TRIAL STATISTICAL ANALYSIS PLAN

c14288633-02

BI Trial No.:	1381.1
Title:	An open-label, Phase I trial to determine the maximum-tolerated dose and investigate safety, pharmacokinetics, and efficacy of BI 754091 in patients with advanced solid tumours Including Protocol Amendments 1, 2, 3, 4, 5 and 6
Investigational Product(s):	BI 754091 (ezabenlimab)
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	17JUN2021- REVISED
Version:	Revised

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[redacted]

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LIST OF TABLES

2 LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
CI	Confidence Interval
CR	Complete Response
CT	Comcomitant Therapy
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End of Treatment
ICH	International Conference on Harmonisation
iCPD	Immune Confirmed Progressive Disease
iCR	Immune Complete Response
iORR	Immune Objective Response Rate
iPFS	Immune Progression-Free Survival
iPR	Immune Partial Response
iRECIST	Immune Response Evaluation Criteria in Solid Tumours

Term	Definition / description
iSD	Immune Stable Disease
iUPD	Immune Unconfirmed Progressive Disease
LLT	Lowest Level Term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MTD	Maximum Tolerated Dose
NE	Not Evaluable
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
P25	25th percentile
P75	75th percentile
PD	Progressive Disease
PD	Protocol Deviation
PDc	Pharmacodynamics
PFS	Progression-Free Survival
PK	Pharmacokinetics
PKS	Pharmacokinetics Analysis Set
PR	Partial Response
PT	Preferred Term
Q1	Lower quartile
Q3	Upper quartile
P10	10th percentile
P90	90th percentile
RECIST	Response Evaluation Criteria in Solid Tumours
REP	Residual Effect Period
RO	Receptor Occupancy
RP2D	Recommended Phase 2 Dose
RPM	Report Planning Meeting
SAE	Serious Adverse Event

Term	Definition / description
SD	Stable Disease
StD	Standard Deviation
SOC	System Organ Class
TNBC	Triple Negative Breast Vancer
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
WHO DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Trial Statsitical 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.

SAS® Version 9.3 or a newer version and Phoenix TM WinNonlin ® version 6.2.1 will be used for PK analyses. SAS® Version 9.4 or a newer version will be used for all other analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The CTP defines the primary endpoint in Phase Ia as number of patients experiencing DLTs graded according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 / 5.0 observed in the first cycle (3 weeks) in order to meet the objective of assessment of the maximum tolerated dose (MTD) of BI 754091. All patients in Phase Ia were assessed by CTCAE Version 4.03 and therefore CTCAE Version 5.0 is not applicable for the primary endpoint in Phase Ia.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary objective of this study is to determine the safety and tolerability of BI 754091 as reflected by the primary endpoint MTD.

The primary endpoint of the Phase Ia dose-escalation portion of the trial is:

- Number of patients experiencing Dose Limiting Toxicities (DLTs) graded according to CTCAE Version 4.03, observed in the first cycle (3 weeks) in order to meet the objective of assessment of the MTD of BI 754091.

The number of patients with DLTs during the MTD evaluation period will be used to determine the MTD. The MTD is defined as the highest dose with less than 25% risk of the true DLT rate being above 33% during MTD evaluation period. For definition of DLTs, see CTP Section 4.1.5. The MTD evaluation period is defined as the first three weeks after a first administration of trial medication to BI 754091.

Patients who were replaced during the MTD evaluation period will not be considered for MTD determination. Those patients that have completed the MTD evaluation period without having been replaced will be referred to as patients evaluable for MTD determination (MTD set).

In addition, the primary endpoints of the Phase Ib dose-expansion portion of the trial are:

- Number of patients with DLTs observed during the entire treatment period, from the first infusion of study treatment to the date of last study treatment administration plus 30 days. See treatment period definition in Table 6:1:1.
- Confirmed objective Response (OR), defined as the best overall response of confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 assessed by the Investigator, where the best overall response is the best time point response recorded from the first administration of BI 754091 until the earliest of disease progression according to RECIST v1.1, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow- up or withdrawal of consent.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

5.2.2.1 Secondary endpoints of the Phase Ia (dose-escalation portion) of the trial

The secondary endpoints of the Phase Ia dose-escalation portion of the trial are:

- The following PK parameters of BI 754091 (if feasible) will be evaluated after the first and after multiple administrations of BI 754091:
  - C_{max}: maximum measured concentration of BI 754091 in plasma
  - AUC_{0-504}: area under the concentration-time curve of BI 754091 in plasma over the time interval from 0 to 504 hours
- Confirmed OR, defined as the best overall response of confirmed CR or PR according to RECIST v1.1 as assessed by the Investigator where the best overall response is the best time point response recorded from the first administration of BI 754091 until the earliest of disease progression according to RECIST v1.1, death or last evaluable tumor assessment before start of subsequent anti-cancer therapy, loss to follow- up or withdrawal of consent.
- Number of patients experiencing DLTs from the start of treatment until end of treatment (in all cycles) as assessed approximately every 3 weeks.

Table 5.2.2.1: 1 Details of confirmed best overall response according to RECIST 1.1 derivation rules

Overall response (time point 1)	**Overall response (>=28 days from time point 1)**	**Confirmed BOR**
CR	CR	CR
CR	PD	SD as long as >=39 days*, otherwise, PD
CR	NE/Missing	SD as long as >=39 days*, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD as long as >=39 days*, otherwise, PD
PR	PD	SD as long as >=39 days*, otherwise, PD
PR/SD	NE/Missing	SD as long as >=39 days*, otherwise, NE
SD	SD/PD	SD as long as >=39 days*, otherwise, PD
NE	NE/Missing	NE

* after first treatment administration

5.2.2.2 Secondary endpoints of the Phase Ib (dose expansion) of the trial

The secondary endpoints of the Phase Ib dose-expansion portion of the trial are:

- Progression-free survival (PFS) defined from date of start administration of BI 754091 to the date of disease progression according to RECIST v1.1 as assessed by the Investigator or death from any cause, whichever is earlier
- Safety will continue to be assessed by the recording of adverse events (AEs), serious adverse events (SAEs) (including DLTs), laboratory evaluations, vital signs, and ECGs as:
  - Percentage of subjects with AEs
  - Percentage of subject with SAEs
  - Percentage of subjects with clinical relevant abnormalities in vital signs, laboratory evaluations or ECG parameters (note that clinically relevant abnormalities are those which have to be reported by the investigator as AEs).

PFS according to RECIST v1.1:
For patients with 'event' as outcome for PFS:

- PFS [days] = date of outcome – date of first treatment administration + 1

For patients with 'censored' as outcome for PFS:

- PFS (censored) [days] = date of outcome – date of first treatment administration+ 1

A patient has an evaluable response assessment if CR, PR, stable disease (SD), or progressive disease (PD) according to RECIST v1.1 has been assigned by the investigator. The censoring rules and applicable dates of outcome are specified in Table 5.2.2.2: 1 below.

If patients would have their radiological examinations over a number of days, i.e. target lesions assessed on day x, non-target lesions assessed on day y and new lesion (if applicable) on day z, the earliest date of the multiple assessments should be considered.

Table 5.2.2.2: 1 Censoring rules for progression-free survival according to RECIST v1.1

Situation	Outcome	Date of outcome
No baseline radiological assessment		
Patient with death on or before first planned post-baseline radiological assessment (≤ Day 64)	Event	Date of death
Patient without death or patient with death after first planned post-baseline radiological assessment (> Day 64)	Censored	First treatment administration
Without post-baseline radiological assessments		
Vital status is unknown or patient is known to be alive	Censored	First treatment administration
Death prior to or on the first planned post-baseline radiological assessment (≤ Day 64)	Event	Date of death
Death beyond the first planned post-baseline radiological assessment (> Day 64)	Censored	First treatment administration
With baseline and post-baseline radiological assessments BUT no other anti-cancer therapy		
Alive and not progressed	Censored	Date of last evaluable radiological assessment
Progressed, no missed radiological assessment window* prior to progression	Event	Date of radiological assessment of progression

Table 5.2.2.2: 1 Censoring rules for progression-free survival according to RECIST v1.1 (cont.)

Situation	Outcome	Date of outcome
Progressed, but one or more consecutively missed radiological assessment window* prior to progression	Censored	Date of last evaluable radiological assessment prior to missed assessment (or first treatment administration if no post-baseline assessment prior to missed assessment)
Death but no progression, no missed radiological assessment window* prior to death	Event	Date of death
Death without progression, but one or more consecutively missed radiological assessment window* prior to death	Censored	Date of last evaluable radiological assessment prior to missed assessments
Initiation of subsequent anti-cancer therapy		
Subsequent anti-cancer therapy started before progression or death	Censored	Date of last radiological assessment before subsequent anti-cancer therapy
No baseline and/or post-baseline imaging and subsequent-anti cancer therapy started prior to death	Censored	First treatment administration

