# Trial Statistical Analysis Plan

**c20394975-05**

| | |
|---|---|
| **BI Trial No.:** | 1218-0091 |
| **Title:** | A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus.<br>The DINAMO™ (main study) and DINAMO™ Mono (ancillary study) studies.<br>Including Revised Protocol (Global Amendment 6) [c03490746-08] |
| **Investigational Product(s):** | Linagliptin (BI 1356)<br>Empagliflozin (BI 10773) |
| **Responsible trial statistician(s):** | [redacted]<br>Phone: +[redacted] |
| **Date of statistical analysis plan:** | 28 JUL 2022 REVISED |
| **Version:** | Revised |

# 1 TABLE OF CONTENTS

LIST OF TABLES

# 2 LIST OF ABBREVIATIONS

| Term | Definition / description |
|---|---|
| ADaM | Analysis Data Model |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine transaminase |
| ANCOVA | Analysis of covariance |
| AP | Alkaline phosphatase |
| ASA | Acetylsalicylic acid |
| AST | Aspartate transaminase |
| ATC | Anatomical-Therapeutic-Chemical classification |
| BI | Boehringer Ingelheim |
| BIcMQ | BI-customised MedDRA query |
| BMI | Body mass index |
| BMI z-score | BMI Standard Deviation Score |
| BOCF | Baseline observation carried forward |
| CEC | Clinical event committee |
| COVID-19 | Corona virus disease – year 2019 |
| CRF | Case report form |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DBL | Database lock |
| DBP | Diastolic blood pressure |
| DKA | Diabetic Ketoacidosis |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| eGFR | Estimated glomerular filtration rate |
| EOS | End of study |
| EOT | End of treatment |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FPG | Fasting plasma glucose |
| Height z-score | Height Standard Deviation Score |

| Term | Definition / description |
|---|---|
| ADaM | Analysis Data Model |
| HbA1c | Glycated haemoglobin |
| HLT | High level term |
| ICH | International Conference on Harmonisation |
| IRT | Interactive Response Technology |
| L | Skewness |
| M | Median |
| MAR | Missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MCMC | Markov Chain Monte Carlo |
| MI | Multiple imputation |
| mITT | Modified intention to treat |
| MMRM | Mixed model for repeated measures |
| MNAR | Missing not at random |
| NCF | Non-completers considered failure |
| NGSP | National Glycohemoglobin Standardization Program |
| NTx | N-terminal cross-linked telopeptide |
| OC | Observed cases |
| OC-AD | Observed cases – all data |
| OC-AD-BOCF | Observed cases - all data and baseline observation carry forward |
| OC-LOCF | Observed cases – Last observation carry forward |
| OC-ROC | Observed cases – rescue observed cases |
| OR | Original results |
| PCSA | Potentially clinically significant abnormalities |
| PD | Protocol deviation |
| PG | Plasma glucose |
| PK | Pharmacokinetics |
| PKS | PK parameter analysis set |
| PMM | Pattern mixed model |
| PPS | Per protocol set |
| PT | Preferred term |

| Term | Definition / description |
|---|---|
| ADaM | Analysis Data Model |
| PD | Protocol deviation |
| Q1 | Lower quartile |
| Q3 | Upper quartile |
| REML | Restricted maximum likelihood |
| RS | Randomised set |
| S | Coefficient of variation |
| SBP | Systolic blood pressure |
| SCR | Screened set |
| SD | Standard deviation |
| SE | Standard error |
| SLR | Sequential linear regression |
| SMQ | Standardised MedDRA query |
| SOC | System Organ Class |
| SSC | Special search category |
| TBILI | Total bilirubin |
| TDMAP | Trial Data Management and Analysis Plan |
| TSactive | Treated set active |
| TSAP | Trial statistical analysis plan |
| UACR | Urine Albumin Creatinine Ratio |
| ULN | Upper limit of normal |
| UTI | Urinary tract infection |
| WHO | World health organisation |
| WHO DD | Word Health Organisation Drug Dictionary |

# 3 INTRODUCTION

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

The Trial Statistical Analysis Plan (TSAP) assumes familiarity with the 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, randomisation.

SAS Version 9.4 or later version will be used for all analyses.

# 4 CHANGE IN THE PLANNED ANALYSIS OF THE STUDY

Analyses updated according to CTP global amendment 6 dated 23 May 2022.

# 5 ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

**DINAMO**

The primary efficacy endpoint is the change in HbA1c [%] from baseline to the end of 26 weeks.

For the definition of baseline HbA1c refer to Section 6.7.

**DINAMO Mono**

The primary efficacy endpoint is the occurrence of treatment failure up to or at Week 26 as a binary endpoint. Treatment failure is defined as meeting at least one of the following criteria:

- Use of rescue medication, see Section 7.6.1, at any time up to Week 26 (including Week 26)
- Increase from baseline in HbA1c by 0.5% (at least 0.5% in absolute value) at Week 26
- Increase from baseline in HbA1c to above 7.0% at Week 26 in patients with baseline HbA1c < 7.0%

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoints

Since there are no key secondary endpoints specified in the CTP, this section is not applicable.

### 5.2.2 Secondary endpoints

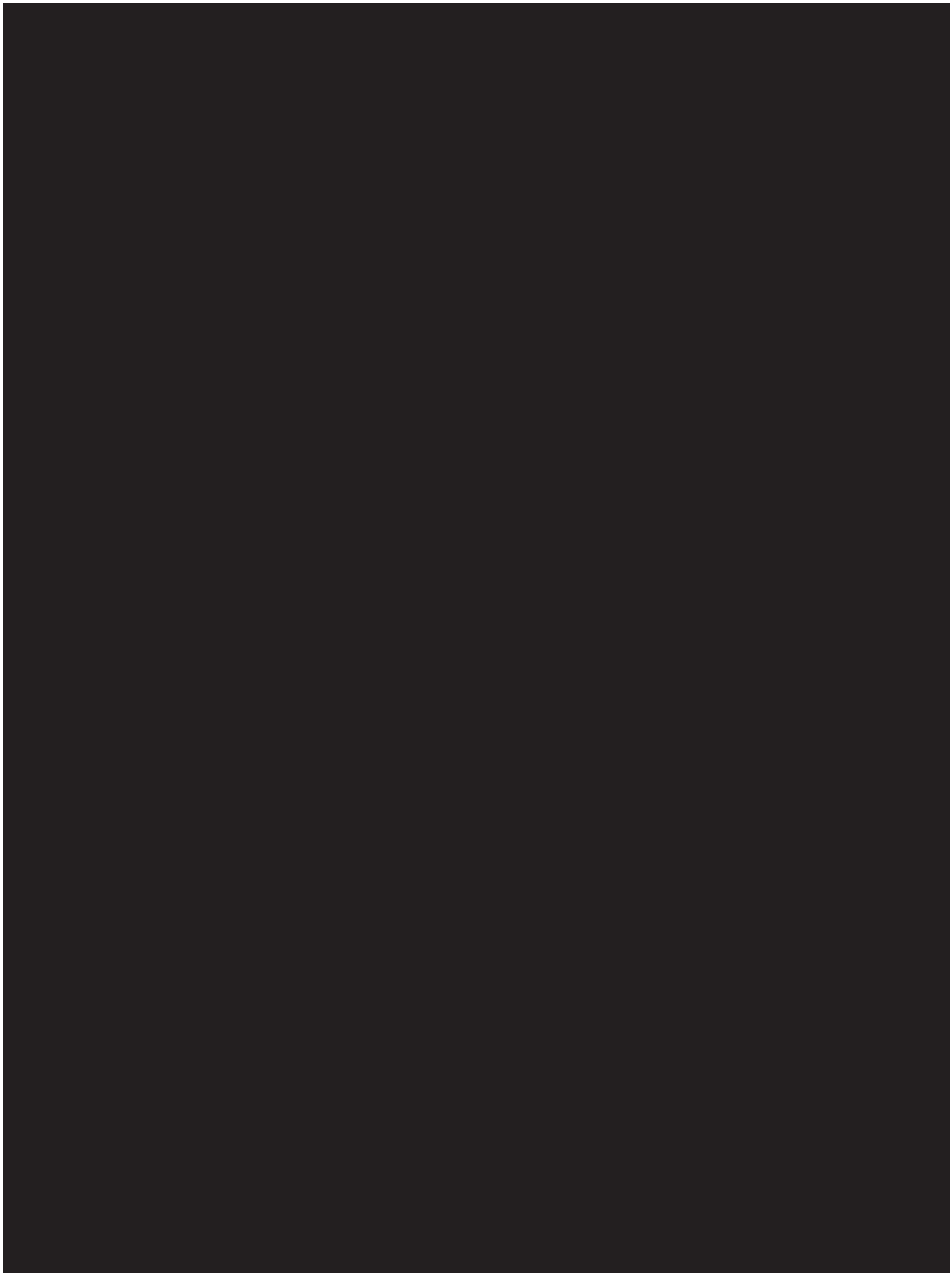
**DINAMO™**

- Change in fasting plasma glucose (FPG) [mg/dl] from baseline to the end of 26 weeks
- Change in body weight [kg] from baseline to the end of 26 weeks
- Change in systolic blood pressure (SBP) [mmHg] from baseline to the end of 26 weeks
- Change in diastolic blood pressure (DBP) [mmHg] from baseline to the end of 26 weeks
- Proportion of patients who achieve HbA1c < 6.5% at the end of 26 weeks
- Proportion of patients who achieve HbA1c < 7.0% at the end of 26 weeks

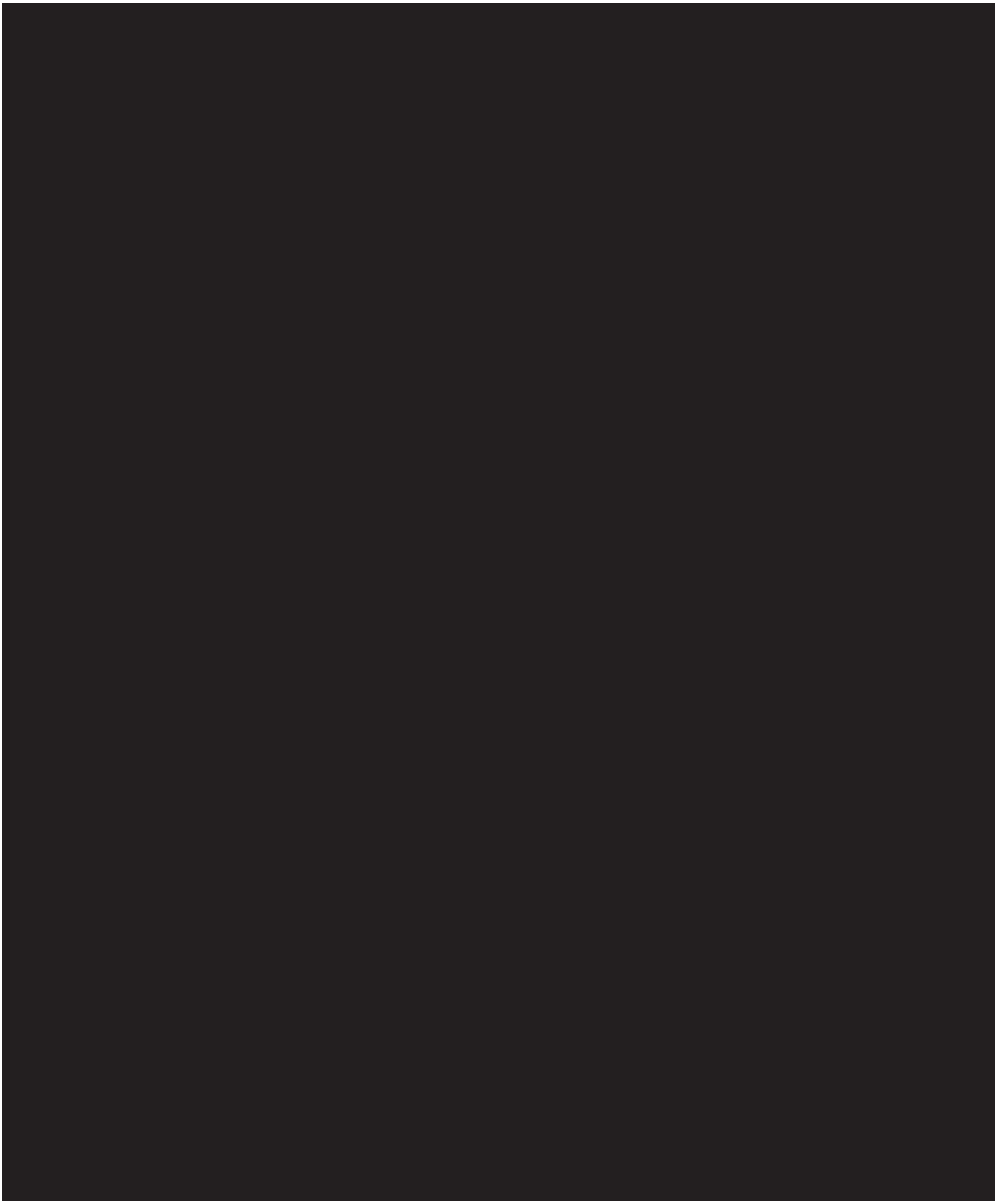
**DINAMO Mono**

- Time to treatment failure
    - Time to treatment failure is the first of the following criteria:
        - Time to first use of rescue medication
        - Time to first increase from baseline in HbA1c by at least 0.5% in absolute value, or
        - Time to first increase from baseline in HbA1c to above 7.0% in patients with baseline HbA1c < 7.0%, or
        - Time to premature discontinuation of treatment
- Change in HbA1c [%] from baseline to the end of 26 weeks
- Change in FPG [mg/dl] from baseline to the end of 26 weeks
- Change in body weight [kg] from baseline to the end of 26 weeks
- Change in SBP [mmHg] from baseline to the end of 26 weeks
- Change in DBP [mmHg] from baseline to the end of 26 weeks
- Proportion of patients who achieve HbA1c < 6.5% at the end of 26 weeks
- Proportion of patients who achieve HbA1c < 7.0% at the end of 26 weeks

For baseline definitions for each endpoint, refer to Section 6.7.



## 5.4 OTHER VARIABLES



[redacted]

### 5.4.4 Safety data

The SBP and DBP will be derived for use in the statistical analysis as the mean of all available SBP and DBP readings, respectively, at the same visit.

Standard adverse event attributes (seriousness, intensity, relationship of AEs, AEs leading to study medication discontinuation), laboratory endpoints, vital signs and BMI z-score will be analysed.

For the full definition of safety endpoints, refer to CTP Section 5.3.

[redacted]

# 6 GENERAL ANALYSIS DEFINITION

## 6.1 TREATMENTS

There will be five analysis phases: screening, placebo run-in, double-blind study treatment phase, post-treatment and post-study, as follows:

- Screening period: Starts from the date of informed consent and ends on the day before the start date of the placebo run-in period (inclusive).
- Placebo run-in period: From the date of first administration of placebo run-in medication up to the first administration of the initial randomised study medication.
- On-treatment period: From the date (and time, if measured) of first administration of the initial randomised study medication up to last administration of study medication plus X days (inclusive). See definition of X in Table 6.7: 1.
- Post-treatment period: From the date of last administration of study medication plus X+1 days up to the last contact date (inclusive). The last contact date is defined as the latest of the following dates (last contact date from end-of-study eCRF page, the last administration of study medication date from end-of-treatment eCRF page, the last visit date). If the last contact date is prior to the date of last administration of study medication plus X+1 days the post-treatment period will not be defined.
- Post-study period: From the last contact date plus 1 day and ends at study database lock date for the corresponding study (i.e. DINAMO or DINAMO Mono).

Both safety and efficacy analyses will follow the intention-to-treat principle in assigning patients to treatment groups, i.e. patients will be analysed in the treatment group to which they were randomised. In addition, AEs with an onset during the time of any incorrect study treatment intake will be listed separately.

The following treatment groupings will be used for the efficacy and safety analyses:

**Treatment grouping 1 (TG1) for Placebo controlled period from Day 1 to Week 26:**

- *Placebo (**Pbo**)*
- *Linagliptin 5 mg (**L5**)*
- *Empagliflozin pooled (**E Pooled**)*, consisting of
    - Empagliflozin 10 mg responders at Week 12 to 10 mg (E10R-10)
    - Empagliflozin 10 mg non-responders at Week 12 to 10 mg (E10NR-10)
    - Empagliflozin 10 mg non-responders at Week 12 to 25 mg (E10NR-25)
    - Empagliflozin 10 mg and not proceed to re-randomisation at Week 14 (E10)

**Treatment grouping 2 (TG2) for Empagliflozin 25 mg titration period from Day 1 to Week 26:**

- *Placebo (**Pbo**)*
- *Empagliflozin titration start with 10 mg and increased dose at re-randomisation if needed (**E Titr25**)*, consisting of
    - Empagliflozin 10 mg responders at Week 12 to 10 mg (E10R-10)
    - Empagliflozin 10 mg non-responders at Week 12 to 25 mg (E10NR-25)
    - Empagliflozin 10 mg and not proceed to re-randomisation at Week 14 (E10)

**Treatment grouping 3 (TG3) for Empagliflozin 10 mg titration period from Day 1 to Week 26:**

- *Placebo (**Pbo**)*
- *Empagliflozin titration start with 10 mg and dose remained at re-randomisation if needed (**E Titr10**)*, consisting of
    - Empagliflozin 10 mg responders at Week 12 to 10 mg (E10R-10)
    - Empagliflozin 10 mg non-responders at Week 12 to 10 mg (E10NR-10)
    - Empagliflozin 10 mg and not proceed to re-randomisation at Week 14 (E10)

**Treatment grouping 4 (TG4) for the period following the administration of the re-randomised medication planned at Week 14 up to Week 26/Week 52:**

- *Empagliflozin 10 mg after initial Empagliflozin 10 mg non-response (**E10NR/10***)*
- *Empagliflozin 25 mg after initial Empagliflozin 10 mg non-response (**E10NR/25***)*

**Treatment grouping 5 (TG5) for long term analysis period from Day 1 to Week 52:**

- *Linagliptin 5 mg (**L5**)*
- *Empagliflozin pooled (**E Pooled**)*, consisting of
    - Empagliflozin 10 mg responders at Week 12 to 10 mg (E10R-10)
    - Empagliflozin 10 mg non-responders at Week 12 to 10 mg (E10NR-10)
    - Empagliflozin 10 mg non-responders at Week 12 to 25 mg (E10NR-25)
    - Empagliflozin 10 mg and not proceed to re-randomisation at Week 14 (E10)

**Treatment grouping 6 (TG6) for active treatment period:**

- *Linagliptin 5 mg active pooled (**L5 active**)*, consisting of
  - Linagliptin 5 mg from the initial randomisation (L5)
  - Linagliptin 5 mg after initial placebo (P/L5*)
- *Empagliflozin active pooled (**E active**)*, consisting of
  - Empagliflozin 10 mg responders at Week 12 to 10 mg (E10R-10)
  - Empagliflozin 10 mg non-responders at Week 12 to 10 mg (E10NR-10)
  - Empagliflozin 10 mg non-responders at Week 12 to 25 mg (E10NR-25)
  - Empagliflozin 10 mg and not proceed to re-randomisation at Week 14 (E10)
  - Empagliflozin 10 mg after initial placebo (P/E10*)
  - Empagliflozin 25 mg after initial placebo (P/E25*)

**Treatment grouping 7 (TG7) for the period following the administration of the re-randomised medication planned at Week 26 up to Week 52:**

- *Linagliptin 5 mg after initial placebo (**P/L5***)*
- *Empagliflozin 10 mg after initial placebo (**P/E10***)*
- *Empagliflozin 25 mg after initial placebo (**P/E25***)*

**Treatment grouping 8 (TG8) for result disclosure from Day 1 to Week 52:**

- *Placebo and not proceed to re-randomisation at Week 26 (**Pbo**)*
- *Placebo to empagliflozin 10 mg at Week 26 (**P-E10**)*
- *Placebo to empagliflozin 25 mg at Week 26 (**P-E25**)*
- *Placebo to linagliptin 5 mg at Week 26 (**P-L5**)*
- *Linagliptin 5 mg (**L5**)*
- *Empagliflozin 10 mg (**E10**)* consisting of
  - Empagliflozin 10 mg responders at Week 12 to 10 mg (E10R-10)
  - Empagliflozin 10 mg non-responders at Week 12 to 10 mg (E10NR-10)
  - Empagliflozin 10 mg and not proceed to re-randomisation at Week 14 (E10)
- *Empagliflozin 10 mg non-responders at Week 12 to 25 mg (**E10NR-25**)*

**Treatment grouping 9 (TG9) for AE result disclosure from Day 1 to Week 52:**

- *Placebo before re-randomisation at Week 26 (**Pbo**)*
- *Linagliptin 5 mg active pooled (**L5 active**)*, consisting of
  - Linagliptin 5 mg from the initial randomisation (L5)
  - Linagliptin 5 mg after initial placebo (P/L5*)
- *Empagliflozin 10 mg active pooled (**E10 active**)*, consisting of
  - Empagliflozin 10 mg and not proceed to re-randomisation at Week 14 (E10)
  - Empagliflozin 10 mg responders at Week 12 to 10 mg (E10R-10)
  - Empagliflozin 10 mg non-responders at Week 12 to 10 mg (E10NR-10)
  - Empagliflozin 10 mg non-responders at Week 12 before re-randomisation to 25 mg (E10NR*/25)
  - Empagliflozin 10 mg after initial placebo (P/E10*)

- *Empagliflozin 25 mg active pooled (**E25 active**)*, consisting of
    - Empagliflozin 25 mg after initial Empagliflozin 10 mg non-response (E10NR/25*)
    - Empagliflozin 25 mg after initial placebo (P/E25*)

The treatment grouping TGx will be used according to the type of analysis, that has been assigned for each analysis throughout the TSAP. The treatment (or a combination of treatments) with the solid bullet point will be used in the analyses and the outputs presentation will use the short name as shown in bold in brackets. Each combination of treatments is defined by a list of treatments identifying the type and timing of the treatment. As a first example, the treatment identifier "E10R-10" means the patient was initially assigned to empagliflozin 10 mg and then carried on to empagliflozin 10 mg as a responder at Week 12, the entire treatment period is included. As a second example, the treatment identifier "E10NR/25*" means the patient was initially assigned to empagliflozin 10 mg and then carried on to empagliflozin 25 mg as a non-responder at Week 12, but only the re-randomised treatment period from Week 14 is included.

## 6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is important if it affects the rights or safety of the study patients, or if it can potentially influence the primary outcome measurement for the respective patients in a way that is neither negligible nor in accordance with the study objectives. The specification and handling of PDs that are determined to be important will be documented in 4-12-01-sdtm-dv-domain-specification located in BIRDS. Not all important PDs will generate exclusion from an analysis population set. The specifications will indicate which important PDs will lead to an exclusion.

The specification document will also list the PDs that have been manually evaluated and determined to be important, and confirmed at the final report planning meeting.

The impact of COVID-19 on important PDs and other COVID-19 related PDs will be also captured.

## 6.3 PATIENT SETS ANALYSED

Screened set (SCR):
This patient set includes all patients screened for the trial, with informed consent given.

Randomised set (RS):
This patient set includes all patients from the screened set who were randomised to study drug, regardless of whether any study drug was taken.

Treated set (TS):
This patient set includes all patients who are treated with at least one dose of randomised study medication. The TS is the basis for safety analyses.

Treated set active (TSactive):
The TSactive is defined as all patients treated with at least one dose of active randomised study medication (linagliptin or empagliflozin) at any time in the study.

Modified Intention-to-Treat Set (mITT):
This patient set includes all randomised patients who are treated with at least one dose of study medication and have a baseline HbA1c measurement. The mITT is the basis for the primary analyses.

Per protocol set (PPS):
This patient set includes all patients in the mITT set who do not have any important PD which can be expected to have a distorting influence on the assessment of the primary endpoint. As the DINAMO primary endpoint is analysed after 26 weeks of study treatment, important PDs related to efficacy that occur after the assessment of the DINAMO primary endpoint measurement will not lead to exclusion from analysis sets. See Section 6.2 for details.

PK parameter analysis set (PKS):
The pharmacokinetic set consists of all treated patients who have at least one evaluable PK plasma concentration measurement.

Table 6.3: 1 Patient sets analysed and treatment groupings

| | **Patient sets** | | | | | |
|---|---|---|---|---|---|---|
| **Class of endpoint** | **SCR** | **TS** | **TSactive** | **RS** | **mITT** | **PPS** |
| Disposition | OR (TG1) | OR (TG4, TG7) | OR (TG6) | OR[1] (TG8) | | |
| Definition of analysis sets | | | (TG6) | (TG1) | | |
| Important protocol deviations | | | | (TG1) | | |
| Demographics | | OR (TG1) | | OR[1] (TG8) | | |
| Baseline efficacy variables | | OR (TG1) | | | | |
| Background antidiabetic therapy at baseline | | OR (TG1) | | | | |
| Antidiabetic medication newly introduced on treatment | | OR (TG1, TG5) | | | | |
| Relevant medical history | | OR (TG1) | | | | |
| Exposure to study medication | | OR (TG1) | OR (TG6) | | | |
| Compliance data by visit | | OR (TG1) | OR (TG6) | | | |

Table 6.3: 1 Patient sets analysed and treatment groupings (continued)

| | Patient sets | | | | | |
|---|---|---|---|---|---|---|
| **Class of endpoint** | **SCR** | **TS** | **TSactive** | **RS** | **mITT** | **PPS** |
| **DINAMO - Primary efficacy endpoint** | | | | | | |
| Primary family of hypothesis - HbA1c [%] CFB - ANCOVA analysis - washout approach | | | | | OC-AD (TG1) | |
| Secondary family of hypothesis - HbA1c [%] CFB - ANCOVA analysis - washout and inverse probability weighting approach | | | | | OC-AD (TG2, TG3) | |
| [redacted] | | | | | | |
| **DINAMO Mono - Primary efficacy endpoint** | | | | | | |
| Occurrence of treatment failure up to or at Week 26 (DINAMO Mono patients only) | | | | | NCF (TG1) | |
| [redacted] | | | | | | |

Table 6.3: 1 Patient sets analysed and treatment groupings (continued)

| | Patient sets | | | | | |
|---|---|---|---|---|---|---|
| **Class of endpoint** | **SCR** | **TS** | **TSactive** | **RS** | **mITT** | **PPS** |
| **Secondary efficacy endpoints** | | | | | | |
| Change in FPG [mg/dl] from baseline - ANCOVA | | | | | OC-AD-BOCF; OC (TG1) | |
| Change in body weight [kg] / SBP [mmHg] / DBP [mmHg] from baseline – MMRM | | | | | OC-AD; OC (TG1) | |
| Proportion of patients who achieve HbA1c goals < 6.5% and < 7.0%. Exact CI | | | | | NCF; OC (TG1) | |

[redacted]

Table 6.3: 1 Patient sets analysed and treatment groupings (continued)

| | Patient sets | | | | | |
|---|---|---|---|---|---|---|
| **Class of endpoint** | **SCR** | **TS** | **TSactive** | **RS** | **mITT** | **PPS** |
| **Further safety endpoints** | | | | | | |
| Shift tables for the Tanner staging score from baseline | | OC-AD (TG1, TG5) | | | | |
| Descriptive statistics over time for growth velocity | | OC-AD (TG1, TG5) | | | | |
| **Safety evaluation** | | | | | | |
| Overall summary of AEs | | TG1, TG5, TG4 | TG6 | | | |
| Freq. of patients with the following AEs by treatment, SOC and PT<br>• AEs<br>• AEs by worst intensity<br>• Drug-related AEs<br>• AEs leading to treatment discontinuation<br>• SAEs<br>• Other significant adverse events<br>• AESIs(except DKA and lower limb amputation) | | TG1, TG5, TG4 | TG6 | | | |
| Incidence rate of patients with AEs by treatment, SOC and PT | | TG1, TG5 | | | | |
| List of patients with AESIs/other significant AE<br>• DKA<br>• Events involving lower limb amputation<br>• Bone fracture | | TS | | | | |
| Freq. of patients with other specific AE by treatment, SOC and PT:<br>• Hypoglycaemic AE<br>• UTI (also investigator assessment, serious and leading to treatment discontinuation)<br>• Genital infection (also investigator assessment, serious and leading to treatment discontinuation)<br>• Acute pyelonephritis or urosepsis<br>• Volume depletion<br>• Ketone measurements | | TG1, TG4 | TG6 | | | |

Table 6.3: 1 Patient sets analysed and treatment groupings (continued)

| | Patient sets | | | | | |
|---|---|---|---|---|---|---|
| **Class of endpoint** | **SCR** | **TS** | **TSactive** | **RS** | **mITT** | **PPS** |
| Freq. of patients with other specific AE by treatment, SOC and PT:<br>• Arthralgia<br>• Pemphigoid in bullous conditions) | | TG1 | TG6 | | | |
| Freq. of patients by characteristics of hypoglycaemia<br>• reported AE<br>• any hypoglycaemia<br><br>Freq. of patients with symptomatic hypoglycaemia AE with plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemia AE by age at randomisation in categories.<br><br>Number of any hypoglycaemia – time at risk | | TG1, TG4 | TG6 | | | |
| Freq. of patients with the following events (investigator assessment) by characteristics of events<br>• UTI<br>• Genital infection<br>• Acute pyelonephritis or urosepsis<br><br>Freq. of patients with genital infection (investigator assessment) by type of the genital infection | | TG1, TG4 | TG6 | | | |
| Freq. of patients with CEC adjudicated events | | TG1 | TG6 | | | |
| Freq. of patients with the following AEs by SOC and PT<br>• AEs<br>• AEs by outcome<br>• SAEs<br>• Drug-related SAEs | | TG1 | TG6 | | | |
| Freq. of patients with AEs by treatment, SOC and PT<br>• Non-serious AE with an incidence in preferred term greater than 5%<br>• SAE | | TG9[1] | | | | |

Table 6.3: 1 Patient sets analysed and treatment groupings (continued)

| | Patient sets | | | | | |
|---|---|---|---|---|---|---|
| **Class of endpoint** | **SCR** | **TS** | **TSactive** | **RS** | **mITT** | **PPS** |
| AEs per treatment arm (including number of patients exposed, affected by SAEs, affected by non-serious AEs with incidence > 5% in any treatment arm for each PT, number of death of all causes, number of deaths resulting from AEs). | | TG9[1] | | | | |
| Non-serious AEs with incidence > 5% in any treatment arm for each preferred term (including number of patients affected, exposed, total occurrences.) | | TG9[1] | | | | |
| SAEs on PT (including number of patients affected, exposed, number of occurrences, occurrences causality related, fatalities, fatalities causally related to treatment.) | | TG9[1] | | | | |
| **Clinical laboratory evaluation** | | | | | | |
| Descriptive statistics of laboratory values at baseline, last value on-treatment, and change from baseline to last value on-treatment (normalised value) and over time<br><br>Freq. of patients within and outside the reference range at baseline and last value on treatment.<br><br>Freq. of patients of categorical laboratory parameters at baseline and last value on-treatment | | TG1, TG5 | | | | |
| Freq. of patients with possibly clinical significant abnormality (PCSA) | | TG1, TG5, TG4 | TG6 | | | |
| Freq. of patients with elevated liver enzymes | | TG1, TG5 | TG6 | | | |

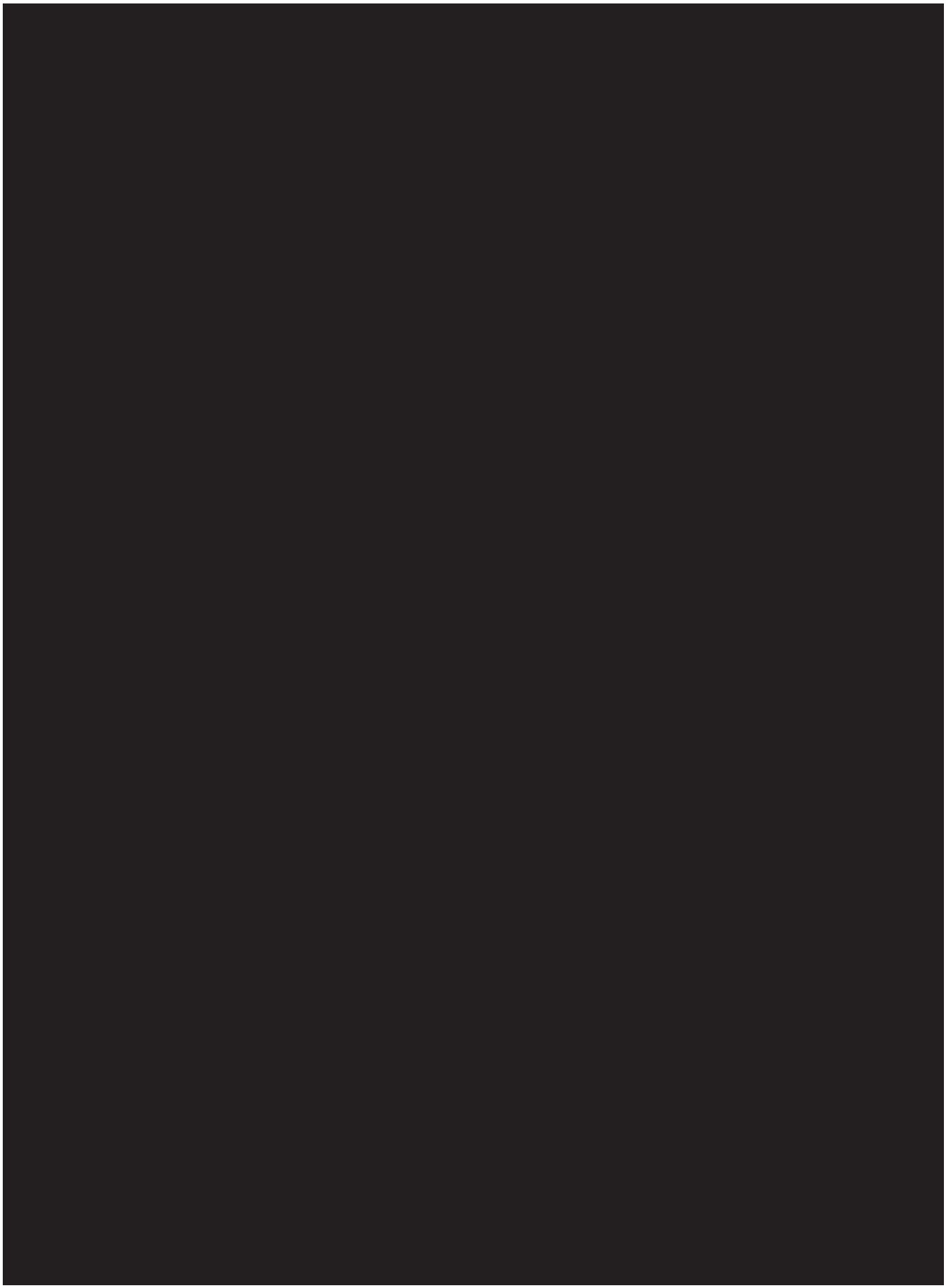
Table 6.3: 1 Patient sets analysed and treatment groupings (continued)

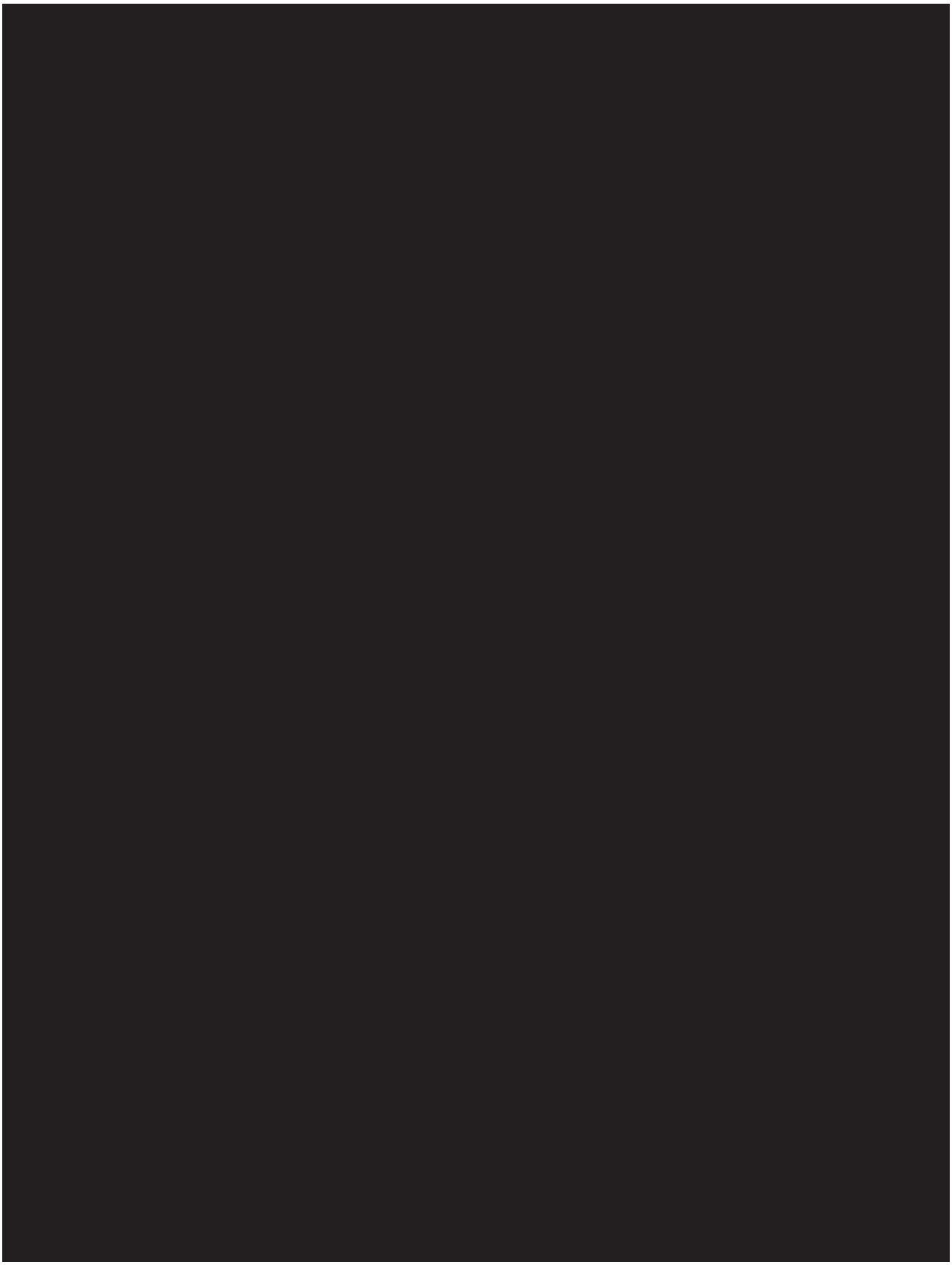
| | Patient sets | | | | | |
|---|---|---|---|---|---|---|
| **Class of endpoint** | **SCR** | **TS** | **TSactive** | **RS** | **mITT** | **PPS** |
| Descriptive statistics over time<br>• Lipid parameters<br>• Renal parameters<br>• Vital signs<br><br>Freq. of patients with increase of serum creatinine shows a >= 2 fold increase from baseline and serum creatinine > upper limit normal | | (OC-ROC)<br>TG1, TG5 | | | | |
| Change from baseline over time - MMRM<br>• Lipid parameters | | (OC-ROC)<br>TG1 | | | | |
| Shift in renal function category from baseline to last and minimum value on treatment | | TG1 | | | | |
| Descriptive statistics<br>• Biomarkers | | (OC-ROC)<br>TG1, TG5<br>(except<br>DPP-4) | | | | |

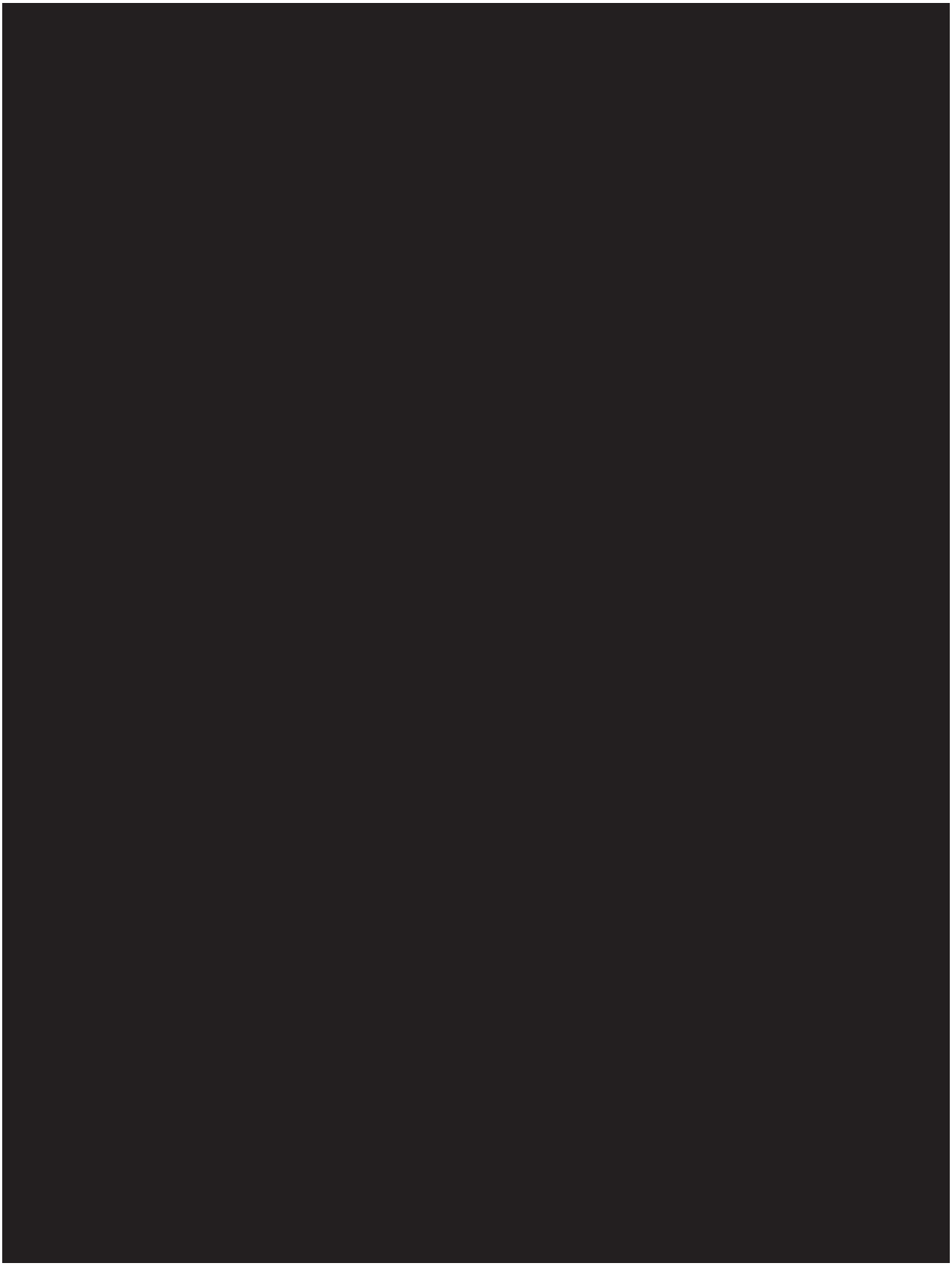
SCR=screened set, RS=randomised set, mITT=modified intention-to treat set, PPS=per protocol set, TS=treated set, TSactive=treated set active; patient sets are defined in Section 6.3
OR=original results, OC=observed cases, OC-AD=observed cases-all data, OC-AD-BOCF=observed cases-all data and baseline observation carry forward, OC-ROC=observed cases-rescue observed cases, NCF=Non-completers considered failures. Handling of missing data is described in Section 6.6. CFB: change from baseline, ANCOVA= Analysis of covariance, SMQ= Standardised MedDRA query, MMRM= Mixed model for repeated measures, HLGT, HLT= High level term, CEC= Clinical event committee
1 Present once at the end of the trial combining both DINAMO and DINAMO Mono data.

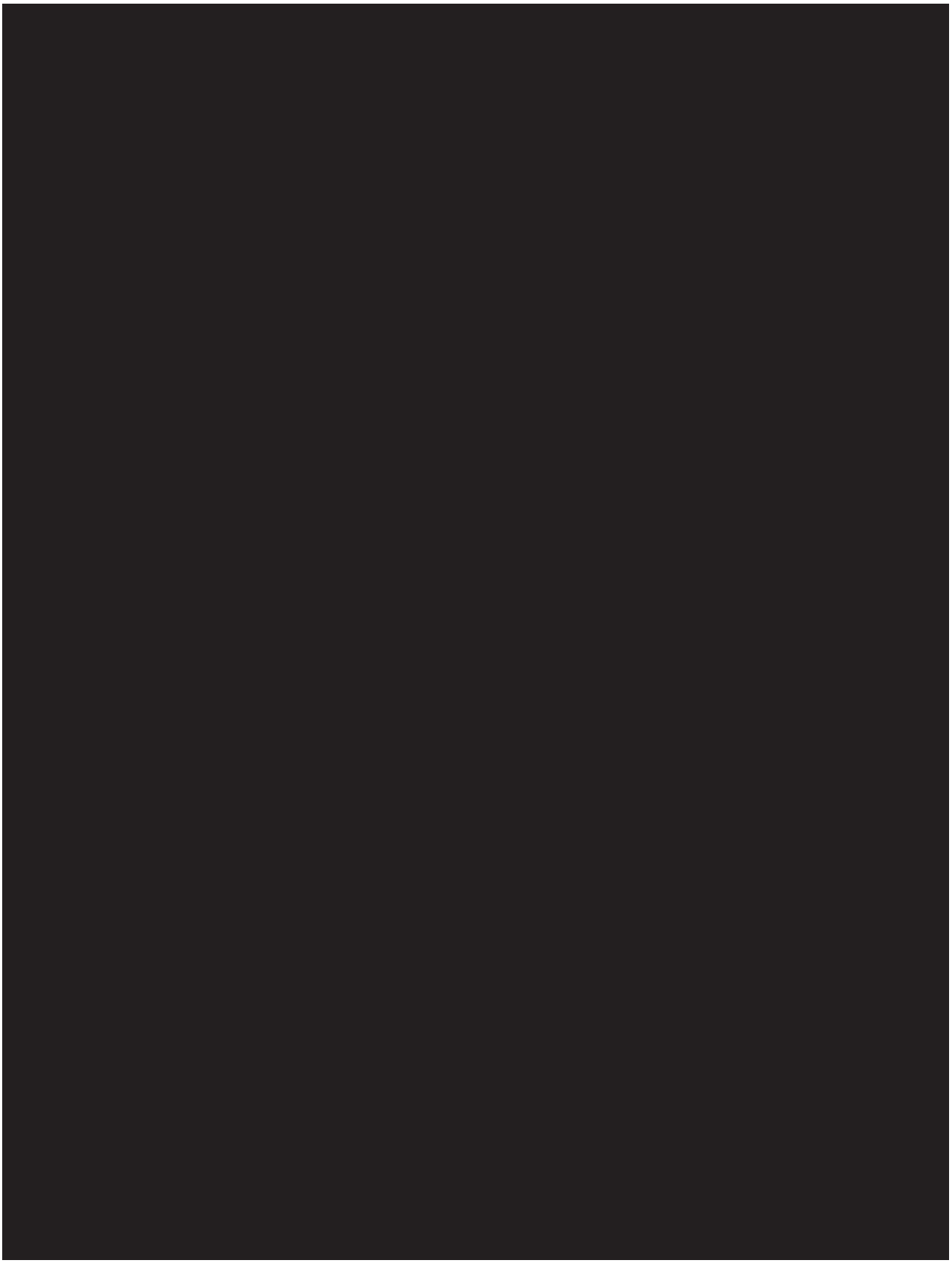
Table 6.3: 2 Patient sets analysed and treatment groupings for COVID-19 related outputs

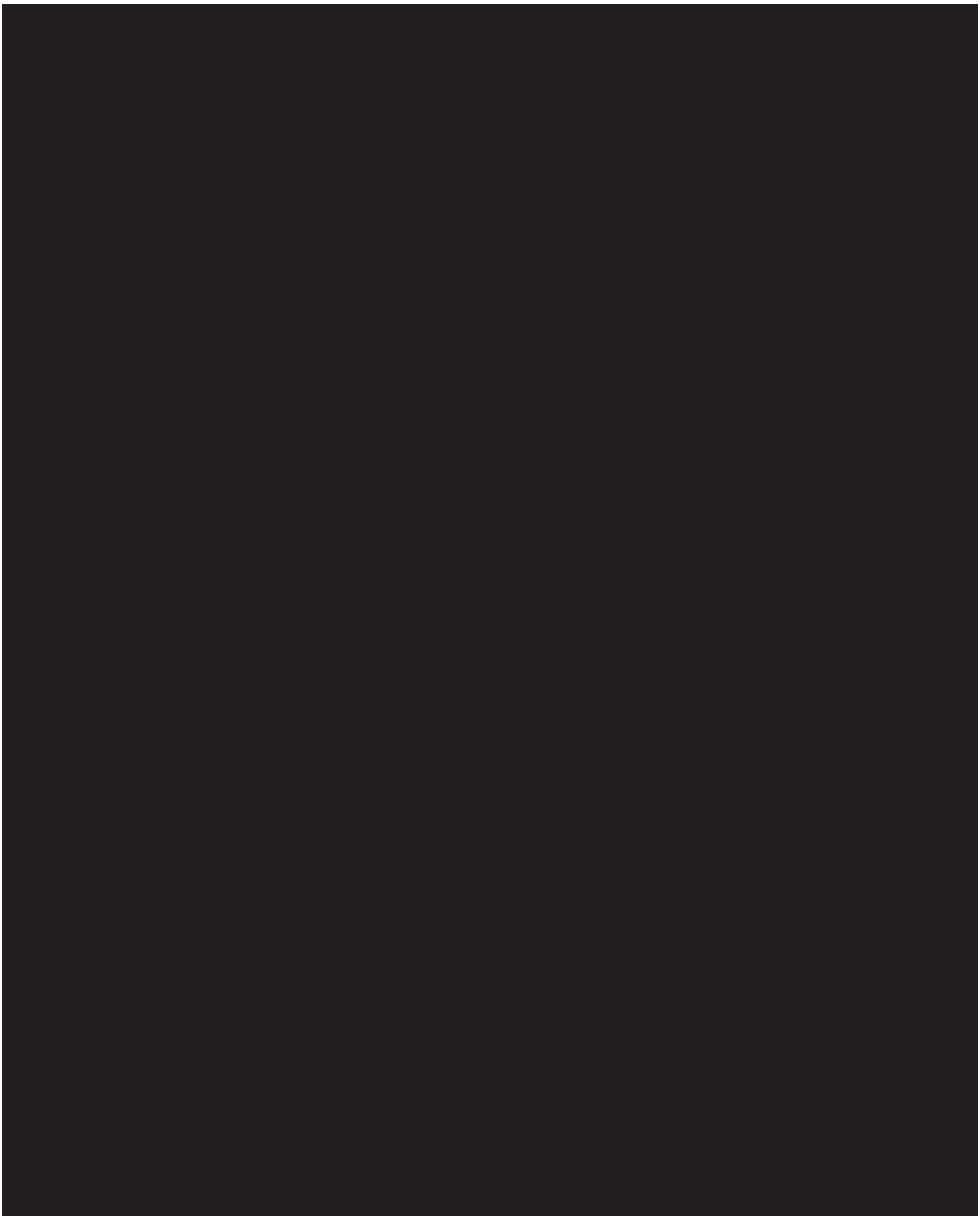
| | **Patient sets** | | | | | |
|---|---|---|---|---|---|---|
| **Class of endpoint** | **SCR** | **TS** | **TSactive** | **RS** | **mITT** | **PPS** |
| Premature discontinuation of trial medication or study | OR (TG1) | | | | | |
| Patient screened and study conduct | OR (TOTAL) | | | | | |
| Protocol deviations | | | | (TG1) | | |
| Demographic data | | OR (TG1) | | | | |
| Baseline efficacy variables | | OR (TG1) | | | | |
| Exposure to study medication | | OR (TG1) | OR (TG6) | | | |
| Compliance data by visit | | OR (TG1) | OR (TG6) | | | |
| Compliance with study medication by visit | | OR (TOTAL) | | | | |
| Freq. of patients and rate of treatment interruptions | | (TG1) | | | | |
| Summary of patients who completed, altered or missed HbA1c sampling at Week 26 visit | | | | | OR (TG1) | |
| Primary family of hypothesis - HbA1c (%) CFB - ANCOVA analysis-multiple imputation with washout approach using a specific COVID-19 imputation | | | | | OC-AD (TG1) | |
| Freq. of patients with COVID-19 intercurrent events | | | | | OC-AD (TG1) | |
| Freq. of patients and rate of AEs before and from the start of COVID-19 disruption | | TG1 | TG6 | | | |
| Sub-population: SARS-CoV-2 infected patients<br>• Overall summary of AEs<br>• Freq. of patients with AEs<br>• Freq. of patients with AEs leading to treatment discontinuation<br>• Freq. of patients with SAEs. | | TG1 | TG6 | | | |











## 6.5 POOLING OF CENTRES

There is no analysis planned by centre due to the small number of patients to be recruited per centre.

## 6.6 HANDLING OF MISSING DATA AND OUTLIERS

Based on the different reasons of patients' data missing for different endpoints, various methods will be used to assess the impact of missing data on the efficacy endpoints of this trial, depending upon the type of the endpoint.

### 6.6.1 Methods of data selection

Original results (OR) analysis
Original result analysis implies the analysis of data exactly as observed. OR analysis will be performed on endpoints where it is not meaningful to apply any imputation rule on them for replacing missing values.

Observed cases (OC) analysis
OC analyses only use the available data that were observed while patients were on-treatment. Any values collected after treatment discontinuation and any values collected after the start of rescue medication will be set to missing.

Observed cases – Rescue observed cases (OC-ROC) analysis

Only the available data that were observed while patients were on-treatment will be considered. Any values taken after rescue medication intake will be kept. Any values collected after treatment discontinuation will be set to missing.

Observed cases – Last observation carry forward (OC-LOCF) analysis
Based on the OC data, the post-baseline missing values, post-treatment values and values after rescue medication will be imputed by the last on-treatment observation without rescue medication carried forward. In case, there is no on-treatment observation without rescue medication, baseline value will be carried forward.

Observed cases - all data (OC-AD) analysis
All available data that were observed are considered. Any values taken after the start of rescue medication and any on- and post-treatment values will be kept.

Observed cases - all data and baseline observation carry forward (OC-AD-BOCF) analysis
Based on the OC-AD data, baseline observation will be carried forward to impute the missing data.

Non-completers considered failure (NCF)
For binary endpoints, like the occurrence of a response, a conservative method to replace missing values is to consider them as "failures". Post-treatment values will be set to missing. Missing data due to early discontinuation of treatment and values after the start of rescue

medication will be replaced as "failure" (e.g. non-responder) up to the planned time point for the analysis.
For binary endpoints that are derived from quantitative endpoints (e.g. HbA1c) missing on-treatment data at the planned time point for the analysis will be replaced by NCF.

### 6.6.2 Imputation methods

A multiple imputations (MI) approach will be considered to impute missing data. Multiple imputation approaches taken are specified in Section 7 within the planned analyses.

Missing safety data will not be replaced.

### 6.6.3 Missing dates and times

Missing or incomplete AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”) (3).

Missing data and outliers of PK data are handled according to (2).

If the date of first drug administration is missing but the patient was randomised, the date of the first drug administration will be set to the date of randomisation. If the date of first administration is partially missing with the month and year present, the day will be set to the date of randomisation if randomisation was in the same month. If randomisation was in the month prior to the first drug administration the missing day will be imputed as the first day of the month.

A missing time of first drug administration will be imputed as 08:00 o'clock in the morning, missing administration times at on-treatment visits will be imputed by 08:00 o'clock in the morning.

The earliest of the listed dates will be picked to impute the missing or incomplete drug stop date:

- Date of End of Treatment (EOT) visit (either premature treatment discontinue visit date or Visit 8 / EOT)
- Last contact date recorded in the EOS page
- Date of death
- Imputation of partial last date of study medication (imputed as last day of the month if only day is missing / last day of year if only year is provided)

For partial start and stop dates for concomitant therapies the following derivations will be used to impute 'worst case' values:

- If the day of the end date is missing then the end date is set to last day of the month.
- If the day and month of the end date are missing then end date is set to 31st December of the year.
- If the day of the start date is missing the start date is set to first day of the month.

- If the day and month of the start date are missing then the start date is set to 1st January of the year.

For other incomplete date information (except to assess the overall compliance, see below) always the midpoint of the possible interval will be used. If only the year is present the day and month will be imputed as 01 July, if year and month is present the day will be imputed as 15. If the year is missing, the date will be considered missing.

All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

### 6.6.4 Missing and incomplete laboratory reference ranges

Incomplete (one-sided) laboratory reference ranges are imputed according to BI standards (see "Handling of incomplete reference ranges") (14).

In case of serum N-terminal cross-linked telopeptide (NTx), central lab reference range was not included in the data transfer as it was based on the Tanner stage score. The Tanner stage score was unknown to the central lab. This missing central lab reference range will be incorporated in the Analysis Data Model (ADaM) dataset based on the Tanner stage score according to the central lab reference ranges (15).

## 6.7 BASELINE, TIME WINDOW, AND CALCULATED VISITS

The term "baseline" refers to the following definitions according to the individual analysis period.

- *Study baseline:* Last observed measurement prior to administration of any initially randomised study medication at Day 1.
- *Titration baseline:* Last observed measurement prior to administration of the re-randomised study medication for the initial empagliflozin patients at Week 14. If last observed measurement is after rescue medication then there is no titration baseline for OC analysis.
- *Safety extension baseline:* Last observed measurement prior to administration of the re-randomised study medication for the initial placebo patients at Week 26.

Note: On or prior to date of randomisation will be used, instead of prior to date of drug administration, for randomised patients who have not taken any blinded study drug.

Both date and time of administration of the randomised study medication are expected to be recorded at Day 1, Week 14 and Week 26. In the determination of baseline for a parameter, if the parameter of interest:

- is collected with date and time: both date and time are used in the calculation of 'last observed measurement prior to administration'. If the dates and times are equal, the parameter will be determined to be prior to administration.

- is collected with only date: the dates are equal, the parameter will be determined to be prior to administration.

The exception to this rule, is HbA1c, whereby even though time of sample is collected, it will be handled as if it was collected only with date.

Measurements taken after the first intake of randomised study drug will be considered on-treatment values if they have been obtained up to the end of the endpoint specific follow-up period as defined in Table 6.7: 1.

Table 6.7: 1 Endpoint specific follow-up period for the assignment to treatment phase

| **Endpoint** | **Last day of assignment to treatment phase (days after study drug stop date)** |
|---|---|
| *Efficacy* | |
| HbA1c | 7 |
| FPG | 1 |
| Body weight | 1 |
| BMI z-score | 1 |
| Blood pressure (systolic, diastolic) | 1 |
| UACR | 7 |
| *Safety* | |
| Adverse events | 7 |
| AESI Hepatic injury [1] | 30 |
| AESI Lower limb amputation | End of study |
| Safety laboratory measurements | 7 |
| AST/ALT/TBILI [2] | 30 |
| Pulse rate | 1 |
| C-peptide | 1 |
| Tanner staging | 1 |

[1] Refers to a specific safety analysis including all hepatic injuries with an onset date up to 30 days after the study treatment stop.
[2] Refers to a specific safety analysis on elevated liver enzymes, for which events with an onset date up to 30 days after the study treatment stop will be included in the analysis. See Section 7.8.2.2.

Measurements taken after the last intake of study drug and
end of the endpoint specific follow-up period will be considered post-treatment values. In efficacy analyses, the words off-treatment and post-treatment are used synonymously.

Efficacy and safety measurements will be assigned to visits based on time windows around the planned visit dates. These time windows are defined based on the planned number of days after the date of first administration of study drug (see Table 6.7: 2).

Table 6.7: 2 Time windows for efficacy and safety measurements at scheduled visits after randomisation

| Visit number | Visit label | Planned days on treatment | Planned days after randomisation | Time window (actual days on treatment) | |
|---|---|---|---|---|---|
| | | | | Start | End[A] |
| 2 | Baseline | 1 | 0[C] | NA | 1[B] |
| 3 | Week 4 | 29 | 28 | 2 | 56 |
| 4A | Week 12 | 85 | 84 | 57 | 91 |
| 4B | Week 14 | 99 | 98 | 92 | 140[B] |
| 5 | Week 26 | 183 | 182 | 141 | Max(Day 141, Visit 5 drug intake date, Min(Day 210, Visit 6 date – 1 day)) |
| 6 | Week 30 | 211 | 210 | Max(Day 141, Visit 5 drug intake date, Min(Day 210, Visit 6 date – 1 day)) + 1 day | 225 |
| 7 | Week 42 | 295 | 294 | 226 | 329 |
| 8 | Week 52 / EoT | 365 | 364 | 330 | Study drug stop date + X days |

[A] In case of premature discontinuation of the study drug an early EoT visit has to be performed. Measurements from the early EoT visit will be assigned to the appropriate visit according to the table. Patients will then be asked to continue in the study according to the visit schedule. Post-treatment measurements will be assigned to visits in the same manner.

[B] Only values taken prior to the start of treatment at Day 1, Week 14 and Week 26, with randomised study drug can be considered study baseline, titration baseline and safety extension baseline accordingly. Time windows will be used for assignment of measurements to scheduled visits.

[C] Reference day (day 0) is day of randomisation

The mid-point between two visits defines the end of a time window, with the midpoint being included in the time window of the preceding visit. The end of the time window of the last on-treatment visit (EoT) is endpoint dependent (cf. Table 6.7: 1). As endpoints are planned to be measured according to different visit schedules, this midpoint algorithm will be applied and the time windows modified accordingly.

Only one observation per time window will be selected for analysis. If there are multiple values within a time-window, the value closest to the CTP planned visit day will be selected. 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 earliest value will be used. 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. For the Week 26 primary analysis, this is applicable if study drug is stopped during the time window of the Week 26 visit.

In addition to the HbA1c values, both National Glycohemoglobin Standardization Program (NGSP) certified and non-NGSP certified HbA1c values, will be used in HbA1c endpoints analyses, given that they are in the same unit. The order of preference for the laboratory values are: (1) NGSP certified central laboratory values, (2) NGSP certified local laboratory values and (3) non-NGSP certified local laboratory values. If a visit window includes a NGSP certified local laboratory value as well as a non-NGSP certified local laboratory value (either both being on- or post-treatment), then the NGSP certified value will be selected rather than the non-NGSP certified value. For study baseline, if none of these preference HbA1c values are available at Visit 2, then Screening data will be used.

For standard descriptive tables of laboratory parameters by visit, in case of multiple measurements within a post-baseline time window for a visit, the worst value of these multiple measurements will be used for calculations.

# 7 PLANNED ANALYSES

Disposition of the patient population participating in the trial, the overall disposition information and the disposition status will be analysed by treatment grouping 1 and 6 separately. Disposition of the patients after re-randomisation of the initial placebo group will be analysed by TG7 and after re-randomisation of the initial empagliflozin group will be analysed by TG4. They will be presented in the clinical trial report as a frequency-distribution.

The number of patients participating (screened, randomised, treated, and prematurely discontinued treatment) in the study by region and country will also be analysed and presented as a frequency distribution. The primary reason for patients failing screening will also be summarised. See Table 9.1: 1 for assignment of countries within region.

In addition, the following analyses will be done for public data disclosure on European Union Drug Regulating Authorities Clinical Trials (EudraCT) and display in Appendix 16.1.13 for both DINAMO and DINAMO Mono together.

- Disposition of patients, including number of patients who discontinued trial medication due to fatal and non-fatal adverse events, by TG8 based on RS
- Number of screened patients by country based on SCR
- Number of screened patients by age (at time of informed consent) groups (Children (2-11 years), Adolescents (12-17 years)) based on SCR

A summary of the number of patients in each randomisation stratum per treatment for each of the 3 randomisations (i.e. Day 1, Week 14 and Week 26) will also be shown. These summaries will be based upon the data received from the IRT provider.

An IPD table will be presented including all CTP deviations leading to exclusion from analysis set (PPS, mITT, TS and/or TSactive) and an additional IPD table will be created to summarise all the IPDs not leading to exclusion from an analysis set using treatment grouping 1 based on RS.

For in-text tables presenting descriptive analysis of the endpoints and other variables, the set of summary statistics is: N (number of patients with non-missing values), mean, standard deviation (SD).

For End-Of-Text tables, the set of summary statistics is: N (number of patients with non-missing values) / Mean / SD / standard error (SE) / Min / Q1 (lower quartile)/ Median / Q3 (upper quartile)/ Max.

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline “Reporting of Clinical Trials and Project Summaries” (4). Figures will be added if deemed necessary.

HbA1c and FPG in conventional unit will be analysed in Appendix 15.2 and SI unit will be analysed in Appendix 16.1.13.1. All analyses of laboratory parameters with SI unit will be analysed in Appendix 15 and the analyses of laboratory parameters with conventional unit will be analysed in Appendix 16.1.13.1.

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.

The following analyses will be performed to assess the impact of COVID-19.

- Premature discontinuation of trial medication or study due to COVID-19 disruption, by TG1 on SCR
- Patients screened and study conduct (assessed HbA1c at Week 26 (regardless on or post-treatment), last intake of study medication, completed study participation) relative to start of COVID-19 disruption by before and from start of COVID-19 disruption on SCR
- Number of patients with protocol deviations associated with COVID-19 disruption, by TG1 on RS
- Listing of patients with COVID-19 related study disruption on SCR

All described outputs, except result disclosure outputs, will be presented separately for DINAMO and DINAMO mono.

All result disclosure outputs will be presented in the final reporting only at the same time as DINAMO Mono reporting.

## 7.1 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

### 7.1.1 Baseline evaluation

Descriptive analysis of the following demographic variables measured at study baseline will be presented:

Sex, race, ethnicity, region, age [years] at informed consent (continuous), age [years] at randomisation (categories), BMI [kg/m$^2$] (continuous and categories), BMI z-score (continuous and categories), height [cm], height z-score, smoking history, time since diagnosis of diabetes [years] (categories), eGFR [mL/min/1.73m$^2$] (Zappitelli) (continuous and categories) and Tanner stages.

See Section 7.8.2.4 for details on the derivation of eGFR endpoints.

Descriptive analysis of the following variables measured at study baseline will be presented:

HbA1c [%] (continuous and categories), FPG [mg/dL] (continuous and categories), FPG [mmol/L] (continuous and categories), weight [kg] (continuous and categories), blood pressure [mmHg] (categories), fasting C-peptide [nmol/L], UACR [mg/g crea] (continuous and categories).

Categories for baseline characteristics are defined in Table 6.4: 1.

Demographic and baseline characteristics tables will be presented using the TS by treatment grouping 1.

The demographic analysis will be repeated on the randomised set by TG8 in Appendix 16.1.13 for disclosure on EudraCT for both DINAMO and DINAMO Mono together.

The following analyses will be performed to assess the impact of COVID-19 for DINAMO only.

- Demographic data by patients randomised before and from the start of COVID-19 disruption, by TG1 based on TS
- Baseline efficacy variables by patients randomised before and from the start of COVID-19 disruption, by TG1 based on TS

## 7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report using the TS and TSactive accordingly.

Concomitant therapy use will be summarised by Anatomical-Therapeutic-Chemical classification level 3 (ATC3) and preferred name. Only therapies under their available ATC3 code(s) will be presented. Summaries will be presented for concomitant therapies taken during randomised treatment which are newly initiated (i.e. new preferred name) during the dedicated randomised treatment period and those taken at baseline (i.e. on day 1) of the dedicated randomised treatment period.

The summary on concomitant therapies during randomised treatment will be presented up to Week 26 by treatment grouping 1 and Week 52 by treatment grouping 6.

Separate summary of use of antihypertensives, ASA, or lipid lowering drugs at baseline will be presented by TG1 and during randomised treatment will be presented up to Week 26 by treatment grouping 1 and Week 52 by treatment grouping 6. The displayed categories and defining ATC levels and ATC codes are shown in Section 9.2.

Concomitant diagnoses and non-drug therapies at any time of the study will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and preferred term (PT). Relevant diabetic medical history will also be presented by treatment grouping 1.

Background antidiabetic treatment at baseline (i.e. on day 1) will be summarised for the DINAMO patients only by treatment grouping 1 presenting number of background antidiabetic treatments (0, 1, 2), background antidiabetic treatment (metformin only, insulin only, metformin and insulin, none (diet and exercise only, metformin not tolerated)), metformin total daily dose [mg] (continuous and categories), and basal insulin total daily dose [IU/day].

Antidiabetic medication newly introduced on treatment will be presented up to Week 26 by treatment grouping 1 and Week 52 by treatment grouping 5. The increase dose of insulin during the on-treatment period is not included in this presentation for the DINAMO patients but it will be presented in the "initiate glycaemic rescue therapy" further efficacy endpoint. The antidiabetic medication newly introduced on treatment will be regarded as rescue medication for the DINAMO Mono patients.

## 7.3 TREATMENT COMPLIANCE

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

Descriptive summary of compliance [%] and frequency distribution of patients with compliance [%] in categories (< 75, 75 to 125, > 125, incalculable (i.e. Not collectable compliance with reason for missing compliance)) will be reported by visit and treatment grouping 1 and 6 using TS and TSactive. Post-treatment period will not be included in the compliance analysis. In case of premature discontinuation of treatment up to Week 26 for the TG1 summary table, premature discontinuation visit or Visit 8/End of treatment compliance will be presented together as 'PTD prior to Week 26'. For up to Week 52 TG6 summary table, all end of treatment visits including premature discontinuation of treatment will be presented together as 'Visit 8/EOT'.

The following analyses will be provided to assess the impact of COVID-19 for DINAMO only.

- Compliance data over time up to Week 26 by visit and permanent discontinuation of study medication or/and completion of Week 26 visit before/from the start of COVID-19 disruption, by TG1 on TS.
- Compliance data over time up to Week 52 by visit and permanent discontinuation of study medication before and from the start of COVID-19 disruption, by TG6 on TSactive.
- Compliance with study medication before and from the start of COVID-19 disruption by visit on TS
- Frequency of patients and rate of treatment interruptions up to Week 26 before and from the start of COVID-19 disruption by TG1 on TS. The time at risk is the entire treatment duration. The time at risk for the period before start of COVID-19 disruption is defined as first dose of treatment until either the day before COVID-19 start date or treatment end date (whichever comes earlier). The time at risk for the

period from start of COVID-19 disruption is defined as COVID-19 start date or treatment start date (whichever comes later) until treatment end date. Treatment interruptions which started during the defined period will be counted toward that specific defined period.

## 7.4 PRIMARY ENDPOINTS

### 7.4.1 DINAMO

The primary endpoint in this trial is the change in HbA1c [%] from baseline to the end of 26 weeks.

#### 7.4.1.1 Primary family of analyses

The primary family of null hypotheses will be tested using alpha level of 5% (two-sided):

For empagliflozin, the following null hypothesis will be tested:

$H_{0,1}$: Mean change in HbA1c [%] from baseline to the end of 26 weeks in the pooled empagliflozin groups
= Mean change in HbA1c [%] from baseline to the end of 26 weeks in the placebo group

For linagliptin, the following null hypothesis will be tested:

$H_{0,2}$: Mean change in HbA1c [%] from baseline to the end of 26 weeks in the linagliptin 5 mg group
= Mean change in HbA1c [%] from baseline to the end of 26 weeks in the placebo group

These confirmatory primary analyses will be performed using an effectiveness “wash-out” approach based on the mITT (OC-AD) set with multiplicity adjustment for simultaneous testing of linagliptin and empagliflozin using the Hochberg procedure by treatment grouping 1. Patients will be assigned to the treatment they were randomised to at the initial randomisation. All randomised treatment groups will be included in the same analysis. The seed used in the DINAMO confirmatory analyses will be 1218009101.

HbA1c values measured after premature discontinuation of study drug or after rescue therapy was initiated will be included in the analyses. All available on- and off-treatment data up to the Week 26 time point will be included.

There will be different types of missing data to be considered for the imputation.

Table 7.4.1.1: 1 "Wash-out" approach – the missing data imputation method

**Randomised treatment group: Placebo**

Missing HbA1c data will be imputed for all scheduled visits up to Week 26, that includes Week 4, Week 12 and Week 26.

| Type of missing data | Data used for imputation | Method to use for | |
|---|---|---|---|
| | | Non-monotone missing data | Monotone missing data |
| On- and off-treatment data | Observed on- and off-treatment HbA1c data in the placebo group, including Baseline, Week 4, Week 12 and Week 26. | MCMC-MI[1] (MAR[3]) | SLR-MI[2] (MAR[3]) |

**Randomised treatment groups: Linagliptin 5 mg and empagliflozin pooled**

Missing HbA1c data will be imputed for Week 26 only.

| Type of missing data | Data used for imputation | Method |
|---|---|---|
| On-treatment data | Observed on-treatment HbA1c data in the respective treatment group, including only Baseline and Week 26. | SLR-MI[2] (MAR[3]) |
| Off-treatment[5] data | Observed on- and off-treatment[5] HbA1c data in the placebo group, including only Baseline and Week 26. | SLR-MI[2] (MNAR[4]) |

[1] Markov Chain Monte Carlo – Multiple imputation (MCMC-MI)
[2] Sequential linear regression – Multiple imputation (SLR-MI)
[3] Missing at random (MAR)
[4] Missing not at random (MNAR)
[5] Missing post-treatment data after permanent treatment discontinuation

**Method of imputation**

For the placebo group, missing HbA1c data, regardless on- or off-treatment, will be imputed for all scheduled visits up to Week 26.

* The non-monotone missing data will be imputed using Markov Chain Monte Carlo (MCMC) simulation and standard techniques; MI will be performed on a data set including on- and off-treatment HbA1c data in the placebo group at baseline, Week 4, Week 12 and Week 26 with baseline HbA1c as a continuous covariate and age at randomisation as binary covariate corresponding to its class categorisation levels (age <15 years or age ≥15 to <18 years). 500 imputations will be performed to ensure adequate efficiency and stability of the estimation for missing data. This step will be referred to as 'MCMC-MI'.

* For the monotone missing data in the placebo group, a sequential linear regression MI approach will be used and referred to as 'SLR-MI'. The MI will be performed on a data set

including on- and off-treatment data and once per imputation from the previous step. This procedure will impute values for all missing time points both on- and off-treatment. The regression models will be fitted with baseline HbA1c as a continuous covariate and age at randomisation as a binary covariate (age <15 years or age ≥15 to <18 years). 500 imputations for the placebo group will be completed.

For the active treatment groups (linagliptin 5 mg and empagliflozin pooled, regardless of the dose level), missing HbA1c data will be imputed for Week 26 only separately for missing on-treatment data and missing off-treatment data.

* To impute the missing on-treatment data at Week 26, the MI will be performed on a data set including only patients who were on active treatment at Week 26, using the baseline and Week 26 (both missing and non-missing values). The regression models will be fitted separately by active treatment group with baseline HbA1c as a continuous covariate and age at randomisation as a binary covariate (age <15 years or age ≥15 to <18 years). 500 imputations for missing on-treatment data in each active treatment group will be completed.

* To impute the missing off-treatment data at Week 26, the MI will be performed on a data set including the baseline of the active treated patients with missing off-treatment HbA1c data at Week 26, and the placebo patients with baseline and the original (i.e. not imputed) on- and off-treatment HbA1c data from Week 26. The regression models will be fitted separately by active treatment group with baseline HbA1c as a continuous covariate and age at randomisation as a binary covariate (age <15 years or age ≥15 to <18 years). 500 imputations for missing off-treatment data in each active treatment group will be completed.

The effectiveness analyses will be performed on these imputed data sets plus the observed HbA1c data at Week 26 using an ANCOVA model with baseline HbA1c as a continuous model term, and with categorical terms for treatment and age at randomisation. Rubin's rules will be used to combine treatment estimates across the 500 complete imputations.

The implicit assumption underlying the imputations and analyses is that unobserved off-treatment patient measurements will lose any treatment effect immediately off-treatment discontinuation in the active treatment groups.

The least square mean differences of the active treatments to placebo, confidence intervals and p-values of change in HbA1c from baseline to the end of 26 weeks will be displayed via forest plots for the primary (primary family of hypotheses) and corresponding sensitivity analyses, refer to Section 7.4.1.3, separately for linagliptin and empagliflozin pooled.

A more technical description of the method can be found in Section 9.4.

#### 7.4.1.2 Secondary family of analyses

After having obtained statistically significant results for both hypotheses $H_{0,1}$ and $H_{0,2}$ of the primary family of hypotheses in the effectiveness "wash-out" approach analysis , the following two hypotheses will be tested in a hierarchical order at significance level $\alpha=0.05$ (two-sided) for the comparison of empagliflozin versus placebo:

$H'_{0,1}$: Mean change in HbA1c [%] from baseline to the end of 26 weeks in regimen starting on empagliflozin 10 mg and either having a dose increase to empagliflozin 25 mg in patients who were non-responders (i.e. patients that did not achieve HbA1c < 7.0%) at Week 12, or who were responders (i.e. patients that did achieve HbA1c < 7.0%) at Week 12 and continue with empagliflozin 10 mg
= Mean change in HbA1c [%] from baseline to the end of 26 weeks in the placebo group.

followed by:

$H'_{0,2}$: Mean change in HbA1c [%] from baseline to the end of 26 weeks in regimen starting on empagliflozin 10 mg and either were responders or were non-responders at Week 12, and continue with empagliflozin 10 mg
= Mean change in HbA1c [%] from baseline to the end of 26 weeks in the placebo group.

The hypotheses $H'_{0,1}$ (by treatment grouping 2) will be tested first and if this hypothesis can be rejected at the significance level $\alpha = 0.05$, the hypotheses $H'_{0,2}$ (by treatment grouping 3) will be tested at the same level. The empagliflozin 10 mg patients who did not proceed to re-randomisation at Week 14 will also be included in the analysis.

In using two sets of hypotheses families in a hierarchical order and using all hypotheses in the primary family as a gatekeeper for the secondary family, the experiment wise Type I error rate across both families is controlled by the significance level $\alpha = 0.05$.

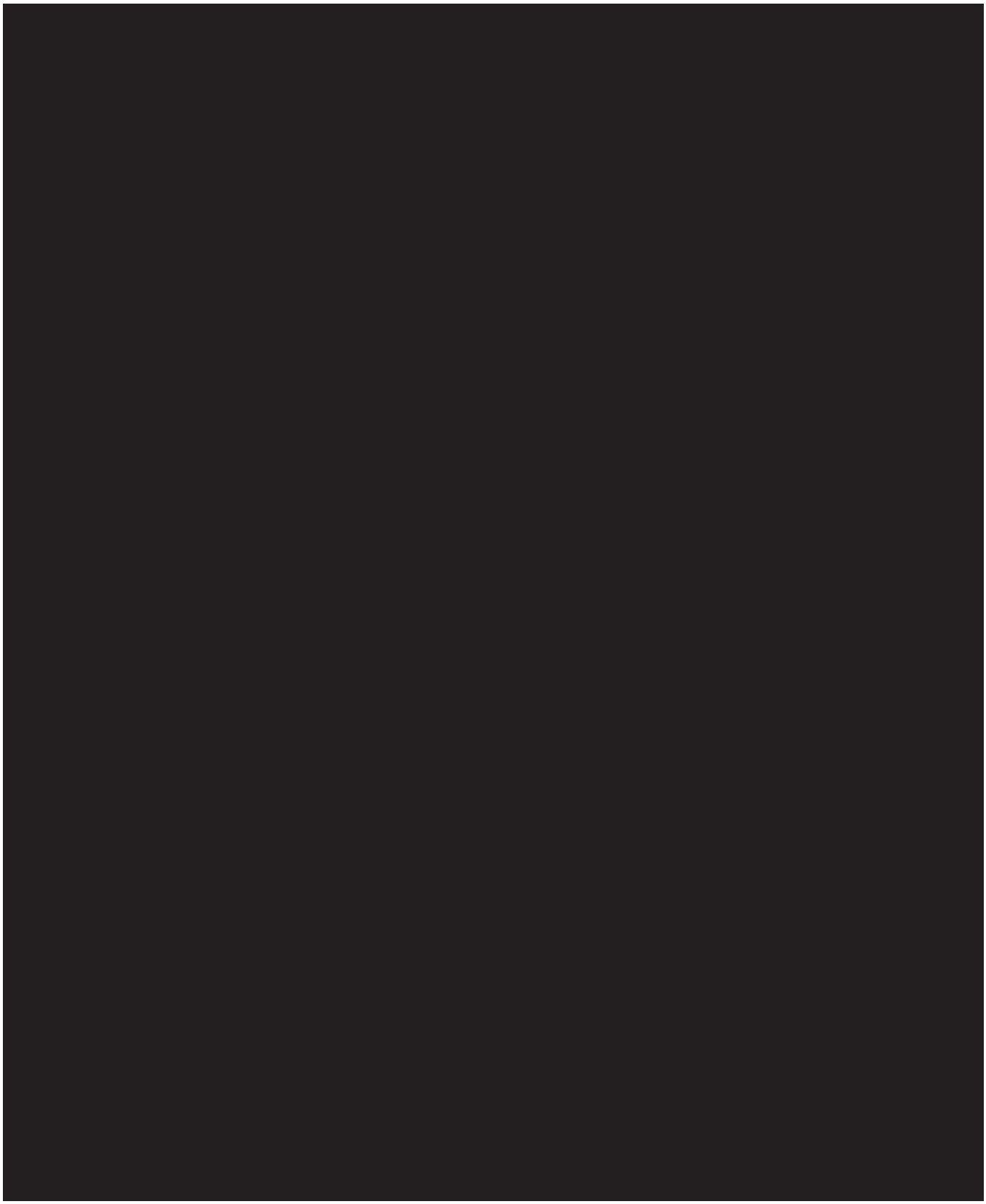
These secondary family of hypotheses for the primary endpoint will be tested using the "wash-out" approach described in Section 7.4.1.1 but the ANCOVA used for analysis of the completely imputed set will apply an "inverse probability weighting" approach based on the mITT (OC-AD) set.

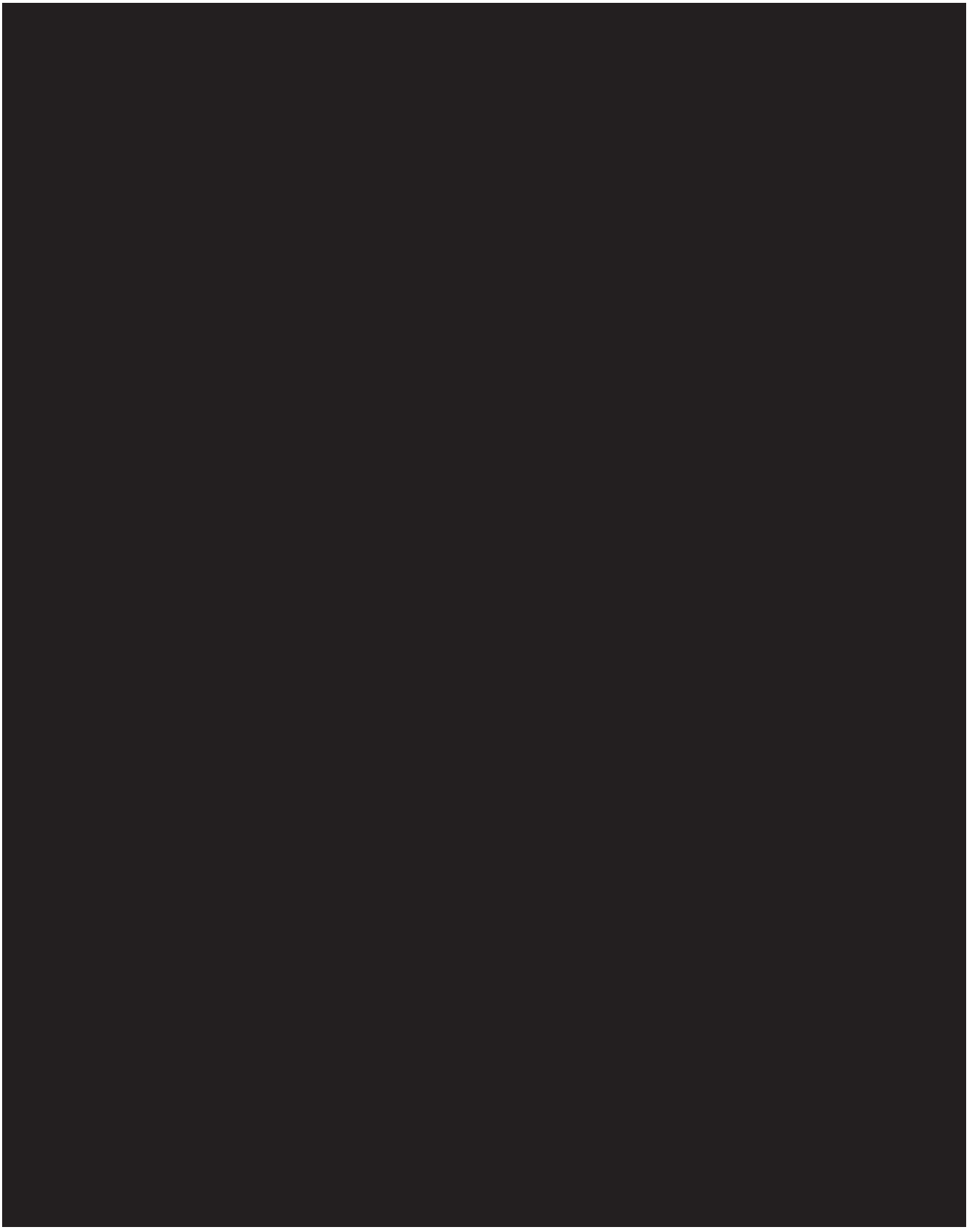
The ANCOVA models will utilise a weight having a value of 0 for the patients who are not in the hypothesis test of interest; a value of 2 for re-randomised patients who are in the hypothesis test of interest and a value of 1 otherwise. The model terms will include baseline HbA1c as a continuous variable, and treatment and age at randomisation as categorical variables. Rubin's rules will be used to combine treatment estimates across the 500 imputations.

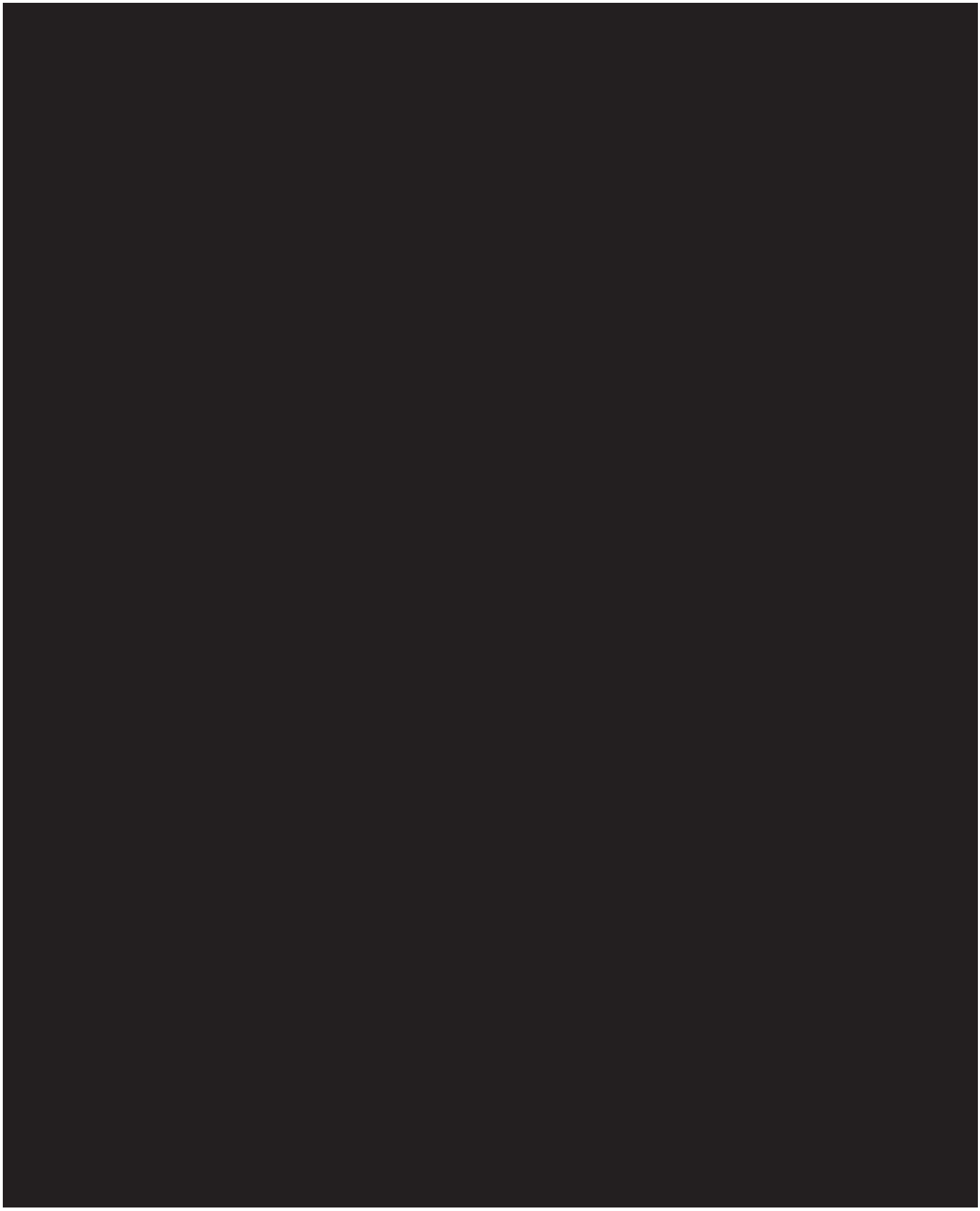
Patients will be assigned to the treatment they were randomised to at the initial randomisation together with the treatment allocation at Week 14 randomisation. HbA1c values measured after premature discontinuation of study drug or after rescue therapy was initiated will be included in the analyses. Patients discontinued from the randomised study medication prior to Week 15 will also be included in the analysis.

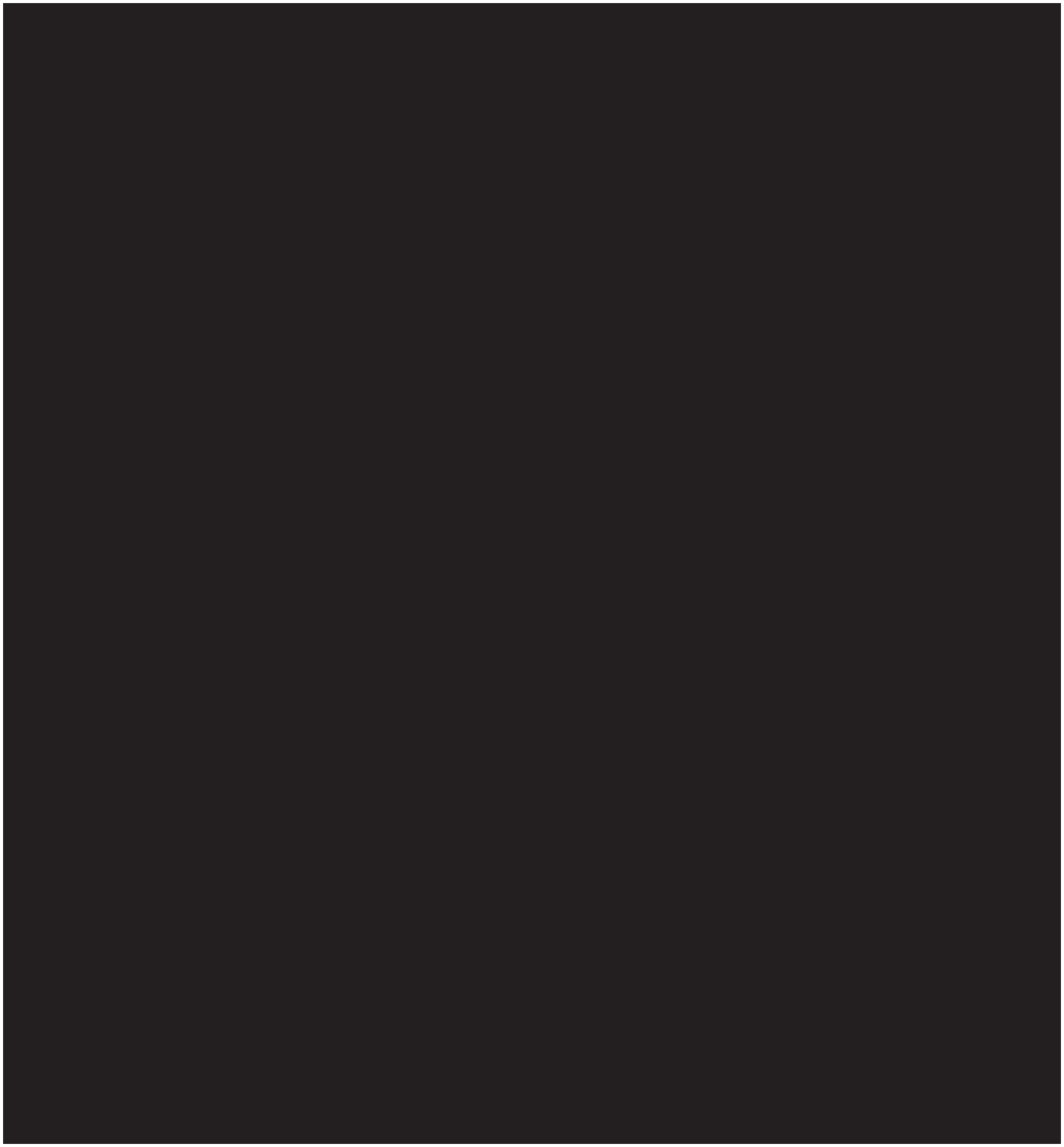
The least square mean differences for each of the empagliflozin doses versus placebo, confidence intervals and p-values of change in HbA1c from baseline to the end of 26 weeks

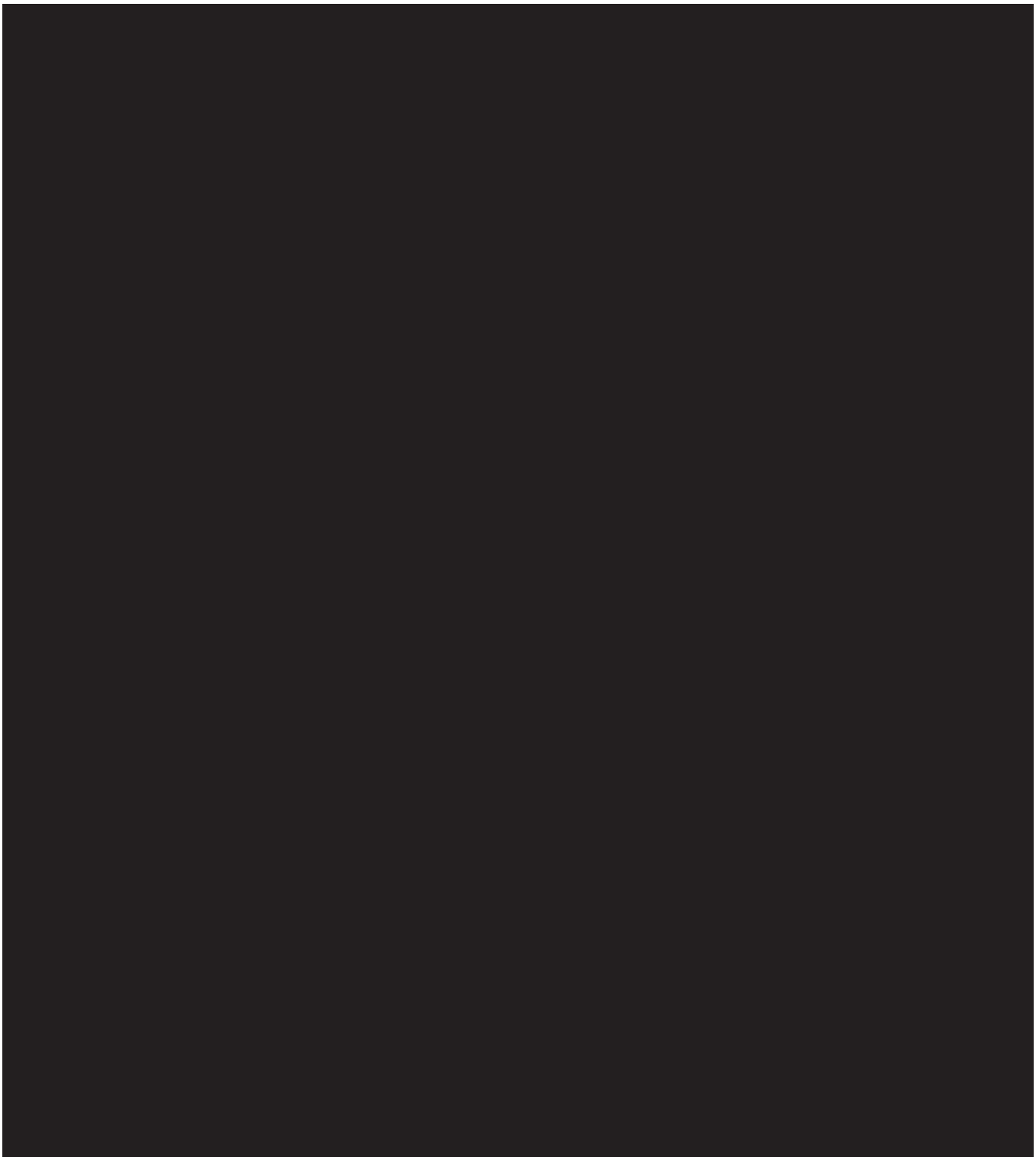
will be displayed via forest plots for the analyses of the secondary family of hypotheses and corresponding sensitivity analyses, refer to Section 7.4.1.3, separately for TG2 and TG3.











7.4.1.4 Effect of centre

There is no analysis planned by centre due to the small number of patients to be recruited per centre.

### 7.4.2 DINAMO Mono

The primary analysis will be a comparison of the treatment failure rates of linagliptin 5 mg, empagliflozin pooled and placebo (i.e. treatment grouping 1) using mITT set (NCF). The risk difference of active treatments versus placebo will be determined and assessed by an exact 2-sided 90% confidence interval based on the method of Chan and Zhang (12). Patients will be assigned to the treatment they were randomised to at the initial randomisation. Non-completers who prematurely discontinue intake of study drug will be considered treatment failures.

[redacted]

### 7.4.3 HbA1c data summary

An overall summary for the availability of HbA1c [%] data at Week 26 will be presented by TG1 on mITT (OC-AD) set showing captured and missing Week 26 data and further classified as on- and off-treatment and within these categories further sub-classified as 'without prior rescue' and 'with prior rescue'.

Frequency of patients who completed, altered or missed the HbA1c [%] measurement at Week 26 will be tabulated by TG1 on mITT set to assess the impact of COVID-19.

## 7.5 SECONDARY ENDPOINTS

### 7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the CTP.

### 7.5.2 (Other) Secondary endpoint(s)

7.5.2.1 DINAMO

For the DINAMO secondary endpoints, the patients initially randomised to empagliflozin (empagliflozin 10 mg and empagliflozin 25 mg pooled) and linagliptin 5 mg will be compared versus placebo (i.e. treatment grouping 1). Analyses will be performed on the mITT set and will apply two approaches.

The *first approach* will use all observed data including data after premature discontinuation of study drug or post rescue medication data up to Week 26 (OC-AD).

Since FPG [mg/dL] is measured only at baseline and Week 26 within the analysis period, OC-AD-BOCF will be considered instead of OC-AD. The change in FPG [mg/dL] from baseline to the end of 26 weeks will be analysed using an ANCOVA model. This analysis will be repeated for FPG [mmol/L] in Appendix 16.1.13.

The statistical model will be:

Change in FPG [mg/dL] from baseline to the end of 26 weeks
= overall mean + treatment + baseline FPG + categorical age at randomisation + random error

Treatment is a fixed classification effect. Baseline FPG is a linear covariate and age at randomisation a categorical covariate. The random error is assumed to be normally distributed with mean 0 and unknown variance $\sigma^2$.

The other continuous secondary endpoints will be analysed based on a REML approach using MMRM. The analyses will include the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous, fixed covariates of baseline of the response variable and baseline of the response variable-by-visit interaction. The covariate visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. The residuals are assumed to have a multivariate normal distribution with zero means and covariance matrix as specified above.

Descriptive statistics up to the end of 26 weeks of FPG [mg/dL], weight [kg], SBP [mmHg] and DBP [mmHg] will be summarised by treatment grouping 1 and subgroup. See Table 6.4:1 for the subgroups.

The proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 weeks will be determined per treatment grouping 1 using mITT (NCF) set and the risk difference of active treatments versus placebo will be determined and assessed by an exact 2-sided 95% confidence interval.

The *second approach* will include only on-treatment values measured prior to the start of any rescue medication up to Week 26 (OC).

The change in FPG [mg/dL] from baseline to the end of 26 weeks will be analysed using the ANCOVA model, which is described in the first approach, but using the second approach data.

For the other continuous secondary endpoints analyses, values measured after rescue therapy was initiated or after premature discontinuation of study drug will be set to missing. The missing data will not be imputed. The MMRM model will handle missing data based on a likelihood method under the "missing at random" assumption.

The proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 weeks will be determined per treatment grouping 1 using mITT (OC) set and the risk difference of active treatments versus placebo will be determined and assessed by an exact 2-sided 95% confidence interval.

#### 7.5.2.2 DINAMO Mono

The secondary endpoint of time to treatment failure will be analysed and graphically described by Kaplan-Meier estimates up to the planned end of the study (Week 52) by placebo in TG1, L5 and E Pooled in TG5. Patients in the placebo group will be censored after 26 weeks unless a prior treatment failure is observed. Data obtained after re-randomisation in the placebo group will not be utilised for the determination of time to treatment failure.

A descriptive Log-rank test will compare linagliptin 5 mg and pooled empagliflozin versus placebo individually up to Week 26 using mITT (NCF) set by treatment grouping 1. Patients will be censored after 26 weeks unless a prior treatment failure is observed.

The change in HbA1c [%] from baseline to the end of 26 weeks will be analysed based on a REML approach using MMRM to assess the effectiveness and efficacy, using the same sensitivity methods as described in Section 7.4.1.3(A) and Section 7.4.1.3(C) respectively. Analysis described in Section 7.4.1.3(C) will be repeated for HbA1c [mmol/mol] in Appendix 16.1.13.

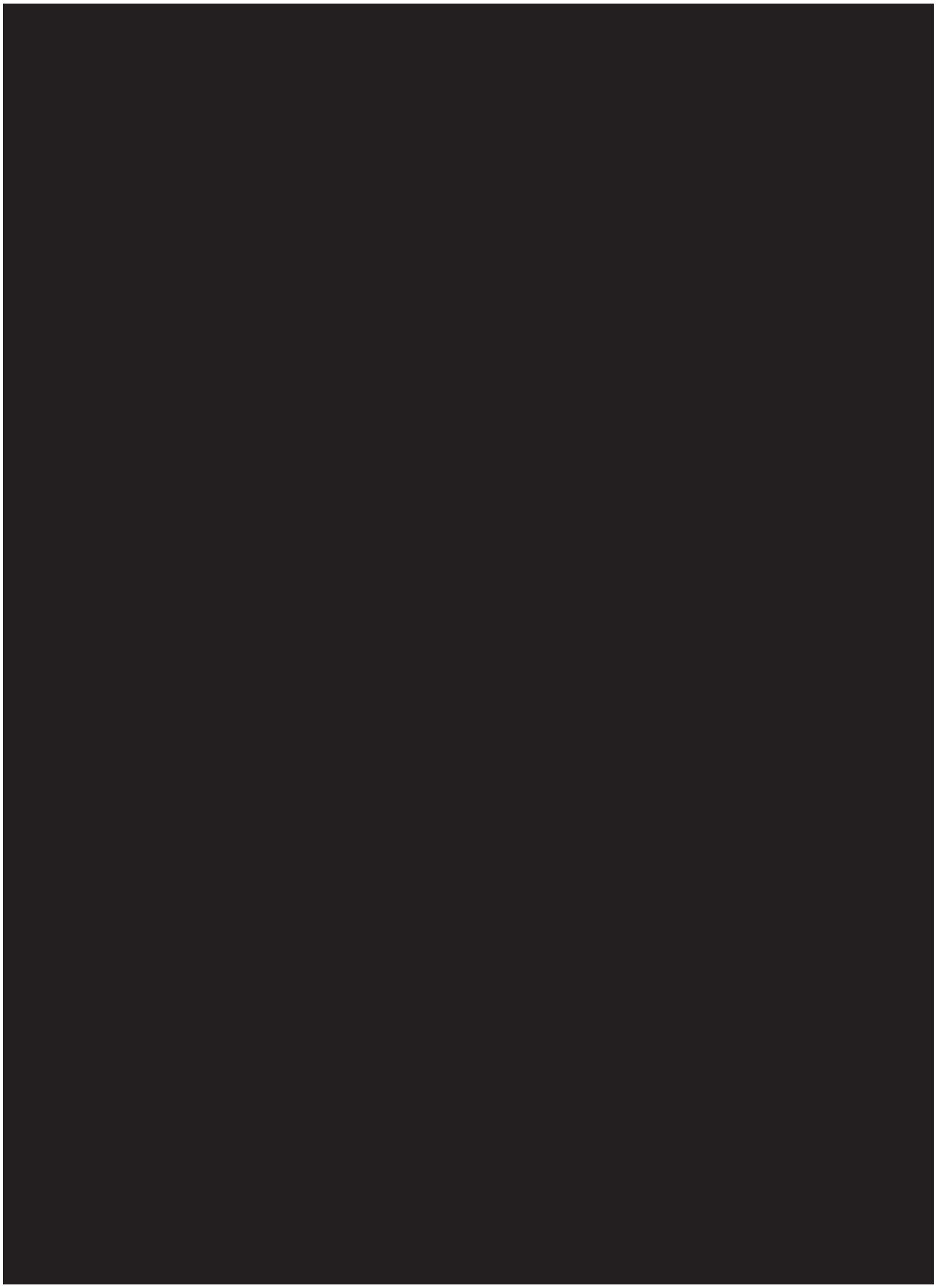
It is expected that a large group of drug naïve patients will require early intervention of rescue medication as early as first on-treatment visit, therefore the change in HbA1c from baseline to the end of 26 weeks will also be analysed using an ANCOVA model including treatment as a fixed classification effect, baseline HbA1c as a linear covariate, and age at randomisation as a categorical covariate using mITT (OC-LOCF) set.

The following continuous secondary endpoints will be analysed using the same methods described in Section 7.5.2.1, excluding the subgroup analyses.

- Change in FPG [mg/dl, mmol/L] from baseline to the end of 26 weeks
- Change in body weight [kg] from baseline to the end of 26 weeks
- Change in SBP [mmHg] from baseline to the end of 26 weeks
- Change in DBP [mmHg] from baseline to the end of 26 weeks

In addition, the change in FPG [mg/dl] from baseline to the end of 26 weeks will also be analysed using an ANCOVA model including treatment as a fixed classification effect, baseline FPG as a linear covariate, and age at randomisation as a categorical covariate using mITT (OC-LOCF) set.

The proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 weeks will be determined by treatment grouping 1 using mITT (NCF, OC) set and the risk difference of active treatments versus placebo will be determined and assessed by an exact 2-sided 90% confidence interval.



## 7.7 EXTENT OF EXPOSURE

An overall descriptive statistics table with mean, SD, median and range of the number of days a patient was on-treatment and patient-years together with the frequency count of on-treatment patients for the exposure in categories and exposure cumulative categories will be provided by TG1 and TG6. See Table 7.7: 1 for the presentation details.

Table 7.7: 1 Details for displays of treatment exposure, including exposure in categories and exposure cumulative categories

| | **Placebo comparisons period** | **Active treatment period** |
|---|---|---|
| **Treatment grouping** | TG1 | TG6 |
| **Period** | Up to Week 26 | Up to Week 52 |
| **Exposure in categories** | >0 to 4 weeks,<br>>4 to 8 weeks,<br>>8 to 16 weeks,<br>>16 to 24 weeks,<br>>24 to 28 weeks,<br>>28 weeks. | >0 to 4 weeks,<br>>4 to 8 weeks,<br>>8 to 16 weeks,<br>>16 to 24 weeks,<br>>24 to 32 weeks,<br>>32 to 40 weeks,<br>>40 to 46 weeks,<br>>46 to 54 weeks,<br>>54 weeks. |
| **Exposure cumulative categories** | ≥1 week,<br>≥4 weeks,<br>≥8 weeks,<br>≥16 weeks,<br>≥26 weeks,<br>≥28 weeks. | ≥1 week,<br>≥4 weeks,<br>≥8 weeks,<br>≥16 weeks,<br>≥26 weeks,<br>≥32 weeks,<br>≥40 weeks, |

| | | |
|---|---|---|
| | | ≥46 weeks,<br>≥54 weeks. |
| **First administration of study drug** | Date of first study drug intake | Date of first active study drug intake |
| **Last administration of study drug** | Date of study drug intake at Week 26 minus 1 day | Date of last active study drug intake |

In addition, the adjusted treatment exposure (treatment exposure minus total number of days of reported treatment interruption in relevant treatment period) will be summarised in descriptive statistics and patient-years by TG1 and TG6.

In order to assess the impact of COVID-19 to the treatment exposure in DINAMO only, the planned analyses for the treatment exposure will be repeated and summarised by permanent discontinuation of study medication or/and completed Week 26 visit before/from the start of COVID-19 disruption for up to Week 26 table and by permanent discontinuation of study medication before and from the start of COVID-19 disruption for up to Week 52 table.

A separate listing will be created of any patients that switched treatment at any time indicating exposure to the actual treatment against the randomised treatment.

All the above mentioned analyses will be presented for DINAMO and DINAMO Mono separately.

## 7.8 SAFETY ANALYSIS

Primary safety analysis (Comparison vs. placebo) (up to Week 26)
The primary safety analysis will be based on the TS. All safety variables will be analysed from start of initial randomised treatment until Week 26 (except for AEs, which will be analysed up to the day before Week 26). The treatment grouping 1 will be used for the comparisons and presented for DINAMO and DINAMO Mono separately.

Safety analysis during active treatment period (up to Week 52)
The safety analysis during active treatments will be based on the TSactive (excluding all data observed while patients were on placebo). All AEs, SAEs, AEs leading to discontinuation, drug related AEs, AESIs and lab PCSAs will be analysed from start of active treatment up to Week 52. The treatment grouping 6 will be presented for DINAMO and DINAMO Mono separately.

Long term safety analysis (up to Week 52)
The long term safety analysis will be based on the TS (excluding patients initially randomised to placebo). All safety variables will be analysed from start of initial randomised treatment up to Week 52. The treatment grouping 5 will be presented for DINAMO and DINAMO Mono separately.

Impact of assessment of up-titration to empagliflozin 25 mg (the period following the administration of the re-randomised medication planned at Week 14 up to Week 26/Week 52)

The up-titration safety analysis will be based on patients initially randomised to empagliflozin in the TS (only patients re-randomised at Week 14) for the assessment of up-titration to empagliflozin 25 mg. All AEs, SAEs, AEs leading to discontinuation, drug related AEs, AESIs, selected other specific AEs (hypoglycaemia, UTI, genital infections, acute pyelonephritis or urosepsis, bone fractures, AE related to reduced intravascular volume, and ketone measurements reported as AE) and lab PCSAs will be analysed. The treatment grouping 4 will be presented for DINAMO and DINAMO Mono separately.

### 7.8.1 Adverse events

AEs will be coded using the latest version of the MedDRA coding dictionary at database lock.

Any clinically significant new finding in the physical examination, vital signs and in the 12-lead ECG starting after Visit 2 (randomisation visit) will be considered as an AE and will be reported as such.

Unless otherwise specified the analyses of adverse events will be descriptive in nature and analyses of AEs will be based on the number of patients with AEs (not the number of AEs). All AEs will be reported according to the BI standard (5).

AE outputs for TG4 and TG5 will be presented for DINAMO only in Appendix 16.1.13 unless otherwise stated.

#### 7.8.1.1 Assignment of AEs to treatment

In general, the analysis of adverse events will be based on the concept of treatment emergent adverse events. This means that all adverse events occurring between first randomised or re-randomised drug intake until 7 days after last drug intake or cut-off (depending on analysis period, see Section 7.8) will be assigned to the randomised treatment.

In general, in-text AE tables will only present AEs assigned to the randomised treatment taken. For listings, AE will be assigned to one of the treatment phases of pre-treatment, treatment groups (depending on treatment grouping), post-treatment, post-study.

The cut off for the AEs outputs presentation period will be defined as the following.

- Prior to Week 26 treatment: Cut off at Visit 5 treatment date. If Visit 5 treatment date is not available, then the minimum of Day 183 or end of study date.
- Up to Week 52 present the whole treatment period plus the residual effect period.

#### 7.8.1.2 Analysis of other significant AEs

Other significant AEs will be reported and summarised according to ICH E3 criteria. Thus, AEs classified as 'other significant' will include those non-serious adverse events with:

- ‘action taken = discontinuation’ or ‘action taken = reduced’, or

- Marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review meeting or Blinded Report Planning Meeting.

Other significant AEs will be performed for the primary safety analysis and the safety during active treatment. See Section 7.8 for details.

#### 7.8.1.3 AE summaries

An overall summary of adverse events will be presented by TG1, TG6, TG5 and TG4.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. AEs will also be reported by intensity. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (6), for patients with serious adverse events, for patients with AEs leading to discontinuation, for patients with drug-related AEs and for patients with selected AESIs and other specific AEs. Incidence rate as defined in Section 7.8.1.8 will apply to frequency tables: overall summary of AEs, patients with AEs, patients with drug-related AEs, patients with other significant AEs according to ICH E3, patients with AEs leading to discontinuation and patients with SAEs. All above mentioned tables will be repeated by TG1, TG6, TG5 and TG4.

The system organ classes will be sorted in descending order of the total frequency count of all treatments then followed by preferred terms in descending order of the total frequency count. Alphabetical ordering will be used for the same total frequency counts on PT level.

Appendix 16.1.13 will include the following analyses by TG1 and TG6:

- Frequency of patients with AEs by SOC and preferred term
- Frequency of patients with SAEs by SOC and preferred term
- Frequency of patients with drug related serious AEs by SOC and preferred term
- Frequency of patients with adverse events by outcome, SOC and preferred term

Additionally, the following analyses will also be reported in Appendix 16.1.13 for disclosure on clinicaltrials.gov and EudraCT:

- Frequency of patients with non-serious adverse events occurring with an incidence in preferred term greater than 5% by treatment, SOC and PT for disclosure on clinicaltrials.gov.

- Frequency of patients with serious adverse events by treatment, SOC and PT for disclosure on clinicaltrials.gov

- AEs per treatment arm for disclosure on EudraCT (Number of patients exposed, affected by SAEs, affected by non-serious AEs with incidence > 5% in any treatment arm for each PT, number of death of all causes, number of deaths resulting from AEs will be presented.)

- Non-serious AEs with incidence > 5% in any treatment arm for each preferred term (grouped by standard SOC terms) for disclosure on EudraCT (Number of patients affected, exposed, total occurrences will be presented.)

- Serious AEs on preferred term (grouped by standard SOC terms) for disclosure on EudraCT (Number of patients affected, exposed, number of occurrences, occurrences causality related, fatalities, fatalities causally related to treatment will be presented.)

These result disclosure AE analyses in Appendix 16.1.13 will be performed using treatment grouping 9 for both DINAMO and DINAMO Mono together. See (13) for details.

#### 7.8.1.4 Protocol-specified AEs of special interest (AESI)

The protocol defines the following adverse events that for analysis purposes will be considered as AESIs:

- Hypersensitivity reactions (narrow SMQ) such as angioedema, angioedema-like events, and anaphylaxis
- Skin lesions (narrow SMQ) such as exfoliative rash, skin necrosis, bullous dermatitis
- Pancreatitis (narrow SMQ, PT)
- Pancreatic cancer (narrow BIcMQ)
- Hepatic injury (narrow sub SMQ)
- Decreased renal function (narrow SMQ)
- Diabetic Ketoacidosis (DKA) (narrow BIcMQ, investigator assessment)
- Events involving lower limb amputation (investigator-determined)

For those selected by SMQs/BIcMQ, the list of AESIs and other specific AEs, which is maintained as a separate file (8-01-tsap-adverse-event-topics) in Section 8 TSAP and Programming in the TDMAP folder “Data Management and Statistics”. The current version at the time of DBL will be used to be in line with the current MedDRA version.

The frequency of patients with AESIs will be summarised by treatment, primary system organ class and preferred term.

These AESI analyses will be performed for the primary safety analysis (TG1), safety during active treatment (TG6), long term safety (TG5) and assessment of up-titration (TG4). See Section 7.8 for details.

Events leading to lower limb amputation and DKA events will be listed only using the TS.

#### 7.8.1.5 Other specific adverse events

The analyses for the other specific adverse events will be performed for the primary safety analysis, safety during active treatment and selected other specific AE will be performed for the assessment of up-titration (Treatment grouping 1, 6 and 4 respectively).

**Hypoglycaemia**

The investigator will record for each AE whether it represents a hypoglycaemic AE and, if so, record additional information to assess the intensity of the hypoglycaemic AE. On the basis of this information the investigator-defined hypoglycaemic AE will be classified as:

- Documented symptomatic hypoglycaemia AE with plasma glucose concentration ≤ 70 mg/dL (< 3.9 mmol/L), as well as asymptomatic hypoglycaemia AE with plasma glucose concentration ≤ 70 mg/dL (< 3.9 mmol/L)
- Documented (any) symptomatic and asymptomatic hypoglycaemia AE with plasma glucose concentration < 54 mg/dL (< 3.0 mmol/L)
- Severe hypoglycaemia AE: event requiring the assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions. (Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.)

Reported hypoglycaemia (investigator-defined hypoglycaemia) adverse event is defined as hypoglycaemia adverse event reported in the eCRF AE page.

Any hypoglycaemia (protocol-defined hypoglycaemia) is defined as reported hypoglycaemia adverse event or asymptomatic hypoglycaemia non-AE that had plasma glucose between >= 54 mg/dL (>= 3.0 mmol/L) and <= 70 mg/dL (< 3.9 mmol/L).
Any hypoglycaemia that occurs on the same day, but, with a different start time, will be handled as a separate hypoglycaemic event.

The number and percentage of patients with reported hypoglycaemia AE will be tabulated by treatment, SOC and preferred term.

The characteristics of the episodes will be presented separately for the reported hypoglycaemia AEs and any hypoglycaemia.

Similarly as for the analysis on patient level, a summary on the number of any hypoglycaemia, descriptive event rate, number of episodes by severity will be produced per patient-years. Only apply to TG1 and TG6.

A frequency table will be provided for number and percentage of patients with symptomatic hypoglycaemia adverse event with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemia AE by baseline age at randomisation in categories. See Table 6.4:1 for the subgroup details.

The treatment phase assignment of any hypoglycaemia (AE and non-AE) is exclusively based on the collected start date. These tables will be summarised up to the day before Week 26 by TG1 using TS, up to Week 52 by TG6 using TSactive and from the start of Week 14 to Week 52 by TG4 using TS (only patients re-randomised at Week 14) unless stated specifically.

**Urinary tract and genital infections**

The following other specific adverse events will be assessed and be tabulated by treatment, SOC, PT:

- Genital infections (narrow sub BIcMQ, investigator assessment)
- Urinary tract infections (UTI) (narrow sub BIcMQ, investigator assessment)

In addition using the narrow sub BIcMQ, serious genital infection events and genital infection events leading to treatment discontinuation will be summarised by treatment, SOC and PT. Similarly, the serious UTI events and the UTIs leading to treatment discontinuation will be summarised by treatment, SOC and PT.

Genital infections based on investigator assessment will be summarised by type (fungal balanitis or fungal vulvovaginitis, genital infection other than fungal balanitis or fungal vulvovaginitis), intensity (mild, moderate or severe), time to onset of first episode (within the first 3 months of treatment or after), duration (<7 days, 7-14 days and >14 days), how the event was treated (no treatment, therapy assigned, hospitalisation), treatment (0, 1, 2, >2 antimicrobials needed to treat), duration of treatment (≤7 days, >7 days), whether leading to discontinuation of treatment, and the number of events per patient.

Furthermore, the above mentioned displays on genital infections based on investigator assessment will be repeated by the type of infection (fungal balanitis or fungal vulvovaginitis, genital infection other than fungal balanitis or fungal vulvovaginitis).

UTIs based on investigator assessment will be summarised by intensity (mild, moderate or severe), time to onset of first episode (within the first 3 months of treatment or after), duration (<7 days, 7-14 days and >14 days), anatomical location (upper UTI (kidney), lower UTI (bladder and below)), how the event was treated (no treatment, therapy assigned, hospitalisation), treatment (0, 1, 2, >2 antimicrobials needed to treat), duration of treatment (≤7 days, >7 days), whether leading to discontinuation of treatment, and the number of episodes per patient.

