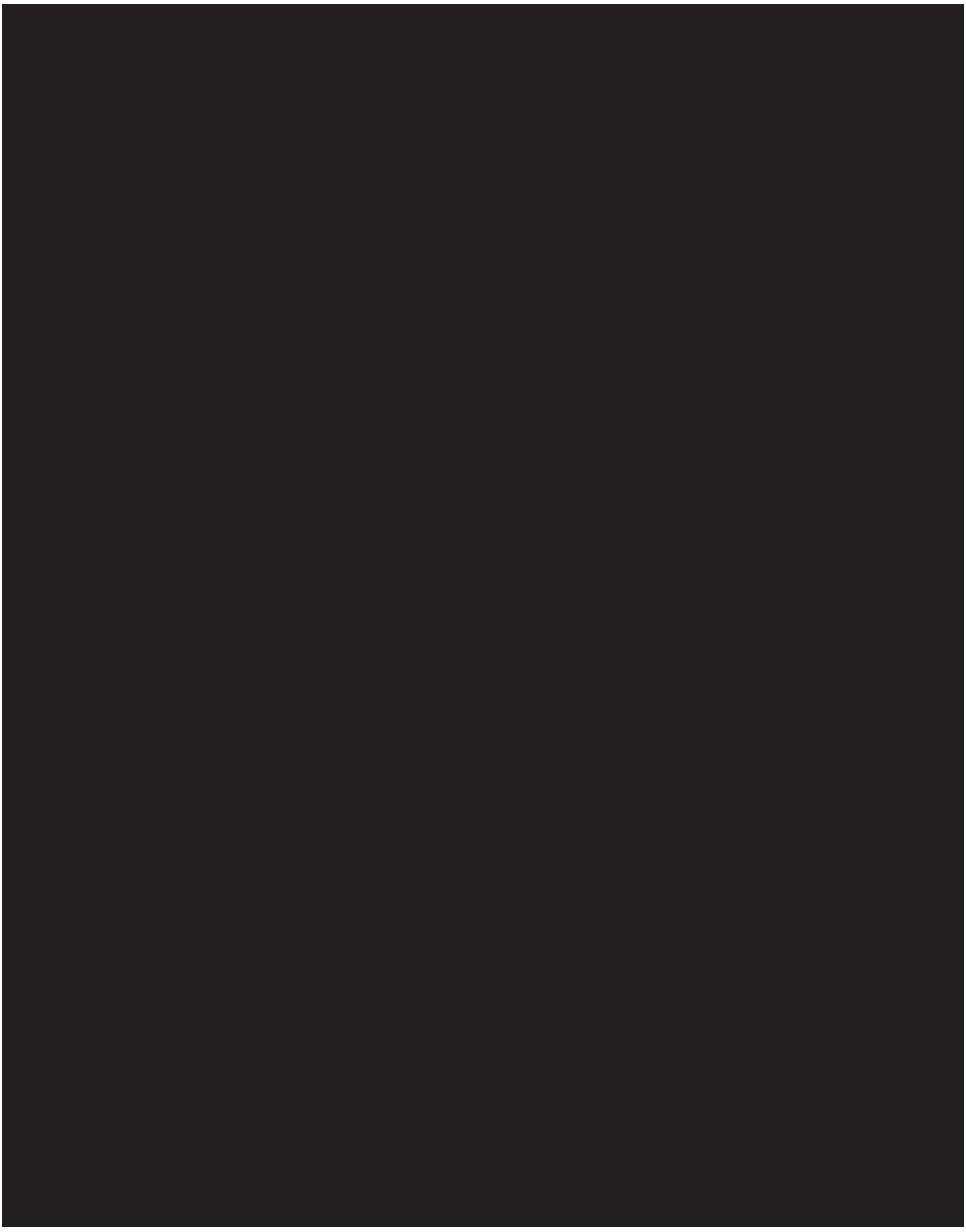

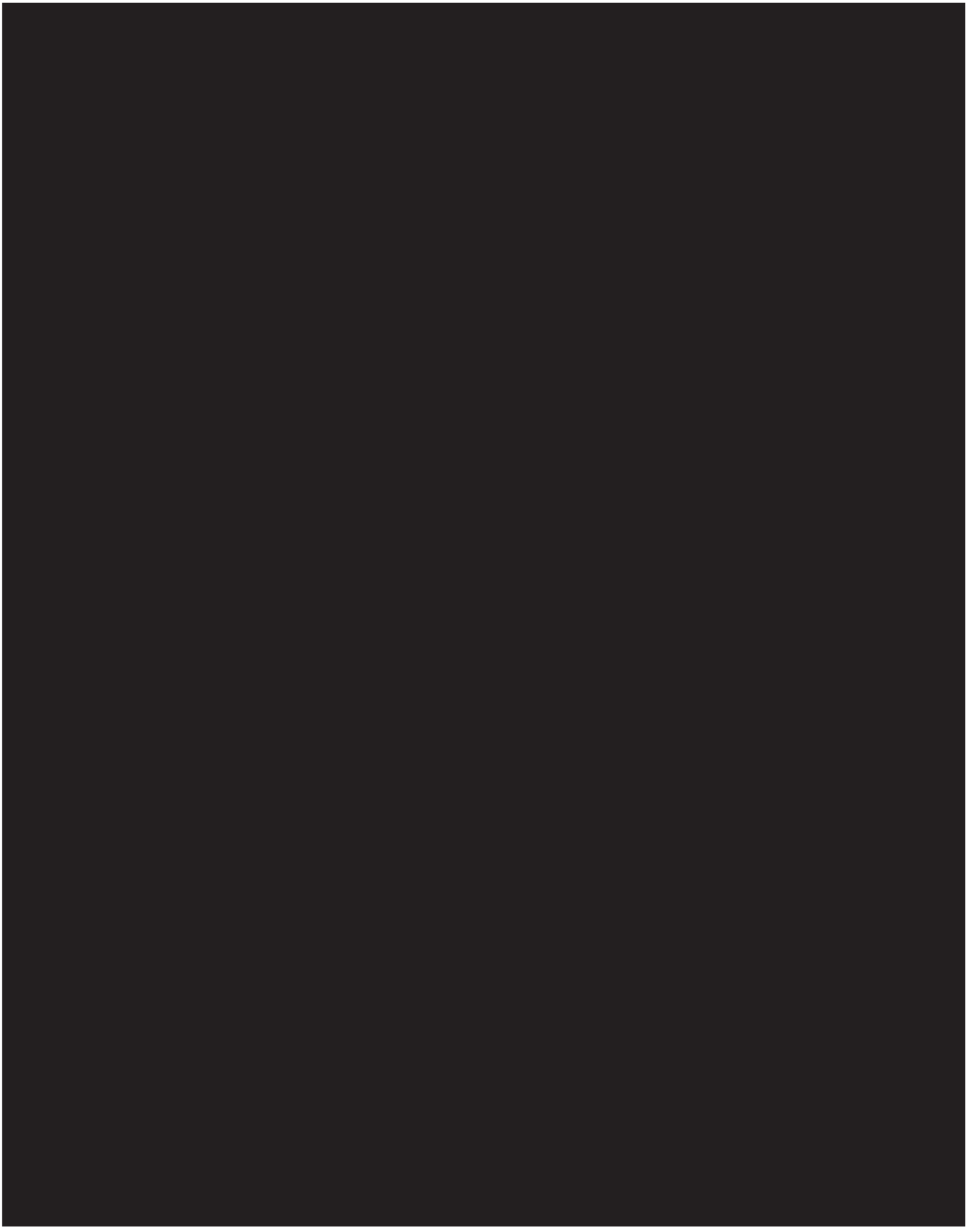

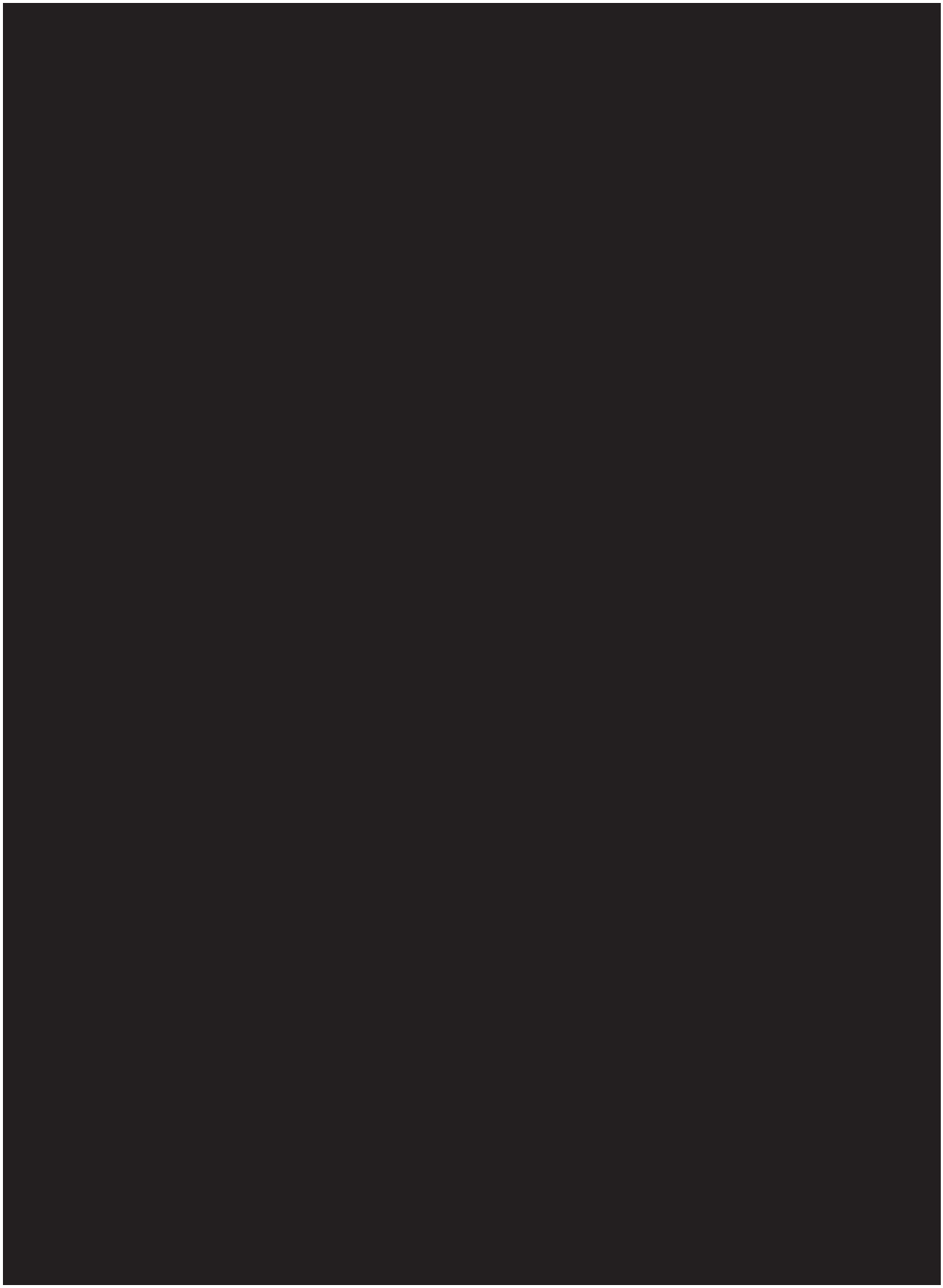

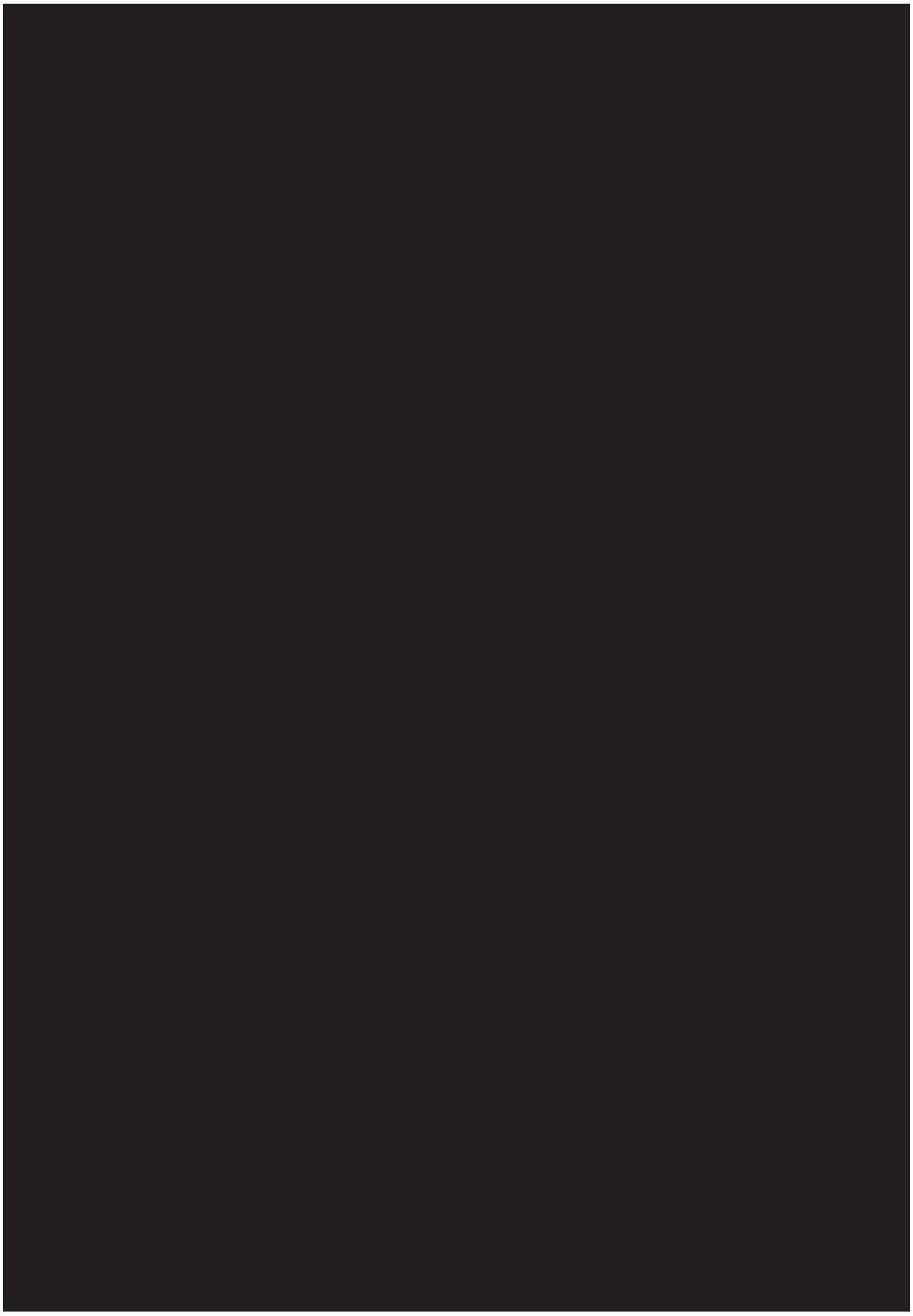

