	Document Number:	**c03490746-08**
EudraCT No.: **EU Trial No:**	2016-000669-21	
BI Trial No.:	1218-0091 (old: 1218.91)	
BI Investigational Product(s):	Linagliptin (BI 1356) Empagliflozin (BI 10773)	
Title:	A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus	
Lay Title:	**DI**abetes study of li**NA**gliptin and e**M**pagliflozin in children and ad**O**lescents (**DINAMO**)	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted] Phone: +[redacted], Fax: +[redacted]	
Coordinating Investigator:	[redacted] Tel: +[redacted] Fax: +[redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment 6))	
Version and Date:	**Version:**	**Date:**
	8.0	**23 May 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Trajenta® Jardiance®	
Name of active ingredient:		Linagliptin (BI 1356) Empagliflozin (BI 10773)	
Protocol date: 11 Oct 2017	**Trial number:** 1218-0091		**Revision date:** 23 May 2022

Title of trial:	A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus
Coordinating Investigator:	[redacted]
Trial site(s):	Multi-centre trial conducted in approximately 15-20 countries
Clinical phase:	III
Rationale:	**DINAMO™ (main study)** The trial is planned to be conducted in children and adolescents treated with diet and exercise and metformin and/or insulin background. Patients not tolerating metformin and treated with diet and exercise only have an unmet medical need for oral antidiabetic drugs beside metformin and are expected to highly benefit from inclusion into this trial. **DINAMO™ Mono:** The TODAY study has shown that the majority of youth with T2DM can be effectively treated with metformin monotherapy during the first 12 months of the disease. However, the TODAY study also demonstrated that metformin monotherapy fails to maintain HbA1c < 8.0% in most adolescents during the second year of treatment, even in the face of substantial residual endogenous insulin. Therefore, studies are warranted to assess whether oral antidiabetic medications can either replace metformin as initial therapy or whether a patients can switch from metformin

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	monotherapy in case of metformin failure to another oral antidiabetic medication instead of initiation of insulin therapy.
Objective(s):	**DINAMO™ (main study)** The objective of this study is to assess the efficacy and safety of an empagliflozin dosing regimen and one dose of linagliptin versus placebo after 26 weeks of treatment in children and adolescents with type 2 diabetes mellitus **treated with metformin and/or insulin** or who are not tolerating metformin. In addition, this study will assess long term safety of empagliflozin and linagliptin after 52 weeks of treatment. **DINAMO™ Mono (ancillary study)** The objective of this study is to explore the effect of an empagliflozin dosing regimen and one dose of linagliptin as **Mono**therapy in children and adolescents with type 2 diabetes mellitus.
Methodology:	Multicentre, randomised, double-blind, placebo-controlled and parallel group design of 3 treatment arms (placebo, linagliptin 5 mg, empagliflozin 10 mg) over 26 weeks with a possible dose increase of empagliflozin 10 mg to 25 mg at Week 14 in patients not achieving HbA1c < 7.0% at Week 12 and a double-blind active treatment safety extension period up to 52 weeks. Patients on placebo will be re-randomised at Week 26 to receive either linagliptin or one of the empagliflozin doses (empagliflozin 10 mg or 25 mg). Since patients and investigators will stay blinded, investigators will have to perform an IRT call for all patients at Week 14 and Week 26 in order to get new trial medication kits assigned.

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No. of patients:	~ 170 (150 patients in DINAMO™ and ~ 20 patients in DINAMO™ Mono)
total entered:	**DINAMO™:** At least 150 patients treated with metformin and/or insulin or patients who are not tolerating metformin. **DINAMO™ Mono:** Approximately 20 drug-naïve patients or patients who are not on active treatment.
each treatment:	**DINAMO™:** at least 50 patients **DINAMO™ Mono**: approximately 6 patients
Diagnosis :	Type 2 diabetes mellitus
Main criteria for inclusion:	Main inclusion criteria: • Patients from 10 to 17 years of age (inclusive) at the time of randomisation (Visit 2) • Documented diagnosis of T2DM at Visit 1A: o DINAMO™: Documented diagnosis of T2DM for at least 8 weeks at Visit 1A. o DINAMO™ Mono: Confirmation of T2DM at Visit 1A. • Insufficient glycaemic control as measured by the central laboratory at Visit 1A: o DINAMO™: HbA1c ≥ 6.5% and ≤ 10.5% o DINAMO™ Mono: HbA1c ≥ 6.5% and ≤ 9.0%

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	• DINAMO™: Patients treated with diet and exercise plus metformin at least 1000 mg/day (or up to a maximal tolerated dose) at a stable dose for 8 weeks prior to randomisation and/or stable insulin therapy (basal or MDI) for 8 weeks prior to randomisation (stable insulin therapy is defined as a weekly average variation of the basal insulin dose ≤ 0.1 IU/kg over 8 weeks prior to randomisation) • Patients not tolerating metformin and treated with diet and exercise only are also eligible for inclusion • DINAMO™ Mono: Drug-naïve patients or patients not on active treatment (including discontinuation of metformin due to intolerance [or previous discontinuation for other reasons] and/or discontinuation of insulin [insulin use must be 8 weeks or less] at investigator's discretion) prior to or at Visit 1A • BMI ≥ 85th percentile for age and sex according to WHO references at Visit 1B • Negative for both islet cell antigen auto-antibodies (IA-2) and glutamic acid decarboxylase (GAD) auto-antibodies as measured by the central laboratory at Visit 1A • Non-fasting serum C-peptide levels ≥ 0.6 ng/ml or ≥ 0.199 nmol/L as measured by the central laboratory at Visit 1A		

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	Main exclusion criteria: • History of acute metabolic decompensation such as diabetic ketoacidosis within 8 weeks prior to Visit 1A and up to randomisation • Diagnosis of monogenic diabetes (e.g. MODY) • Impaired renal function defined as estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1.73m² (according to Zappitelli formula) as measured by the central laboratory at Visit 1A.
Test products:	Linagliptin Empagliflozin
dose:	Linagliptin, 5 mg daily Empagliflozin, 10 mg daily Empagliflozin, 25 mg daily (after Week 14)
mode of administration:	p.o.
Comparator products:	Placebo
dose:	Not applicable
mode of administration:	p.o.
Duration of treatment:	Two-week placebo run in; 26-week treatment period and 26-week safety extension period. For patients on insulin, the insulin therapy will be kept unchanged except for adjustments because of safety reasons.
Endpoints	**DINAMO™:** Primary endpoint: • The primary efficacy endpoint will be the change in HbA1c (%) from baseline to the end of 26 weeks

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Secondary endpoints:

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

DINAMO™ Mono:

Primary endpoint:

- The primary efficacy endpoint will be the occurrence of treatment failure up to or at Week 26 as a binary endpoint, defined as meeting at least one of the following criteria:
  - Use of rescue medication at any time up to Week 26
  - Increase from baseline in HbA1c by 0.5% at Week 26
  - Increase from baseline in HbA1c to above 7.0% at Week 26 in patients with baseline HbA1c < 7.0%

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	Secondary endpoints: • Time to treatment failure • Change in HbA1c (%) from baseline to the end of 26 weeks • Change in fasting plasma glucose (FPG, mg/dL) from baseline to the end of 26 weeks • Change in body weight (kg) from baseline to the end of 26 weeks • Change in systolic blood pressure (SBP, mmHg) from baseline to the end of 26 weeks • Change in diastolic blood pressure (DBP, mmHg) from baseline to the end of 26 weeks • Proportion of patients who achieve HbA1c < 6.5% at the end of 26 weeks • Proportion of patients who achieve HbA1c < 7.0% at the end of 26 weeks
Safety criteria:	**DINAMO™ and DINAMO™ Mono:** • Adverse events after 26 and 52 weeks, including adverse events of special interest (see section 5.3.6.1), genital tract infections, bone fracture, urinary tract infections, arthralgia, bullous pemphigoid, adverse events related to reduced intravascular volume, and ketone measurements reported as AE • Percentage of patients with reported hypoglycaemia after 26 and 52 weeks • Vital signs and heart rate after 26 and 52 weeks • Change from baseline in Tanner staging after 26 and 52 weeks

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	• Change from baseline in serum electrolytes, hematology, biochemistry, lipids, IGF-1 and IGF-BP3 and markers of mineral and bone metabolism after 26 and 52 weeks • Growth velocity (cm/year) after 26 and 52 weeks
Statistical methods:	**DINAMO™:** The primary endpoint will be analysed using an effectiveness "wash-out" approach. The "wash-out" approach will be based on an analysis of covariance (ANCOVA) model with baseline HbA1c as a continuous covariate, and with categorical covariates for treatment and age. The effect of linagliptin and of empagliflozin will be compared to placebo at the overall alpha level of 5% using the Hochberg method to account for multiple testing. The analysis will be based on all randomised patients who are treated with at least one dose of study drug and have a baseline HbA1c value. All available HbA1c measurements up to Week 26 will be included regardless of adherence to treatment or the use of rescue medication. Patients will be assigned to the treatment they were randomised to at the initial randomisation. After achieving statistically significant results for both comparisons in the "wash-out" approach, a secondary family of hypotheses comparing the individual empagliflozin doses versus placebo will be tested using " inverse probability weighting" approach. The first analysis is the comparison of empagliflozin versus placebo in a regimen starting on empagliflozin 10 mg and either having a dose increase in patients who are not at glycaemic target at Week 12 to empagliflozin 25 mg, or continue with empagliflozin 10 mg who are at glycaemic target at Week 12 and the second analysis is the comparison of empagliflozin versus placebo using only empagliflozin 10 mg regardless whether the patients are responder or non-responder at Week 12. These analyses will be hierarchically tested in a confirmatory setting.

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The secondary endpoint of change in FPG from baseline to the end of 26 weeks will be analysed using an ANCOVA model including treatment as a fixed classification effect, baseline FPG as a linear covariate, and age as a categorical covariate.

The other secondary endpoints will be analysed based on a restricted maximum likelihood (REML) approach using mixed effects model for repeated measurements (MMRM). The analyses will include the fixed categorical effects of treatment, visit, and treatment by visit interaction, as well as the categorical covariate age and the continuous, fixed covariates of baseline and baseline by visit interaction. An unstructured covariance structure will be used to model the within-patient measurements. The analysis will be based on all randomised patients who are treated with at least one dose of study drug and have a baseline HbA1c value.

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

DINAMO™ Mono:

The primary endpoint analysis will be a comparison of the treatment failure rates of linagliptin 5 mg, pooled empagliflozin and placebo. The risk difference of active treatments versus placebo will be determined and assessed by an exact 2-sided 90% confidence interval based on the method of Chan and Zhang. Patients will be assigned to the treatment they were randomised to at the initial randomisation.

The secondary endpoint of time to treatment failure will be analysed and graphically described by Kaplan-Meier estimates up to the

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	planned end of the study. A descriptive Log-rank test will compare the linagliptin group and the empagliflozin group versus the placebo group individually up to Week 26. The change in HbA1c from baseline to the end of 26 week will be analysed based on a REML approach using MMRM to access the effectiveness and efficacy. The change in HbA1c from baseline to the end of 26 week will also be analysed using an ANCOVA model including treatment as a fixed classification effect, baseline HbA1c as a linear covariate, and age as a categorical covariate. The secondary endpoints of change in FPG, body weight, SBP and DBP from baseline to the end of 26 week will be analysed in the same way as DINAMO™ with the DINAMO™ Mono data. The proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 week will be determined per treatment group and the risk difference of active treatments versus placebo will be determined and assessed by an exact 2-sided 90% confidence interval.

FLOW CHART

Trial Periods	**Screening**	**Placebo Run-in[1]**	**Randomised treatment period[4]**								**Follow-up**
Visit	**1A**	**1B**	**2[2]**	**3**	**4A**	**4B[3]**	**5[2]**	**6**	**7**	**8[2] EOT[5]**	**9[13]**
Days calculated from the day of first (randomised) treatment	**-21 to -14**	**-14**	**Day 1**	**29**	**85**	**99**	**183**	**211**	**295**	**365**	**386**
Weeks from date of first randomised treatment			**(**)**	**4**	**12**	**14**	**26**	**30**	**42**	**52**	**55**
Time window for visits	+7 days[1 1]	+7 days[1 2]	none	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	+7 days
Informed consent and assent (*)	X										
Demographics	X										
Medical history	X										
Physical examination		X	X				X			X	X
Tanner staging (modified)[6]			X				X			X	
Vital signs (seated)[14]		X	X	X	X		X	X	X	X	X
12 lead-ECG		X					X			X	
Safety Laboratory tests[14]	X[7]		X[2]	X	X		X[2]	X	X	X[2]	X
HbA1c[14]	X		X	X	X		X	X	X	X	
PK blood sampling							X[8]			X[8]	
Fasting plasma glucose (FPG)			X[2]				X[2]			X[2]	

FLOW CHART (cont.)

Trial Periods	**Screening**	**Placebo Run-in[1]**	**Randomised treatment period[4]**								**Follow-up**
Visit	**1A**	**1B**	**2[2]**	**3**	**4A**	**4B[3]**	**5[2]**	**6**	**7**	**8[2] EOT[5]**	**9[13]**
Days calculated from the day of first (randomised) treatment	**-21 to -14**	**-14**	**Day 1**	**29**	**85**	**99**	**183**	**211**	**295**	**365**	**386**
Weeks from date of first randomised treatment			**(**)**	**4**	**12**	**14**	**26**	**30**	**42**	**52**	**55**
IGF-1, IGF-BP3 and markers of bone turnover[14]			X	X[9]			X	X[9]		X	X
DPP-4 activity			X[10]								
Pregnancy test[14]	X		X	X	X		X	X	X	X	
Auto-antibodies for diabetes (IA-2 and GADA)	X										
Serum C-peptide	X		X[2]				X[2]			X[2]	
Height	X						X			X	
Weight[14]		X	X	X	X		X	X	X	X	X
BMI		X					X			X	
Review of in-/exclusion criteria	X	X	X								
Dispense open-label trial drugs		X									
Administer open-label trial drugs		X									
Randomisation			X			X	X				

FLOW CHART (cont.)

Trial Periods	**Screening**	**Placebo Run-in[1]**	**Randomised treatment period[4]**								**Follow-up**
Visit	**1A**	**1B**	**2[2]**	**3**	**4A**	**4B[3]**	**5[2]**	**6**	**7**	**8[2] EOT[5]**	**9[13]**
Days calculated from the day of first (randomised) treatment	**-21 to -14**	**-14**	**Day 1**	**29**	**85**	**99**	**183**	**211**	**295**	**365**	**386**
Weeks from date of first randomised treatment			**(**)**	**4**	**12**	**14**	**26**	**30**	**42**	**52**	**55**
Dispense double-blind trial drugs[16]			X	X	X	X	X	X	X		
Administer double-blind trial drugs[16]			X	X	X	X	X	X	X	X	
Instructions/reminder on blood ketone measurements[15]			X	X	X		X	X	X	X	
Self-blood ketone monitoring[11]			X	X	X	X	X	X	X	X	X
Instructions/reminder on glucometer use[15]		X	X	X	X		X	X	X	X	
Self-blood glucose monitoring (SBGM)		X	X	X	X	X	X	X	X	X	X
Adverse events[15]	X	X	X	X	X	X	X	X	X	X	X
Compliance check[15]			X	X	X	X	X	X	X	X	
Concomitant therapy[15]	X	X	X	X	X	X	X	X	X	X	X
Completion of patient participation (***)											X
Vital status collection[12]											X

1 This visit can be performed on the same day as Visit 1A.

1.1 Visit 1A can occur -28 days before Visit 2 per allowed out of window.

1.2 Visit 1B can occur -21 days before Visit 2 per allowed out of window.

2 Visits to be performed in a fasted state (overnight fast for at least 8 hours).

3 This visit could be either on-site visit or ambulatory visit (nurse/health care professional/validated courier to be assigned for delivering the trial medications at home and retrieving the previous ones dispensed at Visit 4A) as per the investigator's decision. In case of ambulatory visit not performed by a site representative, a phone contact by the investigator or a site staff representative is required to check any new adverse event or concomitant therapy.

4 Additional interactions (phone contact, text messaging or emails, as deemed appropriate) with the patient will be performed a day or two after randomised treatment started and then after 2, 8, 18, 22, 34, 38, 46 and 50 weeks of treatment. Visits 3, 4A, 6, 7, 9 can be done remotely/by telephone/telemedicine under exceptional circumstances due to the Corona Virus Disease-year 2019 (COVID-19) pandemic. Reasons a remote/telephone/telemedicine visit may be performed may include confirmed or suspected COVID-19 infection or unwillingness to return to the investigator site due to concerns of COVID-19 exposure.

5 If a patient discontinues treatment early, an immediate End of Treatment (EOT) visit would be conducted.

6 For patients with Tanner stage V at Visit 2, further assessment is not required at the subsequent visits.

7 Laboratory tests at Visit 1A include TSH, liver enzymes, alkaline phosphatase, serum creatinine, cystatine C, haemoglobin and haematocrit only in addition to HbA1c and C-peptide and do not need to be collected in a fasted state.

8 Blood samples for pharmacokinetic analysis will be collected within 30 minutes prior to drug administration at site (and preferably approximately 24 hours after drug administration on the previous day) and 1.5h ± 15 min after drug administration.

9 IGF-1 and IGF-BP3 will not be measured at this Visit.

10 Blood sample for DPP-4 activity measurement will be collected within 30 minutes prior to trial drug administration.

11 Daily blood ketone measurements in the first 4 weeks of treatment and the 4 subsequent weeks after Visit 5; otherwise at least 3 times per week and in case of intercurrent illness/stress or if deemed necessary by the investigator. In addition, blood ketone levels will be checked by using the meter at clinic visits.

12 Patients who complete an early End of Treatment visit and do not accept to attend all remaining planned visits will be contacted for vital status collection at Week 55. This can be done by phone.

13 Patients who discontinue treatment early should attend Visit 9 at Week 55 in person or by telephone if agreed. At minimum, data on adverse events, concomitant therapies, and vital status should be collected at Visit 9 at Week 55.

14 Vital signs, weight, and local laboratory testing is allowed for Visits 3, 4A, 6, 7, 9 under exceptional circumstances due to the COVID-19 pandemic.

15 Study procedure for Visits 3, 4A, 6, 7, 9 can be done remotely/by telephone/telemedicine/in-home visits under exceptional circumstances due to the COVID-19 pandemic.

16 Shipment/dispensing/administration of study medication to/at the patient's home is allowed for Visits 3, 4A, 6, 7 under exceptional circumstances due to the COVID-19 pandemic and requires discussion with the sponsor first using a sponsor-approved shipment provider. Prior to shipment of study medication to the patient's home, the investigator should first conduct a remote/telephone/telemedicine/in-home visit to discuss adverse events, concomitant therapies, glucose/ketone monitoring, and study medication compliance. The review of local laboratory results can occur after shipment of study medication but within the protocol defined window of the visit. Reasons for shipment of study medication to a patient's home may include unwillingness to return to the investigator site due to concerns of COVID-19 exposure or suspected COVID-19 infection.

(*) All patients' legal representative(s) must sign an informed consent consistent with ICH-GCP guidelines prior to participation in the trial. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. Re-consent can be done remotely/by telephone/telemedicine/in-home visit under exceptional circumstances due to the COVID-19 pandemic. The initial informed consent and assent at Visit 1A must be done in the clinic.

(**) Day of Randomisation / Day of first intake of randomised medication.

(***) Completion of patient participation also needs to be completed if the patient withdraws prematurely following randomisation (see Section 3.3.4).

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine transaminase
AMP	Auxiliary Medicinal Product
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase
AUC	Area under the Curve
BI	Boehringer Ingelheim
MI	Body Mass Index
BOCF	Baseline Observation Carried Forward
BP	Blood Pressure
CA	Competent Authority
CEC	Clinical Event Committee
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
COVID-19	COronaVIrus Disease– year 2019
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Clinical Research Organisation
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database lock
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complications Trial
DILI	Drug Induced Liver Injury
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DPP-4	Dipeptidyl Peptidase-4
ECG	Electrocardiogram
eDC	electronic Data Capturing
ePRO	Electronic Patient Reported Outcome
EDTA	Ethylene Diamine Tetracetic Acid
EMA	European Medicines Agency
EoT	End of Treatment
EudraCT	European Clinical Trials Database
FC	Flow Chart
FDA	Food and Drug Administration
FPG	Fasting Plasma Glucose
FUP	Follow-up
GADA	Glutamic Acid Decarboxylase Auto-antibodies
GCP	Good Clinical Practice
GFR or eGFR	Glomerular Filtration Rate or estimated Glomerular Filtration Rate
GLP-1	Glucagon-like Peptide-1

GMP	Good Manufacturing Practice
HbA1c	Glycated Hemoglobin
IA-2	Islet cell Antigen auto-antibodies
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IFCC	International Federation of Clinical Chemistry
IGF-1	Insulin-like Growth Factor-1
IGF-BP3	Insulin-like Growth Factor-Binding Protein 3
IMP	Investigational Medicinal Product
IPD(s)	Important Protocol Deviation(s)
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LDL	Low Density Lipoprotein
MACE	Major Adverse Cardiac Events
MAR	Missing At Random
MCMC-MI	Markov Chain Monte Carlo - Multiple Imputation
MDI	Multiple Dose Injection
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Multiple Imputation
mITT	modified Intention-to-Treat
MMRM	Mixed Model for Repeated Measurements
MNAR	Missing Not At Random
NGSP	National Glycohemoglobin Standardisation Program
NIMP	Non Investigational Medicinal Product
OPU	Operative Unit
PD	Pharmacodynamics
PDC	Pediatric Diabetes Consortium
PDCO	Paediatric Committee
PIP	Paediatric Investigational Plan
PK	Pharmacokinetics
PMR	Post-Marketing Requirement
p.o.	per os (oral)
PPARγ	Peroxisome Proliferator-Activated Receptors gamma
PPS	Per Protocol Set
q.d.	quaque die (once a day)
REP	Residual effect period
REML	Restricted Maximum Likelihood
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SBGM	Self-Blood Glucose Monitoring
SBKM	Self-blood Ketone Monitoring
SBP	Systolic Blood Pressure
SDS	Standard Deviation Score
SGLT-2	Sodium-Glucose Co-Transporter 2
SI	International System of Units

SLC-5	Sodium-Glucose Co-transport 5
SLR-MI	Sequential Linear Regression – Multiple Imputation
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UACR	Urine Albumin Creatinine Ratio
UGE	Urinary Glucose Excretion
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
WBC	White Blood Cells
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Diabetes is an in prevalence increasing disease with an estimated 415 million affected people worldwide. In high-income countries, up to 91% of adults with the disease have type 2 diabetes mellitus (T2DM) [R16-4703]. Complications associated with chronic hyperglycaemia are currently one of the most frequent causes of adult-onset loss of vision, renal failure, and amputation in the industrialized world. Type 2 diabetes mellitus is associated with macrovascular complications with a 2- to 4-fold increase in cardiovascular disease risk. The high frequency of complications leads to a significant reduction of life expectancy.

T2DM in children and adolescents (youth-onset T2DM) has also become an increasingly important public health concern throughout the world with unique characteristics and demographics in many countries. Youth-onset T2DM occurs most often during the second decade of life and coincides with the peak of physiologic pubertal insulin resistance. T2DM in children and adolescents occurs in all races but at a much greater prevalence in those of non-White European descent, e.g. those of Black African descent, native North American, Hispanic (especially Mexican)-American, Asian, South Asian, and Native Pacific islanders. In the USA and Europe, nearly all youth with T2DM have a body mass index (BMI) above the 85th percentile for age and sex. [P15-01571]. In the USA and Europe, youth-onset T2DM is predominately found in populations characterised by low socioeconomic and educational status whereas in emerging countries like China and India, more affluent children are more likely to develop T2DM than poorer children [P15-01571].

Prevention and reversal of disease progression with diet and exercise is presently the preferred therapeutic approach but is rarely sufficient. Only 10% of children and adolescents with T2DM achieve glycaemic goals through diet and exercise alone. Although several antidiabetic compounds have been developed to improve glucose control in adults, metformin is the only oral agent recommended and approved as the initial pharmacologic treatment for T2DM in youth [P12-09397]. However, metformin is not suitable for all patients, as insufficient efficacy over time has been observed in several paediatric studies [R07-4400; R10-0796]. Insulin can also be used to lower plasma glucose levels but is often unacceptable to patients in the paediatric population due to the injectable route of delivery and the higher rates of hypoglycaemia and weight gain. Therefore there is a medical need for new antidiabetic drugs for children and adolescents for whom lifestyle change is not sufficient.

Empagliflozin is a reversible, highly potent (IC50 1.3 nM) and selective competitive inhibitor of sodium-glucose co-transporter 2 (SGLT-2), a member of a larger group of sodium substrate co-transporters, the sodium-glucose co-transport 5 (SLC5) gene family [R05-0939]. Under normoglycaemia, glucose is 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 glycosuria. This threshold concentration can be decreased by SGLT-2 inhibition [c01678844-17]; an approximately 5000-fold selectivity over human SGLT-1 (IC50 6278 nM), responsible for glucose absorption in the gut, was calculated for empagliflozin [U06-1742].

Linagliptin is a potent inhibitor of DPP-4 activity and prolongs the half-life of GLP-1. This has been shown in vitro, in various animal models, and in clinical trials [c018916941-04].

Both compounds are approved for use as adjunct to diet and exercise as monotherapy and combined with other antidiabetic drugs including insulin. Empagliflozin and linagliptin are expected to show efficacy in terms of glucose control when used alone, as adjunct to diet and exercise and in combination with metformin and/or insulin in children and adolescents with T2DM.

1.2 DRUG PROFILE

1.2.1 Empagliflozin

Empagliflozin is an orally available, potent, and selective inhibitor of the SGLT-2. Its selective inhibition reduces renal reabsorption of glucose and promotes increased urinary glucose excretion (UGE) resulting in reduction of blood glucose levels.

Empagliflozin for the treatment of T2DM is approved in over 100 countries including the European Union and the USA where it is marketed under the brand name Jardiance®.

Non-clinical assessment of safety
Empagliflozin has been extensively tested as part of the adult T2DM program as described in the Investigator's Brochure [c01678844-17].

Clinical pharmacokinetics (PK), pharmacodynamics and safety in children and adolescents
The primary objective of the paediatric empagliflozin trial 1245.87 [c09087100] was to assess the pharmacokinetics of a single dose of empagliflozin (5 mg, 10 mg, and 25 mg) in paediatric patients with T2DM. The secondary objective of this study was to investigate the pharmacodynamics of a single dose of empagliflozin in the same population.

Twenty seven patients with T2DM who were in the age range of 10 to less than 18 years and who had insufficient glycaemic control despite treatment with diet and exercise and/or stable metformin and/or stable basal or multiple dose injection (MDI) insulin therapy were randomised and treated in this paediatric PK single dose trial. Following single dose administration of 5 mg or 10 mg or 25 mg, empagliflozin was rapidly absorbed in paediatric patients with T2DM with median values ranging from 1.25 h to 1.78 h. Empagliflozin exposure (both with respect to AUC and C_{max}) increased with increasing dose. Mean terminal half-life ($t_{1/2}$) was 7 to 8 h for all dose groups. The pharmacokinetic parameters of 10 mg and 25 mg empagliflozin in paediatric patients with T2DM were compared with the results from a previous trial in adults [U09-1970] and with the results from population pharmacokinetic modelling in adult patients with T2DM [c02090424]. The pharmacokinetic exposure was generally comparable between paediatric and adult patients with T2DM, with a slightly lower exposure (with respect to AUC and C_{max}) in paediatric patients in the 10 mg dose group compared with the adult patients. For the 2 doses (10 mg and 25 mg), median t_{max} and mean $t_{1/2}$ were similar in adult and paediatric populations. The slightly lower exposure of paediatric

patients in the 10 mg dose group compared with adult patients may be related to the higher body weight of the paediatric population [c09087100].

In the paediatric patients included in this trial, a dose-dependent increase of UGE in the 24 h following empagliflozin administration was observed, with mean (standard error (SE)) changes from baseline (adjusted for baseline UGE and baseline FPG) of 53.1 (10.2) g/24 h in the 5 mg dose group, 73.0 (10.1) g/24 h in the 10 mg dose group, and 87.4 (9.4) g/24 h in the 25 mg dose group. The effect on UGE in paediatric patients was comparable with the increase seen in a previous trial with adult patients with T2DM [U09-1970].

An exposure-response model, linking AUC_{0-24} to UGE at baseline and to UGE during the first 24 h following empagliflozin administration ($UGE_{0-24,1}$), was developed based on data from 3 clinical trials in adult patients with T2DM [U09-1271; U09-1970; U10-2326] and the data from the 1245.87 trial with paediatric patients. After accounting for all significant covariates, adult and paediatric patients with T2DM had similar exposure-response relationships, following a single oral dose of empagliflozin.

All 3 single doses of empagliflozin were well tolerated in the 1245.87 trial. No new safety signals were observed. The safety results of this trial were consistent with those observed in previous empagliflozin trials in adults [c01678844-17].

Clinical efficacy and safety in adults

Empagliflozin has been studied as part of a global development program with more than 20000 patients with T2DM treated in clinical studies of which more than 13000 were treated with empagliflozin, either alone or in combination with metformin, a sulphonylurea, a PPARγ agonist, dipeptidyl peptidase-4 inhibitors, or insulin.

The Phase III studies in T2DM showed that treatment with empagliflozin 10 mg or 25 mg once daily for up to 24 weeks results in a reduction of HbA1c up to 0.85%, body weight up to 2.2 kg and systolic blood pressure (SBP) up to 4.8 mmHg compared with placebo. This was consistently observed with empagliflozin as monotherapy, add on to metformin, to the combination of metformin and sulphonylurea, to pioglitazone with or without metformin, and to basal insulin with metformin and/or sulphonylurea. One Phase III study up to 204 weeks in T2DM supports the sustained effect of empagliflozin.

In clinical studies, empagliflozin was well tolerated in both healthy volunteers and patients with T2DM up to maximal treatment duration of 208 weeks in completed studies. The frequency of overall adverse events (AEs), AEs leading to discontinuation and serious AE (SAEs) were comparable to that with placebo. There was no significant increase in frequency of hypoglycaemia with empagliflozin compared to placebo except when used in combination with a sulphonylurea or basal insulin. There was an increase in frequency of genital infections with the use of empagliflozin. Empagliflozin treatment also increased urination and thirst. There was a small increase in total cholesterol, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol and no significant changes of LDL/HDL cholesterol ratio and in triglycerides. In addition, increases in haematocrit, haemoglobin and red blood cell were observed with empagliflozin. No clinically relevant changes in electrolytes were observed with empagliflozin.

The safety profile of empagliflozin in patients with renal impairment and decreased eGFR down to 15 mL/min/1.73m^2 was consistent with that reported in patients with normal renal function; there is no experience in patients with endstage renal disease and in patients on dialysis. In the EMPA-REG OUTCOME® study, the overall safety profile of empagliflozin was comparable to the known safety profile of this agent.

In a phase III randomised, double-blind cardiovascular outcome trial (the EMPA-REG OUTCOME® study [c01678844-17]), empagliflozin was shown to be superior in reducing the primary endpoint 3 point Major Adverse Cardiac Events (MACE), a composite of cardiovascular death, non-fatal myocardial infarction (MI), or non-fatal stroke compared to placebo on top of standard of care in patient with T2DM and established cardiovascular disease. Empagliflozin treatment showed a nominally significant reduction in cardiovascular death with no significant change in non-fatal MI or non-fatal stroke. An improved overall survival driven by a reduction in cardiovascular death was also observed. Empagliflozin reduced the risk of hospitalization for heart failure and the composite of cardiovascular death or hospitalization for heart failure compared with placebo. The risk of new or worsening nephropathy (including onset of macroalbuminuria, doubling of serum creatinine and initiation of renal replacement therapy (i.e. haemodialysis)) was reduced in empagliflozin group compared to placebo. Empagliflozin showed a higher occurrence of sustained normo- or microalbuminuria in patients with baseline macroalbuminuria compared with placebo. After an initial drop in eGFR, treatment with empagliflozin slowed progression of renal disease and eGFR returned to baseline 4 weeks after drug discontinuation while the placebo group showed a gradual decline in eGFR during the course of the study with no further change during the 4-week follow-up.

For a more detailed description of the empagliflozin profile, please refer to the respective current Investigator's Brochure (IB) [c01678844-17].

1.2.2 Linagliptin

Linagliptin is a potent inhibitor of DPP-4 activity and prolongs the half-life of GLP-1. This has been shown in vitro, in various animal models, and in clinical trials. Linagliptin is an orally available compound with a low risk for hypoglycaemic episodes [c018916941-04]. Linagliptin for the treatment of T2DM is approved in over 90 countries including the European Union (Trajenta®), the USA (Tradjenta®), and Japan (Trazenta®).

Non-clinical assessment of safety
Linagliptin has been extensively tested as part of the adult T2DM program as described in the Investigator's Brochure [c018916941-04].

Clinical pharmacokinetics, pharmacodynamics, efficacy and safety in children and adolescents
The primary objective of trial 1218.56 [c09060697] was to identify the appropriate dose of linagliptin in paediatric patients with T2DM. Two doses of linagliptin (1 mg and 5 mg) were compared with placebo. A protocol-defined interim analysis was performed, which showed superiority of the linagliptin 5 mg dose over the linagliptin 1 mg dose regarding DPP-4 inhibition at trough at steady state and a plasma DPP-4 inhibition by linagliptin 1 mg of less

than 80%. These results demonstrated inferior DPP-4 inhibition of linagliptin 1 mg and allowed early termination of the trial.

Thirty-eight treated patients between 10 and 17 years were randomised and included in the interim analysis. At final database lock (DBL), 39 patients had been randomised to and treated with placebo (15 patients), linagliptin 1 mg (10 patients) or linagliptin 5 mg (14 patients). Patients had a documented diagnosis of T2DM obtained at least 3 months prior to randomisation and had insufficient glycaemic control despite treatment with diet and exercise and/or metformin with or without concomitant stable basal insulin therapy.

The primary endpoint of the final analysis was the change from baseline in HbA1c (%) after 12 weeks of treatment. Because of the early termination of the study, the trial had limited statistical power. After 12 weeks of treatment, the adjusted mean treatment difference between linagliptin 5 mg and placebo was −0.63 (95% CI: −1.50, 0.23; p = 0.1447). The adjusted mean treatment difference between linagliptin 1 mg and placebo was −0.48 (95% CI: −1.47, 0.51; p = 0.3295). As expected because of the limited power of the trial, a statistically significant difference to placebo could be demonstrated neither for the linagliptin 1 mg dose nor for the linagliptin 5 mg dose. The reduction of −0.63 with linagliptin 5 mg is considered clinically meaningful. The results were in accordance with data from adult patients after 12 weeks of treatment with linagliptin 5 mg. The median change from baseline in HbA1c (%) was +0.50 in the placebo group, -0.05 in the linagliptin 1 mg group, and -0.30 in the linagliptin 5 mg group. The difference to placebo was -0.80 in the linagliptin 5 mg group compared with -0.55 in the linagliptin 1 mg group. The results were consistent with data from adult patients after 12 weeks of treatment with linagliptin 5 mg. In the linagliptin 5 mg group, a reduction in HbA1c compared with baseline was seen over the entire randomised treatment period. In contrast, HbA1c had returned almost to baseline in the linagliptin 1 mg group and had increased beyond baseline HbA1c in the placebo group at Week 12. The percentage of patients with a relative efficacy response (HbA1c lowering by at least 0.5%) was greater in the linagliptin 5 mg group (30.8%) than in the linagliptin 1 mg group (20.0%) or placebo group (14.3%). Furthermore, the proportion of patients who had a baseline HbA1c ≥7% and reached target HbA1c <7% (absolute efficacy response) was greater with linagliptin 5 mg (36.4%) than with placebo (18.2%), whereas it was 10.0% with linagliptin 1 mg. A target HbA1c <7% is more difficult to achieve for patients with a higher baseline HbA1c value than for patients with a lower baseline HbA1c value.

For this trial, DPP-4 inhibition was defined as key secondary endpoint. Baseline DPP-4 activity was similar across treatment groups. DPP-4 inhibition at trough at steady-state was clearly more pronounced for the linagliptin 5 mg dose group than for the 1 mg dose group, with median values of 79% and 38%, respectively. Median DPP-4 inhibition by linagliptin 5 mg in the paediatric patients of trial 1218.56 was similar to the median DPP-4 inhibition obtained with linagliptin 5 mg in adults after 12 weeks of treatment (study 1218.6 [U08-1056]: 85.0%; study 1218.5 [U08-3761]: 82.5%).

Fasting plasma glucose (FPG) was analysed as secondary endpoint. The placebo-corrected adjusted mean change from baseline in the linagliptin 5 mg group was −34.2 mg/dL (95% CI: −77.7, 9.3; p = 0.1189). The placebo-corrected adjusted mean change from baseline in the linagliptin 1 mg group was considerably lower with −5.6 mg/dL (95% CI: −55.5, 44.4; p =

0.8216). The reduction in FPG with linagliptin 5 mg was similar to that in adult patients treated with linagliptin 5 mg. The median change from baseline in FPG was +19.5 mg/dL with placebo, +29.5 mg/dL with linagliptin 1 mg, and -5.0 mg/dL with linagliptin 5 mg. The placebo-corrected median FPG change from baseline at Week 12 was -24.5 mg/dL in the linagliptin 5 mg group and +10.0 mg/dL in the linagliptin 1 mg group. The placebo-corrected median FPG change from baseline of -24.5 mg/dL with linagliptin 5 mg is considered clinically meaningful and was comparable with that in adults receiving linagliptin 5 mg over 12 weeks [U08-1056].

Systemic exposure was assessed based on linagliptin plasma levels. Linagliptin trough levels in the 5 mg dose group were higher than in the 1 mg dose group, with geometric mean (gMean) values of 7.42 and 3.80 nmol/L, respectively.

Linagliptin was well tolerated. No new safety signals were detected in paediatric patients who received linagliptin. The safety profile of linagliptin in paediatric patients was consistent with that in adults [c018916941-04].

Clinical efficacy and safety in adults
Treatment with linagliptin 5 mg q.d. has resulted in clinically meaningful and statistically significant reductions in HbA1c, FPG, and postprandial glucose. There is a consistent pattern in the improvement in HbA1c levels when linagliptin was used in patients with different background therapies. These findings demonstrate efficacy for up to 18 to 24 weeks duration for different background therapies and are further supported by trials of longer duration up to 104 weeks.

The treatment difference to placebo in the HbA1c change from baseline after 24 weeks of treatment was -0.69% (95% CI: -0.85, -0.32) for linagliptin 5 mg monotherapy (trial 1218.16), -0.64% (95% CI: -0.78, -0.50) for linagliptin 5 mg with metformin background therapy (trial 1218.17) and -0.65% (95% CI: -0.74, -0.55) for linagliptin 5 mg with basal insulin background therapy (trial 1218.36) [c018916941-04].

In the phase III studies the overall incidence of AEs, drug related AEs, AEs of severe intensity, AEs leading to discontinuation, and serious adverse events (SAEs) were very similar across studies, with linagliptin being mostly comparable to placebo.
For monotherapy with linagliptin, nasopharyngitis, cough, hypersensitivity, lipase increase and pancreatitis have been identified as adverse drug reactions. In addition, based on post-marketing data, angioedema, urticaria, rash, mouth ulceration and bullous pemphigoid, are other ADRs listed for linagliptin.

Studies in patients on metformin background showed that the percentages of patients with adverse events were comparable between treatments (54.3% placebo plus metformin, 49.0% linagliptin 5 mg plus metformin). The number of patients with SAEs was low in both treatment groups (2.5% placebo plus metformin, 3.0% linagliptin 5 mg plus metformin).
The combination of linagliptin and insulin has been tested in clinical trials in different populations. Studies in patients on insulin background (with or without other oral antidiabetic drugs) had the highest reported frequency of investigator reported hypoglycaemic adverse events in both treatment arms, with comparable rates between the placebo group and

linagliptin. Overall, it has been shown that linagliptin is an effective and safe add-on therapy to insulin in patients with T2DM. This combination therapy was also shown to be safe and effective in vulnerable, elderly T2DM patients and in T2DM patients with renal impairment [P13-14398, c018916941-04].

The growing safety evidence base for linagliptin, including completed Phase III and IV clinical trials, comprises patients treated with background therapies of metformin, sulphonylurea, empagliflozin, and insulin. To date, in Phase III trials in patients with T2DM, linagliptin elicited meaningful glucose-lowering effects and was well tolerated with little intrinsic risk for hypoglycaemia [P10-14001, P11-02847, P11-06845, P11-09378, P11-12477, c018916941-04].

In summary, linagliptin has been shown to be effective and safe as an add-on therapy that can help patients on basal insulin to improve their blood sugar control without weight gain or additional risk of hypoglycaemia.

For a more detailed description of the linagliptin profile please refer to the current Investigator's Brochure (IB) [c018916941-04].

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Empagliflozin (10 mg and 25 mg) and linagliptin (5 mg) are approved for the treatment of adult patients with T2DM.

The paediatric T2DM prevalence is growing and positively correlated with obesity. Prevention and reversal of disease progression with diet and exercise is presently the preferred initial therapy when hyperglycaemia is not considered as severe. However, lifestyle modifications are difficult to implement and require intensive follow-up to be effective. Overall, less than 10% of paediatric patients diagnosed with T2DM can achieve glycaemic targets (HbA1c < 7.0% and FPG < 126 mg/dl) by following lifestyle interventions alone [R07-4402]. As a result, pharmacotherapy is often required and although there are many agents available to improve the metabolic abnormalities, there are little data concerning their use in children and adolescents.

Based on the results from two dose-finding studies in paediatric patients with T2DM with each of the compounds [c09087100 ; c09060697], this phase III trial is planned to confirm the efficacy and safety of empagliflozin and linagliptin in children and adolescents with T2DM.

There is a medical need for new antidiabetic drugs for children and adolescents for whom lifestyle change is not sufficient and as add-on to metformin and/or insulin therapy. In addition, this trial is being conducted to satisfy both the empagliflozin and linagliptin Paediatric Investigation Plans (PIPs) approved by the European Medicines Agency as well as the Post-Marketing Requirements (PMRs) agreed with FDA.

Rationale for background therapies
The trial is planned to be conducted in children and adolescents treated with diet and exercise and metformin and/or insulin background, reflecting the current standard of care. Patients not tolerating metformin (as defined in Section 3.3.2) and treated with diet and exercise only will also be eligible. This subgroup of pediatric patients has a high unmet medical need for oral antidiabetic drugs beside metformin and is expected to highly benefit from inclusion into this trial. Recent data from the Pediatric Diabetes Consortium (PDC) showed that 35% of children and adolescents with T2DM were treated with metformin alone, 19% with insulin alone, 31% with both metformin and insulin, 13% with lifestyle modification alone, and only 3% were treated with other glucose-lowering medications with/without metformin or insulin. Overall, 51% of included patients were on insulin therapy [R16-2240].

Metformin is approved and largely used in youth but insufficient efficacy in terms of durable glycaemic control has been confirmed in a recent paediatric study [R07-4397]. Moreover, metformin is not suitable for all patients, as insufficient efficacy over time has been observed in several paediatric studies [R07-4400; R10-0796]. The alternative option for paediatric patients is the administration of insulin by injection as the only other approved medication for

treating their T2DM. Insulin is often unacceptable in the paediatric population due to the subcutaneous route of delivery and the higher rates of hypoglycaemia and weight gain.

DINAMO™ Mono
The TODAY study has shown that the majority of youth with T2D can be effectively treated with metformin monotherapy during the first 12 months of the disease [R12-3961]. However, the TODAY study also demonstrated that metformin monotherapy fails to maintain HbA1c < 8.0% in most adolescents during the second year of treatment [R18-2686], even in the face of substantial residual endogenous insulin [R18-2687]. Therefore, studies are warranted to assess whether oral antidiabetic medications can either replace metformin as initial therapy or whether a patients can switch from metformin monotherapy in case of metformin failure to another oral antidiabetic medication instead of initiation of insulin therapy.

Therefore, in order to assess the efficacy and safety of empagliflozin and linagliptin as monotherapy, the ancillary study DINAMO™ Mono will be conducted in children and adolescents who are drug-naïve patients or patients not on active treatment (including discontinuation of metformin due to intolerance [or previous discontinuation for other reasons] and/or discontinuation of insulin [insulin use must be 8 weeks or less] at investigator's discretion) prior to or at Visit 1A.

2.2 TRIAL OBJECTIVES

DINAMO™ (main study)
The objective of this study is to assess the efficacy and safety of an empagliflozin dosing regimen and one dose of linagliptin versus placebo after 26 weeks of treatment in children and adolescents with type 2 diabetes mellitus treated with metformin and/or insulin or who are not tolerating metformin.

DINAMO™ Mono (ancillary study)
The objective of this study is to explore the effect of an empagliflozin dosing regimen and one dose of linagliptin as **Mono**therapy in children and adolescents with type 2 diabetes mellitus.

In addition, the trial will assess the long term safety of empagliflozin and linagliptin after 52 weeks of treatment.

2.3 BENEFIT - RISK ASSESSMENT

The clinical development programs in adults showed a favourable benefit-risk ratio for the use of linagliptin and empagliflozin in patients with T2DM. Besides, the linagliptin paediatric dose-finding trial as well as the empagliflozin paediatric PK single dose trial allowed identifying the appropriate dose(s) of each compounds for the paediatric population. Since the paediatric population is considered as a vulnerable population, this combined phase III trial was therefore designed to conduct one confirmatory trial to assess efficacy and the long term safety of empagliflozin and linagliptin in children and adolescents with T2DM.

According to the drug assignment planned in this trial, 67% of the patients will be treated with either linagliptin or empagliflozin up to 52 weeks. These patients might benefit from positive glycaemic effects since they will receive an investigational medication that has already demonstrated favourable HbA1c and fasting plasma glucose changes in adults. Patients initially randomised to placebo treatment will continue treatment with diet and exercise alone or with metformin and/or insulin, reflecting the current standard of care. Due to the study procedures, such as regular visits, it is expected that patients will also benefit during the placebo treatment phase. In case of deterioration of glycaemic control, criteria for initiation of rescue therapy are in place (see Section 4.2.1). However, after 26 weeks of treatment, patients who were initially randomised to placebo will be re-randomised to either linagliptin 5 mg or empagliflozin 10 mg or 25 mg, to ensure a minimum of 26 weeks active treatment for all patients included into this trial.

Patients in the placebo group may have a higher probability of treatment failure, i.e. of increased FPG and HbA1c values. However, the trial eligibility criteria (see Section 3.3.2 and Section 3.3.3) will ensure that unstable patients in terms of glycaemic control are excluded from being randomised. Following randomisation, appropriate criteria (based on HbA1c and blood ketone levels) have been defined for the initiation of rescue medication (please refer to Section 4.2.1 for further details). In addition, the patient safety will be monitored and a number of discontinuation criteria have been defined (see Section 3.3.4 for further details).

The trial design with a two-week placebo run-in phase is a well-established design for T2DM trials [P10-14001]. In this trial, daily monitoring of blood glucose will be performed by patients with a self-blood glucose monitoring (SBGM) device. Thus the risk of the two-week placebo treatment will be minimal.

Blood volumes drawn for safety analysis and efficacy endpoints analysis have been reduced since this trial is conducted in the paediatric population. Furthermore, to minimise pain and distress, local anaesthetic product will be offered to all patients as pain relief for venepuncture. Attempts to draw blood will be limited to three. Children with needle phobia will be excluded from the study.

Due to the mechanism of action of empagliflozin and linagliptin, the risk of hypoglycaemic episodes is considered to be very low. Add-on of empagliflozin and linagliptin to a stable dose of insulin/metformin therapy is deemed acceptable as there are no relevant drug-drug interactions and no potentiated effects are expected. In a study of adult patients receiving linagliptin as add-on therapy to a stable dose of insulin, no significant difference was observed in the incidence of hypoglycaemia between the linagliptin and placebo treated groups. Hypoglycaemia was seen more frequently compared to placebo in adult patients treated with linagliptin on background of metformin+sulfonylurea. Also, the risk of severe hypoglycaemic episodes is considered to be low for empagliflozin (<1%) and similar for empagliflozin and placebo as monotherapy and as add-on to metformin. Compared to placebo when empagliflozin is given as add-on to insulin the number of major hypoglycaemic events may be increased.

However, in order to closely monitor hypoglycaemic events, all patients will be required to perform regular blood glucose measurements (self-blood glucose monitoring – SBGM)

throughout the duration of the trial. Minimum requirements have been defined in the protocol (See Section 5.3.5.2 for further details).

For linagliptin, pancreatitis is an important but uncommon risk. Other important known risks of linagliptin include hypersensitivity and angioedema/urticaria.

Cases of diabetic ketoacidosis (DKA), a serious life-threatening condition requiring urgent hospitalization, have been reported in patients treated with SGLT-2 inhibitors, including empagliflozin. It needs to be taken into account that, due to the insulin independent mode of action, empagliflozin may potentially modify the clinical presentation of DKA. In some of reported cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). 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, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. In patients treated with empagliflozin consider monitoring for ketoacidosis and temporarily discontinuing empagliflozin in clinical situations known to predispose to ketoacidosis (i.e. prolonged fasting due to acute illness or surgery). In these situations, consider monitoring of ketones, even if empagliflozin treatment has been interrupted.

Patients receiving empagliflozin may be at risk to underestimate their need for insulin if blood sugar levels are within individual target ranges or only slightly elevated. Insulin deficiency might lead to ketoacidosis which could be life-threatening if not recognized and appropriately treated. All patients receiving insulin will be made aware of this risk and be instructed not to reduce their insulin dose below investigator recommendations.

In addition to blood glucose monitoring, patients will be equipped with an electronic device to determine their ketone concentration (i.e. a blood glucose monitoring device/meter that is also capable of measuring blood ketones) (for further details see Section 5.3.5.3). Patients will be reminded how to determine ketones in case of any symptoms of DKA, e.g. nausea, vomiting, abdominal pain etc. They will be instructed to do this irrespective of the glucose value in the event of DKA symptoms occurring. More frequent ketone testing (e.g. once daily) will be recommended during the first 4 weeks of the treatment period and during 4 weeks after Visit 5; this will allow patients and investigators to understand baseline ketosis rates and compare them, as appropriate, to the incidence of ketosis following the initiation of study medication. As stated above, a meter will be provided to the patient for this purpose; as an additional safeguard, the meter will also be used to check ketone levels at most clinic visits (see Flow Chart). Patients will be reminded of the interpretation of ketone values measured by the meter, and on appropriate action to be taken in the event of increased ketone levels (see Section 5.3.5.3). In addition, patients with insulin background therapy will be reminded about insulin adjustment during “sick days” and about the importance of keeping themselves hydrated.

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).

Cases of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare, but serious and life-threatening necrotizing infection, have been reported in patients with diabetes mellitus treated with SGLT-2 inhibitors, including empagliflozin. Patients who present with suggestive symptoms are instructed to seek medical attention immediately and should be evaluated for necrotizing fasciitis.

Patients will be carefully selected for the trial in line with the eligibility criteria, to ensure, in the investigator's judgment, that they have a good understanding of their disease and how to manage it. They should also be selected in terms of their ability to be compliant with the demands of the trial.

In the embryo-foetal and fertility studies in rats and rabbits, no effects on early embryonic development, mating, male and female fertility, and bearing live young were observed up to a linagliptin dose of 240 mg/kg and up to a dose of 300 mg/kg with empagliflozin. Therefore, female patients who have reached menarche (i.e. those who have had any vaginal bleeding, however scant or irregular) and are of child-bearing potential will be included in this study provided that they are using adequate contraceptive methods. In addition, regular pregnancy tests will be performed throughout their trial participation.

As with all drugs, the potential for hypersensitivity and allergic reactions have to be taken into consideration when empagliflozin or linagliptin is administered. Other risks to the patients are the risks inherent to any investigational medicinal product used in a clinical trial setting, such as unexpected adverse clinical or laboratory events.

Hence, for sites taking part in this trial, the investigator and designated site personnel must be trained in paediatric emergencies. Patient discomfort will be minimised as far as possible, and all sites selected to take part in this trial will be knowledgeable and skilled in dealing with the paediatric population and its age-appropriate needs. Furthermore, sites will be assessed for a child-friendly infrastructure (e.g. familiar environment, appropriate physical setting, parent(s)/legal guardian allowed to accompany patient during procedures).

Individual patient safety/risks will be minimised by close observation throughout the trial, and by monitoring the patients for adverse events both clinically and by laboratory testing.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.3.6.1.

To continue the assessment of the long-term safety of empagliflozin and linagliptin, an adjudication of cardiovascular, DKA and certain hepatic events will be performed. The progress of the trial will also be assessed at regular intervals by an independent Data Monitoring Committee (DMC). For further details please refer to Section 3.1.1.

Given the safety profile derived from toxicology studies, the good tolerability seen in previous studies in adult and paediatric patients and the monitoring activities including the blood glucose and ketone monitoring described above, the sponsor is of the opinion that the

risks for participating patients are minimised and justified when compared to the potential benefits of a successful development of empagliflozin and linagliptin for children and adolescents with T2DM.

COVID-19 Pandemic
Due to the COVID-19 pandemic, the enrollment of new patients and the initiation of new sites were temporarily put on hold on 17 March 2020 and resumed on a per country level in April 2020. Potential risks with regard to COVID-19 exposure and treatment for patients already enrolled in the trial have been evaluated and described in a specific Benefit-Risk assessment document [c32537051-02 ; c32537611-02].

Based on the pharmacological mechanism of empagliflozin and linagliptin and review of data derived from clinical and post-marketing databases, there is no indication that these investigational drugs could increase the risk of severe viral infections. Moreover, no relevant Drug-Drug Interactions between empagliflozin and linagliptin and the medications currently used for treatment of COVID-19 are expected based on the information in their product labels, nor have they been described in the literature. Please refer to the respective current Investigator Brochures (IB).

As with any acute illness, a Severe Acute Respiratory Syndrome (SARS) CoV-2 infection may increase the risk of DKA. The risk of ketoacidosis in case of acute illness during empagliflozin intake is adequately addressed in the IB. Consistent with the guidance on illness-related treatment discontinuation, the study drug should be discontinued in case of severe COVID-19 disease and re-introduced once the patient has recovered, as described in Section 3.3.4.1.

Patients with diabetes are in general at higher risk of infections and might be at higher risk for severe illness from COVID-19. The majority of patients in the DINAMO trial are randomized to active treatment due to the trial design and would, therefore, be expected to be in a better blood glucose control. Nevertheless, in order to minimize the risk of exposure to COVID-19, physical visits should be avoided depending on the COVID-19 pandemic status of the site. The use of phone visits and local laboratory services for safety and efficacy parameters measurements should be considered when necessary. Furthermore, study drug shipment to patient's homes should also be considered. Investigators should complete study procedures according to the protocol to the extent possible. If protocol-mandated visits, safety laboratory schedules, and/or study drug availability cannot be accomplished, patients should temporarily discontinue study medication.

Based on the above considerations, the Benefit-Risk assessment for trial participants remains positive.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This 3-arm trial compares the efficacy and safety of an empagliflozin dosing regimen and one dose of linagliptin to placebo in children and adolescents with T2DM.

As detailed in the Figure 3.1:1 below, at least 150 and approximately 20 patients with T2DM who meet the entry criteria will be entered (randomised) in DINAMO™ and DINAMO™ Mono respectively.

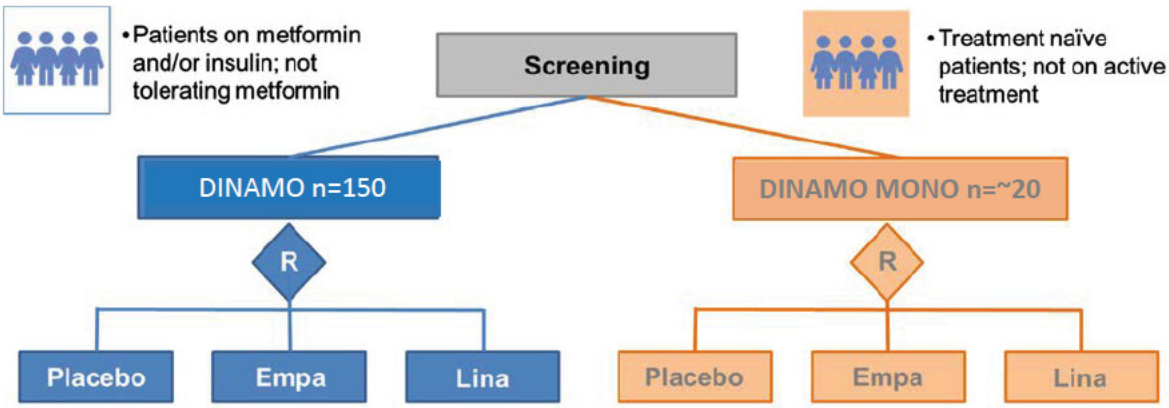


Figure 3.1: 1 Patient repartition into DINAMO™ and DINAMO™ Mono

The randomised treatment period will be double-blind (i.e. each patient will take 3 tablets a day, receiving one active treatment and two placebos matching the alternative treatments or three placebos up to 26 weeks and then 3 tablets a day, receiving one active treatment and two placebos matching the alternative treatments up to 52 weeks).

Patients will be enrolled (screened) in the trial once the appropriate informed consent and assent have been given. All patients who are suitable after screening will undergo a 2-week open-label placebo run-in period before randomisation.

Initial randomisation
Patients who successfully complete the placebo run-in period and still meet the inclusion/exclusion criteria will be randomised to the 26-week double-blind randomised period in which they will receive either linagliptin 5 mg or empagliflozin 10 mg or placebo. Within the study, initial randomisation will be stratified by age (at least 30% but no more than 70% of randomised patients are below 15 years of age). In addition for DINAMO™ only, between 30% and 70% of randomised patients must be girls.

Re-randomisation at Week 14
Patients initially randomised to the empagliflozin 10 mg group and who will not achieve an HbA1c target < 7.0% at Week 12 will be re-randomised at Week 14 to receive either empagliflozin 10 mg or empagliflozin 25 mg. This step will help to evaluate whether

increasing the dose of empagliflozin is beneficial to paediatric patients with T2DM. Since patients and investigators will stay blinded, investigators will have to perform an IRT call for all patients at Week 14 in order to get new trial medication kits assigned (see Section 4.1.4 for further details). The re-randomisation will be stratified by age at baseline (< 15 years; ≥ 15 and < 18 years) as described in Section 7.6.

Re-randomisation at Week 26
After the 26-week treatment period, all patients will enter a double-blind safety extension period up to 52 weeks. Patients who received placebo during the 26-week treatment period will be re-randomised to receive either linagliptin 5 mg or empagliflozin 10 mg or empagliflozin 25 mg. Since patients and investigators will stay blinded, investigators will have to perform an IRT call for all patients at Week 26 in order to get new trial medication kits assigned (see Section 4.1.4 for further details). The re-randomisation will be stratified by age at baseline (< 15 years; ≥ 15 and < 18 years) as described in Section 7.6.

After the 52-week extension period, all patients will enter a 3-week follow-up period during which they will not be treated with study medication. The patient's participation is concluded when he has undergone the last planned visit (i.e. Trial Completion Visit); last-patient-last-visit-primary-endpoint will occur when all patients have completed 26 weeks of treatment. The end of the trial is defined as "last patient out" (i.e. last Trial Completion Visit completed by the last patient in the trial).

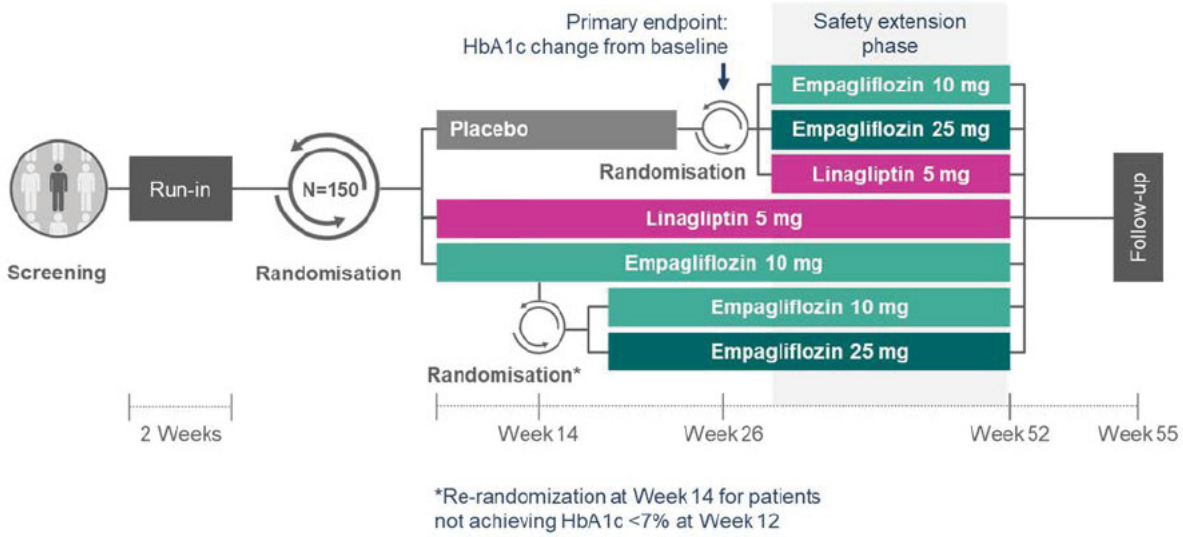
Except for patients who would discontinue the trial treatment for safety reasons, every effort should be made to re-introduce trial treatment after a temporary trial drug discontinuation. For the analysis of this trial it is very important that assessments for each planned visit are still performed in accordance with the Flow Chart even if patients discontinue trial treatment.

Patients who discontinue study drug prematurely should continue study visits until study end. Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception of blood drawing for safety lab tests, HbA1c and FPG, body weight, blood pressure and collection of adverse events and concomitant therapy. Refer to Section 6.2.3 for premature discontinuation of treatment guidance.

Every attempt will be made by the investigator to ensure patients continue participating in the study during interruptions in trial drug intake and after permanent discontinuation of trial drug. The modified Intention-to-Treat (mITT) analysis requires that all trial patients be followed until study end even if the trial drug was temporarily interrupted or discontinued.

For a graphical presentation of the DINAMO™ trial and DINAMO™ Mono trial, see Figure 3.1: 2 below.

a) DINAMO™



b. DINAMO™ Mono

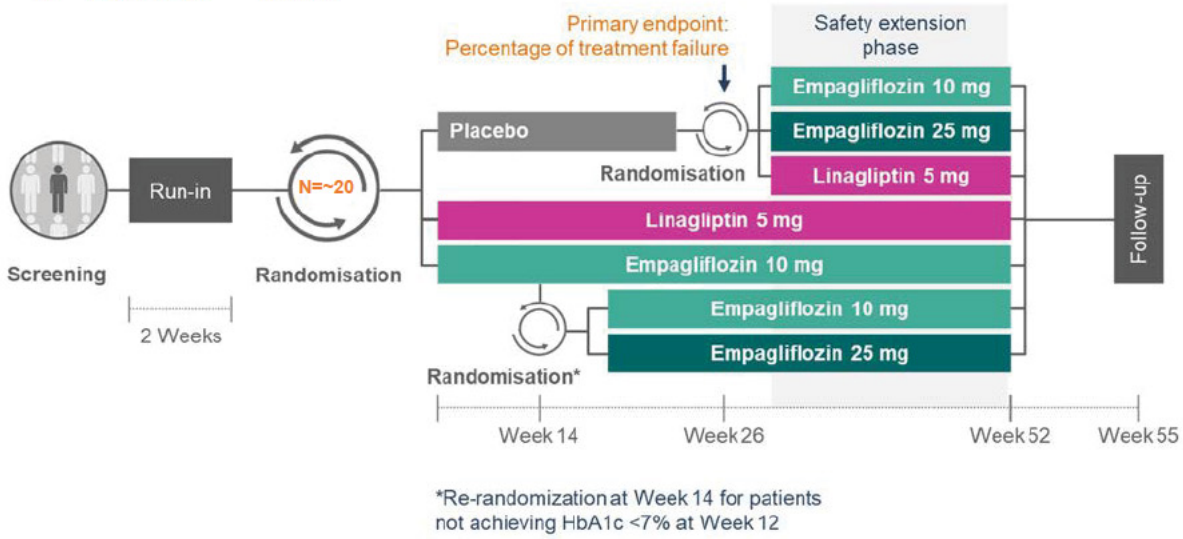


Figure 3.1: 2 Trial duration, primary endpoint, and treatment groups for a) DINAMO™ and b) DINAMO™ Mono

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer-Ingelheim (BI). This is a multi-center trial. The relevant documentation for the principal investigators participating in the trial (i.e. curriculum vitae) will be filed in the ISF. The investigators will have access to the BI portal (Clinergize) to access documents provided by the sponsor. A Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multi-centre trial. Tasks and responsibilities are defined in a contract.

A Steering Committee (SC) was involved in designing this trial and will have a scientific and clinical advisory function in the study. This will include regular oversight of the enrolment

and retention rates in order to make recommendations about actions that could improve these rates. The SC is comprised of university- and sponsor-based scientists with clinical and methodological expertise. Details on the composition of the committee, its procedures and interactions are provided in a separate SC Charter.

A data monitoring committee (DMC), which is independent of the sponsor, will be established to assess the progress of the clinical trial, including an unblinded safety review at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop the trial. The tasks and responsibilities of the DMC will be specified in a separate DMC charter. The DMC will maintain written records of all its meetings.

Boehringer Ingelheim has appointed a Clinical Trial 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 local clinical trial managers (CTMs), Clinical Research Associates (CRAs), and Investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and internal SOPs, or by a Contract Research Organisation (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.

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.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in IRT Manual and Central Laboratory Manual, available in ISF.

3.1.1.1 Clinical Event Committee – cardiovascular events

An independent external committee (Clinical Event Committee, [CEC]) will be established to adjudicate centrally and in a blinded fashion events suspect of stroke, myocardial ischemia (including myocardial infarction), cardiovascular death and other relevant events (e.g. hospitalisation for heart failure) based on the FDA guideline [R09-2151]. Such adjudication is performed in all Phase 2 and 3 clinical trials with empagliflozin and linagliptin. The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.

For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as electrocardiograms (ECGs), laboratory values, angiography, echocardiography reports, CT and/or MRI scans, discharge summaries, and autopsy reports to support the external event adjudication.

The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.

3.1.1.2 Clinical Event Committee – DKA

An independent external committee (CEC) will be established to adjudicate centrally and in a blinded fashion events suspect of DKA. The CEC will evaluate whether pre-specified criteria for adjudication endpoints are met.

For any events that qualify for adjudication, study sites will be asked to provide clinical documentation such as laboratory values, discharge summaries etc. to support the external event adjudication.

The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.

3.1.1.3 Clinical Event Committee – Hepatic external adjudication

Certain hepatic events will be adjudicated by external independent experts for severity and causal relationship with the trial medication in a blinded fashion. The events which will be reviewed will be defined in a charter. Events may either be defined by abnormal laboratory values and/or relevant adverse events or both. For example, assessments will be made for events of hepatic injury events, including liver enzyme elevations.

For qualifying events, relevant source documents generated from any medical evaluations of these events will be requested including laboratory values, histological analysis, results of ultrasound, CT, MRI, scintigraphy, hospital discharge letters, and medical reports from other physicians. All evaluations will be performed in a blinded fashion.

The tasks and responsibilities of the CEC will be specified in a charter. The CEC will maintain the adjudication results in writing.

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

This trial will investigate the efficacy and safety of an empagliflozin dosing regimen and one dose of linagliptin on top of standard treatment in children and adolescents with T2DM.

HbA1c as the primary endpoint has been demonstrated to be a reflection of the glycaemic control over the preceding 12 weeks and maintenance data over a period of approximately 6 months are requested by the different regulatory agencies. Therefore the primary endpoint for DINAMO™ is the change in HbA1c from baseline to the end of 26 weeks of randomised treatment.

For DINAMO™ Mono, the endpoint “occurrence of treatment failure” is selected to evaluate whether an early initial monotherapy is beneficial in children and adolescents with T2DM. A major component of the endpoint is “use of rescue medication”. Virtually all patients in DINAMO™ Mono who will not achieve the glycemic goals defined in guidelines will

require rescue medication and will be classified as failure. Therefore, the study will inform whether the initial monotherapy can bring patients to glycemic target. Comparison with a placebo group is needed to better understand the failure rate of an "untreated population" in order to bring the results for empagliflozin and linagliptin into perspective. A similar endpoint was used in the TODAY study [R12-3961]. Since strict rescue criteria are defined for DINAMO™ Mono, the commonly used endpoint "HbA1c change from baseline" would not be informative. In the placebo group a high rate of rescue medication is expected, i.e. most patients randomised to placebo will benefit from metformin or insulin therapy. Since metformin and insulin are very effective especially in newly diagnosed patients, it is expected to observe no difference in HbA1c after 26 weeks in patients randomised to empagliflozin or linagliptin and placebo (on rescue treatment).

The randomised period is planned for 52 weeks in order to collect one year safety and efficacy data for empagliflozin and linagliptin in patients with T2DM aged 10-17 years (inclusive).

For the linagliptin treatment arm, one dose (i.e. linagliptin 5 mg) will be evaluated for safety over 52 weeks. For empagliflozin, two doses (i.e. empagliflozin 10 mg and 25 mg) will be evaluated as well as whether increasing the dose of empagliflozin 10 mg to 25 mg is beneficial to paediatric patients. So that, patients initially randomised to the empagliflozin 10 mg group who will not achieve an HbA1c target < 7.0% at Week 12 will be re-randomised at Week 14 to receive either empagliflozin 10 mg or empagliflozin 25 mg.

The rationale for the empagliflozin and linagliptin dose selection is described in section 4.1.2.

Patients who were randomised to placebo will be re-randomised after 26 weeks to either linagliptin 5 mg or empagliflozin 10 mg or empagliflozin 25 mg. This reduces the duration of the placebo period in this trial to the requested minimum (26 weeks) and will ensure that all patients will receive active treatment for at least 26 weeks. Moreover, this will generate additional safety and efficacy data over 26 weeks of treatment for both empagliflozin doses and one linagliptin dose.

The design of this trial includes a 2-week open-label placebo run-in period; the intention of this period is to familiarise the patient with the procedures for study medication intake prior to randomisation, giving an opportunity for assessing the patient ability to be compliant with the study medication intake. This is of particular importance within the paediatric population where adherence to medical regimens is often less than desired. The run-in period will therefore ensure that only patients who are likely to be compliant are exposed to the study drugs.

The 3-week follow-up period is considered to be sufficient, as previous studies with empagliflozin and linagliptin have shown that its' PD effect only extends to about 3 and 7 days after the last dose. Furthermore, it will allow for the assessment of reversibility of unexpected long-term side effects.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients with T2DM will be screened to ensure the randomisation of at least 150 and approximately 20 patients from approximately 110 trial sites in DINAMO™ and DINAMO™ Mono respectively. The planned number of patients randomized at each site is at least one patient in DINAMO™ and at least one patient in those sites that participate in DINAMO™ Mono.

If enrolment is delayed, additional sites may be recruited.

At least 30% and not more than 70% of patients should be below 15 year of age. In addition for DINAMO™ only, between 30% and 70% of randomised patients must be girls.

Screening of patients for this trial is competitive across all countries within the trial, i.e. screening for the trial will stop at all sites when the desired number of patients to be randomised in this trial is reached. Investigators will be notified when sufficient patients have been randomised and when screening is complete and will not be allowed to recruit additional patients for the study. Patients who have completed Visit 1A procedures prior to notification of the termination of recruitment will be allowed to continue in the study if they meet all entry criteria and they are able to follow the visit schedule in this Clinical Trial Protocol.

Re-screening and/or re-testing (of assessments) are permitted.

Whilst the information provided below is not an exhaustive list, it provides some guidance as to when such re-screening and/or re-testing would be considered appropriate.

Re-testing:
Re-testing for eligibility criteria is only to be performed for a laboratory test that has been cancelled by the central laboratory (e.g. for specimen not received or received beyond stability) or for a laboratory result thought to be a spurious result based on previously available laboratory results. The re-test should be carried out as soon as possible so the laboratory test results will be received within the next planned visit windows in order to avoid protocol window deviations.

Re-screening:
For patients failing screening due to modifiable exclusion criteria, like HbA1c level too low or too high, unrecognized hypothyroidism (high TSH), re-screening may be considered up to 5 times with at least 8 weeks between screening visits.

The patient should be declared as a screening failure in the eCRF and IRT with their original patient number.

Upon re-screening, a new patient number will be assigned by the IRT. The old patient number, with which the patient failed screening, will be recorded in the eCRF.
The patients' legal representative(s) must be re-consented using the current approved version of the information sheet and consent form. The patient should give again his/her assent.

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

DINAMO™ Mono
Patients could be eligible for DINAMO™ Mono in case of HbA1c ≥ 6.5% and ≤ 9.0% and metformin discontinuation due to intolerance [or previous discontinuation for other reasons] and/or discontinuation of insulin [insulin use must be 8 weeks or less] at investigator's discretion prior to or at Visit 1A.

3.3.1 Main diagnosis for trial entry

Only patients aged 10 to 17 years (inclusive) who meet the following criteria at Visit 1A will be screened for suitability for the study.

- In DINAMO™, patients with documented T2DM for at least 8 weeks
- In DINAMO™ Mono, patients with confirmation of T2DM

Inclusion will be based upon a complete medical history including physical examination, vital signs, 12-lead ECG and clinical laboratory tests.

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. Patients aged 10 to 17 years (inclusive) at the time of randomisation (Visit 2)

2. Male and female patients

3. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient's legal representative information sheet as well as in Section 4.2.2.3.

4. Signed and dated written informed consent provided by the patient's parent(s) (or legal guardian) and patient's assent in accordance with ICH-GCP and local legislation prior to admission to the trial (informed assent will be sought according to the patient's age, level of maturity, competence and capacity)

5. Documented diagnosis of T2DM at Visit 1A:
    a. DINAMO™: Documented diagnosis of T2DM for at least 8 weeks at Visit 1A
    b. DINAMO™ Mono: Confirmation of T2DM at Visit 1A

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

6. Insufficient glycaemic control as measured by the central laboratory at Visit 1A:
    a. DINAMO™: HbA1c ≥ 6.5% and ≤ 10.5%
    b. DINAMO™ Mono: HbA1c ≥ 6.5% and ≤ 9.0%

7. a. DINAMO™: Patients treated with
    - diet and exercise plus metformin at least 1000 mg/day (or up to a maximal tolerated dose) at a stable dose for 8 weeks prior to Visit 2 or not tolerating metformin (defined as patients who were on metformin treatment for at least 1 week and had to discontinue metformin due to metformin-related side effects as assessed by the investigator)
    AND/OR
    - diet and exercise plus stable basal or MDI insulin therapy, defined as a weekly average variation of the basal insulin dose ≤ 0.1 IU/kg over 8 weeks prior to Visit 2

    b. DINAMO™ Mono: Drug-naïve patients or patients not on active treatment (including discontinuation of metformin due to intolerance [or previous discontinuation for other reasons] and/or discontinuation of insulin [insulin use must be 8 weeks or less] at investigator's discretion) prior to or at Visit 1A)

8. BMI ≥ 85th percentile for age and sex according to WHO references at Visit 1B

9. Non-fasting serum C-peptide levels ≥ 0.6 ng/ml or ≥ 0.199 nmol/L as measured by the central laboratory at Visit 1A

10. Compliance with trial medication intake must be between 75% and 125% during the open-label placebo run-in period

11. Negative for both islet cell antigen auto-antibodies (IA-2) and glutamic acid decarboxylase (GAD) auto-antibodies as measured by the central laboratory at Visit 1A

3.3.3 Exclusion criteria

1. Any history of acute metabolic decompensation such as diabetic ketoacidosis within 8 weeks prior to Visit 1A and up to randomisation (mild to moderate polyuria at the time of randomisation is acceptable)

2. Diagnosis of monogenic diabetes (e.g. MODY)

3. History of pancreatitis

4. Diagnosis of metabolic bone disease

5. Gastrointestinal disorders that might interfere with study drug absorption according to investigator assessment

6. Secondary obesity as part of a syndrome (e.g. Prader-Willi syndrome)

7. Any antidiabetic medication (with the exception of metformin and/or insulin background therapy for DINAMO^{TM}) within 8 weeks prior to Visit 1A and until Visit 2

8. Treatment with weight reduction medications (including anti-obesity drugs) within 3 months prior to Visit 1A and until Visit 2

9. History of weight-loss surgery or current aggressive diet regimen (according to investigator assessment) at Visit 1A and until Visit 2

10. Treatment with systemic corticosteroids for > 1 week within 4 weeks prior to Visit 1A and up to Visit 2. Inhaled or topical use of corticosteroids (e.g. for asthma/chronic obstructive pulmonary disease) is acceptable.

11. Change in dose of thyroid hormones within 6 weeks prior to Visit 1A or planned change or initiation of such therapy before Visit 2

12. Known hypersensitivity or allergy to the investigational products or their excipients

13. Impaired renal function defined as estimated Glomerular Filtration Rate (eGFR) < 60 ml/min/1.73m² (according to Zappitelli formula) as measured by the central laboratory at Visit 1A

14. Indication of liver disease defined by serum level of either alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase above 3 fold upper limit of normal (ULN) at Visit 1A as measured by the central laboratory at Visit 1A

15. History of belonephobia (needle phobia)

16. Any documented active or suspected malignancy or history of malignancy within 5 years prior to Visit 1A, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix

17. Blood dyscrasias or any disorders causing haemolysis or unstable red blood cells (e.g. malaria, babesiosis, haemolytic anaemia)

18. Any other acute or chronic medical or psychiatric condition or laboratory abnormality that, based on investigator's judgement, would jeopardize patient safety during trial participation or would affect the study outcome

19. Medical contraindications to metformin according to the local label (for patient on metformin background therapy)

20. Patient not able or cannot be supported by his/her parent(s) or legal guardian to understand and comply with study requirements based on investigator's judgement

21. Previous randomisation in this trial

22. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s)

23. Chronic alcohol or drug abuse within 3 months prior to Visit 1A or any condition that, in the investigator's opinion, makes them an unreliable trial patient or unlikely to complete the trial

24. Female patients who are pregnant, nursing, or who plan to become pregnant in the trial

3.3.4 Removal of patients from therapy or assessments

Patients may be withdrawn from trial treatment or from the trial 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 randomised patients in the trial, if possible on treatment or at least to collect important trial data.

Measures to control the withdrawal rate include but is not limited to careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomisation, investigator's training to clearly explain the consequences of consent withdrawal, regular oversight of retention rates by the SC and the sponsor-based clinical monitors, reimbursement of travel costs, offers for snack or breakfast during clinic visits, option for an ambulatory visit as detailed in the Flow Chart, telephone calls to the patient or the patient's family.
The decision to withdraw from trial treatment or to withdraw consent as well as the reason must be documented in the patient files and CRF.

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient or parent(s) (or legal guardian) wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to start a restricted concomitant therapy that, in the investigator's opinion, poses a safety risk if taken as add-on to the trial medication (see section 4.2.2.1).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- 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 stick to the trial requirements in the future.
- Pancreatitis, bullous pemphigoid, ketoacidosis, arthralgia, or Fournier's gangrene is suspected.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and all subsequent planned visits up to the follow up visit as outlined in section 6.2.3.

For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

Except for patients who would discontinue the trial treatment for safety reasons, every effort should be made to re-introduce trial treatment after a temporary trial drug discontinuation.

For the analysis of this trial it is very important that assessments for each planned visit are still performed in accordance with the Flow Chart even if patients discontinue trial treatment. Patients who discontinue treatment prematurely will be followed up until the end of the study, unless they withdraw their consent for this to happen. All assessments related to the primary and secondary endpoints (i.e., blood drawing for HbA1c and FPG, body weight, blood pressure and collection of adverse events and concomitant therapy) and safety lab tests still have to be performed as if the patient had remained on trial treatment.
Patients who withdraw from the trial treatment after randomisation will not be replaced. However, one exception is patients who discontinue due to the COVID-19 pandemic (i.e. missed visits, SARS CoV-2 infection, withdrawal of consent) may be replaced based on blinded assessment of the number of premature treatment or trial discontinuation.

3.3.4.2 Withdrawal of consent for trial participation

Patients or parent(s) (or legal guardian) may withdraw their consent/assent for trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow-up on safety cannot occur.

If a patient or parent(s) (or legal guardian) wants to withdraw consent/assent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the scientific relevance of their data even if he/she discontinue the trial treatment.

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:

- Failure to meet expected enrolment goals overall or at a particular trial site
- Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk assessment that could significantly affect the continuation of the trial
- Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial

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 study medication will be provided by BI.

Metformin and insulin as background therapies and rescue medications are not considered as part of the clinical trial supplies and therefore will not be provided.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are as shown below.

Table 4.1.1: 1 Test product 1

Substance:	Linagliptin
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	5 mg
Posology	Once daily
Route of administration:	oral

Table 4.1.1: 2 Test product 2

Substance:	Empagliflozin
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	10 mg
Posology	Once daily
Route of administration:	Oral

Table 4.1.1: 3 Test product 3

Substance:	Empagliflozin
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	25 mg
Posology	Once daily
Route of administration:	oral

Table 4.1.1: 4 Reference product 1

Substance:	Placebo matching Linagliptin 5 mg
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	-
Posology	Once daily
Route of administration:	oral

Table 4.1.1: 5 Reference product 2

Substance:	Placebo matching Empagliflozin 10 mg
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	-
Posology	Once daily
Route of administration:	oral

Table 4.1.1: 6 Reference product 3

Substance:	Placebo matching Empagliflozin 25 mg
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim
Unit strength:	-
Posology	Once daily
Route of administration:	oral

4.1.2 Selection of doses in the trial

Empagliflozin will be administered as 10 mg and 25 mg tablets once daily, linagliptin as 5 mg tablet once daily. These doses were selected based on the results from previous dose finding studies in paediatric patients with T2DM (see below) and are the same doses that are approved in adult patients with T2DM.

Empagliflozin
The empagliflozin paediatric PK/PD trial 1245.87 [c09087100] showed that, following a single oral dose of empagliflozin, adult and paediatric patients with T2DM had similar exposure-response relationships after accounting for significant covariates. Therefore, the paediatric dose finding trial results support the use of empagliflozin 10 mg and 25 mg in this phase III trial (the same doses that are approved/used for adult patients with T2DM). See sections 1.2 and 3.2 for further details.

Linagliptin
The linagliptin paediatric dose finding trial 1218.56 [c09060697] interim analysis showed superiority of the linagliptin 5 mg dose over the linagliptin 1 mg dose regarding DPP-4 inhibition at trough at steady state. Besides, the results were consistent with clinical efficacy and safety data for linagliptin in adults. As a consequence, the paediatric dose finding trial findings support the evaluation of the long-term safety and efficacy of linagliptin 5 mg in this phase III trial in children and adolescents (the same dose that is approved/used in adult patients with T2DM). See sections 1.2 and 3.2 for further details.

4.1.3 Method of assigning patients to treatment groups

During Visit 2, eligible patients will be randomised to receive either linagliptin 5 mg or empagliflozin 10 mg or placebo in a 1:1:1 ratio according to a randomisation plan. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

At Visit 4B, patients assigned to the empagliflozin group who do not achieve an HbA1c value < 7% at Week 12 will be re-randomised to receive either empagliflozin 10 mg or empagliflozin 25 mg in a 1:1 ratio. The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

At Visit 5, patients assigned to the placebo group will be re-randomised to receive either linagliptin 5 mg or empagliflozin 10 mg or empagliflozin 25 mg in a 1:1:1 ratio according to a randomisation plan. The assignment will occur in a blinded fashion via IRT.

To ensure double-blind conduct, investigators will have to perform an IRT call for all patients at Week 14 (Visit 4B) and Week 26 (Visit 5).

Access to the codes will be controlled and documented. Technical and statistical features of the process of treatment allocation are described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each patient

The treatment groups and the drug assignment for each patient are outlined in Table 4.1.4:1 below.

Table 4.1.4: 1 Drug assignment and dispensation per treatment group and visits

	Placebo Run-in	Randomised treatment (Double-blind, double dummy)		
Dispensation visits	V1B	V2, V3, V4A	V4B	V5, V6, V7
Treatment duration	2 weeks	14 weeks	12 weeks	26 weeks
Linagliptin 5 mg group	Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg
Empagliflozin 10 mg group	Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Placebo matching linagliptin 5 mg Empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Placebo matching linagliptin 5 mg Empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Placebo matching linagliptin 5 mg Empagliflozin 10 mg Placebo matching empagliflozin 25 mg

Table 4.1.4: 1 Drug assignment and dispensation per treatment group and visits (cont.)

	Placebo Run-in	Randomised treatment (Double-blind, double dummy)		
Empagliflozin 10 mg group – Patients not achieving glycaemic target at week 12	Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Placebo matching linagliptin 5 mg Empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Empagliflozin 25 mg **OR** Placebo matching linagliptin 5 mg Empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Empagliflozin 25 mg **OR** Placebo matching linagliptin 5 mg Empagliflozin 10 mg Placebo matching empagliflozin 25 mg
Placebo group	Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg	Linagliptin 5 mg Placebo matching empagliflozin 10 mg Placebo matching empagliflozin 25 mg OR Placebo matching Linagliptin 5 mg Empagliflozin 10 mg Placebo matching empagliflozin 25 mg OR Placebo matching linagliptin 5 mg Placebo matching empagliflozin 10 mg Empagliflozin 25 mg

All eligible patients will be assigned an open-label placebo run-in kit by the IRT at Visit 1B. As mentioned in Table 4.1.4:1 during the placebo run-in period, patients will take 3 placebo tablets once daily in the morning.

Patients who qualify for randomisation will be randomly assigned by the IRT to one of the treatment groups listed above. Patients will take 3 tablets once daily in the morning up to 52 weeks as detailed in Table 4.1.4: 1 Dispensation of kits by the IRT will begin at Visit 2 for the randomised period (double-blind, double-dummy). Dispensations will occur on 7 occasions over 52 weeks.

Patients initially randomised to empagliflozin 10 mg and who do not achieve an HbA1c value < 7.0% at Week 12 will be re-randomised by the IRT to receive either empagliflozin 10 mg or 25 mg at Visit 4B.

For patients randomised in the placebo group, they will be re-randomised by the IRT to receive either linagliptin 5 mg or one of the empagliflozin doses at Visit 5.

Since patients and investigators will stay blinded, investigators will have to perform an IRT call for all patients at Week 14 and Week 26 in order to get new trial medication kits assigned.
From the start of the placebo run-in period (Visit 1B), patients should be instructed to take their trial medication once daily with approximately 150 ml of water. To ensure a dose interval of 24 hours, the study medication should be taken at the same time every day in the morning. 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. Study medication can be taken with or without food.

Patients should be instructed not to take their trial medication as well as metformin background therapy in the morning of visit days as they will be dosed whilst in the clinic. For visits with PK assessments (as detailed in the Flow Chart), patients who fail to do so should have the visit rescheduled as soon as possible, ideally on the following day. Insulin administration (basal and/or bolus) in the morning of clinic visits will be left to the discretion of the patient and/or investigator and may be dependent on planned meal intake etc. For visits to be performed in a fasted state, visits should be scheduled in the morning, at approximately the same time of day (e.g. 7am to 11am).

Specific requirement before the visits with PK assessments (Visit 5 and 8):
Patients will be asked to record the actual administration date and time of the last 3 doses of trial medication before Visit 5 and 8 on the patient diary. If a dose was missed, the date/time field should be left empty. These data will be transferred to the eCRF. Patients (or their parent(s) or legal guardian, if more appropriate) should be contacted by phone several days before the visit, to remind them to complete the patient diary as requested and to attend for the visit as arranged.

Each medication kit dispensed will include some reserve medications to allow flexibility for the trial visit schedule.

Site personnel will enter the medication numbers dispensed to each patient in the eCRF.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators 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 randomisation code for DINAMO™ and DINAMO™ Mono will be kept secret by Clinical Trial Support up to the corresponding database lock. The bioanalytical lab will remain blinded during the course of the corresponding study. However, in an exceptional case, the bioanalytical lab may receive access to the randomisation code. In that case, bioanalytics will not disclose the randomisation code or the results of their measurements until the corresponding study is officially unblinded.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the 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/or appropriate eCRF page along with the date and the initials of the person who broke the code.

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

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated 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.

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 and are considered as unacceptable, the sponsor must be contacted immediately. Please refer to the ISF for further details.

4.1.8 Drug accountability

The investigator and/or pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,

- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the Principal Investigator
- Availability of FDA Form 1572 (if applicable)

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 and legal representative(s) should be instructed to return unused investigational drug.

The investigator and/or pharmacist and/or investigational drug storage manager 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 product and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator / pharmacist / investigational drug storage manager 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

Background therapy
Throughout the duration of the trial, patients should continue to take their background therapy (metformin and/or insulin). The dose of background therapy at the time of screening will be recorded in the source documentation and on the appropriate pages of the eCRF. If medically appropriate, the dose and dosing frequency should then remain unchanged. For patients on insulin, the weekly average variation of the basal insulin dose should remain ≤ 0.1 IU/kg.

Background therapies will not be provided by BI as part of the clinical trial supplies, unless required by local laws and regulations.

For patients on insulin, investigators are advised to adjust the patient's total insulin dose based on need as assessed by frequent SBGM and close patient follow-up upon initiation of randomised trial medication. In all cases, the actual reduction will be dependent upon individual glucose values. Thereafter and until the end of the trial, further adjustments to insulin therapy (both basal and, MDI insulin) may be implemented as necessary to avoid hypoglycaemia and also hyperglycaemia to ensure that, in the investigator's opinion, the patient is achieving the best standard of care in accordance with local guidelines. In addition,

transfers to another type or brand of insulin as well as changes of the type of insulin pen should be avoided.

For patients on metformin, in case a vascular administration of iodine containing contrast agent is required, metformin should be temporarily discontinued as specified in the SmPC.

Rescue medication
The use of rescue medication will be permitted in this trial and will be metformin and/or insulin. The use of rescue medication will be permitted from the first day of treatment (after randomisation) until the end of the trial.

DINAMO™
Rescue medication (insulin or increased doses of insulin) should be initiated:

1. from the first day of treatment (after randomisation) until Week 52 in case of acute metabolic decompensation accompanied by significant symptoms (e.g., vomiting, dehydration, lethargy) and/or repeatedly elevated blood ketone (beta hydroxybutyrate) values > 1.5 mmol/L measured with the provided electronic device (meter), irrespective of the glucose value (due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of acute metabolic decompensation, e.g. with lower blood glucose values than expected).

   However, in case of sustained hyperglycaemia during SBGM (80% of blood glucose tests are > 300mg/dL (16.6 mmol/L) (non-fasting) or > 200 mg/dL (11.1 mmol/L) (fasting) for 1 week) initiation of rescue therapy should also be considered.

2. from Week 12 (Visit 4A) until Week 52 (Visit 8) if on two successive occasions (separated by at least 4 weeks) HbA1c is ≥ 9.0% and an absolute increase of HbA1c ≥ 1% compared with the baseline value is observed (even in the absence of symptoms related to hyperglycaemia and ketoacidosis).

The type of insulin and its dosage will be left at the investigator's discretion.
If new insulin treatment or insulin treatment at increased doses (i.e. dose increase of basal insulin of more than 0.1 IU/kg above the baseline prescribed dose) continues for more than 21 consecutive days (including the weaning phase) then the patient will be classified as requiring rescue therapy.

DINAMO™ Mono
Rescue medication (metformin and/or insulin) should be initiated:
- at anytime in case of acute metabolic decompensation;
- if HbA1c > 7.0% **AND**
  - there is no HbA1c decrease at Week 12
  - the HbA1c decrease is less than 0.5% at Week 26 and later

In addition, rescue medication could be initiated at any time as per the investigator's judgement. The type of insulin and its dosage as well as the dosage of metformin will be left at the investigator's discretion.

On top of the HbA1c measurements performed at the time points defined in the Flowchart, additional HbA1c measurements can be performed at any time if deemed necessary by the investigator. Besides, additional interactions (e.g. phone calls, text messaging or emails, as deemed appropriate by the investigator and the patient) must be planned every 4 weeks between 2 visits where the interval exceeds 4 weeks.

Furthermore, some patients may require use of insulin due to temporary medical conditions such as hospitalisation or intercurrent illness. Any type or dose of insulin can be used at the discretion of the investigator. In such cases, an attempt is made to withdraw insulin once the acute event has resolved. In the case of a temporary medical condition such as hospitalisation or intercurrent illness, weaning occurs within 2 weeks if the event lasted 2 weeks or less; if the event lasted more than 2 weeks, weaning occurs within 1 month. Withdrawal of insulin occurs regardless of blood glucose values; if metabolic decompensation occurs, appropriate safety procedures are followed as detailed in Section 5.3.5.3.

In the case of hypoglycaemia that may put patient on risk (e.g. repeated symptomatic hypoglycaemia or severe hypoglycaemia), appropriate adjustment of oral antidiabetic therapy and/or insulin therapy such as a dose reduction / discontinuation of ongoing rescue medication or existing background therapy should be initiated. Reduction or discontinuation of ongoing rescue medication should be considered before a reduction in the dose of existing background therapy.

Any rescue medication or dose change in background therapy will be recorded in the source documents and on the appropriate pages of the eCRF.

Any additional treatment that does not qualify as a rescue medication and is considered as deemed necessary for the patient's welfare may be given at the investigator's discretion. Exceptions to this are the restrictions described in section 4.2.2.1.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

With the exception of metformin and insulin used as background therapy, in any other situation than rescue condition, the use of any other antidiabetic agents will be prohibited during the course of the trial. As described in section 4.2.1, insulin is also allowed as rescue medication.

Additionally, weight reduction medications and long-term use of systemic corticosteroids (more than 1 week) are prohibited due to their influence on glucose metabolism. However, therapy with non-systemic corticosteroids such as inhaled or local use will be permitted.

Furthermore, for patients taking thyroids hormones, any dose change should be avoided. If such dose change does occur, it should be recorded in the source documents and onto the appropriate eCRF page.

4.2.2.2 Restrictions on diet and life style

All patients and their families must be encouraged to make dietary changes consistent with healthy eating recommendation, including counselling for weight reduction, reduced carbohydrate and total and saturated fat intake, increased fiber intake and increased physical activity along with decreased sedentary behaviors.

Smoking is not permitted prior to or during any of the visits (from the start of the overnight fast that precedes visits). Any alcohol intake should be avoided within 2 days prior to each visit.

4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient's legal representative information sheet.

In the unexpected and rare cases where women are not of childbearing potential because they are permanently sterilised, they do not need to use contraception to be eligible for the trial. All other female patients are considered to have childbearing potential and must use adequate contraception throughout the trial (from screening until 3 weeks after the last dose of trial medication).

Adequate contraception is defined per ICH M3 (R2) as highly effective or acceptable methods. Highly effective methods of birth control which should be used by women of childbearing potential are those, which alone or in combination, result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, and must be in accordance with local regulations where applicable.

Based on the recommendations of the European Union Heads of Medicines Agency related to contraception and pregnancy testing in clinical trials (CTFG, 2014), the following contraception methods can achieve a failure rate of less than 1% per year when used consistently and correctly:

1. Use of hormonal methods of contraception associated with inhibition of ovulation
    a. Combined (estrogen and progestogen containing) hormonal contraception:
        - Oral
        - Intravaginal
        - Transdermal
    b. Progestogen-only hormonal contraception:
        - Oral
        - Injectable
        - Implantable
2. Placement of intrauterine device or intrauterine system.
3. Bilateral tubal occlusion
4. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
5. Complete sexual abstinence

The list of acceptable contraception methods is also provided in the patient's legal representative information sheet.

Women who become pregnant while participating in the trial must discontinue trial medication immediately.

4.3 TREATMENT COMPLIANCE

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

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

$$\text{Treatment compliance (\%)} = \frac{\text{Number of actually taken} \times 100}{\text{Number of which should have been taken}}$$

Compliance during the open-label placebo run-in period must be between 75% and 125%. If compliance is outside this range, the patient should not be randomised as described in section 3.3.2.

Compliance during the randomised period should also be between 75% and 125%.

Patients who are not compliant with their medication should be carefully interviewed and informed about the purpose and the conduct of the trial. This discussion should be documented.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

DINAMO™
The primary efficacy endpoint will be the change in HbA1c (%) from baseline to the end of 26 weeks.

DINAMO™ Mono
The primary efficacy endpoint will be the occurrence of treatment failure up to or at Week 26 as a binary endpoint, defined as meeting at least one of the following criteria:

- Use of rescue medication at any time up to Week 26
- Increase from baseline in HbA1c by 0.5% at Week 26
- Increase from baseline in HbA1c to above 7.0% at Week 26 in patients with baseline HbA1c < 7.0%.

5.1.2 Secondary Endpoint(s)

The secondary endpoints to assess efficacy are listed below:

DINAMO™

- Change in FPG (mg/dL) from baseline to the end of 26 weeks
- Change in body weight (kg) from baseline to the end of 26 weeks
- Change in SBP (mmHg) from baseline to the end of 26 weeks
- Change in DBP (mmHg) from baseline to the end of 26 weeks
- Proportion of patients who achieve HbA1c < 6.5% at the end of 26 weeks
- Proportion of patients who achieve HbA1c < 7.0% at the end of 26 weeks

DINAMO™ Mono

- Time to treatment failure
- Change in HbA1c (%) from baseline to the end of 26 weeks
- Change in FPG (mg/dL) from baseline to the end of 26 weeks
- Change in body weight (kg) from baseline to the end of 26 weeks
- Change in SBP (mmHg) from baseline to the end of 26 weeks
- Change in DBP (mmHg) from baseline to the end of 26 weeks
- Proportion of patients who achieve HbA1c < 6.5% at the end of 26 weeks
- Proportion of patients who achieve HbA1c < 7.0% at the end of 26 weeks

5.1.3 Further Endpoint(s)

[redacted]

5.1.3.2 Further endpoint to assess safety

Further endpoints to assess safety are listed below for both DINAMO™ and DINAMO™ Mono:

- Adverse events after 26 and 52 weeks, including adverse events of special interest (see section 5.3.6.1), genital infections, bone fracture, urinary tract infections, arthralgia, bullous pemphigoid, adverse events related to reduced intravascular volume, and ketone measurements reported as AE
- Percentage of patients with reported hypoglycaemia after 26 and 52 weeks
- Vital signs and heart rate after 26 and 52 weeks
- Change from baseline in Tanner staging after 26 and 52 weeks
- Change from baseline in serum electrolytes, hematology, biochemistry, lipids, IGF-1 and IGF-BP3 and markers of mineral and bone metabolism after 26 and 52 weeks
- Change from baseline in height (cm) and BMI (kg/m²) after 26 and 52 weeks
- Growth velocity (cm/year) after 26 and 52 weeks

5.2 ASSESSMENT OF EFFICACY

5.2.1 HbA1c and fasting plasma glucose (FPG)

HbA1c and FPG will be analysed by the central laboratory at the time points indicated in the Flow Chart. However, due to the COVID-19 pandemic, HbA1c and FPG may be analysed by the local laboratory.

The samples will be analysed at a central laboratory or its affiliates having a National Glycohemoglobin Standardisation Program (NGSP) Level I certificate. HbA1c results will be reported in both NGSP (%) and International Federation of Clinical Chemistry, IFCC (mmol/mol) units. The relationship between HbA1c results from the NGSP network (% HbA1c) and the IFCC network (mmol/mol) has been evaluated and a master equation has been developed (NGSP = [0.09148*IFCC] + 2.152). This relationship is continuously monitored and any changes are investigated. The NGSP certification process and test results for NGSP-certified methods do not change as a result of the IFCC standardisation of HbA1c, and will continue to be directly traceable to the Diabetes Control and Complications Trial (DCCT) reference and now also the IFCC reference. If a centrally analyzed, NGSP-certified hemoglobin A1c assay is unavailable (e.g. due to the COVID-19 pandemic), an HbA1c assay performed at a local laboratory is acceptable.

Further details about HbA1c sample handling, shipment, and assay procedures can be found in the laboratory manual in the ISF.
Blood samples for the determination of FPG at the central laboratory will be taken after an overnight fast (no food or drinks except for water for at least 8 hours). The samples should be taken before trial medication administration. The samples will be measured at a central laboratory using validated assays. Plasma glucose results will be reported in mmol/l and mg/dl.

Further details about FPG sample handling and shipment can be found in the laboratory manual in the ISF.

5.2.2 Body weight

Body weight measurements should always be done on the same calibrated scales for an individual patient at the time points indicated in the Flow Chart. However, due to the COVID-19 pandemic, body weight measurements may be done at the local laboratory.

In order to get comparable body weight values, it should ideally be performed in the following way:

- fasting (at visits to which a patient has to come fasted, see Flow Chart)
- after bladder voiding
- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc.)

5.2.3 Systolic/diastolic blood pressure (SBP and DBP) and heart rate (vital signs)

SBP and DBP as well as heart rate (electronically or by palpation, count for 1 minute) will be measured at the time points indicated in the Flow Chart with a calibrated electronic sphygmomanometer. The BP measurement should be performed three times at each time point and the mean value of the measurements will be analysed. However, due to the COVID-19 pandemic, vital signs may be done at the local laboratory.

Initially, BP should be taken 3 times in both arms. The arm with the higher average pressure (systolic or – if equal – diastolic) should be used for subsequent measurements; if measurements for both arms are equal, the non-dominant arm should be chosen.

BP measurements should always be performed on the same arm and, if possible, by the same person and using the same device. The same method must be used throughout the trial for a given patient i.e. if a patient receives the first BP measurement for example with an electronic device, the same method and device should be used throughout the study for this patient.

After patients have rested quietly, in the seated position for at least 5 minutes, 3 BP measurements will be taken approximately 2 minutes apart. The seated pulse rate should be from the second BP reading.

BP measurements should be recorded to the nearest 1 mmHg. BP should always be measured before any blood samples are taken.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
The results must be included in the source documents available at the site.

Throughout the physical examination, the privacy of the patient will be respected and local culture/requirements will be taken into consideration (e.g. same sex chaperone or same sex doctor performing the examinations).

For patients on insulin, injection sites should be checked regularly.

5.3.2 Vital signs

Please refer to Section 5.2.3.

5.3.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.3.3: 1 and Table 5.3.3: 2. For the sampling time points please see the Flow Chart.

All analyses will be performed by a central laboratory, or at a local laboratory at designated visits per the Flow Chart under exceptional circumstances due to the COVID-19 pandemic, the respective reference ranges will be provided in the ISF.

For Visit 2, Visit 5 and Visit 8, all safety laboratory samples will be collected from the patient after an overnight fast (i.e. nothing to eat or drink except water for at least 8 hours). When applicable, laboratory samples should be collected before trial medication is taken.

To minimise pain and distress, local anaesthetic product will be offered to all patients before any venepuncture is carried out.

For female patients, pregnancy testing will be performed locally using the urine pregnancy test kits supplied by the central laboratory or local laboratory under exceptional circumstances due to the COVID-19 pandemic. Immediately after the result of a pregnancy test is known, the pregnancy test kit will be discarded at the site. In case of positive result, a serum pregnancy test will be performed by the central laboratory, or at a local laboratory under exceptional circumstances due to the COVID-19 pandemic. The results of the test must therefore be documented in the source documents available at the site for future verification by the CRA.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

Laboratory reports will be provided through the central laboratory web-based system. It is the responsibility of the investigator to retrieve and evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.3.6.2).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.3.6.2 and the DILI Checklist provided in the eDC system). 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 5.3.3: 1 Safety laboratory parameters – blood, serum or plasma

Haematology	
Haematocrit[1]	White blood cells (WBC)/leukocytes
Haemoglobin[1]	Platelet count/thrombocytes
o reticulocyte count (reflex test if haemoglobin is outside normal range)	Differential automatic (relative and absolute count):
Red blood cells (RBC)/erythrocytes	o neutrophils, eosinophils, basophils, monocytes, lymphocytes
Clinical chemistry	
Albumin	Creatine kinase (CK)
Alkaline phosphatase[1]	o troponin I (reflex test if CK is elevated)
o gamma-glutamyl transferase (γ-GT, reflex test triggered by elevated alkaline phosphatase on two sequential measures)	Lactate dehydrogenase
ALT (alanine aminotransferase, SGPT)[1]	Lipase
AST (aspartate aminotransferase, SGOT)[1]	Magnesium
Bilirubin total, fractionated if elevated	Phosphate
Beta-hydroxy-butyrate	Potassium
Bicarbonate	Protein total
Calcium	Sodium
Chloride	TSH (at screening only)
C-peptide[2]	Blood urea nitrogen (BUN)
Creatinine[1]	Uric acid
Cystatin C	
Lipids	
Cholesterol (total)	LDL cholesterol (calculated)
HDL cholesterol	Triglycerides

[1] At the screening visit (Visit 1A) the following parameters are part of the profile: liver transaminases, alkaline phosphatase, serum creatinine, Cystatine C, TSH, haemoglobin, haematocrit and C-peptide only in addition to HbA1c. Blood samples do not need to be collected in a fasted state.

[2] C-peptide will only be assessed at specific visits as described in Section 5.3.5.4.

Table 5.3.3: 2 Safety laboratory parameters – urine

Semi quantitative (dipstick)	**Quantitative urinalysis**
Nitrite[1]	Albumin
Protein	Creatinine
Ketones	Human chorionic gonadotrophin (hCG)[2]
Urine pH	
Leukocyte esterase (for WBC)[1]	
Microscopic urinalysis	
Microscopic analysis will be performed as a reflex test if any of the above semi-quantitative (dipstick) tests except for ketones are abnormal:	
Urine RBC/erythrocyte	
Urine WBC/leukocytes[1]	
Urine sediment microscopic examination	
Urine culture	
Urine culture will be triggered by positive leukocyte esterase (for WBC) and/or nitrite in the semi-quantitative test/dipstick. The culture will include an antibiogram	

[1] Nitrite and leukocyte esterase (for WBC) will be determined both locally on site (not recorded in eCRF) and via the central laboratory. A positive result at site triggers the sampling of mid-stream urine for urine culture

[2] Urine pregnancy testing will be performed locally in female patients of child-bearing potential only according to the timepoints indicated in the Flow Chart. A positive result at site will be confirmed by a serum pregnancy test performed by the central laboratory.

Albumin/creatinine ratio in spot urine will be calculated at the central laboratory.

