Supplemental Material

Appendix 1:

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Appendix 2: Inclusion/Exclusion Criteria

Main Inclusion Criteria:

- Patient had given written informed consent to participate in the study in accordance with local regulations.
- Adult patients, 18 years and older, with a diagnosis of type 1 diabetes made at least 1 year prior to informed consent.
- Patients who were being treated with insulin or insulin analog delivered via continuous subcutaneous insulin infusion or multiple daily injections.
- Willing and able to perform self-monitoring of blood glucose and complete the study diary as required per protocol.
- At the Screening Visit, A1C must have been between 7.0% (53 mmol/mol) and 11.0% (97 mmol/mol), inclusive.
- Females of childbearing potential must have been using an adequate method of contraception and have had a negative pregnancy test.

Main Exclusion Criteria:

- Use of any antidiabetic agent other than insulin or insulin analog at the time of Screening.
- Use of sodium-glucose cotransporter inhibitors within 8 weeks prior to Screening.
- Chronic systemic corticosteroid use.
- Type 2 diabetes mellitus, or severely uncontrolled type 1 diabetes as determined by the Investigator.

Appendix 3: Mitigation Plan for Reduction of Risk of DKA in Clinical Trials of Sotagliflozin

Based on the known experience with SGLT2 inhibitors in type 2 diabetes, steps were taken to ensure that possible DKA was detected as early as possible and interventions employed. The steps taken in the sotagliflozin type 1 diabetes clinical development program included the following:

- Exclusion of patients with a history of recent (i.e., within the month prior to Screening) or recurrent DKA (i.e., more than 2 episodes in the 6 months prior to Screening)
- Information outlining the risk of DKA in the Investigator Brochure and patient informed consent form
- Guidance in the protocols on the recognition and management of DKA (e.g., the potential for occurrence with normal or minimally elevated blood glucose); the potential for masking of DKA symptoms; the need to measure blood or urine ketones in patients presenting with gastrointestinal complaints or other symptoms suggestive of intercurrent illness (i.e., "sick rules"); instructions for the management of ketosis or ketoacidosis with rapid acting insulin via syringe, according to a specified algorithm, until normalization; and fluid and supplemental oral glucose intake.
- Reinforcement of DKA messages via letters to all Investigators and Study Coordinators outlining the risk mitigation plan for DKA in October 2015 with supplemental site training sessions
- Dissemination of communication cards ("wallet cards") to all patients with information about recognizing and treating ketosis

- Provision of dipstick urine ketone tests (e.g., Ketostix®) and, later, point-of-care BHB meters to allow early and active patient evaluation of ketosis at symptom onset
- Blood BHB assessment at every clinic visit (central laboratory and point-of-care), with central laboratory alerts for BHB >0.6 mmol/L to ensure appropriate clinical follow-up of patients
- Ongoing review of the rate of DKA in a blinded fashion, supported by the following:
    - Multifaceted approach to ensure complete capture of all potential DKA cases, including Investigator-reported metabolic acidosis/DKA; ongoing laboratory monitoring of BHB elevations; medical monitoring of reported AEs using broad "trigger terms" to identify potential unreported metabolic acidosis/DKA cases
    - Use of specialized eCRF pages by Investigators to capture all pertinent information regarding potential DKA
    - Blinded adjudication of all metabolic acidosis cases and DKA cases by the CEC to confirm the presence of DKA cases using a uniform definition, and to define the level of evidence supporting this adjudication decision

Appendix 4: Identification of DKA/Metabolic Acidosis

The occurrence of DKA was based on evaluation of the following:

- Absence of typical presenting signs and symptoms did not preclude the diagnosis of DKA
- Elevated blood or urine ketones with specific emphasis on the presence of increased concentration of plasma BHB
- Metabolic acidosis evidenced by the presence of decreased serum bicarbonate concentration, increased anion gap, and decreased blood pH
- Absence of associated hyperglycemia documented by SMBG or plasma glucose testing did not preclude the diagnosis of DKA

All cases of potential metabolic acidosis and DKA were classified using the following scale:

- **Yes, with certainty**: There is sufficient evidence to support such an event.
- **Yes, probably**: The role of other factors could not be excluded (e.g., underlying disease, complications, other medical events, concomitant drugs, or concurrent treatment).
- **No, unlikely**: An alternative explanation is plausible and more likely (e.g., underlying disease, complications, other medical events, concomitant drugs, or concurrent treatment).
- **No, with certainty**: This is a manifestation of other clinical factors or circumstances (e.g., underlying disease, complications, other medical events, concomitant drugs, or concurrent treatment).
- **Unclassifiable**: The clinical characteristics and circumstances related to the event did not allow classification.
- **Insufficient Data**: The information available was inadequate to allow for classification.

Supplemental Tables

Supplemental Table S1. Baseline characteristics and demographics.

	Placebo (N = 526)	**Sotagliflozin 200 mg/day (N =524)**	**Sotagliflozin 400 mg/day (N = 525)**
Age, years	42.5 (13.3)	44.4 (13.7)	44.0 (13.4)
Female, n (%)	255 (48.5)	259 (49.4)	272 (51.8)
Race: White, n (%)	494 (93.9)	493 (94.1)	496 (94.5)
Diabetes duration, years	21.2 (12.0)	21.6 (12.5)	21.5 (12.3)
CSII, n (%)	226 (43.0)	224 (42.7)	224 (42.7)
BMI, kg/m^2	28.5 (5.3)	28.9 (5.6)	28.7 (5.2)
Weight, kg	84.3 (17.6)	84.5 (18.1)	84.2 (18.1)
HbA_{1c}, % [mmol/mol]	7.7 (0.8) [6.3]	7.7 (0.8) [6.3]	7.6 (0.8) [6.3]
Total daily insulin, IU/kg	0.75 (0.33)	0.73 (0.34)	0.73 (0.30)
Median BHB, mmol/L (min, max)	0.13 (0.10, 3.33)	0.13 (0.10, 1.46)	0.14 (0.10, 1.75)

Data are mean (standard deviation) unless otherwise specified.

CSII: continuous subcutaneous insulin infusion; BMI: body mass index; BHB: beta-hydroxybutyrate (Note: for BHB, the lower limit of detection was 0.10 mmol/L).

Supplemental Table S2. Effect of percent change in total daily insulin dose on the incidence of investigator-reported DKA/metabolic acidosis events.

	Placebo	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
Total insulin dose (IU/kg) reduction ≥10%			
Yes	1.7 (2.2, 3.3) n = 309	7.1 (4.3, 9.8) n = 376	9.1 (6.0, 12.2) n = 394
No	1.1 (0.0, 2.5) n = 212	4.0 (0.5, 7.5) n = 141	5.3 (1.1, 9.5) n = 124
Total insulin dose (IU/kg) reduction ≥20%			
Yes	0 n = 157	5.8 (2.6, 8.9) n = 236	10.8 (6.4, 15.0) n = 242
No	2.1 (0.6, 3.7) n = 364	6.7 (1.0, 8.1) n = 281	5.9 (4.1, 7.2) n = 276

Exposure-adjusted incidence rate reported as events per 100 patient-years (95% CI)

Supplemental Table S3. Summary of potential contributing trigger factors for positively-adjudicated DKA events.

	Placebo	**Sotagliflozin**
Positively-adjudicated DKA events, n of events	1	36
Potential Trigger Factors* n		
Insulin reduction/ missed insulin dose	0	6
Insulin pump interruption	0	13
Concomitant illness (infection, injuries, or surgeries)	1	14
Alcohol within 24 hours of event	0	2
Strenuous exercise	0	1
No clear trigger factor identified	0	3

Data are number of events and proportion of events meeting criteria.

* Some events had more than one potential trigger factors.

Supplemental Table S4. Adjudicated DKA by study in the Sotagliflozin Type 1 Diabetes Clinical Program.*

Study Number (Name) **Duration (Reference)**	**Placebo**	**Sotagliflozin 75 mg**	**Sotagliflozin 200 mg**	**Sotagliflozin 400 mg**
204 (inTandem 5)	N = 42			N = 43
12 weeks (1)	1 (2.4)			0
206 (inTandem 4)	N = 36	N = 35	N 35	N = 35
12 weeks (2)	0	0	0	1 (2.9)
309 (inTandem1)	N = 268		N = 263	N = 262
52 weeks (3)	1 (0.4)		9 (3.4)	11 (4.2)
310 (inTandem2)	N = 258		N = 261	N = 263
52 weeks (4)	0		6 (2.3)	9 (3.4)
312 (inTandem3)	N = 703			N = 699
24 weeks (5)	4 (0.6)			21 (3.0)
Total	N = 1,307	N = 35	N = 559	N = 1,302
Adjudicated DKA n (%)	6 (0.5)	0	15 (2.7)	42 (3.2)

Cells filled with black denotes dose not evaluated in specific study.

*203 (Sands et al. Diabetes Care) is not included because formal adjudication process was not implemented at the time of this trial (2 DKA events were reported with sotagliflozin 400 mg and 0 with placebo).

Supplemental Figures

Supplemental Figure S1. Changes in the DKA Risk Mitigation Strategy

Supplemental Figure S2. Annualized DKA incidence before, during, and after implementation of the enhanced risk mitigation plan.*

*The enhanced risk mitigation plan included: 1) distribution of point-of-care BHB meters and testing strips to all patients; 2) revision of patient wallet cards with instructions regarding the need for ketone monitoring and correction and not relying on elevated blood glucose to suspect DKA; 3) a protocol amendment emphasizing the importance of patient adherence to urine and blood ketone monitoring (to be used for screening and confirmation, respectively); and 4) the need for early notification of study site investigators in the event of BHB elevation.

Supplemental Figure S3. Box plot of beta-hydroxybutyrate (mmol/L) with (A) Placebo, (B) Sotagliflozin 200 mg, and (C) Sotagliflozin 400 mg over 52 weeks.

Note: The box represents the 1st to 3rd quartiles, box width varies according to number of patients in each group. The horizontal line within the box is the median. The "+" is the mean. The whiskers extend to the most extreme observations within 1.5 times the interquartile range from the nearest quartile. Outliers >1.5 times the interquartile range are displayed as individual datapoints.

References for Supplemental Appendix

1. Bode BW, Banks P, Sawhney S, Strumph P, The Sotagliflozin JDRF Study Writing Group. Efficacy and safety of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, asadjunct to insulin in young adults with poorly controlled type 1 diabetes (JDRF Study). *Diabetologia.* 2017;60(Suppl 1):S1-S608.
2. Baker C, Wason S, Banks P, et al. Dose-dependent glycometabolic effects of sotagliflozin on type 1 diabetes over 12 weeks: the inTandem4 trial. *Diabetes Obes Metab.* 2019;21(11):2440-2449.
3. Buse JB, Garg SK, Rosenstock J, et al. Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: the North American inTandem1 study. *Diabetes Care.* 2018;41(9):1970-1980.
4. Danne T, Cariou B, Banks P, et al. HbA1c and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: the European inTandem2 study. *Diabetes Care.* 2018;41(9):1981-1990.
5. Garg SK, Henry RR, Banks P, et al. Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N Engl J Med.* 2017;377(24):2337-2348.