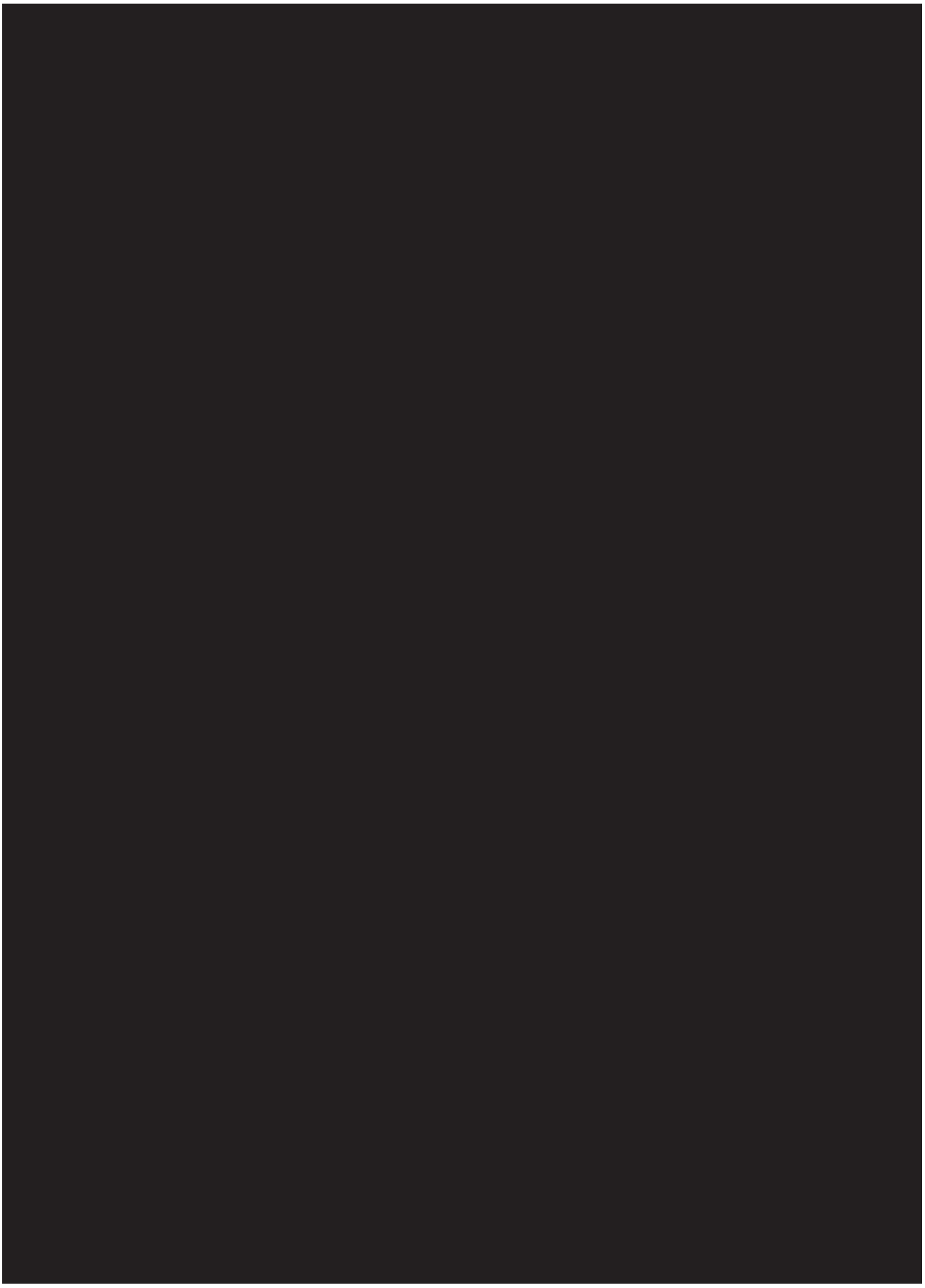

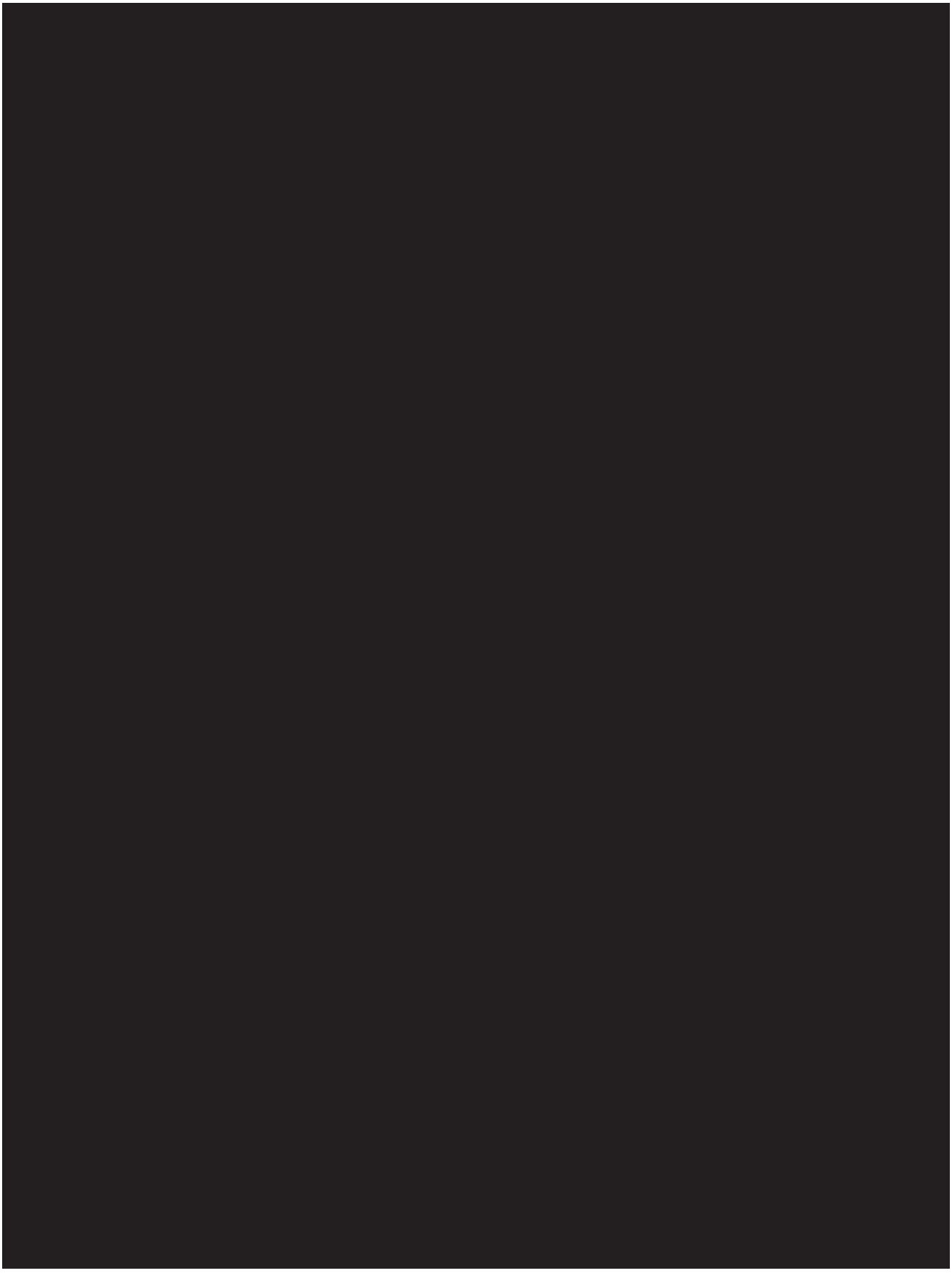

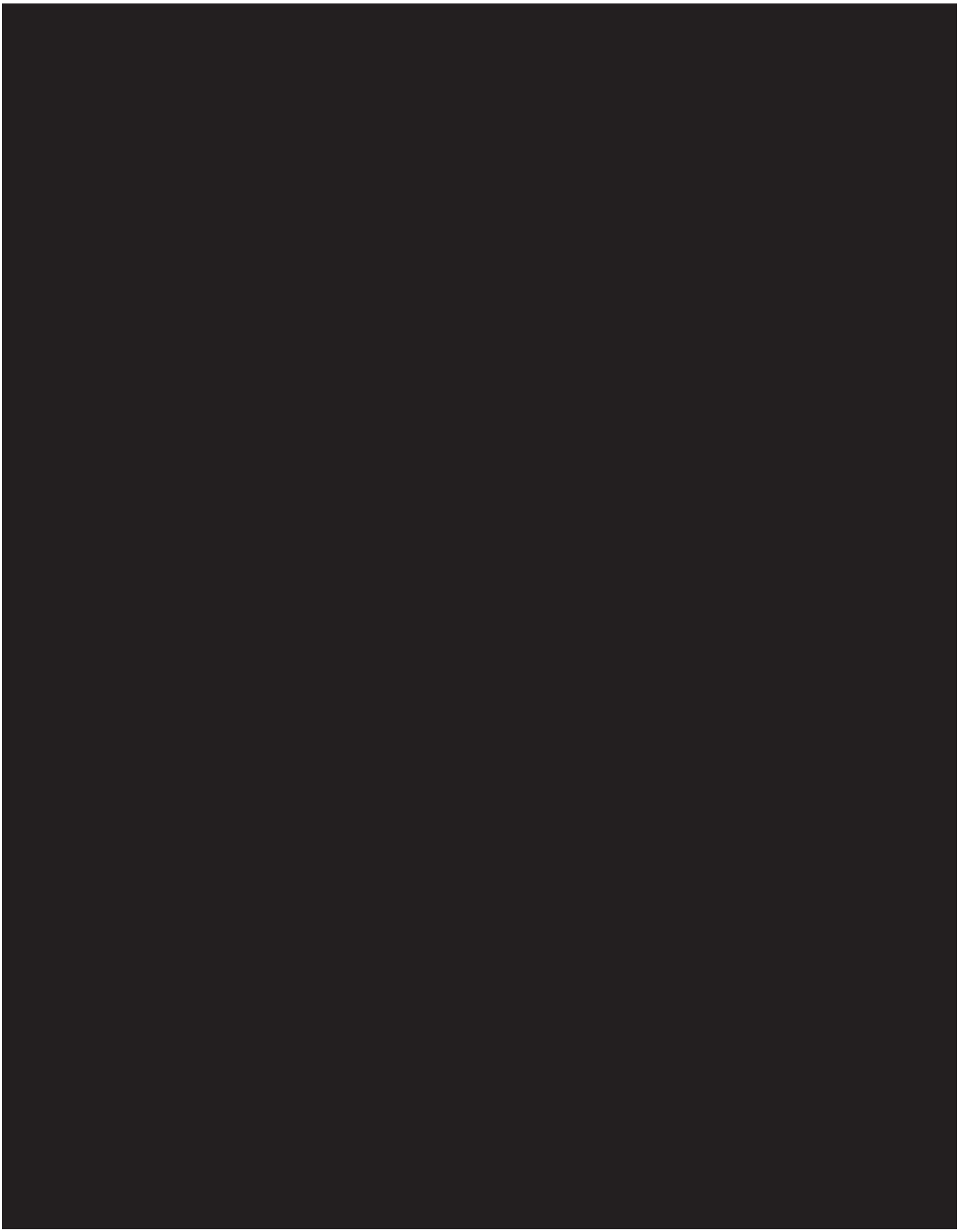

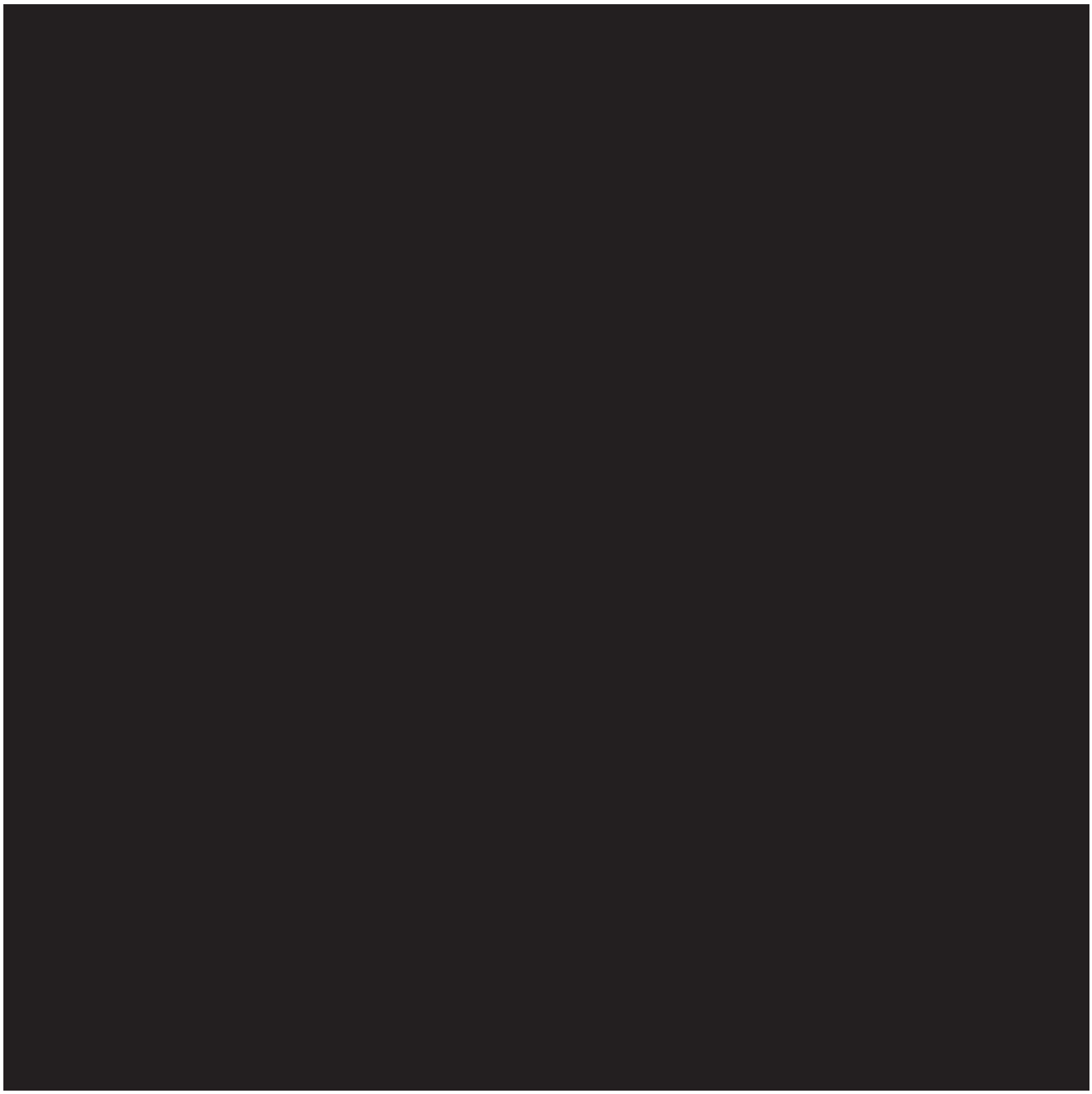

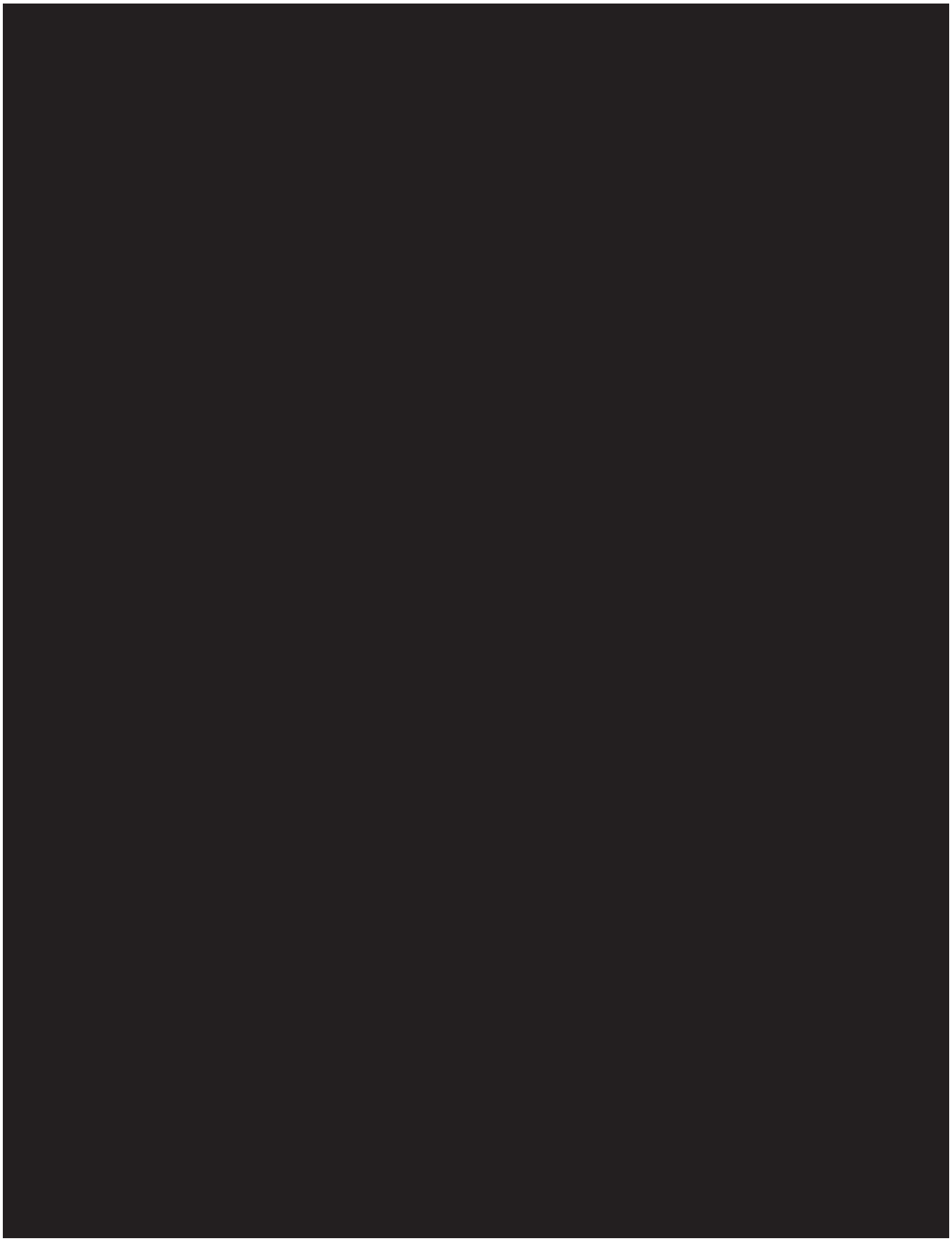

