EMA/2020/46/TDA/19

Specific Contract 01

Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks

(TARGET-EU)

Hypothetical Target Trial Protocol WP3

EU PE&PV research network

Case Study 3:
Dapagliflozin and Major Adverse Cardiovascular Events in Type 2 Diabetes

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1. PROTOCOL SUMMARY

1.1 Protocol Synopsis

Primary objectives and endpoints

The primary objective of this trial is to assess whether dapagliflozin, when added to usual care, reduces the time to first major adverse cardiovascular event (MACE) compared to DPP-4 inhibitors in patients with type 2 diabetes who have established cardiovascular disease or at least two cardiovascular risk factors. The primary endpoint is time to first MACE, defined as a composite outcome that includes myocardial infarction, ischemic stroke, cardiovascular death, and non-cardiovascular death.

Overall Design

Intervention model: Parallel group, active comparator, superiority	***Trial intervention assignment method:*** *1:1 randomisation*
Trial Intervention: Dapagliflozin (Dapa)	***Population Diagnosis or Condition:*** Patients with type 2 diabetes who have or are at risk for atherosclerotic cardiovascular disease
Control Type: Active comparator	***Population age:*** Adult (over 40)
Active comparator: Dipentyl peptidase 4 inhibitor (DPP4-i)	

Number of arms: 2 (dapa vs dpp4-i)

Blinding: Open label

Number of participants: 6,671

Duration: 5 years

1.2 Trial Schema

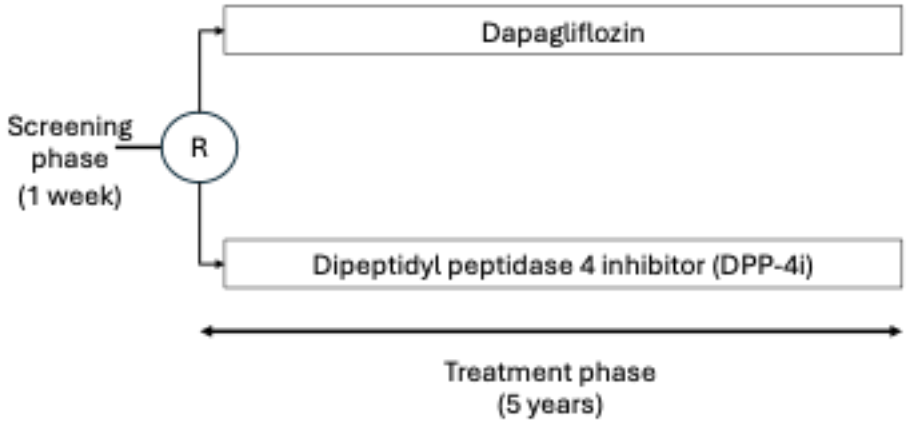

Figure 1. Schematic of Trial Schema

2. INTRODUCTION

2.1 Purpose of the trial

The purpose of this trial is to evaluate the effectiveness of dapagliflozin compared to DPP-4 inhibitors, when added to usual care, in reducing major adverse cardiovascular events (MACE) among patients with type 2 diabetes who have or are at risk for atherosclerotic cardiovascular disease (ASCVD). While initial cardiovascular outcome trials (CVOTs) were primarily designed to assess the safety of glucose-lowering therapies, accumulating evidence — including from the DECLARE-TIMI 58 trial — has demonstrated that dapagliflozin not only meets cardiovascular safety standards but also confers benefits in reducing hospitalization for heart failure and slowing renal disease progression [1]. In contrast, DPP-4 inhibitors have shown a neutral cardiovascular profile, as observed in placebo-controlled CVOTs such as TECOS (sitagliptin) [2] and SAVOR-TIMI 53 (saxagliptin) [3]. Importantly, no large head-to-head randomized controlled trial has directly compared dapagliflozin to a DPP-4 inhibitor for MACE or other cardiovascular outcomes, leaving a significant evidence gap regarding their comparative effectiveness. This trial is therefore designed to address that gap by providing causal, comparative evidence under real-world conditions of use in the post-marketing setting. In doing so, it aligns with the European Medicines Agency's regulatory emphasis on comparative effectiveness [4] and supports evolving clinical guidelines that prioritize SGLT2 inhibitors, like dapagliflozin, in patients with high cardiovascular risk [5,6].

3. TRIAL OBJECTIVES, ENDPOINTS, ESTIMANDS

3.1 Main Objective of the Trial

The primary objective is to assess whether dapagliflozin reduces the time to first major adverse cardiovascular events compared to DPP-4 inhibitors in patients with type 2 diabetes and established cardiovascular disease or at least two cardiovascular risk factors.

3.2 Primary Endpoint

The primary endpoint will be time to the first occurrence of major adverse cardiovascular events (MACE). For this study a modified version of the MACE endpoint will be considered. MACE is a composite endpoint that includes myocardial infarction, ischemic stroke or cardiovascular death. In addition, in this study we will include non-cardiovascular death as part of the endpoint in order to implement a composite strategy to handle non-cardiovascular death (see Estimand Table below).

Table 1. Estimand Table

	Estimand 1 (*Primary estimand*)	**Estimand 2 (*Supplementary estimand*)**	**Estimand 3 (*Supplementary estimand*)**
Population	Patients with type 2 diabetes who have or are at risk for atherosclerotic cardiovascular disease	Patients with type 2 diabetes who have or are at risk for atherosclerotic cardiovascular disease	Patients with type 2 diabetes who have or are at risk for atherosclerotic cardiovascular disease
Treatment Conditions	**Intervention group**: Dapagliflozin (added to usual care) **Control group**: DPP4-I (added to usual care)	**Intervention group**: Dapagliflozin (added to usual care) **Control group**: DPP4-I (added to usual care)	**Intervention group**: Dapagliflozin (added to usual care) **Control group**: DPP4-I (added to usual care)
Endpoint	Time to first MACE (non-fatal MI, stroke, all-cause death)	Time to first MACE (non-fatal MI, stroke, all-cause death)	Time to first MACE (non-fatal MI, stroke, all-cause death)
Summary Measure	Hazard Ratio	Hazard Ratio	Difference in Restricted Mean Survival Time
Intercurrent events and strategies to handle them	Same for both treatment conditions ***Treatment discontinuation***: treatment policy ***Treatment switch***: treatment policy ***Addition of another antihyperglycemic therapy***: treatment policy ***Non-CV death***: composite	Same for both treatment conditions ***Treatment discontinuation***: while on treatment ***Treatment switch***: while on treatment ***Addition of another antihyperglycemic therapy***: while on treatment ***Non-CV death***: composite	Same for both treatment conditions ***Treatment discontinuation***: treatment policy ***Treatment switch***: treatment policy ***Addition of another antihyperglycemic therapy***: treatment policy ***Non-CV death***: composite

3.3 Rationale for why selected strategies to handle intercurrent events are chosen

Intercurrent events such as treatment discontinuation, treatment switching, or initiation of add-on antihyperglycemic therapies are handled using a treatment policy strategy in the Primary Estimand, as this approach aligns with regulatory expectations for estimating effects under usual clinical practice conditions and supports comparative effectiveness evaluations. In contrast, Estimand 2 uses a while-on-treatment strategy to estimate the effect of treatment exposure during the period when patients remain adherent, providing complementary insights into biological treatment responsiveness. For non-cardiovascular death, a composite strategy is used across estimands to ensure that all-cause mortality is captured, reflecting the fact that non-CV death precludes the observation of other MACE components.

3.4 Research questions targeted by the estimands

Estimand 1: What is the HR of MACE for Dapa vs DPP-4i in patients with type 2 diabetes with or at risk for ASCVD regardless of treatment discontinuation, switching or new add-on antihyperglycemic therapy?

Estimand 2: What is the HR of MACE for Dapa vs DPP-4i in patients with type 2 diabetes with or at risk for ASCVD while on treatment (i.e., before treatment discontinuation, switching or new add-on antihyperglycemic therapy)?

Estimand 3: *What is the difference in restricted (at 3 and 5 years) mean survival time (to MACE between Dapa and Dpp4-I* in patients with type 2 diabetes with or at risk for ASCVD regardless of treatment discontinuation, switching or new add-on antihyperglycemic therapy?

4. TRIAL DESIGN

4.1 Description of trial design

This is a randomised, open-label, active-controlled, parallel-group clinical trial comparing the effectiveness of Dapa to Dpp4-I to reduce the risk of MACE.

Description Intervention Model

Patients will be randomised to either Dapa or Dpp4-I and they will be treated with the assigned therapy during the 5-year treatment phase.

Description of Trial Duration

- 5 years in total
  - One week screening period to determine eligibility
  - Randomization and start of 5-year treatment phase

Description of Method of Assignment to Trial Intervention

- Simple 1:1 randomization
- Randomization occurs at the moment when all inclusion criteria for the study have been met (and no exclusion criteria present)

4.2 Rationale for trial design

Rationale for intervention model

- Parallel group: make direct comparisons between dapagliflozin and Dpp-4i
- Active comparator: reflective of treatment given to patients with type 2 diabetes in real-world clinical practice

Rationale for duration

- Sufficient time to capture long-term cardiovascular outcomes and accrue enough MACE events for statistical power.
- Reflects intended long term use of type 2 diabetes treatments.

Rationale for Endpoints

- Components of MACE represent serious, life-threatening events that directly reflect the cardiovascular health of a patient
- All-cause mortality is considered here, but death is expected to be mainly related to cerebrovascular, cardiovascular causes among those with type 2 diabetes

Rationale for comparator

- Active comparator is most representative of real world clinical practice
    - Benchmark safety against another type of medication used to treat this patient population.
    - Would not be ethical to have diabetes patients without treatment for 5 years.
- DPP4i's are a common alternative to SGLT2i's
- DPP4i's are cardiovascular neutral

4.3 Start and End of Trial

Start of trial will be enrolment of first patient meeting eligibility criteria after the eligibility screening period. The end of trial will be 5 years after final patient is randomised.

5. TRIAL POPULATION

5.1 Inclusion Criteria

Inclusion Criteria

1. Documented history or diagnosis of T2D
2. Age 40 and over at the time of eligibility screening
3. Either established **atherosclerotic cardiovascular disease** (ACVD) ***or*** at high risk of ACVD.

Established ACVD defined as history or diagnosis of at least one of the following determined during the 1 year eligibility screening period

- Ischemic heart disease
- Ischemic cerebrovascular disease
- Peripheral arterial disease

High ACVD risk defined as no established ACVD, age ≥ 55 years in men and ≥ 60 in women and one or more of the following:

- Documented history or diagnosis of dyslipidaemia
- Current lipid lowering therapy during
- Documented history or diagnosis of hypertension
- Current anti-hypertensive medication use prescribed for blood pressure lowering
- Tobacco use within the last year prior to randomisation, including current use

Exclusion Criteria

- Treatment with SGLT2i or DPP-4i in the last year prior to randomisation.
- Documented history or diagnosis of acute cardiovascular event in the last year prior to randomisation.
- Documented history or diagnosis of Type 1 diabetes

6. TRIAL INTERVENTION AND CONCOMITANT THERAPY

6.1 Description of trial intervention:

Intervention is oral dapagliflozin at any dose, any regimen, any type which could include:

- Dapa combination therapy as first line therapy, Dapa monotherapy first line therapy, switch to or add on Dapa to any antihyperglycemic background therapy
- Duration of intervention: up to 5 years

Comparator is oral Dpp-4i at any dose, any regimen, any type which could include:

- Dpp-4i - combination therapy as first line therapy, Dpp-4i monotherapy first line therapy, switch to or add on Dpp-4i to any antihyperglycemic background therapy
- Duration of intervention: up to 5 years

6.2 Participant Assignment:

Randomization occurs once all inclusion criteria have been met without the presence of any exclusion criteria.

6.3 Concomitant Therapies:

Permitted

- Anti-hyperglycaemic medication including sulfonylureas, insulin, glucagon like peptide 1 antagonists, metformin
    - Patients should be treated for diabetes with glycemic targets as recommended by current clinical practice guidelines.

Prohibited

- Pioglitazone, rosiglitazone, any SGLT2-I other than dapagliflozin

7. DISCONTINUATION OF TRIAL INTERVENTION AND LOSS TO FOLLOW-UP

7.1 Discontinuation of trial intervention:

- Possible reasons for discontinuation:
    - Patient decision.
        - Patients are free to discontinue from the randomised treatment at any time.
        - Patients who choose to discontinue treatment will continue in the study and data after treatment discontinuation through until the end of the study is of interest
    - Safety or lack of efficacy reasons as judged by the investigator.