The estimated glomerular filtration rate (eGFR) will be calculated according to Zappitelli et al formula (validated for patients from 10 to 20 years of age inclusive) [R16-2476 ; R16-2470]:

eGFR (mL/min/1.73m²) =

$$(507.76 \times e^{0.003 \times height}) / (\text{Cystatine C}^{0.635} \times \text{Serum Creatinine}^{0.547}\ [\mu mol/L])$$

If renal transplant, x 1.165

Follow-up on suspicion for urinary tract infection (UTI) and genital infection

Patients having a history of chronic/recurrent UTI or genital infection or an acute episode of UTI or genital infection at screening will be identified and this condition must be documented as medical history or as a baseline condition in the eCRF, respectively.

Throughout the trial, patients should be closely observed for symptoms of UTI or genital infection. In case these symptoms occur, symptomatic relief and anti-infectives should be provided as appropriate [c01678844-17].

For documentation of acute UTI during trial conduct, the following measures have to be taken. In any case of suspected UTI (symptomatic or asymptomatic), a dipstick test (leukocyte esterase [for WBC] and nitrite) will be performed at the site at the time points indicated in the Flow Chart. In case of a positive result at site, a urine culture sample must be

obtained and sent to the central laboratory for confirmation of the diagnosis and to obtain an antibiogram.

IGF-1, IGF-BP3 and markers of bone turnover
IGF-1, IGF-BP3 and bone metabolism biomarkers will be measured by the central lab at the time points indicated in the Flow Chart.

The following markers of bone turnover will be measured:

- Calcium
- Phosphate
- Alkaline phosphatase
- 25-OH-vitamin D
- Intact parathyroid hormone
- Serum Procollagen type I N-terminal propeptide (PINP) (*for bone formation*)
- Serum N-terminal cross-linked telopeptide (NTx) (*for bone resorption*)

IGF-1 and IGF-BP3 will be measured in samples collected from the patient after an overnight fast (i.e. nothing to eat or drink except water for at least 8 hours).

5.3.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the 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 adverse events and will be followed up and/or treated as medically appropriate.

5.3.5 Other safety parameters

5.3.5.1 Height and Body Mass Index (BMI)

Height and weight will be measured at the time points indicated in the Flow Chart.

Height should be measured using the same stadiometer for one patient.

SDS (Standard Deviation Score), e.g. z-score, values for height and BMI will be calculated by the sponsor for the statistical analysis using the WHO age-specific references.

5.3.5.2 Self-blood glucose monitoring

All patients will be provided with SBGM equipment (i.e. an electronic blood glucose monitoring device/meter that is also capable of measuring blood ketones) and supplies for use

at home during the study for self-measurement of blood glucose. Instructions on the proper use of the SBGM equipment will be provided by the site staff. The patient or his/her parent(s)/legal guardian will be asked to enter data from the device to a patient diary. The investigator or delegated site personnel should also print out the record list and include it in the patient medical records. To avoid additional finger pricks for blood glucose measurement, patients with a continuous glucose monitoring (CGM) device can use relevant readings from the device following the minimum testing requirements below. It is the PI discretion to report clinically relevant readings as adverse events. It is also the PI discretion regarding patient diary management entry as long as the minimum testing requirements below are met.

Only in case of linked adverse events, the single value from the glucometer will be recorded in the eCRF.

SBGM should be performed regularly and ideally its frequency should be individualised as per local clinical guidelines. Especially for patients on insulin, more frequent SBGM may be performed. Nevertheless, minimum requirements are defined by this clinical trial protocol and are as follows:

- Placebo run-in period

Daily SBGM in a fasted state is recommended.

- Randomised treatment period

SBGM at least 3 times per week in a fasted state is recommended.

- Follow-up period

At least one SBGM per week in a fasted state is recommended.

Throughout the trial, additional blood glucose measurements may be performed any time the patient is symptomatic, i.e. experiences signs/symptoms of hyper- or hypoglycaemia.

5.3.5.3 Self-blood ketone monitoring

Patients will be equipped with an electronic device to determine their ketone concentration (i.e. the electronic blood glucose monitoring device/meter that is also capable of measuring blood ketones). The patient or his/her parent(s)/legal guardian will be asked to enter data from the device to a patient diary. The investigator or delegated site personnel should also print out the record list and include it in the patient medical records.

Patients should be instructed to test their ketones in case of any symptoms of DKA, e.g. nausea, vomiting, abdominal pain etc., irrespective of the glucose value. Patients must be reminded about the signs and symptoms of DKA, on the interpretation of ketone values measured via the meter, and on appropriate action to take in the event of increased ketone levels (see below).

Daily measurements before breakfast are recommended during the first 4 weeks of the treatment period and during the 4 subsequent weeks after Visit 5. Otherwise, measurements should be performed at least 3 times per week. In addition, blood ketone levels will be checked by using the meter at most clinic visits (see Flow Chart).

Daily blood ketone monitoring should also be performed in case of concomitant illness/stress or if deemed necessary by the investigator. In the event of increased ketones (> 0.6 mmol/l), patients should contact their trial site. In case of deteriorating ketosis, blood glucose and ketone levels should be checked every 1-2 hours until they are back in a range considered to be normal for the patient. Patients should be instructed to immediately refer themselves to hospital and/or the investigator, or to contact an emergency physician, in case of a blood ketone concentration > 1.5 mmol/L (as indicated in the meter manual). Blood ketone concentration > 1.5 mmol/L should be reported as AE by the investigator and the blood ketone values should be recorded in the eCRF.

In case of a suspected DKA, the investigator should ensure that appropriate tests are performed at the earliest opportunity according to local guidelines, such as a blood gas test (pH, bicarbonate). 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). In accordance with Section 3.3.2, investigators should carefully select patients for the study in terms of their ability to comply with ketone measurement requirements. Patients not adhering to the instructions given by the investigator should be retrained at the earliest possible opportunity.

5.3.5.4 C-peptide

Laboratory samples for C-peptide will be collected at the time points indicated in the Flow Chart.

Except for the screening visit, samples will be collected from the patient after an overnight fast (i.e. nothing to eat or drink except water for at least 8 hours). When applicable, samples should be collected before trial medication is taken.

The analysis will be performed by a central laboratory. Non-fasting serum C-peptide at Visit 1A will be used to check the patient eligibility as described in Section 3.3.1. The respective reference ranges and details about sample handling and shipment will be provided in the laboratory manual in the ISF.

5.3.5.5 Tanner staging (modified)

Tanner staging is a scale of pubertal development in children, adolescents and adults which is routinely used for defining physical measures of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitalia and development of pubic hair. Due to natural variation, individuals pass through the Tanner stages at different rates depending on the timing of puberty.

To assess the stage of puberty of each patient throughout the trial, a modified version of this scale will be used at the time points indicated in the Flow Chart. For patients with Tanner stage V at Visit 2, further assessment is not required at the subsequent visits. For details regarding the modified Tanner staging, please refer to Appendix 10.1.

5.3.5.6 Criteria for hypoglycaemic event

Every episode of plasma glucose equal to or below 70 mg/dl (3.9 mmol/l) should be documented in the eCRF with the respective time and date of occurrence. Any hypoglycaemia with glucose values < 54 mg/dl (< 3.0 mmol/l) as well as all symptomatic and severe hypoglycaemic event (requiring active assistance by another person to administer carbohydrate) should be documented with the respective time and date of occurrence as an AE "hypoglycaemic event".

For the analysis, all hypoglycaemias will be classified according to the following criteria:

- Documented symptomatic hypoglycaemia AE with glucose concentration ≤ 70 mg/dL (< 3.9 mmol/L), as well as asymptomatic hypoglycaemia event ≤ 70 mg/dL (< 3.9 mmol/L)
- Documented any hypoglycaemia AE with glucose concentration < 54 mg/dL (< 3.0 mmol/L)
- Severe hypoglycaemia AE: event requiring the assistance of another person to actively administer carbohydrates, glucagon or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration [R17-0216].

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event
An adverse event (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.

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
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect, or

- 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 considered "Always Serious"
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 5.3.6.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".
In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further 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 eDC system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)
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 Pharmacovigilance Department within the same timeframe that applies to SAEs.

Protocol-specified AESIs (as identified by the investigator based on the below list for adverse events of special interest) can be classified as serious or non-serious but all these AESIs once identified by the investigator must be reported on an SAE form in an expedited manner similar to SAEs, even if they do not meet any of the SAE seriousness criteria (i.e. non serious AESI should be reported as a non-serious event on the SAE form for reporting).

The following events are considered as protocol-specified adverse events of special interest (AESI):

- Hypersensitivity reactions such as angioedema, angioedema-like events, and anaphylaxis (an identified risk with DPP-4 inhibitors)
- Skin lesions such as exfoliative rash, skin necrosis, or bullous dermatitis (a potential risk with DPP-4 inhibitors)
- Pancreatitis (an identified risk with DPP-4 inhibitors)
- Pancreatic cancer (a potential risk with DPP-4 inhibitors)
- Hepatic injury (of potential interest for all investigational drugs)
- Decreased renal function (of potential interest for all investigational drugs)
- Diabetic Ketoacidosis (DKA) (an identified risk with SGLT-2 inhibitors)

- Events involving lower limb amputation (a potential risk with SGLT-2 inhibitors)

Details on hepatic injury, decreased renal function, DKA and events involving lower limb amputation are provided below.

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

- an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample, and/or
- isolated elevation of ALT and/or AST ≥ 5 fold ULN

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

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.

Decreased renal function
Decreased renal function diagnosed as acute kidney injury or defined by a creatinine value showing a ≥ 2 fold increase from baseline and is above the ULN.

For the AESI "decreased renal function" the investigator shall collect an unscheduled laboratory sample for creatinine as soon as possible and initiate follow-up laboratory tests of creatinine according to medical judgement.

Diabetic ketoacidosis (DKA)
DKA is defined by the diagnostic criteria in Table 5.3.6.1: 1 below, and as defined by the American Diabetes Association (ADA) [R14-5435].

Investigators should note that not all criteria in the table below need to apply for the diagnosis of DKA, and clinical judgement should also be taken into consideration. Due to its mechanism of action, empagliflozin may potentially modify the clinical presentation of DKA which may occur at lower plasma glucose levels than stated in Table 5.3.6.1: 1 below (see Sections 1.2.1 and 2.3 for further details).

Table 5.3.6.1: 1 Diagnosis criteria for DKA according to the American Diabetic Association

	DKA		
	Mild	Moderate	Severe
Plasma glucose (mg/dL)	>250§	>250§	>250§
Arterial pH	7.25-7.30	7.00-7.24	<7.00
Serum bicarbonate (mEq/L)	15-18	10 to <15	<10
Urine ketones*	Positive	Positive	Positive
Serum ketones*	Positive	Positive	Positive
Effective serum osmolality (mOsm/kg)**	Variable	Variable	Variable
Anion gap***	>10	>12	>12
Alteration in sensoria or mental obtundation	Alert	Alert/drowsy	Stupor/coma

§ In patients treated with SGLT2-inhibitors, including empagliflozin, a plasma glucose < 250 mg/dl does not exclude the diagnosis of DKA. In these patients DKA may occur at lower plasma glucose levels

* Nitroprusside reaction method

** Calculation: 2[measured Na (mEq/L) + glucose (mg/dL)/18

*** Calculation: (Na+) – (Cl- + HcO3-) (mEq/L)

Events involving lower limb amputation
This definition includes amputation (i.e. resection of a limb through a bone), disarticulation (i.e. resection of a limb through a joint) and auto-amputations (i.e. 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).

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.

In addition to the safety topics defined as AESI above, the following safety topics will be monitored during the trial and assessed: Arthralgia, bullous pemphigoid, genital infections (including mycotic infections, such as vulvovaginal or balanitis), bone fracture, urinary tract infections (including urosepsis or pyelonephritis), AEs related to reduced intravascular volume and osmotic diuresis (including symptomatic hypotension).

Intensity of AEs
The intensity 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

Causal relationship of AEs
Medical judgement should be used to determine the relationship, 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 diminished).

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.

5.3.6.2 Adverse event collection and reporting

AE Collection
The investigator shall maintain and keep detailed records of all AEs in their patient files.

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

- From signing the informed consent onwards until individual patient's end of trial:
  -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 AEs but should only report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the eCRF.

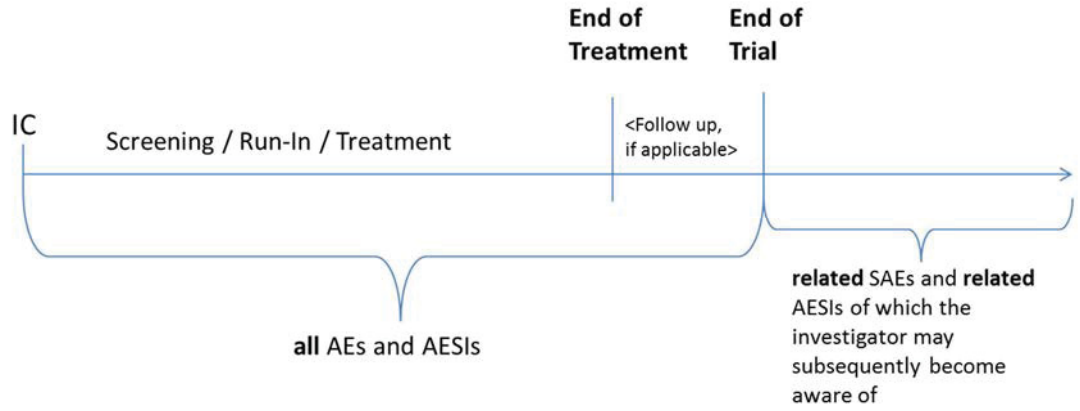


Figure 5.3.6.2: 1 Trial periods for collection of AEs

Patients who discontinue trial medication prematurely and agree to be contacted further, but do not agree to physical visits should be followed up as described in section 3.3.4.1. From the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, related SAEs and related AESIs the investigator becomes aware of.

AE reporting to 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 immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. On 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.

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication and any possible interactions between the trial medication and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP).

The following should also be recorded as an (S)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 and laboratory test results, if they are judged clinically relevant by the investigator.

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

Pregnancy
In rare cases pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

Blood samples for pharmacokinetic analysis will be collected at the following time points (see also the Flow Chart):

Visit 5

- pre-dose: within 30 minutes prior to drug administration at site (and preferably approximately 24 hours after drug administration on the previous day)
- 1.5 h ± 15 min after drug administration

Visit 8 (EoT)

- pre-dose: within 30 minutes prior to drug administration at site (and preferably approximately 24 hours after drug administration on the previous day)
- 1.5 h ± 15 min after drug administration

The date and exact clock time of drug administration and of sampling times have to be recorded and documented in the eCRF by the investigator or designated site-personnel. These

actual dates and times will be used to evaluate pharmacokinetics. Dates and clock times of drug administrations on the 3 days prior to Visit 5 and 8 have to be recorded as well (see Section 4.1.4).

5.4.2 Methods of sample collection

The planned PK analyses will require blood sampling at the time points indicated in the Flowchart. Correct, complete and legible documentation of drug administrations and blood sampling times as well as adequate handling and identification of PK samples are mandatory to obtain data of adequate quality for the PK analysis.

In order to allow the sample identification, the sample tube labels should list at a minimum the following information: BI trial number, patient number, visit number and planned sampling time. Two x 2 plasma aliquots will be obtained from blood samples (two aliquots for empagliflozin analysis, and two aliquots for linagliptin analysis). Each aliquot should contain at least 0.5 mL plasma. All aliquots will be stored at about -20°C or below and be shipped on dry ice.

Further details on sample collection, preparation of plasma aliquots, sample handling, and shipping are provided in the ISF and/or lab manual.

5.4.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of analyte plasma concentrations, blood will be taken from an antecubital or forearm vein into a blood drawing tube that contains potassium EDTA–anticoagulant at the time points indicated in the Flowchart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. If a forearm vein cannot be used for any reason, then the most easily found vein can be used instead. It is recommended to use local anesthetics for the skin to avoid pain upon blood withdrawal. Attempts to draw blood are limited to three.
During the whole trial, a maximum of approximately 16 mL of blood will be drawn for PK purposes. Plasma samples will be obtained by centrifugation. Sample aliquots will be stored at the trial site and at the logistics central laboratory until shipment and at the analytical laboratory until analysis. First and second sample aliquots are to be shipped separately. For further details please refer to the ISF and/or lab manual.

The trial samples will be discarded after completion upon the final study report has been signed.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

This section is not applicable for this trial.

5.5 ASSESSMENT OF BIOMARKER(S)

5.5.1 Biobanking

This section is not applicable for this trial.

5.5.2 DPP-4 activity

Measurement of DPP-4 activity will require blood sampling at the time points indicated in the Flowchart.

In order to allow the sample identification, the sample tube labels should list at a minimum the following information: BI trial number, patient number, visit number and planned sampling time. Two plasma aliquots will be obtained and stored in polypropylene tubes at -20 C° or colder.

Blood will be taken from an antecubital or forearm vein into a blood drawing tube that contains potassium EDTA–anticoagulant. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. If a forearm vein cannot be used for any reason, then the most easily found vein can be used instead. It is recommended to use local anesthetics for the skin to avoid pain upon blood withdrawal. Attempts to draw blood are limited to three.

At Visit 2, at least 4 mL of blood will be drawn. Plasma samples will be obtained by centrifugation. Sample aliquots will be stored at the trial site and at the logistics until shipment and at the analytical laboratory until analysis. First and second sample aliquots are to be shipped separately.

Further details on sample collection, preparation of plasma aliquots, sample handling, and shipping are provided in the ISF and/or lab manual.

The trial samples will be discarded after completion upon the final study report has been signed.

Plasma DPP-4 activity will be measured using a validated fluorescence assay at [redacted].

5.6 OTHER ASSESSMENTS

5.6.1 Auto-antibodies for diabetes

Auto-antibodies can be detected early in the development of type 1 diabetes and are considered as markers of autoimmune beta cell destruction. In conjunction with the measurement of C-peptide levels, the presence of T2DM will be confirmed at Visit 1A in all trial patients by measuring auto-antibodies to IA-2 and glutamic acid decarboxylase auto-antibodies (GADA).

The analysis will be performed by a central laboratory. The details about sample handling and shipment will be provided in the laboratory manual in the ISF.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are considered standard measurements in the clinical development of non-insulin products such as empagliflozin and linagliptin, and/or standard as part of routine care for T2DM [P12-09397]. All defined measurements will be performed in order to monitor safety and tolerability aspects and to determine efficacy in an appropriate way.

A surrogate endpoint (i.e. the laboratory parameter HbA1c) is used as the primary efficacy endpoint, since for the purposes of drug approval and labelling, which will support an indication of glycaemic control, regulatory authorities state that this endpoint, albeit surrogate, is the primary endpoint of choice [R08-2669].

6. INVESTIGATIONAL PLAN

Visits should take place at a location within the clinical site that has a child-friendly infrastructure (e.g. an environment that is familiar to the patients, the setting is physically appropriate, if desired by the patient, parent(s)/legal guardian are allowed to stay with them during the trial procedures). Furthermore, site-personnel should be knowledgeable and skilled in dealing with the paediatric population and its age-appropriate needs. However, Visits 3, 4A, 6, 7, 9 can be done remotely/by telephone/telemedicine under exceptional circumstances due to the COVID-19 pandemic. Reasons a remote/telephone/telemedicine visit may be performed may include a confirmed or suspected COVID-19 infection or unwillingness to return to the investigator site due to concerns of COVID-19 exposure.

6.1 VISIT SCHEDULE

Trial visits should start between 7.00 AM and 11.00 AM and ideally should be scheduled as early as possible when overnight fast is required (at least 8 hours with no food or drink and water only).

Smoking is not permitted prior to or during any of the visits (this includes from the start of the overnight fast that precedes all visits). Excessive food and alcohol intake should be avoided in the 2 days prior to each visit.

All patients are to adhere to the visit schedule as specified in the Flow Chart. Some flexibility is allowed in scheduling the visits according to the visit time windows as specified. The trial medication kits will contain sufficient medication to allow for these protocol-permitted visit windows. All deviations from the planned visit schedule will be documented. If any visit has to be re-scheduled, subsequent visits should follow the original visit schedule (calculated from Visit 2).

If a patient mistakenly takes trial medication in the morning of a visit where blood samples are drawn for PK assessment or comes in non-fasted where a fasting condition is required, the visit should be re-scheduled to the next day reminding the patient about the expected conditions.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart. Study procedures should be performed in the same order as in the Flow Chart. Blood pressure and pulse rate as well as 12-lead ECG should always be measured before any blood samples are drawn. Weight should be measured after urine sampling.

Additional details regarding visit procedures are provided below.

6.2.1 Screening and run-in period(s)

No trial procedure is allowed unless the appropriate consent and assent are in place. Consent and assent must be obtained prior to the screening visit procedures.

Screening Period (Visit 1A to 1B)
Visit 1A is the beginning of the screening period. The patient should be recorded on the enrolment log and be registered in the IRT as a screened patient when Visit 1A is performed. Once Visit 1A procedures are complete and laboratory results are received, inclusion/exclusion criteria must be reviewed. If the patient meets inclusion/exclusion criteria, he/she should be contacted to schedule the next visit.

If the patient does not meet inclusion/exclusion criteria, the patient must be recorded in eCRF as a screen failure. Patient must be registered as a screen failure in IRT.

Run-in Period (Visits 1B to 2)
Visit 1B is the beginning of the run-in period. This visit can be performed on the same day as Visit 1A.

Following completion of Visit 1B procedures, eligible patients will be dispensed a placebo run-in kit for the 2 week run-in period which will be assigned via the IRT system.

The SBGM/SBKM device is delivered to the patient at Visit 1B. Only blood glucose measurements are expected during the run-in period. The measures have to be captured by the patient or his/her legal representative in a paper diary every day during run in period.

Medical History
Any pre-existing medical conditions considered as relevant by the investigator, excluding the indication of the trial, are recorded into the eCRF in the appropriate page. This concern all active pathology, chronic disease or recurrent event.

6.2.2 Treatment period(s)

For patients eligible to be randomised, assessments should be performed as mentioned in the Flow Chart and the respective protocol sections.

Visits 2, 5 and 8 have to be performed in a fasted state (overnight fast for at least 8 hours, no food intake, only water allowed).

Initial randomisation at Visit 2
Eligible patients will be randomised by using the IRT system; all visit assessments should have been completed prior to this, and before the first intake of study medication. First dose of trial drugs will be administered in the clinic (Day 1).

Starting from Visit 2, the SBGM/CGM/SBKM device will also be used by the patient to measure his/her blood glucose concentration and blood ketone concentration before breakfast. He/she or his/her parents/legal guardian should enter the values in the patient diary. Those values will then be reviewed by the investigator or delegated site personnel at each clinic visit. In order to make sure those measurements are well performed, the investigator or a delegated site staff representative should contact the patient or the parent/legal guardian by phone/text message/email a day or two after randomised treatment is started and then after 2, 8, 18, 22, 34, 38, 46 and 50 weeks of treatment.

These measurements should be performed as described in the Flow Chart and in Section 5.3.5.2 and 5.3.5.3.

Next clinic visits will be scheduled after 4, 12, 14, 26, 30, 42 and 52 weeks of treatment (Visit 3 to 8). For detailed description of the trial procedures at each visit and dispensing schedule, please refer to the Flow Chart.

Re-randomisation at Visit 4B (Week 14)
Patients not achieving an HbA1c value < 7.0% at Visit 4A (as measured by the central laboratory) and initially randomised to empagliflozin 10 mg will be re-randomised to receive either empagliflozin 10 mg or empagliflozin 25 mg. In order to maintain the blinding, an IRT call will be performed for all patients. Medication numbers will be assigned through the IRT system based on the HbA1c value at Visit 4A and the age at baseline.

Visit 4B could be a site visit or medication kits could be delivered at the patient's home by a dedicated study nurse/study site staff/delegated courier at the investigator's discretion and as per the local regulations. In case the medication kits would be delivered at the patient's home, a phone contact should be performed by a site staff representative. Following completion of the visit procedures, eligible patients will be re-randomised and the first dose of re-randomised trial drugs should be administered on the same day.

Re-randomisation at Visit 5 (Week 26)
After the 26-week treatment period, all patients will enter a double-blind safety extension period up to 52 weeks.

Patients who received placebo during the 26-week treatment period will be re-randomised to receive either linagliptin 5 mg or empagliflozin 10 mg or empagliflozin 25 mg. The re-randomisation will be stratified by age at baseline. At Visit 5, in order to preserve the trial blinding, the investigator will assign medication kits for all patients through the IRT system. Following completion of the visit procedures, eligible patients will be re-randomised and the first dose of re-randomised trial drugs should be administered on the same day

6.2.3 Follow Up Period and Trial Completion

For patients who complete treatment as planned, a follow-up (FUP) visit should be planned 3 weeks after last trial drug administration. For detailed description of the trial procedures at the FUP visit, please refer to the Flow Chart.

Trial completion
The trial completion eCRF end-of-study page has to be filled-in when the patient has terminated the trial.

The end of the trial is:

- At the end of the follow-up visit for patients who have completed the trial on treatment as planned;
- After the early unscheduled end of treatment (EOT) visit, if a patient did not agree to come to the remaining planned study visits and also disagrees to be contacted at all;
- After the Visit 9/FUP visit (in person or by telephone) at Week 55, for patients who discontinued drug early but agreed to come to the remaining planned study visits, or agree to be contacted/allow access to medical records.

Patients who prematurely discontinued trial medication

Patients who prematurely discontinue study drug (refer to section 3.3.4) before the planned end of treatment at Visit 8, should come to the clinic as soon as possible after last drug intake for an immediate unscheduled early EOT visit. The reason for premature trial drug discontinuation must be documented in the eCRF. For detailed description of the trial procedures at this visit, please refer to the Flow Chart.

In addition patients will be encouraged to attend all subsequent planned visits despite not being under treatment anymore and perform all study procedures except pharmacokinetic sampling.

Study assessments may be omitted if a patient is willing to return to the pre-defined study visits, with exception of blood drawing for safety lab tests, HbA1c and FPG, body weight, blood pressure and collection of adverse events, and concomitant therapy.

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.

Vital status information

In case of early discontinuation of trial medication, if the patient does not agree to come to future visits as planned,every attempt will be made to get information on vital status at Week 55 after his/her randomisation.

Patients and parents/legal guardian will be asked to agree to be contacted by the site personnel, which could be by telephone calls, to allow collection of this information.
If death occurs, the investigator will review the circumstances, including the relevant medical records to ascertain the most likely primary and secondary causes of death.
Collection of vital status will be performed in accordance with national ethical and regulatory guidelines. The need for vital status information will be explained to patients prior to their participation in the trial.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a multinational, randomised, placebo-controlled, double-blind trial to assess the efficacy and safety of pooled empagliflozin (empagliflozin 10 mg and empagliflozin 25 mg) and linagliptin 5 mg versus placebo after 26 weeks of treatment in children and adolescents with T2DM.

7.1.1 DINAMO

The primary endpoint is the change in HbA1c (%) from baseline to the end of 26 weeks. This endpoint will be analysed in a confirmatory way. For the primary analyses, treatment comparisons will be made between the randomised pooled empagliflozin (empagliflozin 10 mg and empagliflozin 25 mg, i.e. independent of patients achieving the glycaemic target at Week 12 and re-randomisation at Week 14) versus placebo and between the randomised linagliptin 5 mg versus placebo according to the initial randomisation. The change in HbA1c (%) from baseline to the end of 26 weeks will be analysed using a "wash-out" approach.

7.1.2 DINAMO Mono

The primary endpoint is the occurrence of treatment failure up to or at Week 26 as a binary endpoint. This endpoint will be analysed in an exploratory way. The primary analysis will be a comparison of the treatment failure rate of linagliptin 5 mg, pooled empagliflozin and placebo. The risk difference of active treatments versus placebo will be determined and assessed by an exact 2 sided 90% confidence interval based on the method of Chan and Zhang [R15-1346]. Patients will be assigned to the treatment they were randomised to at the initial randomisation. Non-completers who prematurely discontinue intake of study drug will be considered treatment failures.

7.2 NULL AND ALTERNATIVE HYPOTHESES

7.2.1 DINAMO

7.2.1.1 Primary family of hypotheses

The following two hypotheses are the set of primary hypotheses in this trial.

For empagliflozin, the following null hypothesis will be tested:

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

For linagliptin, the following null hypothesis will be tested:

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

= Mean change in HbA1c (%) from baseline to the end of 26 weeks in the placebo group

The hypotheses will be tested simultaneously at the study-wise level of $\alpha = 0.05$ (two-sided). The Hochberg-procedure will account for multiple testing within the primary family of hypotheses.

7.2.1.2 Secondary family of hypotheses

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

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

followed by:

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

7.2.2 DINAMO Mono

It is not planned to test specific hypotheses because of the exploratory nature of DINAMO™ Mono.

7.3 PLANNED ANALYSES

The statistical analysis will be based on the following populations.

Treated set

The treated set (TS) will include all patients who are treated with at least one dose of randomised study medication. The TS is the basis for safety analyses.

Modified intention-to-treat set

The modified intention-to-treat set (mITT) will include all randomised patients who are treated with at least one dose of study medication and have a baseline HbA1c measurement. The mITT is the basis for the primary analyses.

Per protocol set

The per protocol set (PPS) will include all patients in the mITT set who do not have any important protocol deviations (IPD) which can be expected to have a distorting influence on the assessment of the primary endpoint. Details regarding the definitions of IPDs will be provided in the Trial Statistical Analysis Plan (TSAP) and the decision to exclude patients from the PPS will be made prior to database lock.

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

- *Study baseline:* Last observed measurement prior to administration of any initially randomised study medication at Day 1.
- *Titration baseline:* Last observed measurement prior to administration of the re-randomised study medication for the initial empagliflozin patients at Week 14.
- *Safety baseline:* Last observed measurement prior to administration of the re-randomised study medication for the initial placebo patients at Week 26.

For analyses up to Week 26, data collected after the first intake of study medication in the extension period will be censored.

Analyses up to Week 12 and Week 52 will be considered exploratory in nature. The study is not powered to compare empagliflozin with linagliptin at Week 12, Week 26 and Week 52, or to compare empagliflozin 10 mg with empagliflozin 25 mg at Week 52. No hypothesis testing is planned, and only descriptive statistics will be provided.

The anticipation for the patients who would have taken the wrong study medication is low. Therefore all analyses will be based on the randomised treatments. All patients with wrong study medication will be listed.

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

7.3.1 Primary endpoint analyses

7.3.1.1 DINAMO

The primary endpoint of DINAMO™ is defined in Section 5.1.1.

7.3.1.1.1 Analysis of the primary family of hypotheses

These confirmatory primary analyses will be performed using an effectiveness "wash-out" approach based on the mITT set with multiplicity adjustment for simultaneous testing of linagliptin and empagliflozin using the Hochberg-procedure. Patients will be assigned to the treatment they were randomised to at the initial randomisation, i.e. linagliptin 5 mg, pooled empagliflozin or placebo. HbA1c values measured after premature discontinuation of study drug or after rescue therapy was initiated will be included in the analyses. All available on- and off-treatment data up to the Week 26 time point will be included.
There will be different types of missing data to be considered for the imputation.

Table 7.3.1.1.1: 1 "Wash-out" approach – the missing data imputation method

Randomised treatment group: Placebo
Missing HbA1c data will be imputed for all scheduled visits up to Week 26, that includes Week 4, Week 12 and Week 26. Baseline will not be imputed.

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

Randomised treatment groups: linagliptin 5 mg and empagliflozin pooled.
Missing HbA1c data will be imputed for Week 26 only.

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

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

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

For the monotone missing data, a sequential linear regression MI approach will be used and referred to as 'SLR-MI'. The MI will be performed on a data set including on- and off-treatment data and once per imputation from the previous step. This procedure will impute values for all missing time points both on- and off-treatment. The regression models will be fitted with baseline HbA1c as a continuous covariate and age as a binary covariate (age < 15 years and age ≥15 to <18 years). 500 imputations for the placebo group will be completed.

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

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

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

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

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

7.3.1.1.2 Analysis of the secondary family of hypotheses

If the "wash-out" approach analysis for both hypotheses in the primary family of hypotheses shows a statistically significant result, the secondary family of hypotheses will be tested as ordered hypotheses at the significance level $\alpha = 0.05$ (two-sided), i.e., the hypotheses $H'_{0,1}$ will be tested first and if this hypothesis can be rejected at the level $\alpha = 0.05$, the hypotheses $H'_{0,2}$ will be tested at the same level.

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

These secondary family of hypotheses for the primary endpoint will be tested using the "wash-out" approach described in Section 7.3.1.1 but the ANCOVA used for analysis of the completely imputed set will apply an "inverse probability weighting" approach based on the mITT set.

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

Patients will be assigned to the treatment they were randomised to at the initial randomisation together with the treatment allocation at Week 14 randomisation. HbA1c values measured after premature discontinuation of study drug or after rescue therapy was initiated will be included in the analyses. All data up to the Week 26 time point will be included.

The treatment comparisons for $H'_{0,1}$ and $H'_{0,2}$ according to Section 7.2.2 are as follows:

For $H'_{0,1}$, this is a contrast between patients who started empagliflozin 10 mg and either having a dose increase in patients who were non-responder at Week 12, or who were responders at Week 12 and continue with empagliflozin 10 mg, and placebo.

For $H'_{0,2}$, this is a contrast between patients who started empagliflozin 10 mg and either were responders or were non-responders at Week 12 and continue with empagliflozin 10 mg, and placebo.

7.3.1.2 DINAMO Mono

The primary endpoint of DINAMO™ Mono is defined in Section 5.1.1.

The primary analysis will be a comparison of the treatment failure rates of linagliptin 5 mg, pooled empagliflozin and placebo. The risk difference of active treatments versus placebo will be determined and assessed by an exact 2-sided 90% confidence interval based on the method of Chan and Zhang [R15-1346]. Patients will be assigned to the treatment they were

randomised to at the initial randomisation. Non-completers who prematurely discontinue intake of study drug will be considered treatment failures.

7.3.2 Secondary endpoint analyses

7.3.2.1 DINAMO

Secondary endpoints of DINAMO™ are defined in Section 5.1.2.

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

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

The change in FPG from baseline to the end of 26 weeks will be analysed using an ANCOVA model. The statistical model will be:

FPG change from baseline to the end of 26 weeks =
overall mean + treatment + baseline FPG + age + random error

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

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

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

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

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

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

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

7.3.2.2 DINAMO Mono

Secondary endpoints of DINAMO™ Mono are defined in Section 5.1.2.

The secondary endpoint of time to treatment failure will be analysed and graphically described by Kaplan-Meier estimates up to the planned end of the study. A descriptive Log-rank test will compare linagliptin 5 mg and pooled empagliflozin versus placebo individually up to Week 26. Patients in the placebo group will be censored after 26 weeks unless a prior treatment failure is observed. Data obtained after re-randomisation in the placebo group will not be utilised for the determination of time to treatment failure.

The change in HbA1c from baseline to the end of 26 weeks will be analysed based on a REML approach using MMRM to access the effectiveness and efficacy, using the same sensitivity methods as described in Section 7.3.4.1.1 and Section 7.3.4.1.3 respectively.

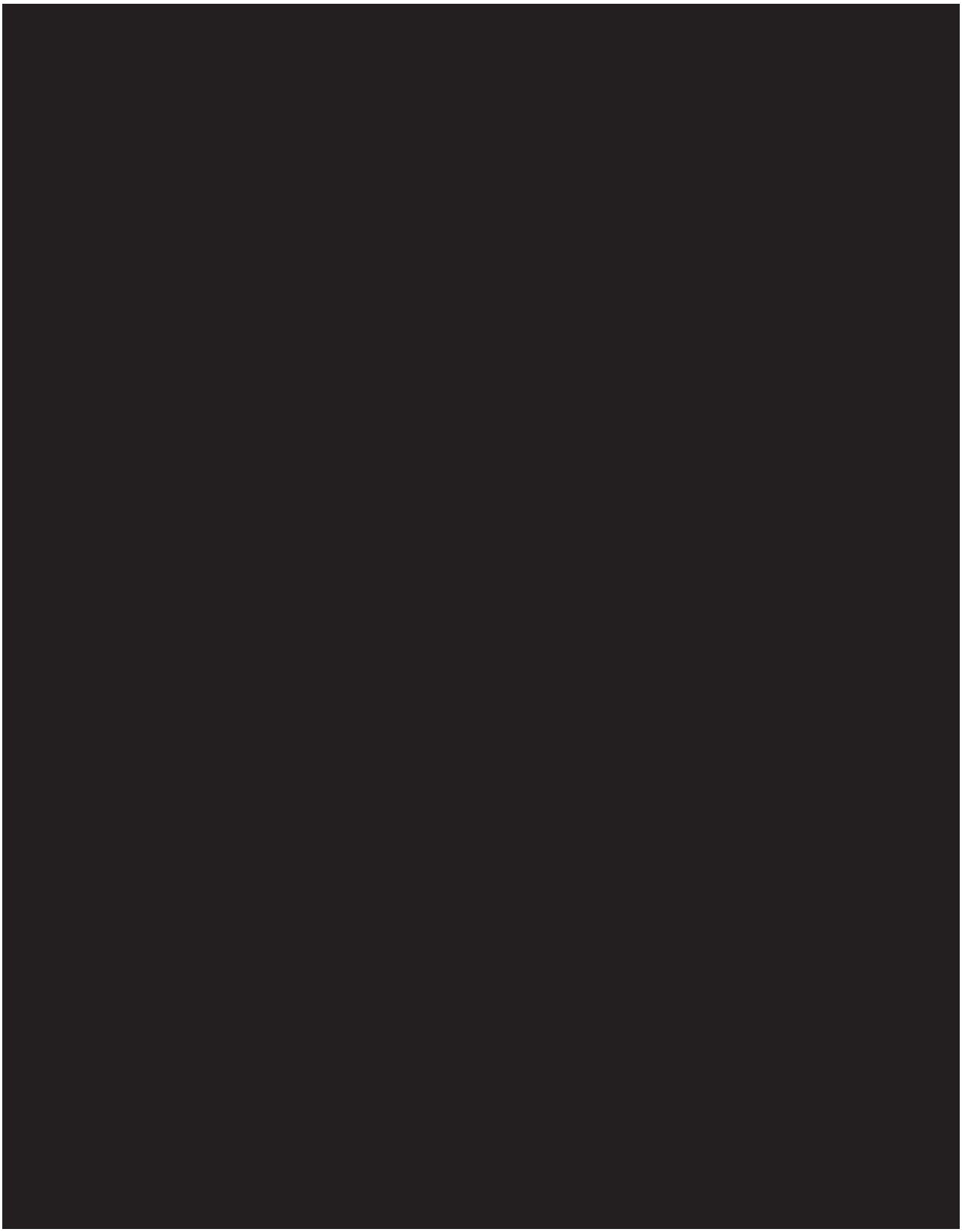
It is expected that a large group of drug naïve patients will require early intervention of rescue medication as early as first on-treatment visit, therefore the change in HbA1c from baseline to the end of 26 weeks will also be analysed using an ANCOVA model including treatment as a fixed classification effect, baseline HbA1c as a linear covariate, and age as a categorical covariate. The missing data will be imputed by the last on-treatment observation without rescue medication carried forwards. In case, there is no on-treatment observation without rescue medication, baseline value will be carried forward.

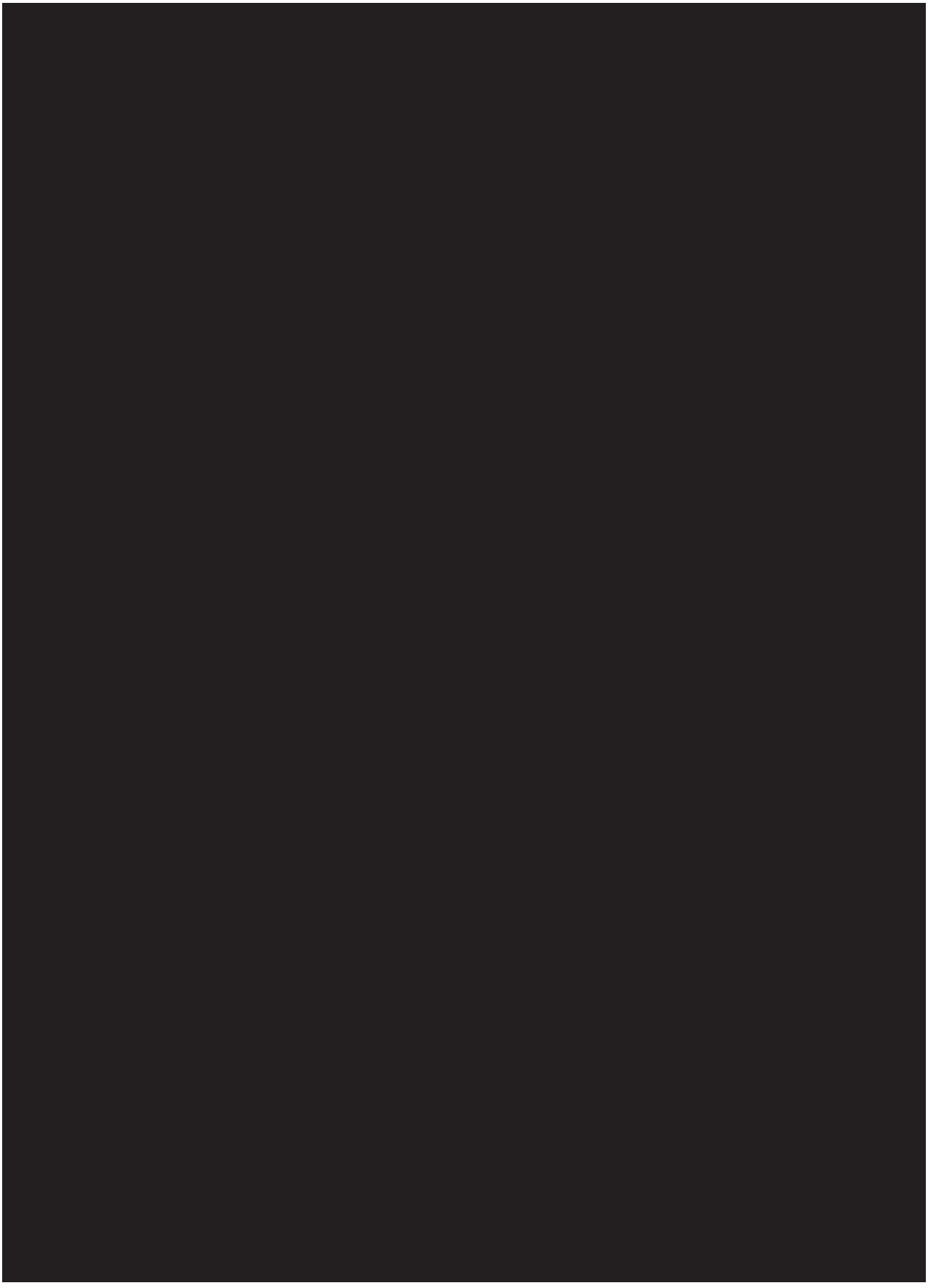
The following secondary endpoints will be analysed using the same methods described in section 7.3.2.1.

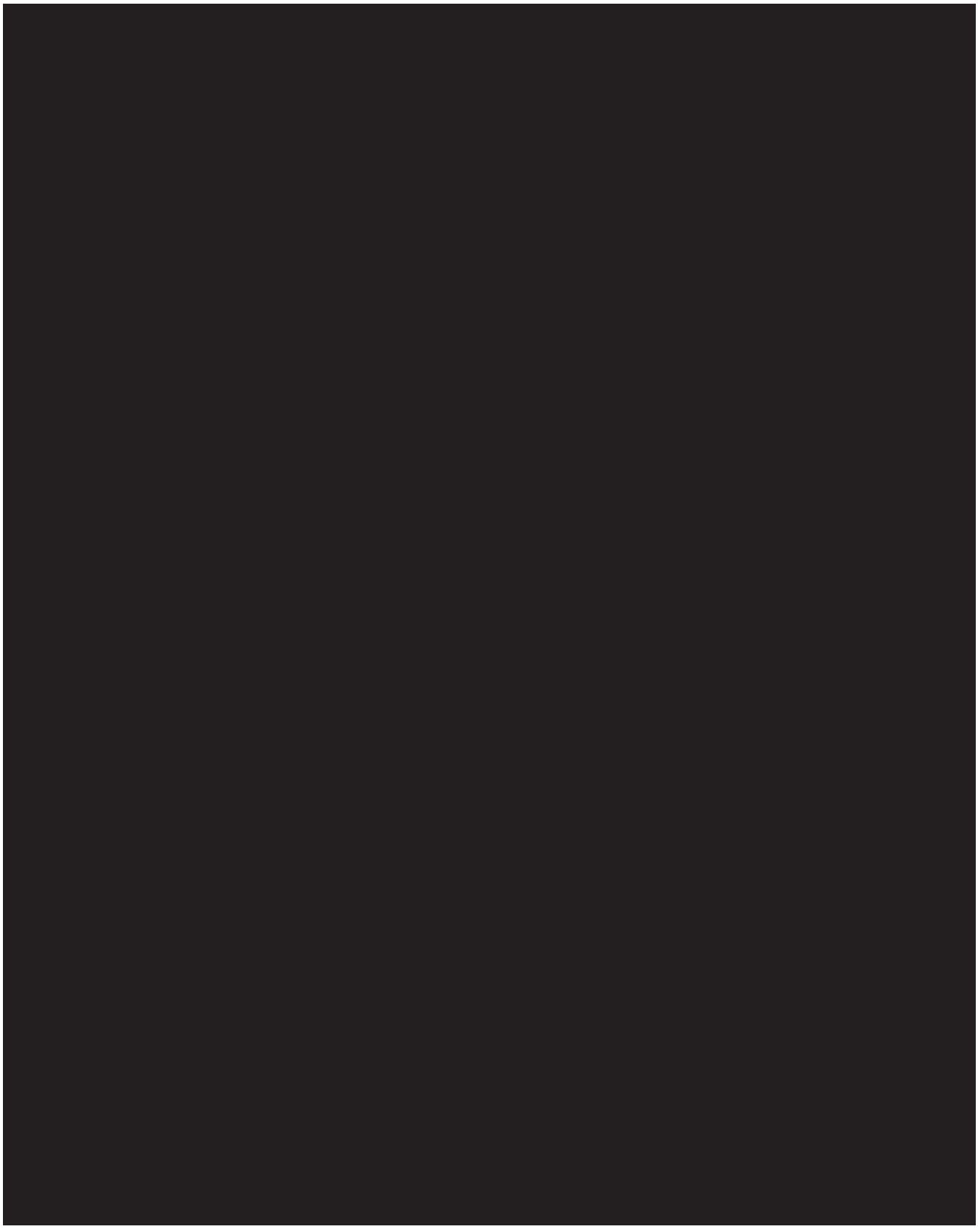
- Change in FPG (mg/dl) from baseline to the end of 26 weeks
- Change in body weight (kg) from baseline to the end of 26 weeks
- Change in SBP (mmHg) from baseline to the end of 26 weeks
- Change in DBP (mmHg) from baseline to the end of 26 weeks

The change in FPG (mg/dl) from baseline to the end of 26 weeks will also be analysed using an ANCOVA model including treatment as a fixed classification effect, baseline FPG as a linear covariate, and age as a categorical covariate. The third approach will have any post-baseline missing values, off-treatment values and values after rescue medication imputed by BOCF since FPG is measured only at baseline and Week 26.

The proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 weeks will be determined per treatment group and the risk difference of active treatments versus placebo will be determined and assessed by an exact 2-sided 90% confidence interval.







7.3.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analyses and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 7 days after the date of the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. All AEs occurring before first study medication intake will be assigned to 'pre-treatment' and all AEs occurring after last study medication intake plus 7 days will be assigned to 'post-treatment'.

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 MedDRA.

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 highlighted in the listings. 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.

The safety analyses will be performed using the following population set and randomised study treatment combinations according to the defined period, separately for DINAMO™ and DINAMO™ Mono.

- **Comparison vs. placebo:** All patients in the TS will be included in the safety analyses up to Week 26 presented by placebo, linagliptin 5 mg and empagliflozin pooled.

- **Safety during active treatment periods:** All patients on active treatment at anytime in the TS will be included in the safety analyses up to Week 52 presented by linagliptin pooled and empagliflozin pooled. For patients on active treatment and initially randomised to placebo at the start of the study, analyses will be restricted to data collected after Week 26.

- **Assessment of up-titration to empagliflozin 25 mg (For DINAMO™ only):** Patients initially randomised to empagliflozin in the TS, excluding the responders at Week 12 and the patients who did not proceed to re-randomisation at Week 14, will

be included in the safety analyses from Week 15 to Week 52 presented by empagliflozin 10 mg and 25 mg non-responder at Week 12 after initial randomisation.

- **Long term safety:** All patients in the TS, excluding patients initially randomised to placebo, will be included in the safety analyses up to Week 52 presented by linagliptin 5 mg and empagliflozin pooled.

7.3.7 Pharmacokinetic and pharmacodynamics analyses

In order to complement the pharmacokinetic characterisations of linagliptin and empagliflozin in paediatric patients with T2DM, in a first step, a descriptive analysis of the plasma concentrations will be performed to allow for a comparison to adults. In a second step, a population PK analysis may be conducted if the descriptive analysis suggests meaningful differences in the PK of adolescents compared to adults.

No pharmacodynamics analyses are planned.
PK analyses will be performed in the treated patients. Further information regarding the statistical analysis will be documented in the TSAP.

7.4 INTERIM ANALYSES

No interim analysis is planned, but the conduct of the trial will be monitored by a DMC.

7.5 HANDLING OF MISSING DATA

The handling of missing data in the primary and secondary analyses is described in Section 7.3.1 and Section 7.3.2 respectively.

Details regarding the imputation rule for further endpoints will be specified in the TSAP.

Missing or incomplete AE data will be imputed according to BI standards. Other missing safety data will not be imputed.

7.6 RANDOMISATION

At visit 2, patients will be randomised in blocks to double-blind treatment. Approximately equal numbers of patients will be randomised to each treatment group. The randomisation will be stratified by age (<15 years; ≥15 to <18 years). It will be monitored and capped so that at least 30% but no more than 70% of the randomised patients are < 15 years. For DINAMO™ only, the randomisation system will also include caps for gender so that at least 30% but no more than 70% of the randomised patients are girls.

At visit 4B, patients from the empagliflozin 10 mg arm who do not achieve an HbA1c < 7.0% at Week 12 will be re-randomised in blocks to double-blind treatment with either empagliflozin 10 mg or empagliflozin 25 mg. This re-randomisation will be stratified by age at baseline (< 15 years; ≥ 15 to <18 years). Practically, an IRT call will be performed for all patients to maintain double-blind conditions but only patients on empagliflozin 10 mg with HbA1c ≥ 7.0% at Week 12 may get new trial treatment re-assigned.

At visit 5, patients from the placebo arm will be re-randomised in blocks to double-blind treatment. Approximately equal numbers of patients will be re-randomised to empagliflozin 10 mg, empagliflozin 25 mg, or linagliptin 5 mg. The re-randomisation will be stratified by age at baseline (<15 years; ≥15 to <18 years). Practically, an IRT call will be performed for all patients to maintain double-blind conditions but only patients on placebo may get new trial treatment re-assigned.

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 so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report (CTR). Access to the codes will be controlled and documented. The method of assigning patients to treatment groups is described in Section 4.1.3.

7.7 DETERMINATION OF SAMPLE SIZE

7.7.1 DINAMO

To support the sample size determination various sample size scenarios were considered. The underlying assumptions and the power estimates for the final sample size are described in details in this section for the "wash out" effectiveness analysis. These estimates are based on available study data in adults with T2DM treated with placebo, linagliptin or empagliflozin.

Sample size calculation for the "wash out" effectiveness analyses

Based on the "wash out" analysis, the superiority of pooled empagliflozin doses (empagliflozin 10 mg, empagliflozin 25 mg) and the superiority of linagliptin 5 mg compared to placebo will be tested simultaneously using the Hochberg procedure at the study-wise alpha level of 0.05 (see section 7.2.1).

For the corresponding power considerations post-rescue data will be included, and it will be assumed that there is no treatment difference for off-treatment patients. Average treatment effects including HbA1c values after the start of rescue therapy can be obtained from the studies quoted below and are summarised in Table 7.7.1: 1. The corrected treatment difference in this table was calculated assuming patients discontinuing active treatment show the same HbA1c change from baseline as the average placebo patient.

In Table 7.7.1: 1 HbA1c results are summarised as a basis for the efficacy analysis. Where available data for Week 24 are quoted, otherwise for Week 18:

- Study 1218.17, patients treated with linagliptin 5 mg or placebo in combination with metformin background therapy [U09-2533-03]
- Study 1218.36, patients treated with linagliptin 5 mg or placebo in combination with basal insulin therapy [c02697848 ; U11-2286-01]
- Study 1245.23, patients treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo in combination with metformin background therapy only [U12-1518-01]

- Study 1245.33, patients treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo in combination with basal insulin therapy [U12-3817]
- Study 1245.49, patients treated with empagliflozin 10 mg, empagliflozin 25 mg, or placebo in combination with insulin or metformin background therapy [U13-2122]

Studies 1218.17, 1218.36 and 1245.23 assessed the change from baseline to Week 24 as primary endpoint, in studies 1245.33 and 1245.49 the primary endpoint was change from baseline to Week 18. For all calculations raw means and standard deviations for the primary endpoint were considered as initial basis for further calculations.

Table 7.7.1: 1 HbA1c (%) change from baseline to Week 18 or 24 for studies with T2DM patients treated with linagliptin or empagliflozin

	Placebo			Active treatment				Corrected treatment difference[4]
Study number	N	Mean[1]	SD[2]	N	Mean[1]	SD[2]	N disc.[3]	Mean Active - Placebo
1218.17 - Week 24 linagliptin 5 mg	156	-0.07	1.03	471	-0.66	0.85	39	-0.54
1218.36 - Week 24 linagliptin 5 mg	560	0.01	0.93	568	-0.66	0.89	36	-0.63
1245.23 – Week 24 empagliflozin 10 mg	183	-0.26	0.79	206	-0.76	0.76	8	-0.48
1245.33 – Week 18 empagliflozin 10 mg	145	0.06	0.89	152	-0.69	0.88	16	-0.68
1245.49 – Week 18 empagliflozin 10 mg	173	-0.59	0.85	170	-1.04	0.79	17[a]	-0.41

[1] Mean change from baseline in HbA1c at Week 18 or 24 based on the observed means in the raw data (including post rescue medication data)

[2] Observed standard deviation in the raw data up to Week 18 or 24 (including post rescue medication data)

[3] Number of patients prematurely discontinuing active treatment prior to endpoint visit according to report disposition table

[4] Assuming placebo response for patients prematurely discontinuing active treatment

[a] Number of patients excluded from full analysis completers set, estimate of treatment discontinuations up to Week 18

Based on these results a mean treatment difference in HbA1c change from baseline of -0.55% with a SD of 0.9% between active drugs and placebo can be assumed. For the effectiveness analysis a covariate adjusted standard deviation of 0.9% can be regarded as the expected scenario, while 0.8% will probably be optimistic. A conservative scenario of 1.0% is added because of the potential of increased variability through the multiple imputations performed for the “wash out”. Power estimates in Table 7.7.1: 2 are based on a two-sided t-test at alpha-level of 0.05. Additionally the power is given for the alpha-level of 0.025 to provide a lower bound of the expected power due to the Hochberg correction for multiplicity.

Table 7.7.1: 2 Power estimates for various scenarios for the "wash out" effectiveness analysis

Alpha (2-sided)	Treatment effect (%)	Covariate-adjusted standard deviation (%)	Sample size per group	Power
0.05	-0.55	1.00	50	77%
0.05	**-0.55**	**0.90**	**50**	**85%**
0.05	-0.55	0.80	50	92%
0.025	-0.55	1.00	50	68%
0.025	**-0.55**	**0.90**	**50**	**78%**
0.025	-0.55	0.80	50	87%

Summary

The final sample size of 50 randomised patients per group was chosen as a balance of clinical, regulatory, ethical, feasibility and statistical considerations. The objective is to minimise exposure of children, given that the available paediatric population is also limited in number, while maintaining acceptable statistical properties.

Calculations were performed using nQuery Advisor® 7.0 statistical package by [redacted]

7.7.2 DINAMO Mono

Data from the empagliflozin Phase III study 1245.20 in adult patients with Type 2 Diabetes were analysed to derive estimates for the treatment failure rate based on the definition in DINAMO™ Mono. Restricted to a study population with a baseline HbA1c from 6.5% to 9.0% the treatment failure rates as in Table 7.7.2:1 were determined.

Table 7.7.2: 1 Treatment failure rate in 1245.20 based on endpoint definition for DINAMO Mono

	Frequency of treatment failure			
	Placebo N (%)	Empagliflozin 10 mg N (%)	Empagliflozin 25 mg N (%)	Sitagliptin N (%)
Analysed patients	207 (100)	195 (100)	201 (100)	203 (100)
Treatment failure	138 (67)	56 (29)	43 (21)	40 (20)

A treatment failure rate between 65% and 85% is expected in the placebo group in DINAMO™ Mono. The initial minimum sample size of 12 patients per group was chosen so that the upper limit of the 90% confidence interval for the risk difference would not include 0 for an approximate risk difference of 40% (see Table 7.7.2: 2).

Table 7.7.2: 2 Exact 90% confidence interval for risk difference scenarios in DINAMO Mono

	Frequency of treatment failure			
N per group	Placebo N (%)	Active treatment N (%)	Risk difference %	Exact 90% CI
6	5 (83.3)	1 (16.7)	-66.7	(-93.9, -12.4)
	5 (83.3)	2 (33.3)	-50.0	(-85.6, 5.5)
8	6 (75.0)	2 (25.0)	-50.0	(-82.0, -3.1)
	6 (75.0)	3 (37.5)	-37.5	(-73.6, 9.7)
10	8 (80.0)	3 (30.0)	-50.0	(-79.2, -8.7)
	8 (80.0)	4 (40.0)	-40.0	(-70.8, -0.5)
	7 (70.0)	3 (30.0)	-40.0	(-72.1, 1.6)
12	**10 (83.3)**	**5 (41.7)**	**-41.7**	**(-69.4, -6.9)**
	9 (75.0)	**4 (33.3)**	**-41.7**	**(-70.9, -4.2)**
	9 (75.0)	5 (41.7)	-33.3	(-63.2, 2.3)
	8 (66.7)	**3 (25.0)**	**-41.7**	**(-70.9, -4.2)**

New patient recruitment for DINAMO™ Mono was prematurely discontinued due only to patient recruitment difficulties. The initially planned recruitment period up to April 2022 was preserved, resulting in a sample size of approximately 20 patients in DINAMO™ Mono.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

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 Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in 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 subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH 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 finalization 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 (Investigator Site File).

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 Institutional Review Board (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 one or both parents of the patient (or the patient's legally accepted representative) according to ICH GCP and to the local regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient/parent(s)-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional parent(s) information must be given to each parent or the patient's legally accepted representative.

In addition to this document, the patient will be provided with an information sheet adapted to his/her age group (two groups: from 10 to 14 years; from 15 to 17 years included). The version prepared for the younger patient should be used for the older patient if judged more appropriate by the investigator) where his/her assent will be collected according to the regulatory and legal requirements of the participating country. Except if the patient is unable to do it, he/she will have to sign or write his/her name on this document and to date it in the day she/he assents to participate.

It is important that the investigator ensure at each visit that the patient still assents to participate in the study. In addition, the refusal of the patient to participate must be accepted independently of the consent of his/her parent(s)/legal guardian.

The patient and his/her parent(s)/legal guardian must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient and his/her parent(s)/legal guardian.

The patient and his/her parent(s)/legal guardian must be informed that the patient's medical records may be examined by authorized monitors (CTM/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. Re-consent can be done remotely/by telephone/telemedicine/in-home visit under exceptional circumstances due to the COVID-19 pandemic. The initial informed consent and assent at Visit 1A must be done in the clinic.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

Case Report Forms (CRF) 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 good documentation practices 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 three documented attempts 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 patients' 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 to ensure patient confidentiality.

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, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient and parent(s)/legal guardian 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.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of on-site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF 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). The CRA and auditor may review all eCRFs 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 ICH GCP.

Remote source data verification in exceptional cases at the time of restricted on-site monitoring visits due to a COVID-19 pandemic, when such decision has been taken centrally

for a trial, must first be discussed with the sponsor before implementation to ensure alignment with local regulations.

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 the national or local requirements (whatever is longer) valid at the time of the end of the trial.

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 regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook. 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 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

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").
The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD 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.

The IEC / competent authority in each participating country will be notified about the trial milestones according to the respective laws.

Two separate clinical trial reports will be written for DINAMO™ and DINAMO™ Mono.

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U12-3817	A phase IIb, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 10773 (10 mg and 25 mg) administered orally, once daily over 78 weeks in type 2 diabetic patients receiving treatment with basal insulin (glargine, detemir, or NPH insulin only) with or without concomitant metformin and/or sulfonylurea therapy and insufficient glycaemic control. 1245.33. 11 January 2013
U13-2122	A phase III, randomized, double-blind, placebo-controlled, parallel group safety and efficacy study of BI 10773 (10 mg and 25 mg administered orally once daily) during 52 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control on MDI insulin regimen alone or with metformin. 1245.49. 20 September 2013

10. APPENDICES

10.1 TANNER STAGING MODIFIED

The evaluation of the Tanner stage will be performed during the physical examination at the time points defined in the Flow Chart to assess the patient's pubertal stage.

To determine the Tanner stage, the investigator should perform a brief check of external primary and secondary sex characteristics during the physical examination. The investigator will then score against the scale after the child has left the examination room. The most advanced pubertal stage will be documented.

Age appropriate explanations will be given, with emphasis that their privacy will be respected at all times. They will be reassured that their research records will be anonymised and only authorized trusted persons will monitor their notes to ensure the research is being conducted properly.

Here is a representation of the Tanner staging scale for both female and male children.

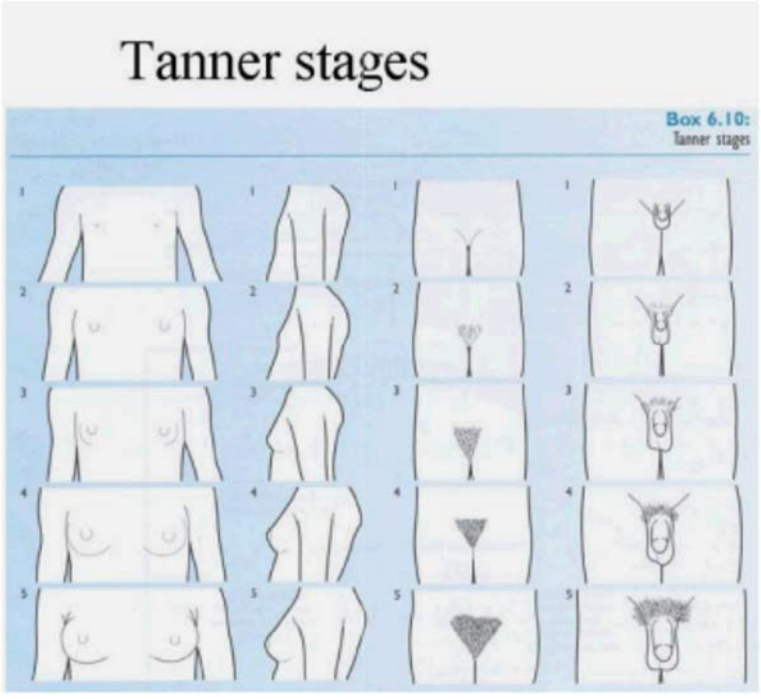

Figure 10.1: 1 Tanner Stages

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		03 Oct 2019
EudraCT number		2016-000669-21
BI Trial number		1218-0091
BI Investigational Product(s)		Linagliptin (BI 1356) Empagliflozin (BI 10773)
Title of protocol		A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		**Title Page**
Description of change		New TCM assignment, updated version and date
Section to be changed		**Synopsis**
Description of change		No. of patients: Number of patients increased in DINAMO. Addition of the number of patients to be included in DINAMO™ Mono.
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA.
Section to be changed		**Synopsis**
Description of change		Trial rationale added

Rationale for change		Consistency with current sponsor CTP template
Section to be changed		**Synopsis**
Description of change		"Treated with metformin and/or insulin" text bolded DINAMO™ Mono objective added
Rationale for change		To clarify the difference between the two studies To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA.
Section to be changed		**Synopsis**
Description of change		Main inclusion criteria: 1. Different patient population (HbA1c ranges and treatment) defined for the inclusion of patients in DINAMO™ and DINAMO™ Mono 2. Additional of DINAMO™ Mono patients 3. Clarification of the criterion related to acute metabolic decompensation 4. Clarification of the criterion related to auto-antibodies
Rationale for change		1. To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA 2. To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA 3. To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA 4. Patients should be negative for both IA-2 and GADA auto-antibodies to be eligible for this trial.
Section to be changed		**Synopsis**
Description of change		Endpoints: Different primary and secondary endpoints defined for DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**Synopsis**
Description of change		Statistical methods: 1. The primary endpoint will be analysed using a Pattern Mixture Model (PMM) only; the efficacy Mixed Model for

		Repeated Measurements (MMRM) will no longer be used. 2. Description of the statistical methods that will be used for DINAMO™ Mono
Rationale for change		1. To reflect the last PIP modification request agreed with EMA/PDCO. 2. To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**Flowchart**
Description of change		Visit window added for V1A and Foot note 1 for out of window allowances at Visits 1A and 1B
Rationale for change		To enable the availability of auto-antibodies results before the Visit 2 in case Visit 1B is performed on the same day as Visit 1A. The turn-around-time is 13 working days for the IA-2 auto-antibodies assay
Section to be changed		**Flowchart**
Description of change		Height to be performed at V1A instead of V1B
Rationale for change		Height is required for eGFR calculation at V1A
Section to be changed		**Flowchart**
Description of change		Administer double-blind trial drugs added at Visit 8
Rationale for change		To ensure consistency in the protocol. Last study drug intake will occur at Visit 8 while the patient is at the clinic.
Section to be changed		**Flowchart**
Description of change		Self-blood glucose and ketone monitoring added at V4B
Rationale for change		To reflect the regular measurements to be performed during the entire treatment period
Section to be changed		**Flowchart**
Description of change		Foot note 4 revised to include additional interactions between the site and the patient (every 4 weeks between each clinic visits)
Rationale for change		To reflect the last PIP modification request agreed with EMA/PDCO
Section to be changed		**Flowchart**
Description of change		Foot note 5: concomitant medication to be collected at subsequent visits in case of premature treatment discontinuation.
Rationale for change		To be consistent with Section 6.2.3.
Section to be changed		**Flowchart**
Description of change		Foot note 7: Clarification on the reduced panel for the screening visit only.

Rationale for change		Upon request of Medicine and Healthcare products Regulatory Agency (MHRA) in UK
Section to be changed		**Flowchart**
Description of change		Footnote 11: Revision of the frequency for blood ketone bodies measurement
Rationale for change		To reflect the last PIP modification request agreed with EMA/PDCO
Section to be changed		**Flowchart**
Description of change		Footnote 13 added
Rationale for change		To clarify the visits to be performed in case of early EOT for patients not accepting to attend subsequent planned visits.
Section to be changed		**Abbreviations**
Description of change		Some abbreviations removed/added
Rationale for change		To reflect the changes in the protocol amendment
Section to be changed		**1.2.1 Drug profile -Empagliflozin**
Description of change		Update on safety information
Rationale for change		To be aligned with the Investigator Brochure version 18
Section to be changed		**2.1 Rationale for performing the trial**
Description of change		Addition of the rationale for conducting DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**2.2 Trial objectives**
Description of change		Addition of DINAMO™ Mono objectives.
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**2.3 Benefit-risk assessment**
Description of change		Details on background therapies and HbA1c ranges removed, references to the appropriate sections are included, and updated important safety information
Rationale for change		To cover the specificities of DINAMO™ Mono and alignment with the Investigator Brochure version 18
Section to be changed		**3.1 Overall trial design and plan**
Description of change		Addition of DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**Figure 3.1:2**

Description of change		To outline the trial duration, primary endpoint, and treatment groups defined for both DINAMO™ and DINAMO™ Mono using two pictorials instead of one
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**3.1 Overall trial design and plan**
Description of change		Increased number of patients randomized in DINAMO™ and number of patients to be randomized in DINAMO™ Mono, clarity on randomization for DINAMO™
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**3.1.1 Administrative structure of the trial**
Description of change		Sponsor template language updated to reference Clinergize portal repository for study documents
Rationale for change		Consistent text with sponsor CTP template
Section to be changed		**3.1.1.1 CEC – cardiovascular events**
Description of change		Removal of hospitalisation for unstable angina from the adjudication process.
Rationale for change		Unstable angina is not a specific safety concern for any of the IMPs and no efficacy endpoint (or part of an endpoint); alignment with other BI trials.
Section to be changed		**3.1.1.3 CEC- Pancreatic events**
Description of change		Section removed.
Rationale for change		Based on linagliptin data in adult T2DM (including large outcome trials) very low rates of pancreatitis anticipated; formal adjudication of isolated cases in the paediatric population to be replaced by case-by-case expert consultation for potential pancreatitis events.
Section to be changed		**3.2 Discussion of trial design, including the choice of control group(s)**
Description of change		Addition of the rationale for the DINAMO™ Mono primary endpoint.
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**3.3 Selection of trial population**
Description of change		Revision of the number of trial site, increased number of patients randomized in DINAMO, and addition of the number of patients to be included

		in DINAMO™ Mono, and estimated patients randomized per site. Protocol violations replaced by protocol deviations. Patients with HbA1c < 6.5% can discontinue metformin and undergo HbA1c retesting after 12 weeks for possible eligibility into DINAMO™ Mono.
Rationale for change		To reflect the actual trial status and the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA To align with BI SOPs and CTP template text. Eligibility for DINAMO™ Mono patients regarding metformin use.
Section to be changed		**3.3.2 Inclusion criteria**
Description of change		1. Revision of inclusion criteria #6 and #7 2. Addition of inclusion criterion #10
Rationale for change		1. To reflect the actual trial status and the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA 2. Patients should be negative for both IA-2 and GADA auto-antibodies to be eligible for this trial.
Section to be changed		**3.3.3 Exclusion criteria**
Description of change		Removal of exclusion criterion #1
Rationale for change		Patients should be negative for both IA-2 and GADA auto-antibodies to be eligible for this trial. Added in the inclusion criteria section.
Section to be changed		**3.3.3 Exclusion criteria**
Description of change		Revision of exclusion criterion #2
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**3.3.4.1 Withdrawal from trial treatment**
Description of change		Addition of criteria (pancreatitis, bullous pemphigoid, arthralgia, Fournier's gangrene, or ketoacidosis) for stopping trial treatment intake
Rationale for change		To reflect the Investigator Brochure guidance
Section to be changed		**4.1.1 Identity of the Investigational Medicinal Products**
Description of change		The words Linagliptin and Empagliflozin capitolized
Rationale for change		Administrative update
Section to be changed		**4.1.3 Method of assigning patients to treatment groups**

Description of change		Correction of visit number at week 26
Rationale for change		To be consistent with the Flowchart
Section to be changed		**4.2.1 Other treatments and emergency procedures**
Description of change		Clarify MDI insulin Revision of the criteria for initiating rescue medication for DINAMO™ (addition of regular interactions between the patient and the site between clinic visits) and addition of specific criteria for initiating rescue medication for DINAMO™ Mono.
Rationale for change		Administrative update To reflect the last PIP modification request agreed with EMA/PDCO and the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**4.2.2.2 Restrictions on diet and life style**
Description of change		New guidance on diet and exercise recommendations to be provided by the site to the patient.
Rationale for change		To reflect the last PIP modification request agreed with EMA/PDCO
Section to be changed		**5.1.1 Primary endpoints**
Description of change		Different primary endpoint for DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**5.1.2 Secondary endpoints**
Description of change		Additional secondary endpoints for DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		

Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		**5.2.3 Systolic/diastolic blood pressure and heart rate**
Description of change		Clarify heart rate will be measured and not just pulse rate
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**5.3.3 Safety laboratory parameters**
Description of change		Clarification of the Table 5.3.3:1 Footnote 1, reduced panel for screening visit only.
Rationale for change		Upon request of Medecine and Healthcare products Regulatory Agency (MHRA) in UK
Section to be changed		**5.3.5.2 Self-blood glucose monitoring**
Description of change		Revision of the minimum requirements (frequency of measurement).
Rationale for change		To reflect the last PIP modification request agreed with EMA/PDCO
Section to be changed		**5.3.5.3 Self-blood ketone monitoring**
Description of change		Revision of the measurement frequency.
Rationale for change		To reflect the last PIP modification request agreed with EMA/PDCO
Section to be changed		**5.3.5.6 Criteria for hypoglycaemic event**
Description of change		Plasma glucose equal to or below 70 mg/dL shall be documented in the eCRF, this guidance is consistent with ADA guidelines
Rationale for change		A value of 70 mg/dL was excluded from reporting erroneously.
Section to be changed		**5.3.6.1 Definitions of AEs**
Description of change		AESI Removal of the section related to the "list of additional search categories for safety topics of interest" available in the ISF/eDC
Rationale for change		To reflect the actual process, list not available in the ISF/eDC
Section to be changed		**5.3.6.1 Definitions of AEs**
Description of change		Addition of bullous pemphigoid, arthralgia and monitoring of safety assessments during the trial.
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA

Section to be changed		**5.3.6.2 Adverse event collection and reporting**
Description of change		**AE collection** Clarification of AE collection for patients who discontinue trial medication prematurely.
Rationale for change		To correct protocol inconsistency.
Section to be changed		**5.3.6.2 Adverse event collection and reporting**
Description of change		**Pregnancy** Removal of the following sentence: Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner
Rationale for change		No risk identified in the Investigator Brochures in case of pregnancy in a partner of a male trial participant, to reflect BI CTP template and Guidance on contraception in clinical trials.
Section to be changed		**5.4.2.1 Plasma sampling for pharmacokinetic analysis**
Description of change		Revision of the volume of blood to be drawn.
Rationale for change		To be consistent with the lab manual
Section to be changed		**6.2.2 Treatment period(s)**
Description of change		Addition of regular interactions with the patient between clinic visits.
Rationale for change		To reflect the last PIP modification request agreed with EMA/PDCO
Section to be changed		**7.1 Statistical design - Model**
Description of change		Removed the efficacy MMRM confirmatory primary analysis for the primary family of hypotheses. Renamed the primary PMM analysis to PMM "jump-to-placebo" analysis. Added new Section 7.1.1 for the existing primary endpoint for DINAMO™ Added new Section 7.1.2 for different primary endpoint for DINAMO™ Mono
Rationale for change		The EMA has requested the same confirmatory primary analysis as the FDA, Therefore the MMRM is no longer required. To clarify the approach used for PMM. To reflect the linagliptin and empagliflozin PPSR agreed with FDA
Section to be changed		**7.2.1 Primary family of hypotheses**
Description of change		Renamed section 7.2.1 Added section 7.2.1.1 for primary family of hypotheses (include the content of the legacy section 7.2.1) and section 7.2.1.2 for secondary

		family of hypotheses (include the content of the legacy section 7.2.2)
Rationale for change		To reflect the linagliptin and empagliflozin PPSR agreed with FDA
Section to be changed		**(New) 7.2.1.1 Primary family of hypotheses**
Description of change		Added "The Hochberg-procedure will account for multiple testing within the primary family of hypotheses."
Rationale for change		To clarify how to address the multiplicity.
Section to be changed		**(New) 7.2.1.2 Secondary family of hypotheses**
Description of change		Renamed the primary PMM analysis to PMM "jump-to-placebo" analysis. Rephrased the treatment groups' description for the hypotheses.
Rationale for change		To clarify the approach used for PMM. To remove the ambiguity of the treatment group description.
Section to be changed		**7.2.2 Secondary family of hypotheses**
Description of change		Renamed section 7.2.2 to DINAMO™ Mono and described the DINAMO™ Mono primary hypothesis.
Rationale for change		To clarify the required hypothesis.
Section to be changed		**7.3 Planned analyses**
Description of change		Section re-organised to consolidated information into the corresponding sections Provided analysis sets definition and new baseline definition.
Rationale for change		Simplified the section to allow clear information for the main and ancillary study.
Section to be changed		**7.3.1.1 Analysis of the primary family of hypothesis for the primary endpoint**
Description of change		Renamed section 7.3.1.1 to DINAMO™ Added section 7.3.1.1.1 Analysis of the primary family of hypothesis (include the content of the legacy section 7.3.1.1) and section 7.3.1.1.2 Analysis of the secondary family of hypothesis (include the content of the legacy section 7.3.1.2)
Rationale for change		To reflect the linagliptin and empagliflozin PPSR agreed with FDA
Section to be changed		**(New) 7.3.1.1.1 Analysis of the primary family of hypotheses**
Description of change		Removed the efficacy MMRM confirmatory primary analysis for the primary family of hypotheses.

		Clarified the PMM "jump-to-placebo" approach by adding Table 7.3.1.1.1: 1 and other wording update.
Rationale for change		To reflect the FDA suggestion To be consistent with Section 7.1
Section to be changed		**(New) 7.3.1.1.2 Analysis of the secondary family of hypotheses**
Description of change		Re-organised section for the ease of understanding. Added new description for the new PMM "inverse probability weighting" approach. Removed the previous MMRM model description to sensitivity analyses.
Rationale for change		To reflect the FDA suggestion
Section to be changed		**7.3.1.2 Analysis of the secondary family of hypotheses for the primary endpoint**
Description of change		Renamed section 7.3.1.2 to DINAMO™ Mono and described the DINAMO™ Mono primary analysis
Rationale for change		To reflect the linagliptin and empagliflozin PPSR agreed with FDA. To be consistent with Section 7.3
Section to be changed		**7.3.1.3 Secondary analyses of the primary endpoint**
Description of change		Section removed. Content added into new section 7.3.4 Sensitivity analysis
Rationale for change		To tidy the section for the ease of understanding.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		**(New) 7.3.2.1 DINAMO™**
Description of change		Swapped the order of the 2 different analysis approaches. Updated 24 weeks to 26 weeks in the FPG model. Moved the paragraph of how to the handle missing data from Section 7.5. Added new secondary endpoints: proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 week.

		Clarify baseline of the response variable
Rationale for change		To be consistent with the primary analysis to analyse the data with off-treatment first. To correct the typo. To line up with the primary analysis which described how to handle the missing data within the section. New endpoints added according to FDA written requests. Clarify what baseline variable is used in the model.
Section to be changed		**(New) 7.3.2.2 DINAMO™ Mono**
Description of change		Described the DINAMO™ Mono secondary analyses Added new secondary endpoints: proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 week. Clarify the reference method is a sensitivity method
Rationale for change		To reflect the linagliptin and empagliflozin PPSR agreed with FDA New endpoints added according to FDA written requests. Clarify what method is used
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		

Description of change		[redacted]
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		**7.3.6 Safety analysis**
Description of change		Section number changed to 7.3.6 from 7.3.4. Added 4 different approaches to present the safely data.
Rationale for change		To clarify how to perform the safety analyses.
Section to be changed		**7.5 Handling of missing data**
Description of change		Moved the FPG missing data handling description to Section 7.3.2. Added reference to Section 7.3.1 and Section 7.3.2 for the primary and secondary endpoints missing data handling.
Rationale for change		To make the content of the protocol easier to follow.
Section to be changed		**7.6 Randomisation**
Description of change		Clarified the gender cap at visit 2 is for DINAMO™ only
Rationale for change		To indicate where the rule should applied
Section to be changed		**7.7 Determination of sample size**
Description of change		Added section 7.7.1 for DINAMO™ (include the original section 7.7 content) and section 7.7.2 for DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin PPSR agreed with FDA

Section to be changed		**(New) 7.7.1 for DINAMO™**
Description of change		Removed sample size calculation for the primary MMRM efficacy analyses. Re-numbered Table 7.7: 3 to Table 7.7.1: 1, and Table 7.7: 4 to Table 7.7.1: 2. Updated Table 7.7.1:2 with 50 patients and new power.
Rationale for change		Primary MMRM efficacy analysis is no longer required by the EMA. Re-organised the table numbers within the section. To agreed FDA written requests to increase the number of patients to 50.
Section to be changed		**(New) 7.7.2 for DINAMO™ Mono**
Description of change		Described the determination of sample size for DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin PPSR agreed with FDA
Section to be changed		**8.6 Trial Milestones**
Description of change		Separate Clinical Trial Reports for DINAMO™ and DINAMO™ Mono.
Rationale for change		To write the DINAMO™ Clinical Trial Report as soon as the last patient last visit milestones is reached for DINAMO™.
Section to be changed		**9.1 Published references**
Description of change		Additional references
Rationale for change		Related to DINAMO™ Mono.

