Supplementary Appendix

Efficacy and safety of the SGLT2 inhibitor empagliflozin versus placebo and the DPP-4 inhibitor linagliptin versus placebo in young people with type 2 diabetes (DINAMO): a multicentre, randomised, double-blind, parallel group, phase 3 trial

Laffel LM, Danne T, Klingensmith GJ, et al.

OVERVIEW OF AMENDMENTS TO THE CLINICAL TRIAL PROTOCOL

Further details regarding protocol amendments are presented in section 11 of the final Clinical Trial Protocol, pages 117-148 of the protocol)

There were 8 versions of the clinical trial protocol (CTP), of which 2 versions (Version 1, dated 29 May 2017, and Version 6, dated 14 Jul 2021) were only submitted to the FDA and never implemented due to the requested changes. A total of 6 global amendments were issued which required approval of the Independent Ethics Committees and/or Institutional Review Boards (IEC/IRB) before implementation. In addition, there were local amendments in Argentina (1 amendment), Germany (4 amendments), Portugal (5 amendments), Thailand (1 amendment), and the United Kingdom (2 amendments); none of them impacted a large number of patients. Major changes in the global amendments are summarized below:

CTP version 1, dated 29 May 2017
This version was only submitted to the FDA and never implemented due to the requested changes.

CTP version 2, dated 11 Oct 2017
This version contained the feedback from the FDA on Version 1 and was the original CTP which was implemented. Changes compared with Version 1 included e.g.:

- In-/exclusion criteria were modified
- Initial randomisation to 25 mg empagliflozin replaced with re-randomisation for non-responders after Week 14
- Length of the primary analysis was prolonged from 24 to 26 weeks
- Statistical method of primary endpoint analysis was adapted

CTP version 3 with Global Amendment 1, dated 3 Oct 2019
Streamlining and clarification of wording and inclusion of authority feedback (FDA proposed paediatric study request, EMA paediatric investigational plan, and Medicine and Healthcare products Regulatory Agency in the UK) as follows:

- Statistical method for primary endpoint changed from MMRM to pattern mixture model (jump-to-placebo and inverse probability
- weighting approach). The previous MMRM became a sensitivity analysis
- Number of patients increased in DINAMO (from 138 to 150 patients)
- Trial part with DINAMO Mono added
- Minor adaptions to the flow chart including additional interactions between patient and site
- Exclusion criterion specified (acute metabolic decompensation)
- Addition of further efficacy endpoint (proportion of patients who achieve HbA1c reduction of >0.5% at the end of 26 and 52 weeks)
- Frequency for blood ketone bodies measurement adapted
- Addition of AESIs arthralgia, bullous pemphigoid, AEs related to reduced intravascular volume
- Removal of hospitalization for unstable angina and of pancreatic events from the adjudication process

- New recommendations on diet and exercise for the patients by the site
- Addition of BMI as new subgroup

CTP version 4 with Global Amendment 2, dated 28 Sep 2020
Streamlining and clarification of wording, inclusion of authority feedback (FDA and EMA), and addition of measures related to the COVID-19 pandemic as follows:
- Updated inclusion criteria: reduction in length of diagnosis of T2DM from 12 to 8 weeks and addition of minimum daily metformin dosage
- Change in primary endpoint analysis from pattern mixture model ('jump-to-placebo' and 'inverse probability weighting' approach) to
- 'wash-out' and 'inverse probability weighting' approach for primary and secondary hypotheses
- Addition of measures related to the COVID-19 pandemic
    - Addition of remote visits
    - Guidance added for patients stopping prematurely (also related to DKA)
    - Addition of local instead of central laboratory testing
    - Shipment of trial medication directly to the patients
    - Possibility added to replace patients to keep a certain sample size despite the pandemic
    - Addition of alternative method for SAE report transmission in certain countries
    - Addition of sensitivity analysis for the primary endpoint
    - Rules implemented for remote source data verification during restricted on-site monitoring visits

CTP version 5 with Global Amendment 3, dated 14 Dec 2020
Administrative changes, streamlining of wording, and addition of further measures related to the COVID-19 pandemic as follows:
- Reconsent could be done remotely due to the COVID-19 pandemic
- Serum pregnancy test could be done at a local laboratory due to the COVID-19 pandemic

CTP version 6 with Global Amendment 4, dated 14 Jul 2021
This version was only submitted to the FDA and never implemented due to the requested changes. It included administrative changes, clarified wording, and incorporated feedback from the FDA on the previous global amendment.
- Time reduced between rescreening visits (from 12 to 8 weeks) to allow earlier inclusion of patients
- Clarification of maintaining the blinded conditions while the bioanalyst required access to the data when migrating from the main trial to the ancillary trial
- If a centrally analysed, NGSP-certified HbA1c assay was unavailable (e.g. due to the COVID-19 pandemic), an HbA1c assay performed at a local laboratory was acceptable. Text added to specify the corresponding sensitivity analyses
- Addition of an alternative means to measure blood glucose concentration
- Clarification of the secondary hypotheses for the ANCOVA

CTP version 7 with Global Amendment 5, dated 28 Sep 2021
This amendment included administrative changes and incorporated feedback from the FDA:

- Clarification that patients with a CGM device could use relevant readings from that device to avoid additional finger pricks
- Further clarification on secondary hypotheses for the ANCOVA

CTP version 8 with Global Amendment 6, dated 23 May 2022
This amendment mainly impacted the ancillary trial DINAMO™ Mono which is still ongoing. Changes regarding DINAMO included addition of bone fracture as further safety endpoint; bone fracture was already introduced via the initial TSAP version.

STEERING COMMITTEE OF THE DINAMO TRIAL

Lori Laffel MD (Chair), Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA

Philip Zeitler MD, Department of Endocrinology, Children's Hospital Colorado, Aurora, CO, USA

Thomas Danne MD, Auf der Bult Kinder- und Jugendkrankenhaus, Hannover, Germany

Steven Willi MD, Perelman School of Medicine at the University of Pennsylvania and Children's Hospital of Philadelphia, PA, USA

Georgeanna Klingensmith MD, Barbara Davis Center, University of Colorado, Aurora, CO, USA

William Tamborlane MD, Department of Pediatrics, Yale School of Medicine, New Haven, CT, USA

DATA MONITORING COMMITTEE OF THE DINAMO TRIAL

Francine K. Welty MD, PhD (DMC Chair), Harvard Medical School, Boston, MA, USA

Tim Clayton MSc (DMC Statistician), London School of Hygiene and Tropical Medicine, London, UK

Klaus G. Parhofer MD (DMC Member), University of Munich, Munich, Germany

Kenneth Copeland (former DMC Member), OUHSC Department of Pediatrics, Oklahoma City, OK

Marc Nicolino MD (former DMC Member), Hôpital Femme Mère Enfant, CHU de Lyon HCL, France

SPONSORS OF THE TRIAL

The sponsors of the trial, Boehringer Ingelheim, had the organizational oversight over the DINAMO trial, which included trial conduct, supervision and monitoring of the enrolling study centers, data collection and storage as well as data storage and data analysis. The trial design was developed by the academic members of the Steering

Committee in cooperation with representatives from Boehringer Ingelheim, who were also represented in the Steering Committee of the trial.

The Steering Committee developed and amended the protocol, oversaw the statistical analysis plan, the recruitment of participants and the quality of follow-up; supervised the analysis of data; and the academic members provided an independent interpretation of the results. The first and last author, who had unrestricted access to the data, prepared the drafts of the manuscript, which were then reviewed and edited by all authors, including representatives of Boehringer Ingelheim.

PRINCIPAL INVESTIGATORS BY COUNTRY WHO HAVE SCREENED AT LEAST ONE PATIENT

Argentina

S.E. Solís, Sanatorio Allende S.A., Nueva Córdoba; M.V. Felipe Gacioppo, Hospital de Clínicas Presidente Dr. Nicolás Avellaneda, San Miguel de Tucumán.

Brazil

R.D.L. Liberatore Jr, Fund. de Apoio ao Ensino, Pesquisa e Assistência do HC da Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto; T.M.B.L. Ferraz, Instituto de Estudos e Pesquisas Clínicas IEP-CE, Fortaleza.

Canada

B.A. Wicklow, University of Manitoba - Health Sciences Centre, Winnipeg; F.H. Mahmud, The Hospital for Sick Children, Toronto.

China

H. Du, The First Hospital of Jilin University, Changchun; H. Wei, Zhengzhou Children's Hospital, Zhengzhou.

Colombia

J.O. Ibarra Gomez, Centro de Diabetes Cardiovascular IPS, Barranquilla; H. Yupanqui Lozno, Dexa Diab Servicios Medicos Ltda-IPS, Bogotá DC.

Germany

K-O. Schwab, Universitätsklinikum Freiburg, Freiburg.

Israel

N. Shehadeh, Rambam Medical Center, Haifa; E. Hershkovitz, Soroka University Medical Center, Beer Sheva.

Republic of Korea

H-S. Kim, Severance Hospital, Seoul; J-H. Choi, Asan Medical Center, Seoul; J. S. Hwang, Ajou University Hospital, Suwon.

Mexico

M. Barrientos Perez, Consultorio Medico, Puebla; F.R. Ramírez Mendoza, CAIMED Investigacion en Salud, S.A. de C.V., Ciudad de México; D. Espinoza Peralta, Investigación Médica Sonora, S.C., Sonora; E.S. Pelayo Orozco, Centro de Investigación Médica de Ocidente, S.C., Zapopan; R.M. Violante Ortiz, Centro de Estudios de Investigación Metabólicos y Cardiovasculares, S.C., Ciudad Madero; L.A. Nevarez Ruiz, Investigación en Salud y Metabolismo S.C., Chihuahua.

Russian Federation

Y. Skorodok, St. Petersburg State Pediatric University, St. Petersburg; I. Bondar, State Novosibirsk Regional Clinical Hospital, Novosibirsk; A. Sobolev, Municipal Institution of Healthcare, Kirov; T. Bardymova, Regional Clinical Hospital 'The Badge of Honor Order', Irkutsk; F. Valeeva, Kazan State Medical University, Kazan; V. Peterkova, Fed. State Budget Instit. "Endocrinology Research Cntr" of MoH of Russia, Moscow; O.A. Malievskiy, Federal State Budget Educational Institution of Higher Education "Bashkir state medical University", Ufa; J. Samoilova, Fed State Budget Educational Instit of Higher Education "Siberian State Med. Univ" MoH of Russian Fed, Tomsk; G. Galkina, Fed. State Budget Educational Instit., Rostov-on-Don; T. Kovalenko, Rep. Childrens Clin. Hosp., Izhevsk; O. Votyakova, Ivanovo Reg. Clin. Hosp., Ivanovo.

Thailand

C. Deerochanawong, Rajavithi Hospital, Krung Thep Maha Nakhon.

United Kingdom

C. Yaliwal, Royal Berkshire Hospital, Reading; M. Chen, St George's Hospital, London.

United States

R.S. Weinstock, SUNY Upstate Medical University, Syracuse; M.E. Gottschalk, Rady Children's Hospital - San Diego, San Diego; L.M.B Laffel, Joslin Diabetes Center, Boston; R.M Wolf, Johns Hopkins Hospital, Baltimore; S.B. Leichter, Columbus Regional Research Institute, Columbus; N. Jain, The University of North Carolina at Chapel Hill, Chapel Hill; B.A. Nelson, Children's Hospital of Richmond at VCU, Richmond; G. Guido, Advantage Clinical Trials, Bronx; L.P. Huerta-Saenz, Penn State Health Milton S. Hershey Medical Center, Hershey; A.A. Hassan, Amir Ali Hassan, MD, P.A., Houston; E. Gonzalez, Oceane7 Medical and Research Center, Inc., Miami; P.A. Velasquez-Mieyer, LifeDoc Research, PLLC, Memphis; M.D. Wheeler, University of

Arizona, Tucson; J.A. Saenz, Saenz Medical Center, La Joya; K.M. Reddy, AdventHealth Medical Group, Pediatric Diabetes and Endocrinology at Winter Park, Winter Park; M.P. Gallagher, New York University Langone Medical Center, New York; W.V. Tamborlane, Yale University School of Medicine, New Haven; E. Tsalikian, University of Iowa, Iowa City; R. Edelen, Monument Health Rapid City Hospital, Inc., Rapid City; J-C.G. Desmangles, Nemours Children's Speciality Care, Pensacola; L. Irizarry Gonzalez, San Juan Bautista School of Medicine - Clinical Research, Caguas; H. Rodriguez, University of South Florida Diabetes and Endocrinology Center, Tampa; M.L. Olson, Phoenix Children's Hospital, Phoenix; K.A. Wintergerst, Norton Children's Endocrinology, Louisville; N.M Dixit, University Of Mississippi Medical Center, Jackson; J.R. Wood, University Hospitals Cleveland Medical Center, Cleveland; P. Bjornstad, Children's Hospital Colorado, Aurora; S.H. Shah, Lucile Packard Children's Hospital at Stanford University, Palo Alto; J. Lynch, Texas Diabetes Institute, San Antonio; A. Muir, Children's Center for Advanced Pediatrics, Atlanta; S.M. Willi, Children's Hospital of Philadelphia, Philadelphia; K. Bethin, UBMD Pediatrics, Buffalo; S. Srinivasan, University of California San Francisco Madison Clinic for Pediatric Diabetes, San Francisco; M. George, University of Oklahoma Health Sciences Center, Oklahoma City; M.A. Clements, The Children's Mercy Hospital, Kansas City; A.H. Shoemaker, Vanderbilt Eskind Diabetes Pediatric Research Laboratory at Vanderbilt University Medical Center, Nashville; V.S. Desai, Pediatric and Adult Research Center, Orlando; D.H. Jelley, University of Oklahoma, Tulsa; M. Daniels, Children's Hospital of Orange County, Orange; J. Colomar, Empire Clinical Research, LLC, Miami Lakes; R. Dillon; Atlanta Center for Medical Research, Atlanta; C. Vance, Rocky Mountain Diabetes and Osteoporosis Center, Idaho Falls.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria

- Participants aged 10 to 17 years (inclusive) at the time of randomisation (Visit 2).
- Male and female participants.
- Women of childbearing potential (WOCBP) 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.
- Signed and dated written informed consent provided by the participant’s parent(s) (or legal guardian) and participant’s assent in accordance with ICH-GCP and local legislation prior to admission to the trial (informed assent will be sought according to the participant’s age, level of maturity, competence, and capacity).
- Documented diagnosis of T2DM at Visit 1A:
    - DINAMO: Documented diagnosis of T2DM for at least 8 weeks at Visit 1A
    - DINAMO Mono: Confirmation of T2DM at Visit 1A.
- Insufficient glycemic control as measured by the central laboratory at Visit 1A:
    - DINAMO: HbA1c ≥6·5% and ≤10·5%
    - DINAMO Mono: HbA1c ≥6·5% and ≤9·0%.

- DINAMO: Participants 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 participants 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.
- DINAMO Mono: Drug-naïve participants or participants 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.
- Non-fasting serum C-peptide levels ≥0·6 ng/ml or >0·199 nmol/L as measured by the central laboratory at Visit 1A.
- Compliance with trial medication intake must be between 75% and 125% during the open-label placebo run-in period.
- 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.

Exclusion criteria

- 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).
- Diagnosis of monogenic diabetes (e.g., MODY).
- History of pancreatitis.
- Diagnosis of metabolic bone disease.
- Gastrointestinal disorders that might interfere with study drug absorption according to investigator assessment.
- Secondary obesity as part of a syndrome (e.g., Prader-Willi syndrome).
- Any antidiabetic medication (except for metformin and/or insulin background therapy for DINAMO) within 8 weeks prior to Visit 1A and until Visit 2.
- Treatment with weight reduction medications (including anti-obesity drugs) within 3 months prior to Visit 1A and until Visit 2.
- History of weight-loss surgery or current aggressive diet regimen (according to investigator assessment) at Visit 1A and until Visit 2.
- 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.
- Change in dose of thyroid hormones within 6 weeks prior to Visit 1A or planned change or initiation of such therapy before Visit 2.
- Known hypersensitivity or allergy to the investigational products or their excipients

- Impaired renal function defined as estimated Glomerular Filtration Rate (eGFR) <60 ml/min/1.73m^2 (according to Zappitelli formula) as measured by the central laboratory at Visit 1A.
- 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
- History of belonephobia (needle phobia).
- 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.
- Blood dyscrasias or any disorders causing hemolysis or unstable red blood cells (e.g., malaria, babesiosis, hemolytic anemia).
- Any other acute or chronic medical or psychiatric condition or laboratory abnormality that, based on investigator's judgement, would jeopardize participant safety during trial participation or would affect the study outcome.
- Medical contraindications to metformin according to the local label (for participant on
- metformin background therapy).
- Participant 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
- Previous randomisation in this trial.
- 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).
- 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 participant or unlikely to complete the trial.
- Female participants who are pregnant, nursing, or who plan to become pregnant in the trial.

Rescue medication

Insulin was the rescue medication, with protocol guidance for initiation. Insulin or increased doses of insulin could be initiated from the first day of treatment until week 52 in case of acute metabolic decompensation and/or repeatedly elevated blood ketone concentrations. In case of sustained hyperglycemia (80% of blood glucose readings greater than 300 mg/dL (16·6 mmol/L) (non-fasting) or greater than 200 mg/dL (11·1 mmol/L) (fasting) for 1 week), initiation of rescue therapy was considered. In addition, rescue could be initiated from week 12 until week 52 if on two successive occasions HbA1c was 9·0% or higher and an absolute increase of HbA1c 1% or higher compared with the baseline value. If new insulin treatment or insulin treatment at increased doses (i.e., a dose increase of basal insulin of more than 0·1 IU/kg above the baseline prescribed dose) continued for more than 21 consecutive days, including the weaning phase, then the participant was classified as requiring rescue therapy.

STATISTICAL METHODS

"Wash-out" approach – missing data imputation methods

Type of missing data	HbA1c data used for imputation	Method
Placebo		
On- and off-treatment data[1]	Observed on- and off-treatment data in the placebo group including baseline, weeks 4, 12 and 26	*Non-monotone missing data:* Markov Chain Monte Carlo-multiple imputation (missing at random)[2] *Monotone missing data:* sequential linear regression-multiple imputation (missing at random)
Linagliptin and empagliflozin		
On-treatment data	Observed on-treatment data in the respective treatment group including baseline and week 26	Sequential linear regression-multiple imputation (missing at random)
Off-treatment data[1]	Observed on- and off-treatment data in the placebo group, including baseline and week 26	Sequential linear regression-multiple imputation (missing not at random)

[1]Missing post-treatment data after permanent treatment discontinuation
[2]Baseline HbA1C as a continuous covariate; age as binary covariates (<15 years; ≥15 to <18 years). 500 imputations were performed to ensure adequate efficiency and stability of the estimation for missing data.

Treatment group definitions

The following treatment groupings were used for the efficacy and safety analyses.

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

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

Treatment grouping 2 (TG2) for Empagliflozin 25 mg titration period from Day 1 to week 26 (see Figure S4 below):

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

Treatment grouping 3 (TG3) for Empagliflozin 10 mg titration period from Day 1 to week 26 (see Figure S5 below):

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

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

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

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

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

Treatment grouping 6 (TG6) for active treatment period:

- *Linagliptin 5 mg active pooled (**L5 active**),* consisting of

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

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

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

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

MEASURES TAKEN DUE TO THE COVID-19 PANDEMIC

During the COVID-19 pandemic, the investigators and trial coordinators were advised that trial procedures should be completed according to the clinical trial protocol (CTP) whenever feasible and appropriate (letter to investigators sent on 17 March 2020). However, it was recognized that in order to protect patient and trial staff safety, sites might have to deviate from the CTP. Global Amendments 2 to 4 (28 Sep 2020, 14 Dec 2020 and 14 Jul 2021) introduced measures to deal with the COVID-19 pandemic in the trial, including the addition of remote visits, guidance added for patients stopping prematurely, addition of local instead of central laboratory testing, shipment of trial medication directly to the patients, possibility added to replace patients to keep a certain sample size despite the pandemic and rules implemented for remote source data verification during restricted on-site monitoring. Furthermore, a sensitivity analysis for the primary endpoint was added excluding non-NGSP (National Glycohemoglobin Standardization Program) certified assay values for HbA1c (if HbA1c assay was unavailable (e.g. due to the COVID-19 pandemic), an HbA1c assay performed at a local laboratory was acceptable). The changes were planned by the sponsor and discussed with the Study Steering Committee. Modification were reviewed and approved by the involved Institutional Review Boards / Institutional Ethics Committees.

Due to the COVID-19 pandemic, the enrolment 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 in the trial were evaluated. Based on the pharmacological mechanism of empagliflozin and linagliptin and review of data derived from clinical and post-marketing databases, there was 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 were expected, nor have they been described in the literature.

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 was adequately addressed in the clinical trial protocol. Consistent with the guidance on illness-related treatment discontinuation, the trial drug was to be discontinued in case of severe COVID-19 disease and re-introduced once the patient had recovered.

All modification to the study based on the COVID-19 pandemic are considered not important (based on the CONSERVE 2021 Statement, *Orkin AM et al. Guidelines for Reporting Trial Protocols and Completed Trials Modified Due to the COVID-19 Pandemic and Other Extenuating Circumstances: The CONSERVE 2021 Statement. JAMA 2021;326:257–265*) since the changes had no meaningful effect on the study's:

- objectives or research question;
- ethical acceptability, including benefits and harms to participants;
- internal validity and generalizability;
- feasibility; or

- analytical methods and statistical power

Impact of COVID-19 pandemic on the trial and results
Before the onset of the COVID-19 outbreak (16 Mar 2020), 111 patients (70.3%) had been randomised in this trial, and 47 patients (29.7%) were randomised thereafter. The primary endpoint assessment at Week 26 occurred for 64 patients (43.8%) before the onset of the COVID-19 outbreak and for 82 patients (56.2%) thereafter. Likewise, the majority of patients (121 patients, 77.1%) took their last dose of trial drug after the onset of the COVID-19 pandemic.

The demographic data of patient groups randomised before and after the start of COVID-19 was comparable. One patient was not randomised due to the COVID-19 pandemic. None of the patients discontinued the trial or trial drug because of a SARS-CoV-2 infection or other COVID-19 related reasons.

The baseline efficacy variables were comparable before and after the start of COVID-19. The exposure to trial medication was generally comparable between patient groups randomised before and after the start of COVID-19. Only patients who discontinued treatment after start of COVID-19 were potentially affected by the pandemic whereas patients who discontinued treatment before start of COVID-19 were clearly not affected by the pandemic. No relevant differences were observed when comparing compliance to trial medication between these 2 patient populations. Further, there was no relevant impact of COVID-19 on the overall compliance of patients.

For the primary endpoint analysis, there we no missing HbA1c data at week 26 due to COVID-19 related reasons. In addition, all HbA1c values were assess by a NGSP certified assay (see table below).

Table. Frequency of patients with COVID−19 related intercurrent events − mITT (TG1)

	Pbo		L5		E Pooled	
	N	%	N	%	N	%
Number of patients in analysis set	53	100.0	52	100.0	52	100.0
Number of patients with at least one COVID-19 related intercurrent events	0	0.0	3	5.8	2	3.8
Affecting the existence of the measurement						
Missing HbA1c at Week 26 due to COVID-19 related reason	0	0.0	0	0.0	0	0.0
HbA1c value is from a non-NGSP certified assay [1]	0	0.0	0	0.0	0	0.0
At Baseline	0	0.0	0	0.0	0	0.0
At Week 4	0	0.0	0	0.0	0	0.0
At Week 12	0	0.0	0	0.0	0	0.0
At Week 26	0	0.0	0	0.0	0	0.0

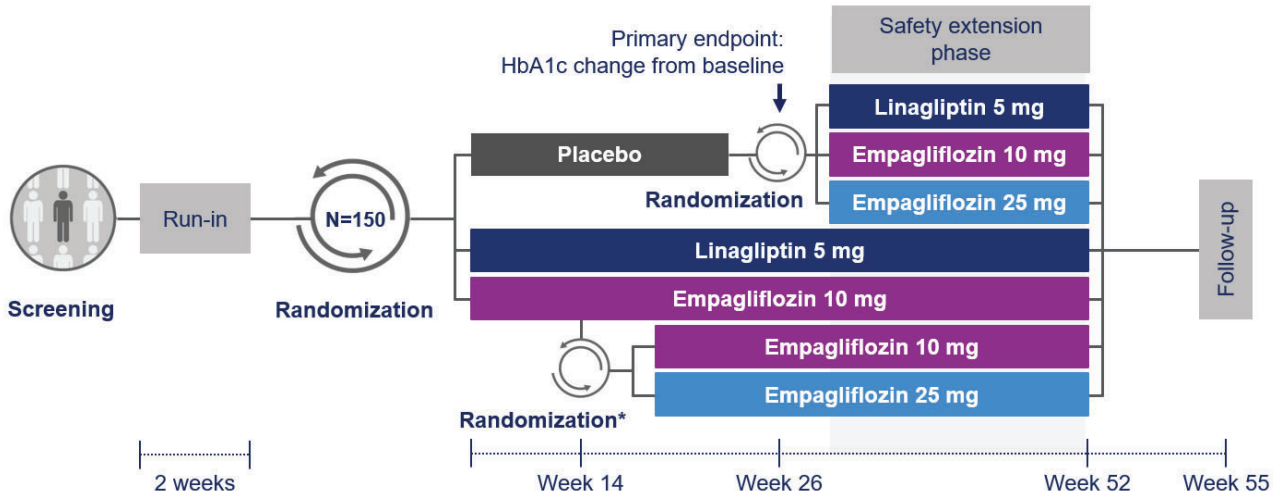
Pbo = Placebo, L5 = Linagliptin 5 mg, E Pooled = Empagliflozin pooled. [1] Except for off−treatment HbA1c values at Week 26 in the active treatment groups after premature treatment discontinuation for reasons unrelated to COVID−19.

Up to Week 26, the rate of overall AEs was balanced between placebo and linagliptin 5 mg or placebo and empagliflozin pooled both before and after the start of the COVID-19 pandemic. No patient in the placebo group, 1 in the linagliptin 5 mg group, and 2 in the

empagliflozin pooled group had SARS-CoV-2 infections. Among these patients, no obvious imbalances were observed between placebo and the active treatment groups with regard to any type of AEs. Up to Week 52, 3 patients in the linagliptin active group and 4 in the empagliflozin active group had SARS-CoV-2 infections.

SUPPLEMENTAL FIGURES AND TABLES

Figure S1: Study design



*Re-randomisation at week 14 for participants not achieving HbA1c less than 7·0% at week 12. HbA1c, glycated haemoglobin.

Figure S2: **DINAMO screening and randomisation over time**

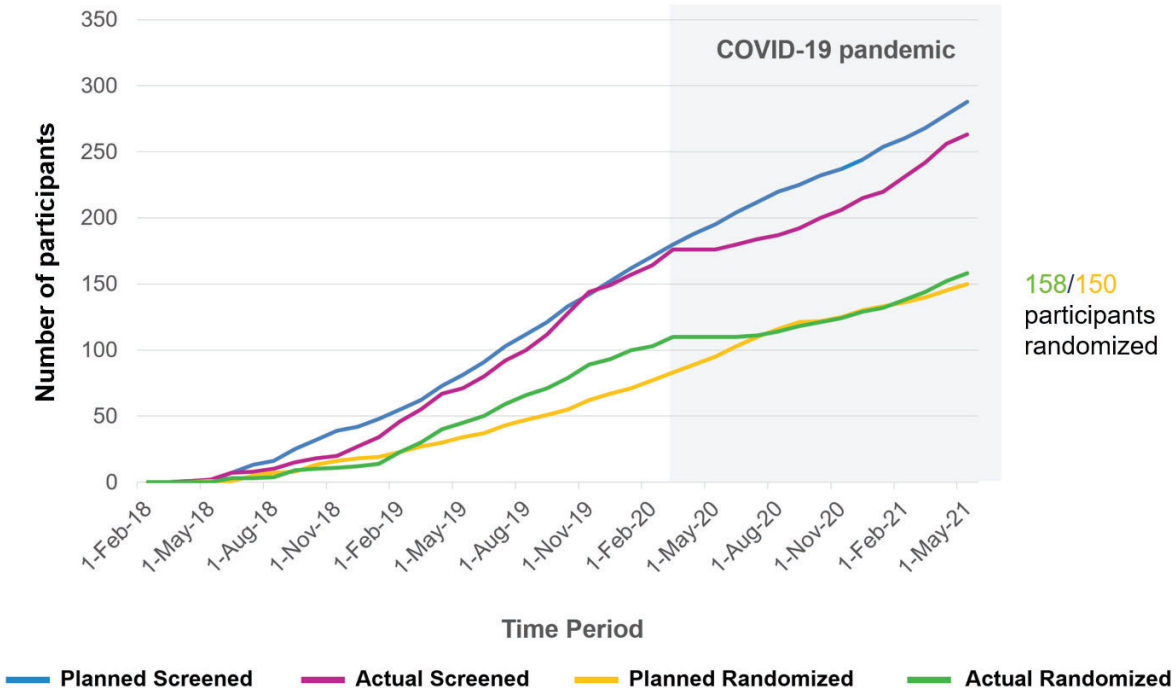
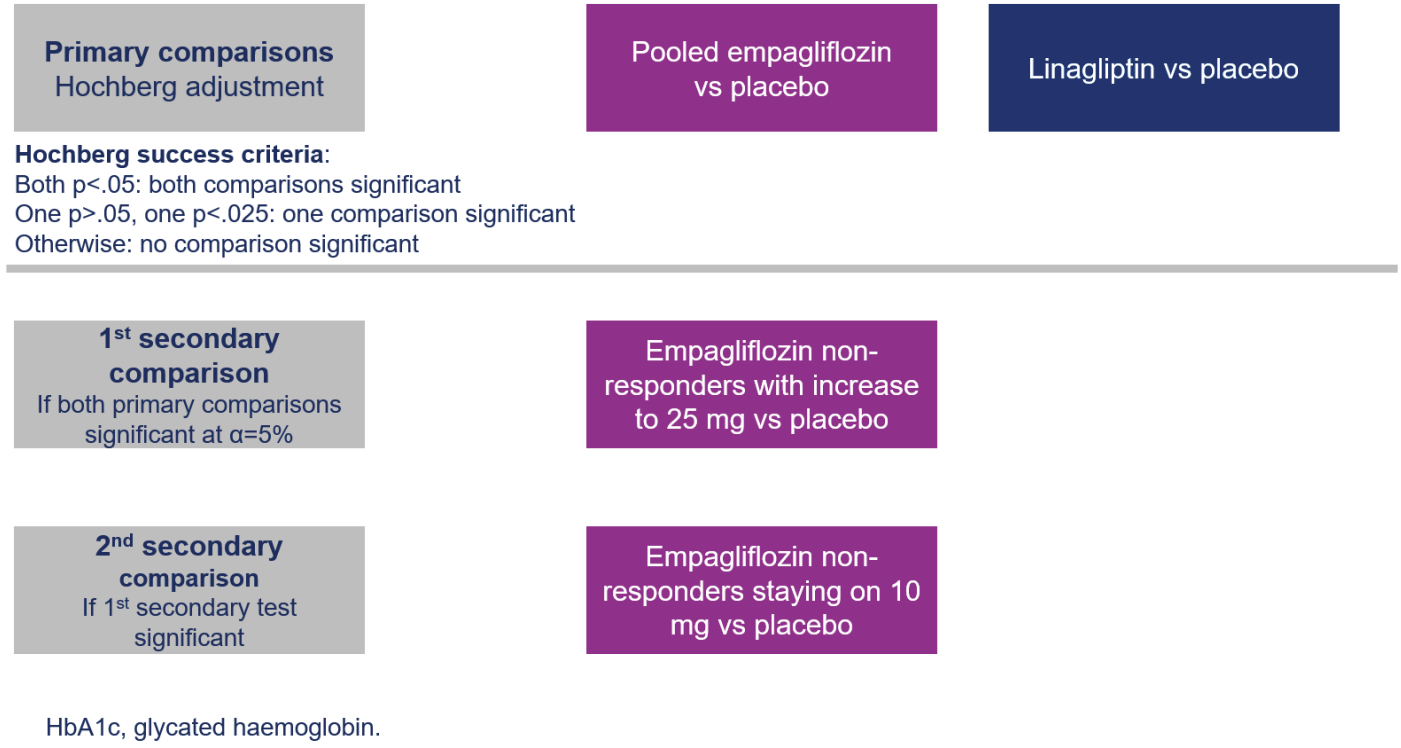
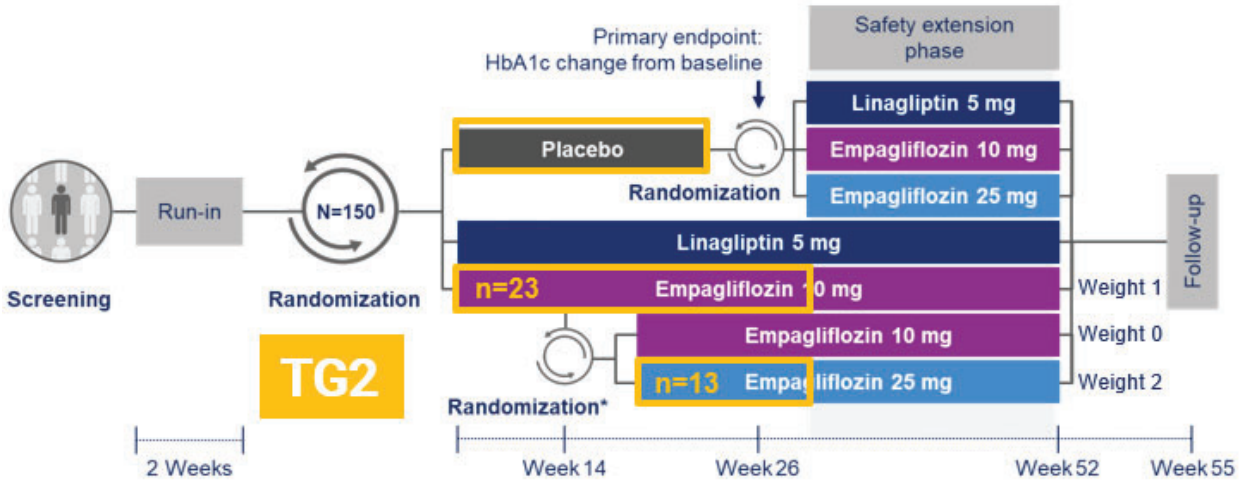


Figure S3: **Confirmatory hypothesis testing of HbA1c change at week 26**



HbA1c, glycated haemoglobin.

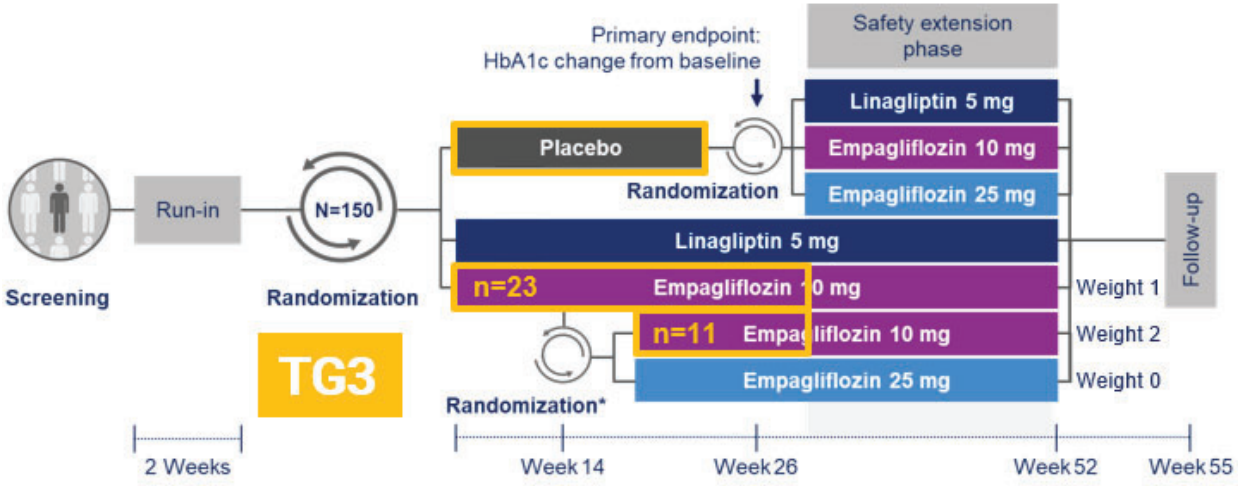
Figure S4: **Treatment grouping 2 (TG2) for empagliflozin 25 mg titration period from day 1 to week 26**



Weighting for the associated secondary hypothesis test:

- Empagliflozin non-responders re-randomised to 25 mg: Weight=2,
  these participants were re-randomised to the 25 mg treatment group *in the hypothesis of interest*
- Empagliflozin non-responders re-randomised to 10 mg: Weight=0,
  these participants were re-randomised to the 10 mg treatment group *not in the hypothesis of interest*
- Empagliflozin responders, not subject to re-randomisation: Weight=1,
  these patients were in the 'otherwise' category
- Placebo patients: Weight=1,
  these patients were in the 'otherwise' category

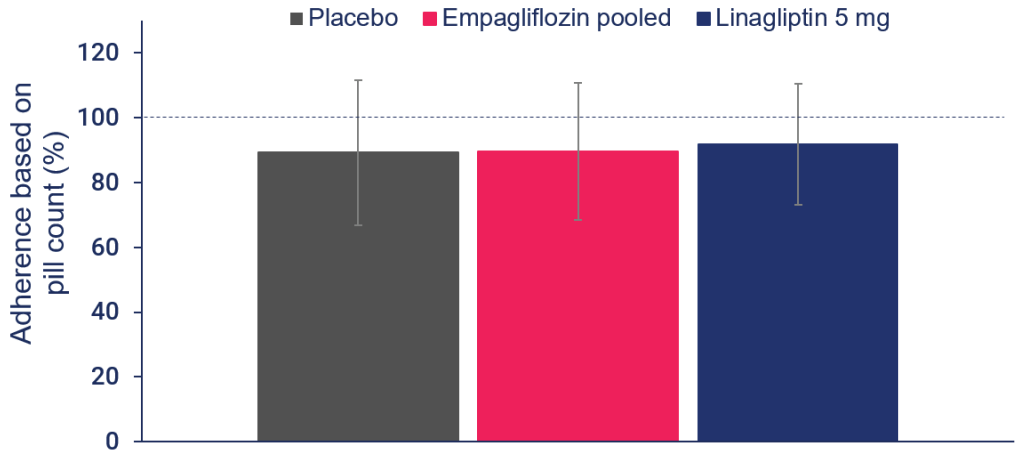
Figure S5: **Treatment grouping 3 (TG3) for empagliflozin 10 mg titration period from day 1 to week 26**



Weighting for the associated secondary hypothesis test:

- Empagliflozin non-responders re-randomised to 10 mg: Weight=2,
  these participants were re-randomised to the 25 mg treatment group *in the hypothesis of interest*
- Empagliflozin non-responders re-randomised to 25 mg: Weight=0,
  these participants were re-randomised to the 10 mg treatment group *not in the hypothesis of interest*
- Empagliflozin responders, not subject to re-randomisation: Weight=1,
  these patients were in the 'otherwise' category
- Placebo patients: Weight=1,
  these patients were in the 'otherwise' category

Figure S6: **Adherence to treatment at week 26 and adherence-related important protocol deviations leading to exclusion from the per-protocol set**

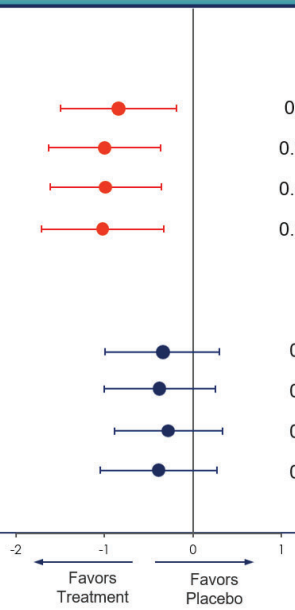


Important protocol deviations before or at Week 26	Placebo	Empagliflozin pooled	Linagliptin 5 mg	Total
Non-adherence, n (%)	8 (15·1)	5 (9·6)	3 (5·7)	16 (10·1)
Non-adherence to study drug intake	7 (13·2)	3 (5·8)	2 (3·8)	12 (7·6)
Treatment interruption for more than 7 consecutive days	2 (3·8)	3 (5·8)	1 (1·9)	6 (3·8)

TS (TG1) population. TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation); TS, treated set.

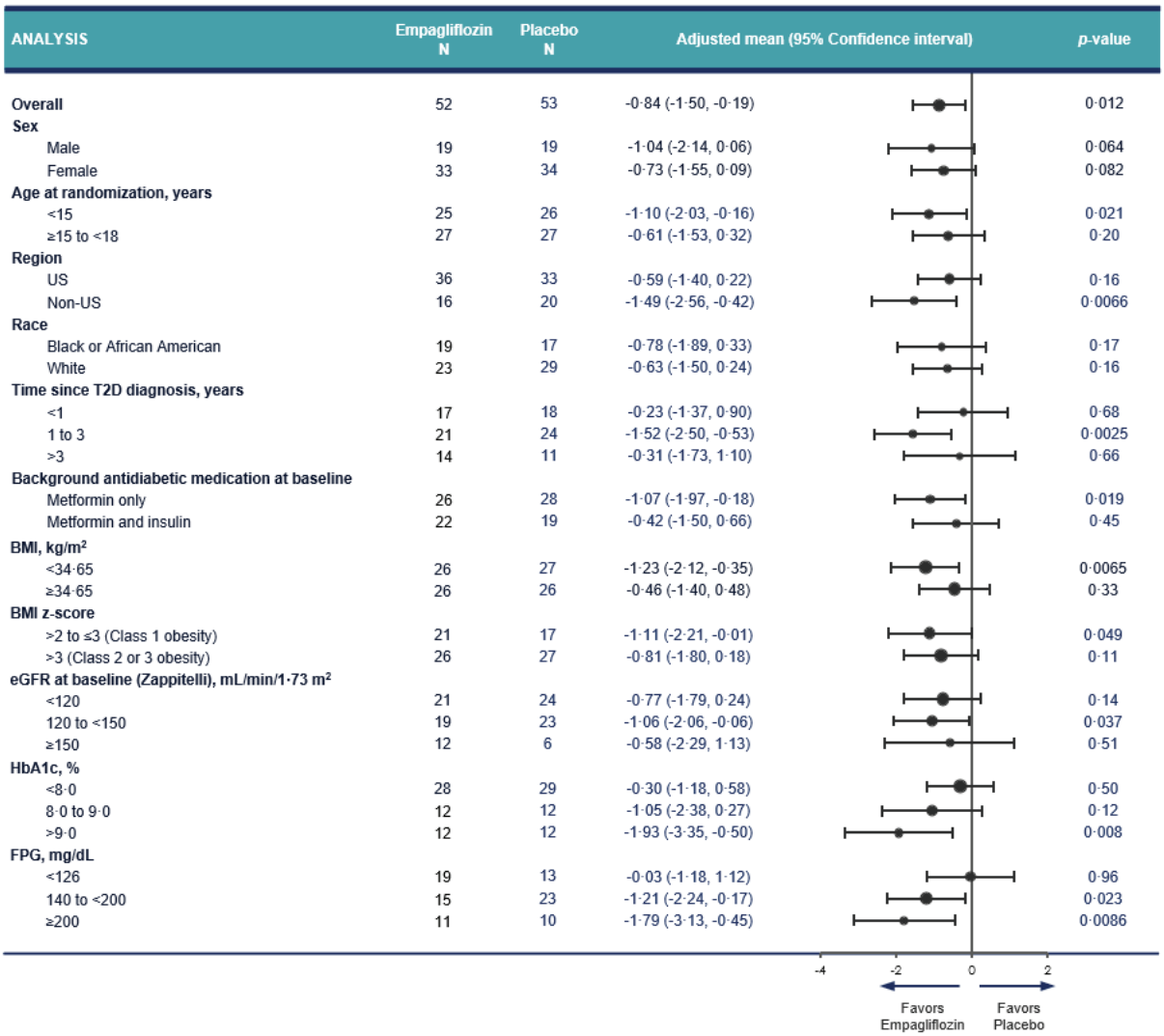
Figure S7: **Primary and sensitivity analysis for primary endpoint**

ANALYSIS	Population	Treatment N	Placebo N	Adjusted mean (95% Confidence interval)	*p*-value
Empagliflozin pooled					
Primary analysis: MI	mITT (OC-AD)	52	53	-0.84 (-1.50, -0.19)	0.012
Sensitivity analysis: MMRM at Week 26	mITT (OC-AD)	47	50	-1.00 (-1.63, -0.37)	0.0022
Sensitivity analysis: MMRM at Week 26	mITT (OC)	41	42	-0.99 (-1.61, -0.36)	0.0022
Sensitivity analysis: MI	PPS (OC-AD)	45	44	-1.02 (-1.71, -0.33)	0.0038
Linagliptin					
Primary analysis: MI	mITT (OC-AD)	52	53	-0.34 (-0.99, 0.30)	0.29
Sensitivity analysis: MMRM at Week 26	mITT (OC-AD)	49	50	-0.38 (-1.00, 0.25)	0.24
Sensitivity analysis: MMRM at Week 26	mITT (OC)	46	42	-0.28 (-0.89, 0.33)	0.37
Sensitivity analysis: MI	PPS (OC-AD)	49	44	-0.39 (-1.05, 0.27)	0.25



TG1 population. MI, multiple imputation with wash-out approach; mITT, modified intention-to-treat; MMRM, mixed model for repeated measurement. OC, observed cases (excluding values after treatment discontinuation and after rescue therapy); OC-AD, observed cases (all data, including values after treatment discontinuation and after rescue therapy); PPS, per-protocol set; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation).

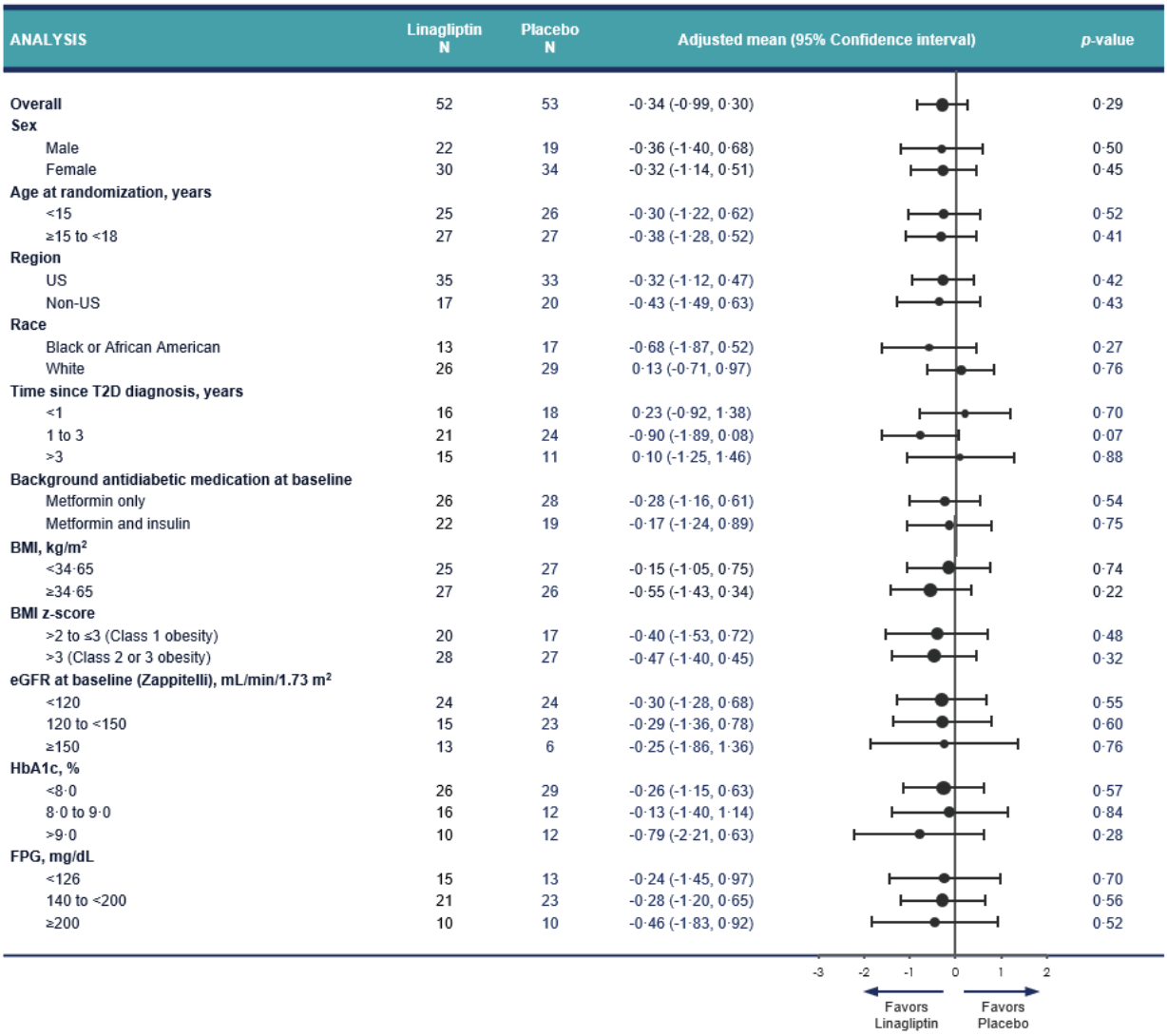
Figure S8: **Subgroup analysis for primary endpoint – empagliflozin**



ANALYSIS	Empagliflozin N	Placebo N	Adjusted mean (95% Confidence interval)	*p*-value
Overall	52	53	-0·84 (-1·50, -0·19)	0·012
Sex				
Male	19	19	-1·04 (-2·14, 0·06)	0·064
Female	33	34	-0·73 (-1·55, 0·09)	0·082
Age at randomization, years				
<15	25	26	-1·10 (-2·03, -0·16)	0·021
≥15 to <18	27	27	-0·61 (-1·53, 0·32)	0·20
Region				
US	36	33	-0·59 (-1·40, 0·22)	0·16
Non-US	16	20	-1·49 (-2·56, -0·42)	0·0066
Race				
Black or African American	19	17	-0·78 (-1·89, 0·33)	0·17
White	23	29	-0·63 (-1·50, 0·24)	0·16
Time since T2D diagnosis, years				
<1	17	18	-0·23 (-1·37, 0·90)	0·68
1 to 3	21	24	-1·52 (-2·50, -0·53)	0·0025
>3	14	11	-0·31 (-1·73, 1·10)	0·66
Background antidiabetic medication at baseline				
Metformin only	26	28	-1·07 (-1·97, -0·18)	0·019
Metformin and insulin	22	19	-0·42 (-1·50, 0·66)	0·45
BMI, kg/m²				
<34·65	26	27	-1·23 (-2·12, -0·35)	0·0065
≥34·65	26	26	-0·46 (-1·40, 0·48)	0·33
BMI z-score				
>2 to ≤3 (Class 1 obesity)	21	17	-1·11 (-2·21, -0·01)	0·049
>3 (Class 2 or 3 obesity)	26	27	-0·81 (-1·80, 0·18)	0·11
eGFR at baseline (Zappitelli), mL/min/1·73 m²				
<120	21	24	-0·77 (-1·79, 0·24)	0·14
120 to <150	19	23	-1·06 (-2·06, -0·06)	0·037
≥150	12	6	-0·58 (-2·29, 1·13)	0·51
HbA1c, %				
<8·0	28	29	-0·30 (-1·18, 0·58)	0·50
8·0 to 9·0	12	12	-1·05 (-2·38, 0·27)	0·12
>9·0	12	12	-1·93 (-3·35, -0·50)	0·008
FPG, mg/dL				
<126	19	13	-0·03 (-1·18, 1·12)	0·96
140 to <200	15	23	-1·21 (-2·24, -0·17)	0·023
≥200	11	10	-1·79 (-3·13, -0·45)	0·0086

mITT (TG1) (OC-AD) population.
Some analyses were not performed due to small patient number, e.g., FPG category 126 to <140. To convert the values for % HbA1c to millimoles per mol, subtract 2·15 and multiply the result by 10·929. To convert the values for plasma glucose to millimoles per liter, multiply by 0·05551. BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; mITT, modified intention-to-treat; OC-AD, observed cases (all data, including values after treatment discontinuation and after rescue therapy; T2D, type 2 diabetes; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation).

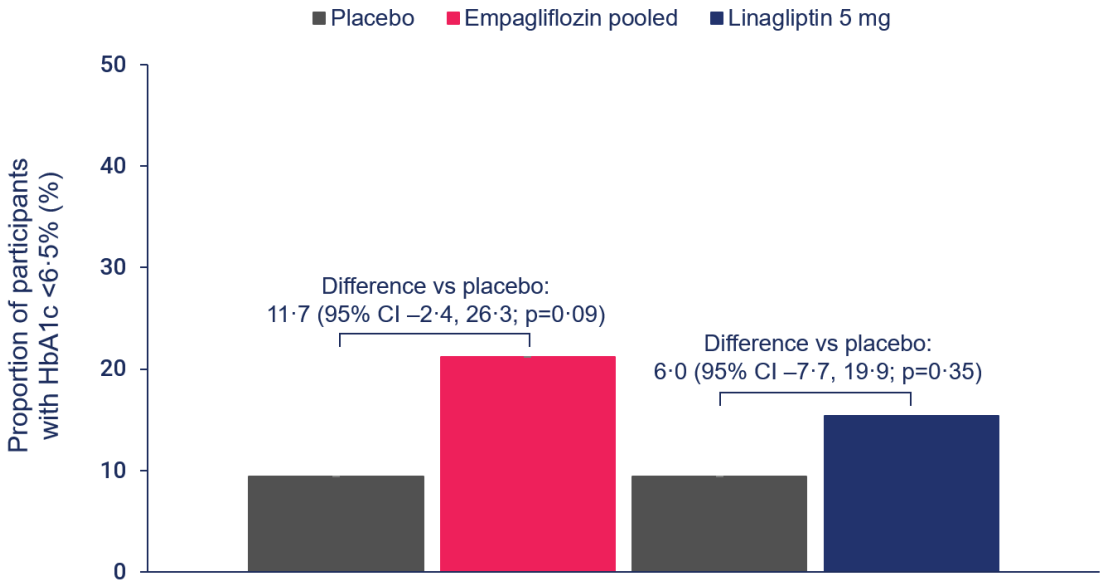
Figure S9: **Subgroup analysis for primary endpoint – linagliptin**



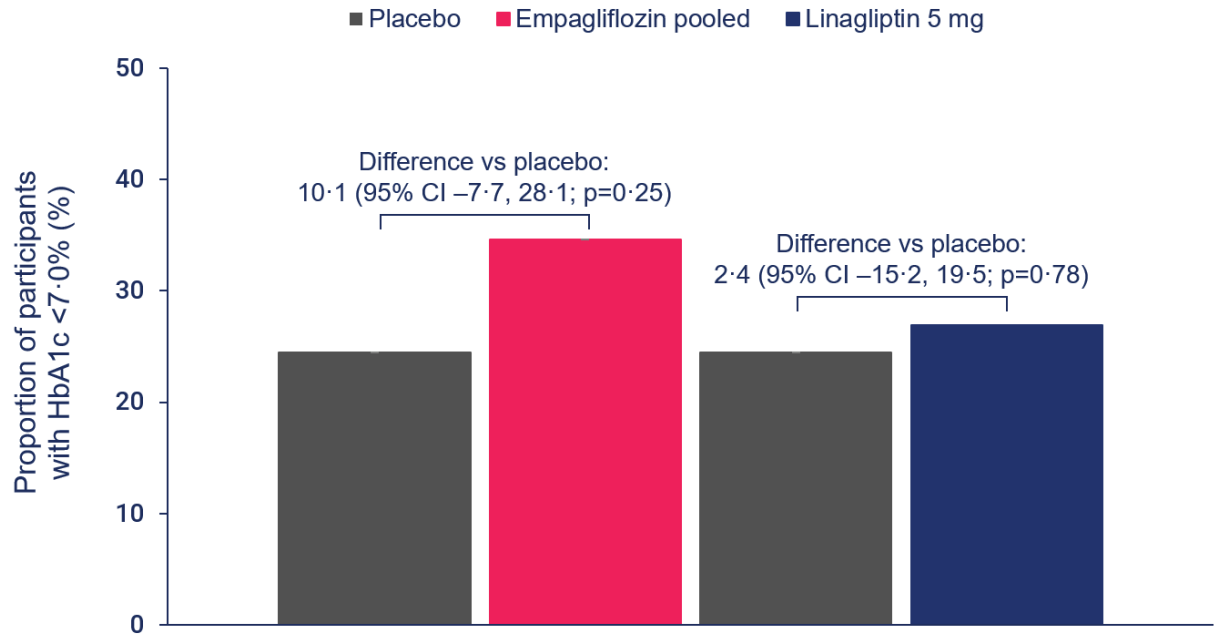
mITT (TG1) (OC-AD) population.
Some analyses were not performed due to small patient number, e.g., FPG category 126 to <140. To convert the values for % HbA1c to millimoles per mol, subtract 2·15 and multiply the result by 10·929. To convert the values for plasma glucose to millimoles per liter, multiply by 0·05551. BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; mITT, modified intention-to-treat; OC-AD, observed cases (all data, including values after treatment discontinuation and after rescue therapy); T2D, type 2 diabetes; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation).

Figure S10: **Proportion of participants who achieved the HbA1c target at week 26 – mITT set**

A. HbA1c <6·5% (<48 mmol/mol). Placebo n=53; empagliflozin pooled n=52; linagliptin n=52.

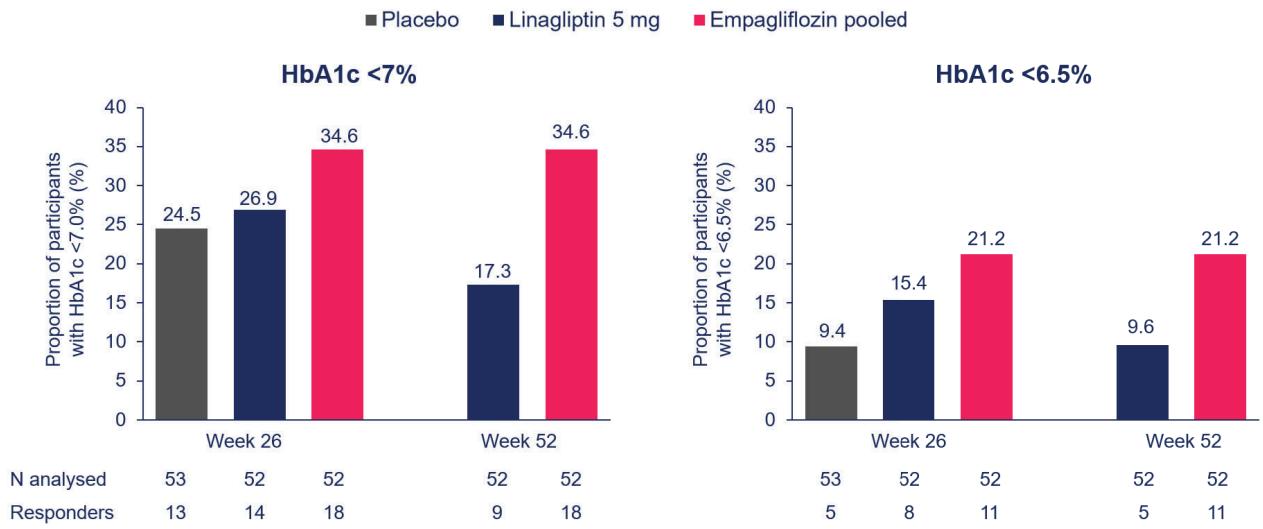


B. HbA1c <7·0% (<53 mmol/mol). Placebo n=53; empagliflozin pooled n=52; linagliptin n=52.



mITT (TG1) (NCF) population. HbA1c, glycated haemoglobin; mITT, modified intention-to-treat; NCF, Non-completers considered failure; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation).

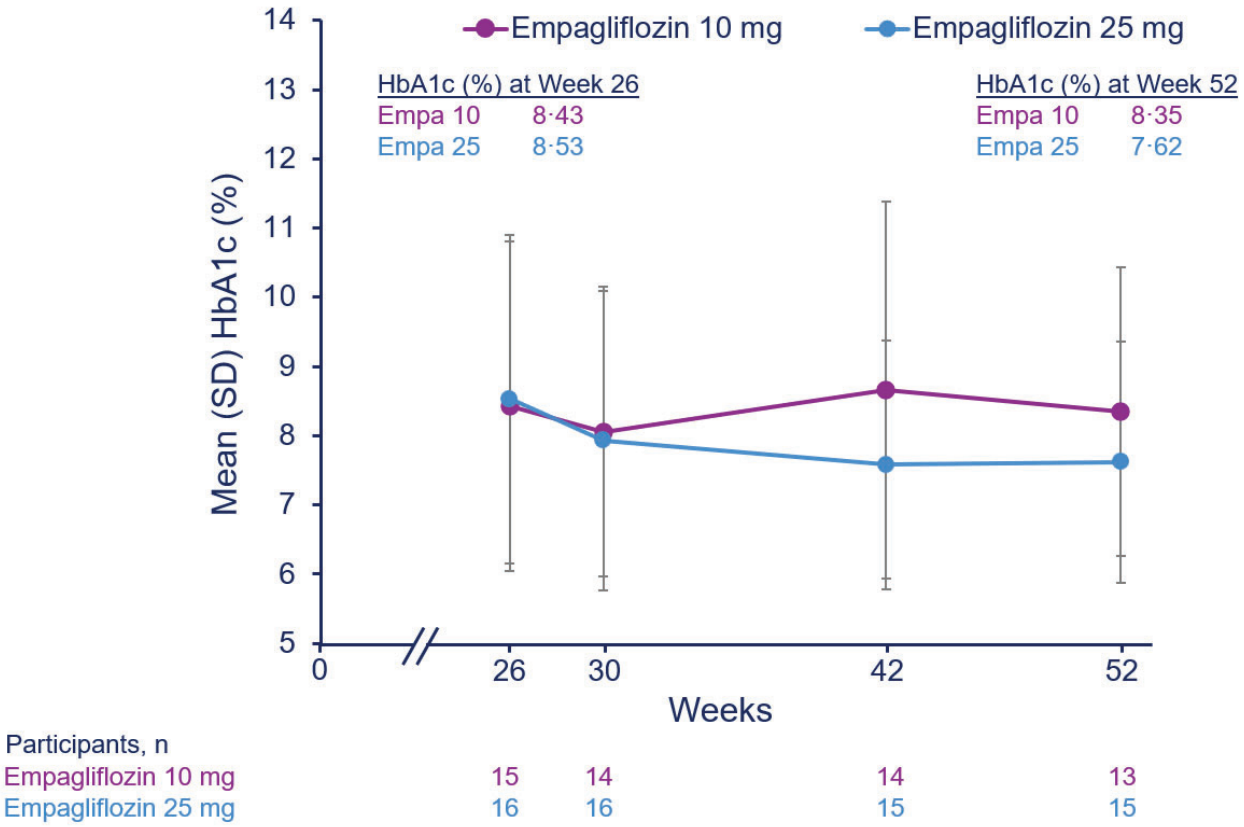
Figure S11: **Proportion of participants achieving HbA1c target <7.0% and <6.5% at weeks 26 and 52**



mITT (NCF) (TG1, TG5). HbA1c, glycated haemoglobin; mITT, modified intention-to-treat; NCF, Non-completers considered failure; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation).

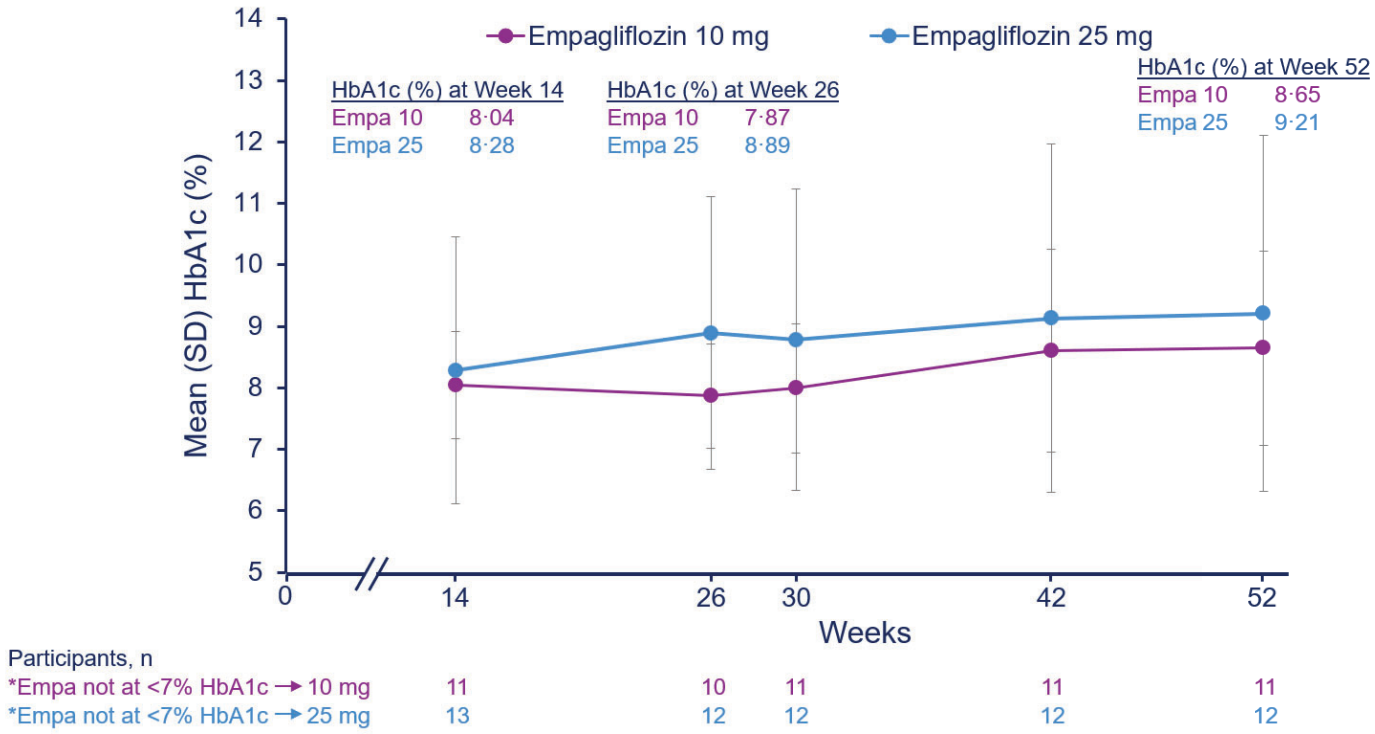
Figure S12: **Change in HbA1c in re-randomised participants**

A. Descriptive data reflecting mean HbA1c over time in participants initially randomised to placebo who were re-randomised at week 26 to receive empagliflozin 10 mg or 25 mg. mITT (TG7) (OC-AD) population.