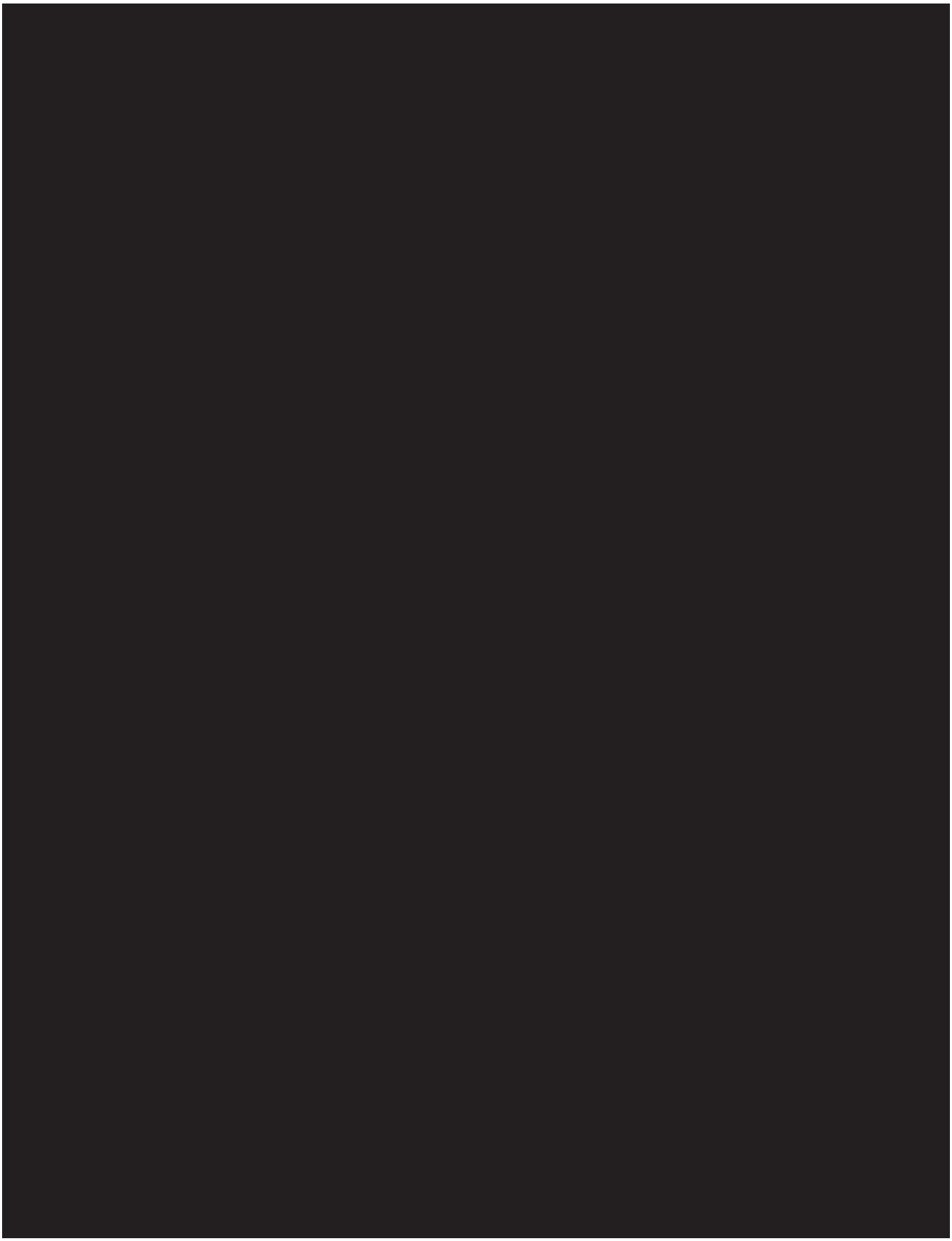

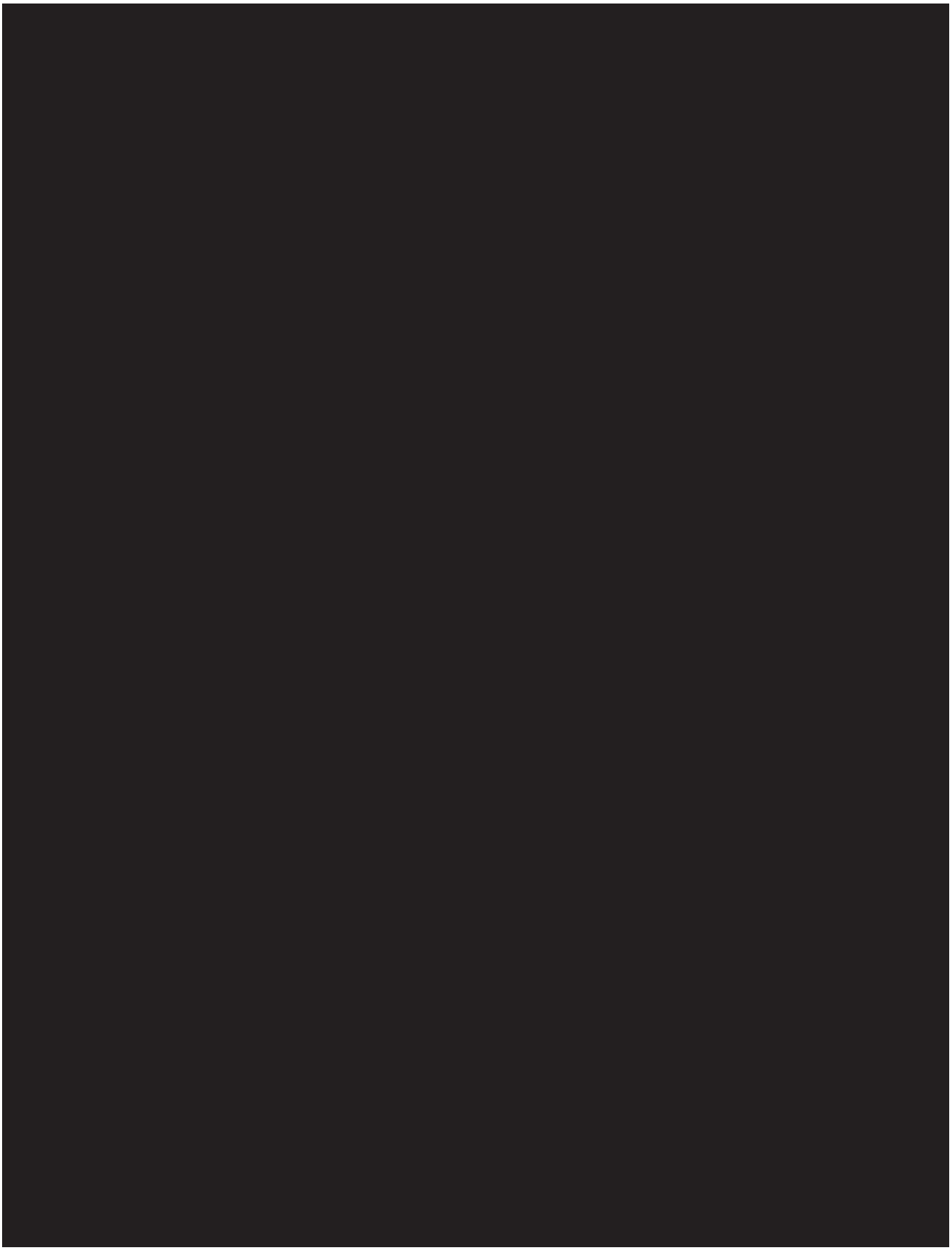

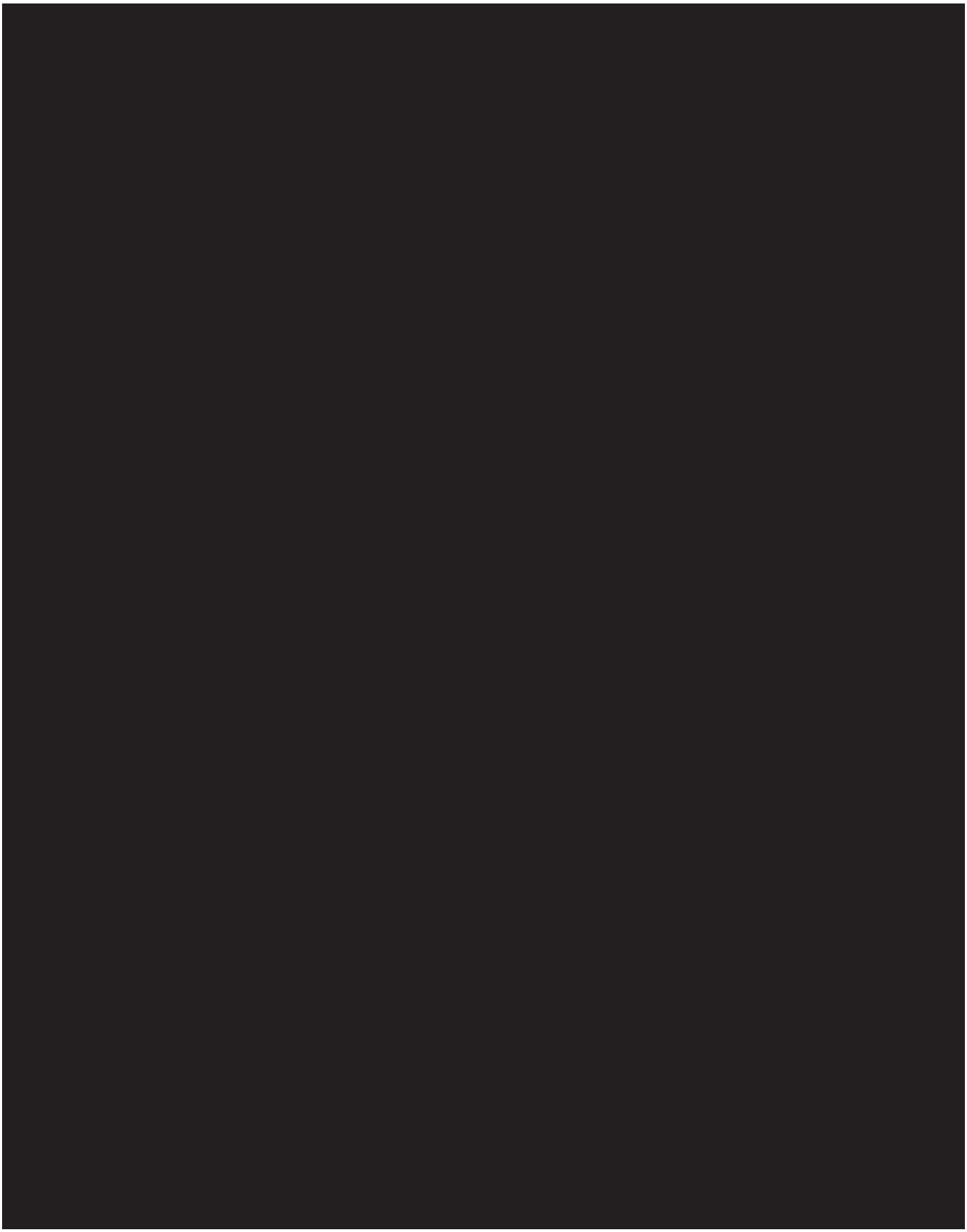

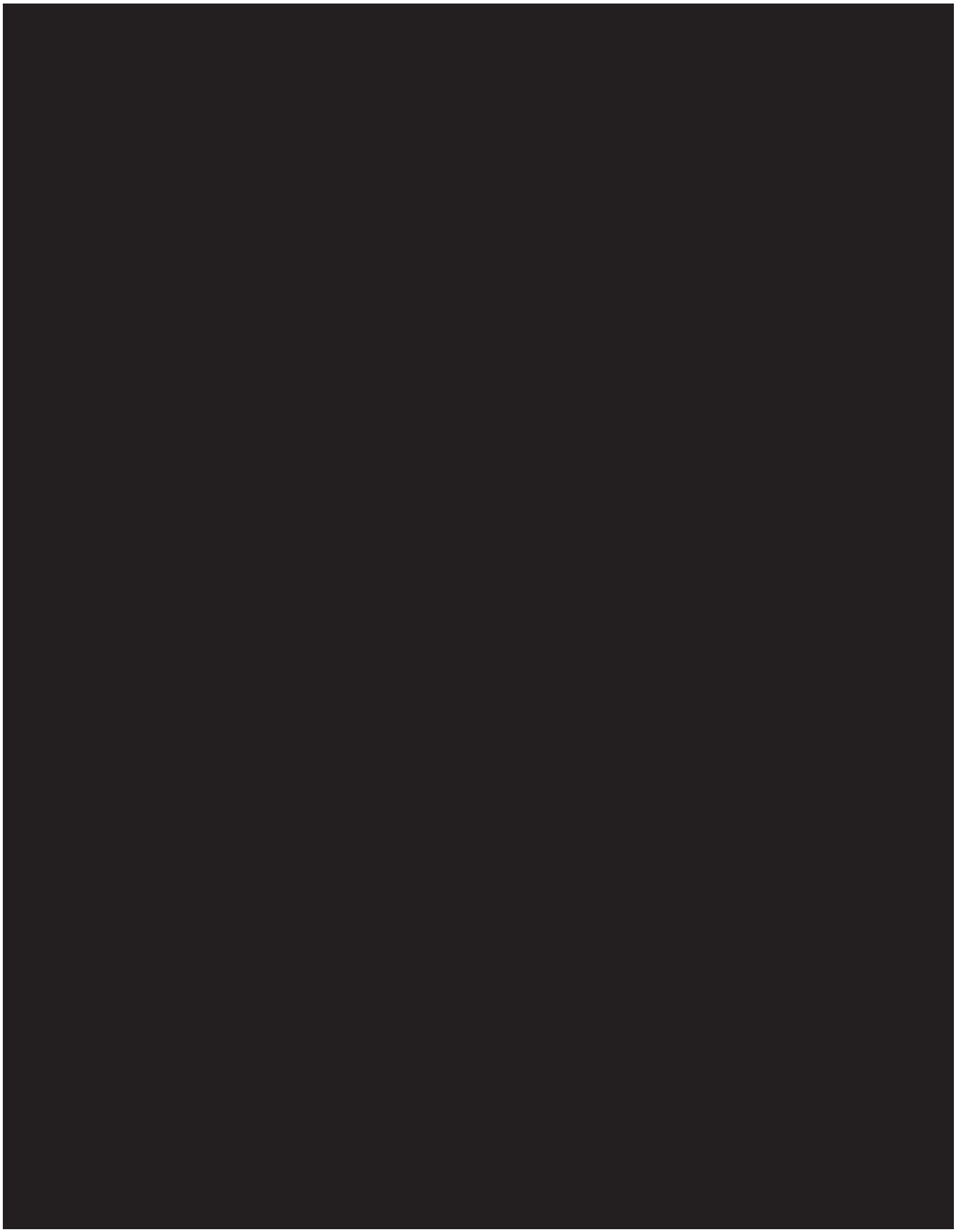