11.2 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		28 Sep 2020
EudraCT number		2016-000669-21
BI Trial number		1218-0091
BI Investigational Product(s)		Linagliptin (BI 1356) Empagliflozin (BI 10773)
Title of protocol		A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus

To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		**Title Page**
Description of change		Updated document number, version, and date
Section to be changed		**Synopsis**
Description of change		1. Updated status and revision date 2. Main inclusion criterion was updated to reduce T2DM diagnosis to 8 weeks; added minimum daily metformin dosage; and for DINAMO Mono: replaced washout of metformin with discontinuation of metformin 3. Updated the primary endpoint analysis from "Pattern Mixed Model (PMM) "Jump-to-placebo" approach" to ""wash-out" approach"
Rationale for change		1. Updated status and revision date 2. Allow patients to screen for the trial at an earlier timeframe; reflect the last PIP modification request agreed with EMA/PDCO; and for better understanding of stopping metformin 3. Based on FDA request
Section to be changed		**Flowchart**
Description of change		1. Footnote 4 updated to allow for remote visits due to exceptional circumstances 2. Footnote 5 updated to clarify actions if a patient terminates treatment prematurely 3. Footnote 13 updated to clarify actions if a patient terminates treatment prematurely 4. Footnote 14 added to allow for vital signs, weight, and local laboratory testing due to exceptional circumstances

		5. Footnote15 added to allow for study procedures to be conducted remotely due to exceptional circumstances 6. Footnote16 added to allow for shipment of study medication to a patient's home due to exceptional circumstances
Rationale for change		1. COVID-19 pandemic alternative process 2. Clarify procedures if a patient discontinues study medication prematurely 3. Clarify procedures if a patient discontinues study medication prematurely 4. COVID-19 pandemic alternative process 5. COVID-19 pandemic alternative process 6. COVID-19 pandemic alternative process
Section to be changed		**Table of Contents**
Description to be changed		7.3.4 – 7.3.7 updated/corrected and 11.1 and 11.2 added
Rationale for change		Correction to section names and addition of new sections
Section to be changed		**Abbreviations**
Description of change		COVID-19, EoT, and SARS added and PMM removed. The abbreviation for "MI" added to MCMC and SLR defintions.
Rationale for change		To reflect the changes in the protocol amendment or prior content not defined
Section to be changed		**1.1 Medical Background**
Description of change		Clarify compounds are now approved as monotherapy for adjunct to diet and exercise
Rationale for change		Updated drug profile
Section to be changed		**1.2.1 Empagliflozin**
Description of change		Updated number of approved countries
Rationale for change		Number of countries that have approved compound use has increased
Section to be changed		**2.1 Rationale for Performing the Trial**
Section to be changed		Clarify results from two dose-finding studies involved both compounds
Rationale for change		Administrative clarification
Section to be changed		**2.3 Benefit-Risk Assessment**
Description of change		1. Administrative corrections/updates and added guidance to consider discontinuation of empagliflozin in cases that predispose ketoacidosis 2. Added section titled COVID-19 Pandemic
Rationale for change		1. Additional ketoacidosis monitoring 2. Due to the pandemic, an assessment was performed and risk management measures added

Section to be changed		**3.1 Overall Trial Design and Plan**
Description of change		Added reference to early treatment discontinuation guidance
Rationale for change		Provide location for source of additional guidance
Section to be changed		**3.1.1.1 Clinical Event Committee – cardiovascular events**
Description of change		Removal of reference to meta-analysis
Rationale for change		Administrative update
Section to be changed		**3.3 Selection of Trial Population**
Description of change		Replaced washout of metformin with discontinuation of metformin
Rationale for change		Allow for better understanding of stopping metformin
Section to be changed		**3.3.2 Inclusion criteria**
Description of change		1. Inclusion criteria 5 was updated to reduce T2DM diagnosis to 8 weeks 2. Inclusion criteria 7A added minimum daily metformin dosage and moved metformin intolerance text to appropriate location 3. Inclusion criteria 7B replaced washout of metformin with discontinuation of metformin 4. Inclusion criteria 11 was changed to inclusion criteria 10
Rationale for change		1. Allow patients to screen for the trial at an earlier timeframe 2. To reflect the last PIP modification request agreed with EMA/PDCO and an administrative update 3. Allow for better understanding of stopping metformin4. To align with the numbering in the eCRFs from CTP2 to avoid a mismatch
Section to be changed		**3.3.4.1 Withdrawal from trial treatment**
Description of change		Added ability to replace patients in exceptional cases due to COVID-19 pandemic
Rationale for change		Trial has a small sample size and this change gives more flexibility to collect sufficient data, if needed
Section to be changed		**4.2.1 Other treatments and emergency procedures**
Description of change		Administrative clarifications
Rationale for change		Administrative clarifications
Section to be changed		**5.2.1 HbA1c and fasting plasma glucose (FPG)**
Description of change		Testing may also be done at a local laboratory
Rationale for change		COVID-19 pandemic alternative process
Section to be changed		**5.2.2 Body weight**
Description of change		Testing may also be done at a local laboratory

Rationale for change		COVID-19 pandemic alternative process
Section to be changed		**5.2.3 Systolic/diastolic blood pressure and heart rate (vital signs)**
Description of change		Testing may also be done at a local laboratory
Rational for change		COVID-19 pandemic alternative process
Section to be changed		**5.3.3 Safety laboratory parameters**
Description of change		Testing may also be done at a local laboratory
Rationale for change		COVID-19 pandemic alternative process
Section to be changed		**5.3.6.2 Adverse event collection and reporting**
Description of change		Removed reference to fax and added in country specific reporting process clarification
Rationale for change		Alternative methods of SAE report transmission are allowed for some countries
Section to be changed		**6. Investigational Plan**
Decription of change		Updated to allow for remote visits due to exceptional circumstances
Rationale for change		COVID-19 pandemic alternative process
Section to be changed		**6.2.3 Follow Up Period and Trial Completion**
Description of change		1. Clarification of which patient group completes FUP visit and what eCRF to complete 2. Clarification of what constitutes the end of trial and timing of EOT visit
Rationale for change		1. Administrative clarifications 2. Administrative clarifications
Section to be changed		**7.1.1 DINAMO™**
Description of change		Updated the primary endpoint analysis from "Pattern Mixed Model (PMM) "Jump-to-placebo" approach" to ""washout" approach"
Rationale for change		Based on FDA request
Section to be changed		**7.2.1.1 Primary family of hypotheses**
Description of change		Added significance level
Rationale for change		To provide more information about the hypotheses
Section to be changed		**7.2.1.2 Secondary family of hypotheses**
Description of change		Added significance level
Rationale for change		To provide more information about the hypotheses
Section to be changed		**7.3 PLANNED ANALYSES**
Description of change		Addressed all analyses are using randomised treatments. Wrong medication will be listed.
Rationale for change		To clarify how to handle wrong medication.
Section to be changed		**7.3.1.1.1 Analysis of the primary family of hypotheses**
Description of change		Updated the primary endpoint analysis from "PMM "Jump-to-placebo" approach" to ""wash-

		out" approach" and description of the new method
Rationale for change		Based on FDA request
Section to be changed		**7.3.1.1.2 Analysis of the secondary family of hypotheses**
Description of change		Updated the primary endpoint analysis from "PMM "Jump-to-placebo" approach" to ""wash-out" approach"
Rationale for change		Based on FDA request
Section to be changed		**7.3.2.1 DINAMO™**
Description of change		Removed the analysis of the proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 weeks from the secondary endpoint analysis first approach
Rationale for change		To be consistent with the TSAP
Section to be changed		**7.3.4.5 Primary family of hypotheses – COVID-19 related intercurrent events (New)**
Description of change		New additional sensitivity analysis for the primary endpoint, hypothetical for COVID-19
Rationale for change		COVID-19 pandemic response to analysis
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		**7.3.6 Safety analyses**
Description of change		Clarified randomised treatments are used in the safety analysis.
Rationale for change		To clarify randomised treatments are in used for the safety analyses.
Section to be changed		**7.3.7 Pharmacokinetic and pharmacodynamics analyses**
Description of change		Added population TS for the PK analysis and further information will be in the TSAP.
Rationale for change		To clarify which population to be used for PK anslysis and the location for further information.
Section to be changed		**7.7.1 DINAMO™**
Description of change		Updated the primary endpoint analysis from "PMM "Jump-to-placebo" approach" to ""wash-out" approach"
Rationale for change		Based on FDA request

Section to be changed		**8.3.2 Direct access to source data and documents**
Description of change		Added new paragraph: Remote source data verification in exceptional cases at the time of restricted on-site monitoring visits due to a COVID-19 pandemic, when such decision has been taken centrally for a trial, must first be discussed with the sponsor before implementing to ensure alignment with local regulations.
Rationale for change		COVID-19 pandemic mitigation
Section to be changed		**8.6 Trial Milestones**
Description of change		Removal of reference of final report submission to the EU database
Rationale for change		Administrative update
Section to be changed		**9.2 Unpublished References**
Description of change		New sources cited regarding risk-benefit and document numbers U09-2533 and U11-2286 corrected to U09-2533-03 and U11-2286-01
Rationale for change		New sources cited and administrative update
Section to be changed		**11.1 Global amendment 1 (new)**
Description of change		Sub section title added for amendment 1 and number of global amendment corrected
Rationale for change		Administrative update
Section to be changed		**11.2 Global amendment 2 (new)**
Description of change		Sub section title added for amendment 2
Rationale for change		Administrative update

11.3 GLOBAL AMENDMENT 3

Number of global amendment		3
Date of CTP revision		14 Dec 2020
EudraCT number		2016-000669-21
BI Trial number		1218-0091
BI Investigational Product(s)		Linagliptin (BI 1356) Empagliflozin (BI 10773)
Title of protocol		A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus

To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		**Title Page**
Description of change		Updated version and date
Section to be changed		**Flow Chart**
Description of change		Footnote * updated to allow for re-consent to be conducted remotely due to exceptional circumstances. Clarification that the initial informed consent and assent at visit 1A are done in the clinic as visit 1A cannot be done remotely due to exceptional circumstances.
Rationale for change		COVID-19 pandemic alternative process
Section to be changed		**Table of Contents**
Description of change		Add new section 11.3
Rationale for change		Addition of new section
Section to be changed		**Abbreviations**
Description of change		EMA, PDCO, PIP added
Rationale for change		Administrative update
Section to be changed		**1.1 Medical Background**
Description of change		Document number in reference to Empagliflozin and Linagliptin Investigator's Brochure updated
Rationale for change		Administrative update
Section to be changed		**1.2.1 Empagliflozin**
Description of change		Document number in reference to Empagliflozin Investigator's Brochure updated
Rationale for change		Administrative update
Section to be changed		**1.2.2 Linagliptin**
Description of change		Document number in reference to Linagliptin Investigator's Brochure updated
Rationale for change		Administrative update
Section to be changed		**3.3.1 Main diagnosis for trial entry**

Description of change		Amend time to diagnosis of T2DM from 12 weeks to 8 weeks to align with inclusion criteria 5 that was updated in CTP4
Rationale for change		Align the time to diagnosis of T2DM in all relevant sections of protocol. The reduction in time to diagnosis will allow patients to be considered for study participation sooner.
Section to be changed		**5.3.3 Safety laboratory parameters**
Description of change		1. In case of a positive urine pregnancy test, a serum pregnancy test can be done at a local laboratory due to exceptional circumstances 2. Update the document number for Empagliflozin Investigator's Brochure
Rationale for change		1. COVID-19 pandemic alternative process 2. Administrative update
Section to be changed		**6.2.2 Treatment period(s)**
Description of change		Additional text added to re-randomization visits 4B and 5 to confirm patients take trial drugs on the same day
Rational for change		Consistency with guidance provided at initial randomization
Section to be changed		**8.1 Trial Approval, Patient Information, Informed Consent**
Description of change		Additional text added to allow for re-consent to be conducted remotely due to exceptional circumstances. Clarification that the initial informed consent and assent at visit 1A are done in the clinic as visit 1A cannot be done remotely due to exceptional circumstances.
Rationale for change		COVID-19 pandemic alternative process
Section to be changed		**9.2 Unpublished References**
Description of change		Update the document number for Empagliflozin and Linagliptin Investigator's Brochure
Rationale for change		Administrative update
Section to be changed		**11.3 Global amendment 3 (new)**
Description of change		Sub section title added for amendment 3 summary of changes
Rationale for change		Administrative update

11.4 GLOBAL AMENDMENT 4 – SENT TO FDA ONLY

Number of global amendment		4
Date of CTP revision		14 Jul 2021
EudraCT number		2016-000669-21
BI Trial number		1218-0091

BI Investigational Product(s)		Linagliptin (BI 1356) Empagliflozin (BI 10773)
Title of protocol		A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		**Title Page**
Description of change		Updated version and date
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Revision date and main criteria for inclusion updated
Rationale for change		Patient recruitment support in DINAMO™ Mono; show both conventional and SI units for entry criteria
Section to be changed		**Table of Contents**
Description of change		Add new sections 7.3.4.6 and 11.4
Rationale for change		Addition of new sections
Section to be changed		**Abbreviations**
Description of change		CGM, CTM, and SI added
Rationale for change		Administrative update
Section to be changed		**1.1 Medical Background**
Description of change		Update the document number for Empagliflozin Investigator's Brochure
Rationale for change		Administrative change
Section to be changed		**1.2.1 Empagliflozin**
Description of change		Update the document number for Empagliflozin Investigator's Brochure

Rationale for change		Administrative change
Section to be changed		**2.1 Rationale for Performing Trial**
Description of change		Removal of metformin discontinuation for at least 12 weeks, adding insulin discontinuation in DINAMO™ Mono
Rationale for change		Representative of clinician actions if metformin is discontinued vs. waiting 12 weeks to start another antidiabetic therapy, clarification for actions if patients are on insulin
Section to be changed		**3.1.1 Administrative structure of the trial**
Description of change		Replaced Trial Clinical Monitor with Clinical Trial Leader, replaced Local Clinical Monitor with Clinical Trial Manager
Rationale for change		Administrative update
Section to be changed		**3.3 Selection of Trial Population**
Description of change		1. Changed time between rescreening visits from 12 to 8 weeks 2. Removal of investigator discretion to withdraw metformin and retest in 12 weeks 3. Removal of metformin discontinuation for at least 12 weeks, adding insulin discontinuation in DINAMO™ Mono
Rationale for change		1. Allows patients to rescreen sooner 2. Representative of clinician actions to mimic real world if metformin is discontinued vs. waiting 12 weeks to retest and start another antidiabetic therapy 3. Representative of clinician actions to mimic real world if metformin is discontinued vs. waiting 12 weeks to start another antidiabetic therapy and clarification for actions if patients are on insulin
Section to be changed		**3.3.1 Main diagnosis for trial entry**
Description of change		Removal of time to diagnosis of T2DM of 8 weeks in DINAMO™ Mono patients
Rationale for change		Allows newly diagnosed patients to enroll sooner and is consistent with pediatric guidelines to start antidiabetic therapy vs. waiting 8 weeks to achieve stable glycemic control with diet/exercise
Section to be changed		**3.3.2 Inclusion criteria**
Description of change		5. Removal of time to diagnosis of T2DM of 8 weeks in DINAMO™ Mono patients 7b. Removal of metformin discontinuation for at least 12 weeks, adding metformin intolerance

		and insulin discontinuation at investigator's discretion in DINAMO™ Mono 9. Addition of SI units of c-peptide laboratory value
Rationale for change		1. Allows newly diagnosed patients to enroll sooner and is consistent with pediatric guidelines to start antidiabetic therapy vs. waiting 8 weeks to achieve stable glycemic control with diet/exercise 2. Representative of clinician actions if metformin is discontinued vs. waiting 12 weeks to start another antidiabetic therapy, clarification for actions if patients are on insulin 3. Provide both conventional and SI central laboratory units for investigators to assess entry criteria
Section to be changed		**4.1.5.1 Blinding**
Description of change		Clarify bioanalyst blinding access for both trials
Rational for change		Clarify bioanalyst blinding access for both trials
Section to be changed		**5.2.1 HbA1c and fasting plasma glucose**
Description of change		Add if a centrally analyzed, NGSP-certified hemoglobin A1c assay is unavailable (e.g. due to the COVID-19 pandemic), an HbA1c assay performed at a local laboratory is acceptable.
Rationale for change		Clarification requested by the FDA in CTP4
Section to be changed		**5.3.3 Safety laboratory parameters**
Description of change		Update the document number for Empagliflozin Investigator's Brochure
Rationale for change		Administrative change
Section to be changed		**5.3.5.1 Height and Body Mass Index (BMI)**
Description of change		Added "e.g. z score" to SDS
Rationale for change		Administrative update to align with TSAP
Section to be changed		**5.3.5.2 Self-blood glucose monitoring**
Description of change		Add continuous glucose monitoring device as an alternative to glucometer measurements
Rationale for change		Patients with a CGM device do not also have to use the SBGM device
Section to be changed		**6.2.2 Treatment period(s)**
Description of change		Add CGM
Rationale for change		An alternative means to measure blood glucose concentration
Section to be changed		**7.3 Planned Analyses**
Description of change		New paragraph added to describe the type of HbA1c values will be used in the analyses.
Rationale for change		Clarification requested by the FDA in CTP4

Section to be changed		**7.3.1.1.1 Analysis of the primary family of hypotheses**
Description of change		Table 7.3.1.1.1: 1 footnote 4 update from "Any instance of a patient permanently discontinuing or changing treatment (excluding change of empagliflozin dose and excluding start of rescue medication) will lead to all future measurements being considered as off-treatment." to "Missing post-treatment data after permanent treatment discontinuation".
Rationale for change		To clarify what off-treatment data is included in the analysis
Section to be changed		**7.3.1.1.2 Analysis of the secondary family of hypotheses**
Description of change		Change from "The ANCOVA model will utilise a weight variable having a value of 0 for the patients who are not in the hypothesis test of interest; a value of 2 for re-randomised patients who are in the hypothesis test of interest and a value of 1 otherwise." to "The ANCOVA models performed for each hypothesis will utilise a weight variable having a value of 2 for re-randomised patients and a value of 1 for all other patients for the respective hypothesis test."
Rationale for change		To clarify the secondary family of hypotheses ANCOVA model.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		**8.1 Trial Approval, Patient Information, Informed Consent**
Description of change		Changed abbreviation of CML to CTM
Rationale for change		Administrative change
Section to be changed		**9.2 Unpublished References**
Desription of change		Update the document number for Empagliflozin Investigator's Brochure
Rationale for change		Administrative change
Section to be changed		**11.4 Global amendment 4 (new)**
Description of change		Sub section title added for amendment 4 summary of changes
Rationale for change		Administrative update

11.5 GLOBAL AMENDMENT 5

Number of global amendment		5
Date of CTP revision		28 Sep 2021
EudraCT number		2016-000669-21
BI Trial number		1218-0091
BI Investigational Product(s)		Linagliptin (BI 1356) Empagliflozin (BI 10773)
Title of protocol		A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		**Title Page**
Description of change		Updated status, version, and date
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Updated date
Rationale for change		Administrative change
Section to be changed		**Table of Contents**
Description of change		Add new section 11.5
Rationale for change		Addition of new section
Section to be changed		**5.3.5.2 Self-blood glucose monitoring**
Description of change		Added “To avoid additional finger pricks for blood glucose measurement.”
Rationale for change		Clarify that subjects with a CGM device may forego additional SBGM in order to avoid additional finger pricks for blood glucose

		measurement, in response to feedback from the FDA.
Section to be changed		**7.3.1.1.2 Analysis of the secondary family of hypotheses**
Description of change		Replaced text with "The ANCOVA model will utilise a weight variable having a value of 0 for the patients who are not in the hypothesis test of interest; a value of 2 for re-randomised patients who are in the hypothesis test of interest and a value of 1 otherwise."
Rationale for change		Revert to original text and reject proposed changes in global amendment 4 based on feedback from the FDA.
Section to be changed		**11.4 Global amendment 4**
Description of change		Added "Sent to FDA Only"
Rationale for change		Clarify that this amendment was sent to the FDA only for initial feedback before implementation in all countries as DINAMO Mono was a written request from the FDA.
Section to be changed		**11.5 Global amendment 5 (new)**
Description of change		Sub section title added for amendment 5 summary of changes
Rationale for change		Provide a summary of the changes implemented.

11.6 GLOBAL AMENDMENT 6

Number of global amendment		6
Date of CTP revision		23 May 2022
EudraCT number		2016-000669-21
BI Trial number		1218-0091
BI Investigational Product(s)		Linagliptin (BI 1356) Empagliflozin (BI 10773)
Title of protocol		A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of		

change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		**Title Page**
Description of change		Updated document number, status, version, and date
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Updated date, reduced DINAMO™ Mono sample size; addition of bone fracture as an additional safety criteria
Rationale for change		Administrative change; analysis of bone fracture is part of the safety analysis
Section to be changed		**Flowchart**
Description of change		"r" from rPK blood sampling removed
Rationale for change		Administrative change
Section to be changed		**Table of Contents**
Description of change		Update section 7.3.4 and add new section 11.6
Rationale for change		Administrative format updates and addition of new section
Section to be changed		**1.1 Medical Background**
Description of change		Updated Empagliflozin Investigator Brochure number
Rationale for change		Administrative change
Section to be changed		**1.2.1 Empagliflozin**
Description of change		Updated Empagliflozin Investigator Brochure number
Rationale for change		Administrative change
Section to be changed		**2.3 Benefit – Risk Assessment**
Description of change		Clarification of no drug-drug interactions for Covid treatments based on product labels
Rationale for change		Administrative change
Section to be changed		**3.1 Overall Trial Design Plan**
Description of change		(1) Reduced DINAMO™ Mono sample size; (2) Figure 3.1:1 and 3.1:2 reduced DINAMO™ Mono sample size
Rationale for change		Sponsor decision to stop new patient enrollment in April 2022, the FDA's view of the value of monotherapy pediatric trials has changed with the evolving standards of care
Section to be changed		**3.3 Selection of Trial Population**
Description of change		Reduced DINAMO™ Mono sample size

Rationale for change		Sponsor decision to stop new patient enrollment in April 2022, the FDA's view of the value of monotherapy pediatric trials has changed with the evolving standards of care
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		**5.3.3 Safety laboratory parameters**
Description of change		Updated Empagliflozin Investigator Brochure number
Rationale for change		Administrative change
Section to be changed		**5.3.6.1 Definitions of AEs**
Description of change		Addition of bone fracture as an additional safety topic
Rationale for change		Analysis of bone fracture is part of the safety analysis
Section to be changed		**7.3.2.2 DINAMO™ Mono**
Description of change		Renumbering of link to section headers
Rationale for change		Administrative change
Section to be changed		**7.3.4 Sensitivity analysis of the primary endpoint (for DINAMO only)**
Description of change		Removal of DINAMO only in section header
Rationale for change		A sensitivity analysis will be performed in DINAMO™ Mono
Section to be changed		**7.3.4.1 DINAMO™ (new)**
Description of change		New section header added specific to DINAMO™
Rationale for change		Administrative change
Section to be changed		**7.3.4.1.1 Primary family of hypotheses – MMRM effectiveness analysis**
Description of change		Renumbering of section headers for DINAMO™
Rationale for change		Administrative change
Section to be changed		**7.3.4.1.2 Secondary family of hypotheses – MMRM effectiveness analysis**
Description of change		Renumbering of section headers for DINAMO™
Rationale for change		Administrative change
Section to be changed		**7.3.4.1.3 MMRM efficacy analysis**
Description of change		Renumbering of section headers for DINAMO™
Rationale for change		Administrative change
Section to be changed		**7.3.4.1.4 Analyses on further patient set**

Description of change		Renumbering of section headers for DINAMO™
Rationale for change		Administrative change
Section to be changed		**7.3.4.1.5 Primary family of hypotheses – COVID-19 related intercurrent events**
Description of change		Renumbering of section headers for DINAMO™
Rationale for change		Administrative change
Section to be changed		**7.3.4.1.6 Primary family of hypotheses – Non-NGSP certified laboratories HbA1c values**
Description of change		Renumbering of section headers for DINAMO™
Rationale for change		Administrative change
Section to be changed		**7.3.4.2 DINAMO™ Mono (new)**
Description of change		New section header added specific to DINAMO™
Rationale for change		Administrative change
Section to be changed		**7.3.4.2.1 Primary analysis with DINAMO eligible patients (new)**
Description of change		Description of DINAMO™ Mono sensitivity analysis
Rationale for change		Inclusion of DINAMO™ patients with no background therapy in the DINAMO™ Mono sensitivity analysis
Section to be changed		**7.7.2 DINAMO™ Mono**
Description of change		(1) Old text: "The minimum sample size of 12 patients per group was chosen … " to new text "The **initial** minimum sample size of 12 patients per group was chosen …"; (2) Added "N per group = 6" into intext Table 7.7.2:2; (3) Added explanation for early termination of patient recruitment in DINAMO™ Mono
Rationale for change		Sponsor decision to stop new patient enrollment in April 2022, the FDA's view of the value of monotherapy pediatric trials has changed with the evolving standards of care
Section to be changed		**8.6 Trial Milestones**
Description of change		Removed reference to the potential for DINAMO™ and DINAMO™ Mono patients finishing at the same time
Rationale for change		Administrative change
Section to be changed		**9.2 Unpublished References**
Description of change		Updated Empagliflozin Investigator Brochure and BI 10773 and Linagliptin Benefit-Risk document numbers

Rationale for change		Administrative change due to updated document versions
Section to be changed		**11.6 Global amendment 6 (new)**
Description of change		Subsection title added for amendment 6 summary of changes
Rationale for change		Provide a summary of the changes implemented

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-08

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

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	27 May 2022 14:21 CEST
Approval-Team Member Medicine		27 May 2022 15:02 CEST
Approval-Therapeutic Area Head		31 May 2022 21:08 CEST
Verification-Paper Signature Completion		02 Jun 2022 23:28 CEST
Approval-Biostatistics		06 Jun 2022 10:52 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed