American Heart Journal 200 (2018) 83–89

Contents lists available at ScienceDirect

American Heart Journal

Trial Design

The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)–TIMI 58 Trial

Stephen D. Wiviott [a,*], Itamar Raz [b], Marc P Bonaca [a], Ofri Mosenzon [b], Eri T Kato [c], Avivit Cahn [b], Michael G Silverman [d], Sameer Bansilal [e], Deepak L Bhatt [a], Lawrence A. Leiter [g], Darren K. McGuire [i], John PH Wilding [h], Ingrid AM Gause-Nilsson [f], Anna Maria Langkilde [f], Peter A. Johansson [f], Marc S. Sabatine [a]

[a] *TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA*
[b] *The Diabetes Unit, Hadassah Hebrew University Hospital, Jerusalem, Israel*
[c] *Kyoto University Hospital, Kyoto, Japan*
[d] *Cardiology Division, Massachusetts General Hospital, Boston, MA*
[e] *Zena and Michael A Weiner Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY*
[f] *AstraZeneca Gothenburg, Mölndal, Sweden*
[g] *Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Ontario, Canada*
[h] *Institute of Ageing and Chronic Disease, University of Liverpool, Liverpool, United Kingdom*
[i] *Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX*

ARTICLE INFO

Article history:
Received 4 August 2017
Accepted 28 January 2018

ABSTRACT

Background: Dapagliflozin is a sodium-glucose co-transporter-2 (SGLT-2) inhibitor that reduces blood glucose in patients with type 2 diabetes mellitus (T2DM) by promoting glycosuria via inhibiting urinary glucose reabsorption. In addition to improving blood glucose control, treatment with dapagliflozin results in glucose-induced osmotic diuresis, weight loss, and blood pressure lowering. Previous trials of SGLT-2 inhibitors showed reductions

RCT# NCT01730534

Disclosures: Dr Wiviott reports grants and personal fees from AstraZeneca, grants and personal fees from Bristol Myers Squibb, grants and personal fees from Eisai, grants and personal fees from Merck, personal fees from Aegerion, personal fees from Angelmed, personal fees from Xoma, personal fees from ICON Clinical, personal fees from Boston Clinical Research Institute, grants and personal fees from Eli Lilly/Daiichi Sankyo, grants from Sanofi-Aventis, other from Merck Research Laboratory, personal fees from Boehringer Ingelheim, grants and personal fees from Amgen, personal fees from Allergan, grants and personal fees from Janssen, grants from Arena, and personal fees from St Jude Medical and Lexicon outside the submitted work. Dr Wiviott's wife is an employee of Merck. Dr. Raz discloses the following relationships: Advisory Board: AstraZeneca, Boehringer Ingelheim, Concenter BioPharma/Silkim Ltd, Eli Lilly and Company, Merck Sharp & Dohme, Novo Nordisk, Inc., Orgenesis, Pfizer, Sanofi, SmartZyme Innovation Ltd, Panaxia; Consultant: AstraZeneca/Bristol-Myers Squibb, Diabetes Medical Center, FuturRx Ltd, Insuline Medical, Medial EarlySign Ltd, CamerEyes, Exscopia, Dermal Biomics Inc; Speaker's Bureau: AstraZeneca/Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly and Company, Johnson & Johnson, Merck Sharp & Dohme Limited, Novartis Pharma AG, Novo Nordisk, Inc., Sanofi, Teva; Stock/Shareholder: Glucome Ltd, Insuline Medical, Orgenesis, DarioHealth, CamerEyes. Dr. Bonaca reports grant support to BWH from AstraZeneca, MedImmune, and Merck; Consulting for Aralez, AstraZeneca, Merck and Bayer. Dr Bhatt discloses the following relationships: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; honoraria: American College of Cardiology (Senior Associate Editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (Editor in Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); other: *Clinical Cardiology* (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); research funding: Abbott, Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Regeneron, Roche, Sanofi Aventis, The Medicines Company; royalties: Elsevier (Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda. Dr Leiter has received research funding from, has provided CME on behalf of, and/or has acted as an advisor to AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Merck, Novo Nordisk, Sanofi, Servier. J. P. H. Wilding has received lecture fees from Astellas, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, Orexigen, Sanofi; consultancy (Institutional) from AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Orexigen; and grants to institution from Takeda, Novo Nordisk and AstraZeneca. Dr Cahn discloses the following relationships: Advisory Board: Novo Nordisk, Eli Lilly, Sanofi, Boehringer Ingelheim, AstraZeneca; research grant support through Hadassah Hebrew University Hospital: AstraZeneca; Speaker's Bureau: AstraZeneca, Novo Nordisk, Eli Lilly, Sanofi, Merck Sharp & Dohme, Boehringer Ingelheim. Stock/shareholder: Glucome Ltd. Dr Nilsson, Dr Langkilde, and Dr Johansson are employees and shareholders of AstraZeneca. Dr Darren K. McGuire discloses the following relationships: honoraria for clinical trials leadership: AstraZeneca, Sanofi Aventis, Janssen, Boehringer Ingelheim, Merck & Co, Novo Nordisk, Lexicon, Eisai, GlaxoSmithKline, Esperion; honoraria for consultancy: AstraZeneca, Sanofi Aventis, Lilly US, Boehringer Ingelheim, Merck & Co, Pfizer, Novo Nordisk. Dr Bansilal is an and employee of Bayer US LLC and reports prior consulting fees from Janssen and AstraZeneca and research grant from AstraZeneca. Dr Kato discloses the following relationships: honoraria from AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Ono Pharmaceutical, and Mitsubishi Tanabe Pharma. Dr Bonaca discloses the following relationships: research grant support to Brigham and Women's Hospital from AstraZeneca, MedImmune, Merck; consulting for Aralez, AstraZeneca, Bayer, Johnson and Johnson, and Merck Dr Mosenzon discloses the following: Advisory Board: Novo Nordisk, Eli Lilly, sanofi, Merck Sharp & Dohme, Boehringer Ingelheim, Jansen and Jansen, Novartis, AstraZeneca; grants paid to institution as study physician by AstraZeneca and Bristol-Myers Squibb; research grant support through Hadassah Hebrew University Hospital: Novo Nordisk; Speaker's Bureau: AstraZeneca and Bristol-Myers Squibb, Novo Nordisk, Eli Lilly, Sanofi, Novartis, Merck Sharp & Dohme, Boehringer Ingelheim.

* Reprint requests: Stephen D. Wiviott.
E-mail address: swiviott@partners.org (S.D. Wiviott).

https://doi.org/10.1016/j.ahj.2018.01.012
0002-87030002-8703/

in cardiovascular (CV) events, including CV death and hospitalization for heart failure, and ischemic events in patients with atherosclerotic cardiovascular disease (ASCVD).

Research design and methods: DECLARE–TIMI 58 (NCT01730534) is a phase 3b randomized, double-blind, placebo-controlled trial designed to evaluate the CV safety and efficacy of dapagliflozin that has completed randomization of 17,160 patients with T2DM and a history of either established ASCVD (n = 6,971) or multiple risk factors for ASCVD (n = 10,189). Patients were randomized in a 1:1 fashion to dapagliflozin 10 mg or matching placebo. The primary safety outcome is the time to the first event of the composite of CV death, myocardial infarction, or ischemic stroke (major adverse cardiovascular events; MACEs). The co-primary efficacy outcomes are the composite of CV death, myocardial infarction, or ischemic stroke and the composite of CV death or hospitalization for heart failure. This event-driven trial will continue until at least 1,390 subjects have a MACE outcome, thereby providing >99% power to test for the primary outcome of safety of dapagliflozin measured by rejecting the hypothesis that the upper bound of the CI >1.3 for the primary outcome of MACE, as well as 85% power to detect a 15% relative risk reduction in MACE and an estimated 87% power to detect a 20% reduction in the composite of CV death or hospitalization for heart failure at a 1-sided α level of .0231.

Conclusion: The DECLARE–TIMI 58 trial is testing the hypotheses that dapagliflozin is safe (does not increase) and may reduce the occurrence of major CV events. DECLARE–TIMI 58 is the largest study to address this question with an SGLT-2 inhibitor in patients with T2DM and with established CV disease and without CV disease but with multiple risk factors.

Patients with diabetes are at increased risk of cardiovascular (CV) disease including heart failure (HF), and among patients with CV disease, those with diabetes have higher rates of acute ischemic events and death.[1] Decades of research have shown that glucose lowering in type 2 diabetes improves microvascular events in a proportional fashion, but uncertainty remains regarding a clear relationship between glucose lowering and macrovascular events such as myocardial infarction and stroke.[2,3] Indeed, currently available clinical trial data suggest that the mechanism of glucose lowering or that the specific therapy chosen may be more important than the extent of glucose lowering on cardiovascular outcomes.[4] With glucose-lowering agents (GLAs), a focus of treatment for type 2 diabetes, concerns regarding the CV safety of several classes of GLAs prompted the United States Food and Drug Administration to introduce guidance that requires the ascertainment of an adequate number of CV events in trials to exclude a CV safety risk with prescribed statistical precision.[5] Because of this guidance, there has been a remarkable increase in the number and size of CV outcomes trials for GLAs. For example, 3 large-scale trials of dipeptidyl peptidase 4 inhibitors have been conducted and results published, evaluating more than 35,000 patients with or at risk for atherosclerotic cardiovascular disease (ASCVD).[6-8] These trials have demonstrated with clarity that there is neither an increase nor a decrease in CV ischemic events with these agents; however, a concern regarding an increase in HF with some but not all members of this class has emerged.[9] This level of precision is in contrast to long-standing, often quoted data from trials such as United Kingdom Prospective Diabetes Study—a trial of multiple agents in patients, with the assertion that metformin improves cardiovascular outcomes based on substudy of fewer than 400 patients randomized to metformin and few cardiovascular events.[10]

Dapagliflozin is among a class of compounds referred to as *sodium-glucose co-transporter-2* (SGLT-2) inhibitors. Dapagliflozin is a highly selective and reversible inhibitor of SGLT-2.[11] SGLT-2 is localized to the renal proximal tubule where it reabsorbs most of the glucose normally filtered through the glomeruli each day.[12] SGLT-2 inhibition leads to pharmacologically promoted glycosuria. Inhibition of urinary glucose reabsorption leads to direct, insulin-independent glycemic effects including lowering of plasma glucose and thus hemoglobin A1c (HbA1c).[13]

Dapagliflozin has beneficial effects on CV risk factors in addition to its glucose-lowering effects.[14] Many potential mechanisms have been proposed for CV benefit of SGLT-2 inhibition.[15,16] Dapagliflozin 10 mg (the dose studied in DECLARE–TIMI 58) lowers systolic blood pressure by 3 to 5 mm Hg compared with placebo.[17] Dapagliflozin also results in loss of body weight compared with placebo or other GLAs, postulated to be related both to changes in fluid volume and to changes in energy balance resulting in fat loss.[15,18]

In a meta-analysis of phase 2 and phase 3 studies of dapagliflozin, there was a suggestion of CV benefit, particularly a tendency toward reductions of a composite of CV events, including CV death, hospitalizations for HF, and MI with no clear effect on stroke.[19] In these studies, a numerically higher rate of bladder cancer was observed with uncertainty regarding whether this finding was related to the drug, to detection bias due to increased urinary symptoms with an SGLT-2 inhibitor, or simply to play of chance.

The DECLARE–TIMI 58 study was designed to test the hypotheses that dapagliflozin (1) does not increase major adverse cardiovascular events (MACEs) and (2) will reduce the incidence of the CV events in patients with type 2 diabetes mellitus (T2DM) with established ASCVD or with multiple risk factors for ASCVD but without established ASCVD. During the course of DECLARE-TIMI 58, new data emerged from 2 other large-scale cardiovascular outcomes trials of SGLT-2 inhibitors: the EMPA-REG OUTCOME trial of empagliflozin[20] and the Canagliflozin Cardiovascular Assessment Study (CANVAS) program for canagliflozin.[21] In the EMPA-REG OUTCOME trial, empagliflozin reduced the composite of CV death, MI, or stroke by 14% over a median follow-up of 3.1 years.[20] This included a marked reduction in CV death by 38%. Also observed was a reduction of hospitalization for HF by 35%. In the CANVAS program, canagliflozin reduced MACE by 14% and hospitalization for HF by 33%; there was a nonsignificant trend toward a reduction in CV death. The MACE efficacy tended to be greater in patients with established cardiovascular disease, although HF reduction was similar.[22] The CANVAS trials program also showed a significant excess of amputations and bone fractures in patients treated with canagliflozin.[21] These external data led to several modifications of the design of DECLARE–TIMI 58 as we note below. Moreover, they set the stage for the study to validate the compelling but unexpected findings with SGLT-2 inhibition reducing CV death and hospitalization for HF, clarify if the magnitude of benefit differs in patient with and without established cardiovascular disease, and provide important information on key safety outcomes such as amputation and bladder cancer.

Study design and population

DECLARE–TIMI 58 (NCT01730534) is a multicenter, multinational, randomized, double-blind, placebo-controlled, phase 3b trial designed

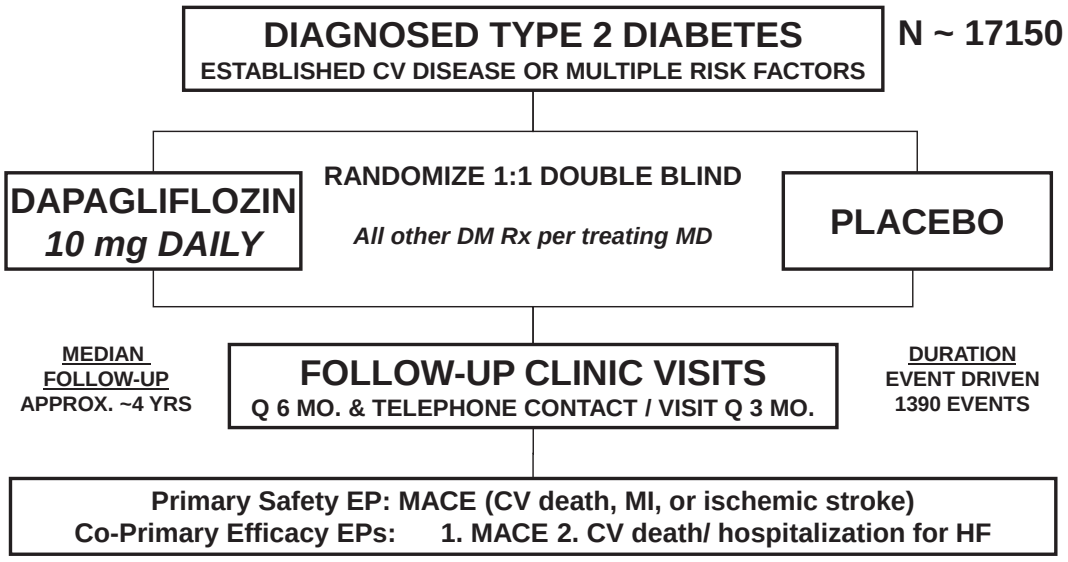

Figure 1. Trial schema.

to evaluate whether treatment with dapagliflozin is safe and effective from a CV standpoint (Figure 1). Safety will first be assessed using a noninferiority analysis of the triple composite end point of MACE with an upper bound of the 95% CI of the hazard ratio < 1.3 of dapagliflozin compared with placebo (primary safety assessment). The trial was originally designed with a primary efficacy assessment to determine whether dapagliflozin reduces MACE, with hospitalization for HF as a key secondary end point. Following presentation of the empagliflozin CV outcomes trial and completion of enrollment in DECLARE–TIMI 58, but *before any Data Monitoring Committee (DMC) efficacy assessments*, the trial Executive Committee (EC) determined, because of compelling outside data, to elevate the composite of CV death or hospitalization for CHF to a co-primary efficacy end point, with an equal split of the α between the 2 outcomes. The intention to make this change was communicated to the US FDA on December 23, 2015, and the protocol was subsequently amended to reflect these changes. The description of the trial herein will be based on the amended protocol.

The duration of the trial was planned to be approximately 6 years, with a median follow-up of 4.5 years. The actual duration of the trial will be based on accrual of at least 1,390 subjects with MACE events. More than 25,000 subjects were enrolled in the run-in period to ultimately randomize 17,190 subjects aged at least 40 years, with a creatine clearance ≥60 mL/min with documented T2DM, HbA1c between 6.5% and <12.0%, and either a history of established CV disease or multiple risk factors for vascular disease but without established CV disease. Full inclusion and exclusion criteria are presented in Appendix A. Subsequently, 30 subjects were excluded from all analyses because of significant Good Clinical Practice violations at a single site in a different trial, casting uncertainty on the validity of this site's data; therefore, the primary total for assessment was 17,160, referred to here as the *randomized total*.

A total of 6,971 subjects were randomized with established CV disease (ischemic heart disease, cerebrovascular disease, or peripheral artery disease). A total of 10,189 subjects were randomized without established CV disease with multiple cardiac risk factors. Multiple risk factor subjects were men aged ≥55 and women aged ≥60 with at least 1 additional traditional CV risk factor including dyslipidemia, hypertension, or tobacco use. Full disease state and risk factor descriptions are detailed in Appendix B.

Key exclusion criteria included acute cardiovascular or cerebrovascular event within 8 weeks of randomization; lifetime history of bladder cancer or recurrent urinary tract infections; history of any malignancy within 5 years; and use of an open-label SGLT2 inhibitor, pioglitazone, or rosiglitazone.

Treatment protocol and follow-up procedures

Eligible patients were enrolled in the run-in period. During the 4- to 8-week run-in period, all subjects were assigned in a single-blind fashion to placebo. Blood and urine tests were performed at the enrollment visit. If blood test revealed a result meeting an exclusion criterion, if patients did not show adequate adherence to therapy, or if patients did not wish to continue, the subject was not randomized. If hematuria was detected on either dipstick or microscopy, it was incumbent on the investigator to exclude bladder cancer using medically appropriate assessment per local standards of care. If bladder cancer was confirmed during run-in or could not be reasonably excluded, the patient was not randomized.

At the randomization visit, subjects were assigned either dapagliflozin 10 mg or matched placebo. The use of all other antihyperglycemic therapies (apart from excluded medications) at baseline and throughout the trial was at the discretion of the treating physician. If unexplained hematuria was detected at randomization or subsequent visits, evaluation for cause was mandated by the protocol. After randomization, subjects return for in-person study visits at 6 months to assess for clinical and safety events and for study drug adherence, and for clinical evaluation and laboratory testing. Subjects are contacted via telephone every 3 months between visits for clinical and safety event assessment and compliance. All subjects are intended to undergo a final visit at completion of the study. Subjects who prematurely discontinue study drug are followed up, ideally in person but, if not possible, by telephone or clinical records until the end of the study.

Based on the findings from other trials of SGLT2 inhibitors, additional efforts were initiated for data collection and characterization of HF. Sites were asked to review each subject's baseline HF status and provide ejection fraction if measured in all subjects, and to report New York Heart Association functional status and cardiac function measurements at each visit. Fracture and peripheral artery, diabetic ketoacidosis, and amputation events were also evaluated in detail with specific data collection and reporting. In addition to these efforts, guidance regarding clinical evaluation and prevention of diabetic ketoacidosis and events leading to amputation was provided.

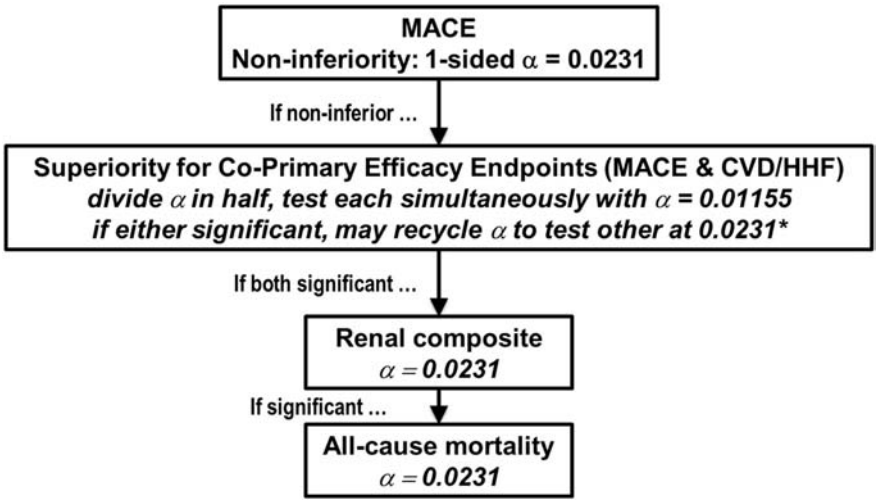

Figure 2. Key outcomes and α allocation. All αs are presented as one-sided. *If either is significant at .01155, α may be recycled and full .0231 can be used for the other co-primary end point according to the Holm procedure.

Study objectives and end points

Primary end point and objectives

The primary safety and co-primary efficacy end point of the trial is the composite end point of CV death, MI, or ischemic stroke (MACE). This primary objective will be evaluated in 2 steps. The first step will determine if dapagliflozin is noninferior to placebo for the incidence of MACE assessed with a noninferiority margin of 1.3. If noninferiority is statistically confirmed, the second step will be to determine if dapagliflozin reduces the incidence of the co-primary efficacy end points.

The co-primary efficacy end points are (1) MACE and (2) the composite of CV death or hospitalization for HF. The event definitions are consistent with the Standardized Definitions for End Points Events in Cardiovascular Trials created by the Standardized Data Collection for Cardiovascular Trials Initiative collaboration between academics, industry, and regulators.[23] Event definitions are found in Appendix C. All elements of the primary safety and efficacy end points will be adjudicated by members of an independent Clinical Events Committee (Appendix D) unaware of treatment assignment. Analytic details are discussed below.

Secondary objectives

Two secondary efficacy objectives are prespecified. The first is to determine whether treatment with dapagliflozin reduces the risk of a composite renal end point consisting of a confirmed, sustained ≥40% decrease in estimated glomerular filtration rate (eGFR) to eGFR <60 mL/min/1.73 m^2 and/or end-stage renal disease (dialysis ≥90 days or kidney transplantation or confirmed sustained eGFR <15 mL/min/1.73 m^2) and/or renal or CV death. The second is to determine whether treatment with dapagliflozin reduces the risk of all-cause mortality.

Additional safety objectives

In addition to the primary safety assessment, safety and tolerability will be assessed from serious adverse events and adverse events of special interest including liver events, fractures, malignancies (particularly bladder), hypersensitivity, urinary and genital infections, volume depletion, and major hypoglycemic events (requiring external assistance due to impairment of consciousness or behavior and with prompt resolution after treatment). Amputations and other vascular events and possible diabetic ketoacidosis will also be prospectively evaluated.

Exploratory objectives

Other efficacy and safety objectives include whether dapagliflozin compared with placebo when added to current background therapy will result in a reduction of the individual components of the co-primary efficacy end points (CV death, MI, ischemic stroke, and hospitalization for HF) and a broader clinical composite end point of cardiovascular death, MI, ischemic stroke, hospitalization for HF, hospitalization for unstable angina pectoris, or hospitalization for coronary or noncoronary revascularization, change in HbA1c, initiation of insulin, increase in antihyperglycemic therapy, major hypoglycemia and/or hospitalization for hypoglycemia, development of albuminuria, regression of albuminuria, change in body weight, and change in blood pressure.

Statistical considerations

The primary analyses for safety and efficacy will be based on time to first event for the noted composite end points in all randomized patients (ie, intent-to-treat principle) using events adjudicated and confirmed by the Clinical Events Committee. Hazard ratios (HRs) and CIs will be derived from a Cox proportional-hazards model with a factor for treatment group in the overall population as well as stratified by (1) CV risk category (established CV disease or multiple risk factors without established CV disease) and (2) baseline hematuria. A sensitivity analysis of the primary objectives will be performed using an on-treatment analysis. Aside from the primary noninferiority safety assessment, all safety outcomes will be assessed using a *safety analysis data set*, defined as all patients receiving at least 1 dose of randomized study treatment with data recorded after the first dose and corrected for actual treatment received in the event of erroneous treatment assignment. Key prespecified subgroups of interest are noted in the statistical analysis plan and include but are not limited to enrollment stratum (CV disease, multiple risk factors), history of HF, renal function, age, gender, duration of diabetes, and diabetes treatments. Subgroups will be assessed without adjustment for multiple testing.

Control of type 1 error

The testing of the primary safety and efficacy outcomes will be assessed in a closed testing procedure to preserve α (Figure 2). To account for 2 data monitoring committee interim analyses to evaluate for overwhelming efficacy at approximately 33% and 67% of anticipated

primary efficacy events, using an O'Brien-Fleming spending rule, an α penalty will be taken leaving a 1-sided α of .0231 (2-sided .0462) to establish nominal significance. First, the primary noninferiority analysis will assess whether the upper bound of the CI of the composite of CV death, MI, or ischemic stroke <1.3 using the full 1-sided α of .0231. If the null hypothesis regarding the noninferiority analysis is rejected, then the α will be split evenly between the 2 co-primary efficacy composites (MACE and CV death or hospitalization for HF). If either is significant at a 1-sided α level of .01155, α recycling will be performed using the Holm procedure[24-26] to allow assessment of the other composite using the full 1-sided α of .0231.

Data safety monitoring

Periodic assessments of safety and efficacy are performed in DECLARE–TIMI 58 by an independent DMC. The DMC is composed of 5 members with appropriate expertise, as noted in Appendix D, and appointed jointly by the sponsor and the academic leadership of the trial. Periodic safety analyses are performed to review for safety including bladder cancers based on accrued enrollment; incident bladder cancers (every 8 events until 32); and accumulation of 33%, 50%, and 67% of efficacy events. Two interim analyses for overwhelming efficacy in terms of reducing MACE and all-cause mortality were prespecified to occur after accrual of 33% and 67% of the planned MACE outcomes. The 1-sided α thresholds for the analyses are .000095 and .00614, respectively, resulting in the α penalties noted above.

Sample size determination

A total of 1,390 subjects with MACE events will be required to have 85% power to demonstrate superiority of dapagliflozin to placebo if the true HR is 0.85, that is, a 15% relative risk reduction, with a 1-sided α of .0231. To achieve this number of MACE events, the study was designed based on the following assumptions. Approximately 17,150 randomized patients will be required for the study, with an assumed annual event rate of 2.1% on placebo and an annual study withdrawal rate of 1.0% over a 3-year accrual period and 3-year minimum follow-up. With above assumptions and 1,390 MACE events, it is estimated to have >99% power to test the hypothesis of noninferiority. The trial was not formally powered for the second of the co-primary end points, CVD or HHF. However, we anticipate that approximately 770 events for this composite will correspond to the 1,390 MACE events. This event number would provide 87% power to detect an HR of 0.80 with a 1-sided α of .0231. As noted above, for the α to be recycled (ie, for a hypothesis to be tested at .0231), the other hypothesis must achieve significance at 1-sided threshold of .01155. At the .01155 level, the power to detect a 20% reduction in CV death or hospitalization for HF is approximately 80%. If a reduction of 25%-30% was seen in CVD/HHF as was observed in EMPA-REG OUTCOME[20] and CANVAS,[21] there would be greater than 90% power at either α level.

The EC of the trial will monitor the aggregate event rate and rate of study drug discontinuation and may alter the number of primary end point events or duration of the trial in accordance with the goals of the trial. Such changes will be made in consultation with the sponsor.

Biomarkers and genetic analyses

Biological samples were collected and stored for future analysis. Future analyses of stored biosamples will be used to assess biomarkers that reflect inflammatory, thrombotic, metabolic, vascular, and hemodynamic markers of risk in subjects with diabetes and atherosclerotic risk. Key objectives will be to evaluate the ability of biomarkers alone or in combination to predict CV risk in the population, to identify groups with a greater absolute/relative benefit of dapagliflozin, and to assess the effects of dapagliflozin on biomarker levels over time. An additional objective was to collect and store serum and deoxyribonucleic acid for future exploratory research into genes/genetic variation that may influence response (eg, distribution, safety, tolerability, and efficacy) to treatment with dapagliflozin or other drugs and genetic factors that may influence susceptibility to T2DM and/or associated cardiovascular conditions and their risk factors.

Study organization

The DECLARE–TIMI 58 Trial is a large-scale CV outcomes trial conducted worldwide with 882 investigative sites in 33 countries. The first patient was enrolled in April 2013. Key participating members are listed in Appendix D. The trial was designed and implemented by an EC which consisted of a collaboration between members of the TIMI Study Group, the Hadassah Medical Organization, additional leading academic medical experts, and the sponsors (initially AstraZeneca [Wilmington, DE and Gothenburg, Sweden] and Bristol Myers Squibb [Princeton, NJ] and subsequently at the time of the protocol update and submission of this manuscript by AstraZeneca alone). The EC was responsible for the protocol design and overall scientific guidance and supervision of the trial. A steering committee including the EC members, worldwide country lead investigators, operational staff, and additional content experts was responsible for scientific guidance and local implementation of the protocol. The authors are responsible for drafting and editing of this design paper and its contents.

Data analysis will be conducted in parallel between the Sponsor and the TIMI Study Group. The TIMI Study Group and The Hadassah Medical Organization will have complete access to the study database, and will submit results for presentation and publication of the primary results in a peer-reviewed medical journal. The trial was funded by and research grants for trial activities were provided to the Brigham and Women's Hospital (TIMI) and the Hadassah Medical Organization by AstraZeneca.

Additional responses to external events

As noted above, the results of 2 other large-scale outcomes trials of SGLT-2 inhibitors (EMPA-REG OUTCOME trial[20] and the CANVAS program[21]) led to changes in the end points and data collection in DECLARE-TIMI 58. In addition, results summaries were prepared and distributed to all sites to ensure all investigators were aware of these external data. In the case of EMPA-REG OUTCOME, with a mortality benefit observed, all subjects were informed and were required to sign an updated informed consent document to continue participation in the trial. The data safety and monitoring board was made aware of external trial results and asked to consider these data (both benefits and risks) in their review of the safety and appropriateness of DECLARE–TIMI 58. In addition, there were interactions with regulators regarding external trial results, ethics of ongoing placebo-controlled study of SGLT-2 inhibitors, safety reviews, and reporting to sites and subjects of updates to drug labels.

Discussion

CV disease is the leading cause of death among people with diabetes[1]; therefore, finding antihyperglycemic therapies that are at the very least safe and ideally effective in reducing risk of CV events in this population is a key treatment goal. In addition to atherothrombotic cardiovascular events, such as MI and stroke, patients with T2DM are at increased risk of morbidity and mortality related to HF.[1,27] Although both ischemic and HF risks have been known for decades, demonstrating CV benefit from oral blood GLAs during treatment has proven elusive in T2DM.

Based on mechanism, SGLT-2 inhibitors represent a promising class of agents for glycemic control with low risk of hypoglycemia in patients with T2DM and CV disease. These agents reduce blood sugar in an insulin-independent manner and tend to have favorable effects on blood pressure, blood volume, and weight.[15] In addition, there are mechanistic

data that suggest that SGLT-2 inhibition may directly improve vascular function and renal function, and have anti-inflammatory effects and favorable effects on the sympathetic nervous system which could be expected to reduce CV events.[12,15] However, there are several classes of drugs where clinical CV outcomes were discordant with mechanistic expectations for both atherothrombotic events and HF.[28]

The EMPA-REG OUTCOME trial demonstrated, for the first-time, in a well-powered trial that an oral GLA could reduce cardiovascular events including cardiovascular death in a population of patients with CV disease.[20] Furthermore, there were early and marked reductions in HF events[29] among patients with and without HF at baseline. Despite these exciting results, uncertainty remains. In the setting of many prior antihyperglycemic agents with neutral or unfavorable CV results, some have remained skeptical of fully accepting the implications of the results of a single trial,[30] especially given that CV mortality was not a prespecified primary or secondary outcome. Although some guidelines have recommended SGLT-2 inhibition for cardioprotection, guideline committees have not uniformly endorsed empagliflozin or SGLT-2 inhibitors as preferred therapy for CVD patients,[3] although the US FDA has granted an indication for the prevention of CV death in patients with established CV disease. The CANVAS program of 10,142 subjects with or at risk for vascular disease affirmed a CV benefit with a significant reduction in CV death, MI, or stroke.[21] Benefits for MACE events seemed to be predominantly seen in patients with established CV disease and not in those with multiple risk factors alone.[22] Based on the hierarchal statistical testing, no definitive statement on significant reduction in HF could be made, but nominal reductions were qualitatively similar to those seen in EMPA-REG and tended to be consistent between primary and secondary prevention. In addition to the benefits seen in CV events, there were also a nearly 2-fold increase in amputations, primarily of the toe or at the level of the metatarsal in patients with and without known peripheral artery disease, and an increase in bone fractures.

The DECLARE–TIMI 58 trial is a large-scale, CV outcomes trial that will determine the cardiovascular safety and efficacy of dapagliflozin. In addition, this trial could both validate and extend the results of prior SGLT-2 inhibitor studies in important ways. If an additional well-powered, rigorously conducted, CV outcomes trial within a class of agents was to show CV benefit, this would increase the level of evidence in support of SGLT-2 inhibition being cardioprotective. Moreover, DECLARE–TIMI 58 is the largest and most well-powered trial to study the effect of SGLT-2 inhibition on CV outcomes in patients with T2DM, with similar numbers of subjects with established CVD as in EMPA-REG OUTCOME and CANVAS as well as with more than 10,000 with multiple risk factors. DECLARE–TIMI 58 is anticipated to report nearly twice the number of CV outcomes compared with the other trials. Further, unlike EMPA REG, DECLARE–TIMI 58 has enrolled large populations of both patients with established CV disease and patients without established CV disease but with multiple risk factors for CV disease. Thus, this trial will have the opportunity to assess whether there is a consistent effect in these 2 important groups of patients with T2DM in contrast to the MACE observations in CANVAS. DECLARE–TIMI 58 will have the largest population of patients without established CV disease treated with SGLT-2 inhibition as primary prevention. In part building off prior data, DECLARE–TIMI 58 will have better characterized assessments of HF history and outcomes than prior studies to provide greater granularity regarding natural history and potential prevention and treatment of coincident HF and T2DM. Furthermore, DECLARE–TIMI 58 has a robust collection of biosamples and genetics that may help to improve the understanding of the pathophysiology of CV disease in patients with T2DM and further increase the understanding of drug effects and benefits and risks in specific populations. Additionally, DECLARE–TIMI 58 can further clarify uncertainty regarding potential risks of SGLT-2 inhibitors that have been raised in large and smaller studies or postapproval monitoring such as volume depletion, acute kidney injury, bladder cancer, limb ischemic events/amputations, and diabetic ketoacidosis.

Summary

DECLARE–TIMI 58 is a global, phase 3b, randomized, double-blind, placebo-controlled CV outcomes trial designed to evaluate the effect of dapagliflozin on CV outcomes in a broad patient population with T2DM and either established CV disease or multiple risk factors for CV disease. The trial is well powered to demonstrate clinical safety and efficacy and has robust data and biosample collection to help extend the understanding of pathobiology of CV disease in diabetes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.01.012.

References

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation 2011;123:e18-e209.
2. Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology—clinical practice guidelines for developing a diabetes mellitus comprehensive care plan—2015. Endocr Pract 2015;21(Suppl 1):1-87.
3. Standards of medical care in diabetes—2016: summary of revisionsDiabetes Care 2016;39(Suppl 1):S4-5.
4. Udell JA, Cavender MA, Bhatt DL, et al. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2015;3:356-66.
5. Guidance for industry diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes. Accessed Januar 12, 2017, at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf 2008.
6. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327-35.
7. Green JB, Bethel MA, Armstrong PW, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232-42.
8. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med 2013;369:1317-26.
9. Scirica BM. The safety of dipeptidyl peptidase 4 inhibitors and the risk for heart failure. JAMA Cardiol 2016;1:123-5.
10. United Kingdom Prospective Diabetes Study (UKPDS). 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. BMJ 1995;310:83-8.
11. Han S, Hagan DL, Taylor JR, et al. Dapagliflozin, a selective SGLT2 inhibitor, improves glucose homeostasis in normal and diabetic rats. Diabetes 2008;57:1723-9.
12. Heerspink HJ, Perkins BA, Fitchett DH, et al. Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications. Circulation 2016;134:752-72.
13. Komoroski B, Vachharajani N, Feng Y, et al. Dapagliflozin, a novel, selective SGLT2 inhibitor, improved glycemic control over 2 weeks in patients with type 2 diabetes mellitus. Clin Pharmacol Ther 2009;85:513-9.
14. Sun YN, Zhou Y, Chen X, et al. The efficacy of dapagliflozin combined with hypoglycaemic drugs in treating type 2 diabetes mellitus: meta-analysis of randomised controlled trials. BMJ Open 2014;4, e004619.
15. Inzucchi SE, Zinman B, Wanner C, et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. Diab Vasc Dis Res 2015;12:90-100.
16. Abdul-Ghani M, Del Prato S, Chilton R, et al. SGLT2 inhibitors and cardiovascular risk: lessons learned from the EMPA-REG OUTCOME study. Diabetes Care 2016;39:717-25.
17. Plosker GL. Dapagliflozin: a review of its use in patients with type 2 diabetes. Drugs 2014;74:2191-209.
18. Henry RR, Rosenstock J, Edelman S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind, placebo-controlled pilot study. Diabetes Care 2015;38:412-9.
19. Sonesson C, Johansson PA, Johnsson E, et al. Cardiovascular effects of dapagliflozin in patients with type 2 diabetes and different risk categories: a meta-analysis. Cardiovasc Diabetol 2016;15:37.
20. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
21. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
22. Mahaffey KW, Neal B, Perkovic V, et al. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). Circulation 2018;137(4):323-34.

23. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). Circulation 2015;132:302-61.
24. Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni-based multiple tests. Stat Med 2009;28:739-61.
25. Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. Stat Med 2009;28:586-604.
26. Multipe endpoints in clinical trials guidance for industry (draft). US Food and Drug Administration, Center for Drug Evaluation and Research. at, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm536750.pdf 2017.
27. Cavender MA, Steg PG, Smith Jr SC, et al. Impact of diabetes mellitus on hospitalization for heart failure, cardiovascular events, and death: outcomes at 4 years from the Reduction of Atherothrombosis for Continued Health (REACH) Registry. Circulation 2015;132:923-31.
28. Fitchett DH, Udell JA, Inzucchi SE. Heart failure outcomes in clinical trials of glucose-lowering agents in patients with diabetes. Eur J Heart Fail 2017;19:43-53.
29. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J 2016;37:1526-34.
30. Kaul S. Is the mortality benefit with empagliflozin in type 2 diabetes mellitus too good to be true? Circulation 2016;134:94-6.