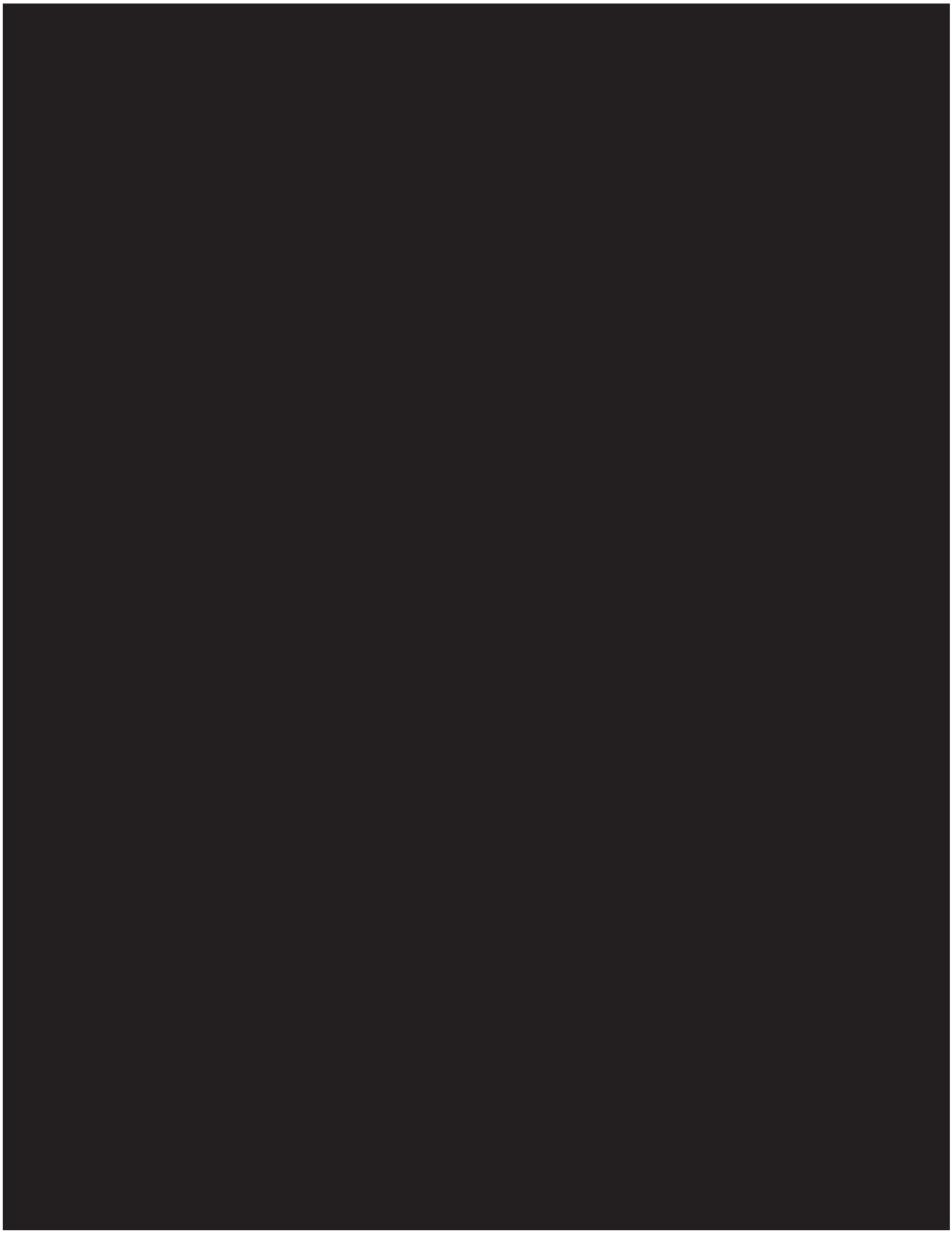

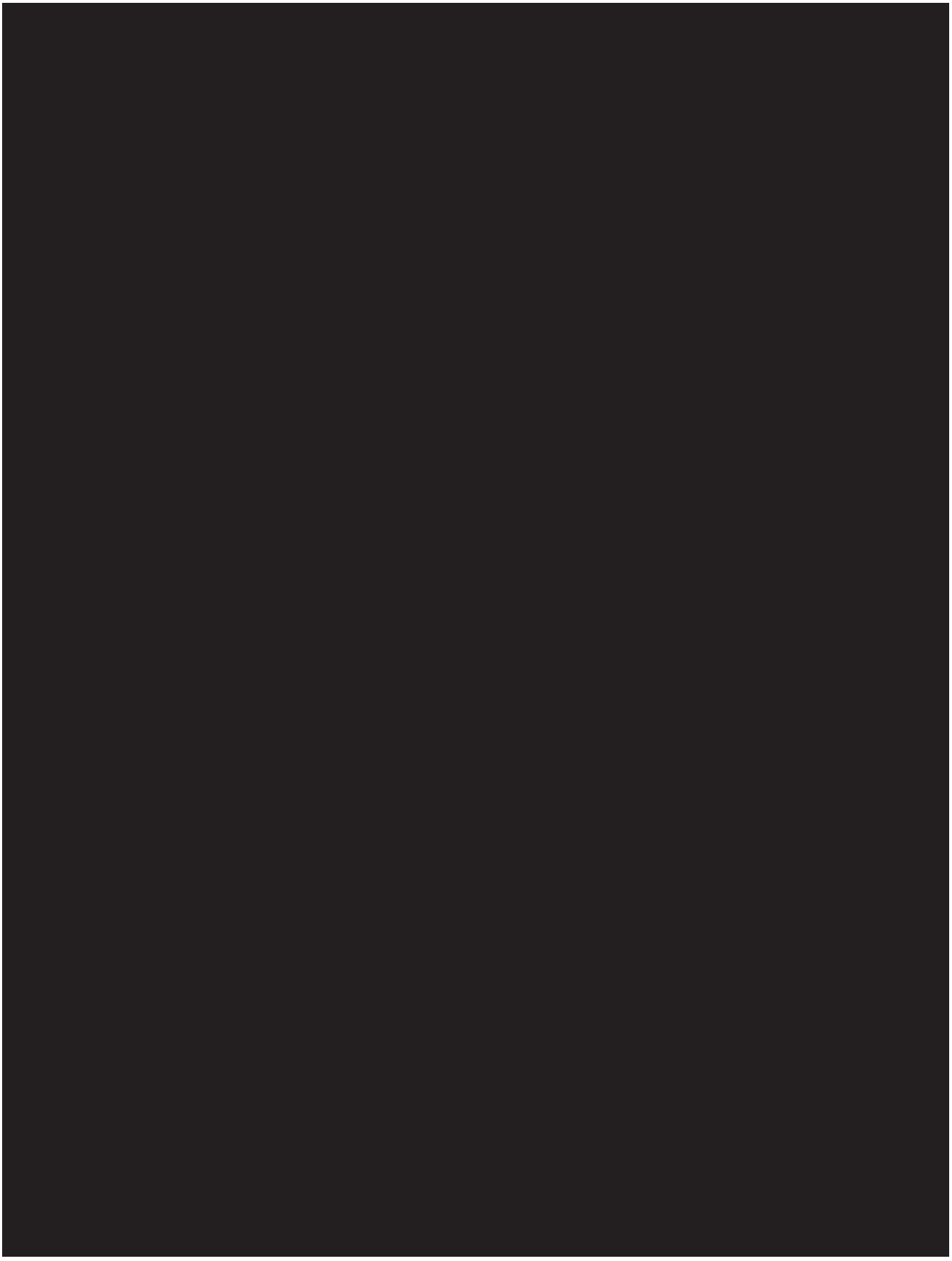

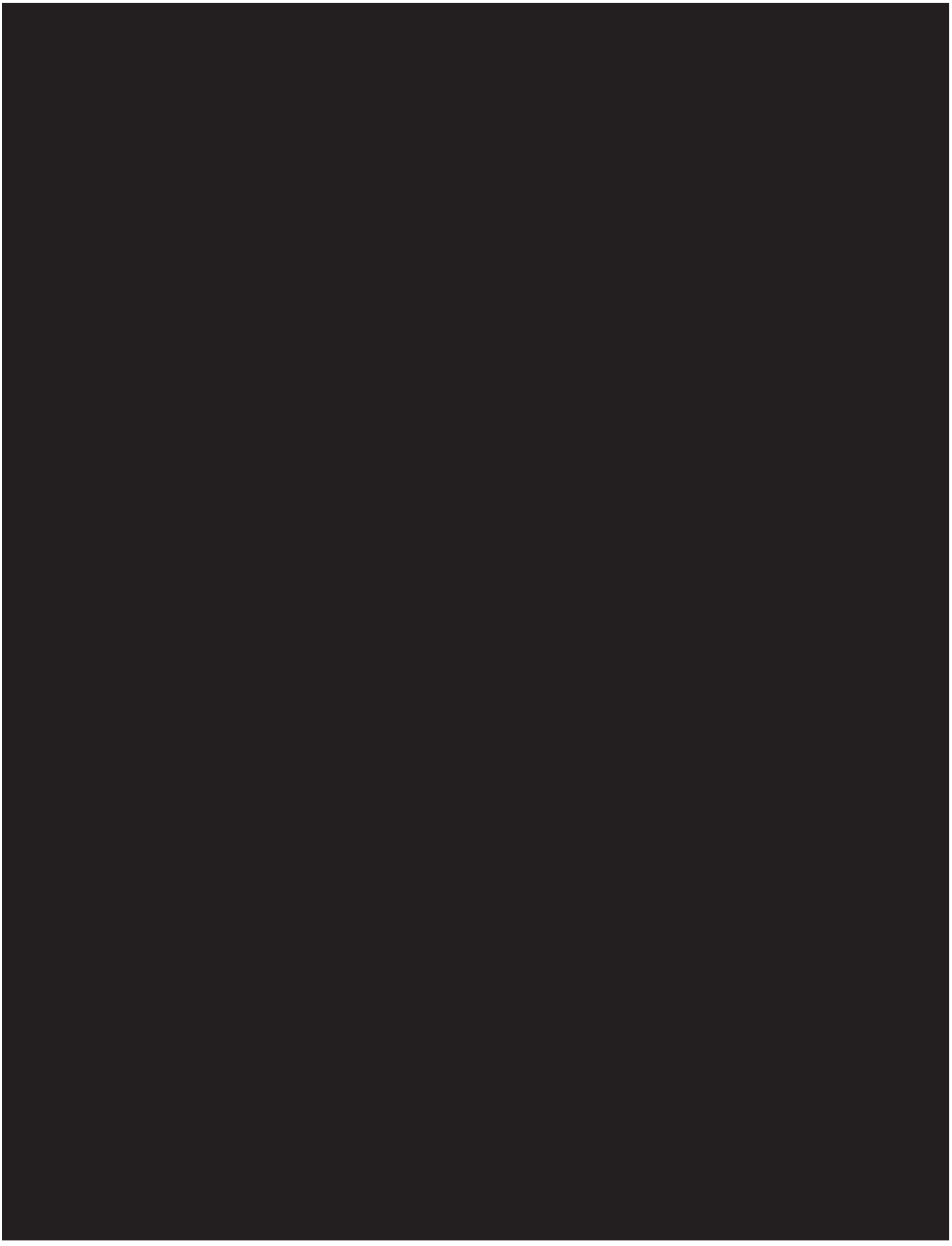

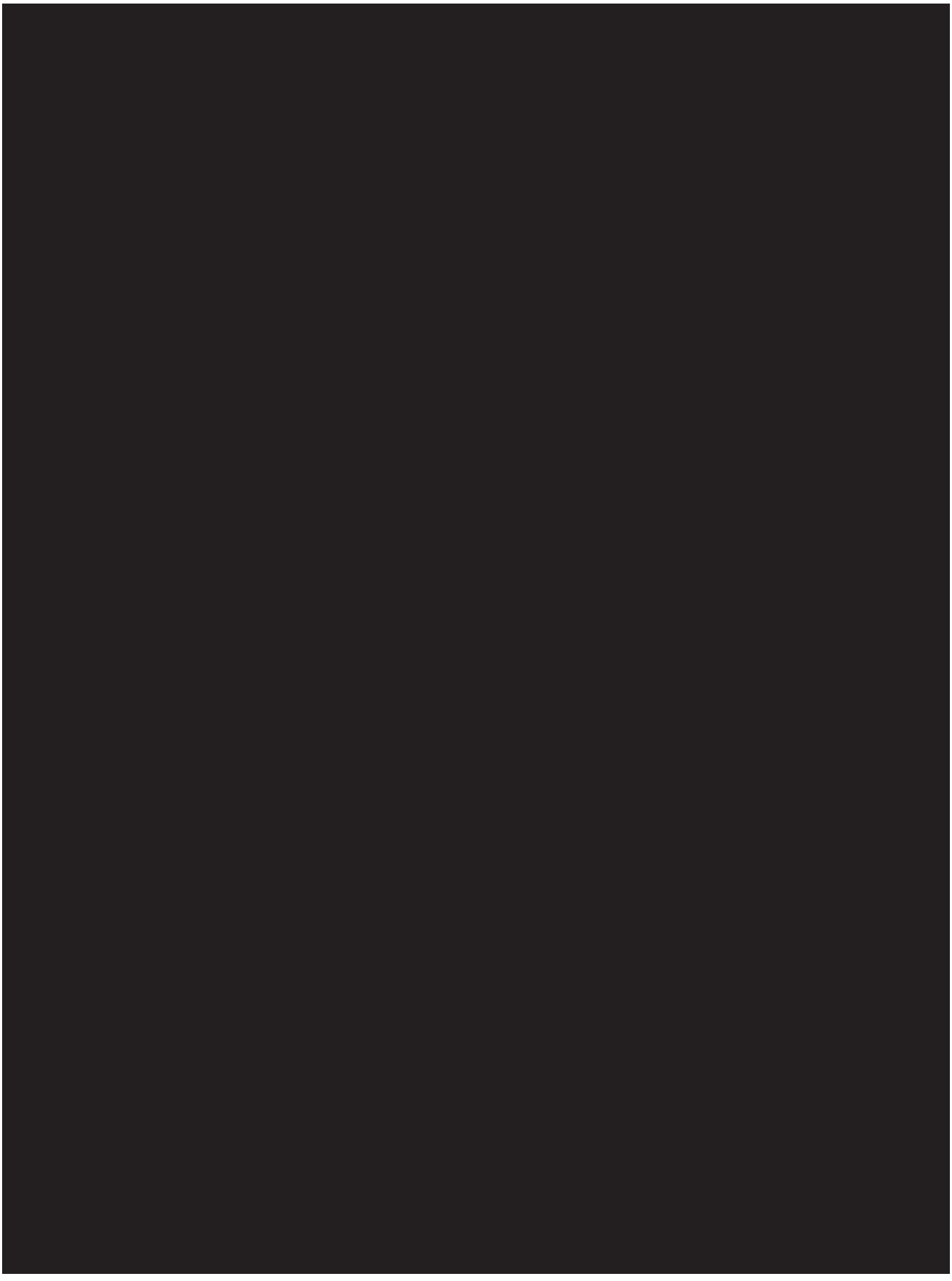

11. HISTORY TABLE

Table 11: 1 History table

Version	Date	Author	Sections changed	Brief description of change
1	**19-JAN-23**	[redacted]	None	This is the final TSAP
2	**26-JAN-23**	[redacted]	Throughout document	To address Checklist comments from the Archiving group

APPROVAL / SIGNATURE PAGE

Document Number: c36236762 **Technical Version Number:2.0**

Document Name: 8-01-tsap

Title: 8-01-tsap

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Medical Writer	[redacted]	27 Jan 2023 13:49 CET
Approval-Biostatistics		27 Jan 2023 13:50 CET
Approval-Project Statistician		27 Jan 2023 13:53 CET
Approval-Clinical Trial Leader		27 Jan 2023 16:18 CET
Author-Trial Clinical Pharmacokineticist		30 Jan 2023 08:36 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed