Boehringer Ingelheim

Clinical Trial Protocol

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EudraCT No. **EU Trial No.**	Not appreciable	
BI Trial No.	1245-0218	
BI Investigational Medicinal Product(s)	Jardiance®, empagliflozin	
Title	A randomised, double-blind, placebo-controlled, parallel group, 52 weeks phase IV trial to evaluate efficacy and safety of oral, once daily empagliflozin in elderly Japanese patients with type 2 diabetes mellitus and insufficient glycaemic control	
Lay Title	A study to test how well empagliflozin works in Japanese people with type 2 diabetes who are older than 65 years	
Clinical Phase	IV	
Clinical Trial Leader	[redacted] Phone: [redacted] FAX: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] FAX: [redacted]	
Version and Date	**Version: 1.0**	**Date: 25 May 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	25 May 2020
Revision date	N/A
BI trial number	1245-0218
Title of trial	A randomised, double-blind, placebo-controlled, parallel group, 52 weeks phase IV trial to evaluate efficacy and safety of oral, once daily empagliflozin in elderly Japanese patients with type 2 diabetes mellitus and insufficient glycaemic control
Coordinating Investigator	[redacted] Phone: [redacted] FAX: [redacted]
Trial site(s)	Multi-center trial conducted in Japan
Clinical phase	IV
Trial rationale	Japan's population is aging, and it is reported that more than 50% of patients with type 2 diabetes mellitus (T2DM) are currently of advanced age (≥60 years old). However, efficacy data is limited in the elderly population (especially those aged ≥75 years), who tends to have a low body mass index (BMI). It is well known that ageing process itself can lead to unfavourable changes related to deteriorations of physical status. There is increasing interest in sarcopenia in elderly patients with T2DM. Poor glycemic control in patients with diabetes may be associated with low muscle mass.The aim of this study is to evaluate efficacy and safety over 52 weeks of empagliflozin therapy in elderly Japanese with T2DM patients whose glycaemia is insufficiently controlled despite of with or without other oral antidiabetic drugs as background treatment.
Trial objective(s)	The main objective of this study is to assess the efficacy of empagliflozin 10 mg after 52 weeks compared to placebo in elderly patients with T2DM. Secondary objectives are to explore if empagliflozin has any impact on patient physical condition compared to placebo in elderly patients with T2DM.
Trial endpoints	The primary endpoint is: • Change from baseline in glycosylated haemoglobin A1c (HbA1c) after 52 weeks of treatment (HbA1c will be measured in the units of % and mmol/mol at all clinical visits; the primary endpoint will use units of %). Secondary endpoints are: • Change of muscle mass from baseline to Week 52 • Change of body fat measurement from baseline to Week 52 • Change of lean body mass from baseline to Week 52 • Change of total body water from baseline to Week 52 • Change of bone mineral content from baseline to Week 52 • Change of skeletal muscle index from baseline to Week 52 • Change of grip strength from baseline to Week 52 • Change of time in the 5-time chair stand test from baseline to Week 52
Trial design	Randomised, double-blind, multi-center, placebo-controlled, parallel group trial
Total number of patients randomised	128
Number of patients on each treatment	64
Diagnosis	The trial will be performed in the elderly Japanese patients (65 years or older) with T2DM. Two populations will be recruited; patients who are treatment naïve and have insufficient glycaemic control, and patients who have insufficient glycaemic control despite of stable antidiabetic treatment.

Main in- and exclusion criteria	**Inclusion criteria** • Japanese patients with diagnosis of T2DM prior to informed consent • HbA1c ≥ 7.0% and ≤ 10.0% for patients at Visit 1 (screening) • If the patient is on treatment with oral antidiabetic drug(s) potentially associated with severe hypoglycaemia (e.g., sulfonylurea or glinides), the following HbA1c value is used as criterion 1) HbA1c ≥7.5% and ≤10.0% for age ≥65 and <75 2) HbA1c ≥8.0% and ≤10.0% for age ≥75 • Patients on diet and exercise regimen who are drug-naïve or on treatment with any oral antidiabetic drug(s) other than glucagon-like peptide-1 (GLP-1) agonists and SGLT-2 inhibitor. Antidiabetic therapy has to be unchanged for 12 weeks prior to randomisation (any thiazolidinedione therapy has to be unchanged for at least 18 weeks prior to informed consent). • Age ≥65 years at informed consent • BMI ≥22 kg/m^2 at Visit 1 (screening) • Male or post-menopausal female patients **Exclusion criteria** • Uncontrolled hyperglycaemia with a fasting glucose level >200 mg/dL (>11.1 mmol/L) during run-in period • Treatment with insulin within 12 weeks prior to informed consent • Impaired cognitive ability as supported by Mini Mental State Examination (MMSE)-J (defined as ≤23) and verified by the investigator at screening • Acute coronary syndrome (ST-elevation myocardial infarction [STEMI], non-STEMI, and unstable angina pectoris), stroke or transient ischemic attack within 12 weeks prior to informed consent • Indication of liver disease, defined by serum levels of either alanine aminotransferase (ALT [SGPT]), aspartate aminotransferase (AST [SGOT]), or alkaline phosphatase (ALP) above 3 x upper limit of normal (ULN) as determined during screening and run-in period • Impaired renal function, defined as estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2 (severe renal impairment, Modification of Diet in Renal Disease [MDRD] formula) as determined during screening and run-in period • Low grip strength defined as <28 kg for male or as <18 kg for female at screening • Short length of calf circumference defined as <34 cm for male or 33 cm for female at screening • Already confirmed diagnose of sarcopenia (based on AWGS algorithm 2019) • Known history of diabetic ketoacidosis • Known contraindications to empagliflozin according to the Japanese label • Disorders causing haemolysis or unstable red blood cells • Treatment with anti-obesity drugs within 12 weeks prior to informed consent or any other treatment at the time of screening (i.e., surgery, aggressive diet regimen (e.g., low- carbohydrate diet), etc.) leading to unstable body weight • Current treatment with systemic steroids (other than inhaled or topical steroids) at informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM
Test product(s)	empagliflozin
dose	10 mg daily
mode of administration	oral

Comparator product(s)	placebo
dose	Not applicable
mode of administration	oral
Duration of treatment	52 weeks
Statistical methods	The primary analysis is a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) comparing the change from baseline in HbA1c (in units of %) after 52 weeks of double-blind treatment. The statistical model will include fixed classification effects for treatment, gender, baseline renal function, visit and visit-by-treatment interaction, and a linear covariate for baseline HbA1c and age. An unstructured covariance structure will be used to model the within-patient errors. Descriptive statistics will be used to analyse the safety endpoints.

FLOW CHART

Period	Screening period	Run-in Period	Double-blind treatment period							Follow up period
Visit[1]	1	2	3	4	5	6	7	Phone contact	8 EOT[2]	9 EOS
Study week	-3	-2	0	4	12	24	36	50	52	1 week from Visit 8 or EOT
Days from randomisation	-28 to -21	-21 to -14	1[3]	29	85	169	253	351	365	EOT+7
Visit window (days)	-	-	N/A	+/-7	+/-7	+/-7	+/-7	N/A	+/-7	+7
Informed Consent	X									
Demographics	X									
Medical history/ Concomitant diagnoses	X									
In-/Exclusion criteria	X	X	X							
Physical examination[4]	C		T			T			C	T
Height	X									
Calf circumference	X									
Body weight	X		X			X			X	
Vital signs[5]	X		X			X			X	X
12-lead-ECG			X							X
Safety lab tests (blood and urine)[6]	X	X	X	X	X		X		X	X
HbA1c	X		X	X	X	X	X		X	
NT-proBNP	X									
Instruction on use of SMBG		X								
SMBG		X	X	X	X	X	X		X	X
[redacted]			[redacted]						[redacted]	
[redacted]			[redacted]						[redacted]	
Body composition measurement[8]			X						X	
Grip strength	X		X						X	
Chair stand test			X						X	
[redacted]		[redacted]						[redacted]		
[redacted]			[redacted]						[redacted]	
[redacted]			[redacted]						[redacted]	
MMSE-J (cognitive function)	X		[redacted]						[redacted]	
Diet and exercise counselling[11]	X	X	X	X	X	X	X	X	X	
IRT call/notification	X	X	X	X	X	X	X		X	
Dispense run-in period medication		X								
Randomisation			X							
Dispense double-blind medication			X	X	X	X	X			
Medication compliance check			X	X	X	X	X		X	
Adverse events[12]	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X		X	X
Termination of trial medication									X	
Trial completion										X

1. Visits should (except Visit 1) be routinely scheduled in the morning, at approximately the same time of day for each visit. All visits except Visit 1 must be performed in fasted state.
2. Patients who discontinue trial treatment prematurely-they will be followed up until the end of study (EOS). If it will not be given patient agreement, it will undergo the End of Treatment (EOT) visit as soon as possible and the EOS visit 7 days thereafter.
3. Day of Randomisation/Day of first administration of randomised trial medication. Drug administration is final procedure after all assessments are completed at Visit 3.
4. Physical examination; C = complete; T = targeted (focus on evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities). For details please see Section 5.2.1.
5. Measurements of vital signs should precede blood sampling.
6. Refer to Section 5.2.3 for more details.
7. All patient reported outcomes (PROs) should be completed by the patient on his/her own in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other trial staff. For the pre-specified order of PROs please refer to Section 5.1.5 and 5.1.6. For details on the PROs please refer to Appendices 10.5.
8. It includes muscle mass, body fat percentage, body fat mass, lean body mass, total body water, and bone mineral content as body composition parameter by using bioelectrical impedance analysis. For details please see Section 5.1.4.
9. [redacted]
10. The investigator and/or site staff (e.g., managerial dietician) will ask the patients about their daily diet during the past 4 weeks prior to Visit 3 and Visit 8 (EOT).
11. Diet and exercise counselling by a diet specialist or trained trial staff will be implemented through the clinical trial. Patients will be reminded about the importance to follow the recommended diet and exercise plan. Through the double-blind treatment period, the trial staff instructs patient to drink appropriate amount of water.
12. After the EOS visit (=individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related adverse event of special interest (AESI)s of which the investigator may become aware of and only via the BI SAE form.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BIA	Bioelectrical impedance analysis
BMI	Body mass index
CA	Competent Authority
CEC	Clinical event committee
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
DBL	Database Lock
DILI	Drug Induced Liver Injury
DKA	Diabetic ketoacidosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
EOT	End of Treatment
EudraCT	European Clinical Trials Database
[redacted]	[redacted]
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GLP-1	Glucagon-Like Peptide-1
GMP	Good Manufacturing Practice
GPSP	Good Post-Marketing Study Practice
GVP	Good Vigilance Practice
IB	Investigator’s Brochure

IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
[redacted]	[redacted]
MMSE	Mini mental state examination
OAD	Oral antidiabetic drug
OPU	Operative Unit
PRO	Patient reported outcomes
REP	Residual Effect Period
SAE	Serious Adverse Event
SGLT-2	Sodium-glucose cotransporter 2
SMBG	Self-monitoring blood glucose
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
ULN	Upper Level of Normal
UTI	Urinary tract infection

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus (T2DM) accounts for 90 to 95% of all cases of diabetes. T2DM is a progressive disease with high morbidity and mortality. Recent estimates suggest that the number of people worldwide with T2DM is currently 382 million and is expected to reach at least 592 million in 2035 [R14-1408].

In Japan, approximately 10 million people are strongly suspected to be affected by T2DM and a further 10 million people have a confirmed diagnosis of T2DM. In total 20 million people are suffering from either T2DM or pre-diabeties [R17-3735].

According to the Japanese Diabetes Society guideline [R17-1515], it is recommended to achieve the glycaemic goal of HbA1c to <7.0%, while less stringent HbA1c goal (<8.0%) is recommended in cases where intensive therapy is not feasible due to side effects such as hypoglycaemia or for other reasons, taking into consideration the age, duration of disease, organ damage, support structure etc..

Diet and exercise therapy should be initiated in T2DM patients. If a patient does not achieve the glycaemic control target after continuing diet and exercise therapy for several months, medication therapy should be initiated. Antidiabetic medications are selected considering age, degree of obesity, degree of complications, liver function, renal function, insulin-distributing ability, and insulin resistance.

Sodium-glucose cotransporter 2 (SGLT-2) is a member of a larger group of sodium substrate co-transporters, the sodium-glucose co-transport 5 gene family [R05-0939]. Under normoglycemia, glucose is almost completely reabsorbed by SGLTs in the kidney, whereas the reuptake capacity of the kidney is saturated at plasma glucose concentrations higher than approximately 10-11 mmol/L, resulting in increasing glycosuria typically seen in patients with diabetes mellitus. The capacity to reabsorb glucose can be decreased by inhibition of SGLT-2. In humans, empagliflozin very selectively blocks glucose transport via SGLT-2 (IC_{50} 1.3 nmol/l), with a 5000-fold selectivity over SGLT-1 (IC_{50} 6278 nmol/l).

Recently, the prevention of sarcopenia, a dysnutrition state accompanying aging or obesity in patients with diabetes, has become a new target of diabetes treatment. Sarcopenia, a recognised geriatric syndrome, is characterised by age-related decline of skeletal muscle plus low muscle strength and/or physical performance [R20-0528]. It is becoming clear that the risk of some symptoms/diseases such as falling, the need for nursing care, the frequency of complications, and death increases when the amount of muscle mass decreases beyond a certain level in elderly people.

For the definition and diagnostic criteria of sarcopenia, consensus by the European Working Group on Sarcopenia in Older People was announced in 2010. The body composition of an average Asian person is apparently different from that of a European person; hence, the diagnostic criteria of sarcopenia for Asian people should be independently developed. With this perspective, consensus by the Asian Working Group on Sarcopenia in Older People was

subsequently announced in 2014 [R20-0528] and updated the criteria to assess and evaluate sarcopenia in 2019 [R20-0617].

In addition to age-related or primary sarcopenia, dysnutrition based on metabolic syndrome with visceral fat accumulation and decreased muscle mass, regardless of age, has been recognized as secondary sarcopenia. It has been shown that patients with poorly controlled glycaemia of diabetes have significantly less muscle volume. Furthermore, the possibility that this muscle loss might be exacerbated even by diabetes treatment has been indicated when measured as total lean mass. It has been recently clarified that sodium–glucose cotransporter 2 (SGLT-2) inhibitors show excellent effects in treating T2DM not only by correcting hyperglycemia and reducing the risk of cardiovascular events, but also by reducing the body fat mass, including visceral fat. Symptoms based on insulin resistance should be therefore further alleviated by this decrease in visceral fat mass. The mechanism for such a reduction in fat mass with the use of SGLT-2 inhibitor is believed to be a result of lipolysis in the adipose tissue due to activation of gluconeogenesis. There is a concern, however, that the activation of the gluconeogenic system should induce not only lipolysis in the adipose tissue, but also proteolysis in the skeletal muscle that supplies amino acids to the liver as a substrate and can therefore lead to sarcopenia. To address this issue, it was carried out a clinical study using luseogliflozin, and SGLT-2 inhibitor, for Japanese patients with T2DM. Luseogliflozin treatment brought about favorable changes in body composition and metabolism of moderately obese Japanese patients with T2DM, accompanied by body fat reduction, and minimal muscle and bone mineral content reduction [R19-1405]. A report on the other study with canagliflozin, another SGLT-2 inhibitor, was also made in which skeletal muscle mass index also showed similar trends [P13-08159].

1.2 DRUG PROFILE

Empagliflozin received its first marketing approval in April 2014 in Australia and is approved for the treatment as an adjunct to diet and exercise to improve glycaemic control in adult patients with T2DM in more than 100 countries. In Japan, empagliflozin has received marketing approval on 26 Dec 2014. The preferred trade name is Jardiance®.

Based on a dedicated cardiovascular outcome trial (EMPA-REG OUTCOME®), a separate indication, reduction of the risk of cardiovascular death in patients with T2DM and established cardiovascular disease, was approved in more than 40 countries including the US, Canada and Australia. In over 50 countries including the EU, the indication was modified and/or the results included in the clinical trial section acknowledging the positive results of the cardiovascular outcome study. In Japan, the indication was not modified and the result is not yet included in the local prescribing information of Jardiance® [R20-0462].

There have been no marketing withdrawals or suspensions, no failures to obtain marketing authorisation renewal, no restrictions placed on the distribution of the product and no clinical trial suspensions for any product containing empagliflozin.

Mode of action

Empagliflozin, an orally available potent selective SGLT-2 inhibitor, has been studied as part of a global development program including more than 15000 patients with type 2 diabetes

treated in clinical studies, of which more than 10000 patients were treated with empagliflozin, either alone or in combination with metformin, a sulfonylurea, a Peroxisome Proliferator-Activated Receptor γ agonist, dipeptidyl peptidase-4 inhibitors, or insulin. This agent lowers both the saturation threshold and the transport maximum of SGLT-2 for glucose, resulting in increased glycosuria, insulin-independent reduction of plasma glucose levels with a low risk of hypoglycaemia, and negative energy balance with weight reduction.

Key pharmacokinetic characteristics

Empagliflozin showed mainly linear pharmacokinetics in humans reaching peak levels at approximately 1.5 hours with a biphasic decline and a terminal elimination half-life of 12.4 hours. Following oral administration of [14^{C}]-empagliflozin, approximately 41.2% and 54.4% of drug-related radioactivity was excreted in faeces and urine, respectively. None of the detected metabolites were major. Empagliflozin tablets can be administered with or without food.

Drug interactions

Empagliflozin does not inhibit, inactivate, or induce CYP450 isoforms. In vitro data suggest that the primary route of metabolism of empagliflozin in humans is glucuronidation by the uridine 5'-diphospho-glucuronosyltransferases UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Empagliflozin does not inhibit UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7. At therapeutic doses, the potential for empagliflozin to reversibly inhibit or inactivate the major CYP450 isoforms and UGT1 isoforms is remote. Drug-drug interactions involving the major CYP450 isoforms and UGT1 isoforms with empagliflozin and concomitantly administered substrates of these enzymes are therefore considered unlikely.

No clinically meaningful interactions were observed when empagliflozin was coadministered with other commonly used medicinal products. Based on results of pharmacokinetic studies no dose adjustment of empagliflozin is recommended when co-administered with commonly prescribed medicinal products.