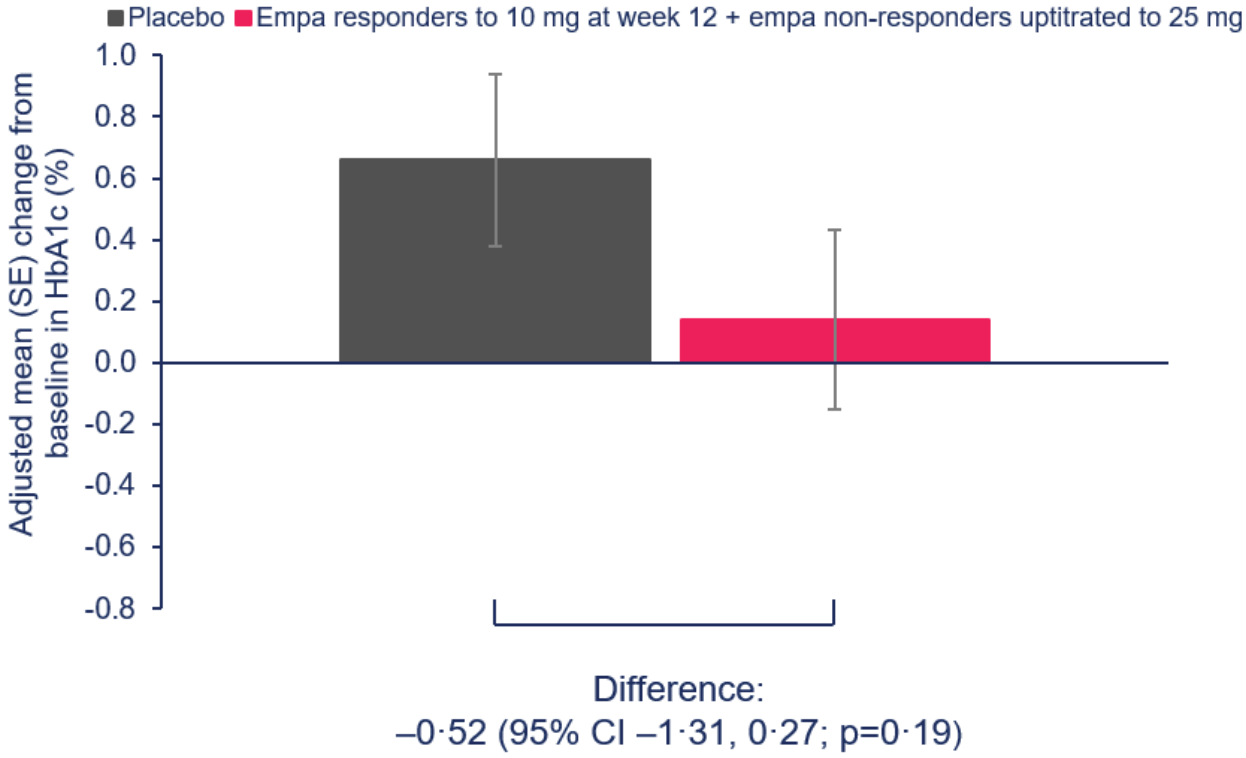
OC-AD, observed cases (all data, including values after treatment discontinuation and after rescue therapy)

B. Descriptive data reflecting mean HbA1c over time in participants initially randomised to empagliflozin who did not achieve a HbA1c target of <7% at week 12 and were re-randomised at week 14 to receive empagliflozin 10 mg or 25 mg. mITT (TG4) (OC-AD) population.



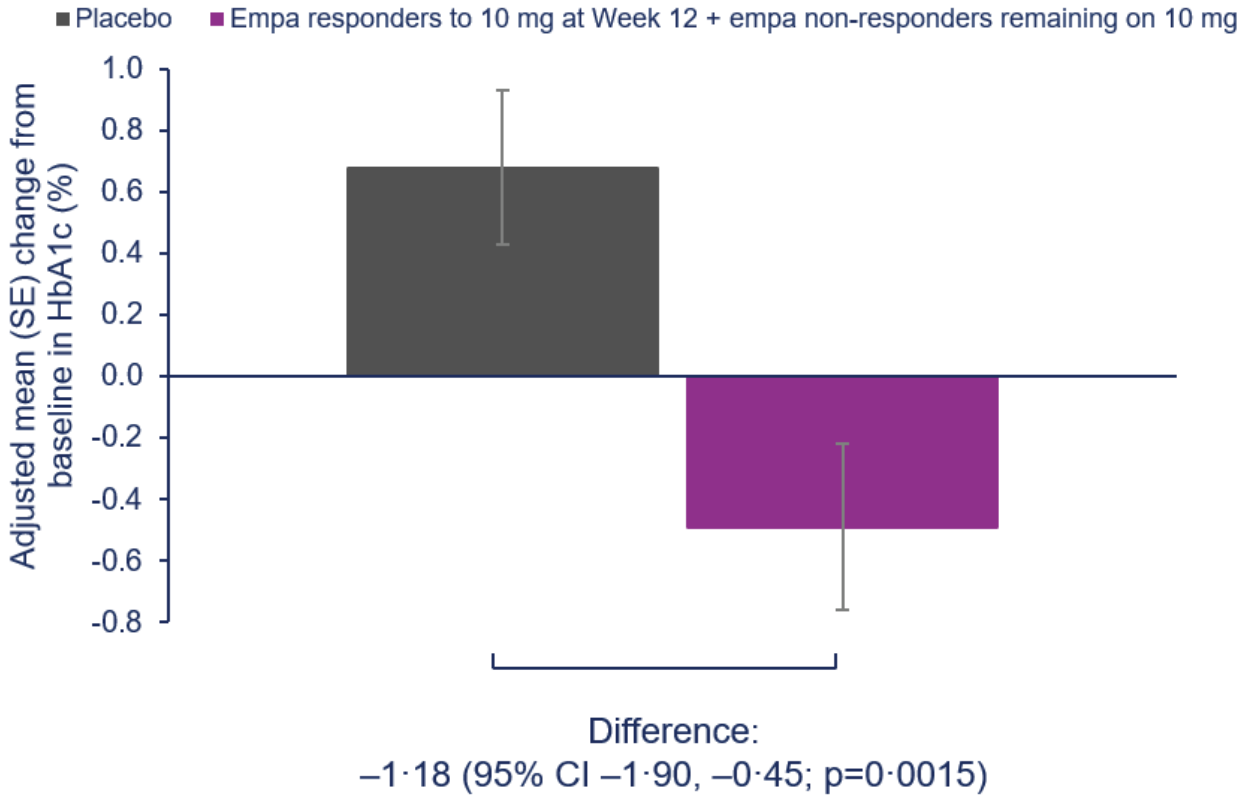
OC-AD, observed cases (all data, including values after treatment discontinuation and after rescue therapy)

C. Change in HbA1c from baseline to week 26 in participants who either achieved a HbA1c target of <7% at week 12 or did not and were re-randomised to empagliflozin 25 mg at week 14. mITT (TG2) (OC-AD) population. Placebo n=53; empagliflozin n=41.



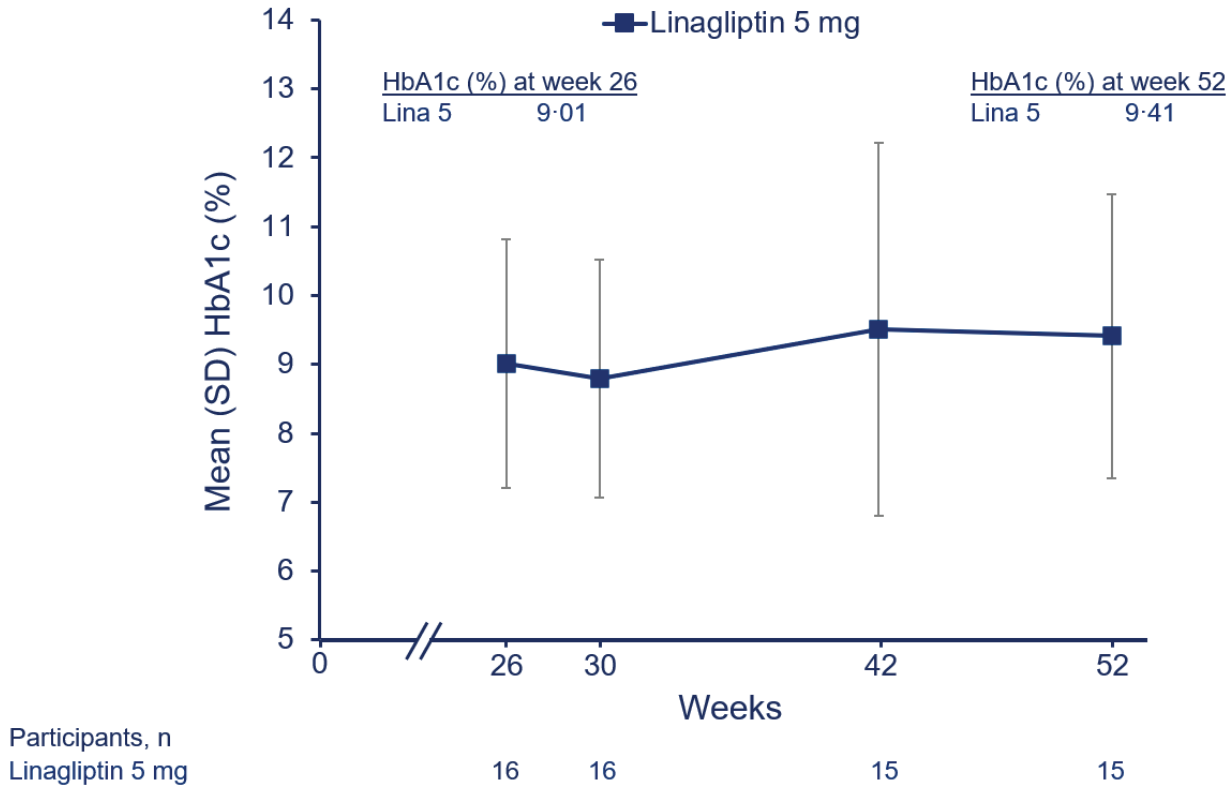
OC-AD, observed cases (all data, including values after treatment discontinuation and after rescue therapy)

D. Change in HbA1c from baseline to week 26 in participants who either achieved a HbA1c target of <7% at week 12 or who did not and were re-randomised to empagliflozin 10 mg at week 14. mITT (TG3) (OC-AD) population. Placebo n=53; empagliflozin n=39.



To convert the values for % HbA1c to millimoles per mol, subtract 2·15 and multiply the result by 10·929. Empa, empagliflozin; HbA1c; glycated haemoglobin; mITT, modified intention-to-treat; OC-AD, observed cases (all data, including values after treatment discontinuation and after rescue therapy); SD, standard deviation; SE, standard error; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation).

Figure S13: **HbA1c over time in participants initially randomised to placebo who were re-randomised at week 26 to receive linagliptin**



Descriptive data reflecting mean HbA1c from weeks 26 to 52 in participants in the placebo group who were re-randomised to linagliptin 5 mg at week 26.
mITT (TG7) (OC-AD) population. To convert the values for % HbA1c to millimoles per mol, subtract 2·15 and multiply the result by 10·929. HbA1c, glycated haemoglobin; Lina, linagliptin; mITT, modified intention-to-treat; OC-AD, observed cases (all data, including values after treatment discontinuation and after rescue therapy; SD, standard deviation; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation).

Table S1: **Baseline characteristics at time 0 of participants who were initially randomised to empagliflozin 10 mg and subsequently re-randomised at week 14 based on treatment response at week 12**

Baseline characteristics at time 0	Empagliflozin responders at week 12 (N=23)	Empagliflozin non-responders at week 12 re-randomised to 10 mg (N=11)	Empagliflozin non-responders at week 12 re-randomised to 25 mg (N=13)
Sex, n (%)			
Male	9 (39·1)	3 (27·3)	5 (38·5)
Female	14 (60·9)	8 (72·7)	8 (61·5)
Region, n (%)			
North America	15 (65·2)	7 (63·6)	9 (69·2)
South America	5 (21·7)	2 (18·2)	2 (15·4)
Europe	3 (13·0)	1 (9·1)	2 (15·4)
Asia	0 (0·0)	1 (9·1)	0 (0·0)
Race, n (%)			
American Indian or Alaska Native	3 (13·0)	0 (0·0)	0 (0·0)
Asian	1 (4·3)	1 (9·1)	0 (0·0)
Black or African American	8 (34·8)	6 (54·5)	4 (30·8)
Native Hawaiian or Other Pacific Islander	0 (0·0)	0 (0·0)	0 (0·0)
White	10 (43·5)	3 (27·3)	7 (53·8)
All other	1 (4·3)	1 (9·1)	2 (15·4)
Ethnicity, n (%)			
Non-Hispanic or Latino	17 (73·9)	7 (63·6)	7 (53·8)
Hispanic or Latino	6 (26·1)	4 (36·4)	6 (46·2)
Age, years, mean ± SD	14·6 ± 1·9	14·6 ± 1·6	13·9 ± 2·2
Median (IQR)	15·0 (13·0, 16·0)	14·0 (14·0, 16·0)	14·0 (12·0, 16·0)
Time since diagnosis of diabetes, n (%)			

<1 year	7 (30·4)	5 (45·5)	4 (30·8)
1 to 3 years	9 (39·1)	5 (45·5)	6 (46·2)
>3 years	7 (30·4)	1 (9·1)	3 (23·1)
BMI, kg/m^2, mean ± SD	35·33 ± 7·21	33·68 ± 9·15	36·06 ± 5·84
Median (IQR)	34·80 (30·09, 38·68)	32·62 (28·21, 36·81)	36·10 (33·35, 41·12)
BMI z-score, n (%)			
>2 to ≤3 (Class 1 obesity)	10 (43·5)	6 (54·5)	4 (30·8)
>3 (Class 2 to 3 obesity)	10 (43·5)	4 (36·4)	8 (61·5)
Weight, kg, mean ± SD	100·17 ± 25·42	93·15 ± 27·52	98·91 ± 21·01
Median (IQR)	94·50 (87·00, 117·00)	91·70 (77·10, 104·60)	94·10 (83·20, 109·80)
Fasting C-peptide, nmol/L, mean ± SD	0·9586 ± 0·3283	0·7657 ± 0·3247	1·1714 ± 0·8332
Median (IQR)	0·9422 (0·7657, 1·1914)	0·7673 (0·5347, 0·9835)	0·8218 (0·7129, 1·4554)
eGFR (Zappitelli), mL/min/1.73 m^2, mean ± SD	123·35 ± 22·05	130·77 ± 22·61	138·84 ± 36·28
Median (IQR)	119·48 (105·48, 143·76)	132·20 (104·50, 151·25)	125·21 (120·41, 137·59)
Tanner scoring score, n (%)			
1	0 (0·0)	0 (0·0)	0 (0·0)
2 to 4	12 (52·2)	4 (36·4)	6 (46·2)
5	11 (47·8)	7 (63·6)	7 (53·8)
HbA1c, %, mean ± SD	7·20 ± 0·91	8·76 ± 1·15	8·24 ± 1·08
HbA1c, n (%)			
<8.5%	21 (91·3)	5 (45·5)	8 (61·5)
≥8.5%	2 (8·7)	6 (54·5)	5 (38·5)
FPG, mg/dL, mean ± SD	131·73 ± 46·08	181·61 ± 44·74	168·80 ± 76·31
Median (IQR)	115·3 (104·0, 144·0)	172·1 (150·1, 210·1)	158·0 (130·6, 215·6)

*Data quoted from descriptive analyses over time by treatment, which did not include study totals.

To convert the values for % HbA1c to millimoles per mol, subtract 2·15 and multiply the result by 10·929. To convert the values for plasma glucose to millimoles per liter, multiply by 0·05551. The BMI is the weight in kilograms divided by the square of the height in metres. BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose, HbA1c, glycated haemoglobin; IQR, interquartile range; mITT, modified intention-to-treat; SBP, systolic blood pressure; SD, standard deviation.

Table S2: **Baseline characteristics of the participants – background antidiabetic treatment – mITT set**

Characteristic	Placebo (N=53)	Empagliflozin pooled (N=52)	Linagliptin 5 mg (N=52)	Total (N=157)
Background antidiabetic treatment, n (%)				
Metformin only	28 (52·8)	26 (50·0)	26 (50·0)	80 (51·0)
Insulin only	2 (3·8)	3 (5·8)	0 (0·0)	5 (3·2)
Metformin and insulin	19 (35·8)	22 (42·3)	22 (42·3)	63 (40·1)
None (diet and exercise only, metformin not tolerated)	4 (7·5)	1 (1·9)	4 (7·7)	9 (5·7)

mITT, modified intention-to-treat.

Table S3: **Adverse events in participants on empagliflozin 10 mg up to week 14, and adverse events across the 3 groups receiving empagliflozin between weeks 15 and 26 in comparison to placebo.**

	Up to week 14		Weeks 15–26			
Header title	Placebo N=53	Empagliflozin 10 mg N=52	Placebo N=49	Responders on empagliflozin 10 mg N=23	Non-responders on empagliflozin 10 mg N=11	Non-responders on empagliflozin 25 mg N=13
Any AE	30 (56·6)	37 (71·2)	17 (34·7)	9 (39·1)	5 (45·5)	3 (23·1)
Severe AE	1 (1·9)	0 (0·0)	1 (2·0)	0 (0·0)	1 (9·1)	0 (0·0)
Drug-related AE (investigator-defined)	5 (9·4)	7 (13·5)	2 (4·1)	3 (13·0)	2 (18·2)	1 (7·7)
AE leading to discontinuation	2 (3·8)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Serious AE	1 (1·9)	1 (1·9)	1 (2·0)	0 (0·0)	1 (9·1)	0 (0·0)
Fatal	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Life-threatening*	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	1 (9·1)	0 (0·0)
Persistent or significant disability/incapacity	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Requiring/prolonging hospitalisation*	1 (1·9)	1 (1·9)	1 (2·0)	0 (0·0)	1 (9·1)	0 (0·0)
Congenital anomaly/birth defect	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Other*	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	1 (9·1)	0 (0·0)
Other significant AEs (according to ICH E3)	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)

AEs of special interest and specific AEs						
Hypersensitivity reactions	1 (1·9)	4 (7·7)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Skin lesions	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Pemphigoid in bullous conditions	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Pancreatitis	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Pancreatic cancer	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Hepatic injury	1 (1·9)	2 (3·8)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Decreased renal function	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Diabetic ketoacidosis	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Increased ketone reported as AE	1 (1·9)	1 (1·9)	1 (2·0)	1 (4·3)	0 (0·0)	0 (0·0)
AEs leading to lower limb amputation	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Hypoglycaemia adverse events	4 (7·5)	11 (21·2)	3 (6·1)	3 (13·0)	0 (0·0)	2 (15·4)
PG <54 mg/dL	2 (3·8)	9 (17·3)	3 (6·1)	0 (0·0)	0 (0·0)	1 (7·7)
Severe hypoglycaemia requiring assistance	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Urinary tract infection	1 (1·9)	1 (1·9)	0 (0·0)	0 (0·0)	1 (9·1)	1 (7·7)
Genital infection	0 (0·0)	0 (0·0)	1 (2·0)	1 (4·3)	0 (0·0)	0 (0·0)
Acute pyelonephritis or urosepsis	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Bone fracture	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Arthralgia	1 (1·9)	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Volume depletion	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Other AEs in at least >5% of participants						
Infections and infestations	10 (18·9)	13 (25·0)	4 (8·2)	3 (13·0)	2 (18·2)	1 (7·7)
Nasopharyngitis	2 (3·8)	3 (5·8)	1 (2·0)	0 (0·0)	0 (0·0)	0 (0·0)

Influenza	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Metabolism and nutrition disorders	10 (18·9)	14 (26·9)	4 (8·2)	5 (21·7)	0 (0·0)	2 (15·4)
Vitamin D deficiency	5 (9·4)	5 (9·6)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Hyperglycaemia	1 (1·9)	0 (0·0)	2 (4·1)	1 (4·3)	0 (0·0)	0 (0·0)
Gastrointestinal disorders	7 (13·2)	12 (23·1)	4 (8·2)	1 (4·3)	0 (0·0)	0 (0·0)
Abdominal pain	2 (3·8)	3 (5·8)	2 (4·1)	0 (0·0)	0 (0·0)	0 (0·0)
Diarrhoea	4 (7·5)	2 (3·8)	1 (2·0)	0 (0·0)	0 (0·0)	0 (0·0)
Vomiting	1 (1·9)	3 (5·8)	1 (2·0)	0 (0·0)	0 (0·0)	0 (0·0)
Nausea	3 (5·7)	3 (5·8)	0 (0·0)	1 (4·3)	0 (0·0)	0 (0·0)
Nervous system disorders	8 (15·1)	10 (19·2)	3 (6·1)	0 (0·0)	1 (9·1)	0 (0·0)
Headache	6 (11·3)	7 (13·5)	1 (2·0)	0 (0·0)	1 (9·1)	0 (0·0)
Dizziness	2 (3·8)	2 (3·8)	1 (2·0)	0 (0·0)	0 (0·0)	0 (0·0)
Respiratory, thoracic and mediastinal disorders	6 (11·3)	2 (3·8)	2 (4·1)	0 (0·0)	0 (0·0)	0 (0·0)
Cough	3 (5·7)	0 (0·0)	1 (2·0)	0 (0·0)	0 (0·0)	0 (0·0)
Epistaxis	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Renal and urinary disorders	3 (5·7)	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Microalbuminuria	1 (1·9)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Skin and subcutaneous tissue disorders	1 (1·9)	4 (7·7)	0 (0·0)	1 (4·3)	0 (0·0)	0 (0·0)
Rash	0 (0·0)	3 (5·8)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Immune system disorders	0 (0·0)	2 (3·8)	0 (0·0)	2 (8·7)	0 (0·0)	0 (0·0)
Seasonal allergy	0 (0·0)	2 (3·8)	0 (0·0)	2 (8·7)	0 (0·0)	0 (0·0)

TS (TG1) population; MedDRA version used for reporting: 25.0. Definition of serious adverse event includes: death, life-threatening, hospitalisation, prolongation of hospitalisation, significant disability, congenital anomaly/birth defect,

medical/surgical intervention. Definition of life-threatening adverse event: participant at risk of death (not an event that might cause death if more severe).
*For serious adverse events defined as life-threatening, requiring/prolonging hospitalisation, or other, the following were reported. Placebo: 1 patient experienced life-threatening events requiring hospitalisation (splenic vein thrombosis, abdominal pain, pancreatitis acute, systemic inflammatory response syndrome, diabetic ketoacidosis, acute kidney injury, acute respiratory failure, hypovolaemic shock); 1 patient required hospitalisation (hyperglycaemia). Empagliflozin: 1 patient experienced life-threatening events requiring hospitalisation (suicidal ideation) and other events (road traffic accident); 1 patient required hospitalisation (skin candida). Linagliptin: 1 patient experienced other events (breast abscess); 1 patient experienced other events (pneumomediastinum).
MedDRA, Medical Dictionary for Regulatory Activities; TG, treatment groupings (see Supplementary Appendix for detailed explanation); TS, treated set.

Table S4: **Overall summary of adverse events up to week 52 for empagliflozin 10 mg, empagliflozin 25 mg and linagliptin 5 mg following re-randomisation at week 26**

Participants, n (%)	Empagliflozin 10 mg after initial placebo (N=15)	Empagliflozin 25 mg after initial placebo (N=16)	Linagliptin 5 mg after initial placebo (N=16)
Any adverse event	11 (73·3)	8 (50·0)	10 (62·5)
Severe adverse events	1 (6·7)	0 (0·0)	0 (0·0)
Drug-related adverse events (investigator-defined)	2 (13·3)	2 (12·5)	3 (18·8)
Adverse events leading to discontinuation	0 (0·0)	0 (0·0)	1 (6·3)
Serious adverse event	0 (0·0)	0 (0·0)	2 (12·5)
Fatal	0 (0·0)	0 (0·0)	0 (0·0)
Life-threatening	0 (0·0)	0 (0·0)	0 (0·0)
Persistent or significant disability/incapacity	0 (0·0)	0 (0·0)	0 (0·0)
Requiring/prolonging hospitalization	0 (0·0)	0 (0·0)	1 (6·3)
Congenital anomaly/birth defect	0 (0·0)	0 (0·0)	0 (0·0)
Other	0 (0·0)	0 (0·0)	1 (6·3)
Other significant adverse events (according to ICH E3)	0 (0·0)	0 (0·0)	1 (6·3)

TS (TG7) (exposure adjusted) population; MedDRA version used for reporting: 25.0
Definition of serious adverse events include: death, life-threatening, hospitalisation, prolongation of hospitalisation, significant disability, congenital anomaly/birth defect, medical/surgical intervention. Definition of life-threatening adverse events: patient at risk of death (not an event that might cause death if more severe).
ICH, International Council for Harmonisation; MedDRA, Medical Dictionary for Regulatory Activities; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation); TS, treated set.

Table S5: **Overall summary of adverse events up to week 52 for empagliflozin 10 mg and empagliflozin 25 mg following re-randomisation at week 14**

Patients, n (%)	**Empagliflozin 10 mg** after initial empagliflozin 10 mg non-responder **(N=11)**	**Empagliflozin 25 mg** after initial empagliflozin 10 mg non-responder **(N=13)**
Any adverse event	9 (81·8)	10 (76·9)
Severe adverse events	1 (9·1)	0 (0·0)
Drug-related adverse events (investigator-defined)	2 (18·2)	1 (7·7)
Adverse events leading to discontinuation	0 (0·0)	0 (0·0)
Serious adverse events	1 (9·1)	0 (0·0)
Fatal	0 (0·0)	0 (0·0)
Life-threatening	1 (9·1)	0 (0·0)
Persistent or significant disability/incapacity	0 (0·0)	0 (0·0)
Requiring/prolonging hospitalization	1 (9·1)	0 (0·0)
Congenital anomaly/birth defect	0 (0·0)	0 (0·0)
Other	1 (9·1)	0 (0·0)
Other significant adverse events (according to ICH E3)	0 (0·0)	0 (0·0)

TS (TG4) (exposure adjusted) population; MedDRA version used for reporting: 25.0
Definition of serious adverse events include: death, life-threatening, hospitalisation, prolongation of hospitalisation, significant disability, congenital anomaly/birth defect, medical/surgical intervention. Definition of life-threatening adverse events: patient at risk of death (not an event that might cause death if more severe).
ICH, International Council for Harmonisation; MedDRA, Medical Dictionary for Regulatory Activities; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation); TS, treated set.

Table S6: Overall summary of adverse events up to week 52 – Treated set (active)

Participants, n (%)	Empagliflozin pooled (N=83)	Linagliptin 5 mg (N=68)
Any adverse event	63 (75·9)	51 (75·0)
Severe adverse event	3 (3·6)	4 (5·9)
Drug-related adverse event (investigator-defined)	14 (16·9)	17 (25·0)
Adverse event leading to discontinuation	1 (1·2)	1 (1·5)
Serious adverse event	3 (3·6)	8 (11·8)
Fatal	0 (0·0)	0 (0·0)
Life-threatening	1 (1·2)	0 (0·0)
Persistent or significant disability/incapacity	0 (0·0)	0 (0·0)
Requiring/prolonging hospitalisation	3 (3·6)	5 (7·4)
Congenital anomaly/birth defect	0 (0·0)	0 (0·0)
Other	1 (1·2)	3 (4·4)
Other significant adverse events (according to ICH E3)	0 (0·0)	1 (1·5)
Adverse events of special interest and specific adverse events		
Hypersensitivity reactions	5 (6·0)	3 (4·4)
Skin lesions	0 (0·0)	0 (0·0)
Pemphigoid in bullous conditions	0 (0·0)	0 (0·0)
Pancreatitis	0 (0·0)	0 (0·0)
Pancreatic cancer	0 (0·0)	0 (0·0)
Hepatic injury	3 (3·6)	5 (7·4)
Decreased renal function	0 (0·0)	1 (1·5)
Diabetic ketoacidosis	0 (0·0)	2 (2·9)
Increased ketone reported as AE	8 (9·6)	8 (11·8)
Adverse events leading to lower limb amputation	0 (0·0)	0 (0·0)
Hypoglycaemia adverse events	16 (19·3)	15 (22·1)
PG <54 mg/dL	15 (18·1)	11 (16·2)
Severe hypoglycaemia requiring assistance	0 (0·0)	0 (0·0)
Urinary tract infection	6 (7·2)	1 (1·5)
Genital infection	1 (1·2)	4 (5·9)
Acute pyelonephritis or urosepsis	0 (0·0)	0 (0·0)
Bone fracture	0 (0·0)	1 (1·5)
Arthralgia	2 (2·4)	5 (7·4)

Volume depletion	0 (0·0)	2 (2·9)
Other adverse events in at least >5% of participants		
Infections and infestations	33 (39·8)	32 (47·1)
Nasopharyngitis	4 (4·8)	6 (8·8)
Upper respiratory tract infection	5 (6·0)	3 (4·4)
Influenza	3 (3·6)	4 (5·9)
Metabolism and nutrition disorders	31 (37·3)	26 (38·2)
Vitamin D deficiency	10 (12·0)	6 (8·8)
Hyperglycaemia	3 (3·6)	6 (8·8)
Gastrointestinal disorders	21 (25·3)	19 (27·9)
Vomiting	7 (8·4)	8 (11·8)
Diarrhoea	5 (6·0)	7 (10·3)
Abdominal pain	4 (4·8)	5 (7·4)
Nausea	3 (3·6)	4 (5·9)
Investigations	18 (21·7)	21 (30·9)
Increased urine albumin/creatinine ratio	2 (2·4)	5 (7·4)
Nervous system disorders	17 (20·5)	14 (20·6)
Headache	13 (15·7)	12 (17·6)
Respiratory, thoracic and mediastinal disorders	9 (10·8)	14 (20·6)
Cough	5 (6·0)	6 (8·8)
Oropharyngeal pain	5 (6·0)	3 (4·4)
Reproductive system and mediastinal disorders	7 (8·4)	4 (5·9)
Dysmenorrhoea	7 (8·4)	2 (2·9)
Musculoskeletal and connective tissue disorders	8 (9·6)	9 (13·2)
Arthralgia	2 (2·4)	4 (5·9)

TSactive (TG6) (exposure adjusted) population; MedDRA version used for reporting: 25.0. Definition of serious adverse events include: death, life-threatening, hospitalisation, prolongation of hospitalisation, significant disability, congenital anomaly/birth defect, medical/surgical intervention. Definition of life-threatening adverse events: patient at risk of death (not an event that might cause death if more severe). ICH, International Council for Harmonisation; MedDRA, Medical Dictionary for Regulatory Activities; TG, treatment groupings (see Treatment group definitions in this Supplementary Appendix for detailed explanation); TS, treated set.

This supplement contains the following items:

Note: The DINAMO CTP and SAP operationally cover a separate ancillary study called DINAMO MONO, which is not the subject of this paper, evaluating the same treatment regimens as in DINAMO but in youth who are treatment naïve or not on active treatment after metformin withdrawal. The DINAMO MONO ancillary study was added during the conduct of the DINAMO study based on a request from regulators. For clarification purposes, sections in the CTP and SAP that are applicable for DINAMO MONO only that do not apply for DINAMO are highlighted in gray.

Overview of Amendments to the Clinical Trial Protocol

(further details regarding protocol amendments are presented in section 11 of the final Clinical Trial Protocol, page 117-148 of this supplement)

There were 8 versions of the clinical trial protocol (CTP), of which 2 versions (Version 1, dated 29 May 2017, and Version 6, dated 14 Jul 2021) were only submitted to the FDA and never implemented due to the requested changes. A total of 6 global amendments were issued which required approval of the Independent Ethics Committees and/or Institutional Review Boards (IEC/IRB) before implementation. In addition, there were local amendments in Argentina (1 amendment), Germany (4 amendments), Portugal (5 amendments), Thailand (1 amendment), and the United Kingdom (2 amendments); none of them impacted a large number of patients. Major changes in the global amendments are summarized below:

CTP version 1, dated 29 May 2017

This version was only submitted to the FDA and never implemented due to the requested changes.

CTP version 2, dated 11 Oct 2017

This version contained the feedback from the FDA on Version 1 and was the original CTP which was implemented. Changes compared with Version 1 included e.g.:

- In-/exclusion criteria were modified
- Initial randomization to 25 mg empagliflozin replaced with re-randomization for non-responders after Week 14
- Length of the primary analysis was prolonged from 24 to 26 weeks
- Statistical method of primary endpoint analysis was adapted

CTP version 3 with Global Amendment 1, dated 3 Oct 2019

Streamlining and clarification of wording and inclusion of authority feedback (FDA proposed pediatric study request, EMA pediatric investigational plan, and Medicine and Healthcare products Regulatory Agency in the UK) as follows:

- Statistical method for primary endpoint changed from MMRM to pattern mixture model (jump-to-placebo and inverse probability weighting approach). The previous MMRM became a sensitivity analysis
- Number of patients increased in DINAMO (from 138 to 150 patients)
- Trial part with DINAMO Mono added
- Minor adaptions to the flow chart including additional interactions between patient and site
- Exclusion criterion specified (acute metabolic decompensation)
- Addition of further efficacy endpoint (proportion of patients who achieve HbA1c reduction of >0.5% at the end of 26 and 52 weeks)
- Frequency for blood ketone bodies measurement adapted

- Addition of AESIs arthralgia, bullous pemphigoid, AEs related to reduced intravascular volume
- Removal of hospitalization for unstable angina and of pancreatic events from the adjudication process
- New recommendations on diet and exercise for the patients by the site
- Addition of BMI as new subgroup

CTP version 4 with Global Amendment 2, dated 28 Sep 2020

Streamlining and clarification of wording, inclusion of authority feedback (FDA and EMA), and addition of measures related to the COVID-19 pandemic as follows:

- Updated inclusion criteria: reduction in length of diagnosis of T2DM from 12 to 8 weeks and addition of minimum daily metformin dosage
- Change in primary endpoint analysis from pattern mixture model ('jump-to-placebo' and 'inverse probability weighting' approach) to 'wash-out' and 'inverse probability weighting' approach for primary and secondary hypotheses
- Addition of measures related to the COVID-19 pandemic
  - Addition of remote visits
  - Guidance added for patients stopping prematurely (also related to DKA)
  - Addition of local instead of central laboratory testing
  - Shipment of trial medication directly to the patients
  - Possibility added to replace patients to keep a certain sample size despite the pandemic
  - Addition of alternative method for SAE report transmission in certain countries
  - Addition of sensitivity analysis for the primary endpoint
  - Rules implemented for remote source data verification during restricted on-site monitoring visits

CTP version 5 with Global Amendment 3, dated 14 Dec 2020

Administrative changes, streamlining of wording, and addition of further measures related to the COVID-19 pandemic as follows:

- Reconsent could be done remotely due to the COVID-19 pandemic
- Serum pregnancy test could be done at a local laboratory due to the COVID-19 pandemic

CTP version 6 with Global Amendment 4, dated 14 Jul 2021

This version was only submitted to the FDA and never implemented due to the requested changes. It included administrative changes, clarified wording, and incorporated feedback from the FDA on the previous global amendment.

- Time reduced between rescreening visits (from 12 to 8 weeks) to allow earlier inclusion of patients
- Clarification of maintaining the blinded conditions while the bioanalyst required access to the data when migrating from the main trial to the ancillary trial

- If a centrally analysed, NGSP-certified HbA1c assay was unavailable (e.g. due to the COVID-19 pandemic), an HbA1c assay performed at a local laboratory was acceptable. Text added to specify the corresponding sensitivity analyses
- Addition of an alternative means to measure blood glucose concentration
- Clarification of the secondary hypotheses for the ANCOVA

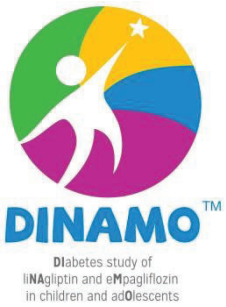
CTP version 7 with Global Amendment 5, dated 28 Sep 2021

This amendment included administrative changes and incorporated feedback from the FDA:

- Clarification that patients with a CGM device could use relevant readings from that device to avoid additional finger pricks
- Further clarification on secondary hypotheses for the ANCOVA

CTP version 8 with Global Amendment 6, dated 23 May 2022

This amendment mainly impacted the ancillary trial DINAMOTM Mono which is still ongoing. Changes regarding DINAMO included addition of bone fracture as further safety endpoint; bone fracture was already introduced via the initial TSAP version.

	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:	Christy Schroeder Boehringer Ingelheim Pharmaceuticals, Inc. 900 Ridgebury Rd., P.O. Box 368 Ridgefield, CT 06877, USA Phone: +1 (203) 798-4722, Fax: +1 (203) 837-5869	
Coordinating Investigator:	Professor Lori Laffel Joslin Diabetes Center Boston, MA 02215, USA Tel: +1 617 732 2603 Fax: +1 617 309 2447	
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:	Professor Lori Laffel Joslin Diabetes Center Boston, MA 02215, USA
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

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

	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.

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

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%

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
	• 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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Protocol date: 11 Oct 2017	**Trial number:** 1218-0091		**Revision date:** 23 May 2022

	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).

TABLE OF CONTENTS

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.

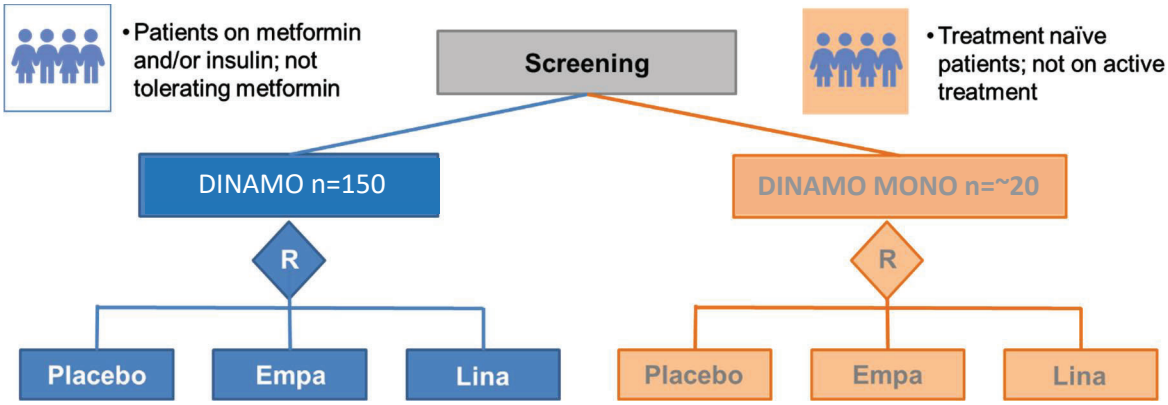


Figure 3.1: 1 Patient repartition into DINAMO™ and DINAMO™ Mono

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).

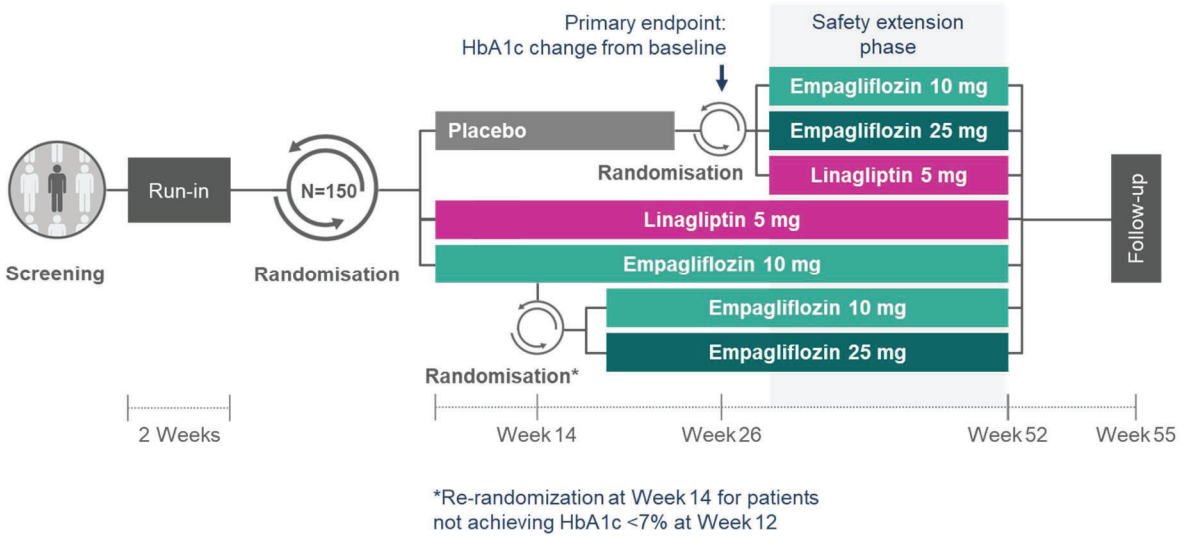
Except for patients who would discontinue the trial treatment for safety reasons, every effort should be made to re-introduce trial treatment after a temporary trial drug discontinuation. For the analysis of this trial it is very important that assessments for each planned visit are still performed in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

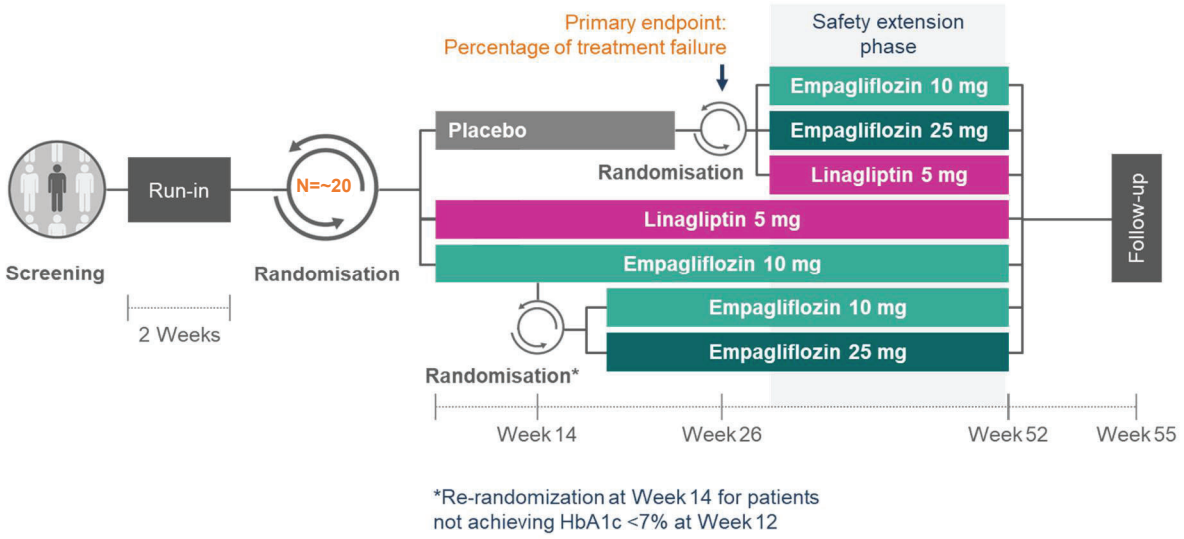


Figure 3.1: 2 Trial duration, primary endpoint, and treatment groups for a) DINAMO™ and b) DINAMO™ Mono

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^{TM}: HbA1c ≥ 6.5% and ≤ 10.5%
    b. DINAMO^{TM} Mono: HbA1c ≥ 6.5% and ≤ 9.0%

7. a. DINAMO^{TM}: 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^{TM} 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™) 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)

5.1.3.1 Further endpoints to assess efficacy

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

- Change in HbA1c (%) from baseline to the end of 12 and 52 weeks

- Change in FPG (mg/dl) from baseline to the end of 52 weeks
- Change in body weight (kg) from baseline to the end of 12 and 52 weeks
- Change in SBP (mmHg) from baseline to the end of 12 and 52 weeks
- Change in DBP (mmHg) from baseline to the end of 12 and 52 weeks
- Proportion of patients who achieve HbA1c < 6.5% at the end of 52 weeks
- Proportion of patients who achieve HbA1c < 7.0% at the end of 52 weeks
- Proportion of patients who achieve HbA1c reduction of > 0.5% at the end of 26 and 52 weeks
- Proportion of patients who initiate glycaemic rescue therapy up to 26 weeks and 52 weeks
    - Note: any new antidiabetic therapy, any dose increase of basal insulin of more than 0.1 IU/kg above the baseline prescribed dose for more than 21 consecutive days will be considered rescue therapy.
- Change in fasting serum C-peptide from baseline to the end of 26 and 52 weeks
- Change in urine albumin creatinine ratio (UACR) (mg/mmol) from baseline to the end of 26 and 52 weeks
- Change in eGFR (mL/min/1.73m²) from baseline to the end of 26 and 52 weeks
- For DINAMO™ only: Change in HbA1c (%) from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and not achieving glycaemic target at Week 12

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

5.1.3.3 Further PK endpoint(s)

Further PK endpoints are listed below for both DINAMO™ and DINAMO™ Mono:

- Empagliflozin and linagliptin trough levels in plasma after 26 and 52 weeks

More details and additional further endpoints may be defined in the trial statistical analysis plan (TSAP).

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, baso-phils, 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 x $e^{0.003 \times height}$) / (Cystatine $C^{0.635}$xSerum Creatinine$^{0.547}$ [µmol/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.

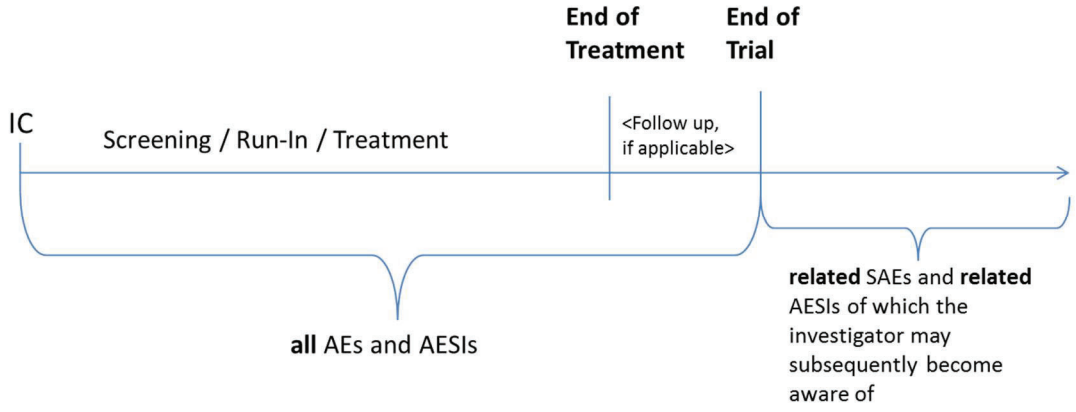


Figure 5.3.6.2: 1 Trial periods for collection of AEs

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.

5.4.3 Analytical determinations

During sample analysis, the bioanalyst will be blinded to patient allocation and will have no access to the random code.

5.4.3.1 Analytical determination of empagliflozin plasma concentration

Empagliflozin concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay at BASi (Bioanalytical Systems Inc.),

West-Lafayette, USA. All details of the analytical method will be available prior to the start of sample analysis.

5.4.3.2 Analytical determination of linagliptin plasma concentration

Linagliptin concentrations will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay at Covance Laboratories Ltd, Harrogate, UK. All details of the analytical method will be available prior to the start of sample analysis.

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 Menal, Im Hausgrün 15, D-79312 Emmendingen, Germany.

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.

7.3.3 Further endpoint analyses

Analyses of all further exploratory endpoints for both DINAMO™ and DINAMO™ Mono as defined in Section 5.1.3 will be performed as follows:

- Descriptive summary statistics will be presented for each continuous endpoint, and at each visit if appropriate. Selected continuous endpoints (to be defined in the TSAP) with the parameter measured at least twice on-treatment will be analysed using an MMRM model, if appropriate.

- Binary endpoints will be tabulated with the frequency and proportion in each treatment group, by visit if appropriate.

Further details about the analysis strategy for all endpoints will be described in the TSAP.

7.3.4 Sensitivity analyses of the primary endpoint

These sensitivity analyses will be performed in an explorative manner, and further details will be specified in the TSAP.

7.3.4.1 DINAMO

7.3.4.1.1 Primary family of hypotheses – MMRM effectiveness analysis

A MMRM on the mITT set will provide a sensitivity analysis for the confirmatory tests of the primary family of null hypotheses. Patients will be assigned to the treatment they were randomised to at the initial randomisation, i.e. linagliptin 5 mg, empagliflozin 10 mg or placebo. All HbA1c values measured after premature discontinuation of study drug or after rescue therapy was initiated will be included in the analysis. Furthermore, only data up to the Week 26 time point will be included.

For the analyses, the mean changes in HbA1c from baseline to the end of 26 weeks will be analysed based on a REML approach using an 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 covariates baseline HbA1c and baseline HbA1c 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. Patient will be included as random effect.

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 treatment comparisons will be the contrasts between active treatments and placebo at Week 26.

7.3.4.1.2 Secondary family of hypotheses – MMRM effectiveness analysis

The same MMRM analysis method as described in Section 7.3.4.1.1 will be applied as a sensitivity analysis for the tests of the secondary family of hypotheses. However, the non-responders at Week 12 who are not in the hypothesis empagliflozin regime will be censored for the analysis.

7.3.4.1.3 MMRM efficacy analysis

An efficacy analysis will be performed on the mITT set. Patients will be assigned to the treatment they were randomised to at the initial randomisation, i.e. linagliptin 5 mg, empagliflozin 10 mg or placebo. All HbA1c values measured after premature discontinuation of study drug or after rescue therapy was initiated will be set to missing for the respective patients. Furthermore, only data up to the Week 26 time point will be included.

For the analyses of efficacy, the mean changes in HbA1c from baseline to the end of 26 weeks will be analysed based on a REML approach using a MMRM model. The analysis will include the fixed categorical effects of treatment, visit, and treatment by visit interaction, as well as the categorical covariate age and the continuous covariates baseline HbA1c and baseline HbA1c 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. Patient will be included as random effect.

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 treatment comparisons will be the contrasts between active treatments and placebo at Week 26.

7.3.4.1.4 Analyses on further patient set

The analyses of the primary endpoint, see Section 7.3.1.1, will be repeated on the PPS using the same statistical model as for the primary effectiveness analyses in order to assess the impact of important protocol deviations.

7.3.4.1.5 Primary family of hypotheses – COVID-19 related intercurrent events

An additional sensitivity analysis will allow to assess the impact of COVID-19 related intercurrent events on the primary analysis. While the primary analysis reflects a treatment policy estimand this sensitivity analysis will include a hypothetical component for COVID-19 related intercurrent events observed prior to the assessment of the primary endpoint.

Intercurrent events will be classified into 2 categories: Not COVID-19 related and COVID-19 related (regardless of logistic or direct infection). Missing data after not COVID-19 related intercurrent events will be handled as described in Section 7.3.1.1, including the use of a wash-out analysis for missing off-treatment data in the active treatment groups.
On-treatment data after COVID-19 related intercurrent events will be included in the sensitivity analysis as observed. Off-treatment data and data after the start of rescue data will be set to missing if they were observed after a COVID-19 related intercurrent event. All

missing on-treatment, off-treatment and data after start of rescue data will be imputed using different methods for the placebo and active groups with the corresponding treatment group data. For the placebo group, MCMC-MI and SLR-MI will be used to impute data according to the missing data type (non-monotone or monotone) for all scheduled visits up to Week 26 as described in Section 7.3.1.1. For the active treatment groups, SLR-MI will be used to impute missing Week 26 data only.

7.3.4.1.6 Primary family of hypotheses – Non-NGSP certified laboratories HbA1c values

This additional sensitivity analysis will allow assessment of the impact of the non-NGSP certified laboratories to determine HbA1c values on the primary analysis. The non-NGSP certified laboratory values will be replaced by multiply imputed HbA1c values assuming the MAR-method as for the placebo group in the primary analysis, based on observed NGSP certified HbA1c values in the respective treatment group (separately for on- and post-treatment values); details will be specified in the TSAP.

7.3.4.2 DINAMO Mono

7.3.4.2.1 Primary analysis with DINAMO eligible patients

The DINAMO Mono primary analysis described in Section 7.3.1.2 will be repeated with addition of DINAMO patients without background medication and fulfilled DINAMO Mono inclusion criteria.

7.3.5 Subgroup analyses (for DINAMO only)

Additional analyses on the primary endpoint will be performed including analyses which investigate interactions of treatments with baseline variables/subgroups. Such analyses will be specified in the TSAP. In general, “wash-out” approach as for the primary analysis will be used. Descriptive statistics will be provided. Subgroup analyses will include:

- Age
- BMI
- BMI z-score
- Sex
- Race
- Region
- Baseline HbA1c
- Baseline FPG
- Baseline eGFR
- Background antidiabetic treatment
- Time since diagnosis of T2DM

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 Statistical Solutions Ltd.

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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c02090424 Population Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Modeling of Empagliflozin in Patients with Type II diabetes mellitus. Mattthew Riggs, Ph.D. Kyle Baron, Ph.D. 06 Feb 2014

c09087100 An open-label, randomised, multicentre, single-dose, parallel group trial to evaluate pharmacokinetics and pharmacodynamics of empagliflozin in children and adolescents from 10 to less than 18 years of age with type 2 diabetes mellitus. Dr Jan Marquard, Dr Dagmar Hobson, Jing Wu, Dr Gudrun Simons, Dr Valerie Nock. 1245.87. 18 May 2016

c09060697 A randomised, double-blind, placebo-controlled parallel group dose-finding study of linagliptin (1 mg or 5 mg administered orally once daily) over 12 weeks in children and adolescents, from 10 to 17 years of age, with type 2 diabetes mellitus. Dr Jan Marquard, Dr Cornelia Hoesl, Guillaume Frappin, Willem Hettema. 1218.56. 02 May 2016

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c02697848 A Phase III randomised, double-blind, placebo-controlled, parallel group efficacy and safety study of Linagliptin (5 mg), administered orally once daily for at least 52 weeks in type 2 diabetic patients in combination with basal insulin therapy. Dr Sabine Pinnetti, Dr Clive Brown, Sudipta Bhattacharya, Dr Christian Friedrich. 1218.36. 11 May 2012

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U08-3761 A randomized, double-blind, placebo-controlled, five parallel group study investigating the efficacy and safety of BI 1356 (0.5 mg, 2.5 mg and 5 mg administered orally once daily) over 12 weeks in drug naïve and treated patients with Type 2 diabetes with insufficient glycemic control (study includes an open-label metformin treatment arm). 1218.5. 20 May 2010.

U09-1970 Safety, tolerability, pharmacokinetics and pharmacodynamics of 4 weeks treatment with three oral doses of BI 10773 as tablets in female and male patients with type 2 diabetes. 1245.4. 23 Sep 2009.

U09-1271 Safety, tolerability, pharmacokinetics and pharmacodynamics of 4 multiple rising oral doses (2.5 mg to 100 mg) of BI 10773 tablets in male and female type 2 diabetic patients. 1245.2. 24 Mar 2009.

U09-2533-03 A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy. 1218.17. 11 Mar 2011.

U10-2326 A Phase II, randomised, double-blind, placebo-controlled, multiple dose study to evaluate pharmacodynamics, pharmacokinetics, safety, and tolerability of once daily oral administration of BI 10773 (1 mg, 5 mg, 10 mg, and 25 mg) for 28 days in Japanese patients with type 2 diabetes mellitus. 1245.15. 23 Aug 2010.

U11-2286-01 Pinnetti S, Bhattacharya S, Brown C. A Phase III randomised, double-blind, placebo-controlled, parallel group efficacy and safety study of Linagliptin (5 mg), administered orally once daily for at least 52 weeks in type 2 diabetic patients in combination with basal insulin therapy. BI trial 1218.36 final report date: 21 September 2011.

U10-1103 A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycaemic control. 1218.16. 15 Mar 2011.

U12-1518-01	A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg, 25 mg) administered orally, once daily over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite treatment with metformin alone or metformin in combination with a sulphonylurea
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.

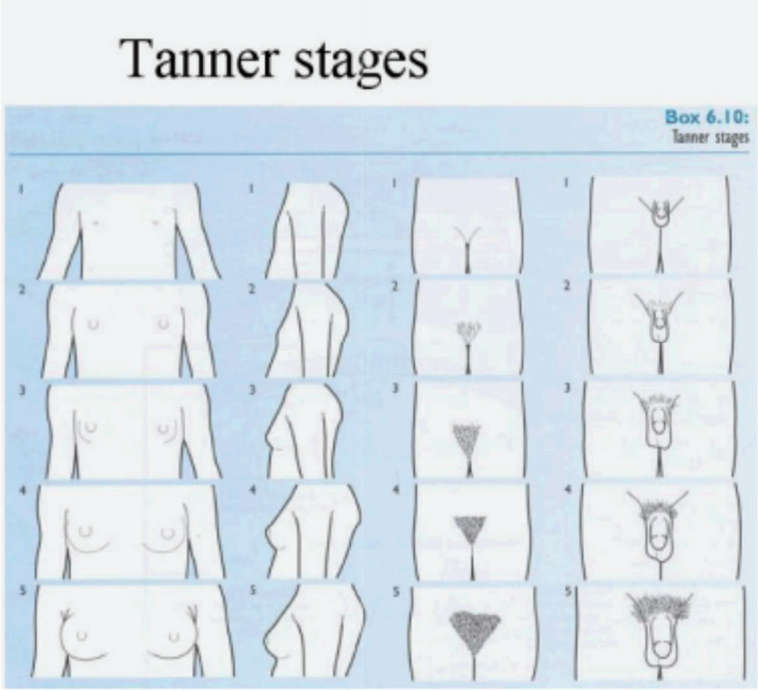

Figure 10.1: 1 Tanner Stages

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^{TM} 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		**5.1.3.1 Further endpoints to assess efficacy**
Description of change		Additional further endpoint and one further endpoint applicable for DINAMO™ only.
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA
Section to be changed		**5.1.3.2 Further endpoint to assess safety**
Description of change		The addition of AESI and further endpoint for DINAMO™ and DINAMO™ Mono.
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA.

Section to be changed		**5.1.3.1 Further PK endpoint(s)**
Description of change		Clarify that endpoint apply to both DINAMO™ and DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin Proposed Pediatric Study Request (PPSR) agreed with FDA.
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		**7.3.1.4 Subgroup analyses**
Description of change		Moved to Section 7.3.5.
Rationale for change		To tidy the section for the ease of understanding.
Section to be changed		**7.3.2 Secondary endpoint analyses**
Description of change		Added sections 7.3.2.1 DINAMO™ (include the original section 7.3.2 content) and section 7.3.2.2 DINAMO™ Mono
Rationale for change		To reflect the linagliptin and empagliflozin PPSR agreed with FDA
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		**7.3.3 Further endpoint analyses**
Description of change		Removed reference to the MMRM primary analysis. Updated some wording for clarification.
Rationale for change		To reflect the removal of the MMRM primary analysis.
Section to be changed		**7.3.4 Sensitivity analyses**
Description of change		Replaced Section 7.3.1.3 with this new section. Described only for DINAMO™ only
Rationale for change		To make the content of the protocol easier to follow.
Section to be changed		**7.3.4.1 Primary family of hypotheses – MMRM effectiveness analysis**
Description of change		Added new sensitivity MMRM effectiveness analysis for the primary family of hypotheses.
Rationale for change		To provide a sensitivity analysis for the confirmatory tests of the primary family null hypotheses.
Section to be changed		**7.3.4.2 Secondary family of hypotheses – MMRM effectiveness analysis**

Description of change		Added new sensitivity MMRM effectiveness analysis for the secondary family of hypotheses.
Rationale for change		To provide a sensitivity analysis for the tests of the secondary family of hypotheses.
Section to be changed		**7.3.4.3 MMRM efficacy analysis**
Description of change		Added new sensitivity MMRM efficacy analysis for the primary endpoint.
Rationale for change		To provide a sensitivity analysis using the MMRM with the data with only the on-treatment values.
Section to be changed		**7.3.4.4 Analyses on further patient set**
Description of change		This section is created from a paragraph in the old Section 7.3.1.3.
Rationale for change		To make the content of the protocol easier to follow.
Section to be changed		**7.3.5 Subgroup analyses**
Description of change		The content of this section came from the legacy Section 7.3.1.4. Added PMM "jump-to-placebo" approach is the main analysis method and "BMI" as a new subgroup. Described for DINAMO™ only
Rationale for change		To make the content of the protocol easier to follow and the analysis method clarification.
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		**7.3.5 Subgroup analyses**
Description of change		1. Updated the primary endpoint analysis from "PMM "Jump-to-placebo" approach" to ""wash-out" approach" 2. Updated "BMI SDS" to "BMI z-score" 3. Updated "Gender" to "Sex"
Rationale for change		1. Based on FDA request. 2. Update the variable name to the correct format. 3. Update the variable name to the correct format.
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		**7.3.4 Sensitivity analyses of the primary endpoint**
Description of change		Added new section 7.3.4.6 Primary family of hypotheses – Non-NGSP certified laboratories HbA1c values.
Rationale for change		To test if the use of non-NGSP certified HbA1c values affect the analyses.
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		**5.1.3.2. Further endpoint to assess safety**
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		**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

Trial Statistical Analysis Plan

c20394975-05

BI Trial No.:	1218-0091
Title:	A double-blind, randomised, placebo-controlled, parallel group trial to evaluate the efficacy and safety of empagliflozin and linagliptin over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus. The DINAMO™ (main study) and DINAMO™ Mono (ancillary study) studies. Including Revised Protocol (Global Amendment 6) [c03490746-08]
Investigational Product(s):	Linagliptin (BI 1356) Empagliflozin (BI 10773)
Responsible trial statistician(s):	Tess Lam Syneos Health 1 Pinehurst Road, Farnborough, Hampshire, GU14 7BE, United Kingdom. Phone: +44 (0)1276 713 571
Date of statistical analysis plan:	28 JUL 2022 REVISED
Version:	Revised

1 TABLE OF CONTENTS

LIST OF TABLES

2 LIST OF ABBREVIATIONS

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

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

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

3 INTRODUCTION

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

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

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

4 CHANGE IN THE PLANNED ANALYSIS OF THE STUDY

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

5 ENDPOINTS

5.1 PRIMARY ENDPOINTS

DINAMO

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

For the definition of baseline HbA1c refer to Section 6.7.

DINAMO Mono

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

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

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

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

5.2.2 Secondary endpoints

DINAMO™

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

DINAMO Mono

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

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

5.3 FURTHER ENDPOINTS

5.3.1 Further efficacy endpoints

Further exploratory efficacy endpoints for both DINAMO and DINAMO Mono are the following:

- Change in HbA1c [%] from baseline to the end of 12 and 52 weeks
- Change in FPG [mg/dl] from baseline to the end of 52 weeks
- Change in body weight [kg] from baseline to the end of 12 and 52 weeks
- Change in SBP [mmHg] from baseline to the end of 12 and 52 weeks
- Change in DBP [mmHg] from baseline to the end of 12 and 52 weeks
- Proportion of patients who achieve HbA1c < 6.5% at the end of 52 weeks
- Proportion of patients who achieve HbA1c < 7.0% at the end of 52 weeks
- Proportion of patients who achieve HbA1c reduction of > 0.5% in absolute value at the end of 26 and 52 weeks

- Proportion of patients who initiate glycaemic rescue therapy up to 26 weeks (including Week 26 visit) and 52 weeks (including Week 52 visit)
    - For DINAMO, the use of rescue therapy is defined as meeting at least one of the following criteria:
        - Any new addition of antidiabetic therapy introduced after the first dose of study treatment.
        - Any total daily dose increase of basal insulin of more than 0.1 IU/kg above the baseline prescribed dose for more than 21 consecutive days.
    - For DINAMO^{TM} Mono, the use of rescue therapy is defined as any use of antidiabetic therapy other than the study treatment.
- Change in fasting serum C-peptide [nmol/L] from baseline to the end of 26 and 52 weeks
- Change in urine albumin creatinine ratio (UACR) [mg/g crea] from baseline to the end of 26 and 52 weeks
- Change in estimated Glomerular Filtration Rate (eGFR) [mL/min/1.73m²], calculated according to Zappitelli et al. formula, from baseline to the end of 26 and 52 weeks
- For DINAMO only, change in HbA1c [%] from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and being not at glycaemic target (HbA1c < 7.0%) at Week 12

5.3.2 Further safety and tolerability endpoints

Further safety endpoints for both DINAMO and DINAMO Mono are the following:

- Adverse events (AE) up to 26 and 52 weeks, including adverse events of special interest (AESI) (see CTP Section 5.3.6.1), genital infections, urinary tract infections, acute pyelonephritis or urosepsis, bone fracture, arthralgia, bullous pemphigoid, adverse events related to reduced intravascular volume and ketone measurements reported as AE
- Percentage of patients with reported hypoglycaemia up to 26 and 52 weeks
- Vital signs and heart rate [bpm] after 26 and 52 weeks
- Change from baseline in Tanner staging after 26 and 52 weeks
- Change from baseline in serum electrolytes, haematology, 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] after 26 and 52 weeks
- Change from baseline in body mass index (BMI) [kg/m^2] after 26 and 52 weeks
- Growth velocity [cm/year] after 26 and 52 weeks

5.3.3 Other endpoints

Further pharmacokinetics (PK) endpoints are listed below for both DINAMO and DINAMO Mono:

- Plasma concentrations of empagliflozin and linagliptin pre-dose and 1.5 hours post-dose after 26 and 52 weeks.

5.4 OTHER VARIABLES

5.4.1 Demographic variables

The following parameters will be derived for use in the statistical analysis of study data:

BMI:

$$BMI\ [kg/m^2] = Weight/Height^2$$

BMI is derived in the BRAVE system for eCRF data capture at specific visits and represented as such in SDTM. For analysis purposes, BMI will also be derived at visits where only weight was collected, using the last available height that was reported prior to the date of weight measurement. In case of missing height at screening, height can be carried backward for the derivation.

The body mass index standard deviation score (BMI z-score) and height standard deviation score (height z-score) will utilise the WHO Reference centile curves for BMI and height. The distribution of BMI and height as they change according to age is shown by the reference centile curves. The changing distribution of three curves representing the median (M), coefficient of variation (S) and skewness (L) which is expressed as a Box-Cox power are summarised by the LMS method (10). The three curves can be fitted as cubic splines with non-linear regression using penalised likelihood, and the amount of smoothing needed can be given in terms of smoothing parameters or equivalent degrees of freedom. BMI LMS references for girls and boys are presented in Table 9.5: 1. Height LMS references for girls and boys are presented in Table 9.5: 2.

The BMI z-score and height z-score of a child is calculated from the L, M and S curves with values appropriate for the child's age and sex:

$$BMI\ or\ Height\ \ z-score = \frac{((BMI\ or\ Height/M)^L - 1)}{(L \times S)}$$

The age in month at informed consent will be used to determine the values of L, M and S.

Growth velocity:

$$Growth\ velocity\ [cm/year] = 365.25\left(\frac{(Height\ at\ Week\ X) - (Height\ at\ baseline)}{(Week\ X\ visit\ date) - (Baseline\ visit\ date)}\right)$$

5.4.2 Treatment exposure

Extent of treatment exposure [days] will be generally calculated as the difference between the last intake of study drug and the first administration of the study drug plus one day (where last and first intake is dependent on treatment grouping time period).

5.4.3 Time since diagnosis

Time since diagnosis of diabetes mellitus type 2 [years] will be calculated as the difference between the informed consent date and the date of diagnosis plus one day. The number of days will be divided by 365.25 and rounded to the nearest 0.1 years.

5.4.4 Safety data

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

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

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

5.4.5 Start of COVID-19 disruption

The start date of COVID-19 disruption will be defined as the earliest date of the following list.

- COVID-19 related protocol deviation
- Discontinuation of a patient's treatment with study drug or trial participation due to COVID-19
- Onset of a SARS-CoV-2 related AE
- COVID-19 related global BI recruitment hold on March 17, 2020

6 GENERAL ANALYSIS DEFINITION

6.1 TREATMENTS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Treatment grouping 6 (TG6) for active treatment period:

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

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

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

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

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

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

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

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

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

6.2 IMPORTANT PROTOCOL DEVIATIONS

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

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

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

6.3 PATIENT SETS ANALYSED

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

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

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

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

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

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

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

Table 6.3: 1 Patient sets analysed and treatment groupings

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

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

	Patient sets					
Class of endpoint	**SCR**	**TS**	**TSactive**	**RS**	**mITT**	**PPS**
DINAMO - Primary efficacy endpoint						
Primary family of hypothesis - HbA1c [%] CFB - ANCOVA analysis - washout approach					OC-AD (TG1)	
Secondary family of hypothesis - HbA1c [%] CFB - ANCOVA analysis - washout and inverse probability weighting approach					OC-AD (TG2, TG3)	
DINAMO - Sensitivity and subgroup analyses						
Primary family of hypothesis – HbA1c [%] CFB – MMRM effectiveness and efficacy analyses					OC-AD; OC (TG1)	
Secondary family of hypothesis – HbA1c [%] CFB – MMRM effectiveness analysis					OC-AD (TG2, TG3)	
Primary family of hypothesis – HbA1c [%] CFB - ANCOVA analysis - washout approach						OC-AD (TG1)
Secondary family of hypothesis – HbA1c [%] CFB - ANCOVA analysis - washout and inverse probability weighting approach						OC-AD (TG2, TG3)
Primary family of hypothesis – HbA1c [%] CFB - ANCOVA analysis - washout approach according to NGSP status					OC-AD (TG1)	
Primary family of hypothesis – HbA1c [%] CFB - ANCOVA analysis-washout approach by subgroups with forest plot					OC-AD (TG1)	
DINAMO Mono - Primary efficacy endpoint						
Occurrence of treatment failure up to or at Week 26 (DINAMO Mono patients only)					NCF (TG1)	
DINAMO Mono – Sensitivity analysis						
Occurrence of treatment failure up to or at Week 26 (DINAMO Mono and suitable DINAMO patients)					NCF (TG1)	

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

	Patient sets					
Class of endpoint	**SCR**	**TS**	**TSactive**	**RS**	**mITT**	**PPS**
Secondary efficacy endpoints						
Change in FPG [mg/dl] from baseline - ANCOVA					OC-AD-BOCF; OC (TG1)	
Change in body weight [kg] / SBP [mmHg] / DBP [mmHg] from baseline – MMRM					OC-AD; OC (TG1)	
Proportion of patients who achieve HbA1c goals < 6.5% and < 7.0%. Exact CI					NCF; OC (TG1)	
DINAMO Mono – Additional secondary efficacy endpoints						
Time to treatment failure during the course of trial based on KM estimate					OR (TG1, TG5)	
Log rank test for time to treatment failure up to Week 26					NCF (TG1)	
Change in HbA1c [%] from baseline - MMRM effectiveness and efficacy analyses					OC-AD; OC; (TG1)	
Change in HbA1c [%] from baseline - ANCOVA model					OC-LOCF (TG1)	
Change in FPG [mg/dl] from baseline - ANCOVA model					OC-LOCF (TG1)	
Further efficacy endpoints						
Descriptive statistics over time for HbA1C [%], FPG [mg/dL], weight [kg], SBP/DBP [mmHg], fasting serum C-peptide [nmpl/L], UACR [mg/g crea] and eGFR [mL/min/1.73m2] (Zappitelli)					OC-AD; OC (TG1,TG5)	
DINAMO only: Descriptive statistics by visit for change in HbA1C [%]					OC-AD (TG4, TG7)	
Freq. table for the proportion of patients who achieve • HbA1c < 6.5% • HbA1c < 7.0%					NCF; OC (TG1)	
Freq. table for the proportion of patients who achieve HbA1c reduction of > 0.5% in absolute value					NCF (TG1, TG5)	
Freq. table for the proportion of patients who initiated glycaemic rescue therapy					OR (TG1, TG5)	

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

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

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

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

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

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

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

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

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

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

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

6.4 SUBGROUPS

Subgroups to be considered in the efficacy analyses will be defined based on the covariates shown in Table 6.4: 1.

Table 6.4: 1 Categories of covariates for displays of baseline characteristics (including demographics), subgroup analyses and statistical models

Subgroup Variable	Analysis	Categories	Endpoint(s) for which subgroup analyses are to be conducted	Comment
Age [years] at randomisation	Baseline characteristics, Descriptive statistics, Statistical modelling.	<15 ≥15 to <18	DINAMO primary (Descriptive statistics only)[2] Weight SBP DBP FPG Hypoglycaemia[1]	
Baseline HbA1c [%]	Baseline characteristics	Version 1 <8.5 ≥8.5		
	Baseline characteristics, Descriptive statistics, Statistical modelling.	Version 2 <8.0 8.0 to 9.0 >9.0	DINAMO primary	Continuous baseline HbA1c will be replaced by categorical baseline HbA1c in all models
	Baseline characteristics	Version 3 <8.0 ≥8.0		
BMI [kg/m2]	Baseline characteristics	Version 1 <25 25 to <30 30 to <35 ≥35		
	Baseline characteristics, Descriptive statistics, Statistical modelling.	Version 2 < median ≥ median	DINAMO primary	Median value to be calculated across all treatment groups, on TS
	Baseline characteristics	Version 3 <30 ≥30		

Table 6.4: 1 Categories of covariates for displays of baseline characteristics (including demographics), subgroup analyses and statistical models (continued)

Subgroup Variable	Analysis	Categories	Endpoint(s) for which subgroup analyses are to be conducted	Comment
BMI z-score [SD]	Baseline characteristics	Version 1 < -2 (Thin) >= -2 to 1 (Normal) > 1 to 2 (Overweight) > 2 (Obese)		Source: WHO BMI-for-age (5-19 years) growth reference.
	Baseline characteristics, Descriptive statistics, Statistical modelling.	Version 2 <= 2 (Underweight, normal or overweight) > 2 to <=3 (Class 1 obesity) > 3 (Class 2 or 3 obesity)	DINAMO primary	
Baseline FPG [mg/dL]	Baseline characteristics, Descriptive statistics, Statistical modelling.	<126 126 to <140 140 to <200 ≥200	DINAMO primary (Descriptive statistics only)[2] FPG	
Baseline FPG [mmol/L]	Baseline characteristics	<7.0 7.0 to <7.8 7.8 to <11.1 >=11.1		
Baseline BP [mmHg]	Baseline characteristics, Descriptive statistics.	SBP ≥140 or DBP ≥90 SBP <140 and DBP <90	(Descriptive statistics only)[2] SBP DBP	
Geographical region	Baseline characteristics.	Version 1 Asia Europe North America South America		
	Baseline characteristics, Descriptive statistics, Statistical modelling.	Version 2 US Non-US	DINAMO primary	
	Baseline characteristics.	Version 3 East Asian South East Asian Other Asian Other		This subgroup based on race and country. Defined in Table 9.1: 1
Sex	Baseline characteristics, Descriptive statistics, Statistical modelling.	Male Female	DINAMO primary	

Table 6.4: 1 Categories of covariates for displays of baseline characteristics (including demographics), subgroup analyses and statistical models (continued)

Subgroup Variable	Analysis	Categories	Endpoint(s) for which subgroup analyses are to be conducted	Comment
Time since diagnosis of diabetes [year]	Baseline characteristics, Descriptive statistics, Statistical modelling.	<1 year 1 year - 3 years >3 years	DINAMO primary	
Background antidiabetic treatment	Baseline characteristics, Descriptive statistics, Statistical modelling.	Metformin only Insulin only Metformin and insulin None	DINAMO primary	
Metformin total daily dose [mg]	Baseline characteristics	<1500 mg >=1500 mg No metformin		
Ethnicity	Baseline characteristics	Hispanic or latino Not hispanic or latino		
Baseline eGFR [mL/min/1.73 m2] (Zappitelli)	Baseline characteristics.	Version 1 <60 60 to <90 90 to <120 120 to <150 ≥150		
	Descriptive statistics, Statistical modelling.	Version 2 <120 120 to <150 ≥150	DINAMO primary	

Race	Baseline characteristics	<u>Version 1 (Race or combination of races)</u>
		• Single race respondents
		  ○ American Indian or Alaska Native
		  ○ Asian
		  ○ Black or African American
		  ○ Native Hawaiian or other Pacific Islander
		  ○ White
		• Multiple race respondents
		  ○ All race categories with non-zero counts
		• Missing race respondents
				Patients are counted only once. All combinations of multiple races that occur in the trial are displayed.

Table 6.4: 1 Categories of covariates for displays of baseline characteristics (including demographics), subgroup analyses and statistical models (continued)

Subgroup Variable	Analysis	Categories	Endpoint(s) for which subgroup analyses are to be conducted	Comment
Race	Baseline characteristics	Version 2 (Race and combinations of races together) • American Indian or Alaska Native • Asian • Black or African American • Native Hawaiian or other Pacific Islander • White		Patients can be counted multiple times, in each race category they select.
	Baseline characteristics, Descriptive statistics, Statistical modelling.	Version 3 • American Indian or Alaska Native • Asian • Black or African American • Native Hawaiian or other Pacific Islander • White • All other respondents (inc. Multiple and missing race respondents)	DINAMO primary	Patients are counted only once. Patients reporting multiple race or race missing are pooled to make a single category called “Multiple race respondents including subjects with missing race data”.
Tanner stage	Baseline characteristics	Version 1 1 2 3 4 5		
	Baseline characteristics	Version 2 1 2 to 4 5		
Weight [kg]	Baseline characteristics	< 70 70 to < 100 100 to < 130 >= 130		
Smoking history	Baseline characteristics	Never smoker Current smoker Former smoker		

Table 6.4: 1 Categories of covariates for displays of baseline characteristics (including demographics), subgroup analyses and statistical models (continued)

Subgroup Variable	Analysis	Categories	Endpoint(s) for which subgroup analyses are to be conducted	Comment
Baseline UACR [mg/g crea]	Baseline characteristics	< 30 (Normal) 30 to 300 (Microalbuminuria) > 300 (Macroalbuminuria)		
COVID-19 disruption (Week 26)	Descriptive statistics	Permanent discontinuation of study medication or completed Wk26 visit before COVID-19 disruption Permanent discontinuation of study medication and completed Wk26 visit from COVID-19 disruption	Exposure Compliance	
COVID-19 disruption (Week 52)	Descriptive statistics	Permanent discontinuation of study medication before COVID-19 disruption Permanent discontinuation of study medication from COVID-19 disruption	Exposure Compliance	
SARS-CoV-2 infection	Frequency tables	With SARS-CoV-2 infection	AEs	Patients with treatment emergent AE in narrow BIcMQ 'SARS-CoV-2 infections' or PT 'Suspected COVID-19'.
Urine Erythrocytes (URBC) and Urine leukocytes (UWBC)	Frequency tables	Normal High		

[1] Defined as rate of symptomatic hypoglycaemic AEs with confirmed plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemic AEs
[2] Refers to endpoint "change in XXX from baseline to the end of 26 weeks".

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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

6.6.1 Methods of data selection

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

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

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

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

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

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

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

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

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

6.6.2 Imputation methods

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

Missing safety data will not be replaced.

6.6.3 Missing dates and times

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

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

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

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

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

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

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

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

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

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

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

6.6.4 Missing and incomplete laboratory reference ranges

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

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

6.7 BASELINE, TIME WINDOW, AND CALCULATED VISITS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Only one observation per time window will be selected for analysis. If there are multiple values within a time-window, the value closest to the CTP planned visit day will be selected. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the earliest value will be used. If an observation

is available on the last day of treatment, this observation will be preferably selected over any later observation that is still within the time window. For the Week 26 primary analysis, this is applicable if study drug is stopped during the time window of the Week 26 visit.

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

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

7 PLANNED ANALYSES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

7.1 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

7.1.1 Baseline evaluation

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

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

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

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

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

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

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

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

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

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

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

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

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

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

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

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

7.3 TREATMENT COMPLIANCE

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

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

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

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

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

7.4 PRIMARY ENDPOINTS

7.4.1 DINAMO

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

7.4.1.1 Primary family of analyses

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

For empagliflozin, the following null hypothesis will be tested:

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

For linagliptin, the following null hypothesis will be tested:

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

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

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

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

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

Randomised treatment group: Placebo

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

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

Randomised treatment groups: Linagliptin 5 mg and empagliflozin pooled

Missing HbA1c data will be imputed for Week 26 only.

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

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

Method of imputation

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

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

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

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

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

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

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

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

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

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

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

7.4.1.2 Secondary family of analyses

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

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

followed by:

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

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

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

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

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

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

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

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

7.4.1.3 Sensitivity analyses

A. Primary family of hypotheses – MMRM effectiveness analyses

A MMRM on the mITT (OC-AD) set will provide a sensitivity analysis for the confirmatory tests of the primary family null hypotheses. Patients will be assigned to the treatment they were randomised to at the initial randomisation. Furthermore, only data up to the Week 26 time point will be included.

For the analyses, the changes in HbA1c from baseline to the end of 26 weeks will be analysed based on a restricted maximum likelihood (REML) approach using an MMRM. The analyses will include the fixed categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the categorical covariate age at randomisation and the continuous covariates baseline HbA1c and baseline HbA1c-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. Patient will be included as random effect.

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.

To avoid non-convergence the methods given in the BI statistical position paper should be followed (11).

The statistical model will be:

Change in HbA1c [%] from baseline
= overall mean + categorical age at randomisation + continuous baseline HbA1c + treatment + visit + baseline HbA1c-by-visit interaction + treatment-by-visit interaction + random error.

The treatment comparisons will be the contrasts between active treatments and placebo at all visits up to Week 26 using the treatment grouping 1.

The treatment response over the treatment period will be illustrated for each visit by plotting the adjusted means (SE) for change from baseline in HbA1c at each visit based on the MMRM models.

B. Secondary family of hypotheses – MMRM effectiveness analyses

The same MMRM analysis method as described in Section 7.4.1.3(A) will be applied as a sensitivity analysis for the tests of the secondary family of hypotheses. The treatment

comparisons will be the contrasts between empagliflozin and placebo at all visits up to Week 26 which are described as the treatment grouping 2 and the treatment grouping 3.

C. MMRM efficacy analysis

The primary family of MMRM analyses, as described in Section 7.4.1.3(A), will be repeated on the mITT (OC) set. In addition, the analysis will be carried out in SI unit in Appendix 16.1.13.1.

D. Analyses on further patient set

The analyses of the primary endpoint, see Section 7.4.1.1 and Section 7.4.1.2, will be repeated on the PPS (OC-AD) using the same statistical model as for the primary effectiveness analyses in order to assess the impact of IPDs.

A descriptive statistics table will be presented for the absolute value of HbA1c [%] and HbA1c [%] change from baseline over time up to Week 26 on the PPS (OC-AD) by treatment grouping 1.

E. Primary family of hypotheses – COVID-19 related intercurrent events

The primary endpoint analysis described in Section 7.4.1.1 will be repeated on the mITT set using a specific COVID-19 imputation for treatment grouping 1.

This additional sensitivity analysis will allow assessment of the impact of COVID-19 related intercurrent events on the primary analysis. While the primary analysis reflects a treatment policy estimand this sensitivity analysis will include a hypothetical component for COVID-19 related intercurrent events observed prior to the assessment of the primary endpoint.

Table 7.4.1.3: 1 COVID-19 related intercurrent events

Intercurrent events (ICEs) will be defined and classified according to the following criteria:

ICE category	**ICE criterion**	**Considered COVID-19 related AND undergoing specific imputation for COVID-19 sensitivity analysis:**
Affecting the existence of the measurement	Missing HbA1c at Week 26	Visit 5 HbA1c measurement • documented as missing because of COVID-19 while patient was still on treatment, or • patient prematurely discontinued study prior to Visit 5 for COVID-19 related reasons. Missing off-treatment HbA1c data at Week 26 for reasons unrelated to COVID-19 will undergo imputation rules as for the primary analysis.
	HbA1c value from a non-NGSP certified assay at baseline, Weeks 4, 12 or 26	Always, except for off-treatment HbA1c values at Week 26 in the active treatment groups after premature treatment discontinuation for reasons unrelated to COVID-19 (these will undergo imputation rules as for the primary analysis).
Affecting the interpretation	Treatment discontinuation prior to Week 26	Treatment discontinuation due to SARS-CoV-2 infection or other COVID-19 related reason.
	Treatment interruption between Week 14 and 26	Treatment interruption between Visit 4b and Visit 5 for more than 7 consecutive days if interruption with COVID-19 related reason started from start of COVID-19 disruption.
	Non-compliance at Week 26	Compliance outside [75%, 125%] at Visit 5 (between Visit 4b and Visit 5) with COVID-19 related reason if start of COVID-19 disruption occurred before Visit 5 (exclusive).

Table 7.4.1.3: 1 COVID-19 related intercurrent events (continued)

ICE category	ICE criterion	Considered COVID-19 related AND undergoing specific imputation for COVID-19 sensitivity analysis:
Affecting the interpretation	Start of rescue medication prior to Week 26	Never
	Patient SARS-CoV-2 infection prior to Week 26	SARS-CoV-2 infection AE with onset before or on the date of Visit 5.
	Patient not re-randomised at Week 14 (affects only interpretation of empagliflozin effect)	Never

Available HbA1c measurements at the first date of or after COVID-19 related ICEs affecting the interpretation will be set to missing and will be imputed together with COVID-related missing HbA1c values at Visit 5 according to the rules in Table 7.4.1.3: 2.

Frequency of patients with COVID-19 related intercurrent events will be presented by TG1.

Table 7.4.1.3: 2 Data imputation method following COVID-19 related intercurrent events

Randomised treatment group: Placebo

Missing HbA1c data, regardless whether is related to COVID-19, will be imputed for all scheduled visits up to Week 26, that includes Week 4, Week 12 and Week 26. Using the same method as in Table 7.4.1.1: 1.

Randomised treatment groups: Linagliptin 5 mg and empagliflozin pooled

Missing HbA1c data due to COVID-19 or HbA1c measurements following COVID-19 related intercurrent events affecting the interpretation will be imputed for Week 26 only. Other missing HbA1c data will be imputed using the same method as in Table 7.4.1.1: 1.

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

[1] Markov Chain Monte Carlo – Multiple imputation (MCMC-MI)
[2] Sequential linear regression – Multiple imputation (SLR-MI)
[3] Missing at random (MAR)

F. Primary family of hypotheses – Non-NGSP certified laboratories HbA1c values

The primary endpoint analysis described in Section 7.4.1.1 will be repeated on the mITT set using a specific imputation without the non-NGSP certified laboratory values for treatment grouping 1. If there are any non-NGSP certified HbA1c values at baseline or Week 26 selected for primary efficacy analysis, the following sensitivity analysis will be performed.

This additional sensitivity analysis will allow assessment of the impact of the non-NGSP certified laboratories to determine HbA1c values on the primary analysis. The non-NGSP certified laboratory values will be replaced by multiply imputed HbA1c values assuming the MAR-method as for the placebo group in the primary analysis, based on observed NGSP certified HbA1c values in the respective treatment group (separately for on- and post-treatment values).

For this sensitivity analysis, study baseline HbA1c will be imputed by the last available HbA1c value from a NGSP-certified assay prior to administration of randomised study medication at Day 1. If no HbA1c value from a NGSP-certified assay is available prior to the intake of the randomised treatment, the patient will be excluded from this sensitivity analysis.

Table 7.4.1.3: 3 Data imputation method following non-NGSP certified laboratory HbA1c values

Randomised treatment group: Placebo

Missing HbA1c data and HbA1c values from a non-NGSP certified laboratory will be multiply imputed for all scheduled visits up to Week 26, that includes Week 4, Week 12 and Week 26.

Type of missing data or non-NGSP certified lab data	**Data used for imputation**	**Method to use for**	
		Non-monotone missing or non-NGSP lab data	**Monotone missing or non-NGSP lab data**
On- and post-treatment Non-NGSP lab data or missing data	On- and post-treatment NGSP certified[5] 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])

Table 7.4.1.3: 3 Data imputation method following non-NGSP certified laboratory HbA1c values (continued)

Randomised treatment groups: Linagliptin 5 mg and Empagliflozin pooled

Missing HbA1c data will be imputed for Week 26 as in the primary analysis.

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

For patients with an HbA1c value at Week 26 from a non-NGSP certified laboratory included in the primary analysis, all included non-NGSP certified laboratory values up to and including the primary endpoint will be set to missing and imputed similarly to the MAR based method applied in the placebo group.

Type of non-NGSP certified lab data or missing data	Data used for imputation	Method to use for	
		Non-monotone missing or non-NGSP certified lab data	Monotone missing or non-NGSP certified lab data
On-treatment non-NGSP certified lab data (any visit) or missing data (Week 4 or Week 12)	Observed on-treatment NGSP certified[5] HbA1c data in the respective treatment group, including Baseline, Week 4, Week 12 and Week 26.	MCMC-MI[1] (MAR[3])	SLR-MI[2] (MAR[3])
Post-treatment non-NGSP certified lab data at Week 26	Observed post-treatment NGSP certified[5] HbA1c data in the respective treatment group, including only Baseline and Week 26.	SLR-MI[2] (MAR[3])	

[1] Markov Chain Monte Carlo – Multiple imputation (MCMC-MI)
[2] Sequential linear regression – Multiple imputation (SLR-MI)
[3] Missing at random (MAR)
[4] Missing not at random (MNAR)
[5] NGSP certified lab data including both central and local laboratory.

7.4.1.4 Effect of centre

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

7.4.1.5 Subgroup analyses

The subgroup analyses of the primary endpoint will be performed using mITT (OC-AD) by treatment grouping 1 based on the "wash-out" approach, see Section 7.4.1.1.

Subgroup analyses will include the subgroups as described in Table 6.4: 1.
Subgroups of the categorical variables with fewer than (7 x number of treatments) patients in total will be excluded from the ANCOVA analyses. If this leaves only one group, the analysis will not be conducted.
Subgroups of the continuous variables with fewer than (7 x number of treatments) patients in total will be considered for pooling and categories will be confirmed at the final reporting planning meeting.

ANCOVA models will be fitted for each subgroup separately by modelling the primary endpoint with baseline HbA1c as a continuous model term, and with categorical terms for treatment and age at randomisation, additional model terms for subgroup and subgroup-by-treatment interaction. Rubin's rules will be used to combine treatment estimates across the 500 imputations.

The statistical model is as follows:

Change in HbA1c [%] from baseline to the end of 26 weeks
= overall mean + baseline HbA1c + treatment + categorical age at randomisation + subgroup + subgroup-by-treatment + random error

While modelling for the baseline HbA1c categories, the continuous baseline HbA1c will be replaced by the categorical baseline HbA1c, the category/subgroup for which the analysis is being conducted.

The least square mean differences of change in HbA1c from baseline to the end of 26 weeks by treatment and subgroup will be displayed via forest plot. Descriptive statistics of HbA1c [%] at Week 26 and change from baseline by subgroup using mITT (OC-AD) will also be provided.

7.4.2 DINAMO Mono

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

7.4.2.1 Sensitivity analysis

The analysis of the DINAMO Mono primary endpoint will be repeated on DINAMO Mono patients plus the drug-naïve DINAMO patients who satisfied the DINAMO Mono HbA1c inclusion criteria limit using the same statistical model.

7.4.3 HbA1c data summary

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

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

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

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

7.5.2 (Other) Secondary endpoint(s)

7.5.2.1 DINAMO

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

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

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

The statistical model will be:

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

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

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

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

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

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

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

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

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

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

7.5.2.2 DINAMO Mono

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

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

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

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

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

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

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

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

7.6 FURTHER ENDPOINTS

7.6.1 Further efficacy endpoints

Descriptive statistics tables will be produced for both DINAMO and DINAMO Mono by visit (where relevant) for the following endpoints:

- Change in HbA1c [%] from baseline to the end of 12 and 52 weeks
- Change in FPG [mg/dl] from baseline to the end of 52 weeks
- Change in body weight [kg] from baseline to the end of 12 and 52 weeks
- Change in SBP [mmHg] from baseline to the end of 12 and 52 weeks

- Change in DBP [mmHg] from baseline to the end of 12 and 52 weeks
- Change in fasting serum C-peptide [nmol/L] from baseline to the end of 26 and 52 weeks
- Change in UACR [mg/g crea] from baseline to the end of 26 and 52 weeks
- Change in eGFR [mL/min/1.73m²] (Zappitelli) from baseline to the end of 26 and 52 weeks
- For DINAMO only: Change in HbA1c [%] from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and being not at glycaemic target at Week 12

Descriptive statistics tables will be presented for endpoints up to Week 26 (including the Week 12 endpoints) by treatment grouping 1 and for endpoints up to Week 52 by treatment grouping 5 using mITT (OC-AD and OC) set. In addition, descriptive statistics for the change of FPG will also be presented using OC-AD-BOCF. Descriptive statistics for the change in HbA1c [%] from Week 12 over time up to the end of 52 weeks will be presented by treatment grouping 4 using mITT (OC-AD) set.

Additional descriptive statistics table will be presented for HbA1c [%] from Week 26 up to Week 52 by treatment grouping 7 using mITT (OC-AD), HbA1c [mmol/mol] over time up to Week 52 by treatment grouping 1 and 5 using mITT (OC, OC-AD) and FPG [mmol/L] over time up to Week 52 by treatment grouping 1 and 5 using mITT (OC, OC-AD, OC-AD-BOCF)in Appendix 16.1.13.

Frequency tables will be produced for the following endpoints:

- Proportion of patients who achieve HbA1c < 6.5% at the end of 52 weeks
- Proportion of patients who achieve HbA1c < 7.0% at the end of 52 weeks
- Proportion of patients who achieve HbA1c reduction of > 0.5% in absolute value at the end of 26 and 52 weeks
- Proportion of patients who initiate glycaemic rescue therapy up to 26 weeks (including Week 26 visit) and 52 weeks (including Week 52 visit)

The use of rescue therapy endpoint will be presented by TG1 for up to Week 26 and TG5 for up to Week 52 using mITT set.

The frequency tables for HbA1c treatment response endpoints will be presented in total and by the baseline HbA1c in categories version 2 using mITT (NCF) set, TG1 is for endpoints at Week 26 and TG5 is for endpoints at Week 52.

7.6.2 Further safety endpoints

Descriptive statistics tables will be produced for both DINAMO and DINAMO Mono by visit for the following endpoints:

- Change from baseline in Tanner staging after 26 and 52 weeks
- Growth velocity [cm/year] after 26 and 52 weeks

Frequency shift tables will be presented for the Tanner staging from baseline to Week 26 and Week 52. Descriptive statistics tables will be presented for growth velocity by treatment grouping 1 at Week 26 and treatment grouping 5 at Week 52 using TS (OC-AD).

The AE related endpoints will be reported as described in Section 7.8.1. The laboratory related endpoints will be reported as described in Section 7.8.2. The vital signs related endpoints will be reported as described in Section 7.8.3.

7.6.3 Further PK endpoints

PK analysis will be based on the PKS. Descriptive statistics of plasma concentrations of empagliflozin and linagliptin at the respective sampling time-points will be presented per treatment. Further subgroup analysis of plasma concentrations e.g. according to age at randomisation, will be performed as deemed necessary.

7.7 EXTENT OF EXPOSURE

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

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

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

		≥46 weeks, ≥54 weeks.
First administration of study drug	Date of first study drug intake	Date of first active study drug intake
Last administration of study drug	Date of study drug intake at Week 26 minus 1 day	Date of last active study drug intake

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

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

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

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

7.8 SAFETY ANALYSIS

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

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

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

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

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

7.8.1 Adverse events

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

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

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

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

7.8.1.1 Assignment of AEs to treatment

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

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

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

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

7.8.1.2 Analysis of other significant AEs

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

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

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

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

7.8.1.3 AE summaries

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

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

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

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

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

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

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

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

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

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

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

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

7.8.1.4 Protocol-specified AEs of special interest (AESI)

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

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

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

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

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

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

7.8.1.5 Other specific adverse events

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

Hypoglycaemia

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

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

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

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

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

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

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

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

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

Urinary tract and genital infections

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

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

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

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

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

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

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

Acute pyelonephritis or urosepsis

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

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

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

Bone fractures

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

Arthralgia

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

Pemphigoid in bullous conditions

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

AE related to reduced intravascular volume (Volume depletion)

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

Ketone measurements reported as AE

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

7.8.1.6 Events qualifying for external adjudication by the Clinical Event Committee

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

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

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

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

7.8.1.7 AEs while patients taking wrong study medication

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

7.8.1.8 AE incidence rates

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

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

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

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

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

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

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

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

7.8.1.9 COVID-19

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

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

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

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

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

7.8.2 Laboratory data

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

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

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

7.8.2.1 General laboratory evaluation

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

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

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

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

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

7.8.2.2 Elevated liver enzymes

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

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

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

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

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

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

7.8.2.3 Lipid parameters

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

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

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

7.8.2.4 Renal laboratory parameters

Creatinine and eGFR

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

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

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

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

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

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

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

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

The UACR will be derived with the following formula.

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

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

7.8.2.5 Biomarkers

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

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

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

7.8.3 Vital signs

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

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

7.8.4 ECG

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

8 REFERENCES

1	CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2	BI-KMED-TMCP-MAN-0012: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED
3	BI-KMED-BDS-HTG-0035: "Handling of missing and incomplete AE dates", current version; KMED.
4	BI-KMED-BDS-HTG-0045: "Reporting of clinical trials and project summaries", current version; KMED.
5	BI-KMED-BDS-HTG-0041: "Analysis and presentation of adverse event data from clinical trials", current version; KMED.
6	CPMP/ICH/137/95: "Structure and content of clinical study reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.
7	BI-KMED-BDS-HTG-0042: "Handling, Display and Analysis of Laboratory Data", current version; KMED.
8	Zappitelli M, Parvex P, Joseph L, Paradis G, Grey V, Lau S, et al. Derivation and validation of cystatin C-based prediction equations for GFR in children. Am J Kidney Dis 2006;48(2):221-230[R16-2470]
9	Carpenter JR, Roger JH, Kenward MG. Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat 2013;23(6):1352-1371 [R15-1829]
10	Cole TJ, Green PJ. Smoothing reference centile curves: The LMS method and penalized likelihood. Stat Med 1992;11:1305-1319 [R21-0301]
11	BI Statistical Position Paper – Standards for Inferential Analyses, 1.1 Analyses of Continuous Endpoints – Parallel Group Studies
12	Chan ISF, Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions, Biometrics 1999;55(4):1202-1209 [R15-1346]
13	BI-KMED-BDS-QRG-0010: "Preparation of tables for results disclosure", current version; KMED.
14	BI-KMED-BDS-MAN-0025: “Handling of incomplete reference ranges”, current version; KMED.
15	Central laboratory reference ranges, current version; TMF.

9 ADDITIONAL SECTIONS

9.1 REGION AND COUNTRIES

The below table summarises to which regions countries are assigned.

Table 9.1: 1 Regions, races and countries

Region v1	Country
Asia	China Korea Thailand
Europe	Germany Netherlands United Kingdom Portugal Russia Israel
North America	Canada United States (including Puerto Rico)
South America	Mexico Brazil Colombia Argentina

Region v3	Race	Country
East Asian	Asian	China Korea
South East Asian	Asian	Thailand
Other Asian	Asian	Other
	Multiple (including Asian as one of the selected race)	Any countries (inc. all Asia countries)
Others	American Indian or Alaska Native Black or African American Native Hawaiian or other Pacific Islander White	Any countries (inc. all Asia countries)
	Multiple (excluding Asian)	Any countries (inc. all Asia countries)

9.2 SPECIAL SEARCH CATEGORIES AND ATC LEVELS FOR CONCOMITANT MEDICATION

The defining ATC levels and ATC codes of the WHO DD Special Search Categories, Standard Drug Groupings (SDG) and BI customised Drug Query (BIcDQ) for the use of antihypertensives, ASA and lipid lowering drugs and are shown in Table 9.2:1.

Table 9.2: 1 WHO DD Special Search Categories (SSC)

SSC	SSC subgroup	Type of code	Code(s)
ASA	ASA	ATC4	B01AC
Antihypertensives	Beta-blockers	ATC3	C07A, C07B, C07C, C07D, C07E, C07F
	ACE inhibitors	ATC3	C09A, C09B
	Diuretics	ATC2, ATC3, ATC4	C03 and missing ATC3 category, C03A, C03B, C03C, C03D, C03E, C03X, C02L, C08G, C07B, C07C, C07D, C09BA, C09DA, C08GA
	ARBs	ATC3	C09C, C09D
	Ca-antagonists	ATC3, ATC4	C08C, C08D, C08E, C08G, C09BB, C09DB
	Other	ATC3, ATC4	C09X, C02A, C02B, C02C, C02D, C02K, C02L, C02N, C07E, C07F, C09DX and missing ATC3 code in C02, C03, C07, C08, C09.

Table 9.2: 1 WHO DD Special Search Categories (SSC) (continued)

SSC	SSC subgroup	Type of code	Code(s)
Lipid lowering drugs	Niacin	ATC4	C10AD [Nicotinic acid and derivatives]
	Fibrates	ATC4	C10AB [Fibrates]
	Statins	SDG	Use of SDG for statins
	Ezetimibe	BIcDQ	
	Other	ATC4	C10AC [Bile acid sequestrants], C10AX [Other lipid modifying agents], C10AW

9.3 ADDITIONAL SUB-GROUP ANALYSIS FOR REGIONAL SUBMISSIONS

There are no additional sub-group analyses planned for regional submissions.

9.4 ALGORITHM FOR IMPUTATION ACCORDING TO 'WASHOUT' METHOD

This algorithm imputes missing data as missing at random, except imputes post-treatment data for active treatment groups as missing not at random.

For the Placebo group:

- Non-monotone missing values are imputed using MCMC-MI and based upon this set of imputations.
- Monotone missing values are imputed using SLR-MI. Only observed and available placebo data are used in the first step.

For the active group(s):

- Missing Week 26 on-treatment data are imputed using available Week 26 on-treatment data within each treatment group, and using SLR-MI.
- Missing Week 26 post-treatment data are imputed using available placebo data at Week 26, and using SLR-MI.

The step-by-step approach is as follows:

1. Select all placebo data, including data points at baseline, Week 4, Week 12 and Week 26.

2. Apply MCMC-MI to impute non-monotone missings, creating a monotone pattern.
    a. 500 imputations are performed
    b. Baseline HbA1c is included as continuous covariate, and age as a binary covariate (age<15, ≥15 to <18)
    c. Multiple chains with 200 burn-in iterations per chain
    d. Jeffrey's prior

```
*** Example SAS code ***;
proc mi data=hba1c_h seed=XXXXXXXXXX nimpute=500 out=OUT_MCMC_PL ;
where trt='Placebo' ;
var Hba1c_bl AGEGRP Hba1c_w4 Hba1c_W12 Hba1c_W26 ;
mcmc chain=multiple impute=monotone nbiter=200;
run;
```

3. To each of these 500 newly imputed datasets, now containing placebo data with monotone missings, apply SLR-MI
    a. One imputation is performed for each of the 500 already available datasets
    b. Baseline HbA1c is included as continuous covariate, and age as a binary covariate (age<15, ≥15 to <18)

```
*** Example SAS code ***;
proc mi data= OUT_MCMC_PL seed=XXXX nimpute=1 out=PLACEBO ;
var Hba1c_BL AGEGRP Hba1c_W4 Hba1c_W12 Hba1c_W26;
monotone reg ;
by _imputation_ ;
run;
```

- 500 datasets for placebo are now complete. “PLACEBO”

4. Select patients on the linagliptin treatment, including data for those that were on-treatment at Week 26, with baseline value and both missing and non-missing Week 26 values only

5. Apply SLR-MI with the following:
    a. 500 imputations are performed for each patient
    b. Baseline HbA1c is included as continuous covariate, and age as a binary covariate (age<15, ≥15 to <18)

```
*** Example SAS code ***;
proc mi data=hba1c_h seed=XXXX nimpute=500 out=ONTRT_LINA  ;
where trt =’Lina’ and on-trt_W26='Yes' ;
var Hba1c_BL AGEGRP Hba1c_W26;
monotone reg ;
run;
```

- 500 datasets for linagliptin patients who completed treatment up to Week 26 with missing on-treatment data are now complete.

6. Repeat Steps 4 and 5 for patients on the empagliflozin treatment, including data for those that were on-treatment at Week 26, with baseline value and both missing and non-missing Week 26 values only.

- 500 datasets for empagliflozin patients who completed treatment up to Week 26 with missing on-treatment data are now complete.

7. To impute for missing Week 26 post-treatment HbA1c values in the active treatment groups, apply the following steps:
   - Select placebo patients with non-missing Week 26 (as the basis for the imputation of the active treatment groups), and,
   - Linagliptin patients with missing Week 26 HbA1c and who did not complete 26 weeks of treatment (for imputation), and,
   - Empagliflozin patients with missing Week 26 HbA1c and who did not complete 26 weeks of treatment (for imputation)
   - To this dataset of placebo and active patients
     a. Apply SLR-MI creating 500 imputations for each patient
     b. Baseline HbA1c is included as continuous covariate, and age as a binary covariate (age<15, ≥15 to <18)

```
*** Example SAS code ***;
proc mi data=hba1c_h seed=XXXXXXXXXX nimpute=500 out=OFFTRT_LINA_EMPA
(where=(trt in ('Lina' 'Empa'))) ;
where (trt='Placebo' and hba1c_w26 ne . ) or (trt in ('Lina' 'Empa') and on-trt_W26='No' and
hba1c_w26=. ) ;
var Hba1c_BL AGEGRP  Hba1c_W26;
monotone reg ;
run;
```

   ➢ 500 datasets for linagliptin and empagliflozin with missing post-treatment are now complete.

8. Patients on active treatment that did not complete treatment to Week 26 but who nevertheless had Week 26 HbA1c recorded are referred to as 'Retrieved dropouts'. The data for these patients needs to be collated with the rest and therefore duplicated so that 500 such datasets are available.

```
*** Example SAS code ***;
data OFFTRT_LINA_EMPA_RETDO ;
 set hba1c_h ;
  if trt in ('Lina' 'Empa') and retdo=1 ;
  do _imputation_=1 to 500 ;
  output ;
 end ;
run ;
```

   ➢ 500 datasets for linagliptin and empagliflozin with available post-treatment data are now complete

9. Bring all the data pieces together, coming from the above steps (3, 5, 6, 7 and 8).

    - PLACEBO
    - ONTRT_LINA
    - ONTRT_EMPA
    - OFFTRT_LINA_EMPA
    - OFFTRT_LINA_EMPA_RETDO

    - 500 datasets for all patients with complete data now available
    - Calculate the change from baseline at Week 26 (DELTA_W26)
    - Perform ANCOVA analysis on each of the 500 datasets with relevant covariates
    - Combine the 500 analyses using Rubin's rules
    - The adjusted mean, differences, confidence interval and p-values are in ODS OUTPUT: Lsmeans, Diffs and SolutionF.

```
*** Example SAS code ***;

proc sort data=COMPLETE ; by _imputation_  usubjid ; run ;

ODS OUTPUT LSMEANS=lsmeans DIFFS=diffs SOLUTIONF=pvalues;
PROC MIXED DATA = COMPLETE cl method=reml covtest;
CLASS trt agegp ;
MODEL delta_w26 = hba1c_bl trt agegp / ddfm=kr solution;
LSMEANS trt / cl diff om alpha=0.05;
by _imputation_;
RUN ;
ODS OUTPUT CLOSE;

*** Select Placebo - Empa combination for simplicity (PFH Test 1) ***;
data PLAC_EMPA ;
 set diffs ;
 if trt='Placebo' and _trt ='Empa' ;
 estimate = estimate * -1 ; *** to have Empa - Placebo ***;
 keep _imputation_ estimate stderr ;
run ;
```

```
ods output ParameterEstimates=PLAC_EMPA_RUBIN ;
proc mianalyze data=PLAC_EMPA ;
modeleffects ESTIMATE;
stderr stderr ;
run;

data PLAC_EMPA_FINAL;
 set PLAC_EMPA_RUBIN (keep=estimate stderr lclmean uclmean probt ) ;
 label estimate = 'Delta W26: Empa - Placebo'
       stderr   = 'SE Delta'
        lclmean  = 'Lower 95% CI'
        uclmean  = 'Upper 95% CI'
        probt    = 'P-value' ;
format estimate lclmean uclmean  6.2 stderr 6.3 probt 6.4 ;
 run ;

title “Primary Family of Hypothesis Test 1 (H0,1)” ;
proc print data= PLAC_ EMPA_FINAL noobs label ;
run ;
```

9.5 WHO BMI LMS REFERENCES FOR GIRLS AND BOYS

The below tables summarise the WHO references for BMI and height median (M), coefficient of variation (S) and skewness (L).

Table 9.5: 1 WHO BMI LMS reference for girls and boys

		Boys			Girls		
Year: Month	Month	L	M	S	L	M	S
9: 0	108	-1.6318	16.0490	0.10038	-1.4650	16.0964	0.11816
9: 1	109	-1.6433	16.0781	0.10082	-1.4688	16.1358	0.11859
9: 2	110	-1.6544	16.1078	0.10126	-1.4723	16.1759	0.11901
9: 3	111	-1.6651	16.1381	0.10170	-1.4753	16.2166	0.11943
9: 4	112	-1.6753	16.1692	0.10214	-1.4780	16.2580	0.11985
9: 5	113	-1.6851	16.2009	0.10259	-1.4803	16.2999	0.12026
9: 6	114	-1.6944	16.2333	0.10303	-1.4823	16.3425	0.12067
9: 7	115	-1.7032	16.2665	0.10347	-1.4838	16.3858	0.12108
9: 8	116	-1.7116	16.3004	0.10391	-1.4850	16.4298	0.12148
9: 9	117	-1.7196	16.3351	0.10435	-1.4859	16.4746	0.12188
9: 10	118	-1.7271	16.3704	0.10478	-1.4864	16.5200	0.12228
9: 11	119	-1.7341	16.4065	0.10522	-1.4866	16.5663	0.12268
10: 0	120	-1.7407	16.4433	0.10566	-1.4864	16.6133	0.12307
10: 1	121	-1.7468	16.4807	0.10609	-1.4859	16.6612	0.12346
10: 2	122	-1.7525	16.5189	0.10652	-1.4851	16.7100	0.12384
10: 3	123	-1.7578	16.5578	0.10695	-1.4839	16.7595	0.12422
10: 4	124	-1.7626	16.5974	0.10738	-1.4825	16.8100	0.12460
10: 5	125	-1.7670	16.6376	0.10780	-1.4807	16.8614	0.12497
10: 6	126	-1.7710	16.6786	0.10823	-1.4787	16.9136	0.12534
10: 7	127	-1.7745	16.7203	0.10865	-1.4763	16.9667	0.12571
10: 8	128	-1.7777	16.7628	0.10906	-1.4737	17.0208	0.12607
10: 9	129	-1.7804	16.8059	0.10948	-1.4708	17.0757	0.12643
10: 10	130	-1.7828	16.8497	0.10989	-1.4677	17.1316	0.12678
10: 11	131	-1.7847	16.8941	0.11030	-1.4642	17.1883	0.12713
11: 0	132	-1.7862	16.9392	0.11070	-1.4606	17.2459	0.12748
11: 1	133	-1.7873	16.9850	0.11110	-1.4567	17.3044	0.12782
11: 2	134	-1.7881	17.0314	0.11150	-1.4526	17.3637	0.12816
11: 3	135	-1.7884	17.0784	0.11189	-1.4482	17.4238	0.12849
11: 4	136	-1.7884	17.1262	0.11228	-1.4436	17.4847	0.12882
11: 5	137	-1.7880	17.1746	0.11266	-1.4389	17.5464	0.12914
11: 6	138	-1.7873	17.2236	0.11304	-1.4339	17.6088	0.12946
11: 7	139	-1.7861	17.2734	0.11342	-1.4288	17.6719	0.12978
11: 8	140	-1.7846	17.3240	0.11379	-1.4235	17.7357	0.13009
11: 9	141	-1.7828	17.3752	0.11415	-1.4180	17.8001	0.13040

Table 9.5: 1 WHO BMI LMS references for girls and boys (continued)

		Boys			Girls		
Year: Month	**Month**	**L**	**M**	**S**	**L**	**M**	**S**
11: 10	142	-1.7806	17.4272	0.11451	-1.4123	17.8651	0.13070
11: 11	143	-1.7780	17.4799	0.11487	-1.4065	17.9306	0.13099
12: 0	144	-1.7751	17.5334	0.11522	-1.4006	17.9966	0.13129
12: 1	145	-1.7719	17.5877	0.11556	-1.3945	18.0630	0.13158
12: 2	146	-1.7684	17.6427	0.11590	-1.3883	18.1297	0.13186
12: 3	147	-1.7645	17.6985	0.11623	-1.3819	18.1967	0.13214
12: 4	148	-1.7604	17.7551	0.11656	-1.3755	18.2639	0.13241
12: 5	149	-1.7559	17.8124	0.11688	-1.3689	18.3312	0.13268
12: 6	150	-1.7511	17.8704	0.11720	-1.3621	18.3986	0.13295
12: 7	151	-1.7461	17.9292	0.11751	-1.3553	18.4660	0.13321
12: 8	152	-1.7408	17.9887	0.11781	-1.3483	18.5333	0.13347
12: 9	153	-1.7352	18.0488	0.11811	-1.3413	18.6006	0.13372
12: 10	154	-1.7293	18.1096	0.11841	-1.3341	18.6677	0.13397
12: 11	155	-1.7232	18.1710	0.11869	-1.3269	18.7346	0.13421
13: 0	156	-1.7168	18.2330	0.11898	-1.3195	18.8012	0.13445
13: 1	157	-1.7102	18.2955	0.11925	-1.3121	18.8675	0.13469
13: 2	158	-1.7033	18.3586	0.11952	-1.3046	18.9335	0.13492
13: 3	159	-1.6962	18.4221	0.11979	-1.2970	18.9991	0.13514
13: 4	160	-1.6888	18.4860	0.12005	-1.2894	19.0642	0.13537
13: 5	161	-1.6811	18.5502	0.12030	-1.2816	19.1289	0.13559
13: 6	162	-1.6732	18.6148	0.12055	-1.2739	19.1931	0.13580
13: 7	163	-1.6651	18.6795	0.12079	-1.2661	19.2567	0.13601
13: 8	164	-1.6568	18.7445	0.12102	-1.2583	19.3197	0.13622
13: 9	165	-1.6482	18.8095	0.12125	-1.2504	19.3820	0.13642
13: 10	166	-1.6394	18.8746	0.12148	-1.2425	19.4437	0.13662
13: 11	167	-1.6304	18.9398	0.12170	-1.2345	19.5045	0.13681
14: 0	168	-1.6211	19.0050	0.12191	-1.2266	19.5647	0.13700
14: 1	169	-1.6116	19.0701	0.12212	-1.2186	19.6240	0.13719
14: 2	170	-1.6020	19.1351	0.12233	-1.2107	19.6824	0.13738
14: 3	171	-1.5921	19.2000	0.12253	-1.2027	19.7400	0.13756
14: 4	172	-1.5821	19.2648	0.12272	-1.1947	19.7966	0.13774
14: 5	173	-1.5719	19.3294	0.12291	-1.1867	19.8523	0.13791
14: 6	174	-1.5615	19.3937	0.12310	-1.1788	19.9070	0.13808
14: 7	175	-1.5510	19.4578	0.12328	-1.1708	19.9607	0.13825
14: 8	176	-1.5403	19.5217	0.12346	-1.1629	20.0133	0.13841
14: 9	177	-1.5294	19.5853	0.12363	-1.1549	20.0648	0.13858
14: 10	178	-1.5185	19.6486	0.12380	-1.1470	20.1152	0.13873
14: 11	179	-1.5074	19.7117	0.12396	-1.1390	20.1644	0.13889

Table 9.5: 1 WHO BMI LMS references for girls and boys (continued)

		Boys			Girls		
Year: Month	**Month**	**L**	**M**	**S**	**L**	**M**	**S**
15: 0	180	-1.4961	19.7744	0.12412	-1.1311	20.2125	0.13904
15: 1	181	-1.4848	19.8367	0.12428	-1.1232	20.2595	0.13920
15: 2	182	-1.4733	19.8987	0.12443	-1.1153	20.3053	0.13934
15: 3	183	-1.4617	19.9603	0.12458	-1.1074	20.3499	0.13949
15: 4	184	-1.4500	20.0215	0.12473	-1.0996	20.3934	0.13963
15: 5	185	-1.4382	20.0823	0.12487	-1.0917	20.4357	0.13977
15: 6	186	-1.4263	20.1427	0.12501	-1.0838	20.4769	0.13991
15: 7	187	-1.4143	20.2026	0.12514	-1.0760	20.5170	0.14005
15: 8	188	-1.4022	20.2621	0.12528	-1.0681	20.5560	0.14018
15: 9	189	-1.3900	20.3211	0.12541	-1.0603	20.5938	0.14031
15: 10	190	-1.3777	20.3796	0.12554	-1.0525	20.6306	0.14044
15: 11	191	-1.3653	20.4376	0.12567	-1.0447	20.6663	0.14057
16: 0	192	-1.3529	20.4951	0.12579	-1.0368	20.7008	0.14070
16: 1	193	-1.3403	20.5521	0.12591	-1.0290	20.7344	0.14082
16: 2	194	-1.3277	20.6085	0.12603	-1.0212	20.7668	0.14094
16: 3	195	-1.3149	20.6644	0.12615	-1.0134	20.7982	0.14106
16: 4	196	-1.3021	20.7197	0.12627	-1.0055	20.8286	0.14118
16: 5	197	-1.2892	20.7745	0.12638	-0.9977	20.8580	0.14130
16: 6	198	-1.2762	20.8287	0.12650	-0.9898	20.8863	0.14142
16: 7	199	-1.2631	20.8824	0.12661	-0.9819	20.9137	0.14153
16: 8	200	-1.2499	20.9355	0.12672	-0.9740	20.9401	0.14164
16: 9	201	-1.2366	20.9881	0.12683	-0.9661	20.9656	0.14176
16: 10	202	-1.2233	21.0400	0.12694	-0.9582	20.9901	0.14187
16: 11	203	-1.2098	21.0914	0.12704	-0.9503	21.0138	0.14198
17: 0	204	-1.1962	21.1423	0.12715	-0.9423	21.0367	0.14208
17: 1	205	-1.1826	21.1925	0.12726	-0.9344	21.0587	0.14219
17: 2	206	-1.1688	21.2423	0.12736	-0.9264	21.0801	0.14230
17: 3	207	-1.1550	21.2914	0.12746	-0.9184	21.1007	0.14240
17: 4	208	-1.1410	21.3400	0.12756	-0.9104	21.1206	0.14250
17: 5	209	-1.1270	21.3880	0.12767	-0.9024	21.1399	0.14261
17: 6	210	-1.1129	21.4354	0.12777	-0.8944	21.1586	0.14271
17: 7	211	-1.0986	21.4822	0.12787	-0.8863	21.1768	0.14281
17: 8	212	-1.0843	21.5285	0.12797	-0.8783	21.1944	0.14291
17: 9	213	-1.0699	21.5742	0.12807	-0.8703	21.2116	0.14301
17: 10	214	-1.0553	21.6193	0.12816	-0.8623	21.2282	0.14311
17: 11	215	-1.0407	21.6638	0.12826	-0.8542	21.2444	0.14320
18: 0	216	-1.0260	21.7077	0.12836	-0.8462	21.2603	0.14330
18: 1	217	-1.0112	21.7510	0.12845	-0.8382	21.2757	0.14340

Table 9.5: 1 WHO BMI LMS references for girls and boys (continued)

		Boys			Girls		
Year: Month	**Month**	**L**	**M**	**S**	**L**	**M**	**S**
18: 2	218	-0.9962	21.7937	0.12855	-0.8301	21.2908	0.14349
18: 3	219	-0.9812	21.8358	0.12864	-0.8221	21.3055	0.14359
18: 4	220	-0.9661	21.8773	0.12874	-0.8140	21.3200	0.14368
18: 5	221	-0.9509	21.9182	0.12883	-0.8060	21.3341	0.14377
18: 6	222	-0.9356	21.9585	0.12893	-0.7980	21.3480	0.14386
18: 7	223	-0.9202	21.9982	0.12902	-0.7899	21.3617	0.14396
18: 8	224	-0.9048	22.0374	0.12911	-0.7819	21.3752	0.14405
18: 9	225	-0.8892	22.0760	0.12920	-0.7738	21.3884	0.14414
18: 10	226	-0.8735	22.1140	0.12930	-0.7658	21.4014	0.14423
18: 11	227	-0.8578	22.1514	0.12939	-0.7577	21.4143	0.14432

Table 9.5: 2 WHO Height LMS reference for girls and boys

		Boys			Girls		
Year: Month	Month	L	M	S	L	M	S
9: 0	108	1	132.5652	0.04535	1	132.4944	0.04612
9: 1	109	1	133.0031	0.04543	1	132.9989	0.04613
9: 2	110	1	133.4404	0.04551	1	133.5046	0.04614
9: 3	111	1	133.8770	0.04559	1	134.0118	0.04615
9: 4	112	1	134.3130	0.04566	1	134.5202	0.04616
9: 5	113	1	134.7483	0.04574	1	135.0299	0.04616
9: 6	114	1	135.1829	0.04582	1	135.5410	0.04617
9: 7	115	1	135.6168	0.04589	1	136.0533	0.04617
9: 8	116	1	136.0501	0.04597	1	136.5670	0.04616
9: 9	117	1	136.4829	0.04604	1	137.0821	0.04616
9: 10	118	1	136.9153	0.04612	1	137.5987	0.04616
9: 11	119	1	137.3474	0.04619	1	138.1167	0.04615
10: 0	120	1	137.7795	0.04626	1	138.6363	0.04614
10: 1	121	1	138.2119	0.04633	1	139.1575	0.04612
10: 2	122	1	138.6452	0.04640	1	139.6803	0.04611
10: 3	123	1	139.0797	0.04647	1	140.2049	0.04609
10: 4	124	1	139.5158	0.04654	1	140.7313	0.04607
10: 5	125	1	139.9540	0.04661	1	141.2594	0.04605
10: 6	126	1	140.3948	0.04667	1	141.7892	0.04603
10: 7	127	1	140.8387	0.04674	1	142.3206	0.04600
10: 8	128	1	141.2859	0.04680	1	142.8534	0.04597
10: 9	129	1	141.7368	0.04686	1	143.3874	0.04594
10: 10	130	1	142.1916	0.04692	1	143.9222	0.04591
10: 11	131	1	142.6501	0.04698	1	144.4575	0.04588
11: 0	132	1	143.1126	0.04703	1	144.9929	0.04584
11: 1	133	1	143.5795	0.04709	1	145.5280	0.04580
11: 2	134	1	144.0511	0.04714	1	146.0622	0.04576
11: 3	135	1	144.5276	0.04719	1	146.5951	0.04571
11: 4	136	1	145.0093	0.04723	1	147.1262	0.04567
11: 5	137	1	145.4964	0.04728	1	147.6548	0.04562
11: 6	138	1	145.9891	0.04732	1	148.1804	0.04557
11: 7	139	1	146.4878	0.04736	1	148.7023	0.04552
11: 8	140	1	146.9927	0.04740	1	149.2197	0.04546
11: 9	141	1	147.5041	0.04744	1	149.7322	0.04541
11: 10	142	1	148.0224	0.04747	1	150.2390	0.04535
11: 11	143	1	148.5478	0.04750	1	150.7394	0.04529

Table 9.5: 2 WHO Height LMS reference for girls and boys (continued)

		Boys			Girls		
Year: Month	Month	L	M	S	L	M	S
12: 0	144	1	149.0807	0.04753	1	151.2327	0.04523
12: 1	145	1	149.6212	0.04755	1	151.7182	0.04516
12: 2	146	1	150.1694	0.04758	1	152.1951	0.04510
12: 3	147	1	150.7256	0.04759	1	152.6628	0.04503
12: 4	148	1	151.2899	0.04761	1	153.1206	0.04497
12: 5	149	1	151.8623	0.04762	1	153.5678	0.04490
12: 6	150	1	152.4425	0.04763	1	154.0041	0.04483
12: 7	151	1	153.0298	0.04763	1	154.4290	0.04476
12: 8	152	1	153.6234	0.04764	1	154.8423	0.04468
12: 9	153	1	154.2223	0.04763	1	155.2437	0.04461
12: 10	154	1	154.8258	0.04763	1	155.6330	0.04454
12: 11	155	1	155.4329	0.04762	1	156.0101	0.04446
13: 0	156	1	156.0426	0.04760	1	156.3748	0.04439
13: 1	157	1	156.6539	0.04758	1	156.7269	0.04431
13: 2	158	1	157.2660	0.04756	1	157.0666	0.04423
13: 3	159	1	157.8775	0.04754	1	157.3936	0.04415
13: 4	160	1	158.4871	0.04751	1	157.7082	0.04408
13: 5	161	1	159.0937	0.04747	1	158.0102	0.04400
13: 6	162	1	159.6962	0.04744	1	158.2997	0.04392
13: 7	163	1	160.2939	0.04740	1	158.5771	0.04384
13: 8	164	1	160.8861	0.04735	1	158.8425	0.04376
13: 9	165	1	161.4720	0.04730	1	159.0961	0.04369
13: 10	166	1	162.0505	0.04725	1	159.3382	0.04361
13: 11	167	1	162.6207	0.04720	1	159.5691	0.04353
14: 0	168	1	163.1816	0.04714	1	159.7890	0.04345
14: 1	169	1	163.7321	0.04707	1	159.9983	0.04337
14: 2	170	1	164.2717	0.04701	1	160.1971	0.04330
14: 3	171	1	164.7994	0.04694	1	160.3857	0.04322
14: 4	172	1	165.3145	0.04687	1	160.5643	0.04314
14: 5	173	1	165.8165	0.04679	1	160.7332	0.04307
14: 6	174	1	166.3050	0.04671	1	160.8927	0.04299
14: 7	175	1	166.7799	0.04663	1	161.0430	0.04292
14: 8	176	1	167.2415	0.04655	1	161.1845	0.04284
14: 9	177	1	167.6899	0.04646	1	161.3176	0.04277
14: 10	178	1	168.1255	0.04637	1	161.4425	0.04270
14: 11	179	1	168.5482	0.04628	1	161.5596	0.04263

Table 9.5: 2 WHO Height LMS reference for girls and boys (continued)

		Boys			Girls		
Year: Month	Month	L	M	S	L	M	S
15: 0	180	1	168.9580	0.04619	1	161.6692	0.04255
15: 1	181	1	169.3549	0.04609	1	161.7717	0.04248
15: 2	182	1	169.7389	0.04599	1	161.8673	0.04241
15: 3	183	1	170.1099	0.04589	1	161.9564	0.04235
15: 4	184	1	170.4680	0.04579	1	162.0393	0.04228
15: 5	185	1	170.8136	0.04569	1	162.1164	0.04221
15: 6	186	1	171.1468	0.04559	1	162.1880	0.04214
15: 7	187	1	171.4680	0.04548	1	162.2542	0.04208
15: 8	188	1	171.7773	0.04538	1	162.3154	0.04201
15: 9	189	1	172.0748	0.04527	1	162.3719	0.04195
15: 10	190	1	172.3606	0.04516	1	162.4239	0.04189
15: 11	191	1	172.6345	0.04506	1	162.4717	0.04182
16: 0	192	1	172.8967	0.04495	1	162.5156	0.04176
16: 1	193	1	173.1470	0.04484	1	162.5560	0.04170
16: 2	194	1	173.3856	0.04473	1	162.5933	0.04164
16: 3	195	1	173.6126	0.04462	1	162.6276	0.04158
16: 4	196	1	173.8280	0.04451	1	162.6594	0.04152
16: 5	197	1	174.0321	0.04440	1	162.6890	0.04147
16: 6	198	1	174.2251	0.04429	1	162.7165	0.04141
16: 7	199	1	174.4071	0.04418	1	162.7425	0.04136
16: 8	200	1	174.5784	0.04407	1	162.7670	0.04130
16: 9	201	1	174.7392	0.04396	1	162.7904	0.04125
16: 10	202	1	174.8896	0.04385	1	162.8126	0.04119
16: 11	203	1	175.0301	0.04375	1	162.8340	0.04114
17: 0	204	1	175.1609	0.04364	1	162.8545	0.04109
17: 1	205	1	175.2824	0.04353	1	162.8743	0.04104
17: 2	206	1	175.3951	0.04343	1	162.8935	0.04099
17: 3	207	1	175.4995	0.04332	1	162.9120	0.04094
17: 4	208	1	175.5959	0.04322	1	162.9300	0.04089
17: 5	209	1	175.6850	0.04311	1	162.9476	0.04084
17: 6	210	1	175.7672	0.04301	1	162.9649	0.04080
17: 7	211	1	175.8432	0.04291	1	162.9817	0.04075
17: 8	212	1	175.9133	0.04281	1	162.9983	0.04071
17: 9	213	1	175.9781	0.04271	1	163.0144	0.04066
17: 10	214	1	176.0380	0.04261	1	163.0300	0.04062
17: 11	215	1	176.0935	0.04251	1	163.0451	0.04058

Table 9.5: 2 WHO Height LMS reference for girls and boys (continued)

		Boys			Girls		
Year: Month	Month	L	M	S	L	M	S
18: 0	216	1	176.1449	0.04241	1	163.0595	0.04053
18: 1	217	1	176.1925	0.04232	1	163.0733	0.04049
18: 2	218	1	176.2368	0.04222	1	163.0862	0.04045
18: 3	219	1	176.2779	0.04213	1	163.0982	0.04041
18: 4	220	1	176.3162	0.04204	1	163.1092	0.04037
18: 5	221	1	176.3518	0.04195	1	163.1192	0.04034
18: 6	222	1	176.3851	0.04185	1	163.1279	0.04030
18: 7	223	1	176.4162	0.04177	1	163.1355	0.04026
18: 8	224	1	176.4453	0.04168	1	163.1418	0.04023
18: 9	225	1	176.4724	0.04159	1	163.1469	0.04019
18: 10	226	1	176.4976	0.04150	1	163.1508	0.04016
18: 11	227	1	176.5211	0.04142	1	163.1534	0.04012

9.6 TREATMENT ASSIGNMENT WITH PATIENT WEIGHTING FOR EFFICACY ANALYSIS

		Period	D1 to Wk26	D1 to Wk26	D1 to Wk26
Initial study treatment to Wk14	**Re-rand study treatment planned at Wk14 to Wk26**	**Re-rand study treatment planned at Wk26 to Wk52**	**Treatment Grouping**		
			TG1	**TG 2**	**TG 3**
Pbo	Pbo	L5	Pbo: 1	Pbo: 1	Pbo: 1
		E10	Pbo: 1	Pbo: 1	Pbo: 1
		E25	Pbo: 1	Pbo: 1	Pbo: 1
L5	L5	L5	L5: 1	0	0
E10	E10 w/o re-rand[1]	E10 w/o re-rand[1]	E Pooled: 1	E Titr25: 1	E Titr10: 1
	E10 with re-rand	E10 with re-rand	E Pooled: 1	0	E Titr10: 2
	E25 with re-rand	E25 with re-rand	E Pooled: 1	E Titr25: 2	0

[1] including patients treated with empagliflozin 10 mg and discontinued prior to the re-randomisation planned at Week 14.

		Period	Wk14 to Wk26/52	D1 to Wk52	D1 to Wk52
Initial study treatment to Wk14	**Re-rand study treatment planned at Wk14 to Wk26**	**Re-rand study treatment planned at Wk26 to Wk52**	**Treatment Grouping**		
			TG4	**TG 5**	**TG 6**
Pbo	Pbo	L5	0	0	L5 active: 1
		E10	0	0	E active: 1
		E25	0	0	E active: 1
L5	L5	L5	0	L5: 1	L5 active: 1
E10	E10 w/o re-rand[1]	E10 w/o re-rand[1]	0	E Pooled: 1	E active: 1
	E10 with re-rand	E10 with re-rand	E10NR/10*: 1	E Pooled: 1	E active: 1
	E25 with re-rand	E25 with re-rand	E10NR/25*: 1	E Pooled: 1	E active: 1

[1] including patients treated with empagliflozin 10 mg and discontinued prior to the re-randomisation planned at Week 14.

		Period	Wk26 to Wk52	D1 to Wk52	D1 to Wk52
Initial study treatment to Wk14	**Re-rand study treatment planned at Wk14 to Wk26**	**Re-rand study treatment planned at Wk26 to Wk52**	**Treatment Grouping**		
			TG7	**TG8**	**TG9**
Pbo	Pbo	[2]	0	Pbo	Pbo
		L5	P/L5*	P-L5	Pbo (up to Wk26), L5 active (from Wk26)
		E10	P/E10*	P-E10	Pbo (up to Wk26), E10 active (from Wk26)
		E25	P/E25*	P-E25	Pbo (up to Wk26), E25 active (from Wk26)
L5	L5	L5	0	L5	L5 active
E10	E10 w/o re-rand[1]	E10 w/o re-rand[1]	0	E10	E10 active
	E10 with re-rand	E10 with re-rand	0	E10	E10 active
	E25 with re-rand	E25 with re-rand	0	E10NR-25	E10 active (up to Wk14), E25 active (from Wk14)

[1] including patients treated with empagliflozin 10 mg and discontinued prior to the re-randomisation planned at Week 14.

[2] including patients treated with placebo and discontinued prior to the re-randomisation planned at Week 26.

9.7 LABORATORY UNITS

Study level CDISC SDTM laboratory data will contain laboratory data in standardised SI units.

Analyses of laboratory data will be based on values standardised in SI units as displayed in Table 9.7: 1, and additionally in US conventional units as indicated.

Table 9.7: 1 Overview of laboratory parameter and their SI and US conventional units

Functional group	**Laboratory parameter**	**SI unit**	**US conventional unit**
HAEMATOLOGY	Haemaglobin A1C	mmol/mol	%
SUBSTRATE	Fasting Plasma Glucose	mmol/L	mg/dL
	Estimated glomerular filtration rate (eGFR-Zapatelli)	mL/min/1.73m**2	mL/min/1.73m**2
AUTO-ANTIBODY	Glutamic Acid Decarboxylase Antibody	U/mL	IU/mL
AUTO-ANTIBODY	Islet Cell 512 Antibody	U/mL	U/mL
CLEARANCE	Creatinine Clearance	mL/min/1.73m**2	mL/min/1.73m**2
CARDIAC MARKER, CLINICAL CHEMISTRY	Troponin I	ug/L	ng/mL
ELECTROLYTES, CLINICAL CHEMISTRY	Bicarbonate	mmol/L	mEq/L
ELECTROLYTES, CLINICAL CHEMISTRY	Calcium	mmol/L	mg/dL
ELECTROLYTES, CLINICAL CHEMISTRY	Chloride	mmol/L	mEq/L

Table 9.7: 1 Overview of laboratory parameter and their SI and US conventional units (continued)

Functional group	Laboratory parameter	SI unit	US conventional unit
ELECTROLYTES, CLINICAL CHEMISTRY	Potassium	mmol/L	mEq/L
ELECTROLYTES, CLINICAL CHEMISTRY	Magnesium	mmol/L	mg/dL
ELECTROLYTES, CLINICAL CHEMISTRY	Phosphate	mmol/L	mg/dL
ELECTROLYTES, CLINICAL CHEMISTRY	Sodium	mmol/L	mEq/L
ENZYMES, CLINICAL CHEMISTRY	Alkaline Phosphatase	U/L	U/L
ENZYMES, CLINICAL CHEMISTRY	Alanine Aminotransferase	U/L	U/L
ENZYMES, CLINICAL CHEMISTRY	Aspartate Aminotransferase	U/L	U/L
ENZYMES, CLINICAL CHEMISTRY	Creatine Kinase	U/L	U/L
ENZYMES, CLINICAL CHEMISTRY	Gamma Glutamyl Transferase	U/L	U/L
ENZYMES, CLINICAL CHEMISTRY	Lactate Dehydrogenase	U/L	U/L

Table 9.7: 1 Overview of laboratory parameter and their SI and US conventional units (continued)

Functional group	Laboratory parameter	SI unit	US conventional unit
ENZYMES, CLINICAL CHEMISTRY	Lipase	U/L	U/L
HORMONES, CLINICAL CHEMISTRY	Fasting C-peptide	nmol/L	ng/mL
HORMONES, CLINICAL CHEMISTRY	Insulin-like Growth Factor 1	nmol/L	ng/mL
HORMONES, CLINICAL CHEMISTRY	Insulin-like Growth Factor Binding Prot3	nmol/L	ng/mL
HORMONES, CLINICAL CHEMISTRY	Parathyroid Hormone, Intact	ng/L	pg/mL
HORMONES, CLINICAL CHEMISTRY	Thyrotropin	mU/L	uIU/mL
HORMONES, CLINICAL CHEMISTRY	25-Hydroxyvitamin D	nmol/L	ng/mL
PROTEINS, CLINICAL CHEMISTRY	Albumin	g/L	g/dL
PROTEINS, CLINICAL CHEMISTRY	Protein	g/L	g/dL
SUBSTRATES, CLINICAL CHEMISTRY	Beta-Hydroxybutyrate	mmol/L	mg/dL

Table 9.7: 1 Overview of laboratory parameter and their SI and US conventional units (continued)

Functional group	Laboratory parameter	SI unit	US conventional unit
SUBSTRATES, CLINICAL CHEMISTRY	Direct Bilirubin	umol/L	mg/dL
SUBSTRATES, CLINICAL CHEMISTRY	Total Bilirubin	umol/L	mg/dL
SUBSTRATES, CLINICAL CHEMISTRY	Indirect Bilirubin	umol/L	mg/dL
SUBSTRATES, CLINICAL CHEMISTRY	Creatinine	umol/L	mg/dL
SUBSTRATES, CLINICAL CHEMISTRY	Cystatin C	mg/L	mg/L
SUBSTRATES, CLINICAL CHEMISTRY	Uric Acid	umol/L	mg/dL
SUBSTRATES, CLINICAL CHEMISTRY	Blood Urea Nitrogen	mmol/L	mg/dL
DIFFERENTIALS, HAEMATOLOGY	Basophils	10^9/L	10^3/uL
DIFFERENTIALS, HAEMATOLOGY	Basophils/Leukocytes	%	%
DIFFERENTIALS, HAEMATOLOGY	Eosinophils	10^9/L	10^3/uL
DIFFERENTIALS, HAEMATOLOGY	Eosinophils/Leukocytes	%	%

Table 9.7: 1 Overview of laboratory parameter and their SI and US conventional units (continued)

Functional group	Laboratory parameter	SI unit	US conventional unit
DIFFERENTIALS, HAEMATOLOGY	Lymphocytes	10^9/L	10^3/uL
DIFFERENTIALS, HAEMATOLOGY	Lymphocytes/Leukocytes	%	%
DIFFERENTIALS, HAEMATOLOGY	Monocytes	10^9/L	10^3/uL
DIFFERENTIALS, HAEMATOLOGY	Monocytes/Leukocytes	%	%
DIFFERENTIALS, HAEMATOLOGY	Neutrophils	10^9/L	10^3/uL
DIFFERENTIALS, HAEMATOLOGY	Neutrophils/Leukocytes	%	%
HEMATOLOGY, HAEMATOLOGY	Haematocrit	%	%
HEMATOLOGY, HAEMATOLOGY	Haemoglobin	g/L	g/dL
HEMATOLOGY, HAEMATOLOGY	Ery. Mean Corpuscular Volume	fL	fL
HEMATOLOGY, HAEMATOLOGY	Platelets	10^9/L	10^3/uL
HEMATOLOGY, HAEMATOLOGY	Erythrocytes (Blood)	10^12/L	10^6/uL
HEMATOLOGY, HAEMATOLOGY	Reticulocytes	10^9/L	10^6/uL
HEMATOLOGY, HAEMATOLOGY	Leukocytes (Blood)	10^9/L	10^3/uL

Table 9.7: 1 Overview of laboratory parameter and their SI and US conventional units (continued)

Functional group	Laboratory parameter	SI unit	US conventional unit
BONE METABOLISM, IGF AND MARKERS OF BONE TURNOVER	N-telopeptide	nmol BCE/L	nmol BCE/L
BONE METABOLISM, IGF AND MARKERS OF BONE TURNOVER	Procollagen 1 N-Terminal Propeptide	ug/L	ng/mL
SUBSTRATES, LIPIDS SI	Cholesterol	mmol/L	mg/dL
SUBSTRATES, LIPIDS SI	HDL Cholesterol	mmol/L	mg/dL
SUBSTRATES, LIPIDS SI	LDL Cholesterol	mmol/L	mg/dL
SUBSTRATES, LIPIDS SI	Triglycerides	mmol/L	mg/dL
URINE ANALYSIS	Urine albumin-to-creatinine ratio (UACR)	mg/g	mg/g
URINE ANALYSIS	Albumin/Creatinine (Urine)	g/kg	mg/g
URINE ANALYSIS	Albumin (Urine)	g/L	mg/dL
URINE ANALYSIS	Creatinine (Urine)	mmol/L	mg/dL
URINE ANALYSIS	Erythrocytes (Urine)	/HPF	/HPF
URINE ANALYSIS	Leukocytes (Urine)	/HPF	/HPF

10 HISTORY TABLE

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
1.0	15-Mar-2018	Anja Hoch, Ulrich Elsasser	None	This is the initial TSAP without any modification.

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	13-Nov-2019	Tess Lam	All	Updated "protocol violation" to "protocol deviation". Updated endpoints from "change from baseline in XXX after 26 weeks" to "change in XXX from baseline to the end of 26 weeks".
		Tess Lam	Cover page	Updated Responsible trial statistician from "Anja Hoch" to "Tess Lam and Anna Unseld" and all the contact details.
		Tess Lam	2	Removed the following abbreviations from list: AUC, CSII, CT, DM&SM, DST, eDiary, EMA, GI, HCRU, ITT, MAGE, MDG, O*C, OC-H, OC-OffT, OC-P. Updated "IVRS" to "IRT", "PD to PV", "TBL to TBILI". Added AP, BOCF, DBL, EudraCT, MAR, MCMC, MI, MNAR, PCSA, PMM, REML, SE, SLR, TSactive.
		Tess Lam	4	Mentioned TSAP amendment version 2 is according to CTP amendment version 3.
		Tess Lam	5.1	Added the current primary endpoint under subsection DINAMO. Added DINAMO Mono primary endpoint.
		Tess Lam	5.2.2	Grouped the existing secondary endpoints under subsection DINAMO. Added "proportion of patients who achieve HbA1c goals < 6.5% and < 7.0% at the end of 26 weeks" as DINAMO secondary endpoints. Added DINAMO Mono secondary endpoints.
		Tess Lam	5.3.1	Clarified this section applied to both DINAMO and DINAMO Mono. Removed "percentage of patients achieving HbA1c goals (< 6.5% and < 7%) after 26 weeks from further endpoints. Updated endpoint name from "percentage of patients …" to "proportion of patients …". Added "proportion of patients who achieve HbA1c reduction of > 0.5% at the end of 26 and 52 weeks to further endpoint. Endpoint "change in HbA1c from Week 12 to the end of 26 weeks" is now only for DINAMO. Updated "(UACR) (mg/mmol)" to "(UACR) (mg/g)" Added the definition of rescue medication for DINAMO Mono to the endpoint

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	13-Nov-2019	Tess Lam	5.3.2	Updated further safety endpoints to fulfil FDA written request. Added arthralgia, bullous pemphigoid, adverse events related to reduced intravascular volume, and ketone measurements reported into AE endpoints, vital signs (including height, heart rate and BMI), haematology and biochemistry endpoints.
		Tess Lam	5.3.3	Clarified this section applied to both DINAMO and DINAMO Mono.
		Tess Lam	5.4.1	Added BMI LMS references for girls and boys. Clarified Age in month collected at Screening will be used. Added the growth velocity formula.
		Tess Lam	5.4.2	Updated to have 2 variation of extent to exposure. One including off-treatment period and the other excluding off-treatment period.
		Tess Lam	5.4.4	Updated reference Section numbers.
		Tess Lam	5.4.5	Updated the text to help the clarity.
		Tess Lam	General analysis definition (6)	Updated Section number from no number to 6.
		Tess Lam	5.5 (6.1)	Updated Section number from 5.5 to 6.1. Added on-treatment period for up to Week 26 and for Week 26 up to Week 52. Updated treatment groups and added new one for analyses and the presentation of the outputs.
		Tess Lam	5.6 (6.2)	Updated Section number from 5.6 to 6.2. Paragraph started with “As the primary endpoint is analysed after 26 weeks, …” has moved to Section 6.3 together with PPS. Consolidate the IPD codes for empagliflozin and linagliptin into a study specific IPD code. Made reference code to the ones for empagliflozin and linagliptin. Updated the inclusion and exclusion numbering according to the change of exclusion 1 to become inclusion 10. Combined columns “Category” and “Code” to “IPD Code”.
		Tess Lam	5.7 (6.3)	Updated Section number from 5.7 to 6.3. Updated the text for the TSactive, mITT and PPS to help the clarity of the definition.

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	13-Nov-2019	Tess Lam	Table 6.3:1	Removed all primary endpoint analyses described as efficacy / effectiveness from the table. Removed primary endpoint sensitivity test (MI). Added DINAMO Primary endpoint analyses: primary & secondary family PMM analyses (mITT, PP); sensitivity primary & secondary family MMRM analyses (mITT); and sensitivity MMRM analysis (mITT). Added DINAMO Mono Primary endpoint NCF analysis. Demographics, baseline variables, concomitant medications, exposure/compliance will be analysed using TS instead of mITT.
		Tess Lam	5.8 (6.4)	Updated Section number from 5.8 to 6.4. Moved the paragraphs on omission efficacy analyses of small subgroups to new Section 7.4.1.4.
		Tess Lam	Table 6.4:1	Updated "Endpoint for which subgroup analyses are to be conducted" from HbA1c (Version 2) to DINAMO primary. Clarified other endpoints under column "Endpoint for which subgroup analyses are to be conducted" for descriptive statistics only. Added baseline HbA1c version 3 for baseline characteristics. Updated the 1st two categories of BMI version 1, from "<20" to "<25" and removed "20 to <25". Added BMI version 3 for baseline characteristics. Added "South America" to Geographical region version 1. Added "None" to background antidiabetic treatment. Added Ethnicity.
		Tess Lam	5.9 (6.5)	Updated Section number from 5.9 to 6.5.
		Tess Lam	5.10 (6.6)	Updated Section number from 5.10 to 6.6.
		Tess Lam	5.10.1 (6.6.1)	Updated Section number from 5.10.1 to 6.6.1.
		Tess Lam	5.10.1.2 (6.6.1.2)	Updated Section number from 5.10.1.2 to 6.6.1.2. Added to exclude any values collected after the start of rescue medication to the OC definition.
		Tess Lam	5.10.1.3 (6.6.1.3)	Updated Section number from 5.10.1.3 to 6.6.1.3. Added to include any values collected after the start of rescue medication to the OC-AD definition.
		Tess Lam	5.10.1.4 (6.6.1.4)	Updated Section number from 5.10.1.4 to 6.6.1.4. Added to consider any values collected after the start of rescue medication as failure to the NCF definition.

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

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

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	13-Nov-2019	Tess Lam	6.4.1.1.2	Removed Section 6.4.1.1.2 Sensitivity analysis of the primary MMRM efficacy analyses.
		Tess Lam	6.4.1.2 (7.4.1.1)	Renamed "Section 6.4.1.2 Primary effectiveness analysis" to "Section 7.4.1.1 Primary family of analyses". Added Table 7.4.1.1:1 PMM "jump-to-placebo" approach – the missing data imputation method. Updated the text to clarify the steps. Updated reference from Appendix 9.4 to 9.5. Moved the primary hypothesis from Section 6.4.1 to the new Section 7.4.1.1.
		Tess Lam	6.4.1.2.1 (7.4.1.2)	Renamed "Section 6.4.1.2.1 Secondary family of effectiveness analyses" to "Section 7.4.1.2 Secondary family of analyses". Updated hypotheses to be the same as CTP. Added the hypotheses will also include Empa 10 mg patients who did not proceed to re-randomisation at Week 14. Updated analysis model used from "MMRM model" to "ANCOVA inverse probability weighting" approach".
		Tess Lam	(7.4.1.3)	Added new Section 7.4.1.3 Sensitivity analyses.
		Tess Lam	(7.4.1.3(A))	Added new Section 7.4.1.3(A) Primary family of hypotheses - MMRM effectiveness analysis. Adapted majority of the content from the old Section 6.4.1.1 such as the analysis model but it is based on OC-AD only.
		Tess Lam	(7.4.1.3(B))	Added new Section 7.4.1.3(B) Secondary family of hypotheses - MMRM effectiveness analysis.
		Tess Lam	(7.4.1.3(C))	Added new Section 7.4.1.3(C) MMRM efficacy analysis.
		Tess Lam	6.4.2.1 (7.4.1.3(D))	Renamed "Section 6.4.2.1 Patients sets" to "Section 7.4.1.3(D) Analyses on further patient set".
		Tess Lam	6.4.2.2	Removed Section as it is a repeat of the further endpoint "change in HbA1c (%) from Week 12 to the end of 26 weeks in patients randomised to empagliflozin 10 mg and not achieving glycaemic target at Week 12".
		Tess Lam	6.4.3 (7.4.1.4)	Updated Section number from 6.4.3 to 7.4.1.4. Added population set and analysis data type.
		Tess Lam	6.4.4 (7.4.1.5)	Replaced old Section 6.4.4 with new Section 7.4.1.5. Subgroup analysis is now carried out by PMM "jump-to-placebo" approach with subgroup ANCOVA model.
		Tess Lam	6.4.5 (7.4.1.6)	Updated Section number from 6.4.5 to 7.4.1.6. Added more population set and analysis data types.

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	13-Nov-2019	Tess Lam	(7.4.2)	Added new Section 7.4.2 DINAMO Mono with DINAMO Mono primary endpoint analysis detail.
		Tess Lam	6.5 (7.5)	Updated Section number from 6.5 to 7.5.
		Tess Lam	6.5.1 (7.5.1)	Updated Section number from 6.5.1 to 7.5.1.
		Tess Lam	6.5.2 (7.5.2)	Updated Section number from 6.5.2 to 7.5.2.
		Tess Lam	(7.5.2.1)	Added new Section 7.5.2.1 DINAMO. Added the content of the old Section 6.5.2. Swapped the order of the first and second approach. Moved paragraph "Baseline Observation Carried Forward (BOCF)… at baseline and week 26 within the analysis period." from second approach (OC) to first approach (OC-AD) as first approach is closer to pure ITT. Added which treatment groups will be used for presentation. Added the analysis of "proportion of patients who achieve HbA1c goals < 6.5% and < 7.0% at the end of 26 weeks".
		Tess Lam	(7.5.2.2)	Added new Section 7.5.2.2 DINAMO Mono with all the analyses details.
		Tess Lam	6.6 (7.6)	Updated Section number from 6.6 to 7.6.
		Tess Lam	(7.6.1)	Added new Section 7.6.1 Further efficacy endpoints. Added the content of the old Section 6.6. Added this Section applied to both DINAMO and DINAMO Mono. Added change in HbA1c (%) from Week 12 to the end of 26 weeks is only for DINAMO. Added the reporting for DINAMO and DINAMO Mono are separate. Added the definition of the use of rescue therapy. Added the use of rescue therapy endpoint will only be summarised using all data OC-AD.
		Tess Lam	(7.6.2)	Added new Section 7.6.2 Further safety endpoints.
		Tess Lam	(7.6.3)	Added new Section 7.6.3 Further PK endpoints.

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

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

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	13-Nov-2019	Tess Lam	6.8.1.5 (7.8.1.5)	Updated Section number from 6.8.1.5 to 7.8.1.5. Added which treatment groups will be used for presentation. Added a subgroup descriptive summary table for Hypoglycaemia. Added Arthralgia. Added Bullous pemphigoid. Added AE related to reduced intravascular volume. Added Ketone measurements reported as AE.
		Tess Lam	6.8.1.7 (7.8.1.7)	Updated Section number from 6.8.1.7 to 7.8.1.7.
		Tess Lam	6.8.2 (7.8.2)	Updated Section number from 6.8.2 to 7.8.2. Added for both DINAMO and DINAMO Mono. Added it will presented for the primary safety analysis with both SI and US units.
		Tess Lam	6.8.2.1 (7.8.2.1)	Updated Section number from 6.8.2.1 to 7.8.2.1. Added further safety endpoint analyses. Removed XLAB related text. Removed table for change from baseline in haematocrit over time including during the follow up period. Added which safety analyses will be carry out.
		Tess Lam	6.8.2.2 (7.8.2.2)	Updated Section number from 6.8.2.2 to 7.8.2.2. Added which safety analyses will be carry out.
		Tess Lam	6.8.2.3 (7.8.2.3)	Updated Section number from 6.8.2.3 to 7.8.2.3. Added which safety analyses will be carry out.
		Tess Lam	6.8.2.4 (7.8.2.4)	Updated Section number from 6.8.2.4 to 7.8.2.4. Added which safety analyses will be carry out.
		Tess Lam	6.8.3 (7.8.3)	Updated Section number from 6.8.3 to 7.8.3. Added further safety endpoint analyses. Added for both DINAMO and DINAMO Mono. Added it will presented for the primary safety analysis.
		Tess Lam	6.8.4 (7.8.4)	Updated Section number from 6.8.4 to 7.8.4. Added for both DINAMO and DINAMO Mono.
		Tess Lam	7 (8)	Updated Section number from 7 to 8. Updated references 3, 4, 5, and 7 from old SOPs to new KMED equivalent. Added reference 12.
		Tess Lam	8 (9)	Updated Section number from 8 to 9.
		Tess Lam	8.1 (9.1)	Updated Section number from 8.1 to 9.1. Removed New Zealand from Table 9.1:1 as it is no longer participating.
		Tess Lam	8.2 (9.2)	Updated Section number from 8.2 to 9.2.
		Tess Lam	8.3 (9.3)	Updated Section number from 8.3 to 9.3.
		Tess Lam	8.4 (9.4)	Updated Section number from 8.4 to 9.4.

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	13-Nov-2019	Tess Lam	8.4.1 (9.4.1)	Updated Section number from 8.4.1 to 9.4.1.
		Tess Lam	8.4.1.1 (9.4.1.1)	Updated Section number from 8.4.1.1 to 9.4.1.1. Updated protocol defined hypoglycaemia criteria from glucose concentration "< 70 mg/dL (< 3.9 mmol/mL)" to "≤ 70 mg/dL (< 3.9 mmol/mL)"
		Tess Lam	8.5 (9.5)	Updated Section number from 8.5 to 9.5.
		Tess Lam	(9.6)	Added new Section 9.6 WHO BMI LMS references for girls and boys. Added Table 9.6:1.
		Tess Lam	9 (10)	Updated Section number from 9 to 10.
		Tess Lam	Whole document	Updated "BMI SDS" to "BMI z-score".

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	23-Jul-2021	Tess Lam	Whole document	Updated "off-treatment" to "post-treatment".
		Tess Lam	5.1 (DINAMO Mono primary endpoint)	Added "(including Week 26)" to the use of rescue medication criteria to clarify what exactly is included in the period. Added "(at least 0.5% in absolute value)" to "Increase from baseline in HbA1c by 0.5% at Week 26" to clarify the meaning of 0.5%.
		Tess Lam	5.2.2	Added criteria for "Time to treatment failure".
		Tess Lam	5.3.1	Clarified the definition of initiate glycaemic rescue therapy. Also clarified the inclusion period to match the DINAMO Mono primary endpoint criteria.
		Tess Lam	5.3.2	From the further safety endpoint, AE, Removed the repeated AE names as they are redundant.
		Tess Lam	5.3.3	Update from "Empagliflozin and linagliptin trough levels in plasma after 26 and 52 weeks." to "Plasma concentrations of empagliflozin and linagliptin pre-dose and 1.5 hours post-dose after 26 and 52 weeks.".
		Tess Lam	5.4.1	Added text to clarify how BMI is derived in the analysis data. Added height z-score
		Tess Lam	5.4.2	Section re-discussed and decided to keep it simple to consider start and end of treatment as the extent of treatment exposure.
		Tess Lam	5.4.4	Added "The SBP and DBP will be derived for use in the statistical analysis as the mean of all available SBP and DBP readings, respectively, at the same visit." to clarify what BP data is used in analyses.
		Tess Lam	(5.4.5)	Added new section 5.4.5 "Start of COVID-19 disruption.".
		Tess Lam	6.1	Re-wrote the treatment periods as found them to be confusing. Also updated the treatment groupings "treatment abbreviation labelling". Added TG7, TG8 and TG9 for the result disclosure.
		Tess Lam	6.2	Moved all IPDs criteria into DV specification, located in BIRDs.
		Juliane Rascher	6.3	Added "PK parameter analysis set (PKS)" Updated Table 6.3:1 (all outputs) and added Table 6.3:2 COVID-19 related outputs.
		Tess Lam	6.4	Added new subgroup Region Version 3 into Table 6.4:1 as required for the PK analysis.

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	23-Jul-2021	Tess Lam	6.4	Updated BMI version 2 to use the median of all data as the cut-off of 2 categories: <median and >= median. Updated subgroup BMI z-score categories from "<0, 0 to <1.28, 1.28 to <2" to "<= 2.0 (underweight/normal/risk of overweight), >2.0 to 3.0 (overweight), >3.0 (obese)". Added new subgroups categories: • Baseline FPG [mmol/L], • Metformin total daily dose [mg], • Smoking history, • Baseline UACR [mg/g crea] • Tanner stage • Weight • COVID-19 disruption • SARS-CoV-2 infection Updated subgroup Ethnicity categories from "Hispanic, No Hispanic" to "Hispanic or latino, Not Hispanic or latino". Region version 1 and baseline eGFR version 1 will not be used for descriptive statistics nor statistical modelling. Added baseline eGFR version 2 for descriptive statistics and statistical modelling. Time since diagnosis of diabetes updated to start from <1 year. Added baseline UACR for baseline characteristics.
		Tess Lam	6.6.1	Updated OC, OC-ROC. Renamed OC-OCF to OC-LOCF. Added OC-AD-BOCF.
		Tess Lam	6.6.3	Section 6.6.3 "Safety and other variables" deleted
		Tess Lam	6.6.4 (6.6.3)	Section 6.6.4 "Missing dates and times" became Section 6.6.3. Updated the rule for imputing the missing/incomplete drug stop date.
		Tess Lam	(6.6.4)	Added new section 6.6.4 "Missing and incomplete laboratory reference ranges".

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

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

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	23-Jul-2021	Tess Lam	7.4.1.2	Text updated from "The ANCOVA model will utilise a weight variable having a value of 0 for the patients who are not in the hypothesis test of interest, a value of 2 for re-randomised patients who are in the hypothesis test of interest and a value of 1 otherwise." to "The ANCOVA models performed for each hypothesis will utilise a weight variable having a value of 2 for re-randomised patients and a value of 1 for all other patients in the treatment grouping for the respective hypothesis test.".
		Tess Lam	7.4.1.3 E	Added details of how to define the COVID-19 ICE and the imputation method.
		Tess Lam	7.4.1.3 F	Added new section for the sensitivity test "Primary family of hypotheses – Non-NGSP certified laboratories HbA1c values".
		Tess Lam	(7.4.3)	Added new section "HbA1c data summary".
		Tess Lam	7.5.2.1	For the first approach FPG analysis, added data type OC-AD-BOCF. Moved the proportion of patients who achieve HbA1c < 7.0% and < 6.5% at the end of 26 weeks will be determined per treatment grouping 1 using mITT (NCF) set to the first approach. Replaced OC for the second approach.
		Tess Lam	7.5.2.2	Added a descriptive Log-rank test comparing linagliptin 5 mg and pooled empagliflozin versus placebo individually up to Week 26 using mITT (NCF) set by TG1.
		Tess Lam	7.6.1	Added the details of all outputs.
		Tess Lam	7.6.2	Updated section to provide shift table for Tanner staging and descriptive summary for growth velocity.
		Tess Lam	7.6.3	Wordings updated.
		Tess Lam	7.7	Re-organised the whole section. Added "for DINAMO only" to the exposure tables by before and from start of COVID-19.
		Tess Lam	7.8	Updated text to present TG4 for DINAMO Mono analyses.
		Tess Lam	7.8.1	Added the location for TG4 and TG5 AEs outputs, where they are relocated into Section 16.
		Tess Lam	7.8.1.1	Text added for the cut off of AEs occurred up to Week 26 and Week 52.
		Tess Lam	7.8.1.3	Added treatment grouping details into text. To clarify which TGX will be used in the table.
		Tess Lam	7.8.1.5	Added Hypoglycaemia derivation. Added text to clarify what outputs to present.
		Tess Lam	(7.8.1.8)	New section "AE incidence rates" added.

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	23-Jul-2021	Tess Lam	(7.8.1.9)	New section "COVID-19" added.
		Tess Lam	7.8.2.1	Section re-organised. Added the bone metabolism biomarkers to the general lab summary table with the normalised values.
		Tess Lam	7.8.2.2	Removed extra details of the liver enzyme elevation as it caused confusion.
		Tess Lam	7.8.2.3	Updated the presentation of the descriptive table to over time instead of baseline and last value only.
		Tess Lam	7.8.2.4	Added a shift table for UACR.
		Tess Lam	(7.8.2.5)	New section "Biomarkers" added.
		Tess Lam	7.8.3	Removed OC analysis from the vital signs parameters analysis.
		Tess Lam	8	Updated reference 8, 9, 10 and 12. Added reference 14 and 15.
		Tess Lam	9.2	Section updated.
		Tess Lam	9.4	Old section 9.4 "Derivation of hypoglycaemia endpoints" is removed.
		Tess Lam	9.5 (9.4)	Old section 9.5 become new section 9.4.
		Tess Lam	9.6 (9.5)	Old section 9.6 become new section 9.5.
		Tess Lam	(9.6)	New section "Treatment assignment with patient weighting for efficacy analysis" added.

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

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

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	7-JUL-2022	Tess Lam	6.1	For TG9, added "active pooled" into the active treatments groups to clarify only active treatments period are included. Old text "The treatment grouping **X** will be …" to New text "The treatment grouping **TGx** will be …". Old text "As a first example, the treatment identifier "E10-10R" means …" to New text "As a first example, the treatment identifier "E10R-10" means…" Old text "As a second example, the treatment identifier "E10/E25NR*" means…" to New text "As a second example, the treatment identifier "E10NR/25*" means…".
		Tess Lam	Table 6.3:1	Updated "Occurrence of treatment failure up to or at Week 26" to "Occurrence of treatment failure up to or at Week 26 (DINAMO Mono patients only)". Added "DINAMO Mono – Sensitivity analysis" Occurrence of treatment failure up to or at Week 26 (DINAMO Mono and suitable DINAMO patients) Updated the following text to make clear the timing of the age. Old text "Freq. of patients with symptomatic hypoglycaemia AE with plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemia AE by **baseline age** in categories" to New test "Freq. of patients with symptomatic hypoglycaemia AE with plasma glucose < 54 mg/dL (< 3.0 mmol/L) and/or severe hypoglycaemia AE by **age at randomisation** in categories"
		Tess Lam	Table 6.4:1	Updated the following subgroup to make clear the timing of the age. Old text "Age [years]" to New text "Age [years] **at randomisation**".

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	7-JUL-2022	Tess Lam	Table 6.4:1	Added the following subgroup to follow the WHO reference. BMI z-score [SD] version 1 (4 categories): < -2 (Thin) >= -2 to 1 (Normal) > 1 to 2 (Overweight) > 2 (Obese) Moved and updated the existing subgroup to be more clear. Old text <= 2.0 (underweight/normal/risk of overweight) > 2.0 to 3.0 (overweight) > 3.0 (obese) New text Version 2 <= 2 (Underweight, normal or overweight) > 2 to <=3 (Class 1 obesity) > 3 (Class 2 or 3 obesity)
		Tess Lam	Table 6.4:1	Added the following subgroup for the PK analysis, based on race and country defined in Table 9.1: 1. Geographical region version 3 (4 categories): East Asian South East Asian Other Asian Other
		Tess Lam	Table 6.4:1	Updated the existing Tanner stage subgroup as Version 1. Added new version 2 for the lab analysis. Version 2 1 2 to 4 5
		Tess Lam	Table 6.4:1	Updated Baseline UACR category from "30 to <= 300 …" to "30 to 300 …".
		Tess Lam	Table 6.4:1	Added new subgroup COVID-19 disruption (Week 26): Permanent discontinuation of study medication or completed Wk26 visit before COVID-19 disruption Permanent discontinuation of study medication and completed Wk26 visit from COVID-19 disruption
		Tess Lam	Table 6.4:1	Subgroup name 'COVID-19 disruption' updated to 'COVID-19 disruption (Week 52)'.
		Tess Lam	Table 6.4:1	Added new subgroup URBC and UWBC as "Normal" and "High" to analyse the lab data more appropriately.

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

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

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

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

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

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

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	7-JUL-2022	Tess Lam	(7.4.2.1)	New section added (Sensitivity analysis for DINAMO Mono) as a result of FDA discussion. "The analysis of the DINAMO Mono primary endpoint will be repeated on DINAMO Mono patients plus the drug-naïve DINAMO patients who satisfied the DINAMO Mono HbA1c inclusion criteria limit using the same statistical model."
		Tess Lam	7.5.2.1	Throughout the section, updated "age" to "age at randomisation". Added unit to the variables. Added additional FPG [mmol/L] analysis to this section: "This analysis will be repeated for FPG [mmol/L] in Appendix 16.1.13.".
		Tess Lam	7.5.2.2	Throughout the section, updated "age" to "age at randomisation". Added additional HbA1c [mmol/mol] analysis to this section: "Analysis described in Section 7.4.1.3(C) will be repeated for HbA1c [mmol/mol] in Appendix 16.1.13.".
		Tess Lam	7.6.1	Added additional HbA1c [mmol/mol] and FPG [mmol/L] summary tables according to FDA request: "HbA1c [mmol/mol] over time up to Week 52 by treatment grouping 1 and 5 using mITT (OC, OC-AD) and FPG [mmol/L] over time up to Week 52 by treatment grouping 1 and 5 using mITT (OC, OC-AD, OC-AD-BOCF)".
		Tess Lam	7.7	Updated subgroup categories from old text: "In order to assess the impact of COVID-19 to the treatment exposure in DINAMO only, the planned analyses for the treatment exposure will be repeated and summarised by permanent discontinuation of study medication before and from the start of COVID-19 disruption.". To new text: "In order to assess the impact of COVID-19 to the treatment exposure in DINAMO only, the planned analyses for the treatment exposure will be repeated and summarised by permanent discontinuation of study medication or/and completed Week 26 visit before/from the start of COVID-19 disruption for up to Week 26 table and by permanent discontinuation of study medication before and from the start of COVID-19 disruption for up to Week 52 table.".

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

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

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

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

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

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

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

Version	Date	Author	Changes in old Section (new Section)	Brief description of change
Revised	7-JUL-2022	Tess Lam	7.8.2.4	Updated the following text with the bold text to clarify what UACR values are used. "A shift table from baseline value to last and maximum values on-treatment will be provided based on the following UACR categories (which used the derived UACR and not the albumin/creatinine ratio values provided by the lab): normal …" Also added the derived UACR formula.
		Tess Lam	7.8.2.5	Added PINP to the biomarkers descriptive tables. Added additional tables "Descriptive statistics by sex and tanner stage category version 2, see Table 6.4:1 for the category, will be summarised over time up to Week 26 by TG1 and up to Week 52 by TG5 on the standard units for PINP, NTx, IGF-1, IGF-BP3.".
		Tess Lam	8	Old text "001-MCS-36-472: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON" to New text "BI-KMED-TMCP-MAN-0012: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; KMED".
		Tess Lam	Table 9.1:1	Updated Table 9.1:1 title with the bold text "Regions, **races** and countries" Updated existing region to region v1. Old text "United States" to New text "United States (including Puerto Rico)". Added region v3 based on races and countries.
		Tess Lam	9.4	In step 9, added clarification where to find the statistics of the analysis. "The adjusted mean, differences, confidence interval and p-values are in ODS OUTPUT: Lsmeans, Diffs and SolutionF".
		Tess Lam	(9.7)	Added new Section 9.7 Laboratory units to clarify the SI and conventional units.

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

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

List of Independent Ethics Committees and/or Institutional Review Boards approvals by countries:

Argentina				
Approval Level: Study Site Only				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
Comité Institucional de Ética en Investigación en Salud (CIEIS) Sanatorio Allende Comité Institucional de Ética en Investigación en Salud (CIEIS) Sanatorio Allende Av. Hipólito Yrigoyen 384 Nueva Córdoba Córdoba X5000JHQ Argentina	Approved	ARG1 - Dr. Silvana Solís		28-Jun-2018
	Approved		Local Protocol Amendment 1.0	10-Sep-2020
	Approved		Global Protocol Amendment CTP 3.0	13-Aug-2020
Comité Independiente de Etica Medica del Noroeste Argentino (CIEM NOA) Comité Independiente de Etica Medica del Noroeste Argentino 4th floor Las Piedras 496 San Miguel de Tucuman Tucumán T4000 BRJ Argentina	Approved	ARG2 - Dr. María Felipe Gacioppo	Initial Approval	26-Dec-2017

Brazil				
Approval Level: Study Country & Study Site				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
Comissao Nacional de Etica Em Pesquisa, SRNTV701, Via W 5 Norte - Edificio PO 700, 3° andar, Asa Norte, Brasilia, (61)3315-5877, conep@saude.gov.br	Approved	BRA4 - Dr Raphael Liberatore Jr	Initial Approval	12-Dec-2017
	Rejected		Global Protocol Amendment CTP v3.0	
Hospital Geral De Fortaleza - HGF/SUS, Rue avila Goulart, n° 900 Sala localizada e identificada, piso terreo do HGF, entrada pela protaria lateral do, Papicu, Fortaleza, (85)3101-7078, cephgf@smail.com	Approved	BRA5 - Dr Tania Maria Ferraz	Initial Approval	01-Aug-2018
	Rejected		Global Protocol Amendment CTP v3.0	

Canada				
Approval Level: Study Site Only				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
University of Manitoba Biomedical Research Ethics Board University of Manitoba Biomedical Research Ethics Board P126 Pathology Building 770 Bannatyne Avenue Winnipeg	Approved	CAN1 - Dr. Brandy Wicklow	Initial Approval	23-Aug-2018
	Approved		Global Protocol Amendment CTP v3.0	18-Feb-2020
	Approved		Global Protocol Amendment CTP 5.0	18-Jan-2021
	Approved		Global Protocol Amendment CTP v4.0	18-Jan-2021
The Hospital for Sick Children - Research Ethics Board The Hospital for Sick Children - Research Ethics Board 555 University Avenue Toronto Ontario M5G 1X8 Canada	Approved	CAN2 - Dr. Farid Mahmud	Initial Approval	14-Aug-2019
	Approved		Global Protocol Amendment CTP v3.0	21-Jun-2020
	Approved		Global Protocol Amendment CTP 5.0	19-Jan-2021
	Approved		Global Protocol Amendment CTP v4.0	19-Jan-2021
	Approved		Global Protocol Amendment CTP 7.0	17-Nov-2021

China				
Approval Level: Study Site Only				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
	Approved	CHN2 - Dr. Hongwei Du	Initial Approval	17-Jan-2019
The First Hospital of Jilin University The First Affiliated Hospital,Jilin University No.71, Xinmin Avenue, Chaoyang District, Changchun,Jilin Province, 130021 Changchun Jilin Province 130021 China	Approved		Global Protocol Amendment CTP v3.0	21-Apr-2020
The First Hospital of Jilin University The First Affiliated Hospital,Jilin University No.71, Xinmin Avenue, Chaoyang District, Changchun,Jilin Province, 130021 Changchun Jilin Province 130021 China	Approved		Global Protocol Amendment CTP v3.0	21-May-2020
	Approved	CHN3 - Prof. Haiyan Wei	Initial Approval	23-Jan-2019
The First Affiliated Hospital of Zhengzhou Unviersity The First Affilicated Hospital of Zhengzhou Meidical University No.1 Jianshe East Road Zhengzhou Henan Province 450052 China	Approved		Global Protocol Amendment CTP v3.0	10-Apr-2020

Colombia				
Approval Level: Study Site Only				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
Clínica de la Costa Ltda. Clínica de la Costa Ltda. Carrera 50 No 80-90 Barranquilla Migration Data 0 Colombia	Approved	COL1 - Dr. Jaime Ibarra Gomez	Initial Approval	01-Feb-2018
Comité de Etica en Investigacion Cientifica DexaDiab Comité de Etica en Investigacion Cientifica DexaDiab Carrera 16A # 79 - 33 Bogota Cundinamarca 110221 Colombia	Approved	COL2 - Dr. Hernán Yupanqui Lozno	Initial Approval	12-Jan-2018
	Notification only		Global Protocol Amendment v3.0	14-Apr-2020

Germany				
Approval Level: Study Country Only				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved	DEU1 - Prof. Dr. Karl-Otfried Schwab	Initial Approval	17-Apr-2018
Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved		Local Protocol Amendment Germany 1.0	09-Jul-2019
Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved		Global Protocol Amendment CTP v3.0	07-Apr-2020
Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved		Local Protocol Amendment Germany, v2.0	07-Apr-2020
Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved		Global Protocol Amendment CTP 5.0	09-Mar-2021

Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved with modifications		Global Protocol Amendment CTP v4.0	09-Mar-2021
Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved		Local Protocol Amendment Germany 3.0	09-Mar-2021
Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved		Global Protocol Amendment CTP 7.0	27-Jan-2022
Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Ethik-Kommission der Albert-Ludwigs-Universität Freiburg Engelberger Str. 21 Freiburg 79106 Germany	Approved		Local Protocol Amendment Germany 4.0	27-Jan-2022

Study Number: 1218-0091

Israel				
Approval Level: Study Site Only				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
Ethics Committee Rambam Medical Center LEC at the Rambam Medical Center 8 Haaliya Hashniya Street Haifa 31096 Israel	Approved	ISR1 - Dr. Naim Shehadeh	Initial Approval	24-Jun-2018
	Approved		Global Protocol Amendment CTP v3.0	30-Apr-2020
	Approved		Global Protocol Amendment CTP v4.0 and 5.0	03-Feb-2021
	Approved		Global protocol Amendment CTP v6.0	20-Jan-22
	Approved		Global Protocol Amendment CTP 7.0	20-Jan-2022
	Approved		Global Protocol Amendment CTP v8.0	21-Aug-2022
Ethics Committee at the Soroka Medical Center Ethics Committee at the Soroka Medical Center Itzchak Rager Blvd. Beer Sheva 84101 Israel	Approved	ISR3 - Prof. Dr. Eli Hershkovitz	Initial Approval	09-Sep-2018
	Approved		Global Protocol Amendment CTP v3.0	21-Apr-2020
	Approved		Global Protocol Amendment CTP v4.0 and 5.0	21-Mar-2021
	Approved		Global Protocol Amendment CTP v6.0 and 7.0	09-Nov-2021

	Approved		Global Protocol Amendment CTP 7.0	31-Jan-2021

Study Number: 1218-0091

Korea, Republic of				
Approval Level: Study Country & Study Site				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
Severance Hospital Severance Hospital, Institutional Review Board 50-1 Yonsei-ro, Seodaemun-gu Seoul 03722 Korea, Republic of		KOR1 - Dr. Ho-Seong Kim	Initial Approval	02-Mar-2018
	Approved		Global Protocol Amendment CTP v3.0	13-Mar-2020
	Approved		Global Protocol Amendment CTP 7.0	10-Dec-2021
	Approved			24-Jan-2022
Asan Medical Center Institutional Review Board Asan Medical Center Institutional Review Board Convergence Innovation Bldg. 88, Olympic-ro 43-gil Seoul 05505 Korea, Republic of		KOR2 - Dr. Jin-Ho Choi	Initial Approval	09-Apr-2018
	Approved		Global Protocol Amendment CTP v3.0	26-Mar-2020
	Approved		Global Protocol Amendment CTP 7.0	25-Nov-2021
	Approved			13-Jan-2022
Ajou University Hospital Ajou University Hospital Institutional Review Board Annex 5F, Clinical Research Ethics Center 164, Worldcup-ro, Youngtong-gu Suwon 16499 Korea, Republic of		KOR3 - Dr. Jin Soon Hwang	Initial Approval	06-Apr-2018
	Approved		Global Protocol Amendment CTP v3.0	31-Mar-2020
	Approved		Global Protocol Amendment CTP 7.0	24-Nov-2021
	Approved			10-Jan-2022

Study Number: 1218-0091

Mexico				
Approval Level: Study Country & Study Site				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
Comite de Etica en Investigacion de Clinica Bajio CLINBA Comite de Etica en Investigacion de Clinica Bajio CLINBA Col. Burocrata Tomas Zavala No. 47 Guanajuato Guanajuato - Guanajuato 36256 Mexico	Approved	MEX1 - Dr. Margarita Barrientos Perez	Global Protocol Amendment CTP v3.0	07-Aug-2020
	Approved		Initial Approval	17-Dec-2019
	Approved		Global Protocol Amendment CTP v4.0 and v5.0	06-Aug-2021
MCCR - Mexico Center for Clinical Research, SA de CV MCCR - Mexico Center for Clinical Research, SA de CV Amores 709, Col de Valle Distrito Federal Ciudad de México 3100 Mexico	Approved	MEX12 - Dr. Fernando Ramírez Mendoza	Initial Approval	26-Dec-2017
	Approved		Global Protocol Amendment CTP v3.0	24-Mar-2020

Comite de Etica en Investigacion de la Unidad de Investigacion en Salud Chihuahua. Comite de Etica en Investigación de la Unidad de Investigación en Salud Chihuahua. Colonia San Felipe Calle Trasviña y Retes No. 1317 Chihuahua Chihuahua – Chihuahua 31203		MEX8 - Dr. Luis Nevarez Ruiz	Initial Approval	19-Dec-2017
			Global Protocol Amendment v3.0	24-Jun-2020
Hospital Hispano, S.A. de C.V. Hospital Hispano, S.A. de C.V. Zona Centro Sector Juárez Pedro Moreno #934 Guadalajara Jalisco – Guadalajara 44100 Mexico	Approved	MEX2 - Dr. Diego Espinoza Peralta	Initial Approval	14-Dec-2017
Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Del. Gustavo A. Madero Col. Tepeyac Insurgentes Montiel 87 Piso 2 CDMX Ciudad de México 07020 Mexico	Approved		Global Protocol Amendment CTP v4.0 and 5.0	20-Mar-2021
Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Del. Gustavo A. Madero Col. Tepeyac Insurgentes Montiel 87 Piso 2 CDMX Ciudad de México 07020 Mexico	Approved		Global Protocol Amendment CTP v3.0	07-Mar-2020

Comite de Etica en Investigacion Unidad Clinica de Bioequivalencia S. de RL de C.V. Unidad Clinica de Bioequivalencia S. de RL de C.V. Colonia Moderna. Av. Alemania 1361 Guadalajara Jalisco – Guadalajara 44190 Mexico	Approved	MEX3 - Dr. Emilia Pelayo Orozco	Initial Approval	13-Dec-2017
Comite de Etica en Investigacion Unidad Clinica de Bioequivalencia S. de RL de C.V. Unidad Clinica de Bioequivalencia S. de RL de C.V. Colonia Moderna. Av. Alemania 1361 Guadalajara Jalisco – Guadalajara 44190 Mexico	Approved		Global Protocol Amendment CTP v4.0 and 5.0	31-May-2021
Comite de Etica en Investigacion Unidad Clinica de Bioequivalencia S. de RL de C.V. Unidad Clinica de Bioequivalencia S. de RL de C.V. Colonia Moderna. Av. Alemania 1361 Guadalajara Jalisco – Guadalajara 44190 Mexico	Approved		Global Protocol Amendment CTP v3.0	23-Mar-2020
Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Del. Gustavo A. Madero Col. Tepeyac Insurgentes Montiel 87 Piso 2 CDMX Ciudad de México 07020	Approved	MEX4 - Dr. Rafael Violante Ortiz	Initial Approval	12-Jan-2018
Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Del. Gustavo A. Madero Col. Tepeyac Insurgentes Montiel 87 Piso 2 CDMX Ciudad de México 07020	Approved		Global Protocol Amendment CTP v4.0 and 5.0	22-May-2021

Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Comité de Ética en Investigación del Centro de Investigación Clínica Acelerada, SC Del. Gustavo A. Madero Col. Tepeyac Insurgentes Montiel 87 Piso 2 CDMX Ciudad de México 07020 Mexico	Approved		Global Protocol Amendment CTP v3.0	03-Jul-2020

Study Number: 1218-0091

Russian Federation				
Approval Level: Study Site Only				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
EC at FSBEI HE, Saint-Petersburg EC at Federal State Budgetary Educational Institution of Higher Education State Pediatric Medical University of MoH 2, Litovskaya Str. Saint-Petersburg 194100 Russian Federation	Approved	RUS1 - Dr. Yulia Skorodok	Initial Approval	14-May-2018
	Approved		Global Protocol Amendment CTP v3.0	29-Jun-2020
FSBEI HE, Novosibirsk State Med.Univ. MoH Federal State Budgetary Educational Institution of Higher Education Novosibirsk State Medical University of the Ministry of Health of the Russian Federation 52, Krasny prospect Novosibirsk 630091 Russian Federation	Approved	RUS10 - Dr. Irina Bondar	Initial Approval	31-May-2018
	Approved		Global Protocol Amendment CTP v3.0	26-Jun-2020
LEC of Kirov Regional State Budget Institution of Healthcare "Kirov clinical hospital #7 n.a.V.I.Urlova" LEC of Kirov Regional State Budget Institution of Healthcare "Kirov clinical hospital #7 n.a.V.I.Url 56, Krasina str. Kirov 610014 Russian Federation	Approved	RUS11 - Prof. Aleksandr Sobolev	Initial Approval	10-May-2018
	Approved		Global Protocol Amendment CTP v3.0	16-Jun-2020

Local Ethics Committee of MoH Rus Fed Irkutsk State Medical Academy of Post-Graduate Education 100, m-n Yubileyny Irkutsk 664049 Russian Federation	Approved	RUS12 - Dr. Tatiana Bardymova	Initial Approval	25-Apr-2019
	Approved		Global Protocol Amendment CTP v3.0	25-Jun-2020
LEC Kazan state medical University, MoH RF Local Ethics Committee of Federal State Budget Educational Institution of Higher Education "Kazan state medical University" of Ministry of Healthcare of Russian Federation 49, Butlerova str. Kazan 420012 Russian Federation	Approved	RUS3 - Prof. Dr. Farida Valeeva	Initial Approval	24-Apr-2018
	Approved		Global Protocol Amendment CTP v3.0	23-Jun-2020
LEC of Federal State Budget Institution "National Medical Research Center of Endocrinology" of MoH of RF LEC of Federal State Budget Institution "National Medical Research Center of Endocrinology" of MoH o 11, Dmitriya Ulyanova, str Moscow 117036 Russian Federation	Approved	RUS4 - Prof. Valentina Peterkova	Initial Approval	10-Oct-2018
	Approved		Global Protocol Amendment CTP v3.0	22-Jul-2020
	Approved		Global Protocol Amendment CTP v4.0 and v5.0	13-Oct-2021
FSBEI HE Bashkirsky State Med.Univ.,MoH Federal State Budget Educational Institution of Higher Education "Bashkirsky state medical University" of Ministry of Healthcare of Russian Federation 3, Lenina Str. Ufa 450008 Russian Federation	Approved	RUS5 - Dr. Oleg Malievskiy	Initial Approval	20-Jun-2018

	Approved		Global Protocol Amendment CTP v3.0	08-Jul-2020
	Approved		Global Protocol Amendment CTP v4.0 and v5.0	22-Sep-2021
EC Siberian State Med.Univ.MoH,HC Ethics Committee under the Federal State Budget Educational Institution of Higher Education "Siberian State Medical University" of the Ministry of Health of Russia 15, Kotovskogo Str. Tomsk 634034 Russian Federation	Approved	RUS6 - Dr. Julia Samoilova	Initial Approval	26-Apr-2018
	Approved		Global Protocol Amendment CTP v3.0	18-Jun-2020
LEC of Federal State Budget Educational Inst. of Higher Education "Rostov State Medical University" of MoH of RF LEC of Federal State Budget Educational Inst. of Higher Education "Rostov State Medical University" 29, Nahichevanskiy pr Rostov-on-Don 344022 Russian Federation	Approved	RUS7 - Dr. Galina Galkina	Initial Approval	13-Sep-2018
	Approved		Global Protocol Amendment CTP v3.0	25-Jun-2020
	Approved		Global Protocol Amendment CTP v4.0 and v5.0	21-Oct-2021
Ethic Committee, Izhevsk State Medical Academy Ethic Committee, Izhevsk State Medical Academy 281, Kommunarov str. Izhevsk 426034 Russian Federation	Approved	RUS8 - Dr. Tatiana Kovalenko	Initial Approval	26-Jun-2018
	Approved		Global Protocol Amendment CTP v3.0	16-Jun-2020
LEC of Federal State Budget Educational Inst. of Higher Education "Ivanovo State Medical Academy" of MoH of Russ.Fed. 8, Sheremetievskiy pr. Ivanovo 153012 Russian Federation	Approved	RUS9 - Dr. Olga Votyakova	Initial Approval	06-Jun-2018

	Approved		Global Protocol Amendment CTP v3.0	09-Sep-2020

Study Number: 1218-0091

Thailand				
Approval Level: Study Country & Study Site				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
The Ethical Review Committee for Research in Human Subjects Ministry of Public Health, Thailand (MoPH) 88/22 Moo 4 Tiwanon Road, Talad-Khwan, Nonthaburi 11000	Approved	THA1 - Dr Chaicharn Deerochanawong	Initial Approval	26-Sep-2018
			Initial Approval, Local CTP v1	26-Sep-2018
	Approved		Global Protocol Amendment CTP v3.0	10-Sep-2020
	Approved		Global Protocol Amendment CTP v5.0	09-Jun-2021
	Approved		Global Protocol Amendment CTP v4.0	09-Jun-2021
Ethics committee Rajavithi hospital Rajavithi Hospital 2, Phayathai Rd. Ratchathewi, Bangkok, Ratchathewi 10400 Thailand	Approved	THA1 - Dr Chaicharn Deerochanawong	Initial Approval, Local CTP v1	18-Oct-2018
	Approved		Global Protocol Amendment	17-Dec-2020
	Approved		Global Protocol Amendment CTP 4.0 and 5.0	16-Sep-2021

Study Number: 1218-0091

United Kingdom				
Approval Level: Study Country Only				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
East of England - Cambridge South REC East of England - Cambridge South REC The Old Chapel, Royal Standard Court Nottingham NG1 6FS United Kingdom	Approved	GBR5 - Dr Chandan Yaliwal GBR7 - Dr Mimi Chen	Initial Approval	08-Aug-2018
	Approved		Local Amendment 1.0 and 2.0	08-Aug-2018
	Approved		Clinical Trial Protocol Amendment V 3.0	10-Jul-2020
	Approved		Clinical Trial Protocol Amendment V 4.0 and 5.0	18-May-2021

Study Number: 1218-0091

United States of America				
Approval Level: Study Country & Study Site				
IRB/IEC (name/address)	**Verdict Type**	**Study Site Number - Investigator**	**Protocol and/or Amendment number(s)**	**Date of Final Approval**
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA106 - Dr. Leichter, Steven	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	11Mar2019 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA4 - Dr. Velasquez-Mieyer, Pedro	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	30Apr2018 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA91 - Dr. Desai, Vivek	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0	20Aug2018 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA74 - Dr. Irizarry-Gonzalez, Lydia	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0	09Jul2018 17Feb2020
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA11 - Dr. Guido, Giancarlo	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0	05Feb2018 17Feb2020

Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA22 - Dr. Hassan, Amir	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0	26Feb2018 17Feb2020 28Dec2020 28Dec2020
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA23 - Dr. Gonzalez, Edgar	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	18Jan2018 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA25 - Dr. Colomar, Javier	Initial Global Protocol v2.0	29Jan2018
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA63 - Dr. Vance, Carl	Initial Global Protocol v2.0	12Feb2018
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA55 - Dr. Dillon, Robert	Initial Global Protocol v2.0	26Mar2018
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA59 - Dr. Saenz, Javier	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	05Feb2018 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
Western Institutional Review Board 1019 39th Avenue SE Suite 120 Payallup, WA, 98374	Approved	USA80 - Dr. Bjornstad,Petter	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0	07Dec2018 25Mar2020 01Apr2021 01Apr2021

United States			Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	25Nov2021 25Nov2021 08Jul2022
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA89 - Dr. Clements, Mark	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	04Feb2019 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
CHOC IRB 1201 W La Verta Avenue Orange, CA 92868 United States	Approved	USA95 Dr. Daniels, Mark	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	05Nov2018 20Apr2020 05Apr2021 05Apr2021 03Jan2022 03Jan2022 15Aug2022
Nemours Institutional Review Board 1600 Rockland Rd Wilmington, DE 19803 United States	Approved	USA72 - Dr. Desmangles, Jean-Claude	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	07Nov2018 16Apr2020 16Feb2021 16Feb2021 03Nov2021 03Nov2021 30Jun2022
Monument Health IRB 353 Fairmont Blvd Rapid City, SD 57701 United States IRB name change from Rapid City Regional Hospital IRB to Monument Health IRB effective 09Sep2020	Approved	USA69 - Dr. Edelen, Rachel	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	12Jun2018 14Apr2020 09Mar2021 09Mar2021 14Dec2021 14Dec2021 04Aug2022
UCSD Human Research Protections Program 9500 Gilman Drive MC0052 La Jolla, CA 92093 United States	Approved	USA102 - Dr. Gottschalk, Michael	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	22Mar2019 07May2020 04Feb2021 04Feb2021 02Dec2021 02Dec2021 21Jun2022
(Effective 13Jul21): Penn State Institutional Review Board	Approved	USA14 - Dr. Huerta-Saenz, Lina	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0	14May2018 20Apr2020

The 330 Building, Suite 205 University Park, PA 16802 United States (Effective 24Jan18): Penn State Milton S. Hershey Medical Center Human Subjects Protection Office IRB 90 Hope Drive, Mailcode A115, ASB Room 1140 Hershey, PA 17033 United States			Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	05Aug2021 05Aug2021 03Nov2021 03Nov2021 30Jun2022
Western IRB (WIRB) 1019 39th Avenue SE Puyallup, WA 98374 United States	Approved	USA108 - Dr. Jain, Nina	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	02Dec2019 12May2020 11Mar2021 11Mar2021 16Nov2021 16Nov2021 18Jul2022
(Effective 27Jul22): The University of Oklahoma Institutional Review Board for the Protection of Human Subjects 865 Research Parkway Suite 400 Oklahoma City, OK 73104 United States (Effective 13Aug18): University of Oklahoma Health Sciences Center 1105 North Stonewall Avenue Library Building Room 176 Oklahoma City, OK 73117 United States	Approved	USA94 - Dr. Jelley, David	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	21Sep2018 18May2020 07Jan2021 07Jan2021 24Jan2022 24Jan2022 08Jul2022
Committee on Human Studies Joslin Diabetes Center One Joslin Place Boston, MA 02215 United States	Approved	USA104 - Dr. Laffel, Lori	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	14Dec2018 15May2020 22Jan2021 22Jan2021 18Nov2021 18Nov2021 22Jul2022
Emory University Institutional Review board 1599 Clifton Road, NE 5th floor Atlanta, GA 30322 United	Approved	USA83 - Dr. Muir, Andrew	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0	12Feb2019 26Mar2020 1Apr2021 1Apr2021

States			Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0	30Nov2021 30Nov2021
Alpha IRB 1001 Avenida Pico Suite C #497 San Clemente, CA 92673 (Effective Date: 11/20/2019) University of South Florida office of Research integrity & Compliance-Medical IRB 3702 Spectrum Blvd Suite 165 Tampa, FL 33612 (Effective Date: 7/5/2018) United States	Approved	USA75 - Dr. Rodriquez, Henry	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	13Nov2018 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
Alpha IRB 1001 Avenida Pico Suite C #497 San Clemente, CA 92673 United States	Approved	USA81 - Dr. Shah, Sejal	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	25Feb2019 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
Vanderbilt Human Research Protection Program 1313 21st Avenue South Suite 504 Nashville, TN 37232 United States	Approved	USA90 - Dr. Shoemaker, Ashley	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	20Dec2018 09Jun2020 21May2021 21May2021 07Dec2021 07Dec2021 30Aug2022
UCSF Human Research Protection Program 3333 California Street Suite 315 Box 0962 San Francisco, CA 94143 United States	Approved	USA87 - Dr. Srinivasan, Shylaja	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	12Nov2019 02Jul2020 11Mar2021 11Mar2021 16May2022 16May2022 02Aug2022
Yale University Human Investigation Committee 25 Science Park 150 Munson Street, 3rd Floor New Haven, CT, USA 06520 United States	Approved	USA67 - Dr. Tamborlane, William	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	13Feb2019 13May2020 10Feb2021 10Feb2021 15Dec2021 15Dec2021 27Jun2022

Western IRB HawkIRB Hardin Library, Office 105 600 Newton Rd Iowa City, IA, 52242 United States	Approved	USA68 - Dr. Tsalikian, Eva	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	03Jan2019 17Apr2020 16Mar2021 16Mar2021 10Nov2021 10Nov2021 13Jun2022
Western Institutional Review Board 1019 39th Avenue SE Suite 120 Payallup, WA, 98374 United States	Approved	USA101 - Dr. Weinstock, Ruth	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	07Feb2019 01Apr2020 14Jan2021 14Jan2021 02Nov2021 02Nov2021 30Jun2022
Children's Hospital of Philadelpia Institutional Review Board Roberts Center for Pediatric Research 2716 South Street, 4th Floor Philadelphia, PA, 19146 United States	Approved	USA84 - Dr. Willi, Steven	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0	12Apr2019 03Mar2021 16Jun2021 16Jun2021 02Feb2022 02Feb2022
Human Subjects Protection Program Med Center One, Suite 200 University of Louisville 501 E. Broadway Louisville, KY, 40202 United States	Approved	USA77 - Dr. Wintergerst, Kupper	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	02Aug2018 14Mar2020 21Apr2021 21Apr2021 23Nov2021 23Nov2021 21Jun2022
John Hopkins Medicine Institutional Review Board 1620 McElderry St. Reed Hall - B130 Baltimore, MD, 21205-1911 United States	Approved	USA105 - Dr. Wolf, Risa	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	11Jun2019 31Mar2020 20Apr2021 20Apr2021 30Nov2021 30Nov2021 05Jul2022
Advarra Institutional Review Board 6940 Columbia Gateway Drive Suite 110 Columbia, MD 21046	Approved	USA79 - Dr. Wood, Jamie	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0	12Oct2018 17Mar2020 03Mar2021 03Mar2021

United States			Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	26Oct2021 26Oct2021 24Jun2022
University of Buffalo Institutional Review Board Clinical and Translational Research Center 875 Ellicott Street, Room 5018 Buffalo, NY 14203 United States	Approved	USA86 - Dr. Bethin, Kathy	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	30Aug2018 14Apr2020 23Feb2021 23Feb2021 06Jan2022 06Jan2022 12Jul2022
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA78 - Dr. Dixit, Naznin	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	10Jun2019 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA64 - Dr. Gallagher, Mary	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	10Dec2018 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022
The University of Oklahoma Institutional Review Board for the Protection of Human Subjects 865 Research Parkway, Suite 400 Oklahoma City, OK 73104 United States	Approved	USA88 - Dr. George, Minu	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	04Dec2018 27Apr2020 26Feb2021 26Feb2021 22Nov2021 22Nov2021 09Jul2022
University of Texas Health Science Center - San Antonio Institutional Review Board 4207 Floyd Curl Drive MC 7830 San Antonio, TX 78229 United States	Approved	USA82 - Dr. Lynch, Jane	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0	28Nov2018 31Mar2020 02Jun2021 02Jun2021
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673	Approved	USA109 - Dr. Nelson, Bryce	Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0	10Aug2020 28Dec2020 28Dec2020 25Oct2021

United States			Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	25Oct2021 20Jun2022
Phoenix Children's Hospital Institutional Review Board 1919 E. Thomas Td Phoenix, AZ 85016 United States	Approved	USA76 - Dr. Olson, Micah	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0	06Dec2018 25jun2020 24Jun2021 24Jun2021 30Nov2021 30Nov2021
Advent Health Orlando Institutional Review Board 901 N. Lake Destiny Road Maitland, FL 32751 United States	Approved	USA62 - Dr. Reddy, Konda	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	15Feb2018 28Apr2020 26Jan2021 26Jan2021 N/A 14Dec2021 07Jul2022
Alpha IRB Alpha IRB Suite C #497 1001 Avenida Pico San Clemente, CA 92673 United States	Approved	USA46 - Dr. Wheeler, Mark	Initial Global Protocol v2.0 Global Protocol Amendment CTP v3.0 Global Protocol Amendment CTP v4.0 Global Protocol Amendment CTP v5.0 Global Protocol Amendment CTP v6.0 Global Protocol Amendment CTP v7.0 Global Protocol Amendment CTP 8.0	30May2018 17Feb2020 28Dec2020 28Dec2020 25Oct2021 25Oct2021 20Jun2022