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Rationale and design of a randomised phase II multicentre crossover trial investigating a sodium-glucose co-transporter 2 inhibitor, dapagliflozin, combined with a novel continuous ketone monitor in adults with type 1 diabetes to reduce the risk of diabetic ketoacidosis: the PARTNER study

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ABSTRACT

Introduction Sodium-glucose co-transporter inhibitors have potential glycaemic and non-glycaemic benefits in people with type 1 diabetes (T1D). However, the increased risk of diabetic ketoacidosis (DKA) limits their widespread use. We hypothesise that dapagliflozin 10 mg daily, combined with the use of continuous ketone monitoring (CKM) and education strategies to mitigate progression to DKA, will demonstrate improved glycaemic control without increasing DKA events.

Methods and analysis PARTNER is a multisite 6-month randomised crossover double-masked study involving Australian adults with T1D who have a Haemoglobin A1c (HbA1c) <85.8 mmol/mol (<10%), minimum total daily insulin dose ≥0.4 IU/kg, consume ≥100 g carbohydrates/day and have not had DKA in the last 3 months. All participants will undergo a 2-week run-in period wearing the Abbott FreeStyle Libre 2 Continuous Glucose Monitor (CGM) and Abbott CKM device. Following this, participants are randomised to receive dapagliflozin or placebo for 12 weeks, followed by crossover for a further 12 weeks separated by a 2-week washout period. The primary effectiveness outcome is the Abbott FreeStyle Libre 2 CGM time in range during the final 2 weeks of each stage. The primary safety outcome is the number of episodes of DKA requiring hospitalisation or emergency department presentation. 60 participants will be recruited across five sites.

Ethics and dissemination The study has received ethical approval from the St Vincent's Hospital Melbourne Human Research Ethics Committee (HREC reference 302/23). The results will be published in peer-reviewed journals and presented at national and international diabetes conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The protocol describes the evaluation of a novel approach to diabetic ketoacidosis prevention in people with type 1 diabetes treated with sodium-glucose co-transporter 2 inhibitor therapy. Double-masking to the study drug or placebo reduces bias and improves reliability of results.
⇒ Involvement of multiple sites including hospital centres and a community centre to increase generalisability of the results.
⇒ Inclusion of a semistructured interview process enabling participants to provide feedback about the investigational continuous ketone monitoring device to inform future development.
⇒ Limitations include the small sample size and potential external factors, such as medication changes, which may impact glycaemia.

Trial registration number ACTRN12624000448549.

INTRODUCTION

Insulin therapy is essential for people living with type 1 diabetes (T1D). Although it enables people with T1D to live longer, the majority are still not achieving the generally recommended glycaemic goals, with global data indicating over 70% have a HbA1c>53 mmol/mol (>7%).[1–4] This means that a large proportion of individuals with T1D are either at high risk or have already

developed microvascular and macrovascular complications of diabetes, for which hyperglycaemia is a major risk factor.[5] Current approaches to insulin therapy are associated with a substantial risk of adverse outcomes such as hypoglycaemia and long-term weight gain, which contribute to poor metabolic and adverse cardiovascular health outcomes in an already high-risk group.[6] Therefore, approaches are being explored to assist more people with T1D to achieve the recommended glycaemic targets while reducing the risk of hypoglycaemia and to protect against chronic diabetes complications.

Sodium-glucose co-transporters are transport proteins that actively transport glucose against its concentration gradient. Sodium-glucose co-transporter 2 (SGLT2) is found in the renal proximal tubules and is responsible for approximately 90% of renal glucose reabsorption. Dapagliflozin is an SGLT2 inhibitor (SGLT2inh), which increases excretion of glucose in the urine. Available data in adults with T1D indicate that dapagliflozin improves glucose control without increasing hypoglycaemia and reduces glycaemic variability.[7–9] Extraglycaemic benefits include insulin dose reduction and weight control.[7–9] There is also substantial evidence in people with T2D that dapagliflozin lowers mortality from cardiovascular causes and hospitalisations for heart failure.[10] Potentially, these cardioprotective benefits may extend to individuals with T1D due to common mechanistic pathways resulting in cardiovascular disease in T1D and T2D.[11] Furthermore, renal benefits with SGLT2inh are emerging with post hoc data revealing improvements in albuminuria in those with pre-existing albuminuria.[12] These glycaemic and extraglycaemic benefits may also extend to other SGLT2inh and SGLT1/2inh.[13]

Despite evidence that SGLT2inh benefit glucose levels, weight and potentially cardiovascular mortality and renoprotection in people with T1D,[13] major regulatory bodies have not yet recommended its use for glycaemic management due to the increased risk of diabetic ketoacidosis (DKA), including euglycaemic ketoacidosis.[14 15] A meta-analysis of randomised controlled trial data of SGLT2inh use in people with T1D demonstrates an elevated DKA risk ratio of 4.49 (95% CI 2.88 to 6.99) relative to placebo.[13] This fourfold increase in risk may be related to mechanisms that decrease insulin relative to glucagon, which stimulates lipolysis and ketosis, for which people with T1D are more susceptible due to autoimmune-related insulin deficiency.[14] Furthermore, DKA risk in T1D is not limited to SGLT2inh but also SGLT1/2inh, such as sotagliflozin, which has been associated with increased β-hydroxybutyrate levels and DKA events.[16]

Effective interventions reducing DKA risk may facilitate the safe use of SGLT2inh in people with T1D. There are a range of limitations to the currently available ketone monitoring methods. Finger-prick blood ketone testing is painful, requires a conscious decision on the part of the person and access to in-date blood ketone test strips and a metre. Urine ketone testing is disliked by people with diabetes,[17] lags hours behind blood levels and is semiquantitative. Both methods often do not occur in a timely manner, as ketone testing strips are often not carried with the person or have passed their expiry date.[18] In addition, the measurement of a ketone level requires a recognition of risk and needs to be initiated by the person or their caregiver. Continuous ketone monitoring (CKM) in conjunction with appropriate education may address some of the shortcomings with conventional monitoring of ketones via urine and capillary blood.

Abbott Diabetes Care (Alameda, California, USA) has developed a CKM device that measures interstitial fluid ketone levels continuously with a dynamic range of 0.0–3.1 mmol/L.[19] The CKM is based on an electrochemical approach using the enzyme β-hydroxybutyrate dehydrogenase to generate a current in the presence of the substrate. The CKM does not require calibration. Accuracy data indicate that for the full range of capillary blood ketone measurements (0–8 mM), 82.4% of values were within 0.225 mM/20% and 91.4% were within 0.3 mM/30% of the reference. The CKM can also report the rate of change of ketones using trend arrows. β-hydroxybutyrate has a lower molecular weight (104 g/mol) in comparison with glucose (180 g/mol), and unlike glucose, there is negligible lag when ketone levels are changing between blood and interstitial fluid. The change in ketone levels in general is slower and of a lower magnitude relative to those observed with glucose.

Human feasibility studies confirm that the sensor has a durability of 14 days and has satisfactory accuracy compared with capillary blood ketone strip measurements using an Abbott ketone meter.[19]

The trial (ACTRN12624000448549) is a multisite 6-month randomised crossover double-masked superiority study. Randomisation to the order of intervention and placebo will be 1:1 at each site. Our main objective is to evaluate the effectiveness and safety of dapagliflozin 10 mg once daily in adults with T1D in comparison with placebo, in conjunction with CKM and education aimed at mitigating the risk of DKA. This study will be the first in-human trial evaluating the use of CKM to reduce DKA risk with adjunctive SGLT2inh therapy in people with T1D. Data from this study may be used to inform the progression to future larger-scale randomised controlled trials to allow this technology to be incorporated into clinical practice. If using CKM can divert ketoacidosis, it may eventually lead to access to SGLT2inh for people with T1D, which could change the trajectory of the disease complications. Secondary aims will examine glycaemic outcomes, safety outcomes, anthropometric outcomes, clinical outcomes and psychological outcomes.

METHODS AND ANALYSIS

Study setting

The trial will occur in five diabetes centres across three Australian states and territories with St Vincent's Hospital Melbourne (SVHM) as the lead site. Four of the study sites are metropolitan tertiary hospitals and academic

Table 1 Eligibility

Inclusion criteria	Exclusion criteria
► Age ≥18 years old. ► T1D of >1-year duration. ► Stable on insulin therapy (either on MDI or IPT). ► HbA1c<86 mmol/mol (<10.0%). ► Minimum total daily insulin dose ≥0.4 IU/kg. ► Access to a mobile phone compatible with the CGM system. ► Willing to adhere to all requirements of the protocol including wearing and responding to information provided by the continuous ketone sensor for the duration of the study.	► Pregnancy or planned pregnancy. ► eGFR <30 mL/minute/1.73 m^2. ► A history of DKA* in the last 3 months. ► Diabetic gastroparesis. ► Tape allergy. ► Unable to exercise (relevant to substudy). ► Use of low carbohydrate diet (defined as <100 g/day).[30] ► Heavy alcohol use (defined as >15 standard drinks per week or binge drinking defined as >5 drinks on one occasion).[55] ► Major medical or psychiatric illness that in the opinion of the investigator would interfere with protocol adherence or impact participant safety.

*DKA is defined as a metabolic state where the individual must have either a glucose concentration of >11.1 mmol/L at presentation or have been previously diagnosed with diabetes; they must have plasma β-hydroxybutyrate concentrations of ≥3.0 mmol/L, or urine ketones of more than 2+ on a standard urine ketone stick; and they must have a pH<7.3 or a serum bicarbonate of <15.0 mmol/L.
CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; HbA1c, Haemoglobin A1c; IPT, insulin pump therapy; MDI, multiple daily injections; T1D, type 1 diabetes.

centres (SVHM, Royal Melbourne Hospital, Austin Health, Canberra Hospital), and one is a public metropolitan community service (Southern Adelaide Diabetes and Endocrine Services). All five participating centres have the required physical infrastructure, human resources and extensive clinical trial experience for follow-up and management of patients with T1D.

Eligibility criteria

See table 1 for full participant inclusion and exclusion criteria. Criteria are focused on excluding those at unacceptably high risk of DKA even in the absence of SGLT2inh therapy. Those included are HbA1c<85.8 mmol/mol (<10%) given exponential increased risk above this threshold[20 21] and minimum total daily insulin dose ≥0.4 IU/kg given the association between insulinopaenia and DKA risk and is in line with current guideline recommendations.[22] Individuals excluded are those with a history of DKA in the last 3 months,[23 24] following a low carbohydrate diet[25] or heavy alcohol use (as defined in table 1).[26 27] Participants may be on multiple daily injections (MDI) or insulin pump therapy (IPT), and at least 40% will be on either therapy, to capture data for the two different insulin delivery modalities used in the real world.

All participants will be adults (≥18 years old), and all women must not be pregnant or planning pregnancy due to the current lack of dapagliflozin safety data for these populations. Participants with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 are excluded given limited experience with dapagliflozin below this threshold, the association with a reduction in glucose lowering efficacy[28] and association with an increased risk of volume-depletion adverse events in patients with moderate renal impairment.[29] Individuals with gastroparesis are excluded as differentiating between nausea and vomiting related to DKA vs that related to gastroparesis would be difficult and could lead to a delay in the diagnosis of DKA. People who are unable to exercise will be excluded as an optional exercise substudy will be conducted to evaluate the impact of high-intensity exercise on ketone levels while on intervention versus placebo. The details of the exercise substudy are not discussed here.

Participants must have a phone compatible with the FreeStyle Libre 2 Continuous Glucose Monitor (CGM)

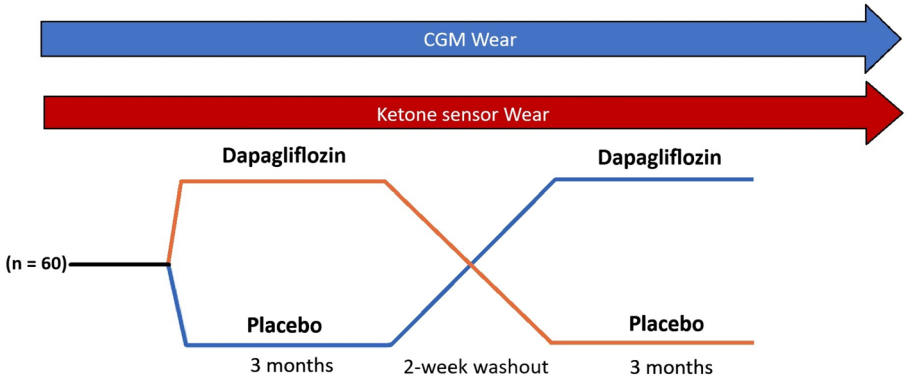

Figure 1 Study design. CGM, continuous glucose monitor.

device, as it is required during the study. Individuals must not be allergic to tape as extra tape may be used to secure the CGM and CKM devices to reduce the risk of device detachment.