Empagliflozin pharmacokinetics was similar with and without co-administration of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, and simvastatin, in healthy volunteers, with or without co-administration of torasemide and hydrochlorothiazide in patients with T2DM. Increases in overall exposure (area under the curve) of empagliflozin were seen following co-administration with gemfibrozil (59%), rifampicin (35%), or probenecid (53%). These changes were not considered to be clinically meaningful.

Empagliflozin had no clinically relevant effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide and oral contraceptives when co-administered in healthy volunteers.

Residual Effect Period

The Residual Effect Period (REP) of empagliflozin is 7 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamics effects still likely to be present.

Data from non-clinical studies

A comprehensive package of safety pharmacology, general toxicology, genetic toxicology, carcinogenicity, reproductive and developmental toxicology studies were conducted in mice, rats, rabbits and dogs to support the chronic administration of empagliflozin to humans. In addition, combination studies have been completed in rats with empagliflozin plus metformin or empagliflozin plus linagliptin. With the exception of the dose range finding and selected safety pharmacology studies, all studies were completed under good laboratory practice conditions.

Data from clinical studies

Empagliflozin was well tolerated in both healthy subjects and patients with T2DM up to maximum treatment duration of 208 weeks in completed T2DM studies Treatment with empagliflozin resulted in a similar percentage of overall AEs, severe AEs, and serious AEs compared to placebo and/or active comparators.

For a more detailed description of the empagliflozin profile, please refer to the current investigator's brochure (IB) [c01678844] and Japanese package insert [R20-0462].

1.3 RATIONALE FOR PERFORMING THE TRIAL

Japan's population is aging, and the proportion of elderly people (≥65 years) is approximately 30% of the total Japanese population [R20-0461]. It is reported that approximately 50% of patients with T2DM are currently of advanced age (≥60 years) [R20-0463].

There is no label restriction for age to use empagliflozin in Japan. However, efficacy data are limited in the elderly population (especially ≥75 years), who tends to have a low body mass index (BMI).

It is well known that ageing process itself can lead to unfavourable changes related to deteriorations of physical status. In Japan there is increasing interest in sarcopenia in elderly patients with T2DM.

Poor glycemic control in patients with diabetes may be associated with low muscle mass. Conversely, adequate glycemic control may increase muscle mass [R19-3669].

This study will investigate the efficacy of empagliflozin in elderly Japanese patients with T2DM. In addition, it will explore how it changes by treatment with empagliflozin on physical performance including grip strength and muscle mass.

1.4 BENEFIT - RISK ASSESSMENT

Empagliflozin is currently indicated for T2DM.

In completed clinical studies, empagliflozin was well tolerated in non-diabetic healthy volunteers and patients with T2DM up to maximal treatment duration of 208 weeks. The frequency of overall adverse events (AEs), AEs leading to discontinuation and serious adverse events (SAEs) were similar to placebo [c01678844].

1.4.1 Benefits

Treatment with empagliflozin 10 mg has been shown to result in clinically meaningful and statistically significant reductions in HbA1c, fasting plasma glucose (FPG), and in body weight in patients with T2DM.

All patients taking part in the trial may derive general medical benefit from careful and close monitoring by medical personnel during the trial. Safety will be ensured by monitoring the patients for AEs both clinically and by laboratory testing, and for hypo/hyperglycaemia by self-monitoring blood glucose (SMBG).

1.4.2 Risks

Table 1.4.2: 1 displays the anticipated side effects of the study drugs, based on the mechanism of action, on the observed clinical data from ongoing studies, and on published clinical data.

Table 1.4.2:1 Known and potential risks of clinical relevance for the study population

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: empagliflozin		
Hypoglycaemia	The risk of hypoglycaemia is considered to be low. However, when empagliflozin is used concomitantly with sulfonylurea and/or glinides, possibly increasing the risk of hypoglycaemia.	Patients in treatment with insulin are excluded from the study. Guidance for the investigator provided in the IB [c01678844]. Blood glucose will be monitored with SMBG.
Volume depletion	Empagliflozin may selectively reduce interstitial volume with minimal change in intravascular volume Polyuria and consequent dehydration and hypotension were identified as risks in	Guidance for the investigator provided in the IB [c01678844]. Information and recommendations for the patients provided in the informed consent form (ICF).

Table 1.4.2:1 Known and potential risks of clinical relevance for the study population (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	patients treated with empagliflozin, especially in patients with known cardiovascular disease, history of hypotension, taking diuretics or other antihypertensive drugs, or elderly patients aged 75 years and older [P19-02151].	
Diabetic ketoacidosis (DKA)	Rare cases of DKA, including fatal cases, were reported in patients treated with SGLT2-inhibitors. In patients treated with SGLT2-inhibitors DKA may occur with lower than usual glucose values. The risk of DKA is increased in patients with lower than needed insulin intake, type 1 diabetes mellitus (T1DM), low carbohydrate intake, acute illness, major trauma, operation, severe dehydration or alcohol use.	Patients with T1DM are excluded from the study. Patients in treatment with insulin are excluded from the study. Guidance for the investigator provided in the IB [c01678844]. Training will be provided to the investigators during investigator meeting. Information and recommendations for the patients provided in the ICF. DKA is an adverse event of special interest (AESI). Cases reported as DKA or metabolic acidosis are adjudicated. (See Sections 4.2.1 and 8.7 details are also described in the adjudication charter).
Complicated urinary tract infections (UTI)	Cases of complicated UTI, including pyelonephritis and urosepsis were reported in	Guidance for the investigator provided in the IB [c01678844].

Table 1.4.2:1 Known and potential risks of clinical relevance for the study population (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	patients treated with empagliflozin.	Information and recommendations for the patients provided in the ICF.
Necrotizing fasciitis of perineum (Fournier's gangrene)	Rare cases of Fournier's gangrene, including fatal cases, were reported in patients treated with SGLT2-inhibitors.	Guidance for the investigator provided in the IB [c01678844]. Information and recommendations for the patients provided in the ICF.
Hypersensitivity	The risks of allergic skin reactions (e.g., rash, urticaria) and angioedema were identified for empagliflozin based on post-marketing experience. As with all drugs, the risk of severe and unexpected allergic reactions cannot be excluded.	Patients with hypersensitivity to empagliflozin are excluded from trial participation.
Drug-induced liver injury (DILI)	No risk of DILI was identified for empagliflozin. However, DILI generally can be severe and lead to fatal outcome or need of liver transplant. Therefore, careful monitoring and assessment of patients for potential DILI are needed.	Parameters for potential liver injury are included in the safety laboratory. Cases of liver impairment are defined as an AESI. Severe cases of liver impairment are adjudicated. (See Sections 5.2.3, 5.2.6.1.4 and 8.7; details are also described in the adjudication charter).
Renal safety	In clinical trials in patients with DM, the incidence of renal impairment was similar to placebo. An initial decrease of estimated glomerular	Parameters for potential renal impairment are included in the safety laboratory.

Table 1.4.2:1 Known and potential risks of clinical relevance for the study population (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	filtration rate (eGFR) was seen in patients treated with empagliflozin, which improved during continuous treatment or discontinuation of empagliflozin. Cases of renal impairment, including those requiring dialysis, were reported in patients using SGLT2-inhibitors. Due to the renal mode of action and risk of volume depletion, the renal safety should be monitored.	Cases of renal impairment are defined as an AESI (see Sections 5.2.3 and 5.2.6.1.4).
Trial procedures		
The patients who take placebo have a higher probability of treatment failure, i.e., of increase in HbA1c.	50% of patients will receive placebo.	This study will have criteria for rescue therapy (refer to Section 4.2.2) and patient discontinuation from study medication to ensure an adequate treatment in case of any clinical concern (refer to Section 3.3.4).
Hyperglycaemia	50% of patients will receive placebo and these patients thus have a higher probability of treatment failure, i.e., of increase in FPG and HbA1c.	Blood glucose will be monitored with SMBG. Appropriate inclusion/exclusion criteria of HbA1c and FPG values, as well as criteria for rescue therapy and patient discontinuation will ensure an adequate treatment in case of any clinical concern.

Table 1.4.2:1 Known and potential risks of clinical relevance for the study population (cont.)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Bruising and pain commonly experienced in association with blood sampling		The frequency of blood sampling during the whole course of the trial is not excessive.
Other risks		
Administration of Placebo	If the patient is randomised to receive a placebo, patients may not be able to control their blood glucose sufficiently during the course of the trial.	If the rescue criteria are met, rescue therapy will be initiated at the investigator's discretion. If the rescue criterion is met and/or investigator judges necessary, the patient will receive rescue therapy.

Known and potential risks in healthy volunteers and patients with T2DM:

For the main risks, please refer to Table 1.4.2:1.

In general there was a small increase in frequency of urinary tract infection (UTI) compared to placebo. There was an increase in frequency of genital infections with the use of empagliflozin. There was a small increase in total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol and no significant changes in triglycerides. No clinically relevant changes in electrolytes were observed with empagliflozin [c01678844].

Other risks to the patients are the risks inherent to any clinical trial such as unexpected adverse clinical or laboratory events.

For more information about clinical efficacy data and adverse drug reactions of empagliflozin reference is made to the current version of the empagliflozin IB [c01678844] and the local prescribing information of Jardiance® [R20-0462].

1.4.3 Discussion

All patients taking part in the trial may derive general medical benefit from careful and close monitoring by medical personnel during the study. Safety will be ensured by monitoring the patients for AEs both clinically, by laboratory testing, and for hypo/hyperglycaemia by SMBG.

Patients who are randomised to placebo group will not benefit from efficacy of investigational drug, but they will continue to receive their standard of care that has been provided before participating in the trial.

During the study, in case blood glucose level meets rescue criteria, patient will receive rescue therapy to ensure their safety (see Section 4.2.1).

Given the safety profile of empagliflozin established in patients with T2DM, the careful monitoring to be conducted during the study visits, and the blood glucose monitoring to be performed by the patients at home during the study, the sponsor considers the risks for the participating patients will be minimised and justified when compared with the potential benefits from this trial.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this study is to assess the efficacy of empagliflozin 10 mg after 52 weeks compared to placebo in elderly patients with T2DM.

Secondary objectives are to explore if empagliflozin has any impact on patient physical condition compared to placebo in elderly patients with T2DM.

2.1.2 Primary endpoint(s)

The primary endpoint in this study is the change in HbA1c from baseline after 52 weeks of treatment. HbA1c will be measured in the units of % and mmol/mol at all clinical visits; the primary endpoint will use units of %.

2.1.3 Secondary endpoint(s)

Secondary endpoints are the following safety endpoints:

- Change of muscle mass from baseline to Week 52
- Change of body fat measurement from baseline to Week 52
- Change of lean body mass from baseline to Week 52
- Change of total body water from baseline to Week 52
- Change of bone mineral content from baseline to Week 52
- Change of skeletal muscle index from baseline to Week 52
- Change of grip strength from baseline to Week 52
- Change of time in the 5-time chair stand test from baseline to Week 52

Please refer to Section 5.1.2, 5.1.3, and 5.1.4, and Appendix 10.1, 10.2, and 10.3 how each item will be measured and evaluated.

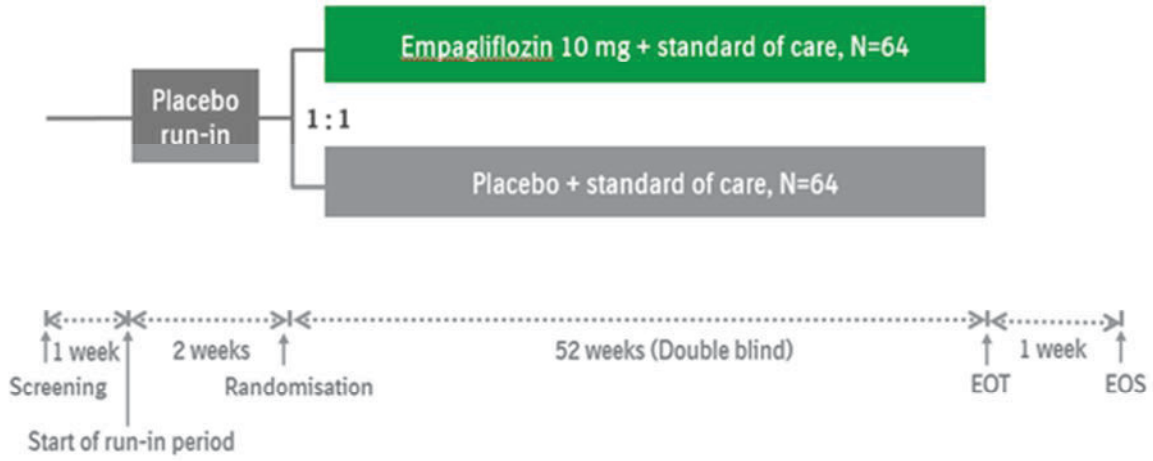
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a randomised, double-blind, placebo-controlled, multi-centre trial. The trial design is illustrated in Figure 3.1: 1.

Approximately 128 male and female eligible patients with T2DM will be randomised (1:1) in the study in Japan.

Each randomised patient will be treated with oral empagliflozin or placebo daily in addition to standard of care. Patients will receive the trial medication for 52 weeks. An End of study (EOS) visit will be performed 7 days after the End of Treatment Visit (EOT).



EOT: end of treatment, EOS: end of study

Figure 3.1: 1 Overall study design

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

Since efficacy data is limited in the elderly population (especially ≥75 years) compare to placebo and there are no studies that have thoroughly investigated how empagliflozin affects muscle mass, grip strength, lower limb function, and physical activity in the elderly patient compared to placebo, the trial design that compare empagliflozin to placebo is appropriate.

As the patients who participate in the study will continue to receive stable standard of care that has been provided prior to screening, and will receive rescue medication if indicated, a placebo-controlled trial is justified. Since patients will continue their baseline treatment, the risk of significant hyperglycaemia is low during the 52 weeks. Additionally, rescue therapies can be applied during this time frame to assure patient safety.

The intention of the run-in period is to ensure central laboratory data availability for randomisation, to assess the compliance of the trial medication administration, to ensure fasting glucose level is stable by a regular monitoring of blood glucose with a SMBG, and to ensure that the patient can continue diet and exercise and background medication according to investigator's instructions.

A double-blind design is adopted in order to minimise bias to evaluate the efficacy and safety of empagliflozin in comparison to placebo. The randomised treatment period is planned for 52 weeks which is considered a relevant observation time for the investigation of the defined endpoints of efficacy and safety, including the variation of physical activity, in special physical activity and grip strength in patients over 75 years of age, in elderly patients in long-term treatment with empagliflozin, .

The one-week follow-up period, after treatment, is considered to be sufficient as the REP of empagliflozin is 7 days.

3.3 SELECTION OF TRIAL POPULATION

Approximately 128 patients are planned to be randomised in Japan and participation of approximately 20 sites is planned. Screening of patients for this trial is competitive, i.e., screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A log of all patients enrolled into the trial (i.e., who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the clinical trial manager (CT Manager) should be contacted immediately.

3.3.1 Main diagnosis for trial entry

The trial will be performed in the elderly Japanese patients with T2DM. Two populations will be recruited; patients who are treatment naïve and have insufficient glycaemic control, and patients who have insufficient glycaemic control despite of stable antidiabetic treatment for 12 weeks (any thiazolidinedione therapy has to be unchanged for 18 weeks).

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Japanese[1] patients with diagnosis of T2DM prior to informed consent

[1] Japanese is defined as patient has parents who are Japanese.

2. HbA1c ≥7.0% and ≤10.0% for patients at Visit 1 (screening)
   If the patient is on treatment with oral antidiabetic drug(s) potentially associated with severe hypoglycaemia (e.g., sulfonylurea or glinides), the following HbA1c value is used as criterion
   1) HbA1c ≥7.5% and ≤10.0% for age ≥65 and <75
   2) HbA1c ≥8.0% and ≤10.0% for age ≥75
3. Patients on diet and exercise regimen who are drug-naïve[2] or on treatment with any oral antidiabetic drug (OAD) other than Glucagon-Like Peptide-1 (GLP-1) agonists and SGLT-2 inhibitor. Antidiabetic therapy has to be unchanged for 12 weeks prior to randomisation (any thiazolidinedione therapy has to be unchanged for at least 18 weeks prior to informed consent).
4. Age ≥65 years at informed consent
5. BMI ≥22 kg/m^2 at Visit 1 (screening)
6. Male or post-menopausal[3] female patients
7. Patient signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

3.3.3 Exclusion criteria

1. Uncontrolled hyperglycaemia with a fasting glucose level >200 mg/dL (>11.1 mmol/L) during run-in period
2. Treatment with insulin within 12 weeks prior to informed consent
3. Impaired cognitive ability as supported by MMSE-J (defined as ≤23) and verified by the investigator at screening
4. Acute coronary syndrome (ST-elevation myocardial infarction [STEMI], non-STEMI, and unstable angina pectoris), stroke or transient ischemic attack within 12 weeks prior to informed consent
5. Indication of liver disease, defined by serum levels of either alanine aminotransferase (ALT [SGPT]), aspartate aminotransferase (AST [SGOT]), or alkaline phosphatase (ALP) above 3 x upper limit of normal (ULN) as determined during screening and run-in period
6. Impaired renal function, defined as eGFR <45 mL/min/1.73 m^2 (severe renal impairment, Modification of Diet in Renal Disease [MDRD] formula) as determined during screening and run-in period
7. Low grip strength defined as <28 kg for male or as <18 kg for female at screening
8. Short length of calf circumference defined as <34 cm for male or 33 cm for female at screening
9. Inability to perform 5 times chair stand test according trial protocol
10. Already confirmed diagnose of sarcopenia (based on AWGS algorithm 2019)

[2] drug-naïve is defined as no antidiabetic drugs for at least 12 weeks prior to informed consent.
[3] Menopause is a point in time 12 months after a woman's last period.

11. Known history of diabetic ketoacidosis
12. Known contraindications to empagliflozin according to the Japanese label
13. Disorders causing haemolysis or unstable red blood cells
14. Any previous (within 2 years prior to informed consent) or planned bariatric surgery (or any other weight loss surgery) or other gastrointestinal surgery that induce chronic malabsorption
15. Medical history of cancer (except for resected non-invasive basal cell or squamous carcinoma) and/or treatment for cancer within the last 5 years
16. Treatment with anti-obesity drugs within 12 weeks prior to informed consent or any other treatment at the time of screening (i.e., surgery, aggressive diet regimen (e.g., low-carbohydrate diet), etc.) leading to unstable body weight
17. Current treatment with systemic steroids (other than inhaled or topical steroids) at informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent or any other uncontrolled endocrine disorder except T2DM
18. Known or suspected allergy or hypersensitivity to trial products or related products (e.g., SGLT-2 inhibitors)
19. Alcohol or drug abuse prior to informed consent that would interfere with trial participation or any ongoing condition leading to a decreased compliance to trial procedures or trial drug intake, in the opinion of the investigator
20. Intake of an investigational drug in another trial within 30 days prior to Visit 1 or participation in the follow-up period of another trial (participation in observational studies is permitted)
21. Any other clinical condition that, in the opinion of the investigator, would jeopardise patient's safety while participating in this clinical trial

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and electronic case report form (eCRF). If applicable, consider the requirements for adverse event collection reporting (please see Sections 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product. Please refer to Sections 4.2.1 and 4.2.2
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, or other diseases).
- Introduction of rescue therapy due to hyperglycaemia as described in Section 4.2.1 does not lead to sufficient treatment efficacy (rescue criteria still met). In this case, the reason for discontinuation will be classified as "lack of efficacy"
- Occurrence of hypoglycaemia that may put the patient at risk with continued participation (e.g., repeated hypoglycaemic episodes)
- Medically significant events that may put the patient at risk with continued participation (i.e., DKA, severe UTI including urosepsis, Fournier's gangrene).

In case of a temporary reason, trial treatment should be restarted if medically justified, please see Section 4.1.4.

Patients who discontinue treatment prematurely will be followed up until the end of the trial as outlined in the flowchart and Section 6.2.2.

A patient can be discontinued from the trial after discussion between the sponsor and the investigator if the eligibility criteria are being violated.

Patients who discontinue or withdraw from the study during placebo run-in period and before being randomised at Visit 3 will be considered a run-in failure. They have to be recorded as in eCRFs and no further follow-up is required (except for AEs, if needed).

Patients who are discontinued from the study after randomisation (Visit 3) and before completing 52 weeks of treatment will be considered as early discontinuations and the reason for the discontinuation must be recorded in the eCRFs. The reason will be included in the trial database and reported. If determined by the investigator as necessary for the patient's safety, a new antidiabetic medication regimen can be started immediately after discontinuation and must be recorded in the eCRFs. In this case, EOT visit must be performed before taking any new antidiabetic drug. If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the flowchart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, and explain the scientific relevance of their data even if he/she discontinue the trial treatment as well as explain the options for continued planned visit up to follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from Good Clinical Practice (GCP), the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in section 3.3.4.1.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by Boehringer Ingelheim Pharma GmbH & Co.KG.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Empagliflozin

Substance:	Empagliflozin
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim GmbH & Co.KG
Unit strength:	10 mg
Posology:	1 tablet once daily
Mode of administration:	Oral

Table 4.1.1: 2 Placebo to empagliflozin

Substance:	Placebo to empagliflozin
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim GmbH & Co.KG
Unit strength:	-
Posology:	1 tablet once daily
Method and route of administration:	Oral

Standard of care will not be provided as part of the clinical trial supplies.

4.1.2 Selection of doses in the trial and dose modifications

Empagliflozin 10 mg and 25 mg are approved in Japan for the treatment of T2DM.

In the ongoing Japanese post-marketing study, approximately 97% of patients who started treatment at 10 mg continue treatment with empagliflozin 10 mg for over a year without uptitration. Therefore, only empagliflozin 10 mg will be given in this study [c15144621].

4.1.3 Method of assigning patients to treatment groups

When a patient is confirmed eligible for entry into the randomised double-blind treatment period, treatment assignment will be by means of a third-party phone/web-based randomisation at Visit 3. This will involve the use of interactive response technology (IRT). To facilitate the use of the IRT, the investigator will receive an IRT manual including all necessary instructions for using the IRT. IRT manual will be available in the ISF.

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups of empagliflozin 10 mg or placebo to empagliflozin according to a randomisation plan in a 1:1 ratio at visit 3 via IRT. The randomisation will be stratified by HbA1c (<8.5% vs. ≥8.5%) as determined from the blood sample taken at Visit 1 and age (≥65 to <75 years vs. ≥75 years) at Visit 1. For further details please refer to Section 7.4.

Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System). The assigned medication number will be entered in the eCRF, and the corresponding medication kit should be given to the patient. Using this procedure, relevant parties will be blinded to the treatment group assignment.

4.1.4 Drug assignment and administration of doses for each patient

Eligible patients will be randomised to empagliflozin 10 mg or placebo. Medication will be dispensed in a double-blind manner. The empagliflozin dosing is described in Table 4.1.4:1.

Patients will be assigned a placebo run-in kit at the beginning of the placebo run-in period (Visit 2), and this kit will contain sufficient medication for the run-in period within visit window. Dispensing of kits for the double-blind treatment period will begin at Visit 3 and occur on 5 occasions over a period of 52 weeks.

From the start of the placebo run-in period (Visit 2), patients should be instructed to take their trial medication, 1 tablet with water, once daily in the morning. To ensure a dose interval of about 24 hours, the medication should be taken at the same time each day. If a dose is missed by more than 12 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken, and dose reductions are not permitted. Empagliflozin can be taken with or without food.

Patients should be instructed not to take their trial medication on the morning of study visits as they will be dosed while patient is in the trial site. Patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day. Visits should be routinely scheduled in the morning, at approximately the same time of day for each visit. The

actual date and time of administration of the medication at the trial visit will be recorded in the eCRF.

Patients will continue with their standard of care throughout the entire study.

Table 4.1.4: 1 Empagliflozin dose administration schedule

		Total units per dose	Timing
Placebo run-in period (open-label)			
All patients	matching placebo	1 tablet	once daily, morning
Randomised treatment period (double-blind)			
10 mg	active drug	1 tablet	once daily, morning
or			
Placebo	matching placebo	1 tablet	once daily, morning

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after database lock.

The access to the randomisation code will be kept restricted until its release for analysis.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the principal investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and appropriate eCRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's pharmacovigilance (PV) group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised PV representatives for processing in the PV database system and will not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated contract research organisation (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

The study medication will consist of packs labelled with the trial identification and medication kit number. Each pack will contain an appropriate number of empagliflozin tablets or placebo to empagliflozin with some reserve (see below) for dosing until the next scheduled visit.

The kit for placebo run-in period, assigned to all patients successfully completing Visit 2, will contain 21 tablets (i.e., sufficient supply for 2 weeks, with 1 week in reserve). Each kit for double-blind treatment period will contain 35 tablets (i.e., sufficient supply for 4 weeks, with 1 week in reserve).

At Visit 3, the patient will receive 1 kit for double-blind treatment period. The patient will receive 2 kits at Visit 4, 3 kits at Visit 5 and 6, and 4 kits at Visit 7.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the clinical research associate (CRA) or CT Manager (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the institutional review board (IRB)
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Notification to the Pharmaceuticals and Medical Devices Agency,
- Availability of the curriculum vitae of the principal investigator,
- Availability of a signed and dated clinical trial protocol,

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch/serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial

patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the clinical trial protocol and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Throughout the duration of the trial, patients should continue to take their previous antidiabetic therapy as permitted by trial protocol, including acceptable OADs with the exception of SGLT-2 inhibitors (treatment with insulin and GLP-1 agonists is excluded as well, see Section 4.2.2). This background medication of OADs should remain unchanged throughout the study. The background medication will not be provided as part of the clinical trial supplies.

The patients can take their background medication as they are used to and should have the same habits of dosing throughout the trial. Morning dose of OADs and study medication should be taken after the visits blood samples are taken.

Hyperglycaemia

Rescue medication can be given if the criterion below is met during the run-in period at the investigator's discretion. Patients who need rescue medication prior to Visit 3 are not eligible for randomisation. Please see Section 3.3.4.1:

- The patient has a glucose level >200 mg/dL (>11.1 mmol/L) after an overnight fast

Rescue medication, for the treatment of hyperglycaemia, can be initiated during the double-blind treatment period of the trial (i.e., from Visit 3 to Visit 8) at the investigator's discretion if the criterion below is met:

- The patient has a glucose level >200 mg/dL (>11.1 mmol/L) after an overnight fast

The above results should be confirmed, meaning that there is a minimum of two measurements, at least second measurement should be performed at the investigational site after an overnight fast (central or local laboratory testing is allowed), and on a different day to the initial measurement.

In order to expedite the rescue medication initiation decision, the investigator may confirm the results (second measurement) at the local or commonly used laboratory. This procedure with its results should be documented in the patient's medical chart. Before initiation of rescue therapy a FPG sample should be drawn and sent to the central lab for analysis.

If the above criteria are met, the initiation of rescue medication is at the Investigator's discretion, based on the patients' current clinical condition (e.g., ongoing illness etc.). If dose of standard of care increase, it should be recognised as rescue medication.

Rescue medication can be used from when it is initiated until the end of the trial. The choice of rescue medication and its dosage will be left to the discretion of the investigator excluding SGLT-2 inhibitors. Regardless of the choice made, rescue medication should be taken in accordance with the prescribing information of that respective medication, taking into account potential contraindications.

In the case of hypoglycaemic event that may put patient on risk (e.g., repeated symptomatic hypoglycaemic events or severe hypoglycaemic event), appropriate adjustment of oral antidiabetic therapy such as a dose reduction/discontinuation of ongoing rescue medication should be initiated.

If, in the investigator's clinical opinion, no further effect from the rescue medication is anticipated, and the patient's hyper- or hypoglycaemia cannot be controlled, the patient should be discontinued from the trial as specified in Section 3.3.4.

Any rescue medications should be recorded in the source documents and on the appropriate pages of the eCRF.

Rescue medication will not be provided as part of the clinical trial supplies.

Special attention must be paid to the prevention of DKA. All patients must be made aware of this risk and need to be instructed to contact the investigator or other healthcare professional in case of symptoms of DKA.

In case of a suspected DKA the investigator should ensure that appropriate tests are performed at the earliest opportunity according to guidelines in Japan, such as a blood gas test (i.e., pH, bicarbonate, anion gap, potassium, blood glucose, etc; the results will be collected on the relevant page of the eCRF) and that the patient is appropriately treated (i.e., hospitalised or referred to emergency treatment) according to treatment guidelines in Japan.

Any additional treatment, that does not qualify as a rescue medication, and is considered necessary for the patient's welfare may be given at the discretion of the investigator. Exceptions to this are the restrictions described in Section 4.2.2.

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Patient can continue any standard of care if patient used it before participating in the trial. Antidiabetic therapy has to be unchanged for 12 weeks prior to randomisation (for thiazolidinedione, therapy has to be unchanged for at least 18 weeks prior to informed consent).

SGLT-2 inhibitors (other than blinded study medication), Insulin, GLP-1 agonists, and any other diabetes drugs other than standard of care will be prohibited during the course of the trial.

Treatment with anti-obesity drugs or systemic steroids will be prohibited due to their influence on glucose metabolism and muscle mass. However, intermittent or short-term use (i.e., ≤2 weeks duration) of systemic steroids will be permitted as well as therapy with non-systemic steroids such as inhaled or local steroids. Furthermore, for patients taking thyroid hormones and testosterone, any change in the dose should be avoided. If dose changes do occur, then they should be recorded in the source documents and in the eCRF.

4.2.2.2 Restrictions on diet and life style

Through the clinical trial, patients will receive diet and exercise counselling by a diet specialist or trained trial staff. The counselling will be based on the diet and exercise recommendations of The Japanese Diabetes Society. The patients will be reminded to follow the agreed diet and exercise plan.

To avoid DKA, extreme diets (e.g., ketogenic diets) have to be avoided.

Through the double-blind treatment period, the investigator and trial staff will instruct the patient to drink appropriate volume of water every day. and it must be ensured particularly in the beginning of use of investigational drug, and caution must be continued during use.

Herbal or nutritional supplements with effect on blood glucose are prohibited throughout trial. Patients using/requiring these supplements should be discontinued from the trial, see Section 3.3.4.1.

Patients also should not take investigational drug in another trial within 30 days prior to Visit 1 in this trial. Furthermore, patients should not participate in another trial (involving an investigational drug) after discontinuing medication in this trial for the remaining trial period.

There are no other restrictions on diet and lifestyle.

4.2.2.3 Contraception requirements

Only male and post-menopausal female participate in this trial. Therefore, there are no special contraception requirements to be followed.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablet actually taken} \times 100}{\text{Number of tablet which should have been taken as directed by the investigator}}$$

If the compliance is smaller than 80% or larger than 120%, site staff will explain a reason in eCRF and remind to the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 HbA1c

HbA1c is considered appropriate to evaluate the efficacy as primary endpoint because HbA1c is an internationally accepted endpoint of stable glycaemic control.

Blood samples for the determination of HbA1c at the central laboratory will be taken at all the visits except Visit 2, the blood sample can be taken at any time during the visit. For the determination of HbA1c, 3 mL of blood will be collected. The samples will be analysed at a central laboratory having a National Glycohaemoglobin Standardisation Program (NGSP) Level I certificate. Further details about sample handling, shipment, and assay procedures can be found in the ISF (Lab manual).

5.1.2 Grip strength

Grip strength is an important function of upper extremities for elderly population, and it is used for the assessment of sarcopenia in AWGS 2019 [R20-0617]. The Sarcopenia Frail Society of Japan recommends to use this criterion of AWGS. Therefore, grip strength is a parameter to evaluate physical condition and assess sarcopenia.

The procedure to measure grip strength is described in Appendix 10.1.

5.1.3 Lower limb function

Lower limb function for elderly population is an important function, and it is used for the assessment of sarcopenia in AWGS 2019 [R20-0617]. The Sarcopenia Frail Society of Japan recommends to use this criterion of AWGS. As same as grip strength, time of chair stand test is a parameter to evaluate physical condition and assess sarcopenia.

The procedure to implement chair stand test is described in Appendix 10.2.

5.1.4 Body composition

Body composition assessment is being increasingly recognised as an important tool in the evaluation of nutritional status in a variety of clinical conditions and for fitness assessment in both research and clinical settings and muscle mass is an important parameter for diagnosing sarcopenia in AWGS 2019 [R20-0617].

Bioelectrical impedance analysis (BIA) is a commonly used method for estimating body composition and it assesses body composition by passing a very small current through the body and assessing differences in impedance caused by the fact that fat and lean tissues have different electrical properties. Since all lean tissue in the limbs is either bone or muscle use of segmental BIA can provide a good proxy for skeletal muscle mass by assessing the composition of limbs alone. BIA is a valid tool for the assessments of total body and

segmental body composition in the general middle-aged population, particularly for the quantification of body lean mass [R20-0698].

The body composition planned to be measured by using BIA includes muscle mass (kg), body fat percentage (%), body fat mass (kg), lean body mass (fat-free mass) (kg), total body water (kg), and bone mineral content (estimated bone mass) (kg). Skeletal muscle index is calculated by dividing the limb muscle mass (kg) by the square of the height (m^2). The procedure to measure body composition is described in Appendix 10.3 and instruction in ISF.

[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the flowchart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

Targeted physical examination will include evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

Measurement of height calf circumference, and body weight will be performed at the time points specified in the flowchart. For calf circumference, the maximum non-dominant calf circumference is measured.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling. Clinically relevant abnormal findings as judged by the investigator will be reported as AE (see Section 5.2.6).

Vital signs include systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1, 5.2.3: 2 and 5.2.3: 3. For the sampling time points please see the flowchart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.

Safety laboratory samples (except screening) will be collected after a full overnight fast (nothing to eat or drink except water for at least 10 hours) and before administration of background antidiabetic therapies and investigational drug as described in the flowchart and Section 6. The blood sample at Visit 1 (screening visit) can be taken with the patient in a fasted or nonfasted state.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the ISF (lab manual).

It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as AE (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (see Section 5.2.6.1 and the DILI checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3: 1 Safety laboratory tests – Haematology

Visit	1	2	3	4	5	6	7	8 EOT	9 EOS
Study week	-3	-2	0	4	12	24	36	52	53*
Haematocrit	X		X	X	X		X	X	X
Haemoglobin	X		X	X	X		X	X	X
Red Blood Cells (RBC)/Erythrocytes	X		X	X	X		X	X	X
WBC/Leukocytes	X							X	
Platelet Count/Thrombocytes	X							X	
Differential Automatic (relative and absolute count): Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes	X							X	

* EOS should be done 1 week after Visit 8 or EOT

Table 5.2.3: 2 Safety laboratory parameters – Clinical Chemistry

Visit	1	2	3	4	5	6	7	8 EOT	9 EOS
Study week	-3	-2	0	4	12	24	36	52	53*
Glucose (fasted)	X	X	X	X	X		X	X	X
Lipase	X		X	X	X		X	X	X
AST (aspartate transaminase, SGOT)	X		X	X	X		X	X	X
ALT (alanine transaminase, SGPT)	X		X	X	X		X	X	X
Alkaline phosphatase	X		X	X	X		X	X	X
Bilirubin total	X		X	X	X		X	X	X
Direct bilirubin, if bilirubin total increased	X		X	X	X		X	X	X
Total Protein	X		X	X	X		X	X	X
Albumin	X		X	X	X		X	X	X
Potassium	X		X	X	X		X	X	X
Sodium	X		X	X	X		X	X	X
Bicarbonate	X		X	X	X		X	X	X
Creatinine	X		X	X	X		X	X	X
Blood urea nitrogen	X		X	X	X		X	X	X
Calcium	X		X					X	
Inorganic phosphorous			X					X	
Uric acid	X		X					X	
Cholesterol (total)			X					X	
HDL cholesterol			X					X	
LDL cholesterol			X					X	
Triglycerides			X					X	
Thyroid stimulation hormone	X								

* EOS should be done 1 week after Visit 8 or EOT

Table 5.2.3: 3 Safety laboratory parameters – urine

Visit	1	2	3	4	5	6	7	8 EOT	9 EOS
Study week	-3	-2	0	4	12	24	36	52	53*
Protein	X		X	X	X		X	X	X
Ketone	X		X	X	X		X	X	X
Leucocytes	X		X	X	X		X	X	X
Erythrocytes	X		X	X	X		X	X	X

* EOS should be done 1 week after Visit 8 or EOT

If the investigator needs safety lab (e.g., to follow an ongoing AE), he/she can perform it in the local lab. The results will not be captured in the eCRF. Clinically significant lab abnormalities will be reported as AE (see Section 5.2.6).

Estimate glomerular filtration rate

The estimated glomerular filtration rate (eGFR) will be derived from serum creatinine* values based on the standard MDRD formula:

eGFR (ml/min/1.73 m^2) = 175 x [Screatinine (umol/L)/88.4]$^{-1.154}$ x [age]$^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is of African origin]

*: creatinine methods calibrated to an IDMS reference method

NT-proBNP will be measured at screening as part of baseline examinations to characterise the patient population in the trial.

5.2.4 Electrocardiogram

The 12-lead electrocardiogram (ECG) must be administered by a qualified technologist and results will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Self-monitoring of blood glucose

All patients will be provided at Visit 2 with SMBG equipment and supplies for use at home throughout trial participation. Instruction on the proper use of the SMBG equipment will be provided by the trial staff. The patient will be asked to record the results of the SMBG test on a SMBG test log and will submit it to site staff at every visit. The log will be included in the

patients source document file. Clinically relevant abnormal findings as judged by the investigator will be reported as AE (see Section 5.2.6). Only in the case of linked AEs or of hypoglycaemia events, the single SMBG values will be recorded in the eCRF.

During the run-in period, SMBG test is recommended to be done daily in the fasted state (before breakfast, i.e., after an overnight fast) and at any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper- or hypoglycaemia. If during this period, results of a fasting SMBG test reveal blood glucose levels meeting rescue criteria (see Section 4.2.1), the patient should contact the site and the investigator should follow the instructions given in Section 4.2.1. During the double-blind treatment period, SMBG test is recommended to be done daily but be performed at least once a week in the same way as in the run-in period.

For the 1 week follow-up period, after the Visit 8 (EOT) up to a time period as judged by the investigator, SMBG test should be performed at least once daily in the fasted state and any time the patient is symptomatic, i.e., experiences signs/symptoms of hyper- or hypoglycaemia. If result of SMBG test reveals blood glucose of >200 mg/dL (11.1 mmol/L) after an overnight fast the patient should contact the site to assess if a change in his/her T2DM treatment is required.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, data on SMBG log and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,

- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

AEs which possibly lead to disability will be reported as SAEs as "deemed serious for any other reason".

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the electronic data capture system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g., the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's PV Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or

- aminotransferase (ALT, and/or AST) elevations ≥5 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Diabetic ketoacidosis (DKA)

The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty in breathing, confusion, and unusual fatigue or sleepiness.

In case of a suspected DKA, the investigator should ensure that appropriate tests are performed at the earliest opportunity according to Treatment Guide for Diabetes [R17-1515], such as blood tests (glucose, blood urea nitrogen/creatinine, and ketone) and blood gas test (pH, bicarbonate, anion gap). The results will be collected on the relevant page of the eCRF.

Investigators should also differentiate deteriorating ketosis/DKA from any mild to moderate increase of ketones which may be seen due to the mechanism of action of empagliflozin, especially in the fasted state (e.g., in the morning).

Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels in patients with DM. The diagnosis of DKA in these patients can be based on arterial pH ≤7.30, serum bicarbonate levels <15 and measurement of serum betahydroxybutrate levels. Other diagnostic criteria which can support the diagnosis of DKA are urine ketones and anion gap >10.

Investigators should note that not all criteria mentioned above need to apply for the diagnosis of DKA, and clinical judgment should also be taken into consideration.

Decreased renal function

Decreased renal function is defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN.

For the AESI "decreased renal function" the patient needs to be followed-up appropriately based on local clinical guidance.

Events leading to lower limb amputation

Any event leading to a lower limb procedure of amputation, auto-amputation or disarticulation as defined below is considered as an AESI.

Amputation is a resection of a limb through a bone. Disarticulation is a resection of a limb through a joint. Auto-amputation is a spontaneous separation of non-viable portion of the lower limb.

Not included in this definition are debridement (removal of callus or dead tissue), procedures on a stump (like stump revision, drainage of an abscess, wound revision etc.) and other procedures (e.g., nail resection or removal) without a concomitant resection of a limb (amputation or disarticulation). (International Working Group of Diabetic Foot, 2015).

Each lower limb amputation, disarticulation, or auto-amputation should be reported separately. The SAE report should include the date of the procedure, the level of amputation or disarticulation, the medical condition(s) leading to the procedure and if the patient had some of the known risk factor(s) for lower limb amputation.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g., pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g., Stevens-Johnson syndrome).
- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g., pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g., after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate eCRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of study (EOS):
  all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g., phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the eCRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must

be followed up until they have resolved, have been assessed as “chronic” or “stable”, or no further information can be obtained.

5.2.6.2.3 Pregnancy

Pregnancy is unlikely to occur as the trial includes only post menopausal women.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Not applicable.

5.4 ASSESSMENT OF BIOMARKER(S)

Not applicable.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

Not applicable.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits except for screening (Visit 1) should take place in the morning. If a patient mistakenly takes trial medication in the morning of a visit before attending the clinic or comes in fed condition where a fasting condition is required, the visit should be rescheduled for another day as soon as possible reminding the patient of the expected conditions. The rescheduled visit must take place in a short enough time-frame so that the patient has sufficient trial medication available.

All patients are to adhere to the visit schedule as specified in the flowchart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. The trial medication kits contain sufficient medication to allow for these time windows. The run-in period must be 14 to 21 days long prior to randomisation.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Trial procedures to be performed at each visit are listed in the flowchart and the respective protocol sections. Explanations of procedures are provided in section 5. Additional details regarding visit procedures are provided below. Please also reference the instructions provided in the ISF for clarification on eCRF issues.

All visits except Visit 1 must be performed in fasted state (at least 10 hours with nothing to eat or drink except water).

At the end of every visit from Visit 2 to 8 the patient must be reminded to bring SMBG test log and the dispensed medication kit at the next scheduled visit. Preferably, a phone call to remind the patient must take place one or two days before the patient's next visit.

Patient reported outcomes (PROs) [redacted] should be completed by the patient on his/her own in a pre-specified order in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other trial staff.

6.2.1 Screening and run-in period

Screening Period

No trial procedures should be done unless the patient has consented to taking part in the trial. Once they have consented, the patient is considered to be enrolled in the trial and should then be recorded in the enrolment log, and screening will be started. The patient should be registered in the IRT and recorded in the eCRF as a screened patient at Visit 1.

Visit 2 should be done no more than 7 days after screening (Visit 1). If needed (e.g., in case of national holiday), the time window for Visit 1 may be extended at the discretion of the CT Manager in conjunction with the clinical trial leader (CT Leader) on a case by case basis.

Demographics:

Informed consent date, age on the day of informed consent (in years), sex (in order to describe the subject`s sex at birth), gender identity (in order to describe how the subject self-identifies regardless of their genotypic or phenotypic sex), ethnicity and race will be collected and reported in the eCRF.

Baseline Conditions

Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding T2DM) will be reported on the baseline condition eCRF page.

Medical History

Medical history will be collected and reported in the medical history eCRF page. Information on clinically significant previous and concomitant illnesses, other than T2DM, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical history at screening on the baseline condition page in the eCRF.

Run-in Period

From this visit on, patients should be fasting (no food or drinks, water only for at least 10 hours) prior to each visit.

Patients who fail the run-in period following Visit 2 procedures should be registered in the IRT (refer to IRT user manual). It is considered as a run-in failure.

For standard of care, details please see Section 4.2.1.

Investigator should monitor adverse events, document it in the medical record and eCRF.

Investigator and site staff instruct patients on the correct use of SMBG for glucose testing during the run-in period.

- Patients should use the SMBG equipment/supplies to test glucose levels in a fasting state. During the run-in period patients should test once a day before breakfast (i.e., after an overnight fast). Additionally, patients should test their glucose levels if they experience signs/symptoms of hypo- or hyperglycaemia. Test results should be documented on the SMBG testing log. More frequent SMBG testing is permitted at the Investigator's and/or patient's discretion.
- If the SMBG test reveals an overnight fasted blood glucose of >200 mg/dl (>11.1 mol/l), the patient should contact the study site for a visit at the next day. The investigator will then draw a new blood sample (overnight fasted samples for FPG determination) to confirm the hyperglycaemia, document the AE if appropriate and decide about the possible exclusion from randomisation (it is considered as run-in failure).

[redacted]

6.2.2 Treatment period

Patients must satisfy all inclusion and exclusion criteria prior to randomisation (see Section 3.3). In addition, if during the run-in period, there is any indication that a patient's conditions of T2DM are not stable enough for the patient to complete the study or that the patient will not be compliant with the study medication or restrictions, the patient should not be randomised to the treatment.

The date of visit should be determined based on the date of Visit 3 and visits should occur within the allowed time frame shown in the flowchart.

The treatment period is from Visit 3 to Visit 8/EOT. Patients will be dispensed medication at each of these visits (except for Visit 8/EOT). Medication number of each occasion will be allocated by IRT (refer to IRT manual).

Patients should not take study medication at home on the morning of trial visits during the treatment period.

Randomisation visit (Visit 3)

Visits should be performed fasting and as indicated in the flowchart and the respective protocol sections.

[redacted]

Patient is instructed not to take study medication and background medications on the morning of next trial visits (Visit 4) as described in Section 4.1.4.

Visits 4-8/EOT

Visits should be performed as mentioned in the flowchart and the respective protocol sections.

Patient is instructed not to take study medication and background medications on the morning of next trial visits as described in Section 4.1.4.

[redacted]

If a patient prematurely discontinues from the 52 weeks treatment period, patient will be followed up until the end of the trial. If a patient will not give his/her agreement, the patient must return to the trial site for EOT (within 7 days of stopping study treatment). The reason for premature trial drug discontinuation must be documented in the eCRF. In addition patients will be encouraged to attend all subsequent planned onsite visits despite not being under treatment anymore and perform all study procedures. If the EOT visit occurs within the time window of a planned visit, the EOT visit will replace the planned visit.

The need for coming to future visits in case of premature discontinuation of trial medication will be explained to patients prior to their participation in the trial.

The investigator may initiate any additional antidiabetic therapy for the patient, based on his or her discretion, no sooner than one day after discontinuing study medication or after Visit 8.

Patients who prematurely discontinue the study should be registered as discontinued, and patients who complete the full 52 weeks double-blind treatment period should be registered as completed in the IRT.

6.2.3 Follow-up period and trial completion

A Follow-up visit will be performed 7 days (+7 day window) after the last dose of trial medication. The assessments to be performed at the follow-up visit are indicated in the flowchart. The follow-up visit marks the completion of the study for the individual patient who completed the study on trial medication.

See section 3.3.4.1 for procedures to be followed in case a patient prematurely discontinues trial treatment.

For patients who early discontinued trial medication but followed up according to the visit schedule, Visit 9 (EOS) marks the completion of the study for the individual patient.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The eligible patients for this trial will be randomised to one of two treatment groups (empagliflozin or placebo) in a 1:1 ratio, stratified according to HbA1c (<8.5% or ≥8.5% at screening), and age (≥65 to <75 years old or ≥75 years old at screening).

7.1 NULL AND ALTERNATIVE HYPOTHESES

The effect of empagliflozin 10 mg will be tested against placebo at a two-sided $\alpha = 0.05$ level of significance.

H0: Mean change from baseline in HbA1c after 52 weeks of treatment with empagliflozin 10 mg = mean change from baseline in HbA1c after 52 weeks of treatment with placebo

against

H1: Mean change from baseline in HbA1c after 52 weeks of treatment with empagliflozin 10 mg ≠ mean change from baseline in HbA1c after 52 weeks of treatment with placebo.

The primary endpoint will use HbA1c units of %.

Secondary endpoints and further endpoints will be evaluated in an exploratory manner.

7.2 PLANNED ANALYSES

7.2.1 General considerations

With regard to each efficacy and safety endpoint during the randomised 52 weeks treatment period, the term "baseline" refers to the last observed measurement prior to the administration of any randomised trial medication.
The statistical analysis will be based on the following populations.

The treated set (TS) will consist of all patients who were randomised and treated with at least one dose of trial drug.

The full analysis set (FAS) will consist of all patients in the TS who had a baseline HbA1c assessment and at least one on-treatment HbA1c assessment during the 52 week double-blind part of the trial.

Per protocol set (PPS) will consist of all patients in FAS who were without important protocol violations (IPVs) for efficacy. The definition of IPVs will be specified in the TSAP.

7.2.2 Primary endpoint analyses

For primary endpoint, refer to Section 2.1.2. The primary analysis will be performed on the FAS with treatment assignment as randomised.

The primary analysis is a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) comparing the change in HbA1c (in units of %) from baseline after 52 weeks of double-blind treatment.

The statistical model will include fixed classification effects for treatment, gender, baseline renal function, visit and visit-by-treatment interaction, and a linear covariate for baseline HbA1c and age. An unstructured covariance structure will be used to model the within-patient errors. If this unstructured covariance structure fails to converge, the following structures will be tested: compound symmetry, variance components and Toeplitz. The covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used.

The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Only the available data that were observed while patients were on treatment will be included in the analysis. Missing data are handled implicitly by the above statistical model, rather than using any imputation. This approach, referred to as observed case (OC), will additionally set all values measured after rescue medication taken to missing.

Sensitivity analyses of the primary endpoint will be performed. Such sensitivity analyses will be specified in the TSAP.

7.2.3 Secondary endpoint analyses

For secondary endpoints, refer to Section 2.1.3. A more detailed description will be provided in the TSAP.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of double-blind treatment and end of the REP, a period of 7 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of double-blind treatment and end of the REP. Adverse events that start before first double-blind drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at database lock. Adverse events of special interest (AESI) will also be summarised.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Further details on the safety analysis will be specified in the TSAP.

7.2.6 Other Analyses

Not required.

7.2.7 Interim Analyses

No interim analysis is planned for this trial.

7.3 HANDLING OF MISSING DATA

As defined for the primary endpoint analysis, missing data are handled implicitly by the statistical model, rather than by using any imputation. This approach will additionally set all values measured after rescue medication taken to missing. Further details will be described in the TSAP.

With respect to safety evaluations, it is not planned to impute missing values.

7.4 RANDOMISATION

The trial will be performed as a double-blind design with respect to the two blinded treatment groups. Randomisation to the two treatment groups of empagliflozin 10 mg and placebo will be 1:1 and will be stratified by following 2 factors:

- HbA1c (<8.5 or ≥8.5%) at Visit 1
- Age (≥65 to <75 or ≥75 years) at Visit 1

The randomisation of patients to the treatment groups will be performed via an IRT system.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation of

treatment will be both reproducible and non-predictable. The block size will be documented in the clinical trial report. Access to the radomisation codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

Based upon previous experiences with these compounds, the difference in HbA1c change from baseline after 52 weeks between the treatment groups can be assumed to be 0.5% with a standard deviation of 0.85%. With a randomisation ratio of 1:1, it is assumed that the sample size of each group (empagliflozin 10 mg and placebo) is 62 patients. Assuming that approximately 3% of patients will not be eligible for inclusion into FAS due to the absence of a post-baseline primary endpoint value, 64 patients for the empagliflozin 10 mg group and 64 patients for the placebo group need to be randomised. With this sample size, a power of 90% for a two-sided test at level α=5% for the primary endpoint will be achieved.

Calculations were performed using nQuery Advisor® 6.1 statistical package by [redacted].

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Guideline for GCP, relevant BI Standard Operating Procedures (SOPs), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), Good Post-Marketing Study Practice (GPSP), Good Vigilance Practice (GVP) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations will be treated as “protocol deviation”.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol , of ICH GCP, or of Japanese GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the clinical trial report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/independent ethics committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of Japan. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient’s own free will with the

informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An integrated quality and risk management plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB/IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to

retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Before providing any copy of patient´s source documents to the sponsor the investigator must ensure that all patient identifiers (e.g., patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the protocol, any corrective action e.g., re-training must be documented in the patient file.

For the eCRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it)
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g., medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial
- [redacted]

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g., FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Not applicable.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is

defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim.

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

An independent external clinical event committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspected of DKA (for further details see Section 5.2.6.1.4) and hepatic events. The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met. For qualifying events, study sites will be asked to provide relevant source documents generated from any medical evaluations of these events will be requested including laboratory values, histological analysis, results of ultrasound, computed tomography, magnetic resonance imaging, scintigraphy, hospital discharge letters, and medical reports from other physicians. All evaluations will be performed in a blinded fashion. The assessments will be analysed based on empagliflozin data combined from multiple trials (i.e., on project level). The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.

Relevant documentation on the participating (principal) investigators (e.g., their curricula vitae) will be filed in the ISF.

The investigators and trial staff will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a CT Leader, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of CT Managers, CRAs, and investigators of Japan.

The organisation of the trial in Japan will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT manual and Lab manual, available in the ISF.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P13-08159 Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, et.al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 weeks results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet. 2013. 382 (9896), 941 - 950.

P19-02151 Verma S, McMurray J.J.V. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia. 2018. 61: 2108–2117.

R05-0939 Wright EM, Turk E. The sodium/glucose cotransport family SLC5. Pfluegers Archiv - European Journal of Physiology 2004; 447 (5), 510 - 518.

[redacted]

R14-1408 Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw, et.al. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract 2014. 103, 137-149.

R17-1515 The Japan Diabetes Society. Treatment Guide for Diabetes 2015-2016. Tokyo: Bunkodo; 2016.

R17-3735 Ministry of Health, Labour and Welfare, Japan, The national health and nutrition survey in Japan, 2016
Website: http://www.mhlw.go.jp/toukei/itiran/gaiyo/k-eisei.html (access date: 7 November 2017)

R19-1405 Sasaki T, Sugawara M, Fukuda M. Sodium-glucose cotransporter 2 inhibitor-induced changes changes in body composition and simultaneous changes in metabolic profile: 52- week prospective LIGHT (Luseogliflozin: the Components of Weight Loss in Japanese Patients with Type 2 Diabetes Mellitus) study, J Diabetes Invest 2019. 10 (1), 108-117

R19-3669 Ken S, Yasuharu T, Hiroshi I, Tasunori T, Kei K. Hyperglycemia in non-obese patients with type 2 diabetes is associated with low muscle mass: The Multicenter Study for Clarifying Evidence for Sarcopenia in Patients with Diabetes Mellitus. J Diabetes Investig. 2019. 10: 1471-1479.

[redacted]

R20-0461 Ministry of Internal Affairs and Communications, Japan, Demographic forecast in Japan, 2017.

R20-0462 Package insert of Jardiance tablet.

R20-0463 Ministry of Health, Labour and Welfare, Japan, The national health and nutrition survey in Japan, 2017
Website: http://www.mhlw.go.jp/toukei/itiran/gaiyo/k-eisei.html (access date: 7 November 2017)

R20-0528 Chen, L.K, Liu, L.K, Woo, J, Assantachai, P, Auyeung, T.W, et.al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J. Am. Med. Dir. Assoc. 2014. 15, 95-101.

R20-0617 Chen, L.K, Woo, J, Assantachai, P, Auyeung, T.W, Chou, M.Y. Asian Working Group for Sarcopenia: 2019 Consensus Update on Sarcopenia Diagnosis and Tratment. JAMDA. 2020. 1-8.

R20-0698 CHY Ling, AJM de Craen, PE Slagboom, DA Gunn, MPM Stokkel, et.al. Accuracy of direct segmental multi-frequency bioimpedance analysis in the assessment of total body and segmental body composition in middle-aged adult population. Clinical Nutrition. 2011. 30 (5), 610-615.

[redacted]

9.2 UNPUBLISHED REFERENCES

c01678844 Investigator's Brochure BI 10773 in type 2 diabetes mellitus, CHF, CKD, paediatric diabetes, and type 1 diabetes mellitus, Current Version

c15144621 Non-interventinal Study Report of 1245.98, [redacted]

10. APPENDICES

10.1 GRIP STRENGTH

A Smedley-type dynamometer is used to measure grip strength.

The site staff instructs the patient to adjust the grip width so that the second joint of the index finger is approximately 90 degrees (almost right angle).

The site staff asks the patient to be careful not to touch the body or clothes with hand while keeping arms down naturally. The site staff makes sure that the patient does not wave the grip dynamometer.

Grip strength is measured twice alternately left and right. Records are rounded down to the nearest kilogram and averaged for the better of the left and right.

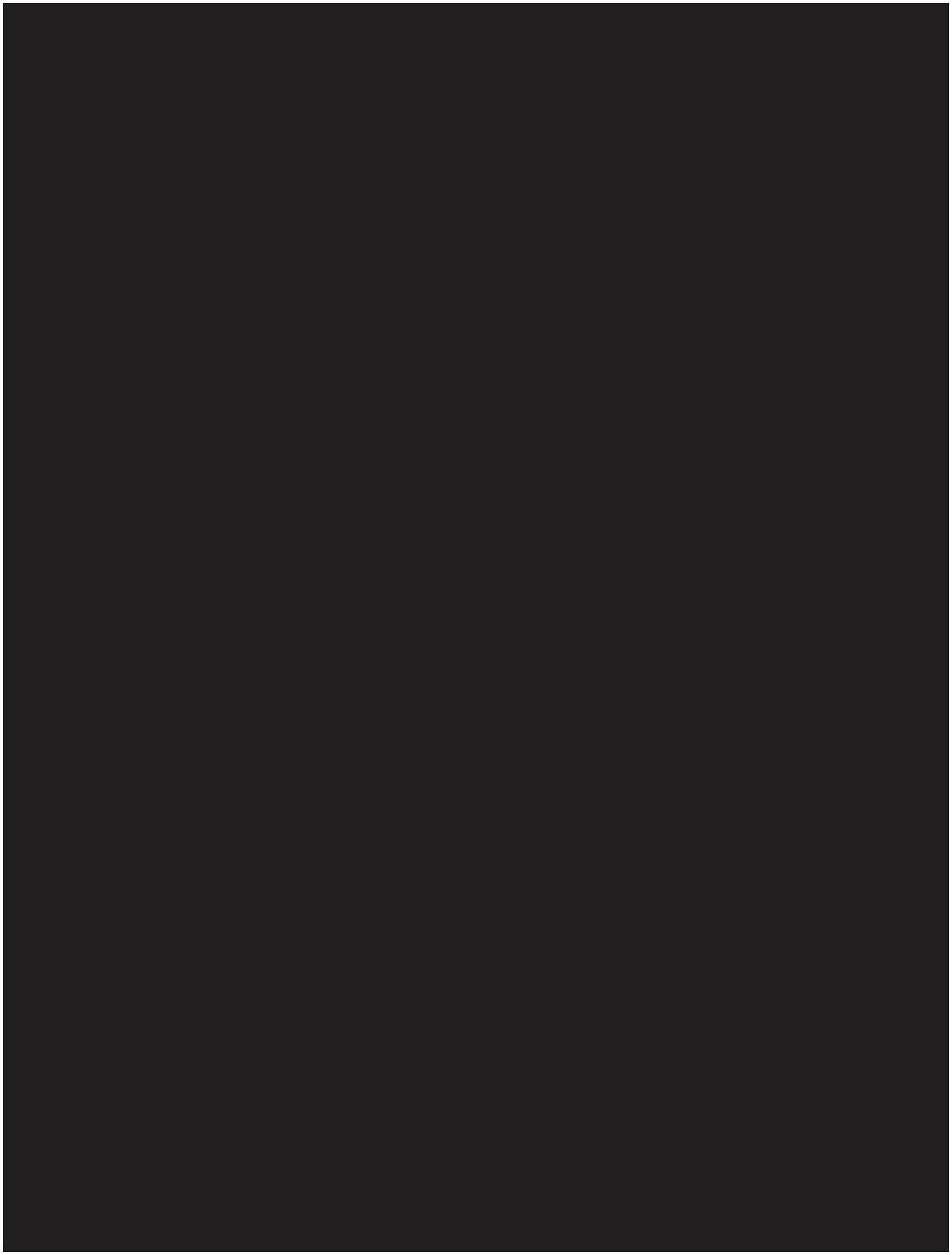
10.2 CHAIR STAND TEST

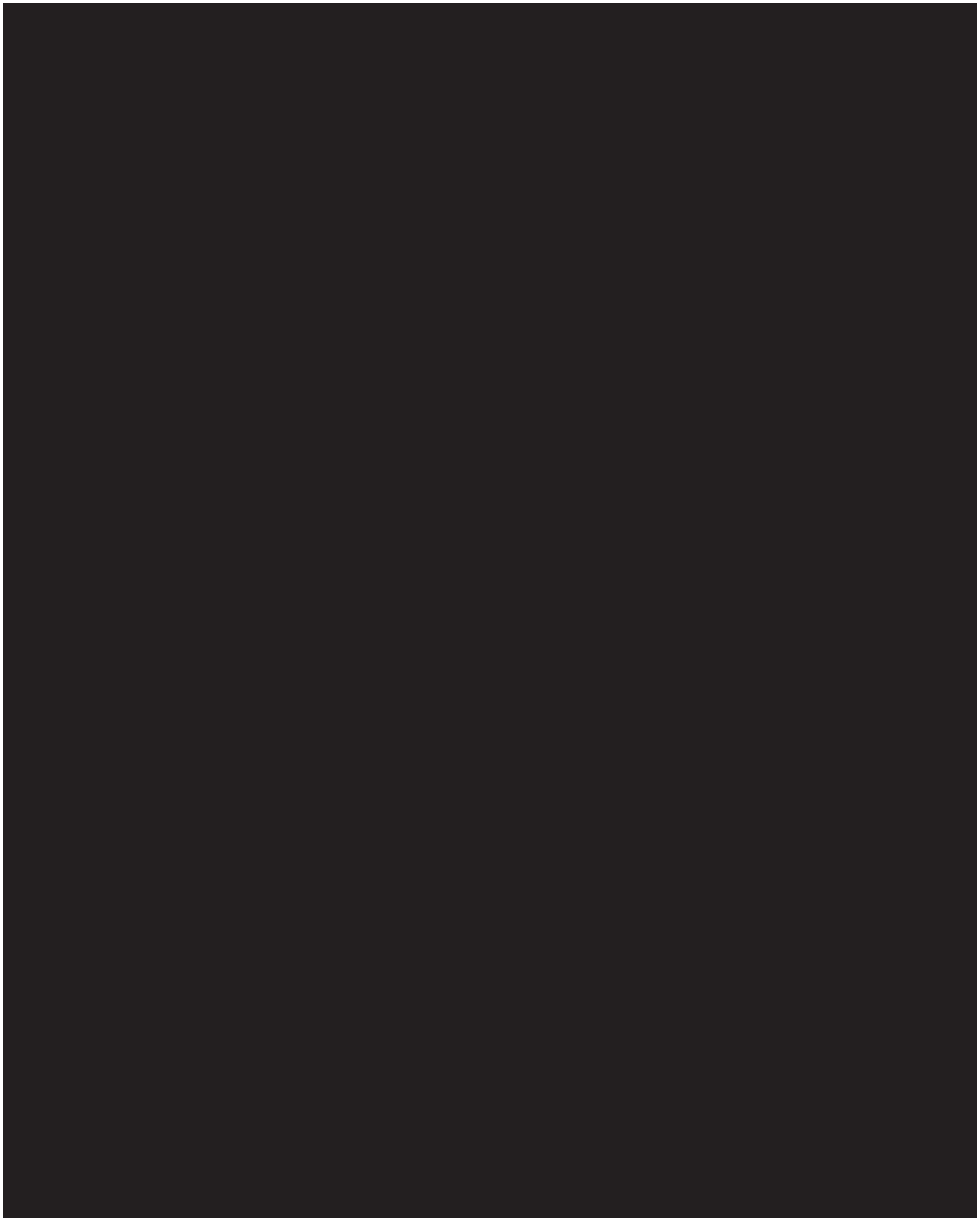
Patients fold their arms across their chest and try to stand up once from a chair. If patients can stand from a chair, they repeat same action five times. It is measured the time required to perform five rise from a chair to an upright position as fast as possible without the use of arms.

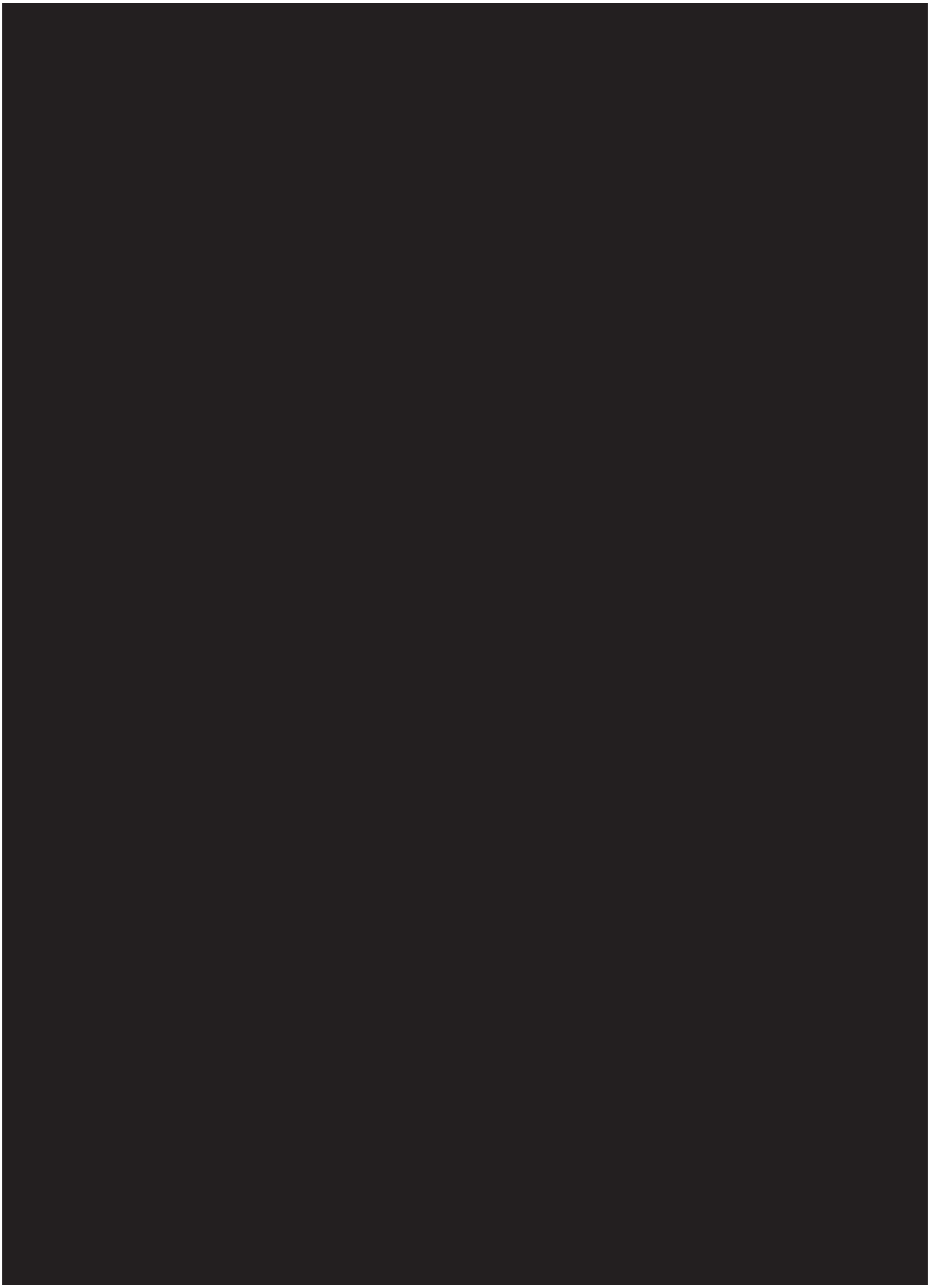
10.3 BODY COMPOSITION

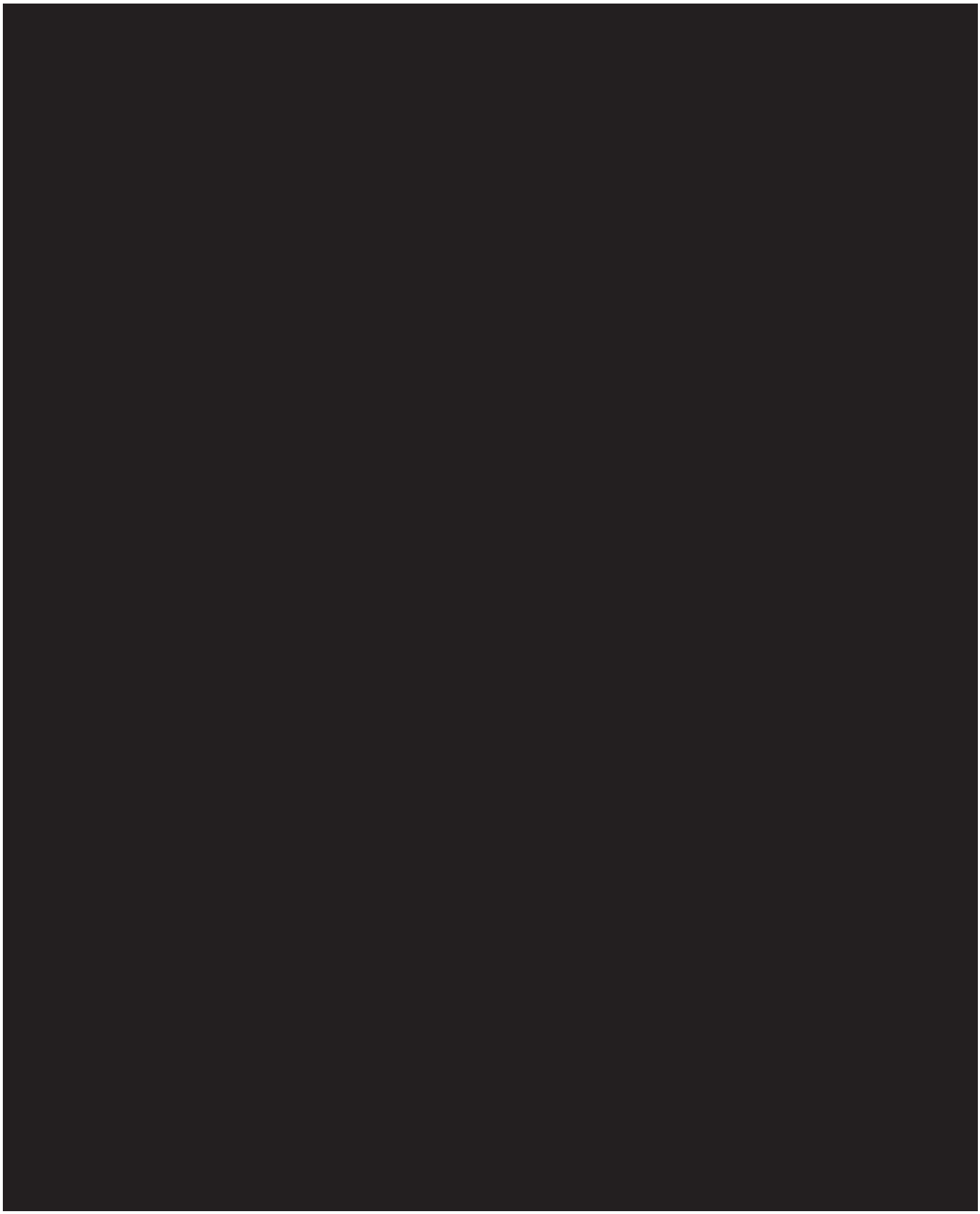
Body composition is measured by using BIA (MC-780A-N, TANITA). The patient barefoot stands on the bench evenly on the toe and heel electrodes and holds the grip on each hand. Note: do not move during the measurement.

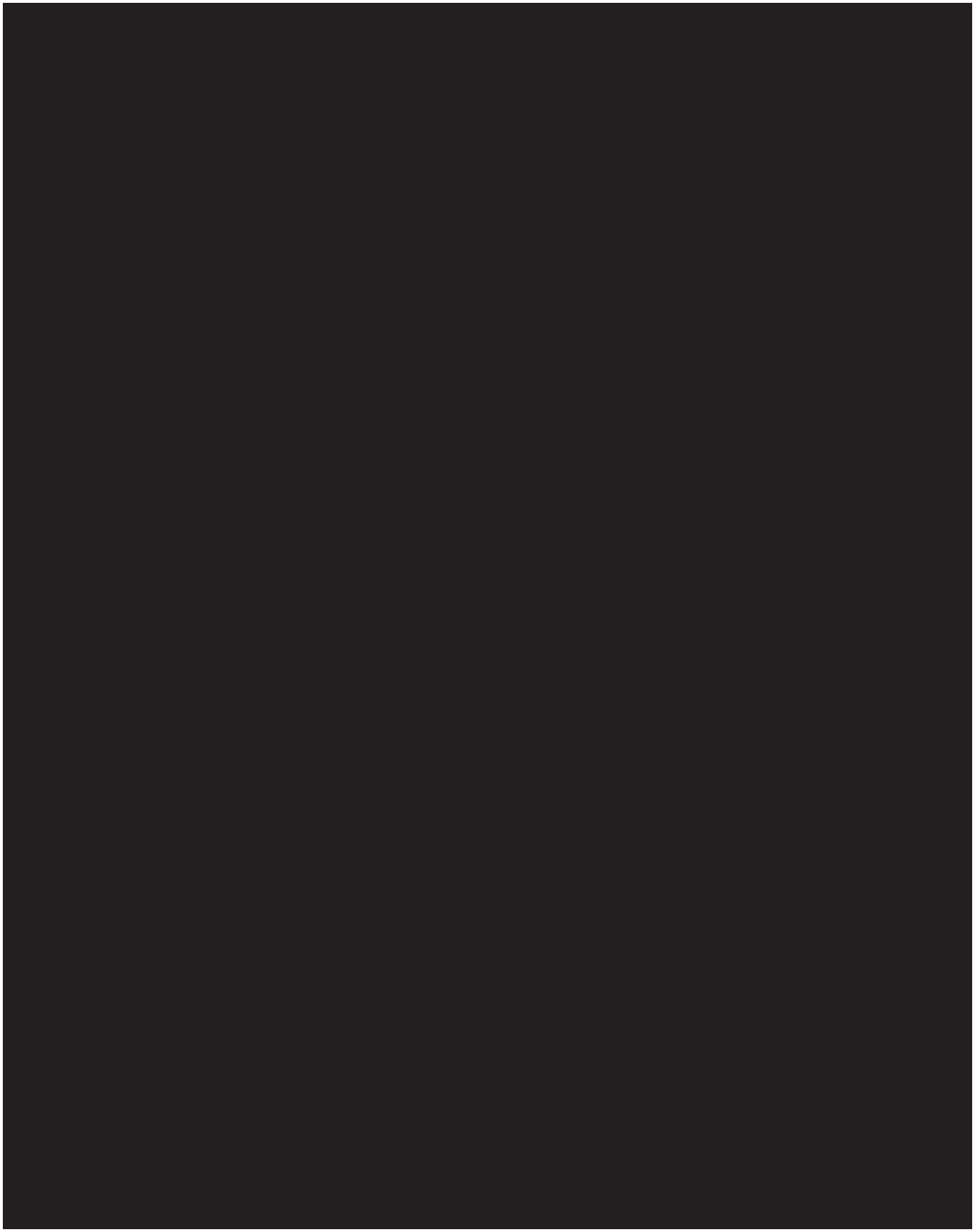
It is recommended that urination and defecation is completed before measurement. For a patient who has dehydration, hypothermia, swelling or fever, the visit to measure body composition has to be rescheduled as soon as possible.

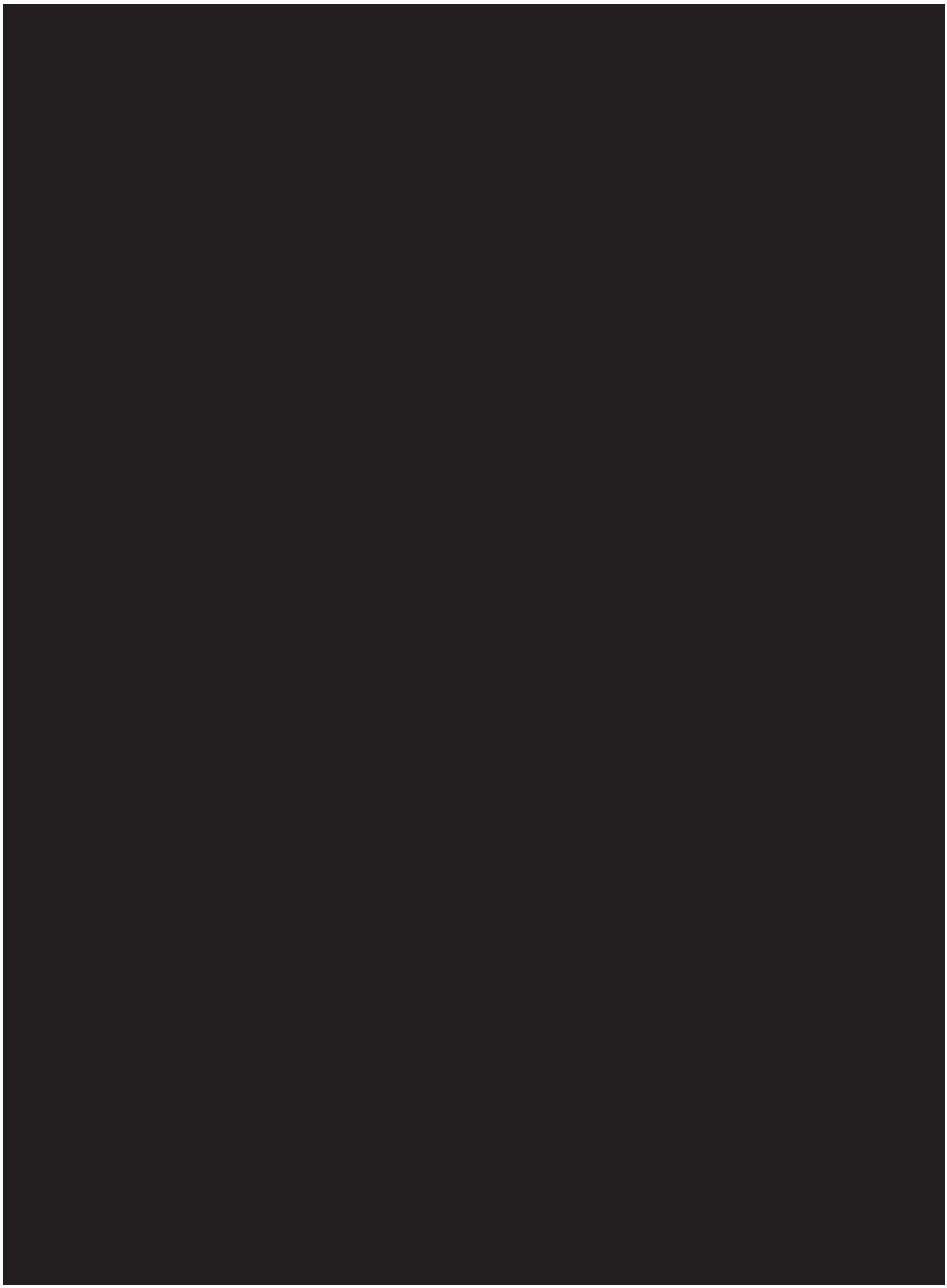


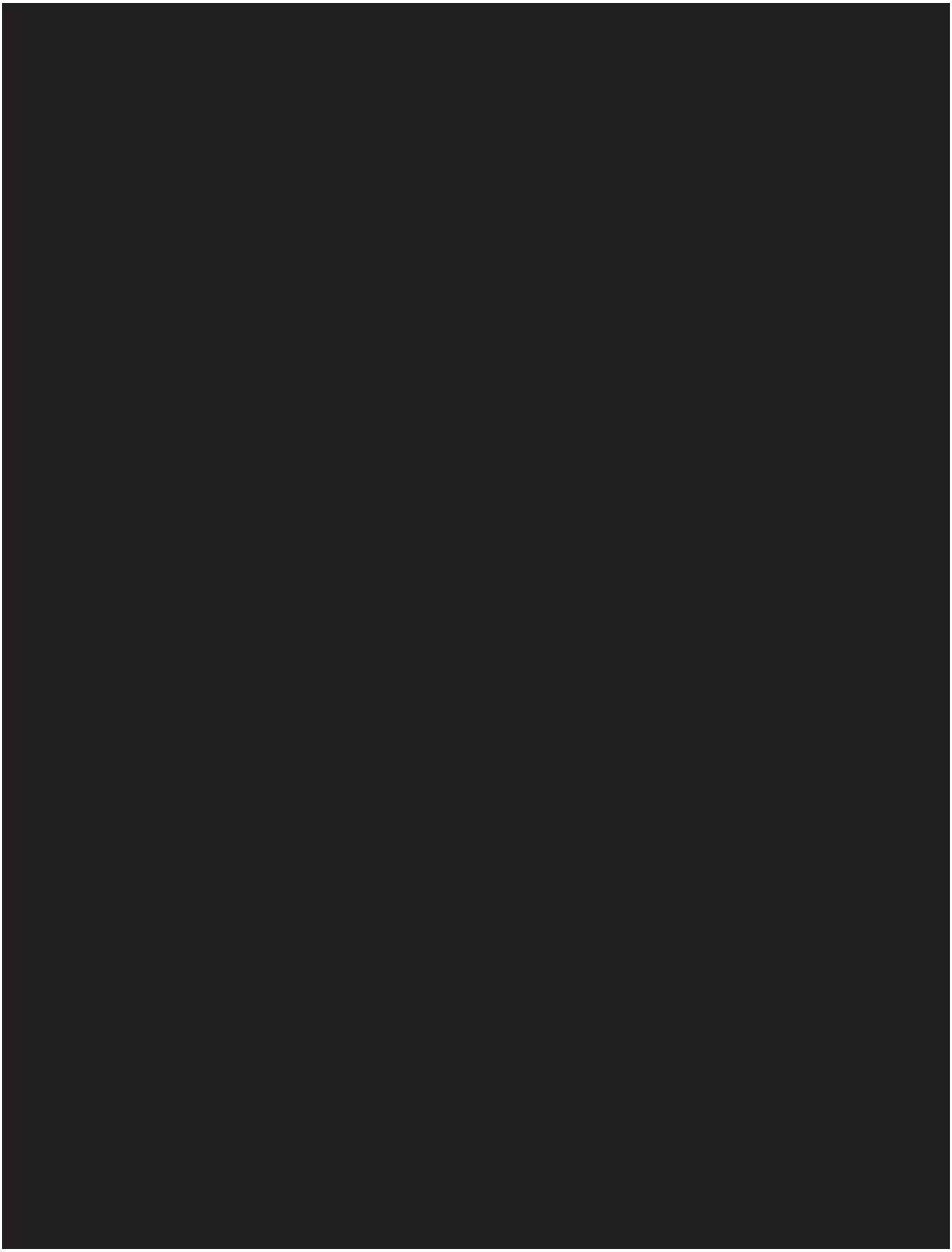


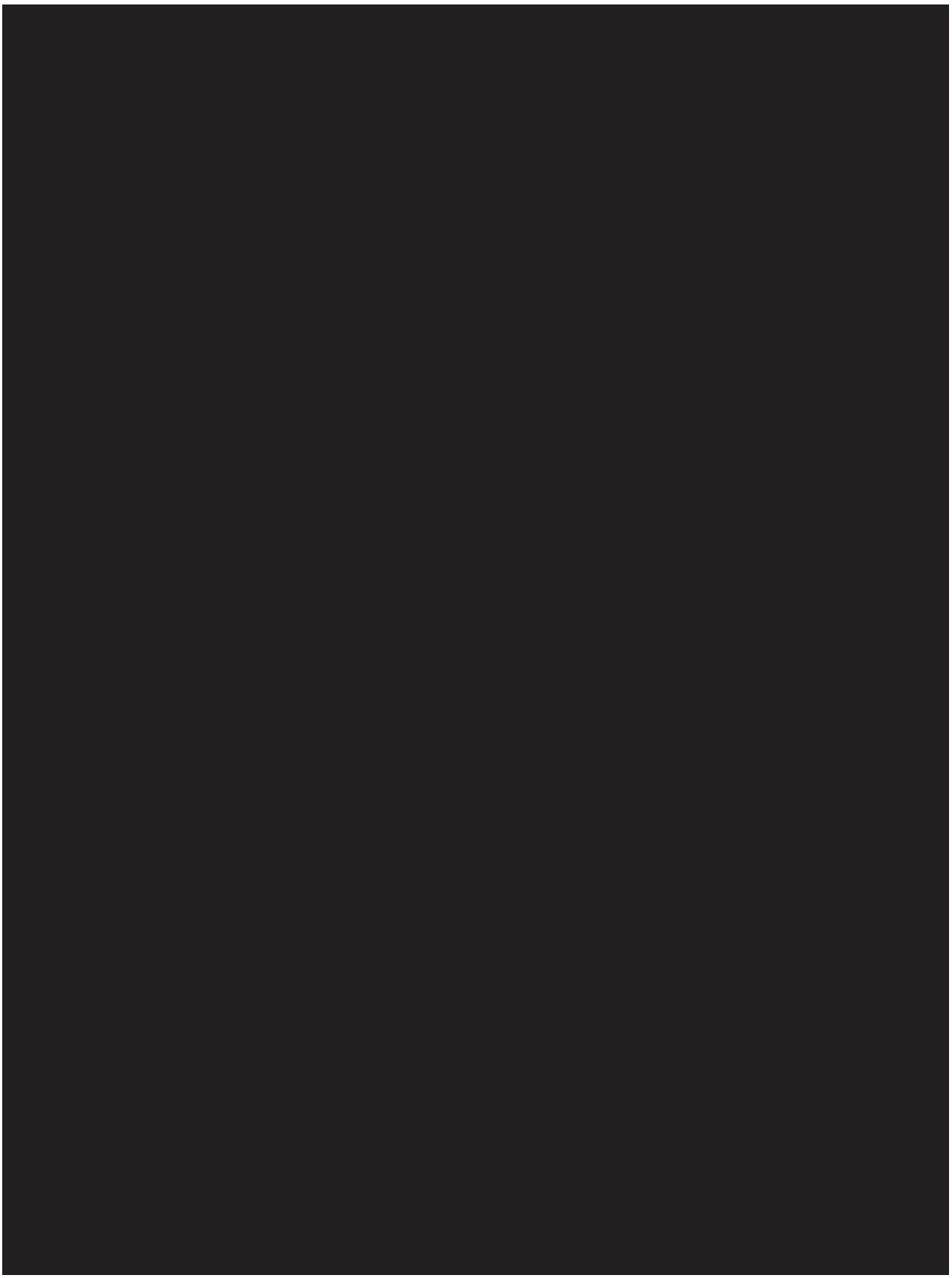


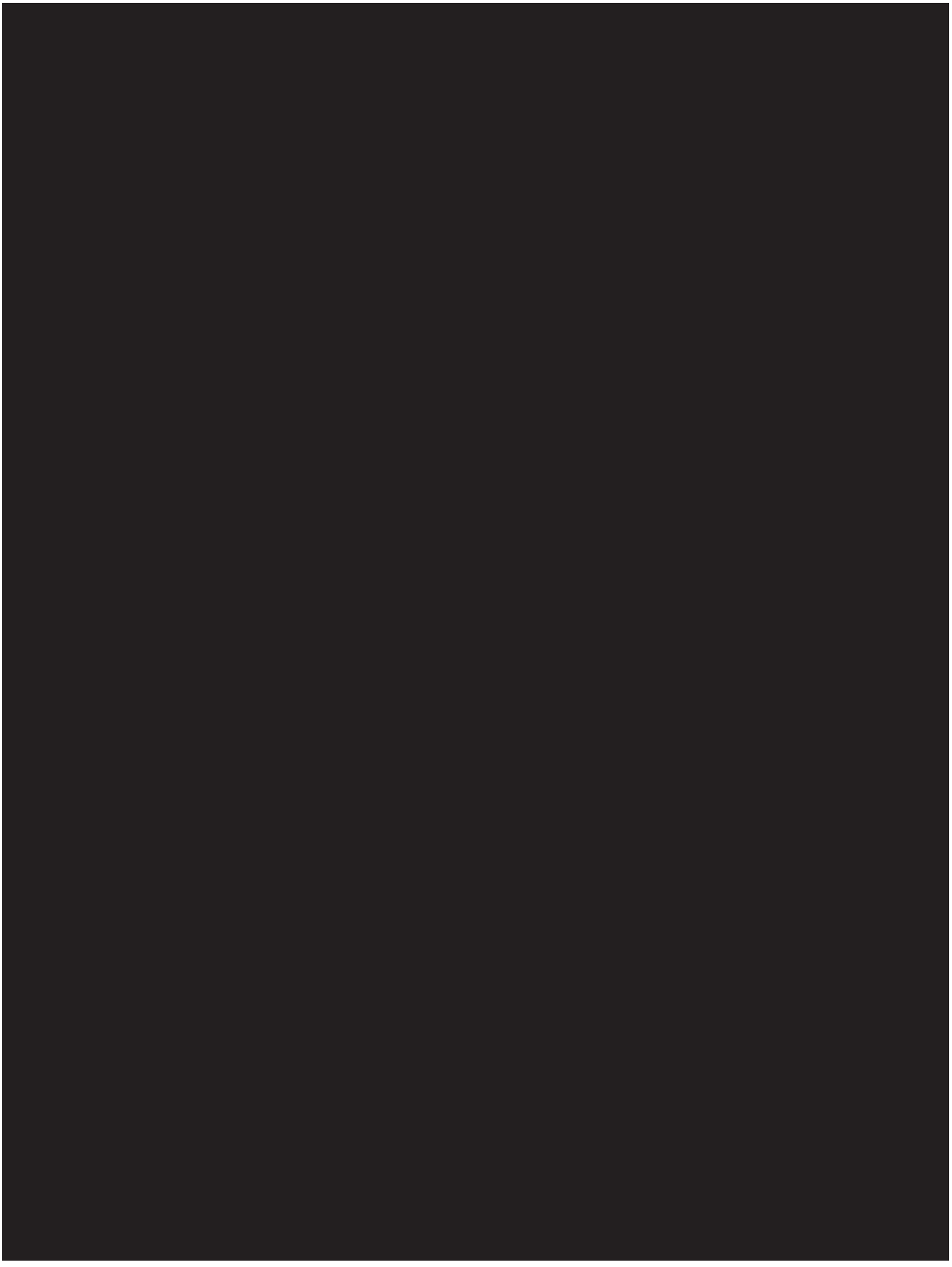


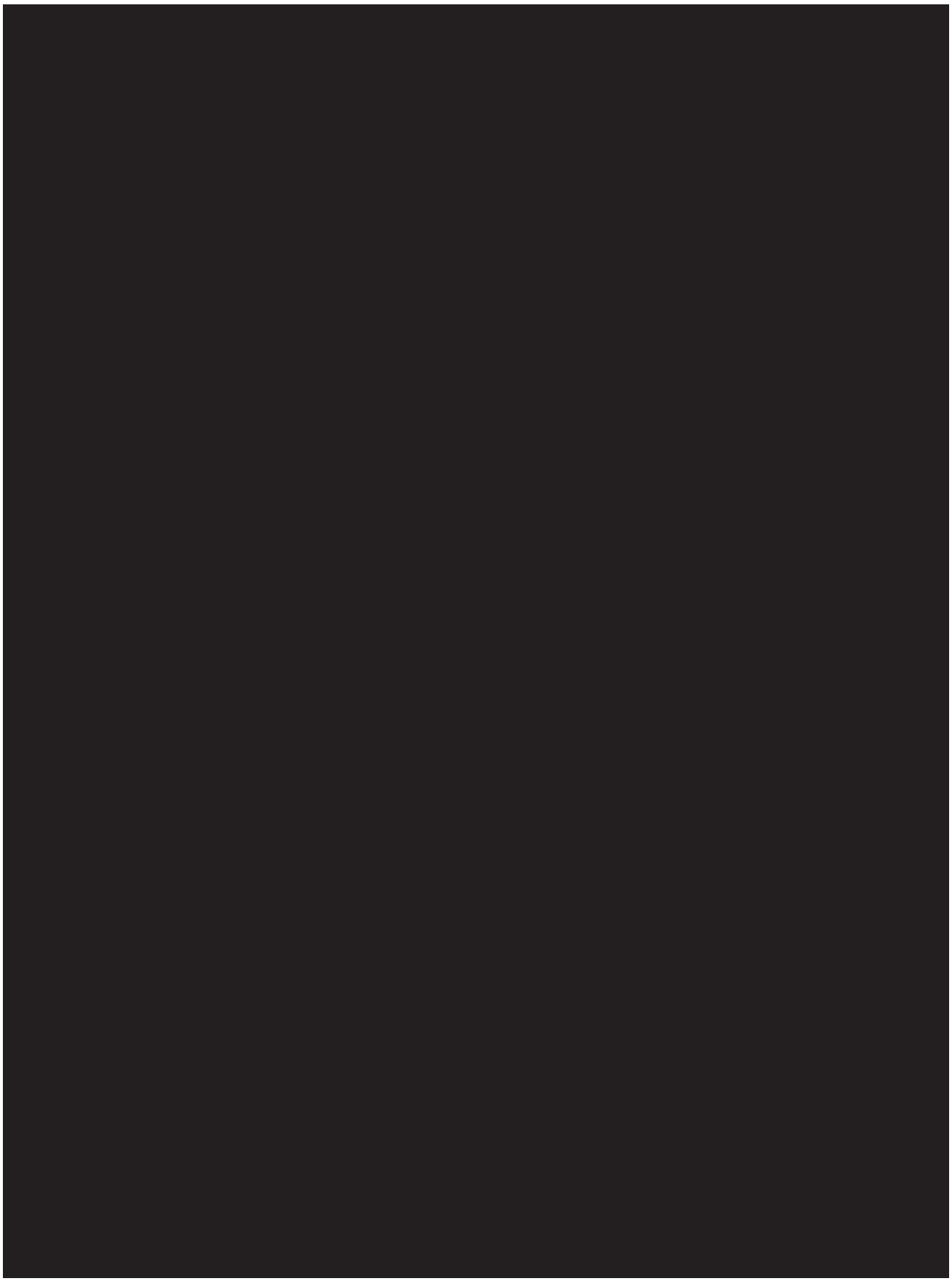


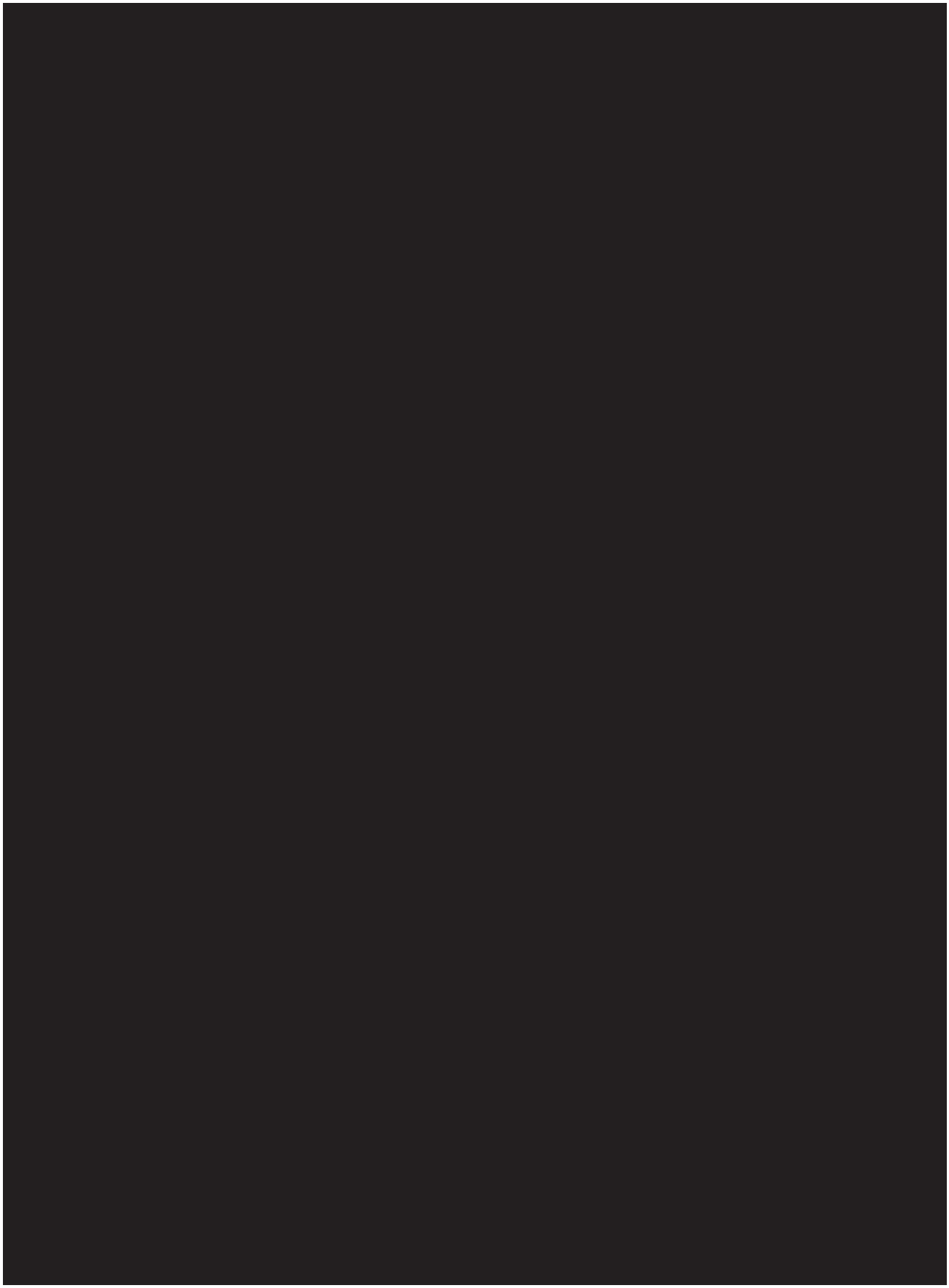


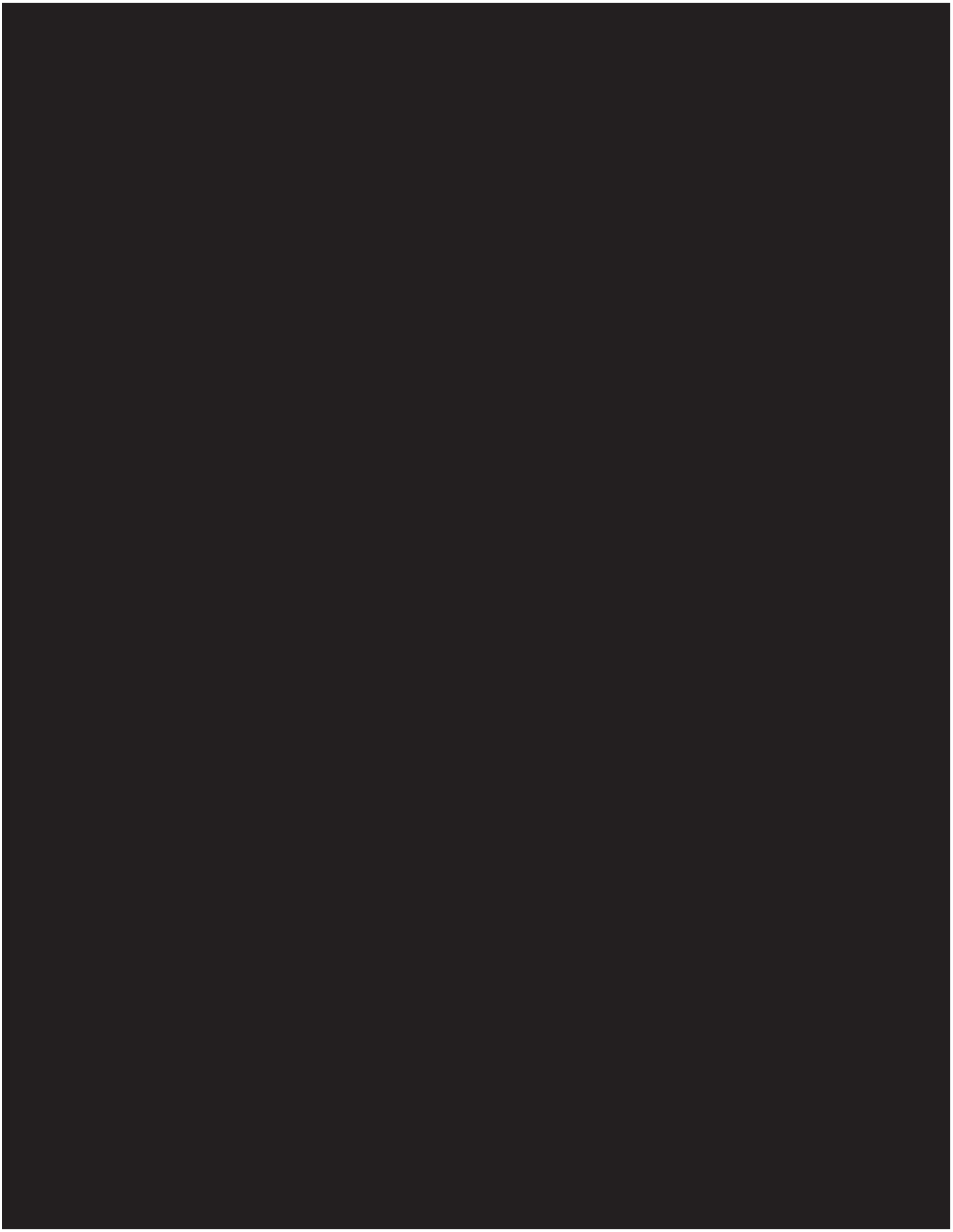


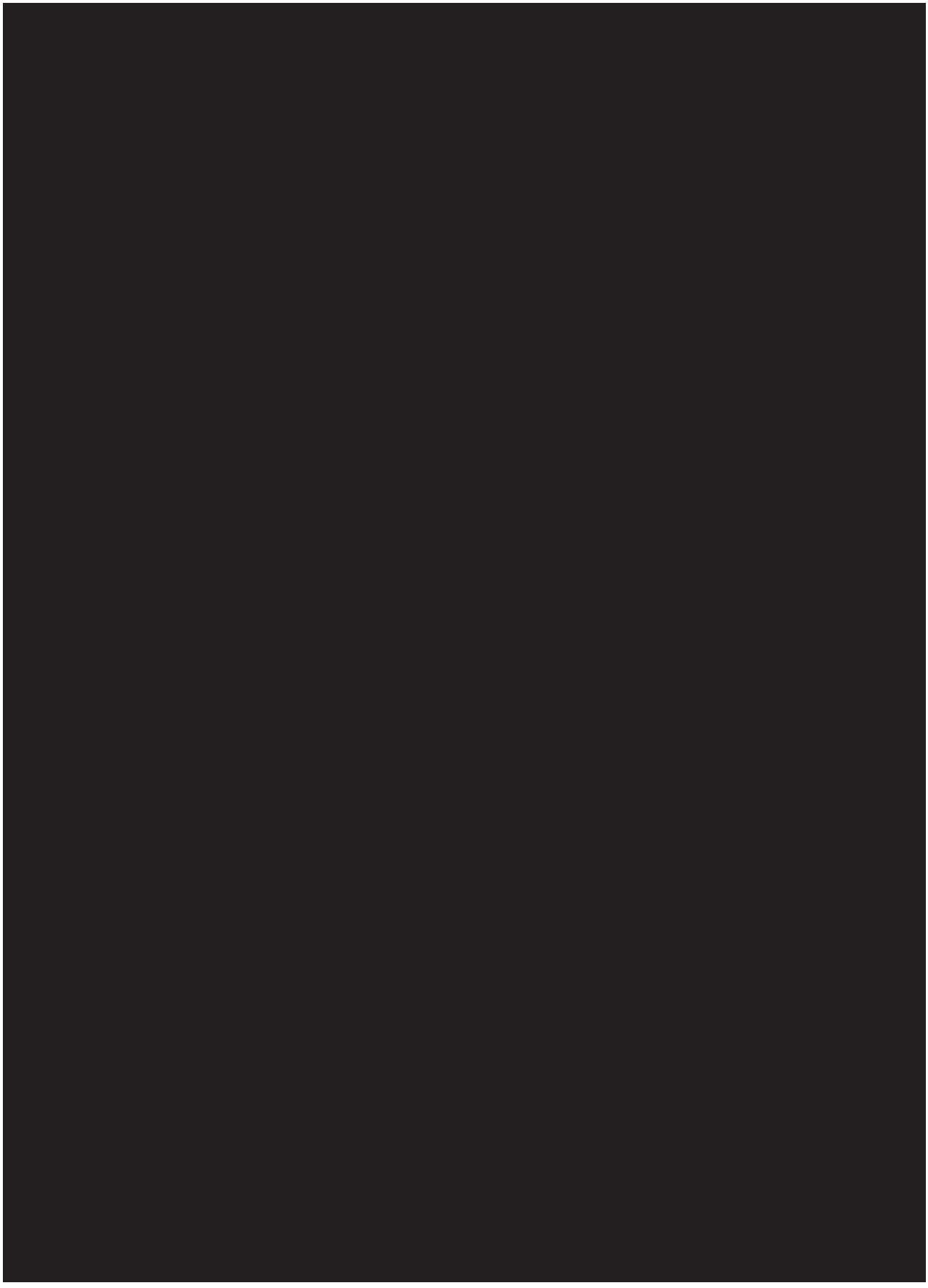


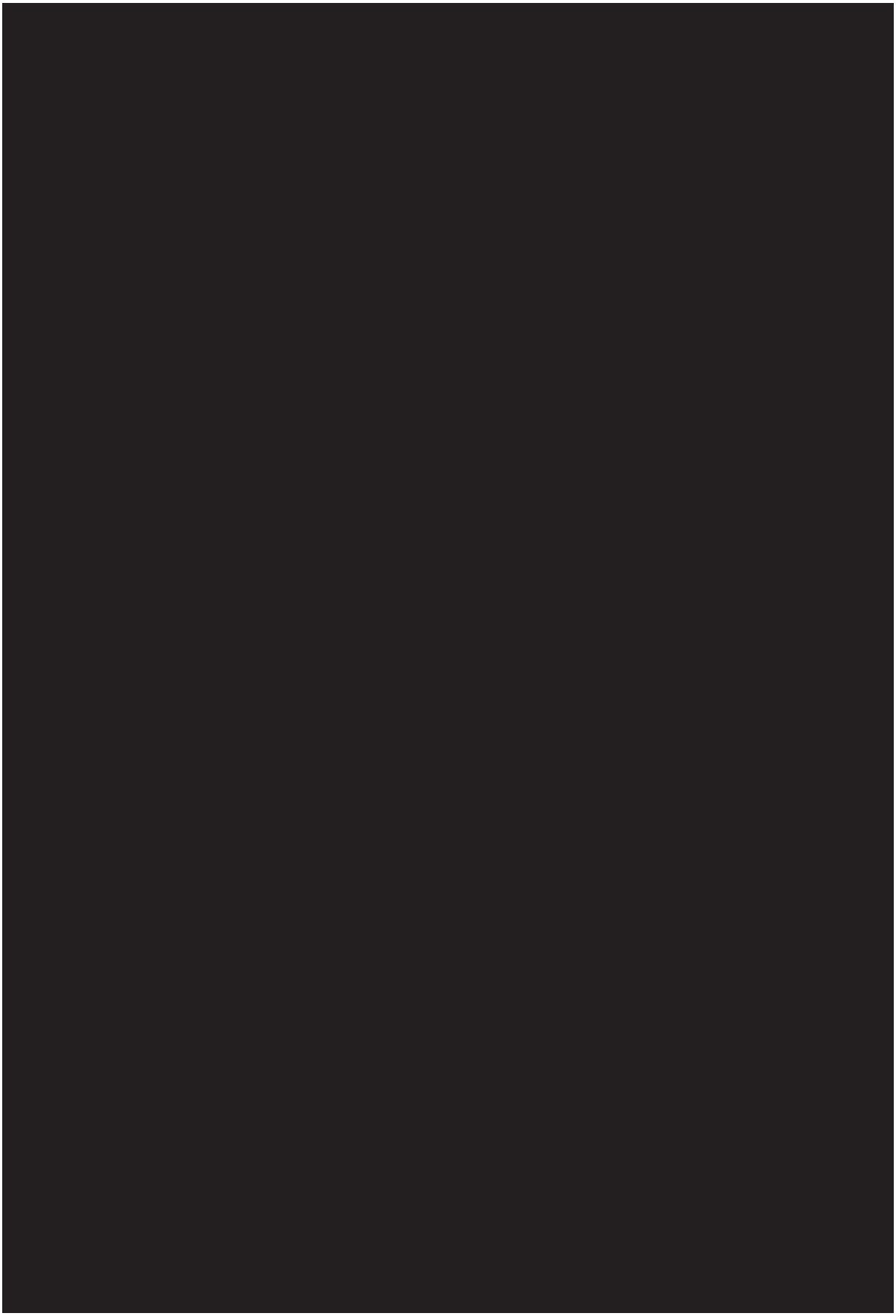


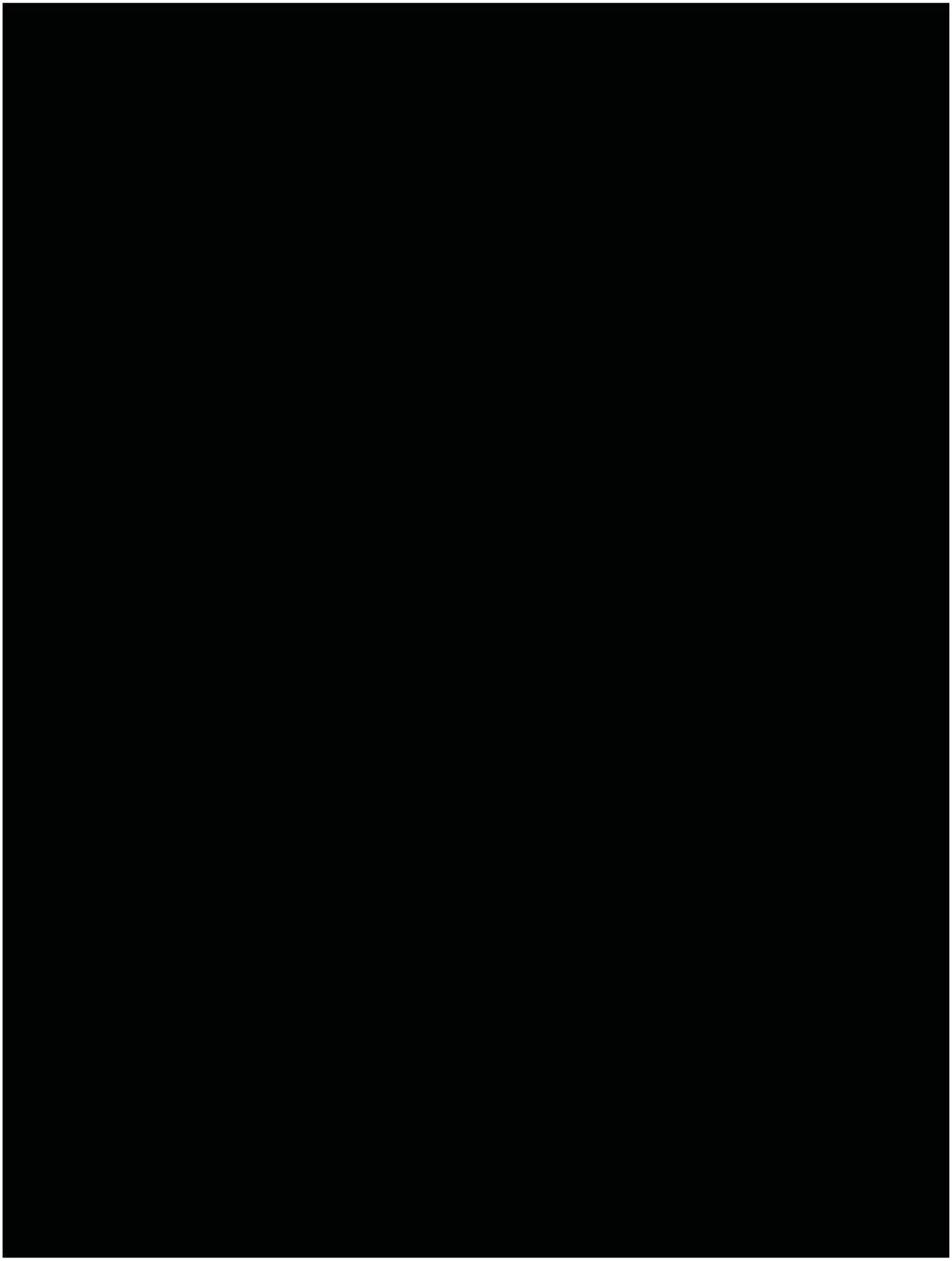


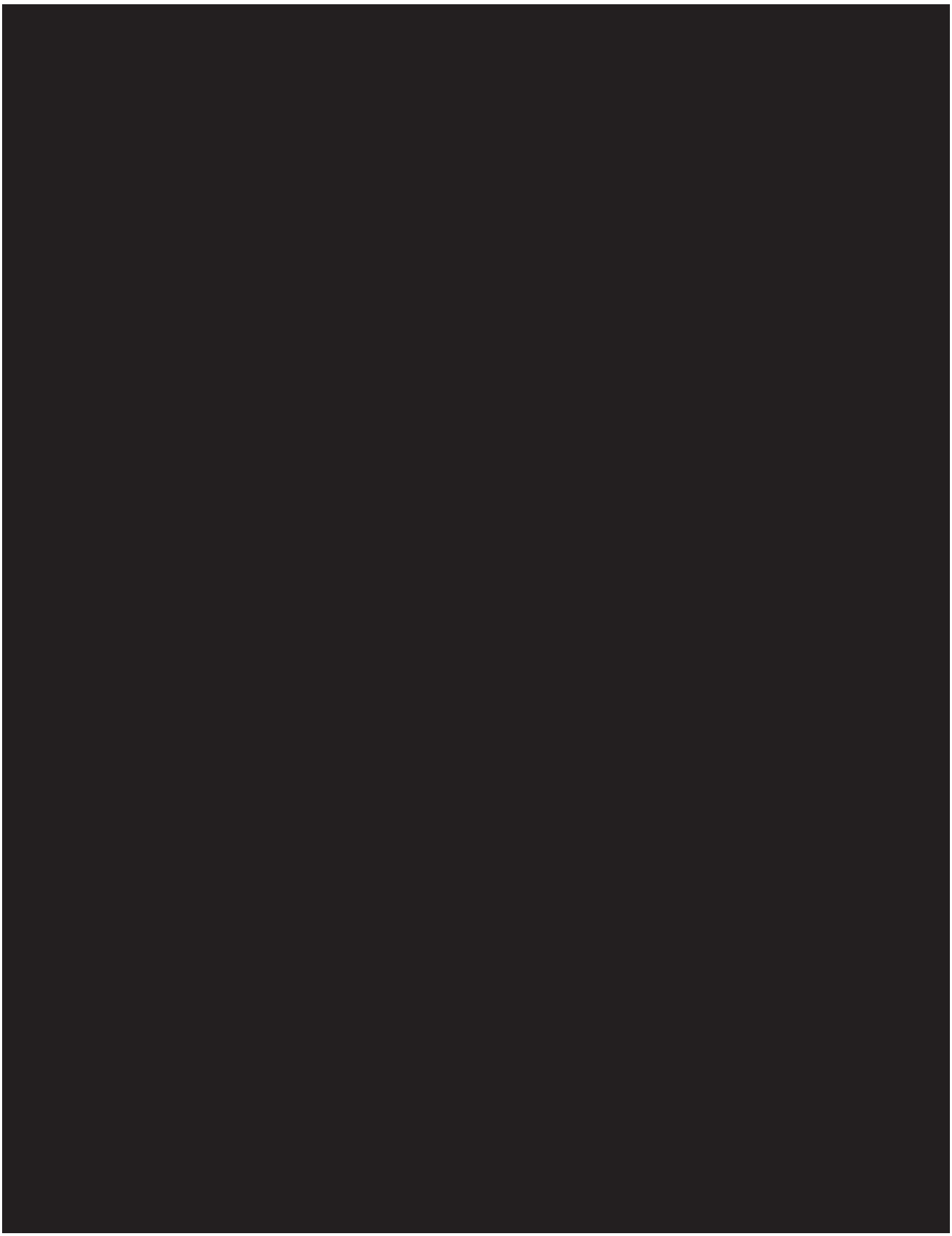


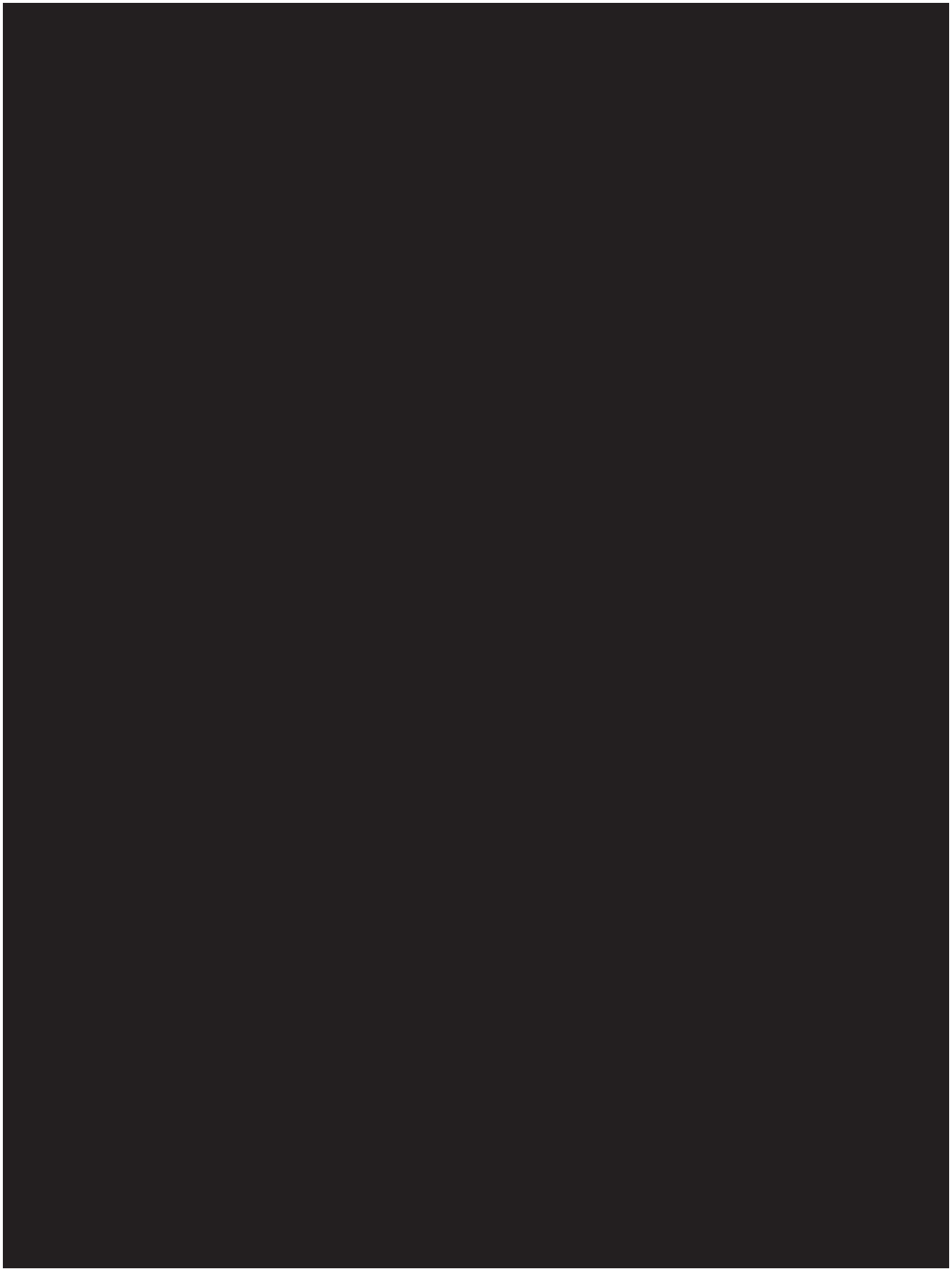


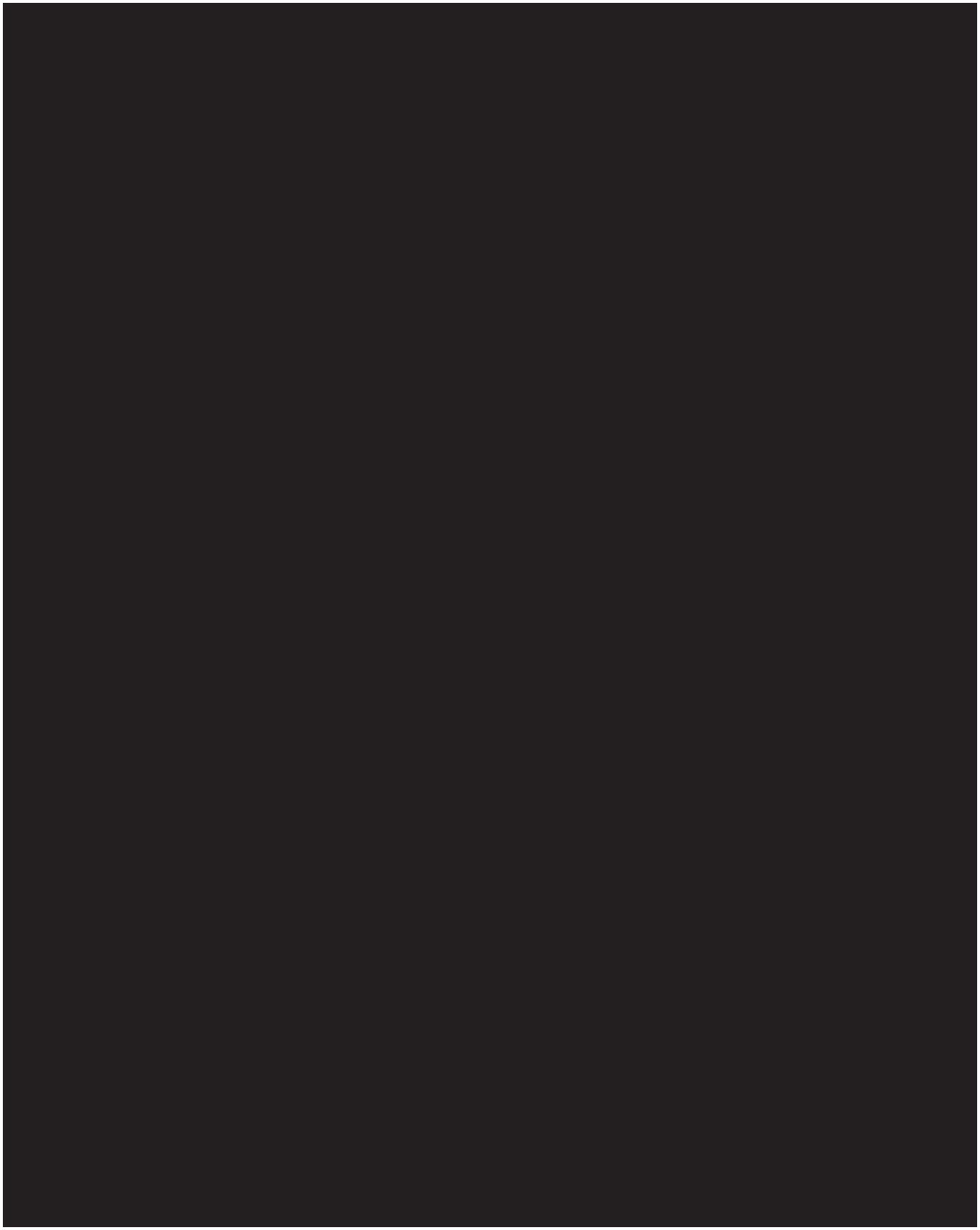












11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

11.1 GLOBAL AMENDMENT 1

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
Global Amendment due to urgent safety reasons		☐
Global Amendment		☐
Section to be changed		
Description of change		
Rationale for change		

11.2 GLOBAL AMENDMENT 2

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Medicinal Product(s)		
Title of protocol		
Global Amendment due to urgent safety reasons		☐
Global Amendment		☐
Section to be changed		
Description of change		
Rationale for change		

12. REFERENCES FOR CTP AUTHORS

Not applicable.

APPROVAL / SIGNATURE PAGE

Document Number: c30966609 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: A randomised, double-blind, placebo-controlled, parallel group, 52 weeks phase IV trial to evaluate efficacy and safety of oral, once daily empagliflozin in elderly Japanese patients with type 2 diabetes mellitus and insufficient glycaemic control

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	26 May 2020 07:21 CEST
Approval-Team Member Medicine		27 May 2020 12:16 CEST
Author-Trial Statistician		28 May 2020 02:31 CEST
Approval-Therapeutic Area [redacted]		28 May 2020 10:45 CEST
Verification-Paper Signature Completion		29 May 2020 12:19 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed