

Optimising the analysis strategy for the CANVAS Program – a pre-specified plan for the integrated analyses of the CANVAS and CANVAS-R trials

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Abstract

Two large cardiovascular outcome trials of canagliflozin, the CANVAS Program, will complete in early 2017: the CANagliflozin cardioVascular Assessment Study (CANVAS) and the CANagliflozin cardioVascular Assessment Study – Renal (CANVAS-R). Accruing data for the sodium-glucose co-transporter 2 inhibitor (SGLT2i) class has identified questions and opportunities that were not apparent when the trials were designed. Accordingly, a series of modifications have been made to the planned analyses. These updates will ensure that the data from the CANVAS Program will maximise advances in scientific knowledge and patient care. The specification of the analysis strategy prior to knowledge of the trial results, their design by the independent scientific trial Steering Committee, the detailed *a priori* definition of the analysis plans and the external review provided by the US Food and Drug Administration, all provide for a maximally efficient and robust utilisation of the data. The CANVAS Program should significantly advance our understanding of the effects of canagliflozin, and the broader SGLT2i class, on a range of important efficacy and safety outcomes.

Introduction

Canagliflozin, an orally active inhibitor of the sodium-glucose co-transporter 2 (SGLT2), was approved for marketing in the United States on 29 March 2013 and is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes

mellitus (T2DM).¹ Three large outcome studies are ongoing to evaluate canagliflozin (Figure 1). Two of these studies complete in the next 12 months: the CANagliflozin cardioVascular Assessment Study (CANVAS)² and the CANagliflozin cardioVascular Assessment Study – Renal (CANVAS-R),³ which comprise the CANVAS Program. The third, the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial, a trial independent of the CANVAS program, will determine the effects of canagliflozin on chronic kidney disease, but is not scheduled to complete until 2020.⁴

As new data have accrued for the sodium glucose co-transporter 2 (SGLT2) inhibitor class, it has become apparent that updating the objectives and analysis plans for the CANVAS Program prior to study completion offers opportunities to enhance the scientific, clinical and regulatory outcomes from the studies.⁵ Accordingly, this paper describes the initial study plan and analysis strategy, the rationale for modifications and the updates that have been made for CANVAS, CANVAS-R and integrated analyses of the CANVAS Program.

The drug development environment for diabetes

Historically, new therapies for diabetes were marketed on the basis of well-tolerated improvements in blood glucose control. The supporting phase 3 programs typically comprised a few thousands of patient-years of follow-up with post-marketing surveillance implemented to protect against medium- to long-term risks. This model has been deemed inadequate following the high-profile withdrawal from the market of several therapies years after marketing was first authorised because of likely serious adverse effects on cardiovascular outcomes.⁶ In December 2008, the US Food and Drug Administration (US FDA) issued new guidance describing an enhanced strategy for ensuring the cardiovascular safety of drugs marketed for the management of diabetes by specifying explicit safety

requirements for initial marketing authorisation, as well as more robust criteria for ensuring medium-term safety.⁷ Specifically, the US FDA has required evidence that the upper 95% confidence interval (CI) for the hazard ratio (HR) of the composite cardiovascular outcome of vascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina (MACE plus) is less than 1.8 at the time marketing authorization is sought. Post marketing requirements made by the US FDA have then further required that clearer evidence of safety is provided within a few years such that the upper 95% CI for the HR of the composite cardiovascular outcome of vascular death, non-fatal myocardial infarction and non-fatal stroke (MACE) is less than 1.3.

Accordingly, the initial marketing authorization for canagliflozin was supported by an analysis of cardiovascular events accrued in the ongoing CANVAS trial and 8 other completed studies that constituted the phase 2 and phase 3 program at that time.⁸ The database within which cardiovascular safety was evaluated comprised 9,632 participants. This analysis demonstrated initial cardiovascular safety for the compound in line with US FDA guidance by excluding an upper 95% CI of the HR for MACE plus of 1.8. At the time of approval, the US FDA also set a post-marketing requirement that the upper bound of the 2-sided 95% CI of the MACE HR be shown to be below 1.3 by —September 2017 based upon a larger patient exposure.⁷ To meet this requirement and following discussions with the US FDA, a study with directly comparable population, procedures and assessments, the CANVAS-R study,³ was commenced in conjunction with the ongoing CANVAS trial such that an adequately powered analysis of the data from the integrated CANVAS Program could be completed within the specified timeframe.

The CANVAS Program

The CANVAS Program comprises two trials, CANVAS and CANVAS-R, and includes a pre-specified integrated analysis of the two. The integrated analysis will enable the sponsor to meet the US FDA post-marketing requirement to determine the cardiovascular safety of canagliflozin, as well as provide an opportunity to evaluate the potential for cardiovascular protection.

CANagliflozin cardioVascular Assessment Study (CANVAS)

The CANVAS study² is a double-blind, placebo-controlled trial that commenced recruitment in 2009 and was designed with the primary objective of evaluating the effects of canagliflozin on the risk of cardiovascular disease in patients with inadequately controlled T2DM and increased cardiovascular risk. As previously described,² the study was initially planned with two stages of study enrolment—the goal of the first stage would be to substantiate the potential for cardiovascular protection by defining effects on key biomarkers and provide the initial cardiovascular safety data required for marketing approval.^{9,10} The second stage would then expand recruitment with the goal of demonstrating protection against serious cardiovascular events.

Fundamental to the original design of CANVAS, and the integrity of the second stage objective of demonstrating cardiovascular protection, was the prevention of release of interim data defining the effects on cardiovascular outcomes. Unblinding of the detailed outcome effect estimate at any point before completion of the study would represent a breach of the trial design principles. The intended strategy had been developed through discussions with the US FDA and other regulatory agencies such that the review of the data for marketing authorisation would require only limited disclosure of the effects on

cardiovascular outcomes (i.e. pass/fail in regard to exclusion of the 1.8 hazard criterion) and trial integrity would be preserved.

First stage recruitment was achieved as planned with 4,330 individuals randomized to placebo, canagliflozin 100 mg or canagliflozin 300 mg. During preparation of the program-wide data for the initial marketing submission, an adverse effect on low density lipoprotein cholesterol was observed.¹ In light of this finding, a decision was made by the sponsor to unblind CANVAS group-level cardiovascular outcome data in January 2012 to provide Health Authorities with the maximum possible insight into the compound during the review of the initial marketing application. Care was taken to ensure that subject-level unblinded data were not available to the Steering Committee, Endpoint Adjudication Committee, Sponsor personnel involved with ongoing conduct of the trial or endpoint processing, the site investigators or the participants. A subsequent disclosure was also made using group level data to November 2012 in response to a request arising during review of the marketing application in Europe. No further unblinding of cardiovascular outcome data has occurred since, and apart from the Independent Data Monitoring Committee, no members of the Steering Committee, Sponsor or study team have seen or had access to any further unblinded data. The second stage of recruitment of the planned additional 14,000 patients did not, however, go ahead due to the unblinding of the interim cardiovascular outcome results. Rather, a second separate study (CANVAS-R) was initiated.

Cardiovascular events and other outcome data continue to accrue amongst the original CANVAS cohort who remain on randomised treatment and now have a median follow-up of about 5.7 years. The US FDA agreed that the vascular outcome data from CANVAS could, in conjunction with additional data from another 'CANVAS-like' study, be used to address the

second cardiovascular safety objective, excluding an upper limit of the 95% CI for cardiovascular risk of 1.3, during the immediate period post-marketing. However, the interim unblinding of the CANVAS data done in 2012 meant that it was unlikely that any regulatory objective beyond excluding the upper limit of the HR of 1.3 could be achieved with the CANVAS data as they stood. Likewise, the decision not to expand CANVAS recruitment for the planned second stage meant that the capacity for CANVAS alone to address the primary objective of cardiovascular protection was severely impacted, because the failure to recruit the additional 14,000 individuals greatly reduced statistical power.

The CANagliflozin cardioVascular Assessment Study – Renal (CANVAS-R)

The CANVAS-R study³ is a second large prospective, randomized, double-blind, placebo-controlled clinical trial of patients with T2DM with a history or at high risk of cardiovascular events. CANVAS-R was initiated following marketing authorisation in the United States and in response to the US FDA regulatory requirement for a 'CANVAS-like' study, the data from which could be combined with data from the ongoing CANVAS trial to address the specified post-marketing safety requirements. CANVAS-R patients have nearly identical inclusion criteria to CANVAS participants and have been assigned to once-daily placebo or canagliflozin 100 mg (with optional up-titration to 300 mg) for a planned average of 2 years of follow-up. The dosing strategy was selected to reflect the labelling instructions in many countries in which canagliflozin is approved. The separate primary objective of CANVAS-R is attenuation of kidney disease progression, as evidenced by fewer transitions from normo- to micro- or macro-, or micro- to macroalbuminuria. The secondary objectives defined in the original protocol were to determine corresponding effects on the regression of albuminuria, on estimated glomerular filtration rate and on albumin creatinine ratio. To enable the study to meet the post-marketing evaluation of cardiovascular safety in the

integrated analysis of data across the CANVAS program, the procedures for recording and managing serious adverse events and endpoint adjudication across the two trials are identical (Table 1), as are the participant characteristics (Table 2). This includes the use of a common independent and blinded Endpoint Adjudication Committee that operates to the same Charter that is used for CANVAS. CANVAS-R completed randomization of 5,812 individuals between January 2014 and May 2015 and median follow-up is currently 1.7 years.

The characteristics of patients enrolled in the CANVAS Program are summarized in Table 2. A total of 10,142 participants were randomized to the studies including 65% with a history of cardiovascular disease and 35% with at least 2 risk factors for cardiovascular disease. The characteristics of the patients enrolled in the CANVAS and CANVAS-R studies were similar with respect to duration of T2DM, microvascular disease and atherosclerotic cardiovascular disease.

Accumulating evidence about the effects of SGLT2 inhibition

Since the design of CANVAS and CANVAS-R, there have been substantial new data reported about the effects of SGLT2 inhibitors on clinical outcomes. This includes evidence about possible new risks such as diabetic ketoacidosis,¹¹ bone fracture^{12,13} and amputation,^{14,15} as well as a possible protective effect for some cardiovascular and renal outcomes. In particular, the 2015 report of the EMPA-REG OUTCOME trial implied large benefits for cardiovascular death, heart failure, total mortality and kidney outcomes.^{16,17} A recent meta-analysis of the totality of the evidence describing the effects of SGLT2 inhibition indicates that the EMPA-REG OUTCOME findings are consistent with the broader evidence base and

that the EMPA-REG OUTCOME results are likely to provide a good approximation of the effects of other agents in this class.⁵ However, many of the analyses were *post hoc*, the numbers of events included in some were small and there is an urgent need to determine their repeatability in adequately powered, prespecified analyses of large new datasets with adjudicated data. The soon-to-be completed CANVAS Program provides a unique near-term opportunity to achieve this but modification of the existing objectives will be required to enable the *a priori* specification of the most important outstanding questions and the robust testing of key hypotheses in the CANVAS program.

Principles underpinning the updated analysis strategy

The accumulating data about SGLT2 inhibitors provides much better insight into the most likely effects of canagliflozin than were available at the time the CANVAS and CANVAS-R trials were designed. In particular, there are now more data about the serious adverse events most likely to be prevented or caused by canagliflozin and the likely magnitudes of the effect sizes that can be anticipated. In light of these data, there are opportunities to modify the initially planned analysis strategies for CANVAS, CANVAS-R and the integrated CANVAS Program to maximise the further scientific insights obtained from the trials. In specifying the changes, a series of methodological, clinical and regulatory issues have been considered.

Maximising statistical power to detect plausible effects of canagliflozin can be achieved by increasing the quantity of data available and/or selecting outcomes for which effects of greatest size are anticipated. The quantity of data available to address hypotheses can be increased by combining the CANVAS and CANVAS-R datasets for integrated analyses across the CANVAS Program and by evaluating the effects of all doses of canagliflozin combined

versus placebo (rather than investigating the separate effects of each dose). These two strategies have been planned from the outset for the evaluation of cardiovascular safety (i.e. ruling out an upper bound of 1.3 on major adverse cardiovascular events [MACE]) and the strategy is now being utilised for the assessment of cardiovascular efficacy. The combined recruitment of 10,142 to the CANVAS and CANVAS-R trials is less than was initially planned for CANVAS (18,000) and this reflects a Sponsor decision to focus on demonstrating cardiovascular safety after second stage recruitment to CANVAS was discontinued. Subsequently, the greater than anticipated effects on vascular outcome reported by the EMPA-REG OUTCOME trial suggests that even with this reduced sample size the CANVAS Program will have reasonable power to test efficacy for several outcomes. Specifically, the apparently large effects of SGLT2 inhibition on vascular death, total mortality, heart failure and kidney disease present opportunities to test hypotheses of protection related to these outcomes that were not previously considered feasible with the quantity of data accrued within CANVAS, CANVAS-R or even across the integrated data from the two trials.

Minimization of the risk of chance findings is being achieved through the use of a sequential testing process, which was also a feature of the original protocols for both CANVAS and CANVAS-R. However, because the updated analysis plan will include testing of both safety and efficacy in the individual and the integrated datasets, a new single sequential testing plan has been defined. This plan covers all the main hypotheses from the integrated and individual study datasets, and will control type I error at 5% across all.

Outcomes for investigation, primary, secondary and exploratory, have been updated to focus on complications of diabetes for which benefits appear likely to be detectable.

Accordingly, analyses of vascular death, total mortality, heart failure and kidney disease have been prioritised. In parallel, analyses of outcomes addressing myocardial infarction for which effects appear lesser or absent, and stroke for which SGLT2 inhibition may cause harm,⁵ have been refined. In terms of multi-component outcomes, the regulatory assessment of cardiovascular safety is reasonably based upon MACE, a broad composite that encompasses the most common serious vascular outcomes experienced by patients with diabetes. However, if there are effects of different magnitude or direction on specific cardiovascular outcomes, the use of a composite will conceal important information about the effects of the agent. As such, in addition to the prescribed safety analyses on composite cardiovascular events, additional analyses investigating effects on cause-specific outcomes are now proposed.

Protection against the risks of bias or confounding has been central to the designs of CANVAS, CANVAS-R and the planned integrated analysis of the CANVAS Program and is achieved through randomisation, blinding and intention-to-treat analysis. Premature discontinuation of treatment by some patients will result in underestimation of the true effects of the drug on most outcomes but the likely impact can be quantified and the direction of effect is known. Considerable efforts are being made to maximise the completeness of follow-up but sensitivity analyses using each of worst case single imputation, multiple imputation and delta methods will be undertaken to identify the range of possible effects of missing data for key outcomes.

There is also a potential for bias that results from the interim unblinding of the CANVAS data, because it is possible that the implementation of the study differed after the data

were revealed (operational bias), or that the decision to continue with the study itself was based upon that knowledge (a statistical bias). In practice, the likelihood of important bias is small since the trial was planned to continue and did, substantive changes to the CANVAS protocol have not been made and the cardiovascular events accrued by November 2012 will be only a small proportion of all events recorded. Reflecting the low level of risk of bias, the US FDA will accept for review the integrated CANVAS and CANVAS-R data to fulfil a post-marketing cardiovascular safety requirement (i.e. rule out an upper bound of 1.3) and also consider the possibility of using the integrated CANVAS Program data to address cardiovascular efficacy. There is, nonetheless, a theoretical risk of bias consequent upon the inclusion of the unblinded interim CANVAS data in a final analysis. As such, the efficacy hypotheses addressing the effects of canagliflozin on vascular death and total mortality in the combined CANVAS Program data from CANVAS and CANVAS-R are proposed to be done on a modified integrated dataset. Specifically, the data from CANVAS that contribute to the integrated dataset used for primary testing of the hypotheses of protection against death will be left-truncated such that all CANVAS study time and mortality events prior to 20 November 2012 will be excluded—the 20 November 2012 date reflecting the last time MACE data from the CANVAS study were unblinded at the request of a health authority.

Left truncation of the data will result in an unbiased estimate of effect for the entire study if the proportional effect of the intervention on the outcome of interest is constant over time, as appears to be the case for fatal outcomes with SGLT2 inhibitors.¹⁶ However, if greater benefits accrue early in treatment than do later, as for example may be the case for the effects of SGLT2 inhibitors on heart failure, then left truncation would result in a biased estimate of the overall treatment effect.¹⁶ The constancy of treatment effects over time,

and the constancy of effects across the two studies, which have different durations of follow-up, will be examined.

Achieving regulatory outcomes - The primary goal of reviewing the analysis strategy for CANVAS, CANVAS-R and the integrated CANVAS program datasets has been to maximise the opportunity to make new scientific discoveries from the data. However, the ultimate goal is to improve the care of patients with diabetes, and the uptake of new therapies by clinicians is importantly determined by their regulatory status. As such, throughout the review process, an additional consideration in updating the analytic approach has been to maximise concurrently the possibility of achieving appropriate new indications to be reflected in labelling.

The updated hypotheses and outcomes for investigation

The initial and updated plans for hypothesis testing in CANVAS, CANVAS-R and the integrated CANVAS Program data are summarised in Table 3. Table 4 shows the full set of primary, secondary and exploratory outcomes that will be evaluated. The strategy for control of the type 1 error at 5% for multiple hypothesis testing is shown in Figure 2. The primary hypothesis test will be of non-inferiority for the HR for MACE at the margin of 1.3 for all canagliflozin versus placebo using the full integrated dataset (null hypothesis, H_0 : the $HR \geq 1.3$, versus the alternative hypothesis, H_1 : the $HR < 1.3$). Cardiovascular safety will be demonstrated if, as compared to placebo, the upper bound of the 95% CI of the HR is less than 1.3. If the null hypothesis H_0 is rejected and the upper bound of the 2-sided 95% CI of the HR is also less than 1.0, it will be concluded that canagliflozin is superior to placebo. Testing of the secondary mortality hypotheses will proceed sequentially conditional on the primary safety hypothesis being met but will be based on the truncated integrated dataset

that excludes the CANVAS study time and mortality events accrued prior to 20 November 2012. For these mortality endpoints, the statistical hypothesis on the HR of canagliflozin over placebo will be tested (null hypothesis, H_0 : the HR ≥ 1.0 , versus the alternative hypothesis, H_1 : the HR < 1.0). Canagliflozin will be deemed to be superior in reducing these mortality endpoints as compared to placebo if the upper bound of 95% CIs of the HR is less than 1.0. Testing will continue at the 5% significance level with assessment of subsequent endpoints proceeding in order, conditional on achieving statistical significance with the prior test.

If the MACE and the mortality endpoints tested on the integrated dataset succeed in rejecting the null hypotheses, all of the alpha for testing (i.e., 5%) will pass to the CANVAS-R dataset for testing of the renal and cardiovascular efficacy hypotheses specified for that study. No alpha is preserved for evaluating hypotheses in CANVAS and only nominal p-values will be reported for all other endpoints assessed in the CANVAS, CANVAS-R and integrated CANVAS program datasets. The truncated integrated dataset will only be used for testing the hypotheses of protection against total mortality and cardiovascular mortality, with the primary outcome and all exploratory outcomes planned for the integrated data to be investigated using the full integrated CANVAS Program dataset.

The anticipated numbers of events, assumed minimum effect sizes and projected statistical power for the hypothesis testing is shown in Table 5. The analyses of mortality outcomes based upon the left-truncated dataset will be carefully examined for evidence of varying effects of the intervention over time. If present, then the focus of reporting for these outcomes will be on the subsidiary analyses based upon the full dataset.

Safety analyses

In the same way that analysis of the integrated data from CANVAS and CANVAS-R will provide for a more precise and reliable assessment of the efficacy of the compound, so too will evaluations of the integrated data provide for a better assessment of non-cardiovascular safety. The safety analyses will be based on an on-treatment analysis set as the approach least likely to favour canagliflozin, unless otherwise specified, and all instances of relevant adverse events collected across the two studies, regardless of whether they were collected in exactly the same way, will be included. That said, the evaluation of clinical laboratory test results and vital signs will be made only at the visits that are commonly scheduled in CANVAS and CANVAS-R. The integrated safety analyses will be based on the observed data with no imputation of missing values and the combined doses of canagliflozin will be compared against placebo for the primary analyses.

Analyses will be of serious adverse events grouped into major categories defined by MedDRA,¹⁸ adverse events that resulted in study drug discontinuation and adverse events of interest. This latter group includes osmotic diuresis, volume depletion, hypoglycaemia, urinary tract infection, female mycotic genital infection, severe hypersensitivity /cutaneous reactions, pancreatitis, hepatic injury, acute kidney injury and renal-related adverse events, male genital infection (balanitis, phimosis, events leading to circumcision), malignancy (renal cell cancer, bladder cancer, pheochromocytoma, Leydig cell tumors, breast cancer), photosensitivity, venous thromboembolic events, diabetic ketoacidosis, amputation, and fracture.

Conclusion

The updates to the analysis strategy for CANVAS, CANVAS-R and the CANVAS Program proposed here will ensure that the completion of these trials results in the maximum possible likelihood of advances in scientific knowledge and patient care. They take a deliberately conservative approach to minimise the likelihood of spurious findings and to maximise the likelihood that any observed effects are real. The specification of these changes prior to knowledge of the trial results, their careful planning by the independent scientific trial Steering Committee, the detailed *a priori* definition of the statistical analysis plans and input provided by the US FDA, all provide for efficient and robust utilisation of the data. The new data from the CANVAS program should significantly advance our understanding of the effects of canagliflozin, and the broader SGLT2 inhibitor class, on a range of efficacy and safety outcomes of key importance to patients with diabetes.

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Figure Legends

Figure 1. Overview of canagliflozin trial timelines.

CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CANVAS, CANagliflozin cardioVascular Assessment Study; CANVAS-R, CANagliflozin cardioVascular Assessment Study—Renal.

*Planned; recruitment ongoing.

[†]Note that the patient populations in CANVAS and CANVAS-R are nearly identical to facilitate an integrated analysis of the data.

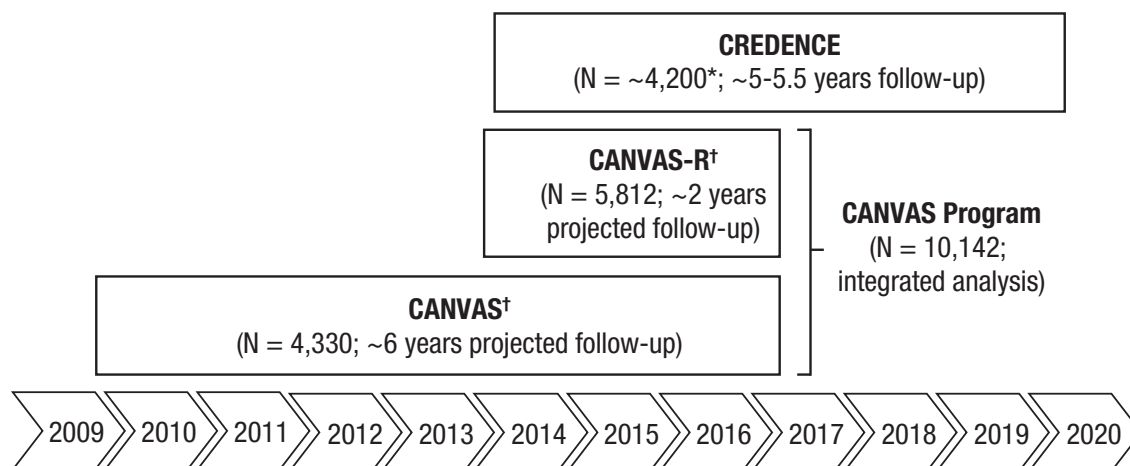


Figure 2. Sequential hypothesis testing plan for the CANVAS program.

MACE, major adverse cardiovascular events; CANVAS, CANagliflozin cardioVascular Assessment Study; CANVAS-R, CANagliflozin cardioVascular Assessment Study–Renal; CANA, canagliflozin; CV, cardiovascular; ACR, albumin:creatinine ratio; HF, heart failure.

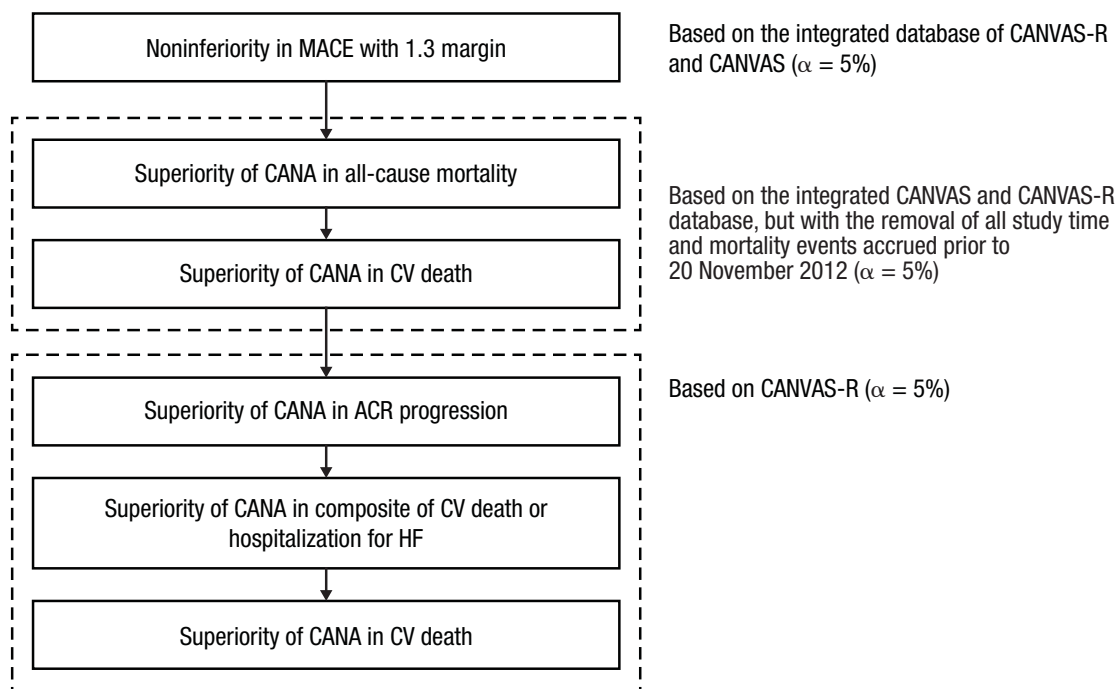


Table 1. Characteristics of the CANVAS and CANVAS-R Trials

	CANVAS	CANVAS-R
Patient population	Men or women with T2DM who have inadequate glycaemic control (HbA1c ≥ 7.0 and $\leq 10.5\%$) with either known CV disease or ≥ 2 risk factors for CV events	
Renal function for trial entry	eGFR ≥ 30 mL/min/1.73m ²	
Renal function for study drug discontinuation	Confirmed eGFR < 15 mL/min/1.73m ²	
AHA background therapy	Drug naïve, AHA monotherapy or combination therapy	
Other background therapy	Standard of care for the treatment of diabetes with treatment individualized as clinically appropriate according to applicable local guidelines	
Scientific governance	Academic Steering Committee, Independent Data Monitoring Committee, Endpoint Adjudication Committee	
Randomised treatment	Placebo, canagliflozin 100 mg, canagliflozin 300 mg	Placebo, canagliflozin 100 or 300 mg (through optional up titration)
Participants	4,330	5,812
Recruitment period	December 2009 to March 2011	January 2014 to May 2015
Projected mean follow-up	Approximately 6 years	Approximately 2 years

AHA, antihyperglycaemic agent; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; T2DM, type 2 diabetes mellitus

Table 2. Participant Characteristics for CANVAS, CANVAS-R and the CANVAS Program

	CANVAS Program N=10,142	CANVAS N=4,330	CANVAS-R N=5,812
Age, years (mean, SD)	63.3 (8.3)	62.4 (8.0)	64.0 (8.4)
Female, n (%)	3633 (35.8)	1469 (33.9)	2164 (37.2)
Race, n (%)			
White	7944 (78.3)	3179 (73.4)	4765 (82.0)
Asian	336 (3.3)	105 (2.4)	231 (4.0)
Black or African American	1284 (12.7)	795 (18.4)	489 (8.4)
Other	578 (5.7)	251 (5.8)	327 (5.6)
Current smoker (%)	1806 (17.8)	776 (17.9)	1030 (17.7)
History of hypertension (%)	9121 (89.9)	3795 (87.6)	5326 (91.6)
History of heart failure (%)	1461 (14.4)	515 (11.9)	946 (16.3)
Duration of diabetes, years (mean, SD)	13.5 (7.8)	13.4 (7.5)	13.7 (7.9)

Drug therapy, n (%)			
Insulin	5093 (50.2)	2174 (50.2)	2919 (50.2)
Sulphonylurea	4356 (43.0)	2029 (46.9)	2327 (40.0)
Metformin	7821 (77.1)	3166 (73.1)	4655 (80.1)
GLP-1 receptor agonist	407 (4.0)	96 (2.2)	311 (5.4)
Statin	7592 (74.9)	3131 (72.3)	4461 (76.8)
Antithrombotic	7455 (73.5)	3098 (71.5)	4357 (75.0)
RAAS inhibitor	8095 (79.8)	3487 (80.5)	4608 (79.3)
Microvascular disease history, n (%)			
Retinopathy	2130 (21.0)	865 (20.0)	1265 (21.8)
Nephropathy	1774 (17.5)	660 (15.2)	1114 (19.2)
Neuropathy	3111 (30.7)	1346 (31.1)	1764 (30.4)
Atherosclerotic vascular disease history, n (%) [*]			
Coronary	5349 (52.7)	2212 (51.1)	3137 (54.0)
Cerebrovascular	1845 (18.2)	683 (15.8)	1162 (20.0)
Peripheral	2043 (20.1)	705 (16.3)	1338 (23.0)
Any	6933 (68.4)	2748 (63.5)	4185 (72.0)
CV disease history, n (%) [†]	6572 (64.8)	2471 (57.1)	4101 (70.6)
Body mass index, kg/m ² (mean, SD)	32.0 (5.9)	32.1 (6.2)	31.9 (5.7)
Systolic BP, mmHg (mean, SD)	136.6 (15.8)	136.3 (15.7)	136.9 (15.8)
Diastolic BP, mmHg (mean, SD)	77.7 (9.7)	77.8 (9.7)	77.6 (9.6)
HbA1c, % (mean, SD)	8.2 (0.9)	8.2 (0.9)	8.3 (1.0)
Total cholesterol, mmol/L (mean, SD)	4.4 (1.2)	4.4 (1.2)	4.4 (1.2)
Triglycerides, mmol/L (mean, SD)	2.0 (1.4)	2.0 (1.4)	2.1 (1.5)
HDL-C, mmol/L (mean, SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
LDL-C, mmol/L (mean, SD)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)
LDL-C:HDL-C ratio (mean, SD)	2.0 (0.9)	2.0 (0.9)	2.1 (0.9)
eGFR, mL/min/1.73 m ² (mean, SD) [‡]	76.5 (20.5)	77.2 (18.9)	75.9 (21.7)
eGFR ≥90 mL/min/1.73 m ² , n (%)	2474 (24.4)	1036 (24.0)	1438 (24.7)
eGFR ≥60 to <90 mL/min/1.73 m ² , n (%)	5620 (55.5)	2573 (59.6)	3047 (52.4)
eGFR ≥45 to <60 mL/min/1.73 m ² , n (%)	1484 (14.6)	544 (12.6)	940 (16.2)
eGFR ≥30 to <45 mL/min/1.73 m ² , n (%)	526 (5.2)	163 (3.8)	363 (6.2)
eGFR ≥15 to <30 mL/min/1.73 m ² , n (%)	26 (0.3)	3 (0.1)	23 (0.4)
eGFR <15 mL/min/1.73 m ² , n (%)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Albumin:creatinine ratio (mean, mg/mmol) [§]	13.0 (49.9)	10.1 (39.7)	15.2 (56.3)
Normoalbuminuria, n (%)	7002 (69.8)	3085 (71.7)	3917 (68.4)
Microalbuminuria, n (%)	2263 (22.6)	966 (22.5)	1297 (22.7)
Nephrotic range macroalbuminuria, n (%)	57 (0.6)	14 (0.3)	43 (0.8)
Non-nephrotic range macroalbuminuria, n (%)	703 (7.0)	236 (5.5)	467 (8.2)

SD, standard deviation; GLP-1, glucagon-like peptide-1; RAAS, renin angiotensin aldosterone system; BP, blood pressure; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate. * Some participants had ≥ 1 type of atherosclerotic disease.

[†]As defined in the protocol.

[‡]Values for eGFR categories calculated based on N of 10,132, 4,320, and 5,812, the integrated dataset, CANVAS and CANVAS-R, respectively.

[§]Values for albuminuria categories calculated based on N of 10,025, 4,301, and 5,724, the integrated dataset, CANVAS and CANVAS-R, respectively.

Table 3. Initial and Updated Outcomes for Hypothesis Testing for CANVAS, CANVAS-R and the Integrated CANVAS Program Data*

	CANVAS	CANVAS-R	CANVAS Program
INITIAL			
Primary	MACE	Albuminuria progression	MACE (safety) on treatment
Secondary [†]	Beta-cell function	Albuminuria regression	MACE on or off treatment
	Albuminuria progression	eGFR	
	Albumin:creatinine ratio	Albumin:creatinine ratio	
	eGFR		
	HbA1c		
	FPG		
	Body weight		
	Systolic and Diastolic BP		
	Fasting plasma lipids (triglycerides, HDL-C, LDL-C, LDL-C/HDL-C ratio)		
UPDATED			
Primary	Unchanged	Unchanged	Unchanged
Secondary	Unchanged	Cardiovascular mortality or hospitalised heart failure	Total mortality [‡]
		Cardiovascular mortality	Cardiovascular mortality [‡]

MACE, major adverse cardiovascular events (i.e. cardiovascular death, nonfatal stroke or nonfatal myocardial infarction); eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

*All hypotheses will test for superiority except for the cardiovascular safety hypothesis which will test for non-inferiority. Note - Initial cardiovascular safety for marketing authorisation was demonstrated using the MACE plus outcome (MACE plus hospitalization for unstable angina) based upon interim data from CANVAS and data from 8 other phase 2 and phase 3 trials of canagliflozin completed by January 2012.

[†]Prespecified substudies in subgroups of subjects receiving protocol-specified dosages of (1) insulin, (2) sulphonylurea monotherapy, or (3) peroxisome proliferator-activated receptor γ (PPAR γ) agonist plus metformin, evaluated the following at week 18: Primary: change from baseline in HbA_{1c}; Secondary: effects on body weight, FPG-lowering efficacy, proportion of subjects reaching HbA_{1c} <7.0%, systolic and diastolic blood pressure, fasting plasma lipids (triglycerides, HDL-C, LDL-C, total cholesterol, and the ratio of LDL-C to HDL-C). The substudies were published previously. The following parameters will be assessed in the substudy populations at weeks 26 and 52: effects on glycaemic efficacy (HbA_{1c} and FPG), body weight, systolic and diastolic blood pressure, and fasting plasma lipids.

[‡]Will be evaluated using left-truncated data from CANVAS and all data from CANVAS-R.

Table 4. All Primary, Secondary and Exploratory Outcomes Planned for CANVAS, CANVAS-R and the Integrated CANVAS Program Data*

	CANVAS	CANVAS-R	CANVAS Program
Primary	MACE	Albuminuria progression	MACE (safety)
Secondary	Beta-cell function (HOMA-B, proinsulin/insulin ratio) [†] Albuminuria progression Albumin:creatinine ratio eGFR HbA _{1c} FPG [§] Body weight [§] HbA _{1c} <7% [§] Systolic and diastolic BP [§] Fasting plasma lipids (triglycerides, HDL-C, LDL-C, LDL-C/HDL-C ratio) [§]	Cardiovascular mortality or hospitalised heart failure Cardiovascular mortality	Total mortality [‡] Cardiovascular mortality [‡]
Exploratory		Albuminuria regression Albumin:creatinine ratio eGFR HbA _{1c} Use of antihyperglycaemic	Nonfatal myocardial infarction Nonfatal stroke

CANVAS	CANVAS-R	CANVAS Program
	therapy	
	40% reduction in eGFR, renal death, or renal replacement therapy [#]	40% reduction in eGFR, renal death, or renal replacement therapy [#]
	40% reduction in eGFR, renal death, renal replacement therapy, or cardiovascular death [#]	40% reduction in eGFR, renal death, renal replacement therapy, or cardiovascular death [#]
	40% reduction in eGFR, macroalbuminuria, renal death, or renal replacement therapy [#]	40% reduction in eGFR, macroalbuminuria, renal death, or renal replacement therapy [#]
		Total hospitalisations
		Hospitalisation for heart failure
		Hospitalisation for heart failure or cardiovascular death
		Albuminuria progression
		Albuminuria regression

MACE, major adverse cardiovascular events (i.e. cardiovascular death, nonfatal stroke or nonfatal myocardial infarction); HOMA-B, homeostatic model assessment of beta-cell function; HbA1c, glycated haemoglobin; FPG, fasting plasma glucose; BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

*Nominal p-values will be provided for outcomes for which hypothesis testing is not specified.

[†] For subjects not receiving insulin at randomization.

[‡] Will be evaluated using left-truncated data from CANVAS and all data from CANVAS-R.

[§] Evaluated at week 18 and at the end of the treatment.

^{||} Using alternative analysis methods.

[#] These outcomes will also be evaluated switching doubling of serum creatinine for 40% reduction in eGFR

Table 5. Anticipated Statistical Power for Hypothesis Testing

Hypothesis	Outcome	Dataset	Anticipated events		Assumed Hazard Ratio	Statistical power	
			Active	Placebo		Individual Test	Hierarchical Test
Primary:	Major adverse cardiovascular	Integrated	515/580	362/433	0.91	99.9%	99.9%
Non inferior			8	3			

to placebo*	ar events						
Secondary: Superiority over placebo	Total mortality	Integrated **	254/566 9	224/424 9	0.72	92.3%	92.2%
	Cardiovascular death	Integrated **	139/566 9	133/424 9	0.68	85.1%	78.5%
	Albuminuria progression	CANVAS-R	430/261 5	581/261 5	0.74	99.8%	78.3%
	Cardiovascular mortality or hospitalised heart failure	CANVAS-R	61/2906	93/2905	0.66	73.2%	57.3%
	Cardiovascular death	CANVAS-R	40/2906	60/2905	0.68	48.7%	27.9%

* With 1.3 hazard ratio as the non-inferiority margin

** Will be evaluated using left-truncated data from CANVAS and all data from CANVAS-R