Interventions

All eligible participants who have successfully completed run-in will be randomly allocated to intervention (dapagliflozin 10 mg daily) or matching placebo (same excipients without the active drug) for 12 weeks (figure 1). Following a 2-week washout period, participants who received dapagliflozin will crossover to placebo for a further 12 weeks and vice versa. Both the participant and the investigator will be masked to the drug intervention throughout the study.

Modifications

Discontinuation of the intervention may be initiated at the request of the participant at any time during the study. An investigator can discontinue the intervention if there are any concerns regarding the safety of the participant (eg, severe hypoglycaemia, DKA, hospital admission, device-related adverse event), non-adherence to the trial protocol or on technical grounds (eg, participant relocates during the study).

Adherence

To maximise protocol adherence, all potential participants will be provided pre-enrolment with an information sheet highlighting important study procedures to set expectations. Only participants who successfully complete the run-in will proceed to randomisation to ensure that those selected are able to fulfil the protocol requirements. Participants will be trained in the completion of an insulin diary and a food diary. Information to be entered into the diaries will be limited to the minimum possible for analysis to reduce burden on participants and to maximise adherence (eg, food diary for 3 days during run-in, insulin diary of total daily insulin dose, total daily basal insulin dose and total daily bolus insulin dose during run-in and the final 2 weeks of each stage). Adherence to the study drug will be reviewed by counting tablets on return of the bottles at the end of each study stage. Participants will be sent automated text message reminders prior to key procedures, including prior to in-person visits and commencement of insulin diaries to optimise protocol adherence. A study team member will be contactable via phone 24/7 throughout the study so that all participants are well supported to adhere to protocol requirements.

Concomitant care

Insulin dose adjustments can occur during the trial after a research team member has performed a clinical assessment of the participant's glucose and ketone data. Insulin titration will occur to maximise safety; that is, to avoid hypoglycaemia and DKA. All other therapies related to the participant's usual medical needs can continue and be adjusted according to clinical review by their usual healthcare provider.

Participant timeline

The study consists of a total of up to eight in-person visits. This occurs at screening (weeks −4 to −2), education and run-in (weeks −2 to 0) and up to three visits during each stage of the intervention period (weeks 0 to 26). There will be a total of 12 phone reviews and 4 mandated remote data reviews with the participant during the intervention period. Additional in-person or phone reviews may be conducted at the discretion of the study team if any issues arise from the phone or remote data reviews. The initial phone review of each stage cannot be delayed for safety reasons, while subsequent phone or data reviews may differ by ±1–2 days as long as no major safety concerns have arisen during earlier reviews. Mid-study visits and end-of-study visits may differ by ±6 days given the number of additional tablets provided during the intervention period (figure 2).

Screening and run-in period

This will involve collection of demographics, medical and detailed diabetes history, physical examination, and laboratory investigations. Questionnaire responses will also be collected. Participants who pass screening will proceed to education and run-in for 2 weeks. This involves provision of and training in the use of all study-related devices and equipment, including the Abbott FreeStyle Libre 2 CGM, Abbott CKM and Abbott FreeStyle Optium Neo Glucose and Ketone Monitor (Abbott, Alameda, California, USA). Participants will also receive in-person education on management strategies for sustained hyperglycaemia and ketosis by qualified diabetes nurse educators and/or endocrinologists to minimise the risk of progression to DKA, which will be individualised according to insulin delivery modality. Handouts of the management algorithm will be provided specific to those on insulin pumps and MDI (online supplemental appendix 1 and 2). Principles of the response strategy to manage ketosis will follow the STOP DKA[30] and STop, Inject, Carbohydrate, Hydration protocols,[31] which include stopping the study drug if unwell, hydration, carbohydrate consumption, insulin administration and blood glucose and ketone monitoring. In addition, participants will receive education and training in the use of an insulin and food diary, which will be used to explore associations between baseline ketone values with insulin dose and carbohydrate intake. Participants who pass run-in (defined as at least 10 out of 14 days of CGM and CKM data) will proceed to randomisation. If required, participants will have two attempts at completing the run-in to demonstrate proficiency in the use of the study devices.

Randomisation

Following successful run-in, participants will proceed with randomisation to 12 weeks of dapagliflozin 10 mg daily or placebo via computer-generated random allocation

		STUDY PERIOD						
	Enrolment	Run-in	Allocation	Post-allocation				Close-out
TIMEPOINT (weeks)	-4	-2	0	10	12	14	24	26
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Clinical assessment	X							
Allocation			X					
INTERVENTIONS:								
Study CGM		←	→	←	→		←	→
Study CKM		←	—	—	—	—	—	→
Study drug			←	—	—	→	←	→
ASSESSMENTS:								
Demographics	X							
Medical history	X				X			X
Physical examination	X		X		X			X
Insulin diary		←	→	←	→		←	→
Food diary		X						
HbA1c	X		X		X			X
C-peptide	X							
Blood pregnancy test	X							
Urine pregnancy test			X			X		
Renal function, electrolytes and magnesium	X		X		X			X
Lipid profile	X		X		X			X
BNP	X		X		X			X
Urine ACR	X		X		X			X
Biobank sample			X		X			X
Questionnaires	X[a]				X			X
Semi-structured interviews								X[b]

Figure 2 SPIRIT figure summarising the study design. [a]All questionnaires administered excluding study specific questions regarding treatment satisfaction (10 items) and ketone sensor usability: System Usability Scale (10 items) and User Experience Questionnaire (26 items). [b]Performed on a subset of participants n=20. ACR, albumin creatine ratio; BNP, brain natriuretic peptide; CGM, continuous glucose monitor; CKM, continuous ketone monitoring; HbA1c, haemoglobin A1c; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.

software stratified by site. Physical examination data collected will include weight and blood pressure. Insulin and food diaries from the run-in will be collected. Laboratory data will be collected including urine albumin creatinine ratio (ACR), HbA1c, lipid profile, renal function, magnesium, brain natriuretic peptide (BNP), blood and urine biomarkers related to renal function, adipokines, inflammation and oxidative stress, and urine pregnancy test (if applicable).

Insulin use will continue as per usual care in both arms. The first rapid-acting insulin dose may be adjusted by up to 20% at the discretion of the investigator, given both participant and study team will be masked to the study drug. Insulin dose adjustments at the time of randomisation in anticipation of commencing study drug or placebo will be determined at the discretion of the investigator at each study site and individualised according to participant glycaemic control and risk assessment of ketosis versus hypoglycaemia.

Postrandomisation

Postcommencement of the study drug or placebo, participants will be reviewed by telephone at day 2, and weeks 1, 2, 3, 4 and 8 (and similarly day 2 post start of stage 2 and weeks 15, 16, 17, 18 and 22 during stage 2). A remote data review of CKM, CGM and blood glucose/ketone meter data will occur at week 6 and week 10 (weeks 20 and 24 during stage 2). A mid-study visit will occur at week 12 (and end of study at week 26). Insulin doses may be adjusted at the discretion of the investigators to ensure participant safety at any of these time points.

Participants not already using the FreeStyle Libre 2 CGM as part of their usual diabetes care will return for an in-person visit at week 10 for insertion of the CGM. Participant's CKM, CGM and meter data will be reviewed, and they will commence a 2-week insulin diary at this visit.

A mid-study visit will occur at week 12, signifying the end of stage 1. This will involve diabetes clinical review, physical examination for weight and blood pressure, laboratory tests, and blood and urine biomarkers. Insulin diaries and data from all study devices will be collected. Psychological questionnaires will be completed. If necessary, participants who do not meet minimum data requirements (defined as at least 10 out of 14 days of CGM and CKM data) may defer the mid-study visit by 2 weeks.

Following the end of stage 1, participants will undergo a 2-week washout prior to randomisation and commencement of stage 2 (week 14). A urine pregnancy test will be performed (if applicable). Those previously assigned to dapagliflozin 10 mg daily will crossover to placebo and vice versa. Stage 2 will be identical to stage 1, with phone reviews (48 hours post, weeks 15–18 and week 22), remote data review (week 20) and an in-person visit for study CGM insertion if required and commencement of a 2-week insulin diary (week 24).

The end of the study visit will occur at week 26. Information collected will be identical to that obtained at the end of stage 1 visit. In addition, semistructured interviews will be conducted with a subset (n=20) of participants focusing on their experiences of using CKM and the education provided regarding DKA risk minimisation.

Box 1 Primary and secondary glycaemic and safety outcomes

Primary efficacy outcome

Continuous glucose monitor (CGM) percentage time in range (TIR) on dapagliflozin versus placebo.

⇒ CGM percentage TIR during the final 2 weeks of each study stage.

Primary safety outcome

Diabetic ketoacidosis (DKA)

⇒ Number of episodes of DKA requiring hospitalisation or emergency department presentation during each study stage.

Secondary outcomes

Glycaemic outcomes

Study CGM metrics during the final 2 weeks of each study stage for the entire day, daytime, night-time and postprandial period

a. Mean CGM glucose.
b. Glucose management indicator.
c. Glycaemic variability (%Coefficient of Variation).
d. Percentage of readings and time >13.9 mmol/L.
e. Percentage of readings and time 10.1–13.9 mmol/L.
f. Percentage of readings and time 3.9–10.0 mmol/L.
g. Percentage of readings and time 3.0–3.8 mmol/L.
h. Percentage of readings and time <3.0 mmol/L.
i. Glycaemic Risk Index.[32]

⇒ Haemoglobin A1c at weeks 0, 12 and 26.

⇒ CGM metrics during weeks 0–12 and weeks 14–26 were measured using Abbott FreeStyle Libre 2 CGM or the participant's own device where relevant.

Safety outcomes

⇒ Continuous ketone monitor (CKM) percentage time with ketone levels above 0.6, 1.5 and 3.0 mmol/L.

⇒ Mean CKM ketone levels for each study stage between 00:00 and 06:00 (likely fasting); 10:00 and 22:00 (likely fed).

⇒ Episodes of severe hypoglycaemia.

Defined as: any low glucose level requiring the assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions.[37]

Outcomes

Primary efficacy outcomes

The primary efficacy outcome is the percentage time in range (TIR) defined as glucose between 3.9 and 10.0 mmol/L as measured using the FreeStyle Libre 2 CGM. It will be calculated as the number of CGM readings within the range divided by the number of total valid readings. This will be determined during the final 2 weeks of each study stage, as previous evidence has confirmed that the most recent 2 weeks of CGM data correlate well with the last 3 months of glycaemic control, particularly for TIR.[32 33] In the event of incomplete data requirements, the participant may repeat the final 2 weeks of each study stage until at least 70% of data are achieved (boxes 1 and 2).

Primary safety outcomes

The primary safety outcome is the number of episodes of DKA requiring hospitalisation or emergency department (ED) presentation during the trial. DKA is a known clinically relevant adverse outcome of SGLT2inh therapy in people with T1D with an attendant risk for increased mortality.[15] It has been an adverse event of special interest in previous randomised controlled trials evaluating dapagliflozin in adults with T1D.[7–9] The diagnosis of DKA requires biochemical confirmation and usually inpatient treatment, and hence will be assessed by adjudication using hospital and ED records.

Secondary outcomes

1. Glycaemic outcomes: This will include standardised CGM metrics, as defined by an international consensus agreement,[34] measured using the study CGM during the final 2 weeks of each study stage (entire 24 hours, day, night and postprandial). These time periods will be analysed based on the international consensus guidelines, and the 2-hour postprandial period defined as a >20 g carbohydrate meal at conventional Australian meal-times (defined as breakfast 06:00–10:00 hours, lunch 11:00–15:00 hours and dinner 17:00–21:00 hours)[35] will be reviewed to evaluate the effect of SGLT2 inhibition on postprandial glycaemic excursions. Additionally, standardised CGM metrics will be measured using the FreeStyle Libre 2 CGM or the participant's own CGM device for 3 months of each study arm. HbA1c will be measured at weeks 0, 12 and 26. A change in HbA1c of 0.3% will be considered clinically significant.[36]
2. Safety outcomes: CKM percentage time with ketone levels ≥0.6, ≥1.5 and ≥3.0 mmol/L throughout each of the two study stages. These ketone thresholds were selected as they correspond to the development of mild ketosis, moderate ketosis and likely DKA, respectively. Additional analyses will include mean CKM ketone levels when participants are likely fasting (00:00–06:00 hours) and likely fed (10:00–22:00 hours), incidence and duration of CKM ketone levels above 0.6, 1.5 and 3.0 mmol/L. The final 2 weeks of each stage of CKM ketone data will be used to relate ketone levels to CGM metrics using the study CGM. It is an assumption that this interval will be reflective of the last 3 months of CKM data, similar to CGM metrics.[32 33] The number of episodes of severe hypoglycaemia[37] will be measured throughout the study.
3. Anthropometric outcomes: Weight and body mass index (BMI) will be assessed given dapagliflozin is known to lower these parameters and has been an outcome of interest in other dapagliflozin randomised controlled trials.[7–9]
4. Other clinical outcomes: These include renal, cardiac and metabolic outcomes as specified in box 2. All hospital admissions will be reviewed as a clinical safety outcome. Urinary tract infections and candida infections are adverse events of special interest that will be analysed throughout the study period. Average total, basal

Box 2 Other secondary and tertiary outcomes

Other secondary outcomes

Anthropometric outcomes
⇒ Weight.
⇒ Body mass index.

Other clinical outcomes
⇒ Estimated glomerular filtration rate.
⇒ Urine albumin-creatinine ratio.
⇒ All presentations with cardiac failure.
⇒ All cardiac ischaemic hospitalisations.
⇒ All hospital admissions.
⇒ B-type natriuretic peptide.
⇒ Urinary tract infections.
⇒ Candida infections.
⇒ Insulin doses
  a. Average total daily insulin dose.
  b. Average daily bolus insulin dose.
  c. Average daily basal insulin dose.
⇒ Blood pressure
⇒ Lipids
  a. Total cholesterol.
  b. Low-density lipoprotein-cholesterol.
  c. High-density lipoprotein (HDL)-cholesterol.
  d. Triglyceride.
  e. Non-HDL-cholesterol.

Psychological outcomes
⇒ Questionnaires:
  a. Treatment satisfaction: Diabetes Medication System Rating Questionnaire Short Form (SF).
  b. Study-specific questions regarding treatment satisfaction at weeks 12 and weeks 24.
  c. Hypoglycaemia awareness: Gold Score.
  d. Sleep disturbances: Pittsburgh Sleep Quality Index.
  e. Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue–SF.
  f. Health-related Quality of Life (general): EuroQol 5 Dimension 5 Level (EQ-5D-5L).
  g. Health-related Quality of Life (diabetes specific): Problem Areas in Diabetes.
  h. General emotional well-being: WHO-5 Well-Being Index.
  i. Hypoglycaemia Fear Survey–SF (HFS-SF).
  j. Ketone sensor usability at week 12 and week 24: System Usability Scale and User Experience Questionnaire.
  k. Physical discomfort: PROMIS pain scale and Adult Sickle Cell Quality of Life Measurement System (ASCQ-Me) v2.0 Stiffness Impact–SF.
⇒ Participant perceptions about the study intervention and the education received for hyperglycaemia and ketosis management assessed via semi-structured interviews.

Tertiary outcomes

Ketone sensor use
⇒ Percentage time of ketone sensor wear.
⇒ Number of skin infections at site of sensor insertion.
⇒ Mean duration of ketone sensor survival before replacement.
⇒ Comparison of blood ketones with CKM values.

Blood and urine biomarkers
⇒ Renal function, adipokines, measure of inflammation and oxidative stress and DNA for markers of oxidative damage which have been associated with diabetes complications.

and bolus insulin doses will be measured at run-in and the final 2 weeks of each study stage.

5. Psychological outcomes: 12 validated questionnaires will be used to assess for treatment satisfaction,[38] hypoglycaemia,[39] sleep quality,[40] health-related quality of life,[41 42] emotional wellbeing[43] and physical discomfort at weeks −4, 12 and 26. Three questionnaires assessing study-specific treatment satisfaction and ketone sensor usability and experience will be performed at weeks 12 and 26. See online supplemental appendix 3 for an overview of the questionnaires and their scoring. In addition, study staff will conduct interviews with a subset of participants (n=20) across all five trial sites at week 26. Development of the interview questions was guided by the study teams' expertise and constructs taken from the Theoretical Framework of Acceptability.[44] These topics will include their trial experience, perceived treatment effectiveness, CKM device usability and

their views on the effectiveness of the education they received for hyperglycaemia and ketosis management. The interviews will be audio recorded and transcribed by a professional human service. These transcripts will undergo a thematic analysis using Braun and Clarke's method, which involves familiarisation, coding, theme development and final reporting.[45] This approach will also be conducted with a framework approach, where initial coding and theme development will be guided by the constructs from the Theoretical Framework of Acceptability that informed the interview guide. This integration ensures that both theory-driven and researcher-led interpretation are both explored, providing a comprehensive understanding of participants' experiences within the trial.

Tertiary outcomes

This includes ketone sensor use outcomes throughout the study and blood and urine biomarkers at weeks 0, 12 and 26 as per box 2.

Subgroup analyses based on insulin delivery modality will be performed on the primary efficacy outcome and CKM ketone outcomes.

Sample size

A TIR difference of >6% is assumed to be clinically meaningful given that a 5% change correlates to approximately one more hour per day spent in range, a reduction in HbA1c of approximately 0.4% and is associated with clinical benefits.[46 47]

Assuming a TIR SD of 15%[46] and correlation between stages of 0.7 (local data), a total of 45 participants are required to detect an absolute difference between stages of at least 5% with 80% power and a two-sided significance level of 5%. To allow for a 20% drop-out rate, a total of 60 participants will be recruited. To aid generalisability of the results, we aim to achieve similar recruitment numbers across all five clinical sites (12 per site) and similar numbers of participants using MDI and IPT for insulin delivery (at least 40% will be on either therapy).

Recruitment

The first participant was enrolled on 6 September 2024, and the anticipated date of the last participant's final visit is 31 December 2025. Participants will be recruited from five major adult diabetes centres. Each centre has been selected based on their track record in conducting similar clinical trials and in providing clinical services to significant numbers of adults with T1D. The estimated total number of people with T1D treated across all five sites is approximately 3500. Hence, it is anticipated that recruitment of 12 participants per site will be achievable. Nevertheless, to enhance participant enrolment, the study will be advertised across several platforms including posters in clinical areas, diabetes websites (Diabetes Victoria, Diabetes Technology Research Group), and social media platforms (LinkedIn, Instagram and Facebook). Given the availability of a large pool of adults with T1D and the use of varied marketing strategies, it is expected that recruitment will take approximately 6 months.

Allocation

After obtaining written informed consent, participants who successfully pass screening and run-in will be randomly assigned to an allocation sequence of either stage 1 dapagliflozin 10 mg daily followed by stage 2 placebo, or stage 1 placebo followed by stage 2 dapagliflozin 10 mg daily, with each stage lasting 12 weeks, separated by a 2-week washout in between. Simple block randomisation stratified by clinical site will be used with a constraint that each site has 50:50 allocation of maximum planned recruited participants (n=12 for each site). The randomisation sequence was computer generated and performed by an independent research team member who is not involved in trial recruitment. The allocation sequence will be recorded in the participant's electronic case report form (eCRF).

Masking

All participants and study team members will remain masked after the assignment of the drug intervention. The active and placebo drugs have the same appearance (yellow, biconvex, diamond and film-coated tablets), and both are packaged in bottles of the same size and appearance. The bottles will be labelled with a randomisation code that does not allow for identification of intervention to the participant or research team members.

Emergency unmasking for an individual participant to facilitate clinical treatment decisions will be permissible after discussion with the lead principal investigator (PI) at SVHM when an unexpected serious adverse event occurs to the participant at any point during the trial. This process would involve the lead PI contacting the holder of the masking information to obtain the intervention allocation for the identified participant only. Additionally, the Data Safety Monitoring Board (DSMB) may request unmasking due to any significant safety concerns. Under these circumstances, the lead PI will contact the unmasked member to provide the entire sequence to a separate unmasked biostatistician for an unmasked analysis to occur. The assignment code will be revealed at the conclusion of the study to determine the effect of the intervention.

Data collection methods and data management

All trial staff members will attend a start-up meeting prior to engagement in study procedures to obtain appropriate training in the study protocol, data collection methods to promote data quality, operation of study devices and uploading procedures to ensure consistency across sites. All device data will be stored on a secure cloud-based central server with access restricted to the study team. Hard copies of all deidentified data will be stored in a locked cupboard and locked office that is only accessible via secure swipe-card access by study team members. All data will be stored for a minimum of 15 years from

the date of final publication as per Australian research standards.

The electronic case report form

Deidentified participant data will be electronically entered on REDCap, which is a secure web-based application database specifically designed for research studies. It enables multisite access over a secure web connection to authorised members of the study team. All user activity and data entry are tracked. REDCap is compliant with the Health Insurance Portability and Accountability Act and Federal Information Security Modernisation Act standards. REDCap will be used at all reviews throughout the study to directly input data into the eCRF to prevent transcription errors from paper forms. Modern-based desktop computers will be used for data entry, and the data will be backed up daily to The University of Melbourne central server. Paper forms will be used in the event the web platform is not accessible. Quality control checks will be performed to ensure accurate data entry. Modifications to previously entered data will be clearly documented, including time/date, reason for modification and person performing the modification.

Diabetes management software

LibreView is a cloud-based online platform compatible with the Abbott FreeStyle LibreLink app and Abbott FreeStyle Optium Neo (Abbott) that allows review of a participant's CGM and point-of-care blood glucose/ketone data. All participants will be set up with a deidentified LibreView account and LibreLink app for study purposes at run-in. CGM data from the LibreLink app will be automatically uploaded to LibreView when the participant's smartphone has internet connection. Blood glucose/ketone meter data will be computer uploaded via a micro-USB cable to LibreView. Participants will be instructed to upload this data from home weekly for the first 4 weeks then 2 weekly thereafter for each stage of the study. The uploaded data will be shared with the study site's LibreView account, with oversight by the lead site at SVHM to ensure consistency of data uploads and to minimise gaps in data.

Continuous ketone monitor data collection

The study investigational device, Abbott CKM (Abbott), is only currently available for premarket clinical investigation. The device monitors interstitial fluid ketone levels, specifically β-hydroxybutyrate, in real-time every minute and transmits the data via Bluetooth to a study-specific smartphone preinstalled with the study ketone app every 5 min. Participants will be required to carry the study-specific smartphone with them at all times for the duration of the trial. If the smartphone is not within the Bluetooth range (6 m), participants will not receive real-time readings from the CKM. However, when the smartphone returns within connectivity range, CKM data will be automatically backfilled. Additionally, all participants will be instructed to save and email the CKM data to a research-specific password-protected Gmail account on a weekly basis to minimise the risk of data loss in case the smartphone is lost. The ketone app will display real-time ketone values, a trend arrow indicating rapidly rising (increasing by ≥0.2 mmol/L per hour), rapidly falling (decreasing by ≥0.2 mmol/L per hour) or steady ketone levels, a 24-hour graph from midnight that is updated every 15 min and time >0.6 mmol/L over a 24-hour period. An audible alarm will sound on the smartphone when ketone levels are ≥1.0 mmol/L and ≥1.5 mmol/L every 5 min. Data on the ketone app will always be available for participant review throughout the study to enable a response strategy to be promptly implemented in the event ketone levels rise. The sensing range is between 0.0 and 3.1 mmol/L with a durability of 15 days. It is designed to be worn on the posterior upper arm. The size of the CKM is similar to the currently commercially available FreeStyle Libre 2 CGM. Smartphone CKM data will be saved and transferred on a weekly basis via unique password-protected study-specific Gmail accounts to a centralised study Gmail account that is only accessible to research team members, with oversight by the SVHM research team.

Laboratory tests

Samples for HbA1c measurement will be analysed by the local study site Diabetes Control and Complications Trial (DCCT)-aligned laboratory. DCCT-measured HbA1c is a validated standardised method that is routinely used in clinical and research settings.[37] Renal function, magnesium, BNP, lipid profile and urine ACR will be analysed by a National Association of Testing Authorities-accredited laboratory at the local study site. Blood and urine biomarkers will be processed at the Baker Heart and Diabetes Institute, who have extensive experience in conducting the assays.

Retention

The study team will make all reasonable efforts to follow up a participant once they are recruited in the study. Participants will be provided with an outline of all scheduled study reviews at the first visit to set expectations and promote retention. 24/7 telephone support by qualified medical practitioners will be provided to all participants, and all queries and concerns will be answered in a timely manner so that participants are supported and likely to remain engaged during the study.

Statistical methods

The primary outcome will be analysed by a mixed effects linear regression model using restricted maximum likelihood estimation with unstructured covariance. Participants will be entered as random intercepts, while intervention (intervention vs placebo) and stages (stage 1 vs 2) will be entered as fixed effects. Model fit will be evaluated by visual inspection of the residuals, and the outcomes will be transformed using natural logarithm, if required. Results will be presented as mean difference in

TIR between intervention and placebo with 95% CIs. A p<0.05 will be considered statistically significant.

Continuous secondary outcomes will be analysed in the same manner, while mixed effects negative binomial regression will be used for count outcomes and mixed effects logistic regression will be used for binary outcomes. There will be no adjustments for multiple comparisons of secondary outcomes. However, the results will be interpreted based on their clinical relevance, and not solely statistical significance. The semistructured interviews will be interpreted using Braun and Clarke's reflexive thematic analysis and guided by the constructs of the Theoretical Framework of Acceptability.[44]

A subgroup analysis by baseline insulin delivery modality will be performed in the form of an interaction term in the regression model or by stratifying analysis if non-parametric methods are required. Outcomes assessed include the primary outcome and CKM ketone outcomes.

Regression models will be used to evaluate the association of primary and CKM ketone outcomes with the following variables: age, sex, duration of diabetes, BMI, comorbidities, carbohydrate intake, C-peptide, insulin dose (total daily, basal and bolus doses), insulin delivery modality (MDI vs IPT including automated insulin delivery vs non-automated insulin delivery systems) and glucose parameters (CGM metrics, HbA1c, fasting plasma glucose). The type of statistical model will be chosen based on the distribution of each outcome. Data may be transformed if that will improve model fit.

Data monitoring

A DSMB consisting of five members including three Australian qualified endocrinologists who have clinical trial and diabetes technology experience, one intensive care specialist and one biostatistician will be appointed. All members of the DSMB will be independent of the trial investigators. The DSMB will convene in person or via teleconference every 3 months after trial commencement to monitor for adverse events, trial safety data, site monitoring and audit outcomes. A masked report will be prepared by the trial statistician and communicated to the lead investigators at each clinical trial site. Unmasked reports will be prepared by an independent statistician and will not be shared outside DSMB. The trial may be terminated early on the advice of the DSMB if any unexpected serious harm to participants is identified.

Harms

All adverse events will be reported in line with local clinical research ethical requirements and the Therapeutic Goods Administration (TGA). All clinical trial staff will be appropriately trained in the standard operating procedures for reporting all adverse events, investigational device-related adverse events and medical product-related adverse events. All adverse events will be recorded in the participant eCRF and local site adverse event log. All serious adverse events will be reported to the lead PI at SVHM within 24 hours. Subsequently, the SVHM Human Research Ethics Committee (HREC) will be notified within 24 hours or 7 days if the adverse event is related to the investigational CKM device or study drug, or not related to the investigational CKM device or study drug, respectively. The HREC will be responsible for notifying the TGA within 7 days for fatal or life-threatening serious adverse events and 15 days for all other serious adverse events. If deemed appropriate, interventions will be implemented by the study team, or a referral will be made to a relevant specialist team to address the adverse event. The nature and resolution of the adverse event will determine the duration of follow-up.

Auditing

A data entry and compliance officer who is independent of the study will remotely audit data entry monthly at all sites to ensure that the study is conducted according to protocol and compliant with Good Clinical Practice standards. In addition, the lead site will perform weekly teleconference reviews with all sites to communicate and address issues in a timely manner.

ETHICS AND DISSEMINATION

Research ethics approval

The PARTNER study has received ethical approval (HREC reference 302/23) from the SVHM HREC which operates in accordance with the National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research (2023), International Conference on Harmonisation Guidelines for Good Clinical Practice, the Health Privacy Principles described in the Health Records Act 2001 (Vic) and Section 95A of the Privacy Act 1988. Approval has been given in accordance with the research conforming to the NHMRC Act 1992 and the NHMRC National Statement on Ethical Conduct in Human Research (2023). Ethics approval for the multisite PARTNER study is centralised to the SVHM HREC. In addition, all sites have received study governance approval.

Protocol amendments

All protocol amendments will be submitted to the SVHM HREC for ethical approval. Following ethical approval, a team member at SVHM will communicate via email the protocol modification to all relevant parties including the four other sites and trial participants in a timely manner. If applicable, the Australian New Zealand Clinical Trials Registry will be informed about the amendment via updating the online registration record.

Consent

Participant information sheets will be provided in advance to all participants who potentially fit eligibility criteria. This will contain detailed information about the purpose of the research, study procedures, risk and potential benefits of the study and information about the research data collected. Participants will present to their

local trial site and be provided with ample opportunity to ask questions prior to informed written consent being obtained. All participants will be provided with a copy of the written signed consent form, and it will be filed in the participant's hard copy study records and uploaded to the local site electronic medical record.

Participants will also be provided with a participant information sheet for optional future research for collection of blood and urine samples for biobanking. The procedure for obtaining informed written consent for optional future research will be the same as the main study consent process (online supplemental appendix 4 and 5).

Confidentiality

The confidentiality of all participants will be maintained at all times before, during and after the trial. All participants will be allocated a unique study identification number that will not contain any personal identifying information. This number will be used for the transfer of all data throughout the study. Confidential data will be retained at the local study sites in a study file stored in a secure locked office that is swipe-card accessible only by relevant team members. Electronic data will be stored on a secure central university server with password-protected access restricted to study personnel. Reports, meetings and publications will not include identifiable participant information.

Access to data

The lead PI at SVHM and study biostatistician at the University of Melbourne will have access to the final dataset at all trial sites. PIs at each participating centre will have access to their local site dataset.

Ancillary and post-trial care

All participants in the study are indemnified through State or Territory of the Commonwealth of Australia insurance programmes. Any participant who suffers injury from participation in the trial may seek compensation as per the Australian pharmaceutical industry compensation guidelines if applicable or via the Australian law system. After the trial, patient care will be transferred back to the participant's usual healthcare team via written communication including a copy of glucose and insulin data and routine laboratory investigations.

Dissemination policy

Run-in and final trial data from all study sites will be analysed and reviewed by all coauthors. Publication of both run-in and final trial data in a peer-reviewed journal is anticipated. Authorship will be based on contributions to the conception, design and execution of the study as well as construction and review of the planned manuscripts.

Deidentified ketone data may be shared with Abbott Diabetes Care (Alameda) for the purposes of education, research and development, product designs and improvements, regulatory submissions, publication and/or product surveillance purposes. In addition, the results of the study are anticipated to be presented at national and international diabetes conferences.

DISCUSSION

While SGLT2inhs have proven glycaemic and non-glycaemic benefits in people with T1D,[13] these medications are currently not approved in this population due to the unacceptable increased risk of DKA.[15] If a strategy to monitor ketones and prevent progression to DKA was implemented and proven to be effective, there is the potential for SGLT2inh use to be re-visited as an adjunctive therapeutic option in this high-risk cohort.

Ketone testing has been recognised as an important component of DKA risk management in an international consensus statement.[48] CKM devices have been developed to fill the limitations of current self-monitoring methods. No studies to date have evaluated the use of CKM as part of a strategy to minimise progression to DKA while on SGLT2inh therapy. This is the first study evaluating the improvement in glucose control in people with T1D with adjunctive use of CKM in conjunction with supporting education to minimise DKA risk.

The study design has several novel aspects. In collaboration with Abbott Diabetes Care (Alameda), the study team provided input into the development of the CKM app, including ketone data display, ketone trend arrows and inclusion of a ketone alarm threshold at ≥1.0 mmol/L to allow for early intervention aiming to prevent DKA. The CKM used in this study reports changes in ketone levels between 0.6 and 3.1 mmol/L,[19] which is the relevant range allowing the person to intervene prior to the onset of frank DKA.[49] Ketone levels <0.6 mmol/L have been recognised as unlikely to progress to DKA and sensor accuracy at these low ketone levels is diminished. Therefore, people should not be responding to fluctuations in ketone levels in this low range of questionable clinical significance. Conversely, it has been optimised for ambulatory care and ketone levels >3.1 mmol/L indicate likely DKA, and under these circumstances, the person is best managed in a hospital or ED. In light of the aforementioned, we suggest that the information provided by the CKM is accurate, timely and relevant, allowing an appropriate response strategy to be implemented. The study involved the development of a ketosis response strategy based on insulin delivery modality that will be used to educate participants on responding to CKM information (online supplemental appendix 1 and 2).[50]

This study is a crossover trial which is advantageous in removing intersubject variability and enabling high statistical power with a smaller sample size when compared with a parallel group design. Each stage of the trial will occur for 12 weeks to allow for glycaemic outcomes to be appropriately evaluated after commencement of intervention. A single dose of dapagliflozin 10 mg oral has a half-life of 12.9 hours,[51] hence a 2-week washout period will ensure elimination of any carryover drug effect, given the standard convention for washout is approximately five half-lives.

The five trial sites selected include both hospital-based diabetes services and a community-based diabetes service to ensure that a representative sample of people with T1D who engage in differing models of diabetes care are included in the study. The involvement of multiple sites will enable rapid recruitment, a more diverse sample and increase the generalisability of the results to impact clinical practice. All team members at all sites will undergo training prior to performing participant education activities to ensure that education regarding DKA risk minimisation is uniform. A standardised hyperglycaemia and ketosis response algorithm will also be provided to all sites, and they will be instructed to use this as part of the education process.

CKM and CGM data will be visible to participants throughout the study. This is to encourage regular review of data, allow for early recognition of any ketone or glucose changes and enable response strategies to be promptly implemented to ensure participant safety throughout the trial. We acknowledge that this will alter participant behaviour during the run-in period, and hence ketone outcomes may not be entirely reflective of a 'normal' profile for an individual with T1D. However, in the absence of a ketosis-inducing event, it is expected that elevated ketone levels will be rare;[52] therefore, participant behaviour is unlikely to be modified during the run-in period.

The primary efficacy outcome is a validated and clinically relevant method of assessing glycaemic efficacy that provides valuable information about day-to-day glycaemic control. It is not subject to the limitations of HbA1c measurement such as lack of reflection of glycaemic excursions and is not confounded by conditions affecting red cell survival (eg, anaemia, iron deficiency, pregnancy) and glycation (eg, haemoglobinopathies).[34] Furthermore, there is an increasing body of evidence supporting TIR as an important clinical glycaemic marker that is strongly associated with the development of chronic diabetes complications.[53 54] Hence, an improvement in TIR is predicted to reduce the development of microvascular complications, making it a valuable outcome metric in clinical research.

The primary safety outcome has been chosen for its clinical importance both in randomised controlled trials and in the real world. If the intervention is proven to be efficacious and significant in reducing SGLT2inh-related DKA, it has the potential to influence policy and clinical practice.

Additionally, an assessment of psychological outcomes using validated questionnaires and semistructured interviews will be beneficial in understanding participants' perceived benefits of the intervention, education strategies and suitability in the real world, given that this is the first study of this nature. Furthermore, the usability of the CKM device will provide crucial insights into user experience, identifying potential areas for improvement.

In summary, the PARTNER study is the first in-human double-masked randomised controlled trial evaluating the use of CKM in Australian adults with T1D to mitigate the risk of DKA while on adjunctive SGLT2inh therapy. This trial will provide important preliminary data on the effectiveness of a CKM strategy in reducing DKA, which may inform future larger-scale longer duration studies to potentially shift the benefit–risk profile of SGLT2inhs in favour of benefit and allow it to be used in clinical practice to improve health outcomes for people with T1D.

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