* Windows for radiological assessments are defined in Table 6.7: 1

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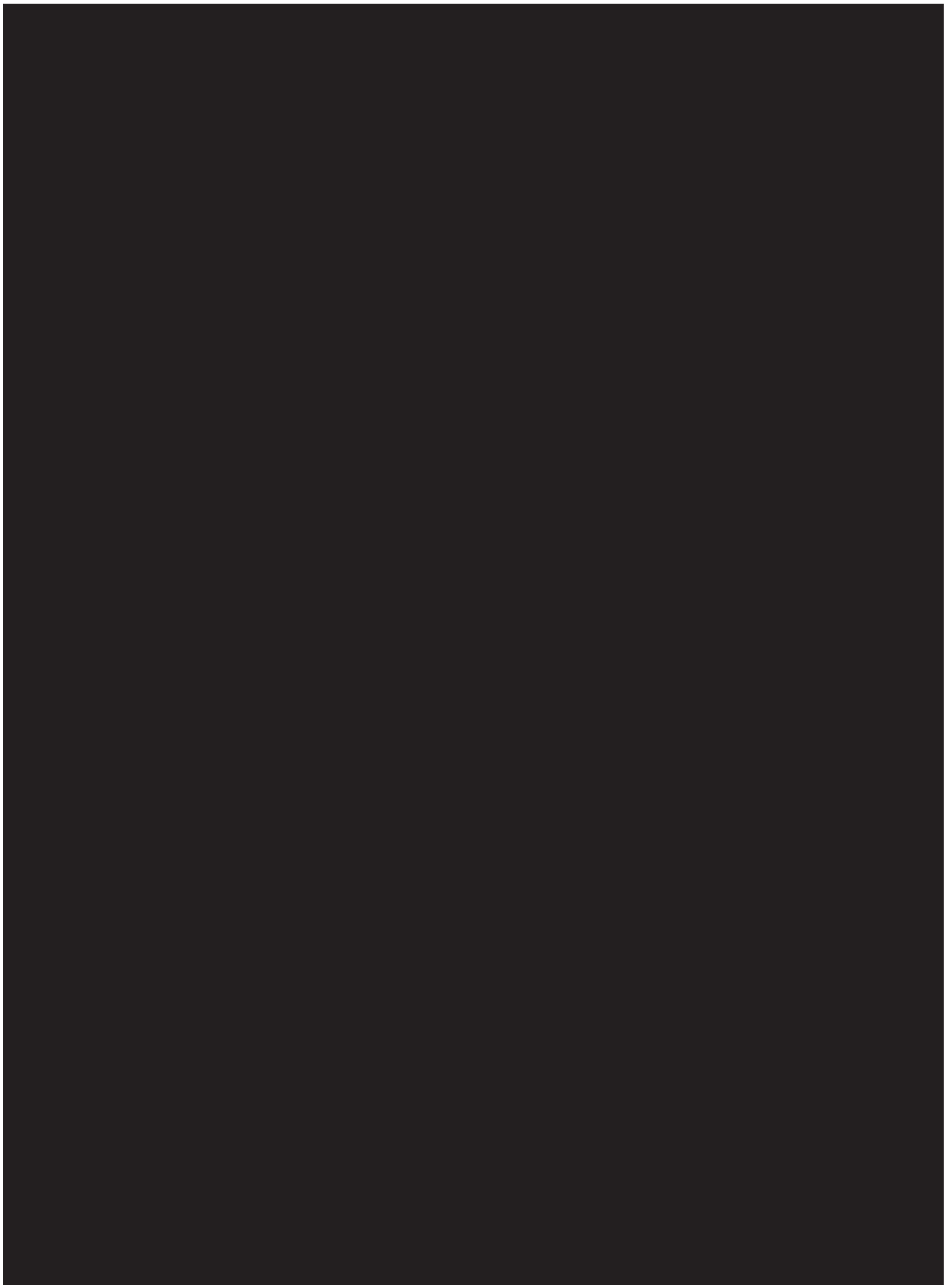
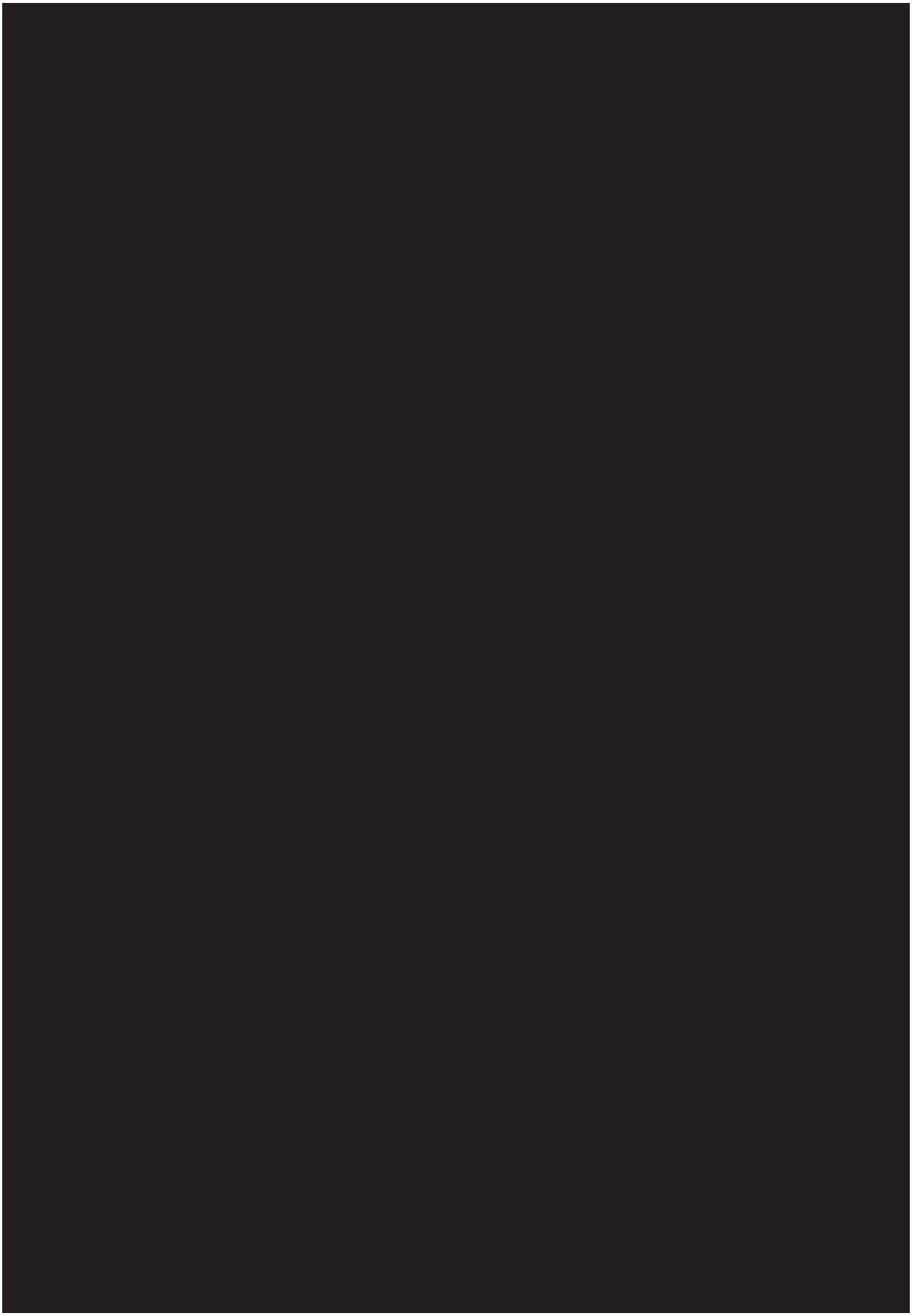