7.2 Withdrawal from the study:

Patients are at any time free to completely withdraw their informed consent and stop participation the study.

7.3 Loss to Follow-up:

A patient will be classified as lost to follow up only if they have failed to return for the required study visits and their health condition and vital status remains unknown despite multiple attempts to contact them.

8. STATISTICAL CONSIDERATIONS

8.1 Analysis Set

Estimand 1

- Do not exclude data after the occurrence of intercurrent events

Estimand 2

- Exclude data occurring after the occurrence of the following intercurrent events: treatment discontinuation, switching or add-on in either the intervention or comparator arm.

Estimand 3

- Do not exclude data after the occurrence of intercurrent events

8.2 Analyses

Analyses supporting Estimand 1 & Estimand 2

Statistical Model, and method of analysis

- Cox Proportional Hazards model
- Endpoint: time from randomization to occurrence of first MACE
- Censoring: loss to follow-up (non-administrative censoring), study end without MACE (administrative censoring)
    - For estimand 2 only, censor at treatment modifying events (administrative censoring): treatment discontinuation, switching, add on
- Covariates: Treatment group (Dapa vs. DPP-4i)

Assumptions & diagnostics

- Proportional hazards
    - Diagnostics: log-cumulative hazard plots
- Censoring is non-informative

- Diagnostic: compare baseline characteristics of censored vs uncensored individuals
    - However, this assumption cannot be formally tested or verified from observed data.

Reporting

- Tables summarizing event counts, incidence rates (e.g., per 100 person-years)
- Hazard Ratios (HR) with 95% Confidence Intervals

Analyses supporting Estimand 3

Statistical Model, and method of analysis

- *Accelerated failure time model with Weibull distribution*
    - Endpoint: time from randomization to occurrence of first MACE
    - Censoring: loss to follow-up (non-administrative censoring), study end without MACE (administrative censoring)
    - Covariates: Treatment group (Dapa vs. DPP-4i)

Assumptions

- Survival times follow Weibull distribution
    - Diagnostic: Plot log(-log(S(t))) vs log(t): Should be linear if Weibull holds.
- Censoring is non-informative
    - Diagnostic: compare baseline characteristics of censored vs uncensored individuals
        - However, this assumption cannot be formally tested
- Log linear relationship between covariates and lot linear survival time
    - Diagnostic: Q-Q plot of residuals normally distributed

Reporting

- Restricted mean (95% CI) MACE free time in dapagliflozin group and mean (95% CI) MACE free time in DPP4-I group over all as well as difference in RMST (with 95% CI)
    - And at year 3 & year 5 of follow-up (restricted mean survival time)

8.3 Handling of intercurrent events

Estimand 1 & Estimand 3

- Treatment discontinuation: do not censor subject, continue following
- Treatment switch: do not censor subject, continue following

- Addition of another antihyperglycemic therapy: do not censor subject, continue following
- Non-CV death: Include as part of MACE outcome

Estimand 2

- Treatment discontinuation: censor subject administratively at the time of the occurrence of the intercurrent event.
- Treatment switch: censor subject administratively.
- Addition of another antihyperglycemic therapy: censor subject administratively.
- Non-CV death: Include as part of MACE outcome

8.4 Handling of Missing Data

- Censored time to event data (handled by the model, contributes partial information)
    - The Cox regression model implicitly assumes censoring occurs at random

8.5 Sensitivity analysis

Sensitivity analysis under the Censoring Not At Random (CNAR) assumption will be carried out.

8.6 Supplemental analysis

Report HR (and 95% CI) for each year of follow-up for estimands 1 & 2

8.7 Sample size determination

Assuming an alpha of 0.05, a 9% risk of MACE over 5 years (from placebo group of DECLARE trial), a 1% withdrawal rate over the entire study period, and a HR=0.85 (HR for dapa vs placebo from DECLARE), 13,341 patients (i.e., 6,671 per arm) would need to be randomized (1,189 events) to achieve 80% power.

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