These tables will be summarised up to the day before Week 26 by TG1 using TS, up to Week 52 by TG6 using TSactive and from the start of Week 14 to Week 52 by TG4 using TS (only patients re-randomised at Week 14).

**Acute pyelonephritis or urosepsis**

Frequency of acute pyelonephritis (narrow sub BIcMQ) or urosepsis (PT) will be tabulated by treatment, SOC and PT.

Acute pyelonephritis or urosepsis based on investigator assessment will be summarised overall and by intensity, and by additional treatment required (0, 1, 2, >2 antimicrobials needed to treat).

These tables will be summarised up to the day before Week 26 by TG1 using TS, up to Week 52 by TG6 using TSactive and from the start of Week 14 to Week 52 by TG4 using TS (only patients re-randomised at Week 14).

**Bone fractures**

Bone fractures (narrow BIcMQ) will be listed using TS.

**Arthralgia**

Arthralgia (HLGT (primary path)) will be summarised by treatment, SOC and PT using TS (TG1) for up to the day before Week 26 and TSactive (TG6) for up to Week 52.

**Pemphigoid in bullous conditions**

Pemphigoid in bullous conditions (HLT(primary path)) will be summarised by treatment, SOC and PT using TS (TG1) for up to the day before Week 26 and TSactive (TG6) for up to Week 52.

**AE related to reduced intravascular volume (Volume depletion)**

Volume depletion (narrow BIcMQ) will be listed and summarised by treatment, SOC and PT using TS (TG1) for up to the day before Week 26, TSactive (TG6) for up to Week 52 and TS with only patients re-randomised at Week 14 (TG4) from the start of Week 14 to Week 52.

**Ketone measurements reported as AE**

Ketone measurements (narrow BIcMQ) reported as AE will be summarised by treatment, SOC and PT using TS (TG1) for up to the day before Week 26, TSactive (TG6) for up to Week 52 and TS with only patients re-randomised at Week 14 (TG4) from the start of Week 14 to Week 52.

#### 7.8.1.6 Events qualifying for external adjudication by the Clinical Event Committee

Independent external Clinical Event Committee (CEC) regularly review cardiovascular, neurology, hepatic and ketoacidosis events and evaluate whether pre-specified criteria for these adjudication endpoints are met. Details on composition of the CECs, responsibilities and clinical event definitions are provided in separate CEC charters. Events qualifying for adjudication will be selected based on the latest CEC charter versions.

The CECs will be provided with additional, specified background material on the patients with these events and perform an assessment of the events. Result of adjudication assessments will be incorporated to the database.

Frequency table will be provided for adjudicated cardiovascular and neurological events, adjudicated hepatic events and adjudicated ketoacidosis events. All adjudication events and results will be listed.

This analysis will be performed for the primary safety analysis (TG1) and the safety during active treatment (TG6). For definition of safety analyses see Section 7.8.

#### 7.8.1.7 AEs while patients taking wrong study medication

A listing using the TS will be provided for AEs that occurred while a patient was taking the wrong medication (planned and actual treatment taken) for DINAMO and DINAMO Mono separately.

#### 7.8.1.8 AE incidence rates

In addition to the frequency tabulations, time-adjusted adverse event analyses will be performed for on-treatment AEs and on-treatment AEs by SOC, respectively HLT and PT.

The time at risk in patient years for an AE is derived as follows:

Patients with AE:
time at risk (AE) in days = date of start of AE with specified PT/SOC/HLT – initial randomised treatment start date + 1

Patients without AE:
time at risk (AE) in days = end date of time at risk – initial randomised treatment start date + 1,
where end date of time at risk is the minimum of date of last study drug intake + x days and date of death, if applicable.

The standard approach will be x=7 days, but for certain AEs in addition other approaches will be used.

Total AE-specific time at risk per treatment group is then derived as:
Time at risk (AE) [years] = Sum of time at risk [days] over all patients in a treatment group/365.25

For ‘each row of a table’ (e.g. displaying an SOC), time at risk is calculated using start of first AE summarised in this row; e.g. for patient with AE in a specified SOC, time at risk = date of start of AE with specified PT in this SOC – start of initial randomised treatment + 1.

The AE incidence rate per 100 patient years at risk will then be calculated as follows:
Incidence rate per 100 patient years (pt-yrs) = 100*number of patients with AE / time at risk (AE) [years].

#### 7.8.1.9 COVID-19

In order to assess the impact of COVID-19 on the reporting of any adverse events, frequency of patients and rate of AEs before and from the start of COVID-19 disruption up to the day before Week 26 by TG1 and up to Week 52 by TG6 will be presented for DINAMO only. In general, the time at risk is the entire treatment duration plus residual effect period. The time at risk for the period before start of COVID-19 disruption is defined as first dose of treatment until either the day before COVID-19 start date or Treatment end date plus residual effect

period (whichever comes earlier). The time at risk for the period from start of COVID-19 disruption is defined as COVID-19 start date or treatment start date (whichever comes later) until treatment end date plus residual effect period. The residual effect period is within 7 days of treatment end date for treatment groups without a re-randomised treatment to follow on. Treatment emergent AEs occurred in the residual effect period after end of treatment will be counted toward the specific defined period based on the COVID-19 start date. For TG1, the residual effect period will not be added for patients who are still on treatment at Week 26 and the cut off for the AEs prior to Week 26 treatment will also apply.

Patients with a SARS-CoV-2 infection will be identified based on the narrow BIcMQ ‘SARS-CoV-2 infections’ plus the PT ‘Suspected COVID-19'. A listing of these AEs will be provided. The patients with such on-treatment AEs will define the subgroup of SARS-CoV-2 infected patients and for this subgroup the following AE analyses will be provided for TG1 and TG6:

- Overall summary of AEs
- Number of patients with AEs by SOC and PT
- Number of patients with AEs leading to discontinuation by SOC and PT
- Number of patients with SAEs by SOC and PT

To provide all available AE information on COVID-19 testing or infection status an additional listing will present all AEs related to SARS-CoV-2 infection based on the broad MedDRA SMQ ‘COVID-19’.

### 7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature for DINAMO and DINAMO Mono separately. The results will be performed for the primary safety analysis (TG1) and long term safety (TG5), presented based on SI units. The naming of the lab parameters will follow CTP. Some selected analyses will be repeated in conventional units and presented in Appendix 16.1.13.1.

The process of normalisation as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data (7). All analyses considering multiple of times upper limit of normal (ULN) will be based on original and not normalised data.

Only patients with at least one available on-treatment value regardless of intake of rescue medication (OC-ROC) will be included in the analysis of an individual laboratory parameter. All individual data will be presented in listings.

#### 7.8.2.1 General laboratory evaluation

The following general laboratory evaluations will be performed for all laboratory data captured in the study including bone metabolism biomarkers (Calcium, phosphate, alkaline phosphatase, 25-OH-vitamin D, intact parathyroid hormone, serum N-terminal cross-linked telopeptide (NTx)). But excluding HBA1C, FPG, C-peptide and UACR that are separately

described in the planned efficacy analysis, and other biomarkers that are separately described in Section 7.8.2.3, 7.8.2.4 and 7.8.2.5):

- For quantitative lab results, descriptive statistics per treatment group at baseline, last value on-treatment, and change from baseline to last value on-treatment (in both SI and conventional units)
    - If both the BI adult standard and the central lab standard ranges are available, the descriptive statistics will be performed on the normalised value.
        - Exception to NTx: the central lab standard range of female with tanner stage 5 will be used as the BI standard reference range.
    - Otherwise, the descriptive statistics will be performed on the standardised value
- For qualitative lab results, frequency tables per treatment group will be presented at baseline and at last value on treatment (only in SI unit).
    - Erythrocytes and leukocytes in urine analysis will be analysed as categorical data with 2 categories (“Normal” and “High”).
- Frequency table per treatment group will summarise the number of patients within and outside the reference range at baseline and the last measurement on treatment (only in SI unit).
    - The age dependent reference range used for post-baseline values by the lab will be replaced by the reference range as provided for the respective patients' baseline measurement, and re-categorised.
    - Exclude parameters only measured occasionally.
- Frequency tables (include a patient listing) per treatment group will summarise the number of patients with any potentially clinically significant abnormality (PCSA) using company standard clinically significant criteria. PCSA will be determined based on SI units and only be counted in tables if the patient had no PCSA value at baseline.

  All the above analyses will be performed on the appropriate treated set for TG1 and TG5. The PCSA tables will additionally be produced for TG6 and TG4 (from Week 14 up to Week 52).

- For quantitative lab results (as described above), descriptive statistics tables will be displayed per treatment group and per analysis visit over time for TG1 and TG5 in Appendix 16.1.13.

#### 7.8.2.2 Elevated liver enzymes

Special attention will be paid to parameters characterising liver function. These include liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP)) and total bilirubin (TBILI).

The frequency of the number of patients with AST/ALT elevations >= 3xULN, >= 5xULN, >= 10xULN, and >= 20xULN will be displayed.

To support analyses of liver related adverse drug effects, patients with AST and/or ALT >= 3xULN with concomitant or subsequent TBILI >= 2xULN in a 30 day period after AST/ALT elevation are of special interest.

Patients with elevations as defined above by ALT and/or AST, total bilirubin and AP combinations, will be summarised and further classified by AP < 2xULN and >= 2xULN, where AP is the maximum value in the 30 day period.

This analysis will be performed for the primary safety analysis (TG1), long term safety (TG5) and the safety during active treatment (TG6). For the definition of safety analyses see Section 7.8.

Details on patients with elevated liver enzymes will be listed using the TS.

#### 7.8.2.3 Lipid parameters

Descriptive statistics over time up to 26 weeks by treatment grouping 1 and up to 52 weeks by treatment grouping 5 for the treated set (OC-ROC).

For each lipid parameter, see CTP in-text Table 5.3.3:1, separate MMRM models for change from baseline up to Week 26 will be fitted on the treated set (OC-ROC) by TG1. The models will include treatment, visit and visit-by-treatment interaction as fixed categorical effects, as well as the categorical covariate age at randomisation and the continuous covariates baseline lipid parameter, baseline HbA1c, baseline lipid parameter by visit, baseline HbA1c by visit. An unstructured (co)variance structure will be used to model the within patient measurements, and the same other options as used for the primary family of MMRM analysis model, as described in Section 7.4.1.3(A), will apply.

All analyses in this section will be repeated for parameters in conventional unit and presented in Appendix 16.1.13.

#### 7.8.2.4 Renal laboratory parameters

Creatinine and eGFR
All calculations for the grading of renal function will be based on the originally measured laboratory values, not on normalised values with BI standard reference ranges.

The glomerular filtration rate will be estimated according to Zappitelli (8):

$$\text{eGFR } [\text{mL/min/1.73m}^2] = \frac{(507.76 \text{ x } e^{0.003(\text{height})})}{(\text{Cystatin C}^{0.635} \text{ x Serum Creatinine}^{0.547})}$$

If renal transplant, x 1.165
(With height in cm, Cystatin C in mg/L and Serum Creatinine in µmol/L)

For the analysis of eGFR and for the covariates in the efficacy statistical modelling the values calculated from the above formula using the serum creatinine values from the central laboratory will be used, and not the eGFR values provided by the central laboratory.
The endpoint will be derived at the visits where both serum creatinine and serum cystatin C are measured at the central laboratory.

A shift table from baseline to last value on treatment, (and from baseline to minimum value on treatment) will be provided for the time period up to 26 weeks.

Descriptive statistics will also be created for creatinine and eGFR values over time up to 26 weeks by treatment grouping 1 and up to 52 weeks by treatment grouping 5.

Additionally, summary tables will be created representing the number of patients per treatment group (i.e. TG1 (up to 26 weeks) and TG5 (up to 52 weeks)) who experienced a doubling in creatinine on treatment as compared to baseline and who were out of the normal range.

The UACR will be derived with the following formula.

$$\text{UACR [mg/g crea]} = \frac{\text{Urine Albumin [g/L] x 100}}{\text{Urine Creatinine [mmol/L] x 0.011312217195}}$$

A shift table from baseline value to last and maximum values on-treatment will be provided based on the following UACR categories (which used the derived UACR and not the albumin/creatinine ratio values provided by the lab): normal (< 30 mg/g crea), microalbuminuria (30 to <= 300 mg/g crea), macroalbuminuria (> 300 mg/g crea) by TG1 and TG5.

#### 7.8.2.5 Biomarkers

Descriptive statistics will be summarised over time up to Week 26 by TG1 and up to Week 52 by TG5 on the standard units for PINP, IGF-1, and IGF-BP3.

Descriptive statistics by sex and tanner stage category version 2, see Table 6.4:1 for the category, will be summarised over time up to Week 26 by TG1 and up to Week 52 by TG5 on the standard units for PINP, NTx, IGF-1, IGF-BP3.

Descriptive statistics of DPP-4 activity pre-dose measurement at Day 1 will be summarised by TG1 on the standard unit.

### 7.8.3 Vital signs

In addition to the analysis of body weight, SBP and DBP as secondary endpoints, descriptive statistics will be presented for the other vital signs as further safety endpoints, such as height (cm), heart rate (bpm) and BMI ($kg/m^2$), together with their change from baseline over time

up to Week 26 by treatment grouping 1, up to Week 52 by treatment grouping 5 based on the treated set (OC-ROC).

### 7.8.4 ECG

12-lead ECG measurements will be taken during placebo run-in, at Week 26 and at EoT (Week 52). Any clinically significant new findings in the ECG measurement after the first ECG will be considered as AEs and analysed as planned in Section 7.8.1.

# 8 REFERENCES


| | |
|---|---|
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| 2 | BI-KMED-TMCP-MAN-0012: "Standards and processes for analyses performed within Clinical<br>Pharmacokinetics/Pharmacodynamics", current version; KMED |
| 3 | BI-KMED-BDS-HTG-0035: "Handling of missing and incomplete AE dates", current version; KMED. |
| 4 | BI-KMED-BDS-HTG-0045: "Reporting of clinical trials and project summaries", current version; KMED. |
| 5 | BI-KMED-BDS-HTG-0041: "Analysis and presentation of adverse event data from clinical trials", current version; KMED. |
| 6 | CPMP/ICH/137/95: "Structure and content of clinical study reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version. |
| 7 | BI-KMED-BDS-HTG-0042: "Handling, Display and Analysis of Laboratory Data", current version; KMED. |
| 8 | Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, et al. Derivation and validation of cystatin C-based prediction equations for GFR in children. Am J Kidney Dis 2006;48(2):221-230[R16-2470] |
| 9 | Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat 2013;23(6):1352-1371 [R15-1829] |
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| 11 | BI Statistical Position Paper – Standards for Inferential Analyses, 1.1 Analyses of Continuous Endpoints – Parallel Group Studies |
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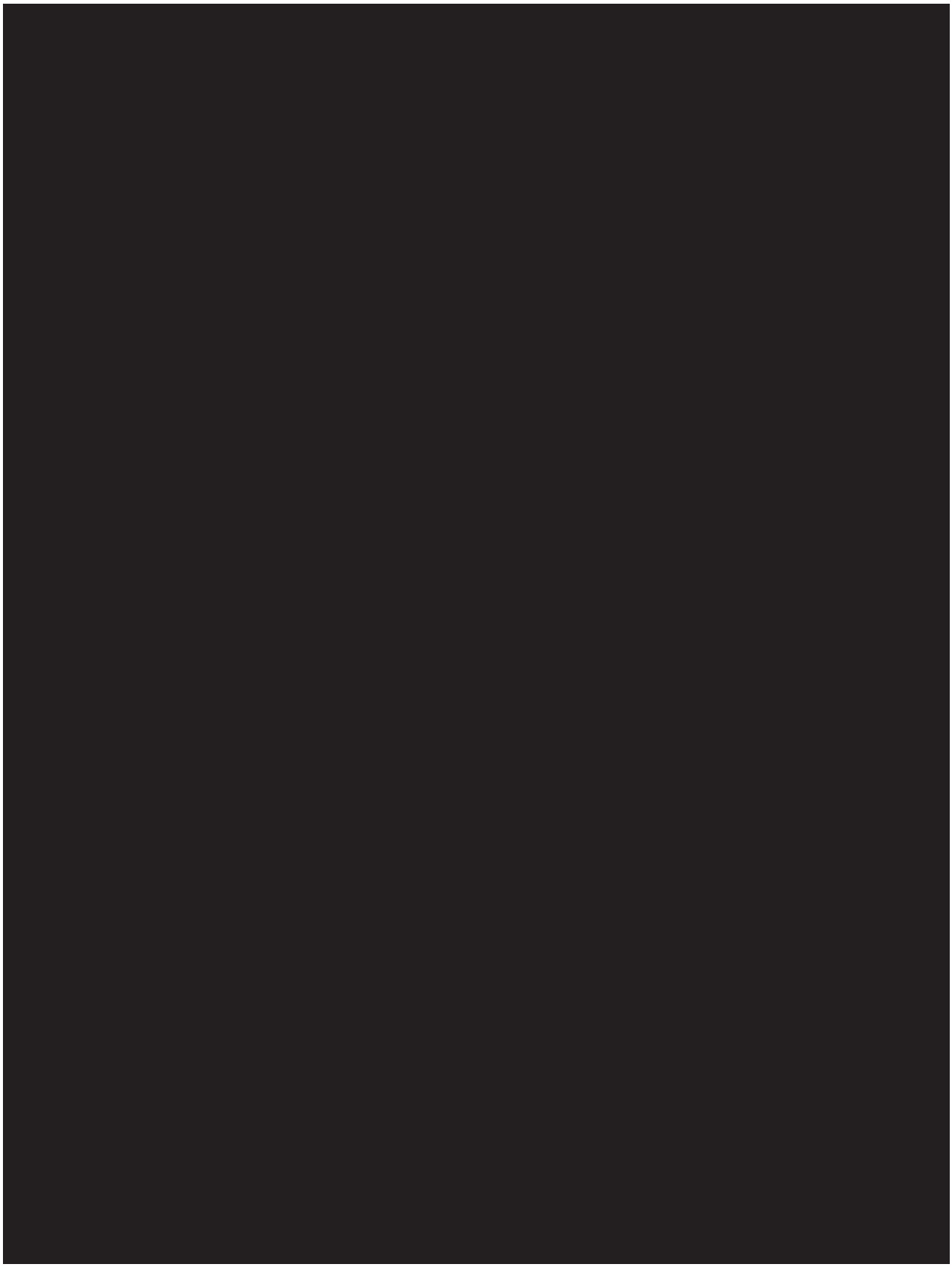
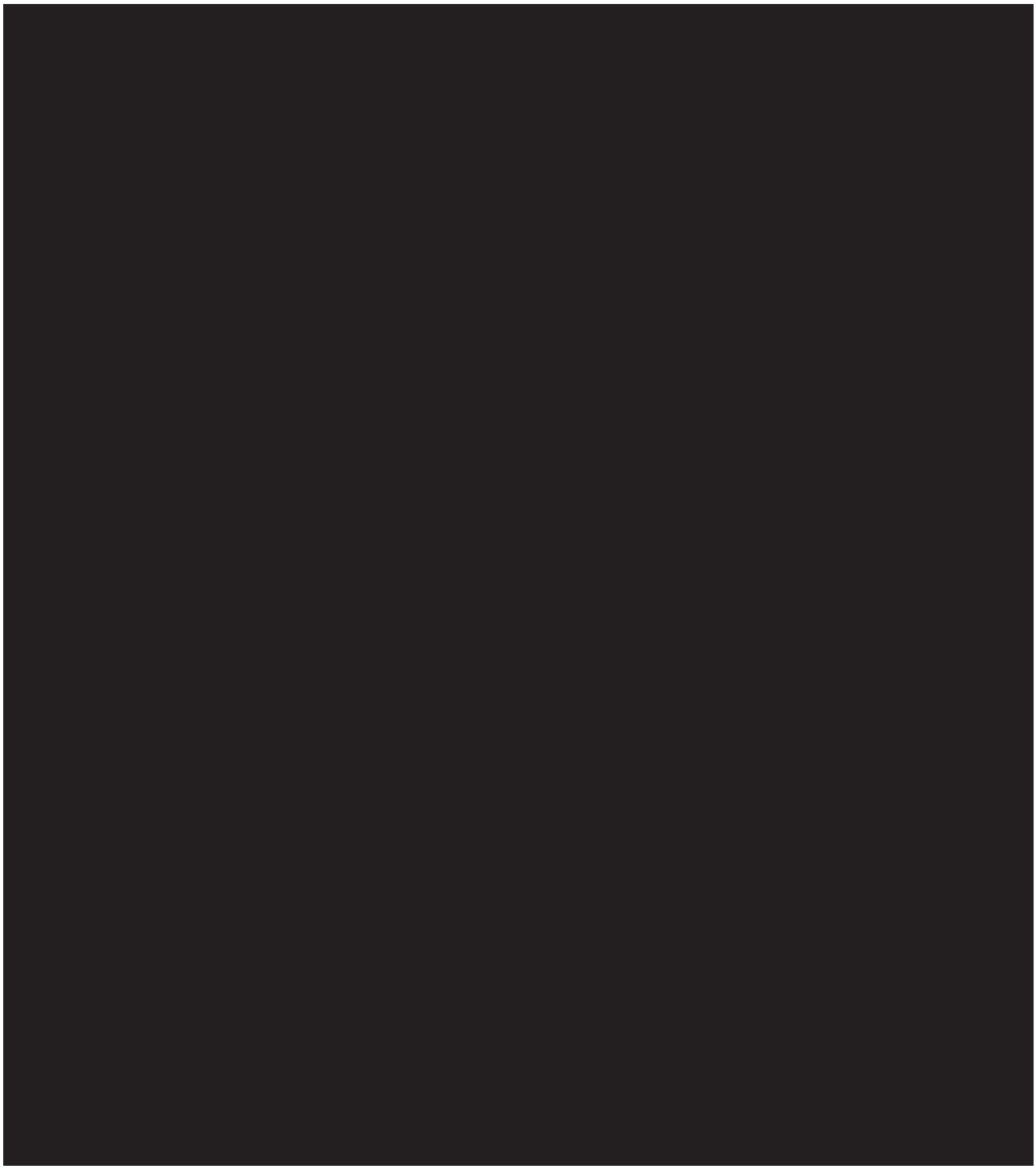
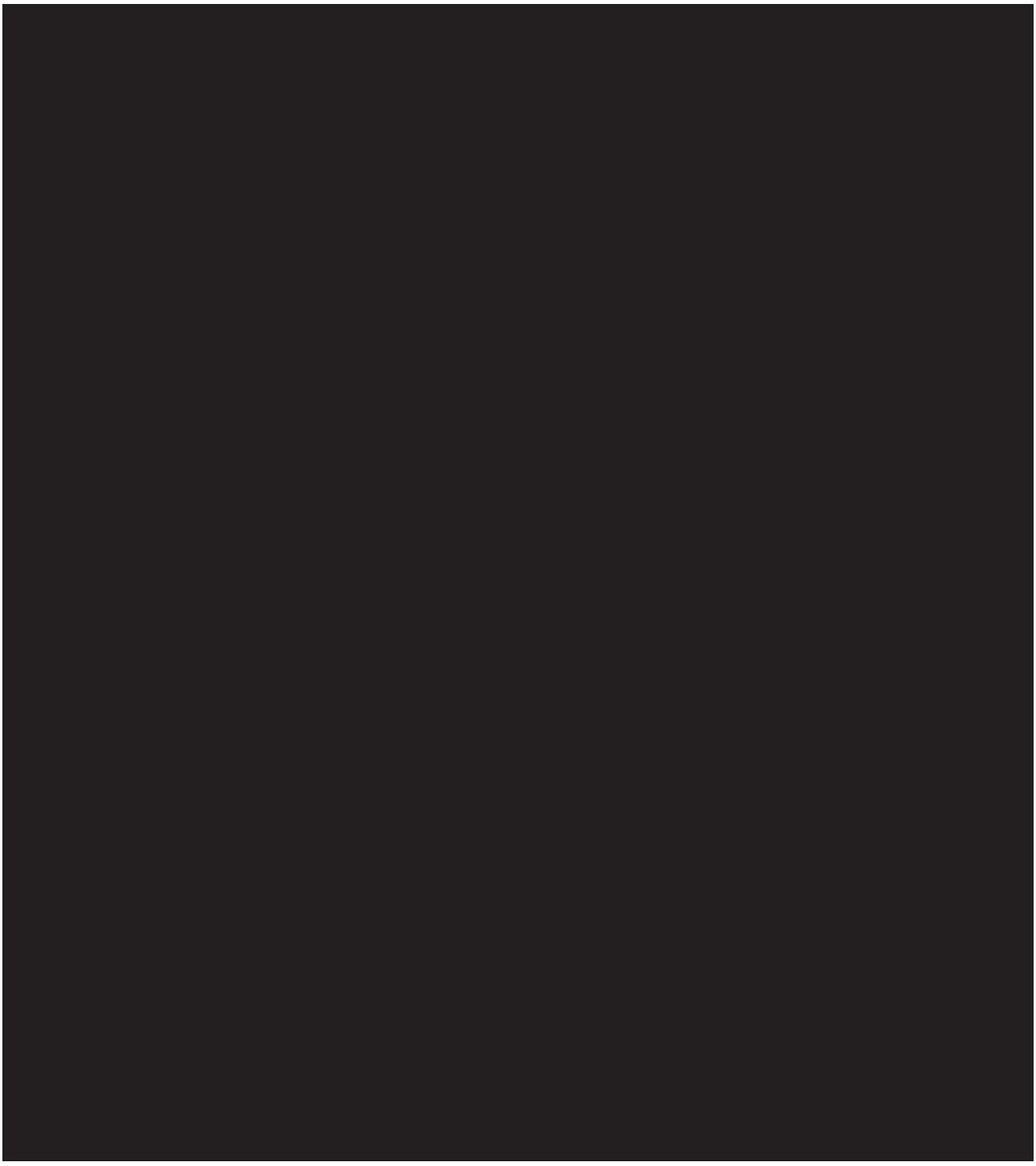
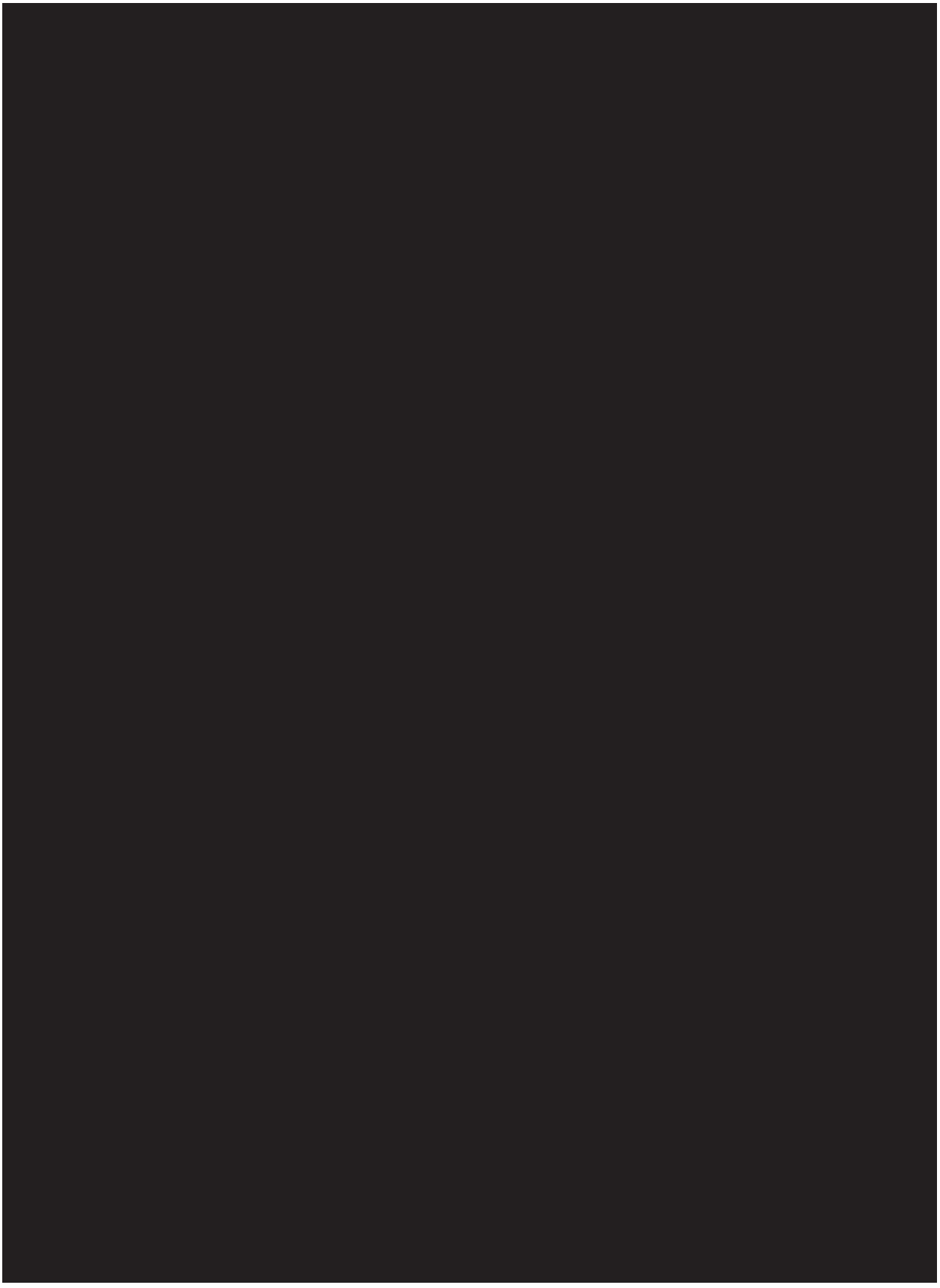
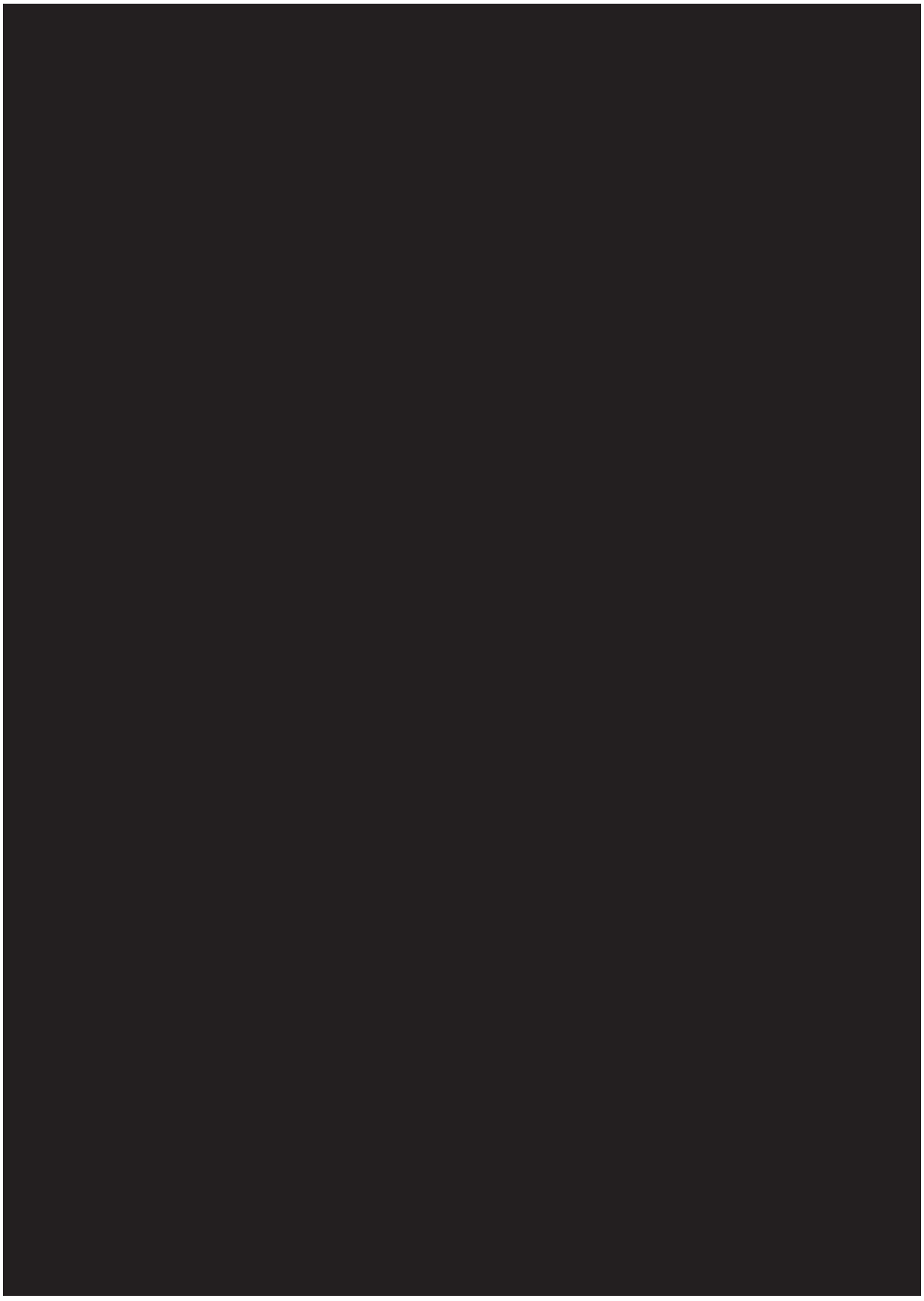
| 14 | BI-KMED-BDS-MAN-0025: “Handling of incomplete reference ranges”, current version; KMED. |
| 15 | Central laboratory reference ranges, current version; TMF. |

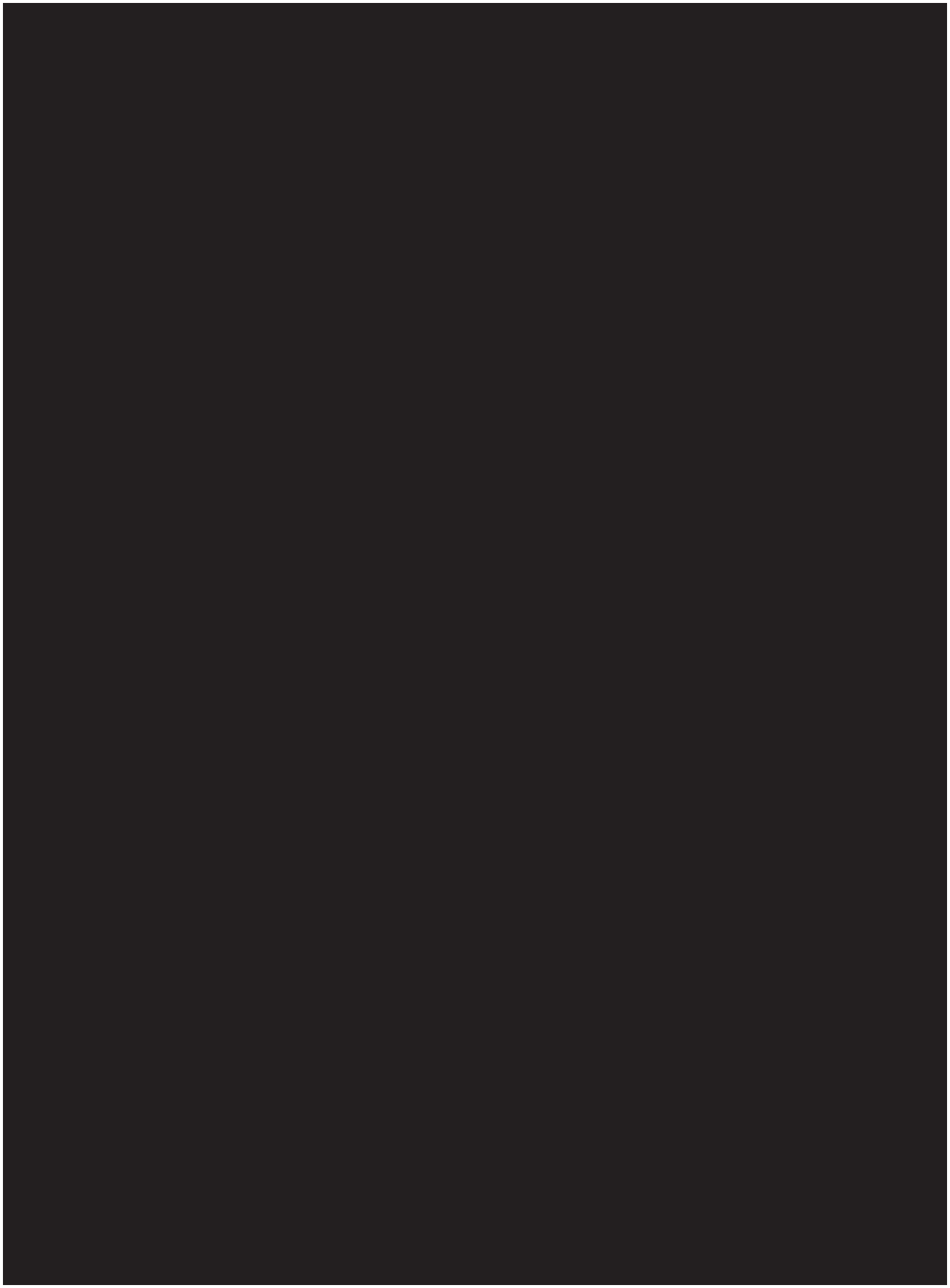


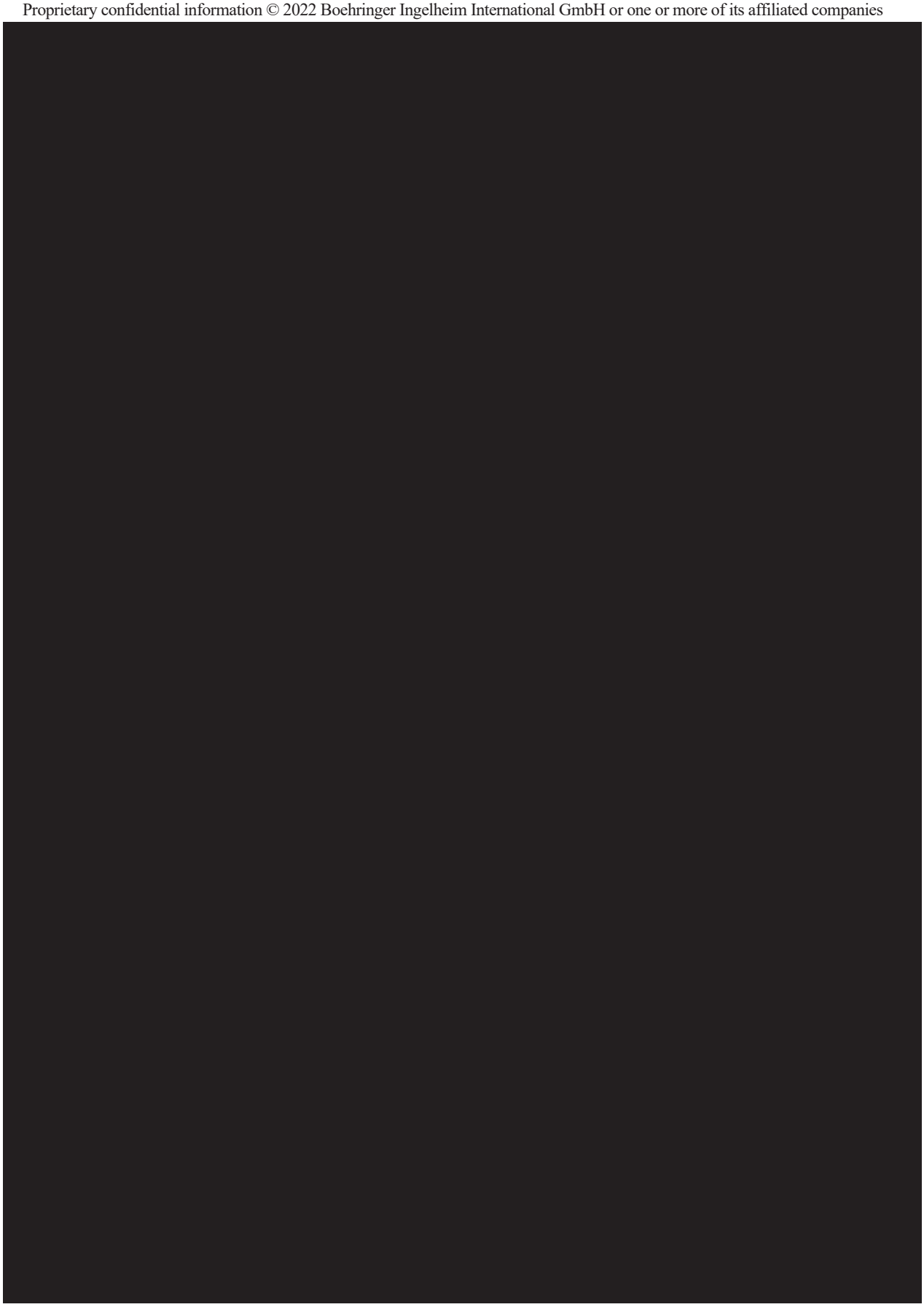


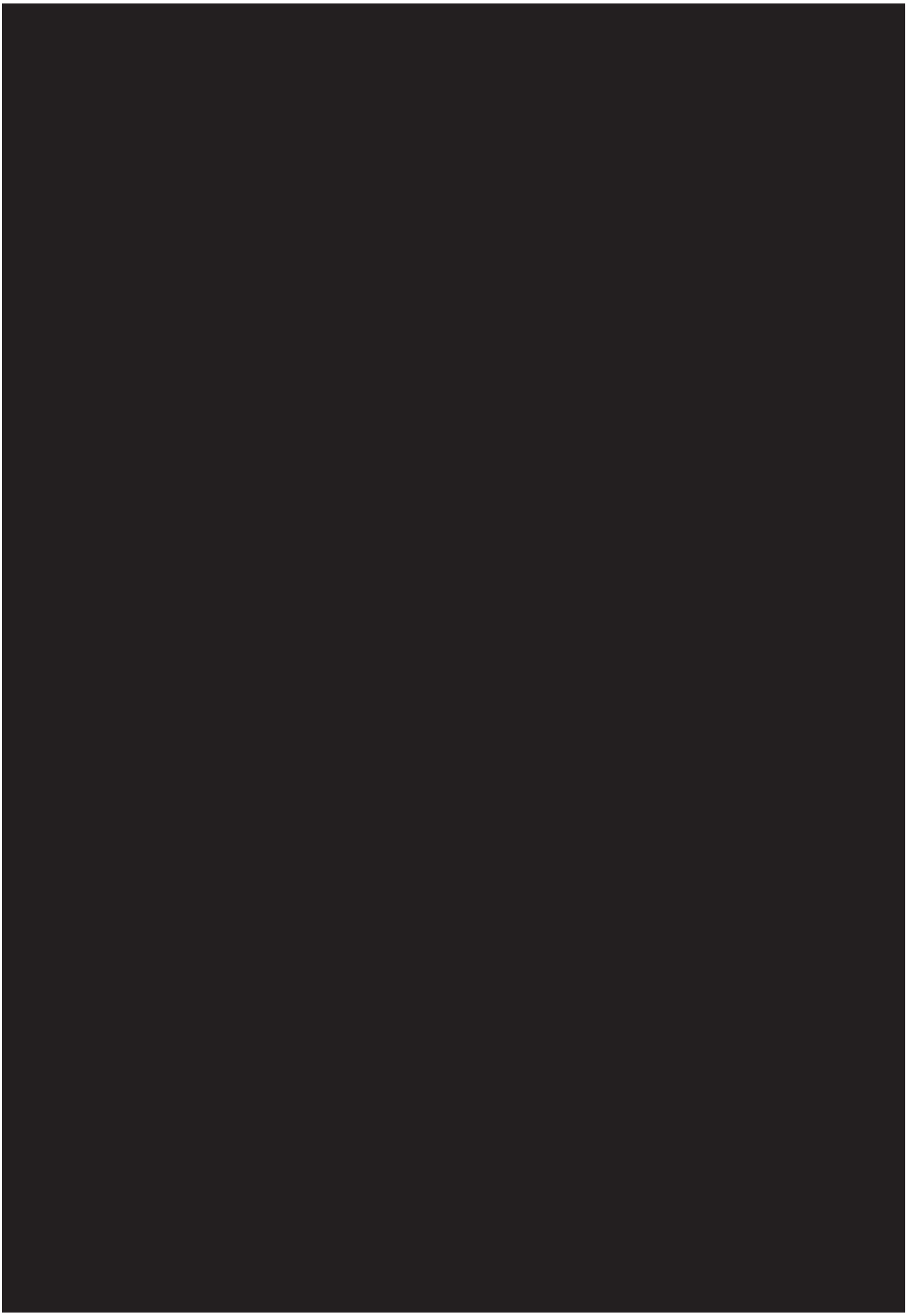


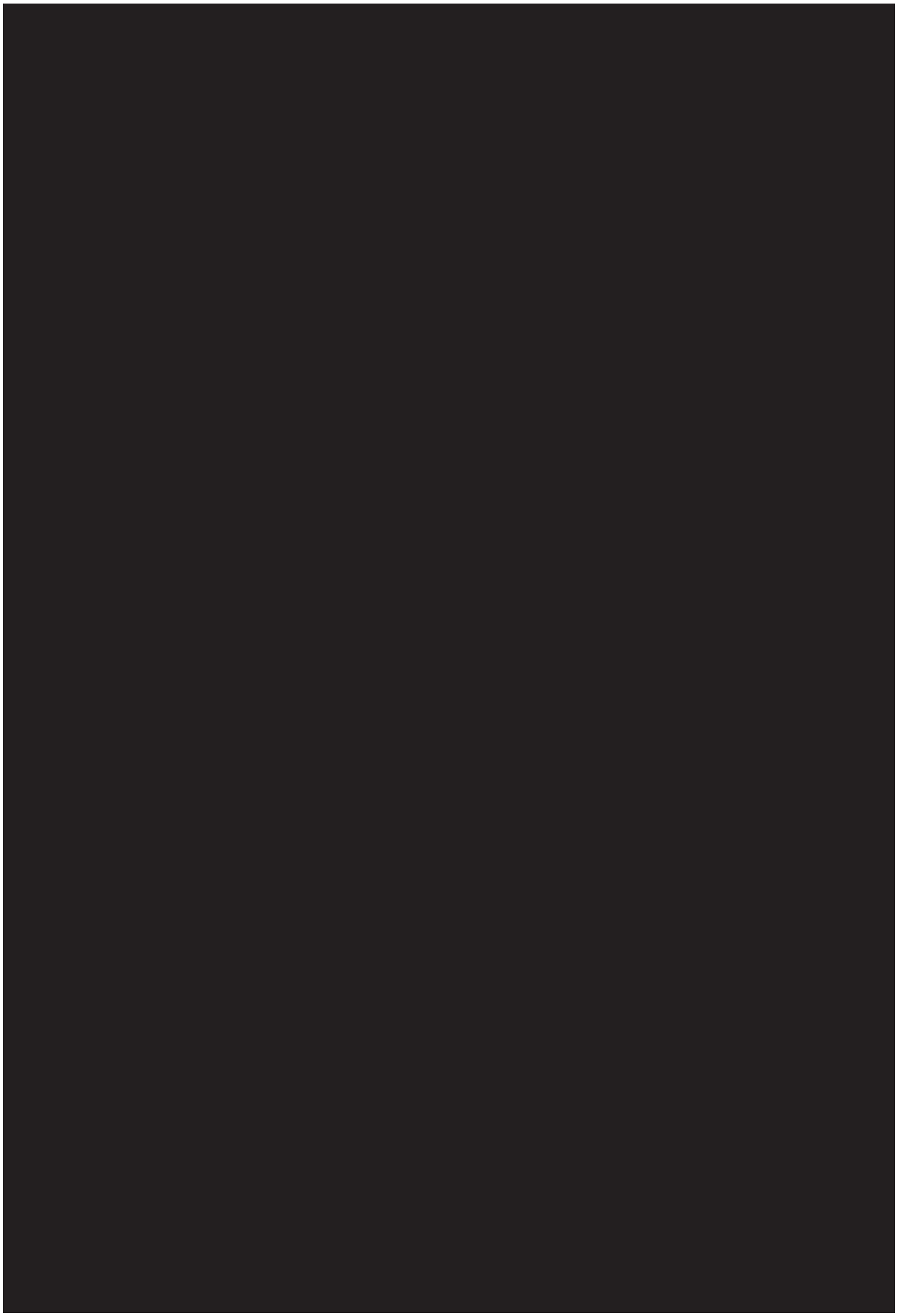


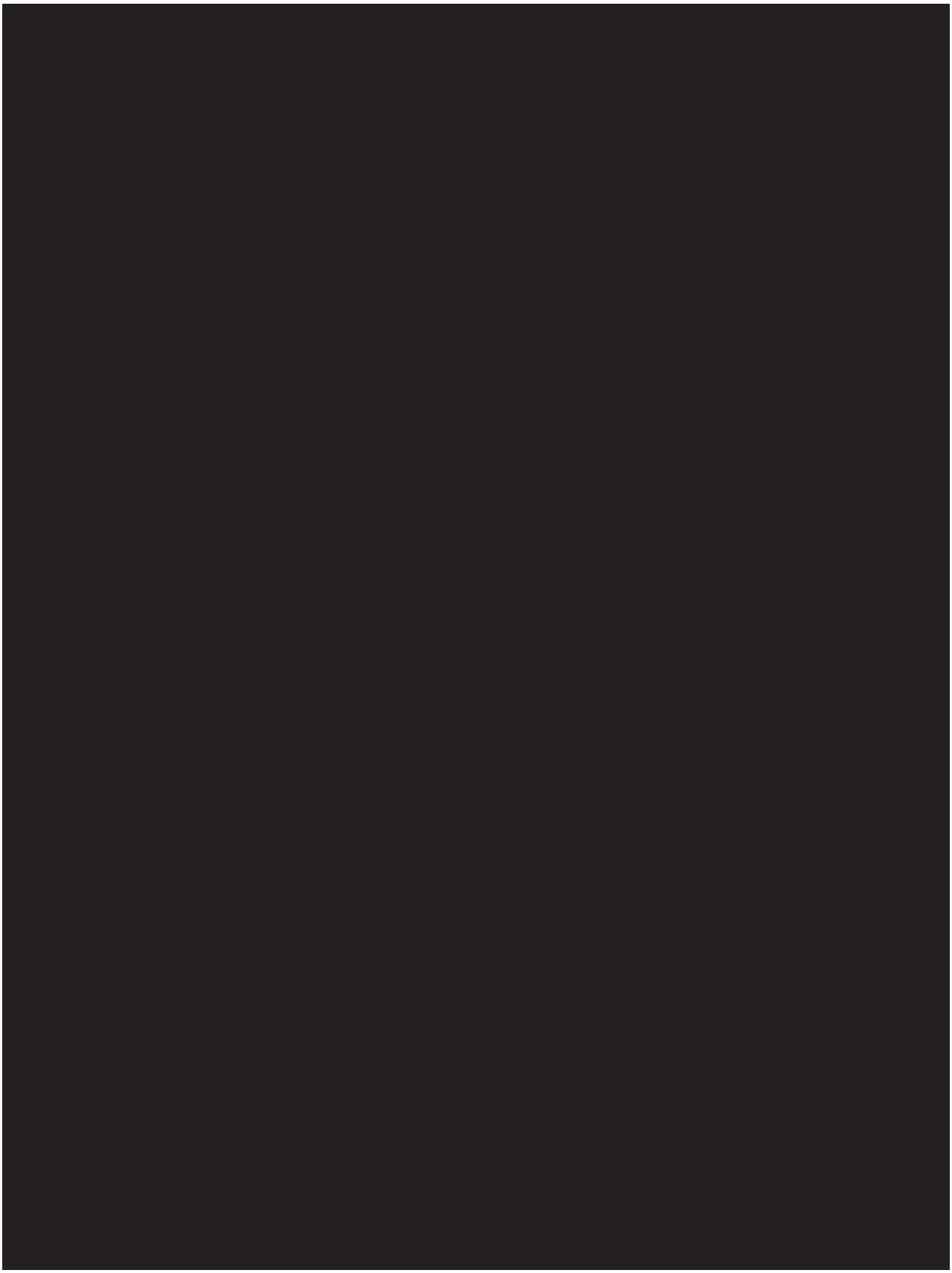


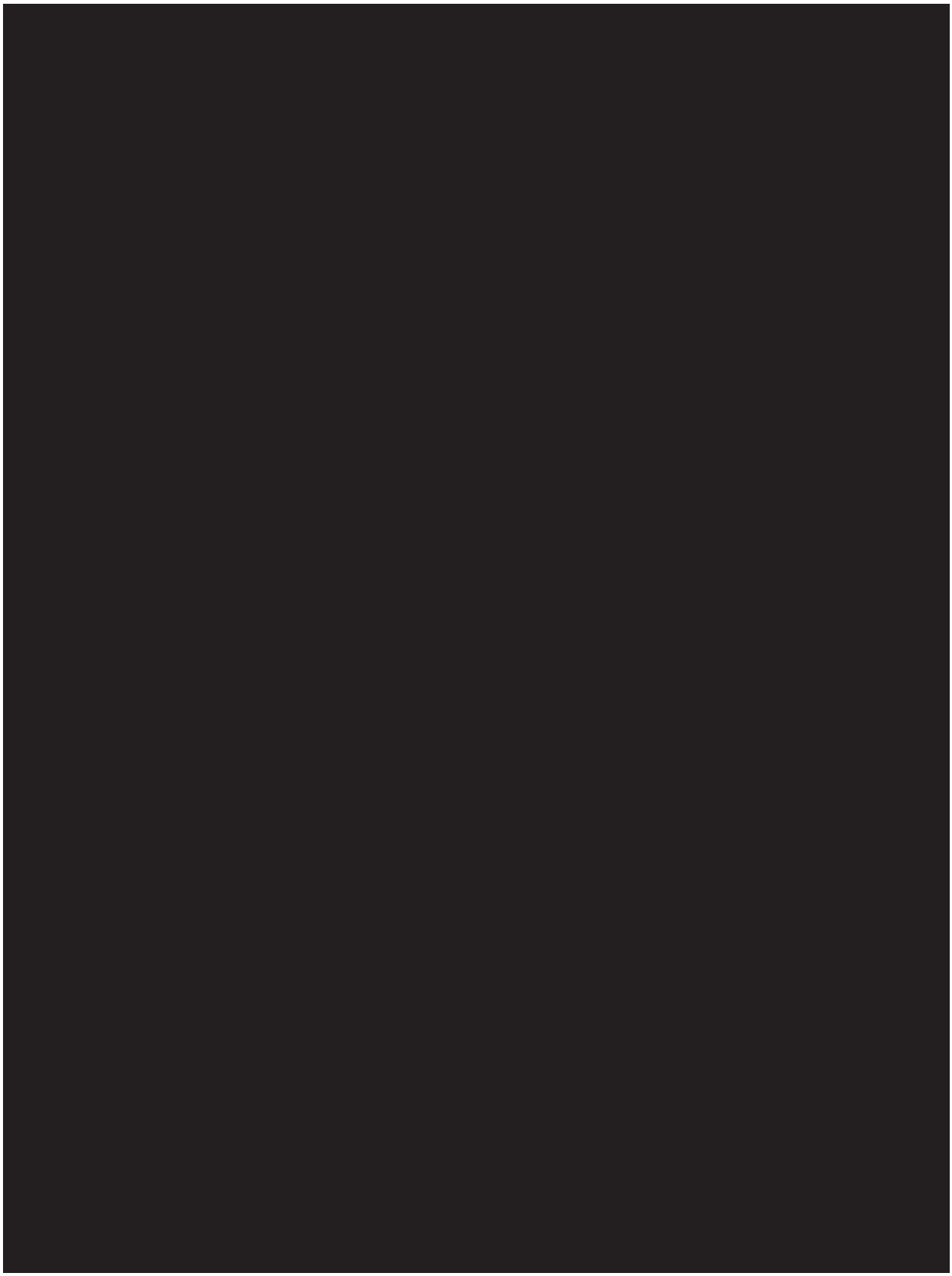


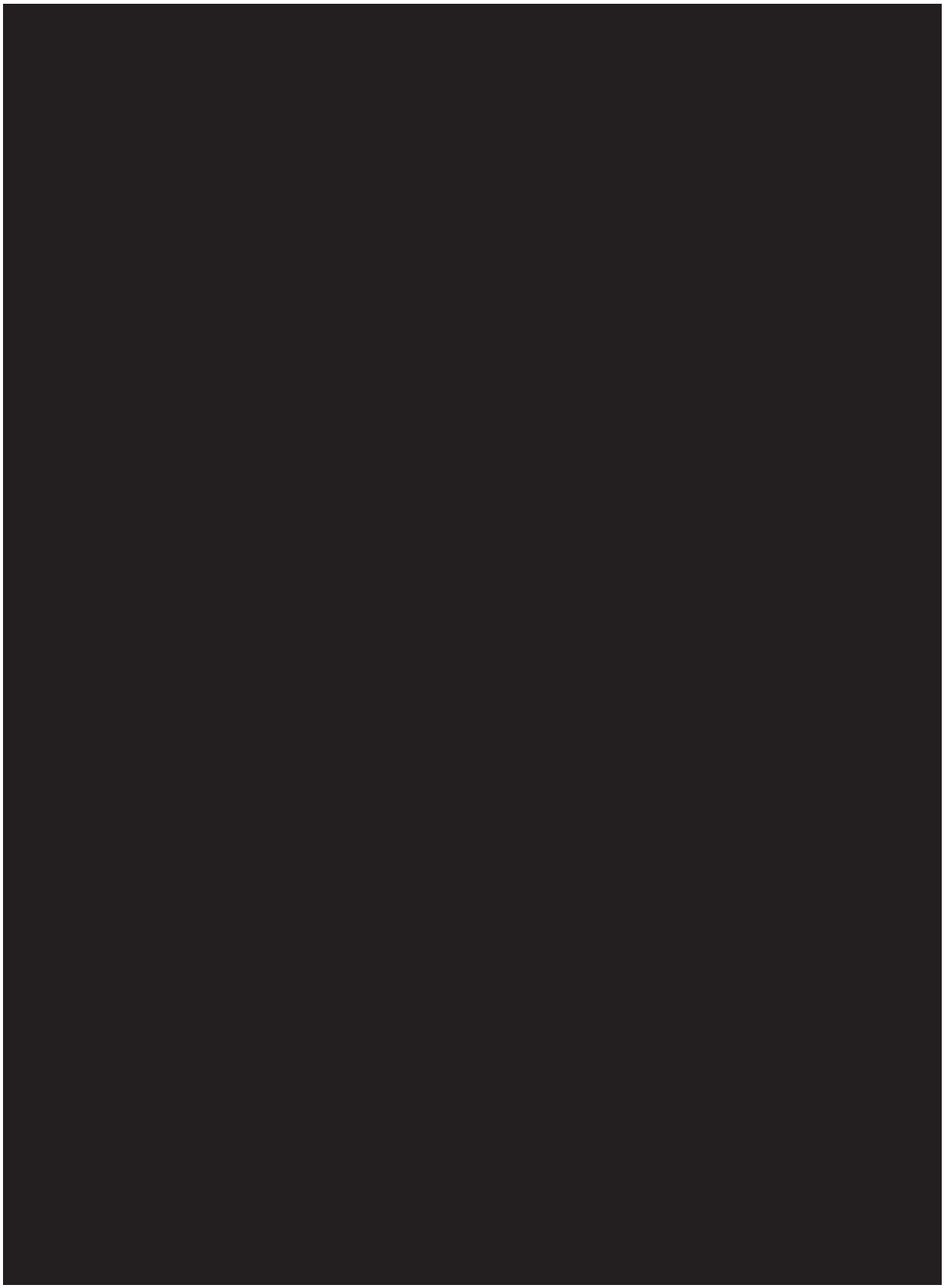


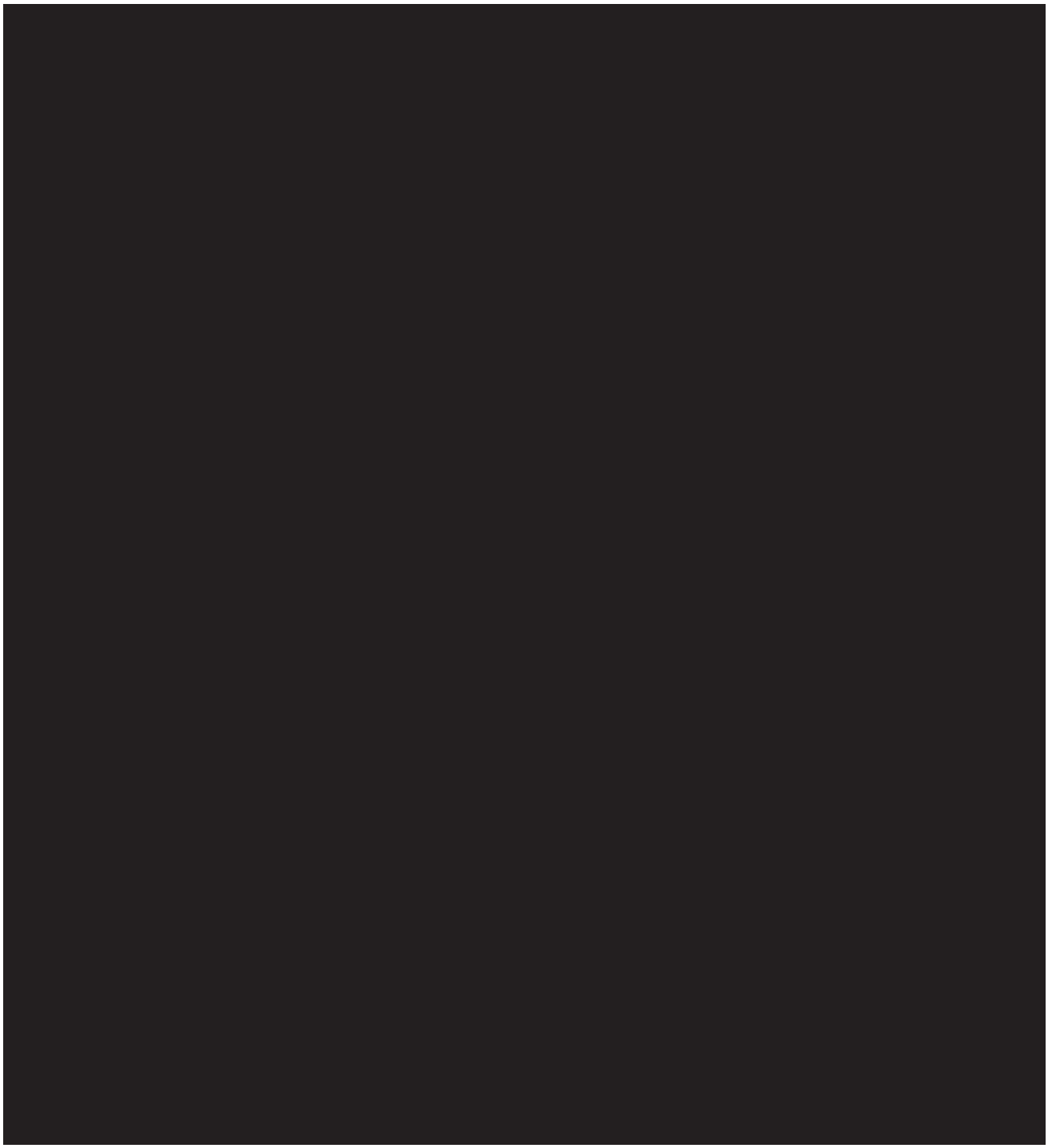


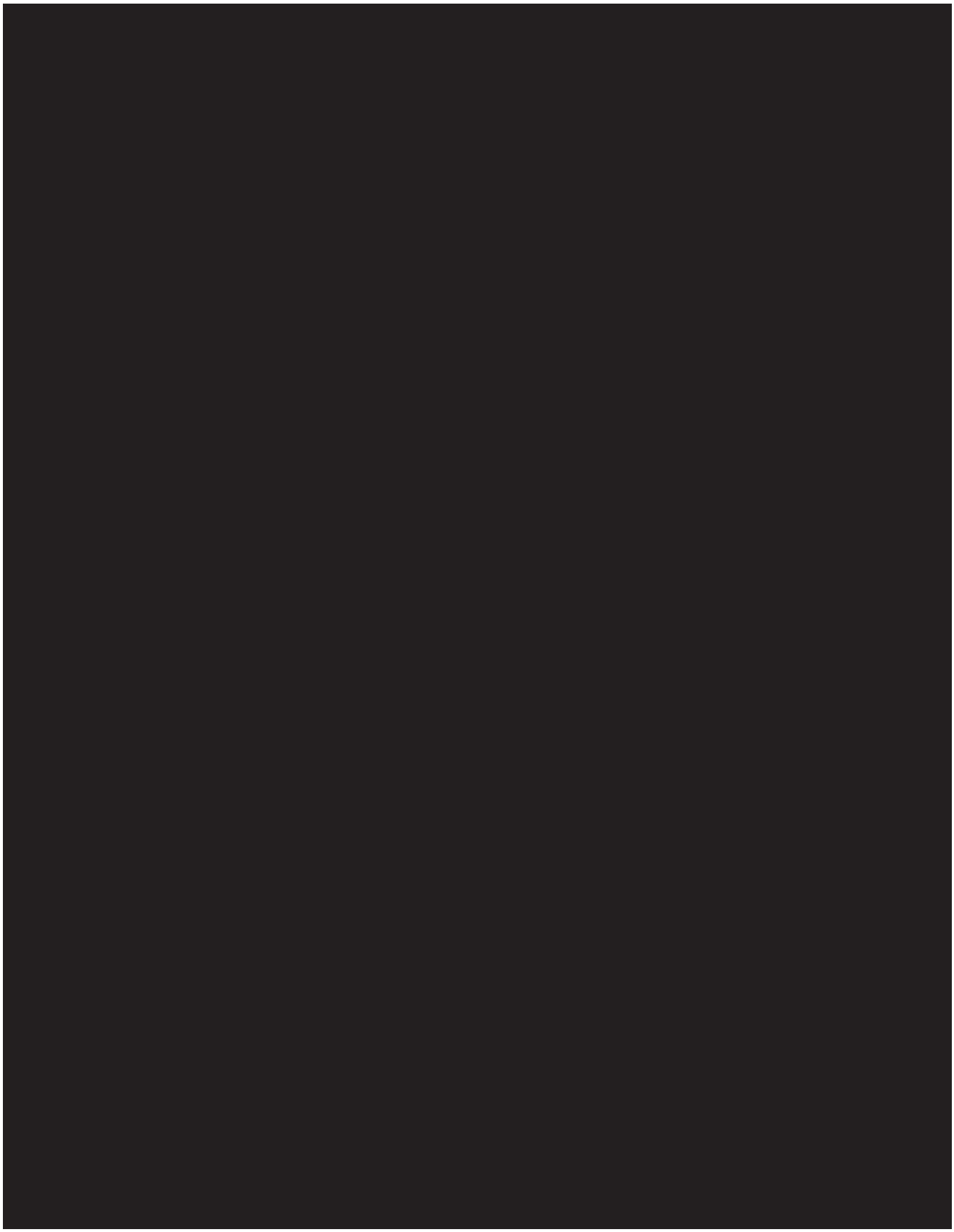


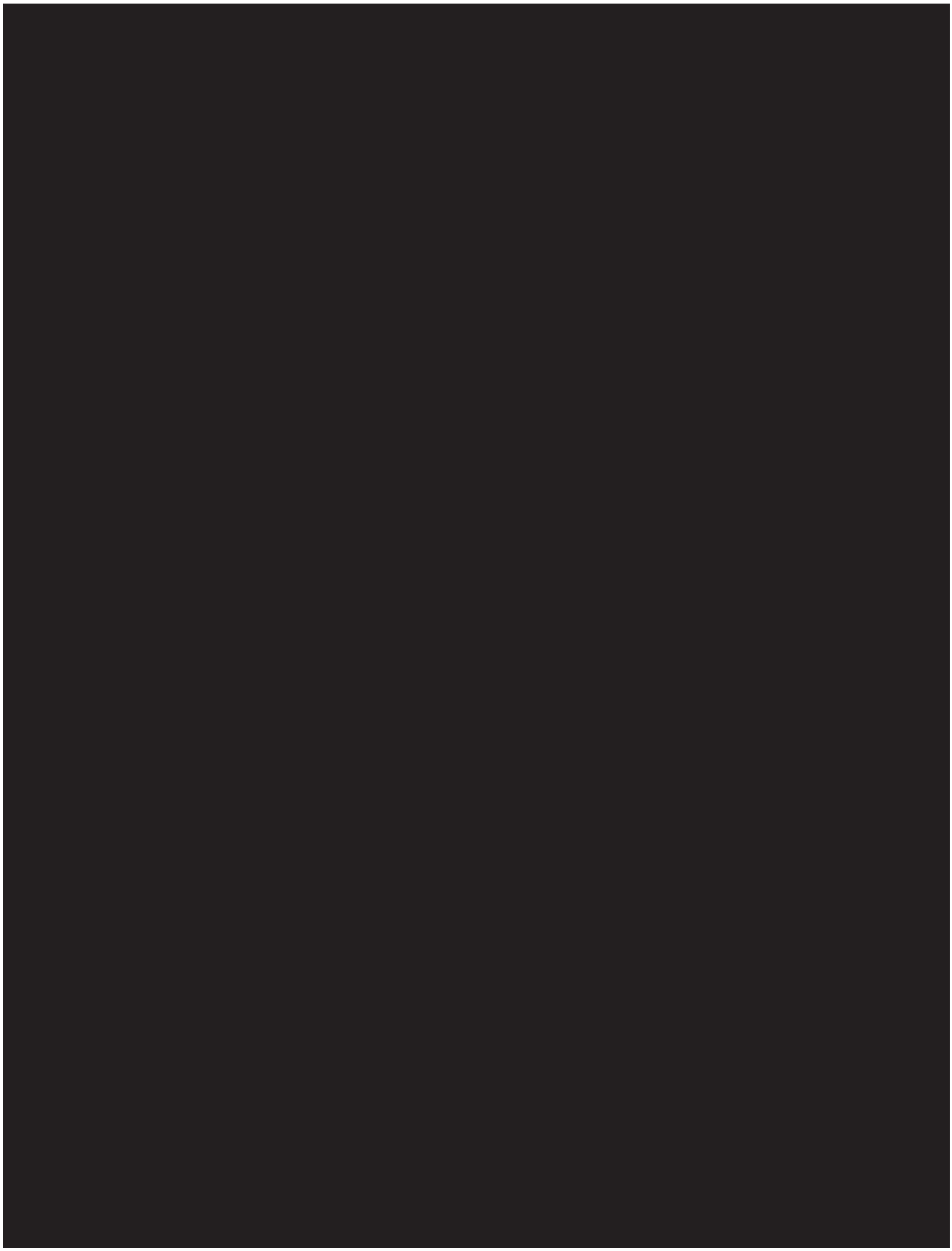


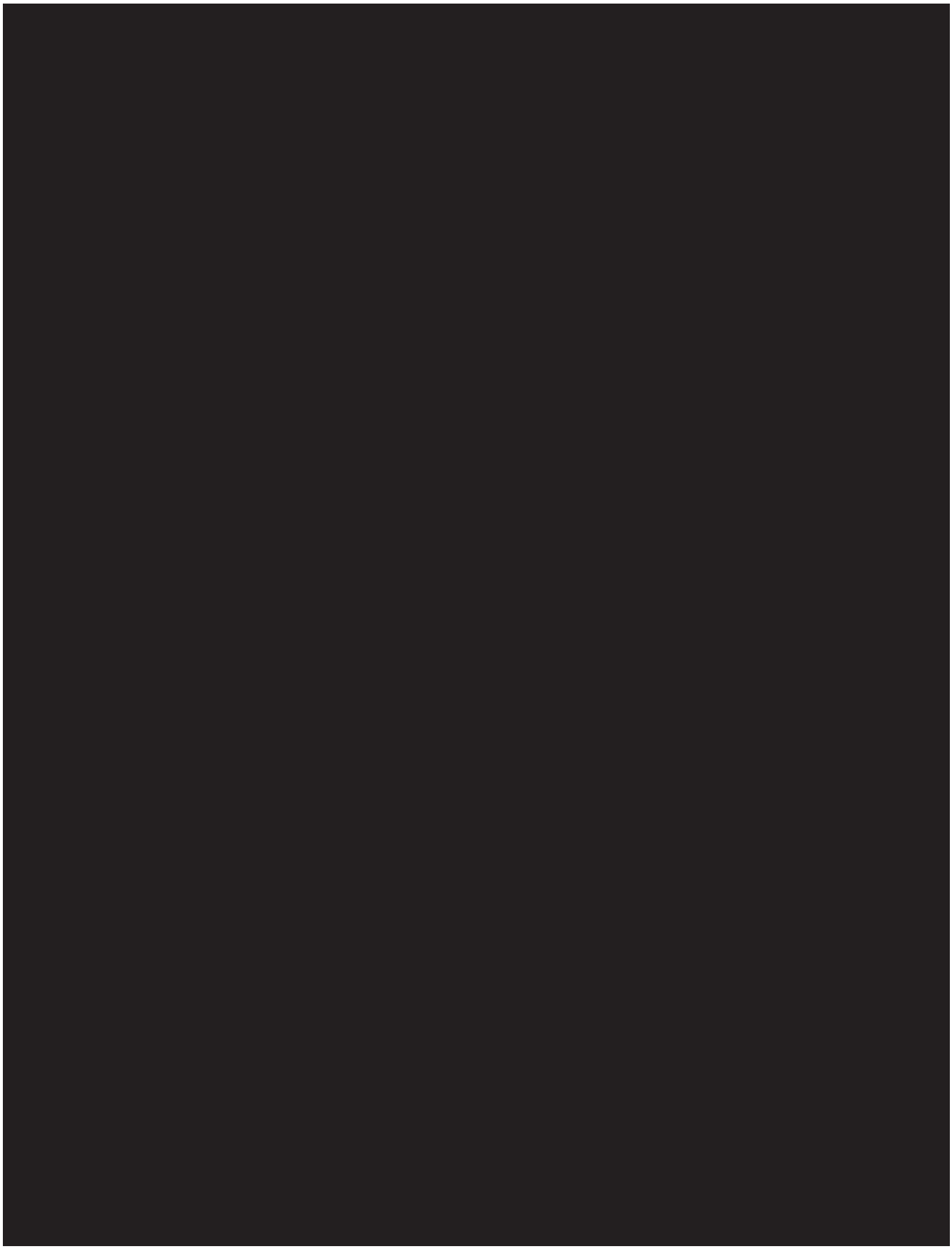


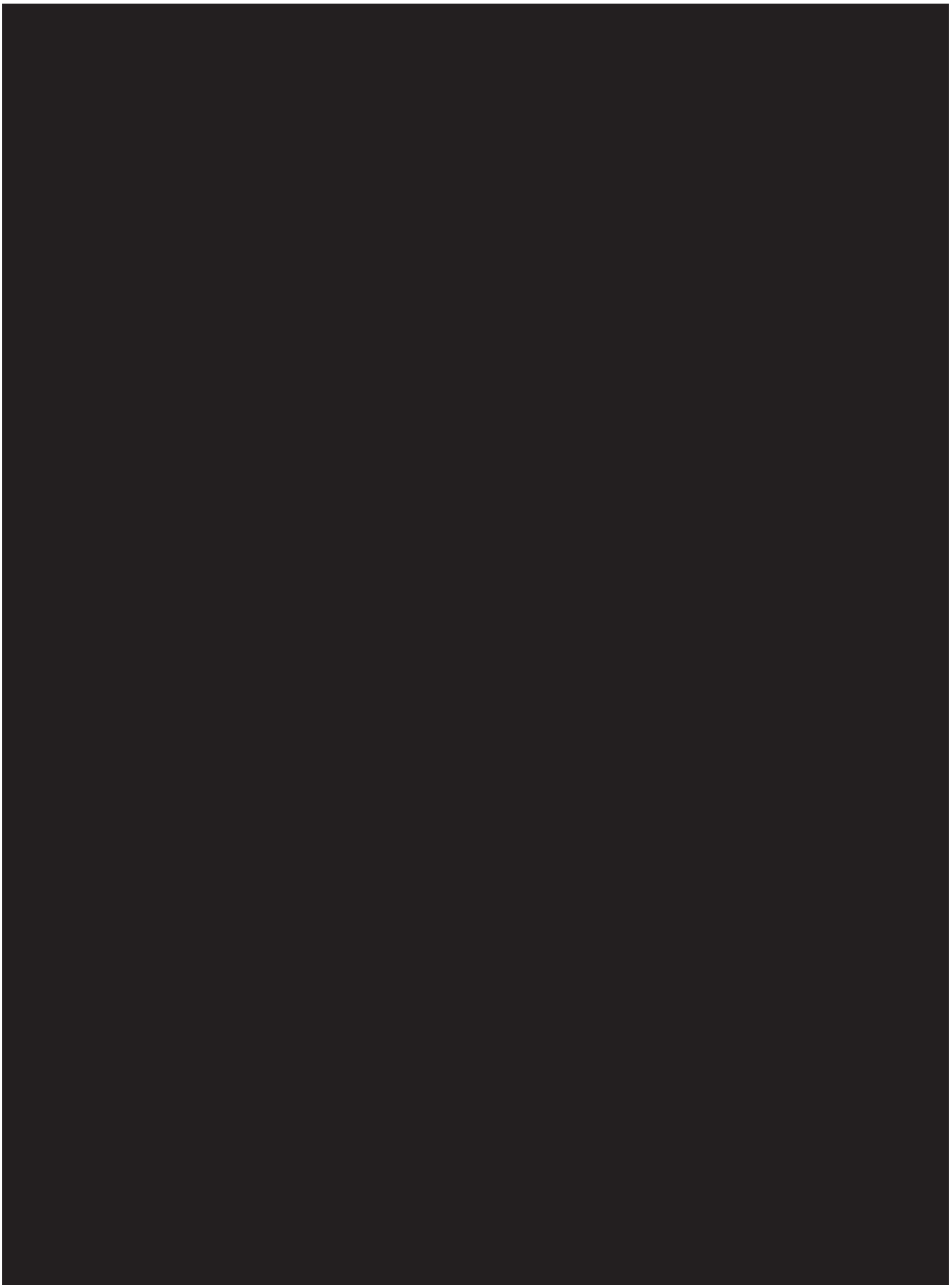


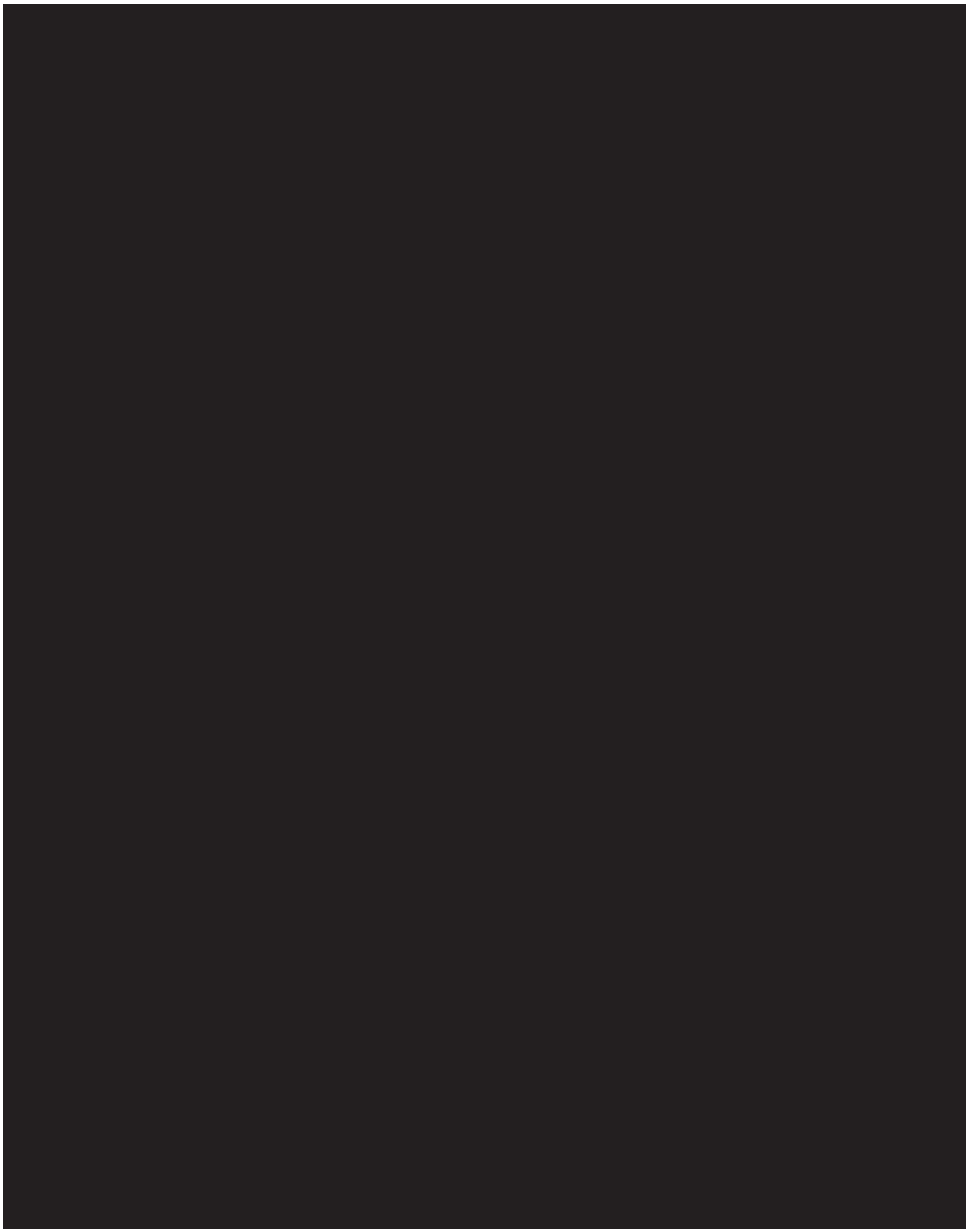


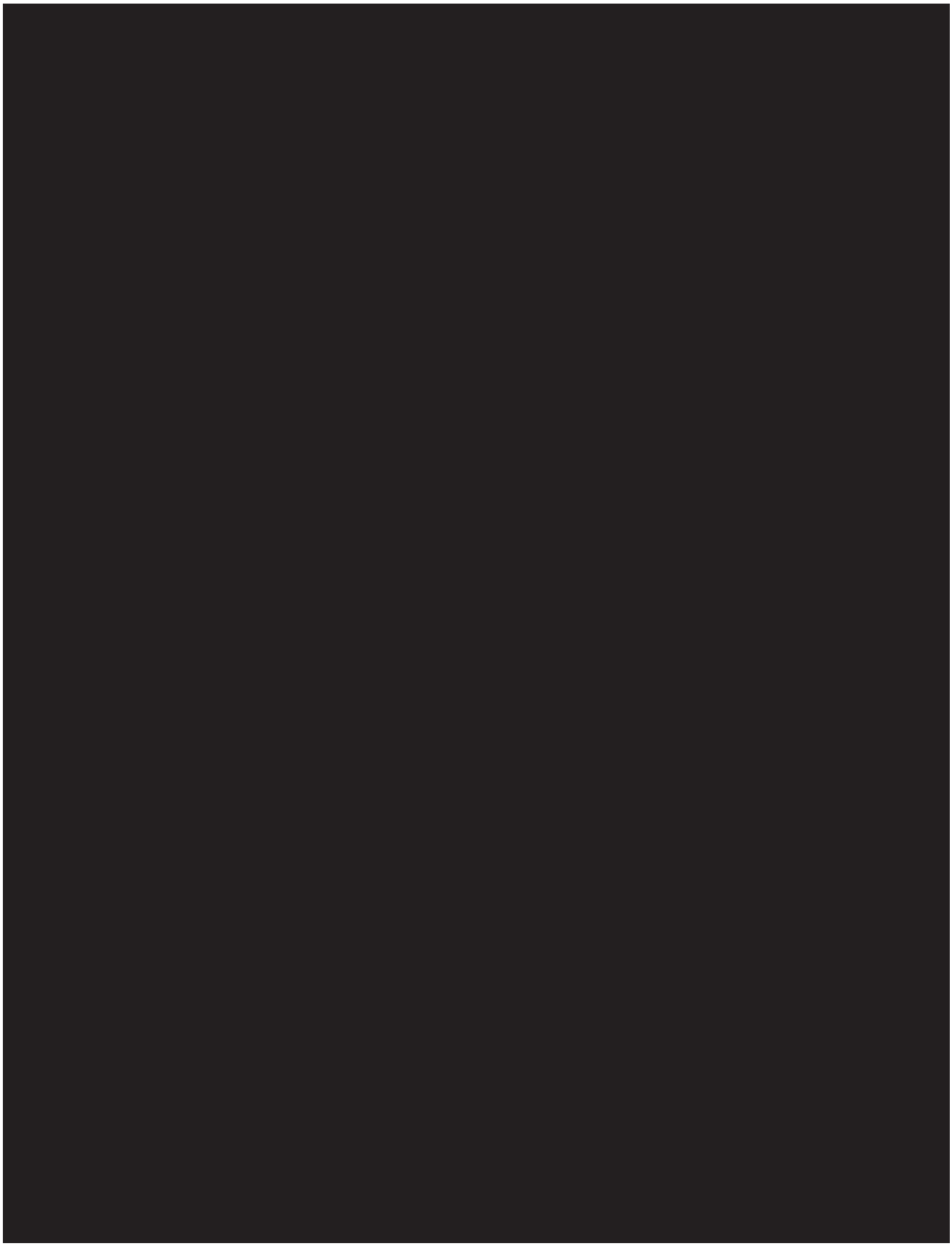












# 10 HISTORY TABLE

Table 10: 1 History table for TSAP version 1.0 dated 15th Mar 2018

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| 1.0 | 15-Mar-2018 | [redacted] | None | This is the initial TSAP without any modification. |

Table 10: 2 History table for TSAP revised version dated 13th Nov 2019

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | All | Updated "protocol violation" to "protocol deviation".<br>Updated endpoints from "change from baseline in XXX after 26 weeks" to "change in XXX from baseline to the end of 26 weeks". |
| | | | Cover page | [redacted] |
| | | | 2 | Removed the following abbreviations from list: AUC, CSII, CT, DM&SM, DST, eDiary, EMA, GI, HCRU, ITT, MAGE, MDG, O*C, OC-H, OC-OffT, OC-P.<br>Updated "IVRS" to "IRT", "PD to PV", "TBL to TBILI".<br>Added AP, BOCF, DBL, EudraCT, MAR, MCMC, MI, MNAR, PCSA, PMM, REML, SE, SLR, TSactive. |
| | | | 4 | Mentioned TSAP amendment version 2 is according to CTP amendment version 3. |
| | | | 5.1 | Added the current primary endpoint under subsection DINAMO.<br>Added DINAMO Mono primary endpoint. |
| | | | 5.2.2 | Grouped the existing secondary endpoints under subsection DINAMO.<br>Added "proportion of patients who achieve HbA1c goals < 6.5% and < 7.0% at the end of 26 weeks" as DINAMO secondary endpoints.<br>Added DINAMO Mono secondary endpoints. |
| | | | [redacted] | |

Table 10: 2 History table for TSAP revised version dated 13th Nov 2019 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | [redacted] | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | | |
| | | | General analysis definition (6) | Updated Section number from no number to 6. |
| | | | 5.5 (6.1) | Updated Section number from 5.5 to 6.1.<br>Added on-treatment period for up to Week 26 and for Week 26 up to Week 52.<br>Updated treatment groups and added new one for analyses and the presentation of the outputs. |
| | | | 5.6 (6.2) | Updated Section number from 5.6 to 6.2.<br>Paragraph started with "As the primary endpoint is analysed after 26 weeks, …" has moved to Section 6.3 together with PPS.<br>Consolidate the IPD codes for empagliflozin and linagliptin into a study specific IPD code.<br>Made reference code to the ones for empagliflozin and linagliptin.<br>Updated the inclusion and exclusion numbering according to the change of exclusion 1 to become inclusion 10.<br>Combined columns "Category" and "Code" to "IPD Code". |
| | | | 5.7 (6.3) | Updated Section number from 5.7 to 6.3.<br>Updated the text for the TSactive, mITT and PPS to help the clarity of the definition. |

Table 10: 2 History table for TSAP revised version dated 13th Nov 2019 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | Table 6.3:1 | Removed all primary endpoint analyses described as efficacy / effectiveness from the table.<br>Removed primary endpoint sensitivity test (MI).<br>Added DINAMO Primary endpoint analyses: primary & secondary family PMM analyses (mITT, PP); sensitivity primary & secondary family MMRM analyses (mITT); and sensitivity MMRM analysis (mITT).<br>Added DINAMO Mono Primary endpoint NCF analysis.<br>Demographics, baseline variables, concomitant medications, exposure/compliance will be analysed using TS instead of mITT. |
| | | | [redacted] | |
| | | | [redacted] | |
| | | | 5.9 (6.5) | Updated Section number from 5.9 to 6.5. |
| | | | 5.10 (6.6) | Updated Section number from 5.10 to 6.6. |
| | | | 5.10.1 (6.6.1) | Updated Section number from 5.10.1 to 6.6.1. |
| | | | 5.10.1.2 (6.6.1.2) | Updated Section number from 5.10.1.2 to 6.6.1.2.<br>Added to exclude any values collected after the start of rescue medication to the OC definition. |
| | | | 5.10.1.3 (6.6.1.3) | Updated Section number from 5.10.1.3 to 6.6.1.3.<br>Added to include any values collected after the start of rescue medication to the OC-AD definition. |
| | | | 5.10.1.4 (6.6.1.4) | Updated Section number from 5.10.1.4 to 6.6.1.4.<br>Added to consider any values collected after the start of rescue medication as failure to the NCF definition. |

Table 10: 2 History table for TSAP revised version dated 13th Nov 2019 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | 5.10.2 (6.6.2) | Updated Section number from 5.10.2 to 6.6.2.<br>Updated the text to where to locate the missing data imputation approaches. |
| | | | 5.10.3 (6.6.3) | Updated Section number from 5.10.3 to 6.6.3. |
| | | | 5.10.4 (6.6.4) | Updated Section number from 5.10.4 to 6.6.4. |
| | | | 5.11 (6.7) | Updated Section number from 5.11 to 6.7.<br>Added three baseline definitions: Study baseline, titration baseline and safety extension baseline.<br>Clarified data from scheduled visit(s) will always be selected if they are collected correctly. |
| | | | Table 6.7:2 | Updated title from "Time window for HbA1c measurements at…" to "Time window for efficacy and safety measurements at…"<br>Rename Week 12 from Visit "4" to "4A".<br>Rename Week 14 from Visit "5" to "4B".<br>Rename Week 26 from Visit "6" to "5".<br>Rename Week 30 from Visit "7" to "6".<br>Rename Week 42 from Visit "8" to "7".<br>Rename Week 52/EOT from Visit "9" to "8".<br>Updated footnote B according to the newly defined baseline definitions.<br>Removed reference to BI XLAB2 macro. |
| | | | 6 (7) | Updated Section number from 6 to 7.<br>Updated the name of the treatment groups.<br>Added that DINAMO and DINAMO mono will be reported separately. |
| | | | 6.1 (7.1) | Updated Section number from 6.1 to 7.1. |
| | | | 6.1.1 (7.1.1) | Updated Section number from 6.1.1 to 7.1.1.<br>Added BMI continuous variable and Tanner stage for the demographic summary.<br>Removed blood pressure continuous variable from the baseline characteristic summary.<br>Updated unit of UACR from "mg/gcrea" to "mg/g".<br>Updated that the outputs will be presented by treatment group 1. |
| | | | 6.2 (7.2) | Updated Section number from 6.2 to 7.2.<br>Updated that the outputs will be presented by treatment group 1 and 6 |
| | | | 6.3 (7.3) | Updated Section number from 6.3 to 7.3.<br>Updated reference Section 6.6.3 to Section 6.6.4.<br>Updated that the outputs will be presented by treatment group 1 and 6. |
| | | | 6.4 (7.4) | Updated Section number from 6.4 to 7.4. |
| | | | 6.4.1 (7.4.1) | Updated Section from 6.4.1 to 7.4.1 DINAMO. |
| | | | 6.4.1.1 | Removed Section 6.4.1.1 Primary MMRM efficacy analysis. |
| | | | 6.4.1.1.1 | Removed Section 6.4.1.1.1 Model diagnostics. |

Table 10: 2 History table for TSAP revised version dated 13th Nov 2019 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | 6.4.1.1.2 | Removed Section 6.4.1.1.2 Sensitivity analysis of the primary MMRM efficacy analyses. |
| | | | 6.4.1.2 (7.4.1.1) | Renamed "Section 6.4.1.2 Primary effectiveness analysis" to "Section 7.4.1.1 Primary family of analyses".<br>Added Table 7.4.1.1:1 PMM "jump-to-placebo" approach – the missing data imputation method.<br>Updated the text to clarify the steps.<br>Updated reference from Appendix 9.4 to 9.5.<br>Moved the primary hypothesis from Section 6.4.1 to the new Section 7.4.1.1. |
| | | | 6.4.1.2.1 (7.4.1.2) | Renamed "Section 6.4.1.2.1 Secondary family of effectiveness analyses" to "Section 7.4.1.2 Secondary family of analyses".<br>Updated hypotheses to be the same as CTP.<br>Added the hypotheses will also include Empa 10 mg patients who did not proceed to re-randomisation at Week 14.<br>Updated analysis model used from "MMRM model" to "ANCOVA inverse probability weighting" approach". |
| | | | [redacted] | [redacted] |
| | | | [redacted] | [redacted] |
| | | | [redacted] | [redacted] |
| | | | [redacted] | [redacted] |
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| | | | [redacted] | [redacted] |
| | | | [redacted] | [redacted] |
| | | | [redacted] | [redacted] |

Table 10: 2 History table for TSAP revised version dated 13th Nov 2019 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | (7.4.2) | Added new Section 7.4.2 DINAMO Mono with DINAMO Mono primary endpoint analysis detail. |
| | | | 6.5 (7.5) | Updated Section number from 6.5 to 7.5. |
| | | | 6.5.1 (7.5.1) | Updated Section number from 6.5.1 to 7.5.1. |
| | | | 6.5.2 (7.5.2) | Updated Section number from 6.5.2 to 7.5.2. |
| | | | (7.5.2.1) | Added new Section 7.5.2.1 DINAMO.<br>Added the content of the old Section 6.5.2.<br>Swapped the order of the first and second approach.<br>Moved paragraph "Baseline Observation Carried Forward (BOCF)… at baseline and week 26 within the analysis period." from second approach (OC) to first approach (OC-AD) as first approach is closer to pure ITT.<br>Added which treatment groups will be used for presentation.<br>Added the analysis of "proportion of patients who achieve HbA1c goals < 6.5% and < 7.0% at the end of 26 weeks". |
| | | | (7.5.2.2) | Added new Section 7.5.2.2 DINAMO Mono with all the analyses details. |
| | | | [redacted] | |
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Table 10: 2 History table for TSAP revised version dated 13th Nov 2019 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | 6.7 (7.7) | Updated Section number from 6.7 to 7.7.<br>Added an overall exposure table.<br>Added which treatment groups will be used for presentation. And how to count the exposure of the re-randomised treatments for both placebo and empagliflozin patients.<br>The exposure categories and exposure cumulative categories of the assessment of up-titration to empa 25 mg updated to use the primary safety analysis categories.<br>Added the analysis period to each of the analysis type.<br>Updated section to apply for the 2 newly defined extent to exposure. One including off-treatment period and the other excluding off-treatment period. |
| | | | 6.8 (7.8) | Updated Section number from 6.8 to 7.8.<br>Added long term safety analysis.<br>Added which treatment groups will be used for presentation.<br>Added the reporting for DINAMO and DINAMO Mono are separate.<br>Added details of what would be presented. |
| | | | 6.8.1 (7.8.1) | Updated Section number from 6.8.1 to 7.8.1.<br>Removed AE collapsing rule, replaced by following BI guideline. |
| | | | 6.8.1.1 (7.8.1.1) | Updated Section number from 6.8.1.1 to 7.8.1.1.<br>Updated reference from "…see section 6.8), except…" to "…see Section 7.8), except…".<br>Updated reference from "…see section 5.5." to "…see Section 6.1". |
| | | | 6.8.1.2 (7.8.1.2) | Updated Section number from 6.8.1.2 to 7.8.1.2.<br>Added which treatment groups will be used for presentation. |
| | | | 6.8.1.3 (7.8.1.3) | Updated Section number from 6.8.1.3 to 7.8.1.3.<br>Added which treatment groups will be used for presentation.<br>Added the reporting for DINAMO and DINAMO Mono are separate. |
| | | | 6.8.1.4 (7.8.1.4) | Updated Section number from 6.8.1.4 to 7.8.1.4.<br>Added bullous pemphigoid and arthralgia as AESI.<br>Added which treatment groups will be used for presentation.<br>Updated the location of the project level AESI list. |

Table 10: 2 History table for TSAP revised version dated 13th Nov 2019 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | 6.8.1.5 (7.8.1.5) | Updated Section number from 6.8.1.5 to 7.8.1.5.<br>Added which treatment groups will be used for presentation.<br>Added a subgroup descriptive summary table for Hypoglycaemia.<br>Added Arthralgia.<br>Added Bullous pemphigoid.<br>Added AE related to reduced intravascular volume.<br>Added Ketone measurements reported as AE. |
| | | | 6.8.1.7 (7.8.1.7) | Updated Section number from 6.8.1.7 to 7.8.1.7. |
| | | | 6.8.2 (7.8.2) | Updated Section number from 6.8.2 to 7.8.2.<br>Added for both DINAMO and DINAMO Mono.<br>Added it will presented for the primary safety analysis with both SI and US units. |
| | | | 6.8.2.1 (7.8.2.1) | Updated Section number from 6.8.2.1 to 7.8.2.1.<br>Added further safety endpoint analyses.<br>Removed XLAB related text.<br>Removed table for change from baseline in haematocrit over time including during the follow up period.<br>Added which safety analyses will be carry out. |
| | | | 6.8.2.2 (7.8.2.2) | Updated Section number from 6.8.2.2 to 7.8.2.2.<br>Added which safety analyses will be carry out. |
| | | | 6.8.2.3 (7.8.2.3) | Updated Section number from 6.8.2.3 to 7.8.2.3.<br>Added which safety analyses will be carry out. |
| | | | 6.8.2.4 (7.8.2.4) | Updated Section number from 6.8.2.4 to 7.8.2.4.<br>Added which safety analyses will be carry out. |
| | | | 6.8.3 (7.8.3) | Updated Section number from 6.8.3 to 7.8.3.<br>Added further safety endpoint analyses.<br>Added for both DINAMO and DINAMO Mono.<br>Added it will presented for the primary safety analysis. |
| | | | 6.8.4 (7.8.4) | Updated Section number from 6.8.4 to 7.8.4.<br>Added for both DINAMO and DINAMO Mono. |
| | | | 7 (8) | Updated Section number from 7 to 8.<br>Updated references 3, 4, 5, and 7 from old SOPs to new KMED equivalent.<br>Added reference 12. |
| | | | [redacted] | |
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Table 10: 2 History table for TSAP revised version dated 13th Nov 2019 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 13-Nov-2019 | [redacted] | [redacted] | |
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| | | | 9 (10) | Updated Section number from 9 to 10. |
| | | | Whole document | Updated “BMI SDS” to “BMI z-score”. |

Table 10: 3 History table for TSAP revised version dated 23rd Jul 2021

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 23-Jul-2021 | [redacted] | Whole document | Updated “off-treatment” to “post-treatment”. |
| | | | 5.1 (DINAMO Mono primary endpoint) | Added “(including Week 26)” to the use of rescue medication criteria to clarify what exactly is included in the period.<br>Added “(at least 0.5% in absolute value)” to “Increase from baseline in HbA1c by 0.5% at Week 26” to clarify the meaning of 0.5%. |
| | | | 5.2.2 | Added criteria for “Time to treatment failure”. |
| | | | [redacted] | |
| | | | 6.1 | Re-wrote the treatment periods as found them to be confusing.<br>Also updated the treatment groupings “treatment abbreviation labelling”.<br>Added TG7, TG8 and TG9 for the result disclosure. |
| | | | 6.2 | Moved all IPDs criteria into DV specification, located in BIRDs. |
| | | | 6.3 | Added “PK parameter analysis set (PKS)”<br>Updated Table 6.3:1 (all outputs) and added Table 6.3:2 COVID-19 related outputs. |
| | | | [redacted] | |

Table 10: 3 History table for TSAP revised version dated 23rd Jul 2021 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 23-Jul-2021 | [redacted] | [redacted] | [redacted] |
| | | | 6.6.1 | Updated OC, OC-ROC.<br>Renamed OC-OCF to OC-LOCF.<br>Added OC-AD-BOCF. |
| | | | 6.6.3 | Section 6.6.3 “Safety and other variables” deleted |
| | | | 6.6.4 (6.6.3) | Section 6.6.4 “Missing dates and times” became Section 6.6.3.<br>Updated the rule for imputing the missing/incomplete drug stop date. |
| | | | (6.6.4) | Added new section 6.6.4 “Missing and incomplete laboratory reference ranges”. |

Table 10: 3 History table for TSAP revised version dated 23rd Jul 2021 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 23-Jul-2021 | [redacted] | 6.7 | Added "If last observed measurement is after rescue medication then there is no titration baseline for OC analysis." to Titration baseline.<br>Added "In efficacy analyses, the words off-treatment and post-treatment are used synonymously." To clarify the meaning of off- and post-treatment.<br><br>Added more details of how to handle HbA1c data. |
| | | | 6.7:1 | Added AESI Hepatic injury and lower limb amputation. |
| | | | 6.7:2 | Updated time window cut-off.<br>Added how to select the HbA1c data for analysis (NGSP or not) |
| | | | 7 | Deleted "For efficacy analyses, patients will be analysed according to the patient information given in the eCRF in the case of potentially erroneous data entered into the IRT system" as age used in analysis came from the IRT system. |
| | | | 7 | Added "All result disclosure outputs will be presented in the final reporting only at the same time as DINAMO Mono reporting." to clarify when the result disclosure outputs will be provided. |
| | | | 7.1.1 | Added height z-score<br><br>Removed Background antidiabetic treatment at study baseline from the baseline descriptive table.<br><br>Added "for DINAMO only" to the demographic and baseline efficacy variables tables by before and from start of COVID-19. |
| | | | 7.2 | Added "Only therapies under their available ATC3 code(s) will be presented." to the concomitant therapy paragraph.<br><br>Added "during randomised treatment" for use of antihypertensive for TG1 and TG6. |
| | | | 7.3 | Added details of how to handle the visit of premature discontinuation of treatment in the compliance summary.<br><br>Added "for DINAMO only" to the compliance tables by before and from start of COVID-19. |

Table 10: 3 History table for TSAP revised version dated 23rd Jul 2021 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 23-Jul-2021 | [redacted] | 7.4.1.2 | Text updated from "The ANCOVA model will utilise a weight variable having a value of 0 for the patients who are not in the hypothesis test of interest, a value of 2 for re-randomised patients who are in the hypothesis test of interest and a value of 1 otherwise." to "The ANCOVA models performed for each hypothesis will utilise a weight variable having a value of 2 for re-randomised patients and a value of 1 for all other patients in the treatment grouping for the respective hypothesis test.". |
| | | | 7.4.1.3 E | Added details of how to define the COVID-19 ICE and the imputation method. |
| | | | 7.4.1.3 F | Added new section for the sensitivity test "Primary family of hypotheses – Non-NGSP certified laboratories HbA1c values". |
| | | | (7.4.3) | Added new section "HbA1c data summary". |
| | | | 7.5.2.1 | For the first approach FPG analysis, added data type OC-AD-BOCF.<br><br>Moved the proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 weeks will be determined per treatment grouping 1 using mITT (NCF) set to the first approach. Replaced OC for the second approach. |
| | | | 7.5.2.2 | Added a descriptive Log-rank test comparing linagliptin 5 mg and pooled empagliflozin versus placebo individually up to Week 26 using mITT (NCF) set by TG1. |
| | | | [redacted] | |
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| | | | 7.7 | Re-organised the whole section.<br><br>Added "for DINAMO only" to the exposure tables by before and from start of COVID-19. |
| | | | 7.8 | Updated text to present TG4 for DINAMO Mono analyses. |
| | | | 7.8.1 | Added the location for TG4 and TG5 AEs outputs, where they are relocated into Section 16. |
| | | | 7.8.1.1 | Text added for the cut off of AEs occurred up to Week 26 and Week 52. |
| | | | 7.8.1.3 | Added treatment grouping details into text. To clarify which TGX will be used in the table. |
| | | | 7.8.1.5 | Added Hypoglycaemia derivation.<br>Added text to clarify what outputs to present. |
| | | | (7.8.1.8) | New section "AE incidence rates" added. |

Table 10: 3 History table for TSAP revised version dated 23rd Jul 2021 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 23-Jul-2021 | [redacted] | (7.8.1.9) | New section "COVID-19" added. |
| | | | 7.8.2.1 | Section re-organised.<br>Added the bone metabolism biomarkers to the general lab summary table with the normalised values. |
| | | | 7.8.2.2 | Removed extra details of the liver enzyme elevation as it caused confusion. |
| | | | 7.8.2.3 | Updated the presentation of the descriptive table to over time instead of baseline and last value only. |
| | | | 7.8.2.4 | Added a shift table for UACR. |
| | | | (7.8.2.5) | New section "Biomarkers" added. |
| | | | 7.8.3 | Removed OC analysis from the vital signs parameters analysis. |
| | | | 8 | Updated reference 8, 9, 10 and 12.<br>Added reference 14 and 15. |
| | | | [redacted] | [redacted] |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | Title page | Updated the document number "c20394975-03" to "c20394975-04".<br><br>Updated CTP version "Including Protocol Amendment 1-8" to "Including **Revised** Protocol **(Global** Amendment **6)**". |
| | | | 4 | Updated CTP amendment version from "…CTP amendment version 6.0 dated 14 Jul 2021" to "…CTP **global** amendment **6** dated **23 May 2022**". |
| | | | 5.2.2, 5.3.1 | Updated "Proportion of patients who achieve HbA1c **goals** …" to "Proportion of patients who achieve HbA1c …". To follow CTP. |
| | | | 5.3.1 | For proportion of patients who initiate glycaemic rescue therapy up to 26 weeks and 52 weeks, the word "(insulin)" has removed from DINAMO criteria and "(metformin and/or insulin)" has removed from DINAMO MONO criteria as to include all antidiabetic therapies as rescue medications and not limited to the allowed ones. |
| | | | 5.3.2 | Updated "Adverse events (AE) up to 26 and 52 weeks, including adverse events of special interest (AESI) (see CTP Section 5.3.6.1)" to "Adverse events (AE) up to 26 and 52 weeks, including adverse events of special interest (AESI) (see CTP Section 5.3.6.1), genital infections, urinary tract infections, acute pyelonephritis or urosepsis, bone fracture, arthralgia, bullous pemphigoid, adverse events related to reduced intravascular volume and ketone measurements reported as AE". |
| | | | 5.4.1 | Updated the following texts to align with project level reporting.<br>Old text" For analysis purposes, BMI will also be derived at visits where only weight was collected, using the last available height that was reported prior to the date of weight measurement." to<br>New text "For analysis purposes, BMI will also be derived at visits where only weight was collected, using the last available height that was reported prior to the date of weight measurement. **In case of missing height at screening, height can be carried backward for the derivation.**"<br><br>Old text "The age in month at **Screening** will be used to determine the values of L, M and S." to<br>New text "The age in month at **informed consent** will be used to determine the values of L, M and S.". |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | 6.1 | For TG9, added "active pooled" into the active treatments groups to clarify only active treatments period are included.<br><br>Old text "The treatment grouping **X** will be …" to<br>New text "The treatment grouping **TGx** will be …".<br><br>Old text "As a first example, the treatment identifier "E10-10R" means …" to<br>New text "As a first example, the treatment identifier "E10R-10" means…"<br><br>Old text "As a second example, the treatment identifier "E10/E25NR*" means…" to<br>New text "As a second example, the treatment identifier "E10NR/25*" means…". |
| | | | Table 6.3:1 | Updated "Occurrence of treatment failure up to or at Week 26" to "Occurrence of treatment failure up to or at Week 26 (DINAMO Mono patients only)".<br><br>Added "DINAMO Mono – Sensitivity analysis" Occurrence of treatment failure up to or at Week 26 (DINAMO Mono and suitable DINAMO patients)<br><br>Updated the following text to make clear the timing of the age.<br>Old text "Freq. of patients with symptomatic hypoglycaemia AE with plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemia AE by **baseline age** in categories" to<br>New test "Freq. of patients with symptomatic hypoglycaemia AE with plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemia AE by **age at randomisation** in categories" |
| | | | [redacted] | |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | [redacted] | [redacted] |
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Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | 6.7 | Added the following text to clarify how the baseline is defined for the not treated but randomised patients.<br>"Note: On or prior to date of randomisation will be used, instead of prior to date of drug administration, for randomised patients who have not taken any blinded study drug."<br>Removed the repeated words.<br>Old text "Measurements taken after the last intake of study drug and **after the** end of the endpoint specific follow-up period will be considered post-treatment values…." to<br>New text "Measurements taken after the last intake of study drug and end of the endpoint specific follow-up period will be considered post-treatment values….". |
| | | | 7 | Updated the disclosure table title to clarify what AGE should be used.<br>Old text "Number of screened patients by age groups …"<br>New text "Number of screened patients by age (at time of informed consent) groups …".<br>Also added the following text to include both laboratory units: SI and Conventional units as requested by FDA.<br>And added "Figures will be added if deemed necessary".<br>"HbA1c and FPG in conventional unit will be analysed in Appendix 15.2 and SI unit will be analysed in Appendix 16.1.13.1. All analyses of laboratory parameters with SI unit will be analysed in Appendix 15 and the analyses of laboratory parameters with conventional unit will be analysed in Appendix 16.1.13.1." |
| | | | 7.1.1 | Separated age [years] in demographic summary table into 2 variables: age [years] ay informed consent (continuous) and age [years] at randomisation (categories). |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | 7.3 | Updated the subgroup from old text: "<br>• Compliance data over time up to Week 26 and up to Week 52 by visit and permanent discontinuation of study medication before and from the start of COVID-19 disruption, by TG1 on TS, TG6 on TSactive.".<br>To new text: "<br>• Compliance data over time up to Week 26 by visit and permanent discontinuation of study medication or/and completed Week 26 visit before/from the start of COVID-19 disruption, by TG1 on TS.<br>•Compliance data over time up to Week 52 by visit and permanent discontinuation of study medication before and from the start of COVID-19 disruption, by TG6 on TSactive.". |
| | | | 7.4.1.1 | Throughout the section, updated "age" to "age at randomisation".<br><br>Also added "The seed used in the DINAMO primary family of analyses will be 1218009101".<br><br>Also added "The least square mean differences of the active treatments to placebo, confidence intervals and p-values of change in HbA1c from baseline to the end of 26 weeks will be displayed via forest plots for the primary (primary family of hypotheses) and corresponding sensitivity analyses, refer to Section 7.4.1.3, separately for linagliptin and empagliflozin pooled.". |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | 7.4.1.2 | Updated "The ANCOVA models performed for each hypothesis will utilise a weight variable having a value of 2 for re-randomised patients and a value of 1 for all other patients in the treatment grouping for the respective hypothesis test. The model terms will include baseline HbA1c as a continuous variable, and treatment and age as categorical variables. Rubin's rules will be used to combine treatment estimates across the 500 imputations" to "The ANCOVA models will utilise a weight having a value of 0 for the patients who are not in the hypothesis test of interest; a value of 2 for re-randomised patients who are in the hypothesis test of interest and a value of 1 otherwise. The model terms will include baseline HbA1c as a continuous variable, and treatment and age at randomisation as categorical variables. Rubin's rules will be used to combine treatment estimates across the 500 imputations" to follow the update in CTP v7.0 and clarify what AGE category will be used in the model.<br><br>Also added "The seed used in the DINAMO secondary family of analyses will be 1218009102 for hypothesis H'0,1 and 1218009103 for hypothesis H'0,2.".<br><br>Also added "The least square mean differences for each of the empagliflozin doses versus placebo, confidence intervals and p-values of change in HbA1c from baseline to the end of 26 weeks will be displayed via forest plots for the analyses of the secondary family of hypotheses and corresponding sensitivity analyses, refer to Section 7.4.1.3, separately for TG2 and TG3.". |
| | | | 7.4.1.3 | Throughout the section, updated "age" to "age at randomisation".<br><br>In C, added "In addition, the analysis will be carried out in SI unit in Appendix 16.1.13.1." according to the FDA request. |
| | | | 7.4.1.5 | Throughout the section, updated "age" to "age at randomisation". |
| | | | 7.4.2 | Added the following text after FDA confirmation. "Patients will be assigned to the treatment they were randomised to at the initial. Non-completers who prematurely discontinue intake of study drug will be considered treatment failures." |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | (7.4.2.1) | New section added (Sensitivity analysis for DINAMO Mono) as a result of FDA discussion. "The analysis of the DINAMO Mono primary endpoint will be repeated on DINAMO Mono patients plus the drug-naïve DINAMO patients who satisfied the DINAMO Mono HbA1c inclusion criteria limit using the same statistical model." |
| | | | 7.5.2.1 | Throughout the section, updated "age" to "age at randomisation".<br><br>Added unit to the variables.<br><br>Added additional FPG [mmol/L] analysis to this section: "This analysis will be repeated for FPG [mmol/L] in Appendix 16.1.13.". |
| | | | 7.5.2.2 | Throughout the section, updated "age" to "age at randomisation".<br><br>Added additional HbA1c [mmol/mol] analysis to this section: "Analysis described in Section 7.4.1.3(C) will be repeated for HbA1c [mmol/mol] in Appendix 16.1.13.". |
| | | | [redacted] | [redacted] |
| | | | 7.7 | Updated subgroup categories from old text: "In order to assess the impact of COVID-19 to the treatment exposure in DINAMO only, the planned analyses for the treatment exposure will be repeated and summarised by permanent discontinuation of study medication before and from the start of COVID-19 disruption.".<br>To new text: "In order to assess the impact of COVID-19 to the treatment exposure in DINAMO only, the planned analyses for the treatment exposure will be repeated and summarised by permanent discontinuation of study medication or/and completed Week 26 visit before/from the start of COVID-19 disruption for up to Week 26 table and by permanent discontinuation of study medication before and from the start of COVID-19 disruption for up to Week 52 table.". |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | 7.8.1 | In response to the DINAMO Mono sample size reduction, TG4 and TG5 AE outputs are no longer required.<br><br>Updated "AE outputs for TG4 and TG5 will be presented in Section 16.1.13 unless otherwise stated.<br>" to "AE outputs for TG4 and TG5 will be presented **for DINAMO only** in Section 16.1.13 unless otherwise stated." |
| | | | 7.8.1.1 | Removed the following text as no longer required.<br>"Appendix 16.1.13 will display in addition AEs observed 'pre-treatment' (including AEs observed during screening and placebo run-in regardless of treatment group). Selected summaries will be created to include an analysis where AEs and SAEs are assigned to the following phases: pre-treatment, each treatment group (according to the type of analysis), and post-treatment." |
| | | | 7.8.1.3 | Updated paragraph to include more exposure adjusted AE tables according to FDA request:<br>"Incidence rate as defined in Section 7.8.1.8 will apply to frequency tables: overall summary of AEs, patients with AEs, patients with drug-related AEs, patients with other significant AEs according to ICH E3, patients with AEs leading to discontinuation and patients with SAEs. All above mentioned tables will be repeated by TG1, TG6, TG5 and TG4.".<br><br>Updated the sorting order for the AE table:<br>Old text "The system organ classes will be sorted in descending order of frequency then followed by preferred terms in descending order of frequency. Alphabetical ordering will be used for same frequency counts on PT level." to<br>New text "The system organ classes will be sorted in descending order of **the total** frequency **count of all treatments** then followed by preferred terms in descending order of **the total** frequency **count**. Alphabetical ordering will be used for **the** same **total** frequency counts on PT level.". |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | 7.8.1.4 | Updated the following text:<br>Old text "Diabetic Ketoacidosis (DKA) (narrow BIcMQ)" to<br>New text "Diabetic Ketoacidosis (DKA) (narrow BIcMQ, investigator assessment)".<br><br>Old text "Lower limb amputation and DKA events will be listed only using the TS.". to<br>New text "Events leading to lower limb amputation and DKA events will be listed only using the TS.". |
| | | | 7.8.1.5 | Throughout the section, updated "age" to "age at randomisation".<br><br>Added this text to clarify how to classify the Hypoglycaemia "Any hypoglycaemia that occurs on the same day, but, with a different start time, will be handled as a separate hypoglycaemic event."<br><br>Added this text to clarify how to derived the start date of Hypoglycaemia.<br>"The treatment phase assignment of any hypoglycaemia (AE and non-AE) is exclusively based on the collected start date."<br><br>Updated Arthralgia (HLGT) to Arthralgia (HLGT (primary path)).<br><br>Updated Pemphigoid in bullous conditions (HLT) to Pemphigoid in bullous conditions (HLT (primary path)). |
| | | | 7.8.2 | Added the following text according to FDA request: "Some selected analyses will be repeated in conventional units and presented in Appendix 16.1.13.1". |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | 7.8.2.1 | Remove "serum-procollagen type I N-terminal propeptide (PINP)" from this laboratory evaluation section.<br><br>Updated to include both SI and conventional units for the quantitative lab results.<br><br>Added "Exception to NTx: the central lab standard range of female with tanner stage 5 will be used as the BI standard reference range." for the normalised values tables.<br><br>Updated to include only in SI unit for the qualitative lab results and by reference tables.<br><br>Added the special categories for URBC and UWBC "Erythrocytes and leukocytes in urine analysis will be analysed as categorical data with 2 categories ("Normal" and "High")."<br><br>Updated to exclude parameters only measured occasionally for the by reference tables. |
| | | | 7.8.2.1 | Added the bold text into the PCSA bullet point.<br>• Frequency tables (include a patient listing) per treatment group will summarise the number of patients with any potentially clinically significant abnormality (PCSA) using company standard clinically significant criteria. **PCSA will be determined based on SI units and only be counted in tables if the patient had no PCSA value at baseline.**<br>In order to clarify how the count should be done. |
| | | | All sections | Updated "AGE" to "age at randomisation" for all AGE in category, as this is the correct time point. And "AGE" to "age at inform consent" for all continuous AGE. |
| | | | 7.8.2.3 | Added the conventional unit tables according to FDA request: "All analyses in this section will be repeated for parameters in conventional unit and presented in Appendix 16.1.13.". |

Table 10: 4 History table for TSAP revised version dated 7th Jul 2022 (continue)

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 7-JUL-2022 | [redacted] | 7.8.2.4 | Updated the following text with the bold text to clarify what UACR values are used. "A shift table from baseline value to last and maximum values on-treatment will be provided based on the following UACR categories (which used the derived UACR and not the albumin/creatinine ratio values provided by the lab): normal …"<br><br>Also added the derived UACR formula. |
| | | | 7.8.2.5 | Added PINP to the biomarkers descriptive tables.<br><br>Added additional tables "Descriptive statistics by sex and tanner stage category version 2, see Table 6.4:1 for the category, will be summarised over time up to Week 26 by TG1 and up to Week 52 by TG5 on the standard units for PINP, NTx, IGF-1, IGF-BP3.". |
| | | | 8 | Old text "001-MCS-36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON" to<br>New text "BI-KMED-TMCP-MAN-0012: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED". |
| | | | [redacted] | |
| | | | | |
| | | | | |

Table 10: 5 History table for TSAP revised version dated 28th Jul 2022

| Version | Date | Author | Changes in old Section (new Section) | Brief description of change |
|---|---|---|---|---|
| Revised | 28-JUL-2022 | [redacted] | 7.4.1.1 | Updated to use one seed for the missing data imputation for all confirmatory analyses.<br>OLD Text … The seed used in the DINAMO **primary family of** analyses will be 1218009101.<br>NEW Text … The seed used in the DINAMO **confirmatory** analyses will be 1218009101. |
| | | | 7.4.1.2 | Removed the seeds from this section in order to use the seed mentioned in section 7.4.1.1.<br>Deleted OLD Text … **The seeds used in the DINAMO secondary family of analyses will be 1218009102 for hypothesis H'$_{0,1}$ and 1218009103 for hypothesis H'$_{0,2}$.** |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c20394975** **Technical Version Number:5.0**

**Document Name:** 8-01-tsap-core

**Title:** A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Author-Statistician | [redacted] | 28 Jul 2022 18:53 CEST |
| Approval-Medical Writer | | 28 Jul 2022 19:29 CEST |
| Approval-Clinical Trial Leader | | 28 Jul 2022 19:41 CEST |
| Approval-Project Statistician | | 28 Jul 2022 20:16 CEST |
| Approval-Clinical Pharmacokinetics | | 28 Jul 2022 22:19 CEST |
| Approval | | 29 Jul 2022 09:43 CEST |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|