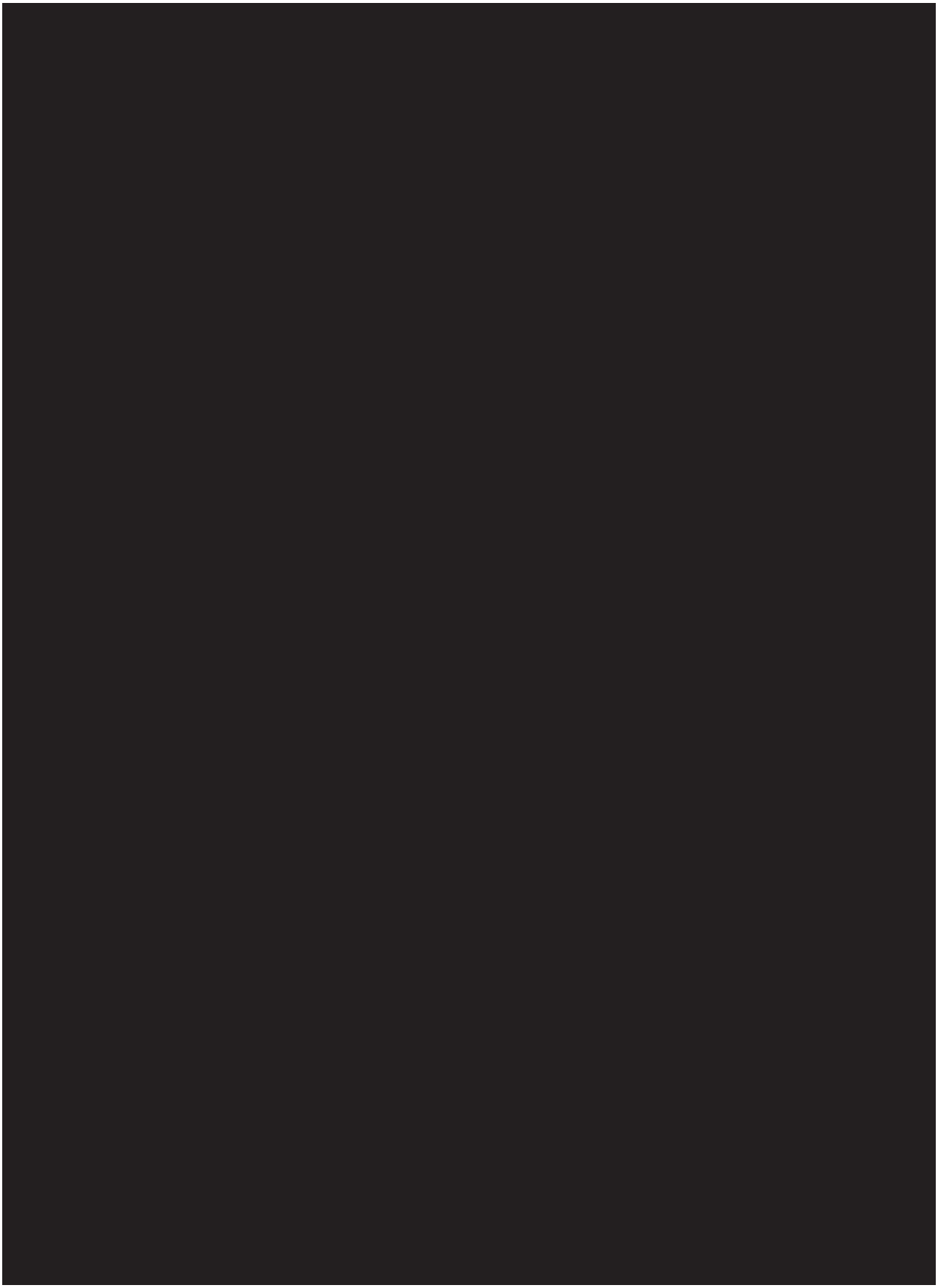
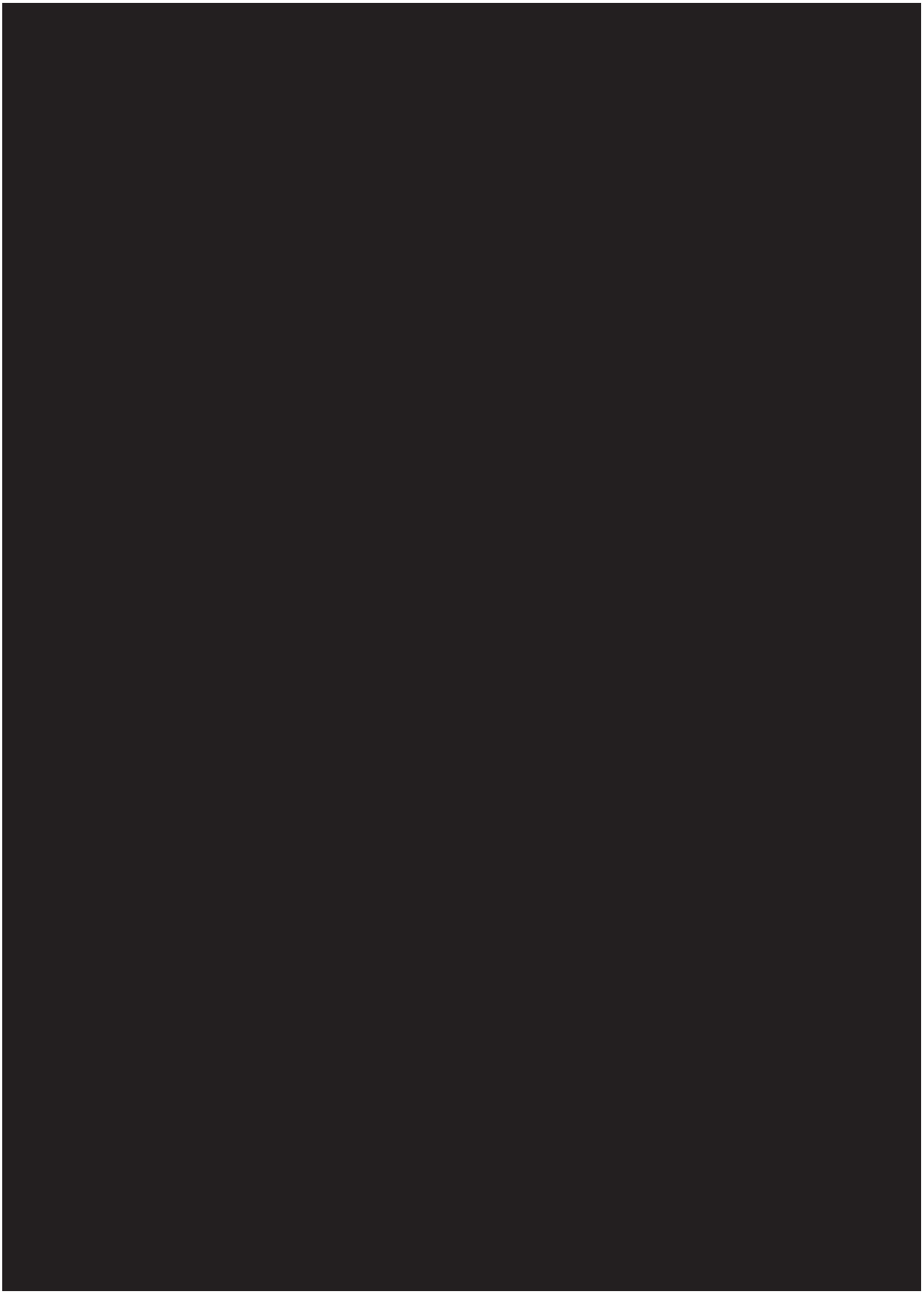
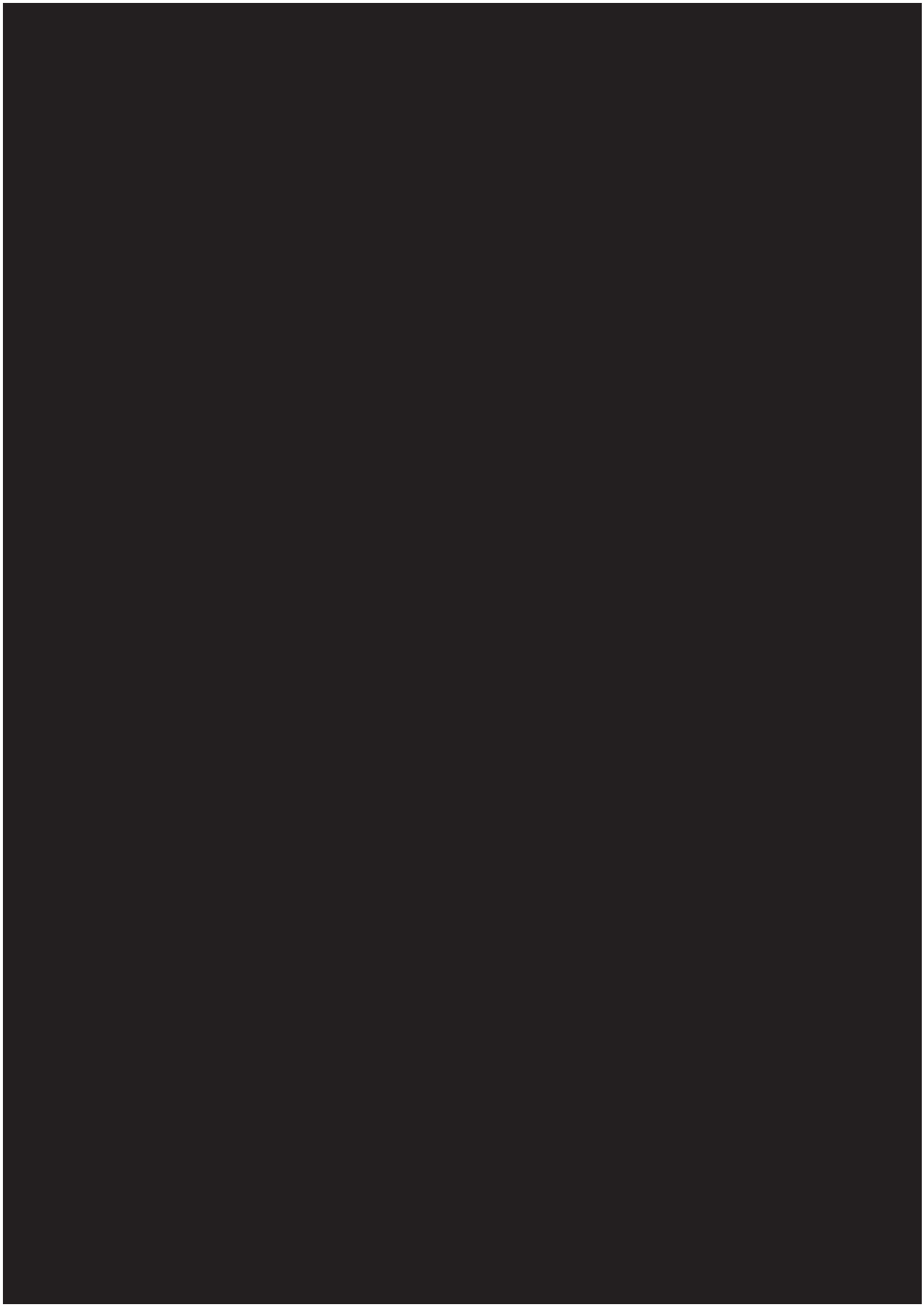
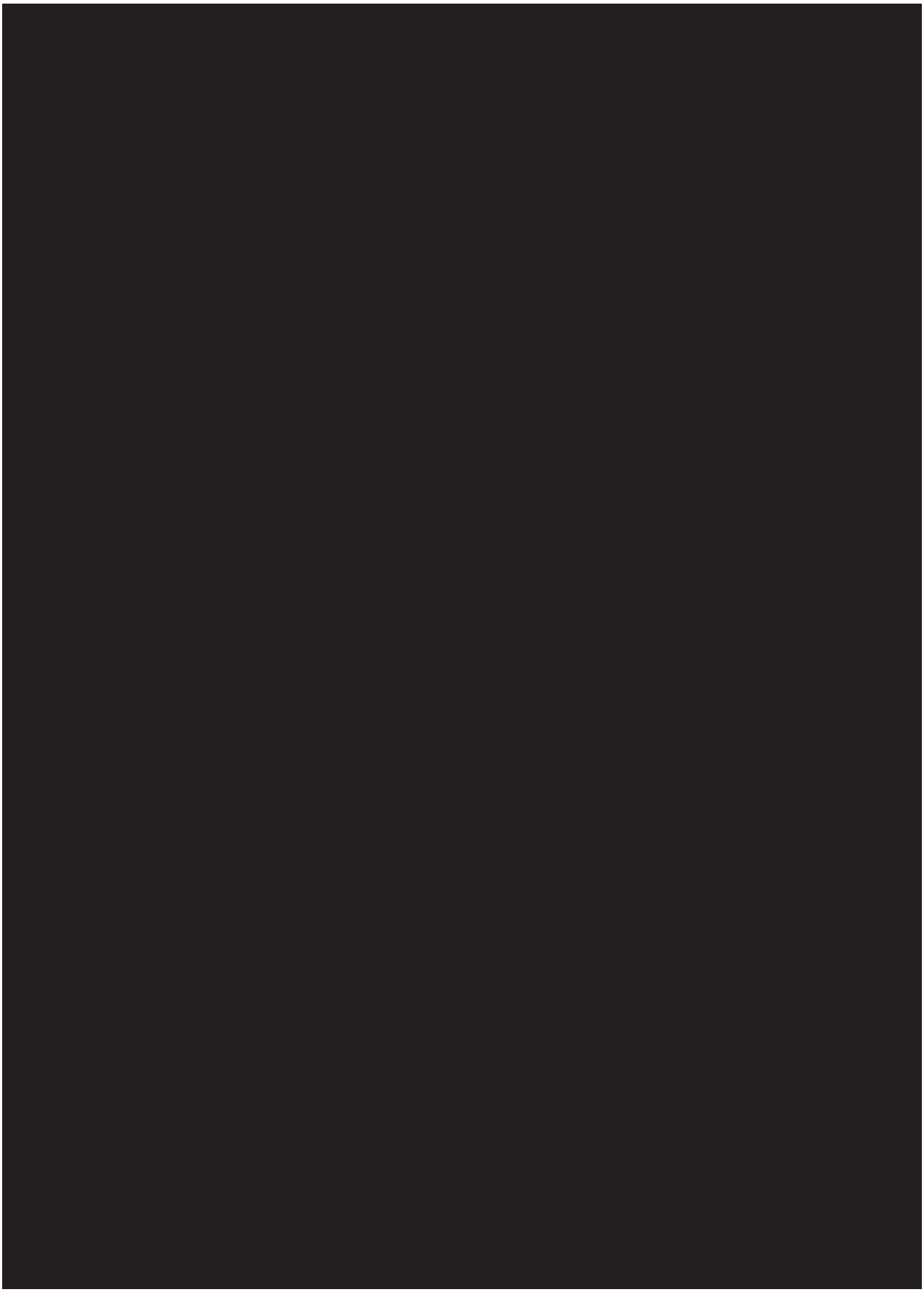


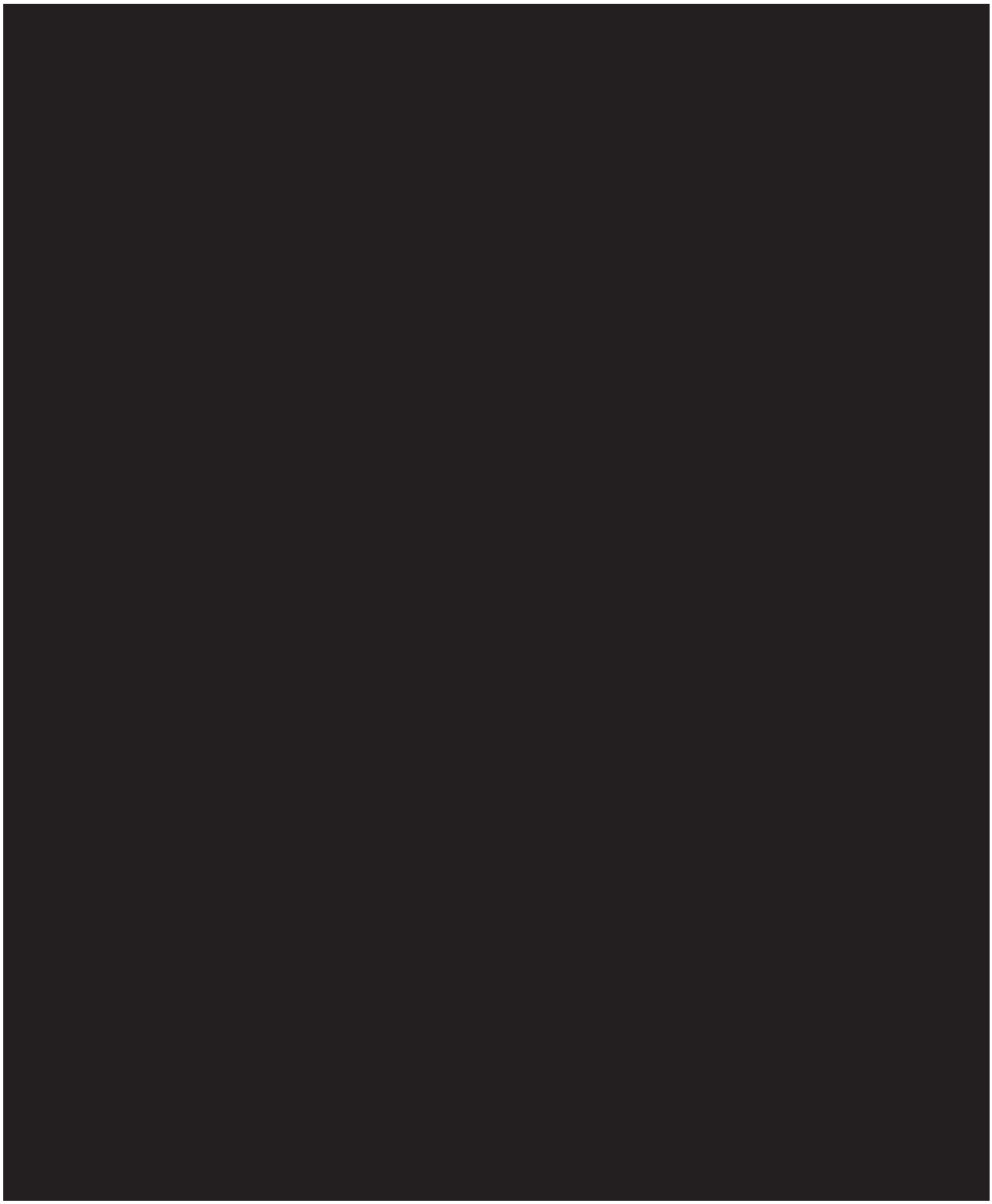


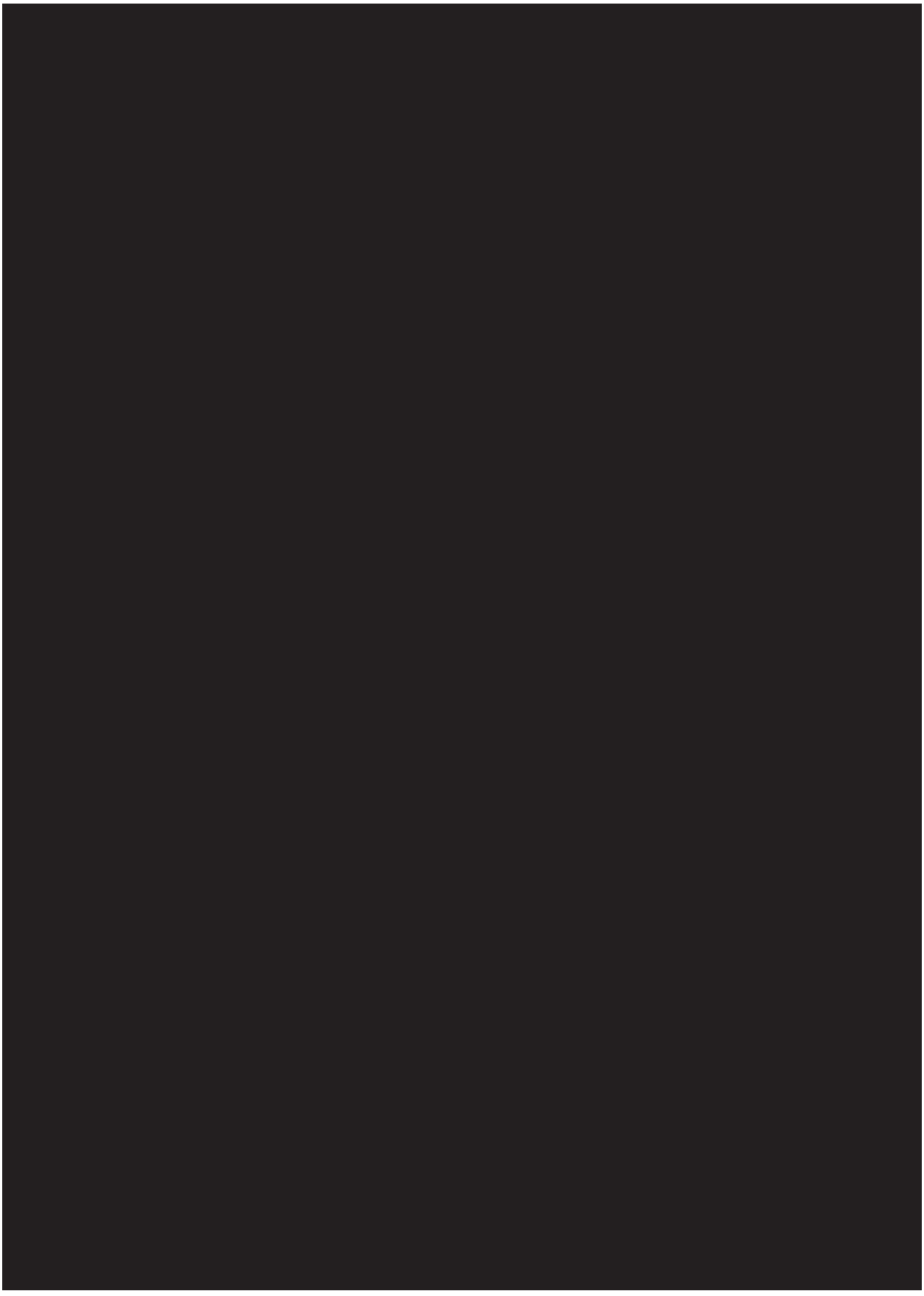












6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

In this Phase I trial, treatments are not randomized. Different dose levels of BI 754091 will arise in phase Ia and there is only one dose level in the 4 cohorts of phase Ib. Data of phase Ia and phase Ib will be displayed separately. In addition, for both phase Ia and phase Ib, data will be presented for all cohorts separately.

For phase Ia, the initial trial medication (i.e. dose level) assigned at the beginning of the first treatment cycle will be used as label of the analysing treatment.

Table 6.1: 1 Definition of analysing treatment periods for safety analysis

Analysing Treatment Period	**Start Date**	**Stop Date**
Screening	Date of informed consent	Date/Time of the first administration of trial treatment
On-treatment	Date/Time of the first administration of trial treatment	Date of the last administration of trial treatment + 30 days (residual effect period)
Follow-up	Date of the last administration of trial treatment + 31 days	Date of the last per protocol visit

Note: a 30-day residual effect period (REP) is defined for this trial.

For safety analyses, AEs will be classified to one of the following time periods: “Screening”, “On-Treatment” or “Follow-up.” This will be applied for all adverse events. Detailed rule for assigning AEs to these time periods are listed below:

- If the date of informed consent ≤ AE onset date < date/time of first administration of BI 754091, then the AE is assigned to “Screening”;
- If date/time of first administration of BI 754091 ≤ AE onset date ≤ date of last administration of BI 754091 + 30 days, then theAE is assigned to “On-Treatment”;
- If AE onset date > date of last administration of BI 754091 + 30 days, then the AE is assigned to “Follow-up”

6.2 IMPORTANT PROTOCOL DEVIATIONS

According to (1) important safety protocol deviations (PDs) are those that potentially affect the rights or safety of study subjects. Important PDs are those that can potentially influence the primary outcome measure(s) for the respective patients in a way that is neither negligible nor in accordance with the study objectives.

No per protocol set is defined for this phase I trial, but patients with important protocol deviations (iPD) will be identified and reported in the clinical trial report (CTR). Potential Important PDs are defined in Table 6.2: 1. The final list of important PDs will be confirmed at the last report planning meeting (RPM) before DBL.

Covid-19 related important and non-important PDs will be listed.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
A		**Entrance criteria not met**			
	A1.1	Patients potential for pregnancy or < 18 years	Inclusion criteria 2, 7 or 8 not met	None	Automatic
	A1.2a	Phase Ia - Patients do not have a histologically confirmed diagnosis of advanced, unresectable, and/or metastatic solid tumours (any type).	Inclusion criteria 3 not met during Phase Ia	None	Automatic
	A1.2b	Patients do not have measurable lesions according to RECIST v1.1 and iRECIST or life expectancy <12 weeks after start of treatment.	Inclusion criteria 3, 4, 6 not met	None	Automatic
	A1.3a	Phase 1a - Patients with PD-1 experience do not have a minimum of 60 days between the last dose of the previous PD-1 and Cycle 1 Day 1 of BI 754091 treatment.	Inclusion criteria 3 not met during Phase Ia	None	Automatic
	A1.3b	Phase 1b - patients who are anti-PD-1 naïve but have failed conventional treatment (excluding anti-PD-1 treatment), or for whom no therapy of proven efficacy exists, or who are not amenable to standard therapies.	Inclusion criteria 4 not met during Phase Ib	None	Automatic
	A1.4	Eastern Cooperative Oncology Group (ECOG, R01-0787) score > 1	Inclusion criteria 5 not met	None	Automatic
	A2.1	Major surgery performed within 12 weeks prior to first trial treatment or planned within 12 months after screening	Exclusion criteria 1 met	None	Automatic

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
A		**Entrance criteria not met**			
	A2.2	Intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial	Exclusion criteria 2 met	None	Automatic
	A2.3	Previous enrolment in this trial	Exclusion criteria 3 met	None	Automatic
	A2.4	Use of investigational or antitumour treatment within 30 days prior to the initial administration of BI 754091	Exclusion criteria 4 met	None	Automatic
	A2.5	History within the last 5 years of an invasive malignancy other than the one treated in this trial. Refer to protocol for the exception.	Exclusion criteria 5 met	None	Automatic
	A2.6	Untreated brain metastasis(es) that may be considered active.	Exclusion criteria 6 met	None	Automatic
	A2.7	Inadequate organ function or bone marrow reserve as demonstrated by the laboratory values in CTP Section 3.3.3	Exclusion criteria 7 met	None	Automatic
	A2.8	Improper cardiac criteria according to CTP Section 3.3.3	Exclusion criteria 8 met	None	Automatic
	A2.9	History of pneumonitis within the last 5 years	Exclusion criteria 9 met	None	Automatic
	A2.10	History of severe hypersensitivity reactions to other mAbs	Exclusion criteria 10 met	None	Automatic
	A2.11	Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of BI 754091	Exclusion criteria 11 met	None	Automatic
	A2.12	Active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy	Exclusion criteria 12 met	None	Automatic

Table 6.2: 1 Important protocol deviations (cont.)

Category / Code		Description	Comment / Example	Excluded from	Automatic/ Manual
A					
	A2.13	Known history of human immunodeficiency virus infection or an active hepatitis B or C virus infection	Exclusion criteria 13 met	None	Automatic
	A2.14	Interstitial lung disease	Exclusion criteria 14 met	None	Automatic
B		**Informed consent**			
	B1	Informed consent not available/not done	Inclusion criteria 1 not met	None	Automatic
	B2	Informed consent too late	Inclusion criteria 1 not met-Informed consent obtained later than the initiation of treatment	None	Automatic
C		**Trial medication**			
	C1.1	Non-compliance with BI 754091 per protocol	Incorrect trial medication dose taken or wrong dose schedule, i.e. wrong infusion time; this will be the decision at MQRM	None	Automatic and manual
	C1.2	Discontinuation of trial medication not following the protocol	Decision at MQRM	None	Automatic and manual
D		**Concomitant medication**			
	D1.1	Prohibited medication use	Review concomitant medications for prohinbited medication use; also refer to Section 4.2.2.2 of the protocol	None	Manual
E		**Study Specific**			
	E1	Incorrect study procedure(s) performed.	Any deviation from protocol not defined above deemed important to document in study report by trial team.	None	Manual

Note: MQRM – Medical and Quality Review Meeting

6.3 SUBJECT SETS ANALYSED

Screened Set:
This patient set includes all patients who have signed the informed consent. The screened set will be used for patient disposition tables.

Treated Set (TS):
This patient set includes all patients who were documented to have received at least one dose of BI754091. The TS is used for both efficacy analyses and safety analyses.

MTD set:
This patient set includes all patients enrolled in a Ia dose finding cohort of the trial who were not replaced within the MTD evaluation period

PK Analysis Set (PKS):
This patient set includes all patients in the TS who provide at least one evaluable observation for at least one PK endpoint and no PK relevant protocol deviations. PKS will be used for statistical pharmacokinetical analyses.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards.
Missing data and outliers of PK data are handled according to (2).

Potential outliers will be reported and analysed as observed. In general, missing data not discussed in (2) and BI standards will not be imputed unless required for the following analyses and definitions. Then the rules as described below apply.

1) **Change of laboratory values from baseline**

   Laboratory values at baseline: For missing laboratory data at cycle 1 day 1 (before the first administration of any study medication) the data of preceding visits will be used if available.

2) **Definition of on-treatment period and actual treatment**

   Date of permanent discontinuation of study medication: All reasonable efforts should be undertaken during the study to obtain the dates of permanent discontinuation of study medication. However, if the date of the very last administration is missing this will be imputed with:

   - If only month and year are given, the last day of the month will be used for imputation
   - If only the year is given, the 31st of December of this year will be used for imputation

   If the imputed date leads to a date that is later than the date of the EOT visit, then the imputed date is the date of the EOT visit. If the imputed date leads to a date that is later than the death date, then the imputed date is the date of death.

3) Partial death dates

If a partial (year and month) death date is reported, the date will be imputed with the end of the month for the analysis of PFS. This is in line with the imputation of partial dates for the analysis of AEs.

4) Partial or missing start date of subsequent anti-cancer therapy/subsequent radiotherapy

If the day of the start date of subsequent systemic therapy/subsequent radiotherapy is missing, then the 1st of the month will be imputed unless this leads to a date before the stop date of study medication. In this case the stop date of study medication +1 day will be imputed.

If day and month, or day and month and year are missing, it will be distinguished whether the start date of subsequent systemic therapy/subsequent radiotherapy is required for censoring of PFS or for other descriptive statistics:

- For censoring of PFS or DoR: If only the year is reported, the 1st of January of this year will be imputed unless this leads to a date before the stop date of study medication. In this case the stop date of study medication +1 day will be imputed. In case of a completely missing start date of subsequent anti-cancer therapy/subsequent radiotherapy and the patient did not have any post-baseline tumour assessment or did not progress or die, the PFS of this patient will be censored at the day of first administration of BI 754091. Additionally, all imputed start dates of subsequent anti-cancer therapy/subsequent radiotherapy should be before death date, if available.

- For descriptive statistics: Dates will not be imputed if more than only the day of the date is missing.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified baseline is defined as the time point closest to but prior to the first administration of any study medication. If no time is specified and the date is the same as the first administration date, then it will still be considered baseline if not specified otherwise. If there is no measurement earlier than the first administration of study medication, then no baseline will be derived.
Study day will be calculated relative to the date of the first administration of study drug. The day prior to first administration of study drug will be ‘Day -1’ and the day of first administration of study drug will be ‘Day 1’; therefore ‘Day 0’ will not exist.

Imaging time windows:
Time windows and visits will be calculated to determine the planned day of tumour measurement and response status, based on the protocol-specified tumour imaging schedule.

For the presentation of tumour response data which will follow a calculated visit approach

based on the protocol specified tumour imaging schedule. Imaging will be performed at screening and every 6 weeks after BI 754091 infusion (i.e. Week 6, 12, 18 …etc.), then every 9 weeks after 6 months of treatment; image data will be slotted to Week 6, 12, 18 etc. based on their relative day (from start of treatment) and using a ±3 week window (images taken in the first 3 weeks from start of treatment will be assigned to Week 6). If two or more images for a patient are assigned to one interval then the last assessment will be used to ensure progressive disease is not missed.
In order to identify whether consecutive imaging time points are missing for a given patient, a nominal time point (i.e. Week 6, 12, 18 … etc.) will be assigned to each and every image. This is achieved by creating windows for every radiological response assessment. These windows are defined in Table 6.7: 1.

Table 6.7: 1 Nominal time points and windows for imaging

Nominal time point (weeks from start of study medication)	**Due date of scans (days)***	**Window (days)**
6	43	1 to ≤ 64
12	85	65 to ≤ 106
18	127	107 to ≤ 148
24	169	149 to ≤ 200
33	232	201 to ≤ 263
42	295	264 to ≤ 326
51	358	327 to ≤ 389
Etc., 9 week interval	Etc.	Etc.

* The date of the first dose of study medication is Day 1

If a patient does not have an image in one of the windows described above, he/she will be considered to have missed an assessment for that time point.

Laboratory values:
Baseline is defined as the latest time point before the very first administration of any study medication. For laboratories where not only the examination date but also time are recorded, examination time has to be taken into account when defining baseline. That is, a laboratory value on the same date as the first administration of study medication is considered as baseline value if and only if the time of laboratory assessment is before or the same as the time of first study drug administration.

If any of these times is missing and the date of laboratory assessment is equal to the date of first administration of study medication, then the laboratory assessment will be considered as according to protocol, i.e. as prior to first study medication.

Laboratory time windows:

Time windows and visits will be calculated to determine the planned day of laboratory assessment, based on the protocol-specified laboratory assessment schedule.

For the presentation of a descriptive summary analysis over time for a laboratory parameter the laboratory data will be displayed by calculated visit instead of actual visit reported to ensure a common handling of all laboratory assessments and to account for unscheduled visits representing a repeated laboratory measurement. As Phase Ia and Phase Ib have a different laboratory assessment schedule, the time windows for the calculated visits will be different for Phase Ia and Phase Ib.

Table 6.7: 2 Calculated visits, nominal time points and windows for laboratory assessments in Phase Ia

Calculated visit	**Nominal time point (weeks from start of study medication)***	**Window (days)**
Cycle 1 Day 1	1	1 to ≤ 4
Cycle 1 Day 8	8	5 to ≤ 11
Cycle 1 Day 15	15	12 to ≤ 18
Cycel 2 Day 1	22	19 to ≤ 32
Cycle 3 Day 1	43	33 to ≤ 53
Cycle 4 Day 1	64	54 to ≤ 74
Etc., 21 days interval	Etc.	Etc.

* The date of the first dose of study medication is Day 1

Table 6.7: 3 Calculated visits, nominal time points and windows for laboratory assessments in Phase Ia

Calculated visit	**Nominal time point (weeks from start of study medication)***	**Window (days)**
Cycle 1 Day 1	1	1 to ≤ 11
Cycel 2 Day 1	22	12 to ≤ 32
Cycle 3 Day 1	43	33 to ≤ 53
Cycle 4 Day 1	64	54 to ≤ 74
Cycel 5 Day 1	85	75 to ≤ 95
Cycle 6 Day 1	106	96 to ≤ 116
Cycle 7 Day 1	127	117 to ≤ 137
Cycel 8 Day 1	148	138 to ≤ 158

Table 6.7: 3 Calculated visits, nominal time points and windows for laboratory assessments in Phase Ia (cont.)

Calculated visit	**Nominal time point (weeks from start of study medication)***	**Window (days)**
Cycle 9 Day 1	169	159 to ≤ 179
Cycle 12 Day 1	232	180 to ≤ 1263
Cycel 15 Day 1	295	264 to ≤ 326
Cycle 18 Day 1	358	327 to ≤ 389
Etc., 21 days interval	Etc.	Etc.

* The date of the first dose of study medication is Day 1

Biomarker time windows:
The time windows used for biomarker analysis are defined as follows.

[redacted]

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / Standard deviation (StD) / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to Mean, StD, Min and Max.

For time-to-event analysis tables the set of statistics is: number of patients [N(%)], number of patients with event [N(%)], <time to event> [months] followed by P25 (25th percentile), median, P75 (75th percentile) and number of patients censored [N(%)]. If not specified otherwise the duration as well as the time to event will be displayed in months.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

Sort order for general categorical variables: If categories correspond to the collected categories on the eCRF and the table shells do not explicitly specify the ordering, the “default ordering” defined by the eCRF is to be used in such cases. If categories are derived, the ordering as specified in the table shell document should be used; in general ordinal data (e.g. categorised continuous data) are to be displayed in ascending order.Abbreviations (e.g. Wors.) should not be displayed without any explanations. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

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

- Weeks = Days / 7
- Months = (Days * 12) / 365.25
- Years = Days / 365.25

[redacted]

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

[redacted] history, prior anti-cancer therapies, medical history and baseline disease assessment.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Concomitant diseases will be coded similarly as adverse events based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version. Concomitant therapies (CTs) will be coded according to World Health Organization Drug Dictionary (WHO DD). CTs will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorise 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, patients receiving CTs with more than one possible ATC level 3 category will be counted more than once. Footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

Not applicable in this study.

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

In order to identify the MTD and the recommended dose for the Phase Ib dose expansion phase, the number of patients with DLTs at each dose level during the Phase Ia MTD evaluation period (first three weeks) must be presented. Patients who discontinue during the first treatment course for reasons other than a DLT will be excluded from the determination of the MTD.

The analysis of the MTD is based on a BLRM guided by the escalation with overdose control principle. The MTD is defined as the highest dose for a given schedule that is expected to cause less than 25% risk of the true DLT rate being above or equal to 33% during the MTD evaluation period. Estimation of the MTD during the dose escalation phase of the study will be based upon the estimation of the posterior probability of the incidence of DLT in toxicity categories during the MTD evaluation period for all evaluable patients. The model to be used is specified in CTP Section 7.

Tables and bar charts displaying the posterior probabilities of the true DLT rates being in either the underdosing interval, the targeted toxicity interval or the over toxicity interval will be produced.

For Phase Ib dose expansion, OR according to RECIST v1.1 will be analysed in terms of

objective response rate (ORR), defined as the proportion of patients with best overall response of CR or PR. ORR according to RECIST v1.1 will be summarised descriptively with 95% exact Clopper-Pearson confidence intervals (CIs).

[redacted]

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 protocol.

7.5.2 (Other) Secondary endpoint(s)

7.5.2.1 Phase Ia

PK parameters evaluated after the first and after multiple administrations of BI 754091

The PK parameters will be evaluated using noncompartmental analysis methods according to 001-MCS-30-476 (2). Tables and figures for concentration values and PK parameters will be created according to 001-MCS-30-476 (2).

Descriptive statistics will be calculated for all concentration time points and PK parameters. The following descriptive statistics will be calculated for BI 754091 concentrations: N (number of patients with non-missing values), arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation and for PK parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, tenth percentile (P10), Q1, Q3, ninetieth percentile (P90), arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation.

The PKS will be used for PK analysis. Non evaluable patients will be listed with their individual PK parameters, but such data will not be included when calculating descriptive statistics.

Objective response according to RECIST v1.1

Objective response will be analysed in terms of ORR, defined as the proportion of patients with best overall response of CR or PR.

ORR according to RECIST v1.1 will be summarised descriptively with 95% exact Clopper-Pearson CIs.

Number of patients experiencing DLTs from the start of treatment until end of treatment

Number of patients with DLT(s) which occurred during the entire treatment period will be summarised for each dose cohort.

7.5.2.2 Phase Ib

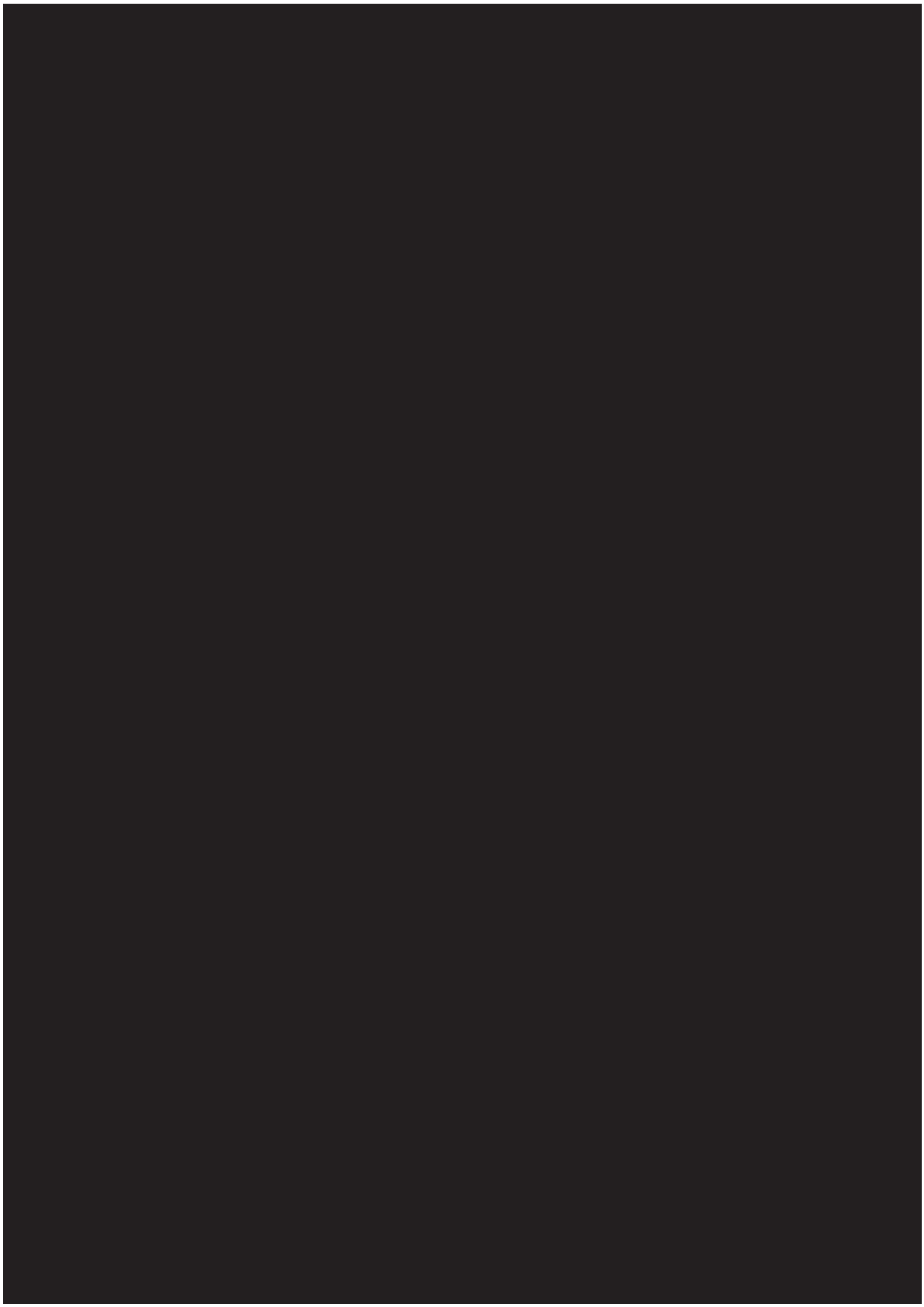
Progression-free survival by RECIST 1.1

PFS will be summarized descriptively by quartiles with 95% confidence interval (based on the Greenwood's method) calculated from Kaplan-Meier estimate.

Safety

Number of patients with AEs, SAEs and clinical relevant abnormalities in vital signs, laboratory evaluations or ECG parameters as reported by the investigator as AEs will be summaries for each cohort.

[redacted]



Please refer to Section 7.5.2.1.

7.7 EXTENT OF EXPOSURE

The total number of administrations, total number of cycles initiated and treatment duration of BI 754091 will be summarized descriptively for each dose cohort. Results of Ia and Ib will also be presented separately.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set (TS). Treated patients will be analysed according to their initial treatment.

Safety data recorded during the Residual Effect Period (REP) of 30 days will be considered as on-treatment.

Patients who were replaced within the MTD evaluation period will be excluded from the determination of the MTD but will be considered for all other safety evaluations.

7.8.1 Adverse Events

The analyses of AEs will be descriptive in nature. All analyses will be based on the number of patients with AEs (not on the number of AEs). The analysis will be based on BI standards. AEs will be coded using the most recent version of MedDRA. The severity of AEs was assessed according to CTCAE Version 4.03 up to Amendment 4 and according to CTCAE Version 5.0 thereafter. AEs will be analysed as reported by the investigator and pooled independent of CTCAE version used if applicable.

The analyses of AEs will be based on the concept of treatment-emergent AEs, where a treatment-emergent AE has an onset in the analysing treatment period. The AE analysis will be based on the on-treatment period which starts with the date of the first administration of study medication and ends 30 days after the last administration of study medication. AEs with an onset date in the screening period (time between informed consent date and date of the first administration of study medication) or follow-up period (time after the on-treatment period) will be listed separately.

The actual planned dose of BI 754091 will be derived and included in the listings. AEs will be reported with start day and end day as calculated from the first day of treatment with study medication. For listings displaying AEs during the screening or follow-up period, the start and stop day are calculated from the start of the respective analysis period.

An overall summary of AEs will be presented.

Adverse events will be displayed by the initial dose of study medication administered on the first day of treatment.

The frequency of patients with adverse events during on-treatment period will be summarised by treatment, primary system organ class (SOC) and preferred term (PT) and by PT only (if at least 2 patients observed a repsecitve AE) for each of the following AE tables:

- DLTs
- All AEs by highest CTCAE grade
- Serious AEs by highest CTCAE grade
- Investigator assessed related AEs by highest CTCAE grade
- Investigator assessed related SAEs by highest CTCAE grade
- Investigator assessed AESI by highest CTCAE grade
- Investigator assessed immune-related AEs by highest CTCAE grade
- AEs leading to treatment discontinuation by highest CTCAE grade
- AEs leading to death

The SOC will be sorted alphabetically, preferred terms will be sorted by frequency (within SOC). Adverse events that are immune mediated can potentially begin more than 30 days after treatment. Additional tables will summarize all immune related events, including events with onset more than 30 days after the last treatment.

AEs leading to death during the on-treatment period will be tabulated by SOC and PT. Reported fatal AEs during follow-up period will be listed.

7.8.2 Laboratory data

The analysis of laboratory data will be descriptive in nature and will be based on BI standards. The same on-treatment period as considered for the analysis of adverse events will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed in a new category "missing CTCAE grade at baseline" for those laboratory parameters where CTCAE grading is applicable. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE Version 5.0.

7.8.2.1 Analysis

The Laboratory tests will be classified into the following categories:

- Primary- full analysis
- Secondary- listing of possible clinically significant values
- Diagnostic- listing of all observed values
- Not analysed

The following outputs will be presented for primary laboratory tests:

- Descriptive statistics, including changes from baseline
- Frequency of patients with shifts from baseline
    - Shifts will be defined in terms of
        - CTCAE grades will be used for laboratory tests with CTCAE grades defined
        - The upper and lower reference limits will be used for laboratory tests without CTCAE grades
- Frequency of patients with possible clinically significant abnormalities (definitions see Section 7.8.2.2)

The analysis of secondary laboratory tests will be limited to tabulation of the frequency of patients with possible clinically significant abnormalities (definitions see Section 7.8.2.2).

Laboratory tests classified as "diagnostic" are recorded as a follow-up to abnormalities of associated lab tests for diagnostic purposes i.e. amylase and lipase would be measured to investigate possible pancreatitis. These values will be presented in a separate listing. No other analyses will be performed

Analyses of descriptive statistics should use normalized lab values and will be displayed by calculated visit instead of actual visit reported to ensure a common handling of all laboratory assessments and to account for unscheduled visits representing a repeated laboratory measurement (see Table 6.7: 2 and Table 6.7: 3).

Analyses of frequencies of patients with potential clinical significance, analyses of shift, and liver function categories tables should use converted values.

Baseline for safety laboratory parameters will be the last available measurement before the start of study drug. Laboratory measurements taken up to 30 days after the last administration of study drug will be considered as on-treatment.

Primary laboratory test results will be presented in CTR section 15.
Secondary laboratory test results will be included in Appendix 16.1.13.1.
Diagnostic laboratory test results will be listed in Appendix 16.1.13.1.
Laboratory test that are not analysed will be listed in Appendix 16.2.8.

Handling of CTCAE grade -1 and -9 laboratory parameters:
Generally, in case only one direction of worsening (high or low laboratory value) is specified in the CTCAE document, there is no need to examine the other direction. Therefore, for calculating the change in CTCAE grade, patients with a CTCAE grade of -9 (no CTCAE grade defined) will be automatically treated as CTCAE grade 0 for all analyses. In laboratory listings, the CTCAE grade will be displayed as -9.
There are certain parameters for which CTCAE grades can only be differentiated by taking physiological consequences into account. These laboratory values will be coded as -1. As these definitions aggregate laboratory data and adverse events or concomitant therapies no analyses based on CTCAE grades will be done. Instead standard laboratory analyses as for laboratory parameters without CTCAE grade definitions will be done.

Corrected calcium:
The grading of hypocalcemia is based on corrected calcium as calcium can be falsely low if hypoalbuminemia is present. The following corrective calculation will be performed:

Corrected calcium (mg/dL) = Total Calcium (mg/dL) – 0.8 [Albumin (g/dL) - 4g/dL]

No correction of the reference range has to be done. The reported reference range of total calcium will be used for analyses.
Corrected calcium can be only derived at a certain time point in case both laboratory values total calcium and albumin have been reported for the patient in the same laboratory sample.

Differential blood count:
Differential blood counts were to be measured in absolute values according to the CTP. In case a subject's differential blood count is reported in percentage, the following conversion will be applied:

Differential [10^9/L] = Differential [%] * (White blood cell count value / 100)
The corresponding reference ranges of the converted differential blood values are not allowed to be converted like the individual laboratory measurements. The reference range is taken from the BI standard reference range definition.

Liver Function tests and potential Hy's Law
A listing of all liver function tests will be provided for all patients who meet the following criteria at any time:

- ALT or AST ≥3xULN and elevation of total bilirubin ≥2xULN at within +/- 30 days

In addition, tables of liver function test abnormalities will be produced.

7.8.2.2 Classification of laboratory tests

Table 7.8.2.2: 1 Primary Laboratory tests[1]

Label	**Lab test name**	**Direction of interest**	**Potential Clinical significance rule**
ALKP	Alkaline Phosphatase	High	CTCAE Grade 2 or higher[4]
BILI	Total Bilirubin	High	CTCAE Grade 2 or higher[4]
BILDIR	Direct Bilirubin	High	CTCAE Grade 2 or higher[4] using grades defined for Total Bilirubin
CK	Creatinine Kinase	High	A[2,3]
CREJIDMS	Creatinine	High	>1.5xULN and >baseline ambiguous CTCAE not used[4]
FT3	Triiodothyronine, Free	Low[5], High[5]	<LLN and <baseline or >ULN and >baseline No CTCAE defined
FT4V	Thyroxine, Free	Low[5], High[5]	<LLN and <baseline or >ULN and >baseline No CTCAE defined
GLUB	Glucose	Low, High[5]	Low: A[2,3] High: >10mmol/L and > baseline No CTCAE defined
HGB	Hemoglobin	Low	A[2,3] (listed in CTCAEv5 as "Anemia")
K	Potassium	Low[5], High	Low: < 3 mmol/L and <baseline High: A[2,3]
LDH	Lactate Dehydrogenase	High[5]	≥ 3xULN and > baseline No CTCAE defined
LYMABS	Lymphocytes	Low	A[2,3]
NA	Sodium	Low[5], High	High: A[2,3] Low: < 130mmol/L and < baseline
NEUABS	Neutrophils	Low	A[2,3]
PLTCT	Platelets	Low	A[2,3]
SGOT	Aspartate Aminotransferase	High	CTCAE Grade 2 or higher[4]
SGPT	Alanine Aminotransferase	High	CTCAE Grade 2 or higher[4]

Table 7.8.2.2: 1 Primary Laboratory tests1 (cont.)

Label	Lab test name	Direction of interest	Potential Clinical significance rule
TPONI	Troponin I	High[5]	>ULN and > baseline CTCAE based upon AE
TPONTULT	Troponin T	High[5]	>ULN and > baseline CTCAE based upon AE
TSH	Thyrotropin	Low[5], High[5]	<LLN and <baseline or >ULN and >baseline No CTCAE defined
UREAN	Blood Urea Nitrogen	High[5]	> 10 mmol/L and > baseline No CTCAE defined
WBC	Leukocytes	Low	A[2,3]

[1]Shift tables, descriptive statistics, and potential clinically significant values will be presented.
[2]A= CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline
[3]Separate shift tables for the low and high directions, when both directions are specified. Shift tables compare baseline vs. on-treatment CTCAE grades. CTCAE grading will not consider symptoms.
[4] CTCAE grades will not be defined for baseline values for ALKP, SGPT, SGOT, BILI (Total and Direct) and baseline and post-basline values for CREJIDMS. Special categories are defined for shift tables.
[5]Separate shift tables for the low and high directions, when both directions are specified. Shift tables compare baseline vs. on-treatment using the three categories 1.) below reference range, 2.) within reference range, and 3.) above reference range.

Table 7.8.2.2: 2 Secondary Laboratory tests[1]

Label	Lab test name	Direction of interest	Potential Clinical significance rule
ALB	Albumin	Low	A[2]
CA	Calcium	Low, High	A[2]
CHOL	Cholesterol	High	A[2]
CL	Chloride	Low, High	<80 mmol/L and <baseline or >120 mmol/L and >baseline No CTCAE defined
CPEP	C-peptide	Low	<LLN and <baseline No CTCAE defined
EOSABS	Eosinophils	High	>1.0 10**9/L and > baseline No CTCAE defined
P	Phosphate	Low, High	H: > 1.7 mmol/L and >baseline, L: < 0.7 mmol/L and <baseline
PROT	Serum Protein	Low	<LLN and <baseline No CTCAE defined
TRIGL	Triglycerides	High	A[2]

Table 7.8.2.2: 2 Secondary Laboratory tests1 (cont.)

Label	Lab test name	Direction of interest	Potential Clinical significance rule
UREA	Urea	High	> 1.5 x ULN and > baseline No CTCAE defined
URIC	Uric Acid	High	Females: > 600umol/L and >baseline Males: > 650umol/L and >baseline CTCAE based upon AE

[1]The frequencies of potential clinically significant values will be tabulated, and values that meet the criteria will be listed. No other analyses will be performed.
[2]A= CTCAE grade 2 or greater with an increase of at least one CTCAE grade from baseline
[3] CTCAE grading will not consider symptoms such as presence of bleeding or use of anticoagulation.

Table 7.8.2.2: 3 Diagnostic Laboratory tests[1]

Label	Lab test name	Direction of interest	Potential Clinical significance rule
AMYL	Amylase	High	> 2x ULN and > baseline
LIPASE	Lipase	High	> 2x ULN and > baseline

[1]Values will be displayed in a listing. No other analysis will be performed.

Table 7.8.2.2: 4 Laboratory tests that will not be analyzed

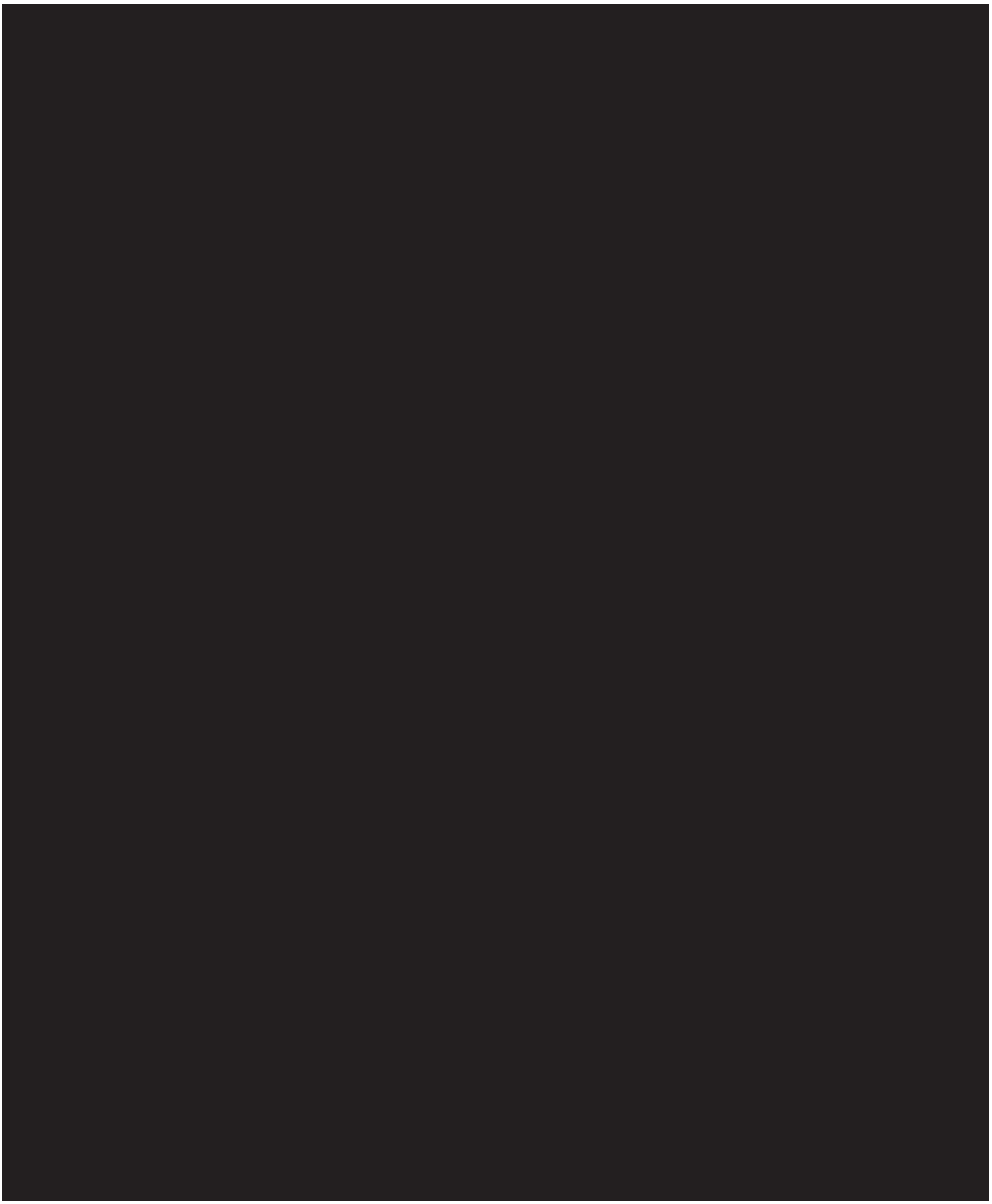
Label	Lab test name
BASABS	Basophils
BICARBV	Bicarbonate
CKMBABS	Creatinine Kinase MB
HCT	Hematocrit
HDL	HDL Cholesterol
LDL	LDL Cholesterol
MCV	Ery. Mean Corpuscular Volume
MONABS	Monocytes
PREG	Choriogonadotropin Beta
RBC	Erythrocytes
UGLU	Urine Glucose
UNIT	Urine Nitrite
UPH	Urine pH
UPRO	Urine Protein
URBCZ	Urine Erythrocytes
UWBCZ	Urine Leukocytes

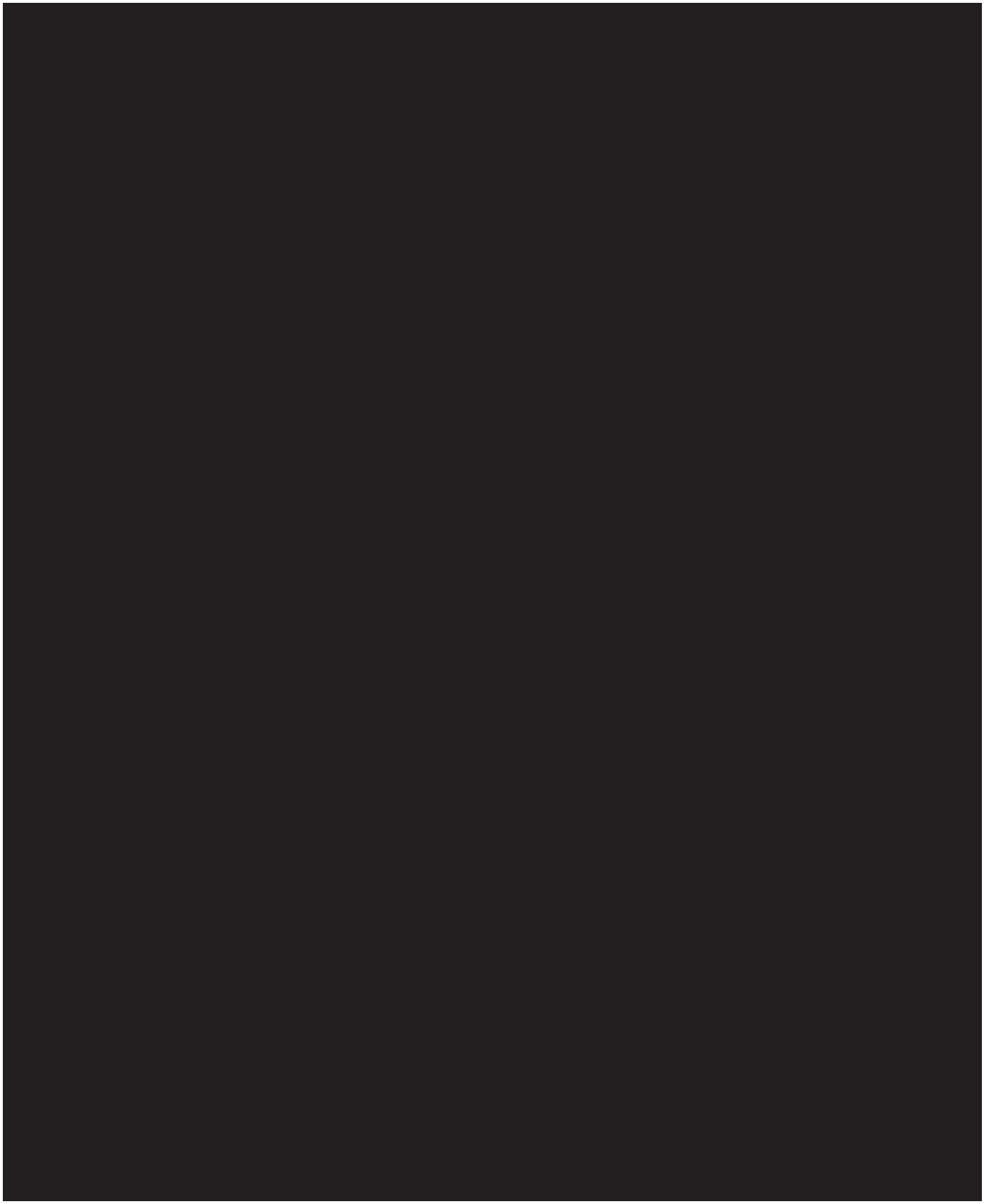
7.8.3 Vital signs

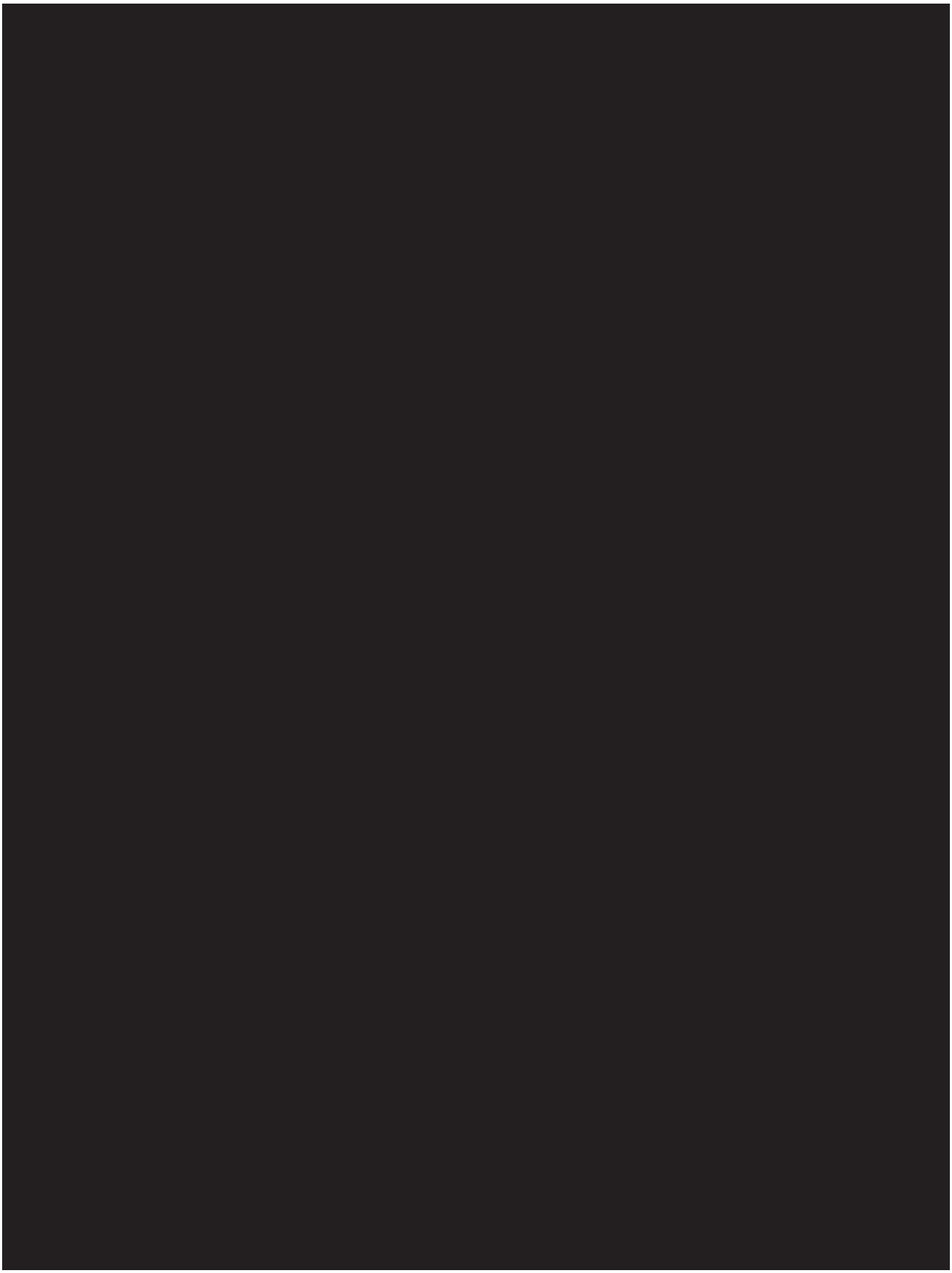
Only descriptive statistics are planned for this section of the report.

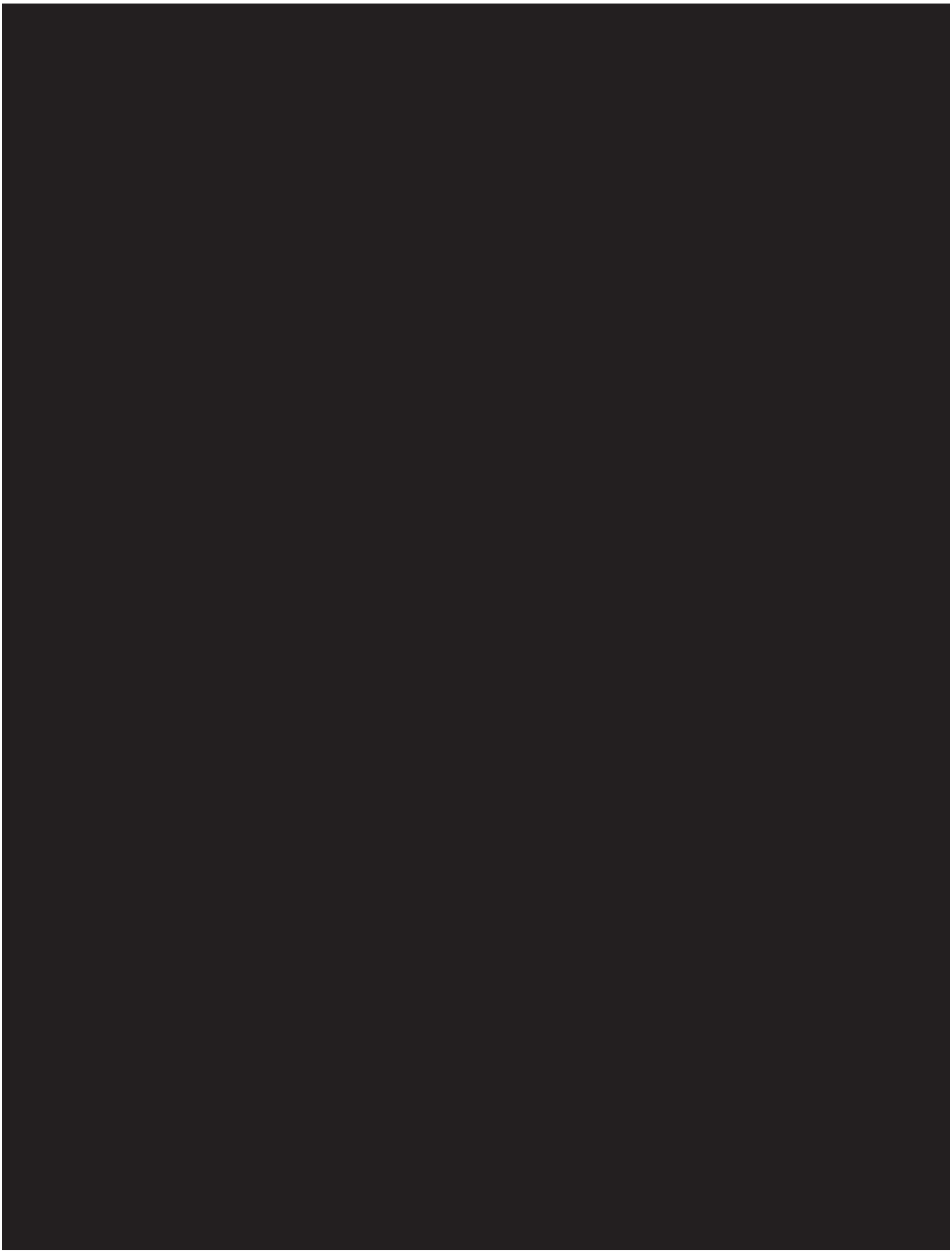
7.8.4 ECG

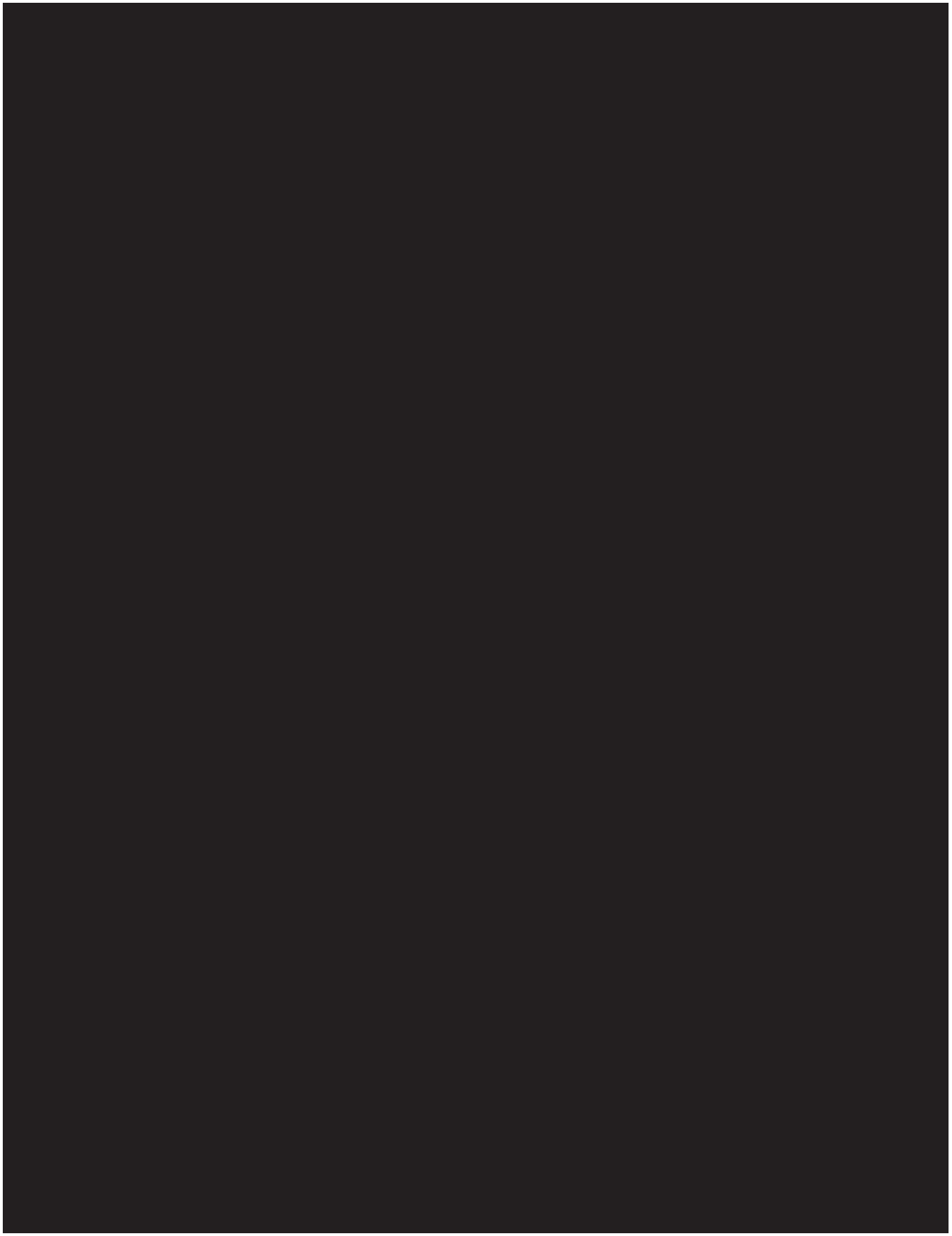
Patients with abnormal ECG data will be provided.





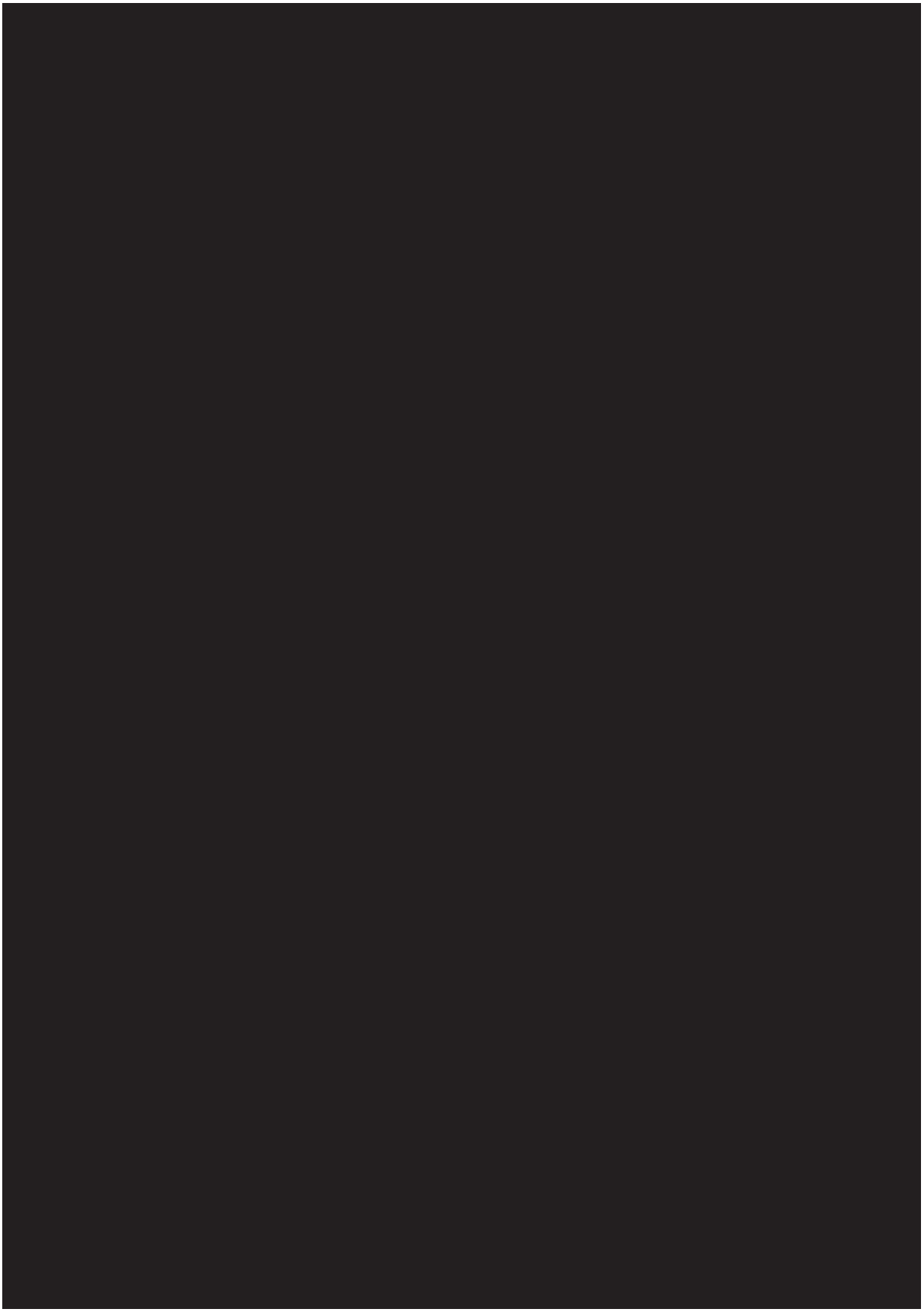


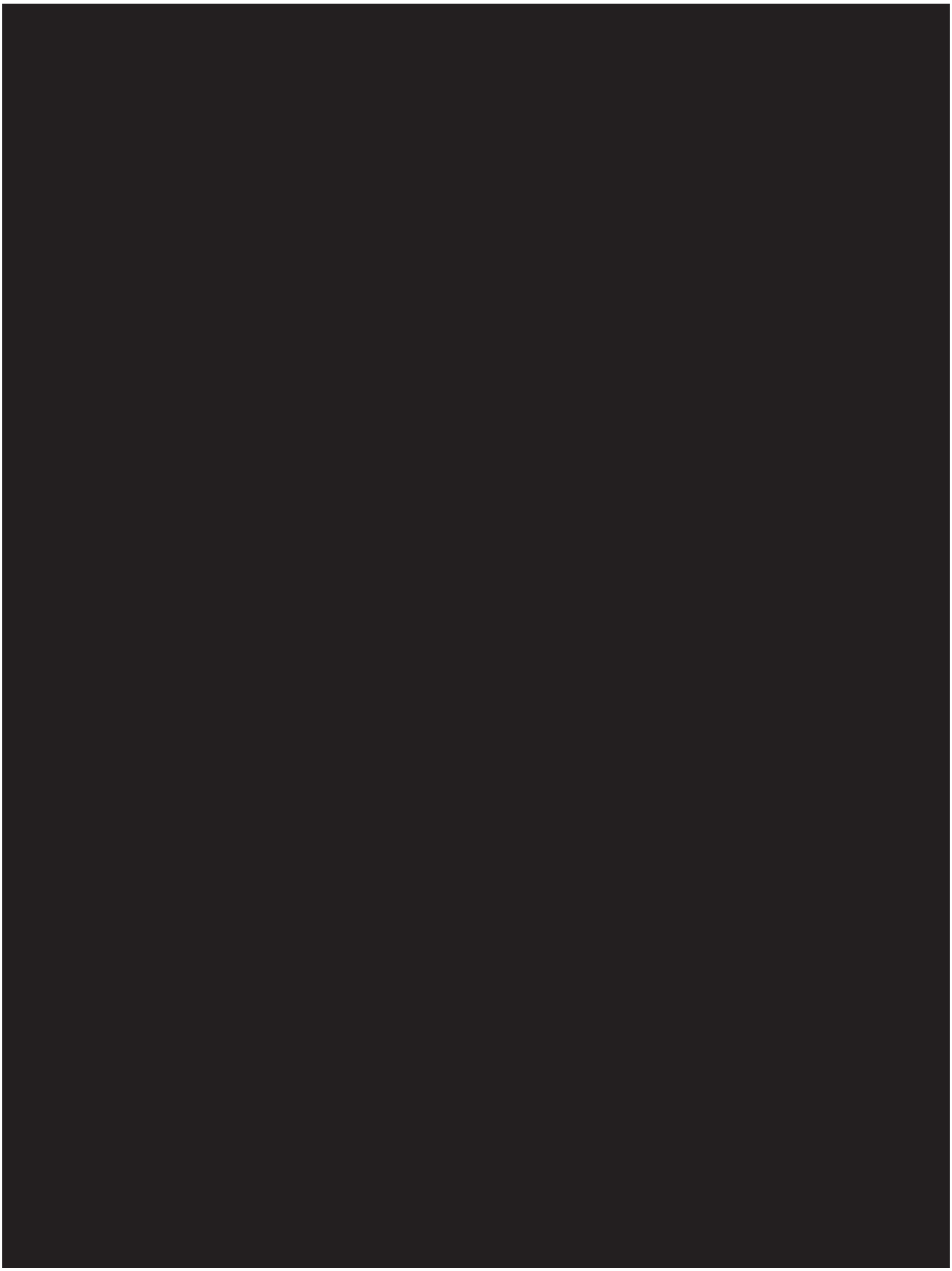




8. REFERENCES

1	*001-MCS-40-413:* "Important Protocol Deviations", current version; IDEA for CON
2	*001-MCS-30-476*: "TMCP Data Analysis", current version; IDEA for CON.





10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**26-JUL-17**	[redacted]	None	This is the TSAP based on CTP amendment 2
2.0	**17-JUN-21**			TSAP updated based on CTP amendment 6 with additional cohorts in expansion phase and biomarker analysis.