Sotagliflozin as an Adjunct to Insulin for Type 1 Diabetes

January 17, 2019
Sanofi / Lexicon Pharmaceuticals
Endocrinologic and Metabolic Drugs Advisory Committee
Introduction

Rene Belder, MD
Vice President
Diabetes and Cardiovascular Clinical Development
Sanofi
Insulin: Life-Saving But Difficult to Dose Correctly

Underdosing

↑ Hyperglycemia
↑ Diabetic ketoacidosis (DKA)

Overdosing

↑ Hypoglycemia
↑ Weight gain

Imprecision

↑ Glucose Variability
↑ Distress
Sotagliflozin: Dual Inhibitor of SGLT1 and SGLT2

- SGLT1 inhibition blunts and delays glucose absorption and reduces postprandial glucose (PPG) excursions\(^1\)
- SGLT2 inhibition reduces glucose reabsorption, lowering blood glucose\(^2\)

Sotagliflozin Proposed Indication and Dosing

- Sotagliflozin, an inhibitor of the sodium-dependent glucose co-transporters (SGLT) 1 and SGLT2, is indicated as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus who have failed to achieve desired glycemic control despite optimal insulin therapy.

- Recommended dose
  - 200 mg orally, once daily before first meal
  - Dose may be increased to 400 mg in patients who tolerate 200 mg and need additional glycemic control
Sotagliflozin Clinical Development Program
Largest to Date in Adults with T1D

- 30 clinical studies including 4,010 adults

<table>
<thead>
<tr>
<th>Phase 3 Study</th>
<th>Total Duration</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>309 (North America)</td>
<td>52 weeks</td>
<td>793</td>
</tr>
<tr>
<td>310 (Europe and Israel)</td>
<td>52 weeks</td>
<td>782</td>
</tr>
<tr>
<td>312 (Global)</td>
<td>24 weeks</td>
<td>1,405</td>
</tr>
</tbody>
</table>
Sotagliflozin – Effective Adjunct to Insulin Therapy

- Provides statistically significant and clinically important reductions in A1c
- Improves glycemic control with lower risk of hypoglycemia
- Favorable effects on other glycemic endpoints
  - Time in range, PPG, fasting plasma glucose (FPG)
- Improves cardiovascular risk factors
  - Body weight, blood pressure
- Decreases disease burden
Sotagliflozin – Safety Profile

- Well-tolerated
- > 80% of patients completing 52 weeks
- Lower risk of hypoglycemia than insulin alone
- Higher risk of diabetic ketoacidosis (DKA)
DKA Known Risk in T1D

- Occurs with absolute insulin deficiency (e.g. missed doses) or relative insulin deficiency (e.g. stress, illness)
  - Increases glucose levels
  - Metabolic shift to fat burning
  - Increase of ketones or ketosis and potentially DKA
- DKA risk mitigation and management already standard of care
SGLT2 Inhibition Increases Risk of DKA in T1D

- DKA, on or off SGLT2, caused by same mechanism
  - Absolute or relative insulin deficiency
- Traditionally recognized through symptoms and hyperglycemia
- SGLT2 inhibitors lower glucose levels independent of insulin
  - Hyperglycemia not as reliable an indicator of DKA
- Important to measure and rely on ketones
Proposed Risk Management Program to Reduce Risk of DKA

- Based on current practice guidelines
  - Patient selection, ketone monitoring, insulin management, recognizing at-risk situations, and use of sick-day rules
- Communicate risk of DKA to HCPs and patients
  - Educational materials and patient leaflets
Agenda

Unmet Medical Need in Adults with Type 1 Diabetes
Steven Edelman, MD
Clinical Professor of Medicine
UC San Diego

Clinical Efficacy Results
Pablo Lapuerta, MD
Executive Vice President and Chief Medical Officer
Lexicon Pharmaceuticals

Clinical Safety Results
Klaus Henning Jensen, MD
Head of Diabetes, Cardiovascular and Metabolism Development
Sanofi

Clinical Perspective
Juan Pablo Frias, MD
Medical Director and Principal Investigator
National Research Institute
## Additional Experts

<table>
<thead>
<tr>
<th>Specialization</th>
<th>Expert Name</th>
<th>Credentials and Affiliations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic Ketoacidosis</td>
<td>Ketan Dhatariya, MBBS, MSc, MD, MS, FRCP, PhD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consultant Physician</td>
<td>Norfolk and Norwich University Hospitals NHS Foundation Trust U.K.</td>
</tr>
<tr>
<td>Biostatistics</td>
<td>LJ Wei, PhD</td>
<td>Professor of Biostatistics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Harvard T.H. Chan School of Public Health</td>
</tr>
<tr>
<td>Cardiology</td>
<td>Darren McGuire, MD</td>
<td>Professor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>UT Southwestern Medical Center</td>
</tr>
<tr>
<td>Principal Investigator European Trial</td>
<td>Thomas Danne, MD</td>
<td>Diabetes Center</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Auf der Bult”, Hannover Medical School, Germany</td>
</tr>
<tr>
<td>Translational Medicine</td>
<td>Ele Ferrannini, MD, PhD</td>
<td>Professor of Internal Medicine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>University of Pisa</td>
</tr>
<tr>
<td>Pharmacoepidemiology</td>
<td>Elizabeth Andrews, PhD</td>
<td>Vice President, Pharmacoepidemiology and Risk Management</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RTI Health Solutions</td>
</tr>
</tbody>
</table>
Unmet Medical Needs in Adults with Type 1 Diabetes

Steven Edelman, MD
Clinical Professor of Medicine
University of California San Diego School of Medicine
Founder and Director, Taking Control of Your Diabetes, a 501(c)3 Not-for-Profit Organization
Type 1 Very Different from Type 2 Diabetes

- Etiology and treatment strategies
- Autoimmune disease
- Absolute insulin deficiency
- Require intensive insulin therapy
- Glycemic unmet needs go far beyond A1c
Discovery of Insulin Significantly Changed and Prolonged Lives of Patients with T1D

Ted Ryder Before Insulin

Ted Ryder 5 Months After Insulin
Limitations of Insulin Therapy

- Hypoglycemia
- Weight gain
  - Hypertension and other co-morbidities
  - Premature cardiovascular disease
- Insulin contributes to unpredictable swings in glucose values
Less than 1/4 of Patients with T1D Reach ADA Goal of A1c < 7.0%

A1c Ranges

- < 7.0: 21%
- 7.0 - < 8.0: 31%
- 8.0 - < 9.0: 23%
- 9.0 - < 10.0: 12%
- ≥ 10.0: 13%

Beck et al, 2012
Trade-Off Between Microvascular Complications and Hypoglycemia

Rate of Progression of Retinopathy (per 100 Patient Years)

Rate of Severe Hypoglycaemia (per 100 Patient Years)

Relative Risk of Microvascular Complications

HbA$_1c$ (%)
A1c Gold Standard for Predicting Microvascular Complications

- Does not capture day-to-day patients’ disease control
- Other glycemic indices better reflection of patient experience
  - Time in range (between 70 and 180 mg/dL)
Glucose Variability Has Important Impact on Patients with T1D

Fluctuations in Daily Glucose Levels in Two Different Patients

- Measuring A1c alone gives no information on variability\(^1-^4\)
- Importance of avoiding extreme hyperglycemia and dangerous hypoglycemia
- Improvement in time in range significantly reduced retinopathy and nephropathy\(^5\)

Severe Hypoglycemia in T1D

- Between 4% and 10% of deaths in T1D due to severe hypoglycemia\textsuperscript{2}

1. The T1D Exchange Clinic Registry, 2018; 2. Seaquist E et al, 2012
More Patients with T1D Overweight and Obese

1/1/2016 – 3/31/2018

The T1D Exchange Clinic Registry, 2018
Increased Risk of Hypertension and Cardiovascular Disease in T1D Population

- ~3 times higher prevalence of hypertension\(^1\)
- 10 times greater risk of cardiovascular disease\(^2\)
- 4 times greater risk of hospitalization for heart failure\(^3\)
- Cardiovascular disease leading cause of death\(^4\)

DKA – Known Severe Risk in T1D

- Patients with T1D, especially those on pumps, taught sick-day rules to mitigate and treat themselves
- Sick day rules to prevent ER visit or hospitalization
  - Enhanced monitoring
  - Early insulin dosing
  - Fluids and carbohydrates
- Incidence up to 5.1 per 100 patient years\textsuperscript{1,2}

\textsuperscript{1} Bohn B et al, 2015; \textsuperscript{2} Hoshina S et al, 2018
Unmet Needs in T1D

- Reaching A1c goal without hyperglycemia and hypoglycemia
- Reducing glycemic variability and improving time in range
- Controlling blood pressure and reducing heart disease
- Preventing and controlling weight gain
- High emotional and physical burden
Clinical Efficacy Results

Pablo Lapuerta, MD
Executive Vice President and Chief Medical Officer
Lexicon Pharmaceuticals
Phase 3 Studies Support Sotagliflozin Proposed Indication

Pivotal Studies
2,980 T1D Patients

Optimized Insulin
- Study 309
  - N=793
  - Placebo, 200 and 400 mg QD
- Study 310
  - N=782
  - Placebo, 200 and 400 mg QD

Global Study
- Study 312
  - N=1,405
  - Placebo, 400 mg QD

- Sotagliflozin QD added to insulin resulted in significant A1c reduction
- Benefits beyond A1c
- Not achieved with insulin alone
Studies 309 / 310: Clinical Design

- **Sotagliflozin 200 mg**
- **Sotagliflozin 400 mg**
- **Placebo**

Weeks
- **Week 24**
- **Week 52**

**Double-blind Core Treatment**

**Double-blind Extension**

**Insulin Optimization**

**Follow-up 30 days after last dose**

**IDMC review / A1c masked**

**Single-blind placebo run-in**

**Screening A1c**

**Day 1 Baseline A1c**

**Week 24 Primary Endpoint A1c Assessment**

**IDMC = Insulin Dose Monitoring Committee**
Studies 309 / 310: Key Inclusion Criteria

- ≥ 18 years
- Diagnosis of T1D ≥ 1 year prior to informed consent
- Screening A1c 7.0% to 11.0%
- Insulin pump or multiple daily injections (MDI) therapy
- History of DKA and severe hypoglycemia (SH) allowed
  - No DKA or SH in 1 month before screening
  - ≤ 2 DKA in past 6 months before screening
Studie 309 / 310: Primary and Secondary Endpoints

- Primary endpoint
  - Change from Baseline to Week 24 in A1c

- Secondary endpoints*
  - Net benefit at Week 24
    - Proportion of patients with A1c < 7.0% without SH or DKA
  - Body weight
  - Bolus insulin dose
  - FPG
  - PROs

*Alpha protected
Studies 309 / 310: Efficacy Results
## Studies 309 / 310: > 80% Completion Rate in All Groups

<table>
<thead>
<tr>
<th></th>
<th>Study 309</th>
<th></th>
<th>Study 310</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo 200 mg</td>
<td>Sotagliflozin 200 mg</td>
<td>Placebo 200 mg</td>
<td>Sotagliflozin 200 mg</td>
</tr>
<tr>
<td></td>
<td>Placebo 400 mg</td>
<td>Sotagliflozin 400 mg</td>
<td>Placebo 400 mg</td>
<td>Sotagliflozin 400 mg</td>
</tr>
<tr>
<td>Randomized (N)</td>
<td>268</td>
<td>263</td>
<td>262</td>
<td>258</td>
</tr>
<tr>
<td>Core treatment</td>
<td>33 (12%)</td>
<td>23 (8.7%)</td>
<td>26 (9.9%)</td>
<td>22 (8.5%)</td>
</tr>
<tr>
<td>discontinuations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal by patient</td>
<td>18</td>
<td>14</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>AE</td>
<td>8</td>
<td>7</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Long-term extension</td>
<td>17 (6.3%)</td>
<td>12 (4.6%)</td>
<td>15 (5.7%)</td>
<td>11 (4.3%)</td>
</tr>
<tr>
<td>discontinuations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Withdrawal by patient</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>AE</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Completed study</td>
<td>218 (81%)</td>
<td>228 (87%)</td>
<td>221 (84%)</td>
<td>225 (87%)</td>
</tr>
</tbody>
</table>
# Studies 309 / 310: Demographics Balanced Between Groups and Representative of Patients with T1D

<table>
<thead>
<tr>
<th>Age, mean (years)</th>
<th>Study 309</th>
<th>Study 310</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=268</td>
<td>Sotagliflozin 200 mg N=263</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>47</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Race</th>
<th>Study 309</th>
<th>Study 310</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=268</td>
<td>Sotagliflozin 200 mg N=263</td>
</tr>
<tr>
<td>White</td>
<td>91%</td>
<td>92%</td>
</tr>
<tr>
<td>Black / African-American</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Other</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Sex, female</td>
<td>49%</td>
<td>52%</td>
</tr>
<tr>
<td>Body weight, mean (kg)</td>
<td>87</td>
<td>87</td>
</tr>
<tr>
<td>BMI, mean (kg/m²)</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>
Studies 309 / 310: A1c Efficacy Observed Through Week 52 for Sotagliflozin Treated Patients

A1c, LS Mean Change from Baseline (% [SE])

**Study 309**

- Screening = 8.2% - 8.3%
- Baseline = 7.5% - 7.6%
- Placebo
- Sotagliflozin 200 mg
- Sotagliflozin 400 mg

**Study 310**

- Screening = 8.4%
- Baseline = 7.7% - 7.8%
- Placebo
- Sotagliflozin 200 mg
- Sotagliflozin 400 mg

Time (weeks)
Studies 309 / 310: Sotagliflozin Reduced Total Insulin Dose at Week 24

Study 309

<table>
<thead>
<tr>
<th>Baseline (IU/Day)</th>
<th>Study 309</th>
<th>Study 310</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=268</td>
<td>N=258</td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
<td>66.8</td>
<td>61.9</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
<td>65.1</td>
<td>60.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>64.2</td>
<td>61.4</td>
</tr>
</tbody>
</table>

Insulin Dose, LSM Change from Baseline (%)

![Graph showing the change in insulin dose for Studies 309 and 310 with different Sotagliflozin doses compared to Placebo.](image)
Studies 309 / 310: Sotagliflozin Produced Statistically Significant A1c Decrease vs Placebo at Week 24

**Study 309**

<table>
<thead>
<tr>
<th>A1c,</th>
<th>Baseline (%)</th>
<th>Week 24 (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7.5</td>
<td>7.5</td>
<td>268</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
<td>7.6</td>
<td>7.2</td>
<td>263</td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
<td>7.6</td>
<td>7.1</td>
<td>262</td>
</tr>
</tbody>
</table>

**Study 310**

<table>
<thead>
<tr>
<th>A1c,</th>
<th>Baseline (%)</th>
<th>Week 24 (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>7.8</td>
<td>7.8</td>
<td>258</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
<td>7.7</td>
<td>7.4</td>
<td>261</td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
<td>7.7</td>
<td>7.4</td>
<td>263</td>
</tr>
</tbody>
</table>

* p < 0.001 vs placebo
Studies 309 / 310: Sotagliflozin Provided Greater Net Benefit at Weeks 24 and 52

*\(p = 0.002\) vs placebo; **\(p < 0.001\) vs placebo, ***\(p = 0.049\) vs placebo, ****\(p = 0.001\) vs placebo

**Study 309**

- Week 24:
  - Placebo: 22
  - Sotagliflozin 200 mg: 34*
  - Sotagliflozin 400 mg: 44**
- Week 52:
  - Placebo: 19
  - Sotagliflozin 200 mg: 26**
  - Sotagliflozin 400 mg: 32**

**Study 310**

- Week 24:
  - Placebo: 15
  - Sotagliflozin 200 mg: 31**
  - Sotagliflozin 400 mg: 32**
- Week 52:
  - Placebo: 14
  - Sotagliflozin 200 mg: 26****
  - Sotagliflozin 400 mg: 27**
Studies 309 / 310: Sotagliflozin Significantly Reduced Body Weight at Weeks 24 and 52

**Study 309**
- Placebo: -2.7 kg*, -1.9 kg
- Sotagliflozin 200 mg: -1.6 kg*, -1.9 kg
- Sotagliflozin 400 mg: +0.8 kg, +1.2 kg

**Study 310**
- Placebo: -2.5 kg*, -1.9 kg
- Sotagliflozin 200 mg: +0.1 kg
- Sotagliflozin 400 mg: +0.3 kg

p < 0.001 vs placebo
Sotagliflozin Reduced Fat Mass vs Placebo

Results of body composition measured by DXA from Pooled Studies 309 / 310
Studies 309 / 310: Sotagliflozin Significantly Decreased FPG

<table>
<thead>
<tr>
<th>Study 309</th>
<th>Study 310</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mg/dL)</td>
<td>Baseline (mg/dL)</td>
</tr>
<tr>
<td>153.7</td>
<td>155.1</td>
</tr>
<tr>
<td>148.2</td>
<td>160.5</td>
</tr>
<tr>
<td>163.7</td>
<td>165.5</td>
</tr>
</tbody>
</table>

LS Mean Change from Baseline at Week 24 (mg/dL) [95% CI]

- Placebo
- Sotagliflozin 200 mg
- Sotagliflozin 400 mg

* p < 0.001 vs placebo
Studies 309 / 310: More Patients on Sotagliflozin Reported Improvement in Treatment Satisfaction

**Study 309**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients with ≥3 Point Improvement in DTSQs Total Score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>28</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
<td>54</td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
<td>52</td>
</tr>
</tbody>
</table>

**Study 310**

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients with ≥3 Point Improvement in DTSQs Total Score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>29</td>
</tr>
<tr>
<td>Sotagliflozin 200 mg</td>
<td>41</td>
</tr>
<tr>
<td>Sotagliflozin 400 mg</td>
<td>43</td>
</tr>
</tbody>
</table>
Studies 309 / 310: Sotagliflozin Reduced High Distress

Change from Baseline to Week 24 in Proportion of Patients with High Distress in DDS2 (%)

**Study 309**
- Placebo: 5
- Sotagliflozin 200 mg: -14
- Sotagliflozin 400 mg: -11

**Study 310**
- Placebo: 3
- Sotagliflozin 200 mg: -12
- Sotagliflozin 400 mg: -10
CGM Sub-Study

Pooled data from Studies 309 / 310
Pooled 309 / 310: CGM Sub-Study Design

- N = 278
  - n = 93 placebo
  - n = 89 sotagliflozin 200 mg
  - n = 96 sotagliflozin 400 mg
- Monitored with blinded-CGM device
  - Week -1 to Baseline, Week 3-4, Week 11-12, Week 23-24
- Assessment of PPG
Pooled 309 / 310: Sotagliflozin Increased Time in Range

Placebo

- Baseline
  - < 70 mg/dL
  - 70 – 180 mg/dL (target)
  - > 180 mg/dL

- Week 24
  - +1 h, 17 min vs placebo p = 0.026

Sotagliflozin 200 mg

- Baseline
  - 24 h
  - 12 h
  - 1 h
  - 25 min

- Week 24
  - +2 h, 49 min vs placebo p < 0.001

Sotagliflozin 400 mg

- Baseline
  - 24 h
  - 12 h
  - 1 h
  - 18 min

- Week 24
  - 24 h
## Pooled 309 / 310: Dose Response on Endpoints Beyond A1c

<table>
<thead>
<tr>
<th>Improvements Beyond A1c</th>
<th>Parameter</th>
<th>Treatment Difference vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>200 mg</td>
</tr>
<tr>
<td>Daily Glycemic Control</td>
<td>Time in range</td>
<td>+ 1h 17m</td>
</tr>
<tr>
<td></td>
<td>FPG (mg/dL)</td>
<td>-15.7</td>
</tr>
<tr>
<td></td>
<td>PPG (mg/dL)</td>
<td>-34.8</td>
</tr>
<tr>
<td></td>
<td>Severe hypoglycemia (per 100 PY)*</td>
<td>-2.0</td>
</tr>
<tr>
<td>Other Benefits</td>
<td>SBP (mmHg)</td>
<td>-2.0</td>
</tr>
<tr>
<td></td>
<td>Body weight (kg)</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

*Risk Reference of EAIR, 52 week data
Study 312: Design and Efficacy Results
Study 312: Clinical Design

- **Screening**: Single-blind placebo run-in
- **W-4**: Run-in
- **W-2**: Run-in
- **Day 1**: Baseline
- **Double-blind treatment**: Sotagliflozin 400 mg (N=700)
- **Placebo (N=705)**
- **Follow-up**: 30 days after last dose
- **Week 24 End of Treatment**

Primary endpoint: Net benefit
  - Proportion of patients with A1c < 7.0% at Week 24 without SH or DKA
Study 312: Net Benefit Greater for Sotagliflozin 400 mg vs Placebo

Week 24

Placebo
N=703

Sotagliflozin 400 mg
N=699

Patients with A1c < 7.0% Without SH or DKA (%)

Placebo: 15.2
Sotagliflozin 400 mg: 28.6*

*p < 0.001 vs placebo
### Study 312: Secondary Endpoints Results

<table>
<thead>
<tr>
<th></th>
<th>Sotagliflozin 400 mg</th>
<th>Difference from Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c change from Baseline at Week 24 (%)</td>
<td>-0.46</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body weight change from Baseline at Week 24 (kg)</td>
<td>-3.0</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SBP change from Baseline (≥ 130 mmHg at Baseline) at Week 16 (mmHg)</td>
<td>-3.5</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Bolus insulin change from Baseline at Week 24 (IU/day)</td>
<td>-2.84</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Hypoglycemia
Positive Findings for Hypoglycemia with Sotagliflozin

- Safety endpoint
  - Examined on basis of MoA, rates, and incidences

- Key findings
  - More hypoglycemic events with blood glucose ≤ 55 mg/dL on placebo
  - More patients with investigator-reported and positively-adjudicated severe hypoglycemia on placebo
Evaluation of Hypoglycemia

- Hypoglycemia detected through SMBG measurements uploaded to central database
  - > 2 million values
  - Presence or absence of hypoglycemic symptoms noted on special collection form
- Severe hypoglycemia detected through reporting and independently adjudicated
  - Defined as requiring help from others, loss of consciousness, or seizure
## More Documented Symptomatic Hypoglycemia Events (≤ 55 mg/dL) with Placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Sotagliflozin 200 mg</th>
<th>Sotagliflozin 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled 309 / 310</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>6,551</td>
<td>5,190</td>
<td>5,115</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td></td>
<td>0.78 (0.68, 0.88)</td>
<td>0.80 (0.70, 0.91)</td>
</tr>
<tr>
<td>Nominal p-value</td>
<td></td>
<td>p = 0.0001</td>
<td>p = 0.0006</td>
</tr>
<tr>
<td><strong>Study 312</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events</td>
<td>3,310</td>
<td></td>
<td>2,479</td>
</tr>
<tr>
<td>Rate ratio (95% CI)</td>
<td></td>
<td>0.76 (0.68, 0.86)</td>
<td></td>
</tr>
<tr>
<td>Nominal p-value</td>
<td></td>
<td>p &lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>
More Patients with Positively-Adjudicated Severe Hypoglycemia over 52 Weeks on Placebo

- Placebo: 7.4%
- Sotagliflozin 200 mg: 5.7%
- Sotagliflozin 400 mg: 4.4%

Cox Model
- HR 0.75, p=0.2434
- HR 0.58, p=0.0377

FDA GLM*
- HR 0.75, p=0.2696
- HR 0.58, p=0.0370

*FDA Briefing Book; GLM: generalized linear model
Sotagliflozin Added to Insulin Provided
Improvement in Glycemic Control vs Insulin Alone

- Significant reductions in A1c vs placebo at Weeks 24 and 52
- Benefits beyond A1c reduction
  - PPG and time in range
  - Reductions in body weight and systolic blood pressure
  - Improvement in PROs
- Hypoglycemia data relevant
  - Glycemic control without higher symptomatic and severe hypoglycemia seen on insulin alone
  - Supports use of sotagliflozin
Clinical Safety Results

Klaus Henning Jensen, MD
Head of Diabetes, Cardiovascular and Metabolism Development
Sanofi
Safety Overview

- Sotagliflozin generally well-tolerated
- Class-related effects (genital mycotic infection, volume depletion) consistent with SGLT2 inhibitor class
- Increased risk of ketosis and DKA
  - Risk consistent with off-label SGLT2 inhibitor use
- DKA effectively managed through risk management plan
  - Learnings from clinical trial, off-label SGLT2 use, and expert clinical guidance
## Safety Exposure

- Safety database included 30 clinical studies

<table>
<thead>
<tr>
<th></th>
<th>Patients Treated with Sotagliflozin</th>
<th>Sotagliflozin Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Patient Years</td>
</tr>
<tr>
<td>Phase 3 Studies 309 / 310 T1D (52 weeks)</td>
<td>1,049</td>
<td>957</td>
</tr>
<tr>
<td>Phase 2 / 3 Studies T1D</td>
<td>1,915</td>
<td>1,290</td>
</tr>
<tr>
<td>Phase 2 / 3 Studies T1D and T2D</td>
<td>2,175</td>
<td>1,343</td>
</tr>
</tbody>
</table>
## Pooled 309 / 310: Overview of Adverse Events

<table>
<thead>
<tr>
<th>Patients with AEs</th>
<th>Placebo N=526</th>
<th>Sotagliflozin 200 mg N=524</th>
<th>Sotagliflozin 400 mg N=525</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE</strong></td>
<td>71.1%</td>
<td>75.0%</td>
<td>74.3%</td>
</tr>
<tr>
<td><strong>Any AE leading to discontinuation</strong></td>
<td>3.8%</td>
<td>4.4%</td>
<td>6.7%</td>
</tr>
<tr>
<td><strong>DKA</strong></td>
<td>0%</td>
<td>0.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>0.4%</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td><strong>Any SAE</strong></td>
<td>7.0%</td>
<td>10.1%</td>
<td>9.5%</td>
</tr>
<tr>
<td><strong>DKA</strong></td>
<td>0.6%</td>
<td>3.6%</td>
<td>5.0%</td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td>1.0%</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td><strong>Deaths (all Phase 2 / 3 studies)</strong></td>
<td>3 (0.2) (0.2)</td>
<td>0 (0)</td>
<td>1 (0.08)</td>
</tr>
</tbody>
</table>

*DKA, diarrhea, hypoglycemia shown here are investigator-reported events*
Events of Special Interest (EOSI) Evaluated in Sotagliflozin T1D Program

- Documented and Severe Hypoglycemia*
- DKA*
- Major Adverse Cardiovascular Events (MACE)*
- Drug induced liver injury (DILI)*
- Genital mycotic infection
- Volume depletion
- UTI
- Amputation
- Renal events
- Bone fracture
- Diarrhea
- Malignancy

* Events Adjudicated by Clinical Events Committees (CECs)
Changes in Early Clinical Features of DKA with SGLT2 Inhibitors

Early symptoms and signs
- High blood glucose levels
- Increased urination
- Increased thirst
- High ketone levels

Later ketosis-related symptoms and signs
- Weakness, sleepiness
- Dry, flushed skin
- Nausea, vomiting, abdominal pain
- Difficulty breathing, fruity breath

Phase 2 / 3 T1D Studies: CEC Assessment of Potential DKA Events

<table>
<thead>
<tr>
<th>All ketosis-related AEs</th>
<th>Placebo Patients N=1,307</th>
<th>Sotagliflozin Patients N=1,896</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>36 Patients (2.8%)</td>
<td>194 Patients (10.2%)</td>
</tr>
<tr>
<td></td>
<td>(41 events)</td>
<td>(274 events)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Possible DKA / metabolic acidosis EOSI</th>
<th>Placebo Patients</th>
<th>Sotagliflozin Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17 Patients (1.3%)</td>
<td>103 Patients (5.4%)</td>
</tr>
<tr>
<td></td>
<td>(17 events)</td>
<td>(109 events)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positively-adjudicated metabolic acidosis</th>
<th>Placebo Patients</th>
<th>Sotagliflozin Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 Patients (0.7%)</td>
<td>64 Patients (3.4%)</td>
</tr>
<tr>
<td></td>
<td>(9 events)</td>
<td>(65 events)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positively-adjudicated DKA</th>
<th>Placebo Patients</th>
<th>Sotagliflozin Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 Patients (0.5%)</td>
<td>57 Patients (3.0%)</td>
</tr>
<tr>
<td></td>
<td>(6 events)</td>
<td>(58 events)</td>
</tr>
</tbody>
</table>
## All Phase 2 / 3 T1D Studies: Incidence of Positively-Adjudicated DKA

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>All Sotagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1,307</td>
<td>N=1,896</td>
</tr>
<tr>
<td><strong>Frequency of patients with DKA</strong></td>
<td>6 (0.5%)</td>
<td>57 (3.0%)</td>
</tr>
<tr>
<td><strong>EAIR for DKA, per 100 PY</strong></td>
<td>0.7 (0, 1.4)</td>
<td>4.1 (3.0, 5.2)</td>
</tr>
<tr>
<td><strong>Relative Risk of the EAIR, vs placebo</strong></td>
<td>-</td>
<td>6.6 (3.0, 17.1)</td>
</tr>
<tr>
<td><strong>Risk Difference of EAIR, minus placebo</strong></td>
<td>-</td>
<td>3.6 (2.5, 4.8)</td>
</tr>
</tbody>
</table>

EAIR: Exposure Adjusted Incidence Rate
Rates, ratios, and risk differences calculated using stratification to take into account differences in protocol design across phase 2 / 3 studies.
**Pooled 309 / 310: Numerical Increase in DKA Risk**

<table>
<thead>
<tr>
<th></th>
<th>Placebo N=526</th>
<th>Sotagliflozin 200 mg N=524</th>
<th>Sotagliflozin 400 mg N=525</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of patients with DKA</strong></td>
<td>1 (0.2%)</td>
<td>15 (2.9%)</td>
<td>20 (3.8%)</td>
</tr>
<tr>
<td><strong>EAIR for DKA, per 100 PY</strong></td>
<td>0.2 (0.6)</td>
<td>3.1 (1.5, 4.7)</td>
<td>4.2 (2.4, 6.0)</td>
</tr>
<tr>
<td><strong>Relative Risk of the EAIR, vs placebo (95% CI)</strong></td>
<td>- (2.7, 315.0)</td>
<td>14.8 (2.7, 315.0)</td>
<td>19.9 (3.7, 416.3)</td>
</tr>
<tr>
<td><strong>Risk Difference of EAIR, minus placebo (95% CI)</strong></td>
<td>2.9 (1.3, 4.5)</td>
<td>4.0 (2.1, 5.9)</td>
<td></td>
</tr>
<tr>
<td>DKA Events</td>
<td>Placebo N=6</td>
<td>All Sotagliflozin N=58</td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------</td>
<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Classified as SAE</td>
<td>5 (83%)</td>
<td>56 (97%)</td>
<td></td>
</tr>
<tr>
<td>Fatal</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>5 (83%)</td>
<td>54 (93%)</td>
<td></td>
</tr>
<tr>
<td>Mean DKA duration, days</td>
<td>5.5</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Event severity*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3 (50%)</td>
<td>8 (14%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>3 (50%)</td>
<td>30 (52%)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>20 (34%)</td>
<td></td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>1 (17%)</td>
<td>23 (40%)</td>
<td></td>
</tr>
</tbody>
</table>

* Presented severity data using modified ADA Consensus severity criteria (without glucose criterion > 250 mg/dl), rather than investigator-reported severity.
## Pooled 309 / 310: No Events of DKA in Patients with BG < 150 mg/dL

<table>
<thead>
<tr>
<th>Blood Glucose Level</th>
<th>Placebo N=1</th>
<th>Sotagliflozin 200 mg N=16</th>
<th>Sotagliflozin 400 mg N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 250 mg/dL (&gt; 13.9 mmol/L)</td>
<td>1 (100%)</td>
<td>8 (50%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>150 to 250 mg/dL (8.3 to 13.9 mmol/L)</td>
<td>0</td>
<td>8 (50%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>&lt; 150 mg/dL (&lt; 8.3 mmol/L)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Plasma Glucose and BHB Levels During Control and Canagliflozin Treatment Studies

Recreated from Figure 1 from Patel et al., Diabetes Technology & Therapeutics, 2017
## Phase 2 / 3 T1D Studies: DKA Triggers Inform Risk Management Strategy

<table>
<thead>
<tr>
<th>DKA Triggers</th>
<th>Placebo N=6</th>
<th>All Sotagliflozin N=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute infection or illness</td>
<td>2 (33%)</td>
<td>26 (45%)</td>
</tr>
<tr>
<td>Insulin reduction or interruption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin reduction / missed dose</td>
<td>1 (17%)</td>
<td>9 (16%)</td>
</tr>
<tr>
<td>Pump interruption</td>
<td>1 (17%)</td>
<td>18 (31%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>2 (33%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Low carb diet</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Excess exercise</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>No identified triggers</td>
<td>1 (17%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>
Evaluation of Potential DKA Risk Factors

- Analyses performed to evaluate potential DKA risk factors
  - Baseline patient characteristics
  - Relationship between insulin dose and DKA
- No subgroup identified with substantial increase in DKA risk above general trial population
- Several factors independent of sotagliflozin, identified with modest association to DKA risk
  - Higher risk: Prior DKA history, insulin pump use, and female
  - Lower risk: Higher insulin doses or no insulin dose reduction
- Findings used to inform DKA risk management strategy
Postmarketing DKA Reports with SGLT2 Inhibitors (MarketScan Database)

- Experience from off-label use of available SGLT2 inhibitors
- Evaluation of incidence rates of hospitalization for DKA
- MarketScan: large US-based healthcare claims database
- Incidence rates for DKA in patients with T1D using SGLT2 inhibitors vs patients not on these drugs
Hospitalized DKA in Adult T1D Patients Stratified by Use of SGLT2 Inhibitors (MarketScan Database, 2013-2017)

Incidence Rate (per 100 PY)

- **SGLT2 inhibitor cohort**
  - 2013: 15.7
  - 2014: 4.9
  - 2015: 7.9
  - 2016: 7.0
  - 2017: 5.1

- **Non-SGLT2 inhibitor cohort**
  - 2013: 4.9
  - 2014: 5.0
  - 2015: 6.0
  - 2016: 5.3
  - 2017: 4.2

Number of patients at risk

<table>
<thead>
<tr>
<th>Year</th>
<th>SGLT2 inhibitor cohort</th>
<th>Non-SGLT2 inhibitor cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>411</td>
<td>124,742</td>
</tr>
<tr>
<td>2014</td>
<td>2,049</td>
<td>117,262</td>
</tr>
<tr>
<td>2015</td>
<td>2,341</td>
<td>89,062</td>
</tr>
<tr>
<td>2016</td>
<td>1,842</td>
<td>85,283</td>
</tr>
<tr>
<td>2017</td>
<td>1,327</td>
<td>73,682</td>
</tr>
</tbody>
</table>

**FDA Warning and community awareness of euglycemic DKA**
Measures Taken in Clinical Program to Minimize DKA Risk

- Initial steps
  - Exclusion of patients with recent DKA or elevated screening BHB
- Following FDA DKA warnings (2015)
  - Communication about Euglycemic DKA risk with SGLT2 inhibitors
  - Additional education for patients and investigators
    - Signs and symptoms for ketosis / DKA
    - Circumstances which may increase risk (surgery, infection, etc)
    - Guidance on early intervention and avoidance of progression
  - Provision of urine ketone sticks and blood BHB meters
Effect of Enhanced Risk Mitigation on DKA Rate in Clinical Trials (2015-2017)

Mean Rate of DKA (per 100 PY) [95% CI]

Before March 31, 2016
21 events | 376.3 patient-years
Mean Rate: 5.6

After April 1, 2016
37 events | 1068.3 patient-years
Mean Rate: 3.5
Risk Management Strategy

- Patient Selection
- Ketone Monitoring
- Adequate Insulin Dosing

Broad Risk Communication
Appropriate Patient Selection

- Disease not controlled on SOC (intensive insulin therapy)
- Engaged patients capable of day-to-day management of T1D
  - Adept at managing insulin dose adjustments
  - Recognize at-risk situations and apply sick-day rules
  - Willingness to monitor ketones essential
- Do not start sotagliflozin
  - Recent or recurrent DKA
  - Ketosis at baseline
  - Risk for ketosis (e.g. excessive alcohol use, ketogenic diets)
Ketone Monitoring and Management

- Check ketones before and after starting treatment
- Insulin pump patients check ketones 3-4 hours after infusion set or component changes
- Stop sotagliflozin and seek medical attention
  - Mildly elevated ketones with clinical symptoms of ketosis / DKA
  - Moderately elevated ketones regardless of symptoms
- Consider restarting sotagliflozin
  - Complete event resolution
  - Correction of precipitating factors
Maintenance of Adequate Insulin Dosing

- Optimize insulin prior to starting therapy
- Cautious insulin reductions after starting sotagliflozin to avoid ketosis / DKA
- Consider discontinuing sotagliflozin if adequate insulin dosing cannot be achieved
Risk Communication Plan Targeting Both Healthcare Providers and Patients

**Healthcare Providers**
- Product Labeling
  - Core of DKA risk communication
- HCP Communication Letter
  - Sent within 60 days of approval
  - DKA identification and management
  - Target 1 million HCPs

**Patients**
- Patient Alert Card
  - In product carton
  - Signs / symptoms, triggers, and management
  - Portable - shown to HCPs in acute care setting
- Medication Guide and Website
  - Distributed with each prescription fill
  - Complete information on product safety and DKA
# Broad Risk Communication to Further Enhance DKA Messaging

## Healthcare Providers

- Scientific programs to discuss T1D and DKA management
- Educational materials delivered to HCPs
- Publications
- National Congress Meetings
- Promotional speaker programs

## Patients

- Patient Alert Card
- Education and messaging at point of care
- Patient tip sheet
- Patient education video
- Nurse outreach via the PSP
- Welcome email communication
- PSP SMS messaging
Post-Marketing Assessments to Evaluate Effectiveness of DKA Risk Mitigation

- Post-Authorization Safety Study (PASS)
  - Further monitor DKA risk in real-world setting
  - Compare risk of DKA with sotagliflozin to insulin alone
- Drug utilization study
  - Evaluate prevention, diagnosis, and treatment of DKA in patients treated with sotagliflozin
- Prescriber survey to assess effectiveness of risk communication
Sotagliflozin Safety Supports Use as Adjunct to Insulin in Patients with T1D

- Well-tolerated
- Safety profile largely consistent with SGLT2 class
- Less hypoglycemia vs insulin alone
- Increased risk of DKA
  - 3-4 excess cases per 100 PY
  - Well-characterized and consistent with class
  - Anticipated based upon MoA
  - Predictable with recognized triggers amenable to enhanced “for cause” ketone monitoring to prevent progression
Risk Management Plan Developed to Effectively Mitigate DKA Risk

- Feasibility suggested by SGLT2 inhibitor experience
  - Incidence rates comparable to standard of care therapy
- Plan focused on appropriate patient selection, targeted ketone monitoring, and maintenance of adequate insulin dosing
  - Supported through broad communication plan targeting key medical and patient stakeholders
Clinical Perspective

Juan Pablo Frias, MD

Medical Director and Principal Investigator
National Research Institute
Majority of Adults with T1D Not Achieving Glycemic Goals

- Challenges of insulin therapy
  - Weight gain, excessive glycemic variability, and hypoglycemia
- Hypoglycemia a leading cause of diabetes-related death in patients with T1D
- Patients and HCPs need adjunctive therapeutic agents
- Sotagliflozin meets needs in appropriate patients with T1D
Appropriate Patients for Sotagliflozin

- Not achieving glycemic targets with insulin alone
- Significant glycemic variability
- Frequent hypoglycemia
- Because of known risk of DKA
  - Engaged patients
  - Willingness and ability to optimize insulin
  - Monitor ketones
  - Communicate to HCP
Patients NOT Appropriate for Sotagliflozin

- Not achieved best possible results with insulin alone
- Recurrent or unexplained DKA
- Ketogenic diet
- Not demonstrated ability to self-manage disease
- Difficulties complying with treatment plan
How I Will Use Sotagliflozin in Practice

- Instruct patients on risks and how to prevent, recognize, self-treat, and when to contact clinic
- Prevention and treatment of DKA in T1D ongoing practice
- STICH Protocol\(^1\)
  - Treatment and prevention of DKA in patients using SGLT inhibitors

1. Garg, 2018
Proposed Safety Plan Will Mitigate DKA Risk

- Proposed steps commonplace in clinical care
  - Appropriate selection, patient education, and monitoring
- Sponsor’s plan will further educate patients and HCPs and help reduce DKA
- MarketScan claims data reassuring that awareness and education over time will reduce incidence of DKA
Positive Benefit / Risk Ratio of Sotagliflozin

- Addresses unmet need in patients with T1D
- Reductions in A1c, body weight, and systolic blood pressure
- Improvement in time in range
- Patients more satisfied and less distressed than insulin alone
- Sotagliflozin much needed tool for HCPs
Sotagliflozin as an Adjunct to Insulin for Type 1 Diabetes

January 17, 2019
Sanofi / Lexicon Pharmaceuticals
Endocrinologic and Metabolic Drugs Advisory Committee
BACK-UP SLIDES SHOWN
Study 309 / 310: Time in Range (70 - 180 mg/dL)

**Study 309**
- N=45
- LS Mean Change from Baseline in Time in Range (% [95% CIs]:
  - Placebo: -1.8 (-26 mins)
  - Sotagliflozin 200 mg: 1.2 (17 mins)
  - Sotagliflozin 400 mg: 8.6* (124 mins)

**Study 310**
- N=48
- LS Mean Change from Baseline in Time in Range (% [95% CIs]:
  - Placebo: -0.7 (-10 mins)
  - Sotagliflozin 200 mg: 7.8** (112 mins)
  - Sotagliflozin 400 mg: 12.7* (183 mins)

* Nominal p-value < 0.001
** Nominal p-value = 0.044
### 2-Item Diabetes Distress Screening Scale (DDS2)

Listed below are 2 potential problem areas that people with diabetes may experience.

Each of the 2 items may have distressed or bothered you DURING THE PAST MONTH and circle the appropriate number.

<table>
<thead>
<tr>
<th>Item</th>
<th>Not a problem</th>
<th>A Slight Problem</th>
<th>A Moderate Problem</th>
<th>Somewhat Serious Problem</th>
<th>A Serious Problem</th>
<th>A Very Serious Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling overwhelmed by the demands of living with diabetes.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>2. Feeling that I am often failing with my diabetes routine.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
Pooled 309 / 310: A1c Reduction (%) at Week 24 by Baseline A1c

Baseline A1c

≤ 7.0% to < 7.5% 7.5% to < 8.0% 8.0% to < 8.5% 8.5% to < 9.0% ≥ 9.0%

LS Mean Change in A1c from Baseline (%)

[95% CI]

N=95 100 97 141 122 143 129 126 131 72 96 78 53 47 40 36 33 36

Placebo Sotagliflozin 200 mg Sotagliflozin 400 mg
## Risk Difference of DKA and Severe Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Risk Difference per 100 PY (95% CI) at Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DKA</strong></td>
<td></td>
</tr>
<tr>
<td>N=524 200 mg vs placebo</td>
<td></td>
</tr>
<tr>
<td>N=525 400 mg vs placebo</td>
<td></td>
</tr>
<tr>
<td><strong>Severe hypoglycemia</strong></td>
<td></td>
</tr>
<tr>
<td>N=524 200 mg vs placebo</td>
<td></td>
</tr>
<tr>
<td>N=525 400 mg vs placebo</td>
<td></td>
</tr>
</tbody>
</table>

- Favors Sotagliflozin
- Favors Placebo
## Pooled 309 / 310: Sotagliflozin 200 mg and 400 mg Dose Comparison

<table>
<thead>
<tr>
<th>Improvements Beyond A1c</th>
<th>Parameter</th>
<th>Treatment Difference vs Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg</td>
<td>400 mg</td>
</tr>
<tr>
<td>Daily Glycemic Control</td>
<td>Time in range</td>
<td>+ 1h 17 m</td>
</tr>
<tr>
<td></td>
<td>FPG (mg/dL)</td>
<td>-15.7</td>
</tr>
<tr>
<td></td>
<td>PPG (mg/dL)</td>
<td>-34.8</td>
</tr>
<tr>
<td></td>
<td>Severe hypoglycemia (per 100 PY)*</td>
<td>-2.0</td>
</tr>
<tr>
<td>Other Benefits</td>
<td>SBP (mmHg)</td>
<td>-2.0</td>
</tr>
<tr>
<td></td>
<td>Body weight (kg)</td>
<td>-2.2</td>
</tr>
</tbody>
</table>

*Risk Reference of EAIR, 52 week data
## Additional DKA Risk Mitigation Measures: Beyond Clinical Trial Activities

<table>
<thead>
<tr>
<th>More specific patient selection</th>
<th>- Willingness and ability to perform ketone monitoring. Strong T1D disease management understanding.</th>
</tr>
</thead>
</table>
| More specific ketone monitoring and mitigation instructions | - Start treatment only if values normal at baseline. Check after initiation of treatment  
- Assess ketones: e.g. with changes to diet or exercise, pump set changes or during acute illness  
- Hold Sotagliflozin:  
  - If BHB between 0.6 to ≤ 1.5 or urine ketones = 1+ and symptoms  
  - If BHB > 1.5 or urine ketone ≥ 2  
- Hydrate, take carbs, insulin and call doctor when holding Sotagliflozin |
| Insulin dose guidance | - Maintain Adequate insulinization  
- Insulin dose reductions should be done cautiously to avoid ketosis and diabetic ketoacidosis |
| Extensive and specific risk communication | - Educate on risk, importance of ketone monitoring, mitigation  
- Communication to prescribers, non-prescribers, and patients  
- Publications |
### Phase 2 / 3 T1DM Studies: Treatment-Emergent Genital Mycotic Infections – Safety Population

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>Sotagliflozin 200 mg</th>
<th>Sotagliflozin 400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>N=1324</td>
<td>N=559</td>
<td>N=1321</td>
</tr>
<tr>
<td>Female</td>
<td>N=672</td>
<td>N=274</td>
<td>N=660</td>
</tr>
<tr>
<td>Exposure-adjusted Incidence Rate (EAIR) per 100 Subject-years</td>
<td>6.4 (3.9, 8.9)</td>
<td>17.1 (11.9, 22.4)</td>
<td>22.3 (17.6, 26.9)</td>
</tr>
<tr>
<td>Male</td>
<td>N=652</td>
<td>N=285</td>
<td>N=661</td>
</tr>
<tr>
<td>Exposure-adjusted Incidence Rate (EAIR) per 100 Subject-years</td>
<td>1.2 (0.2, 2.3)</td>
<td>3.2 (1.0, 5.4)</td>
<td>5.8 (3.4, 8.1)</td>
</tr>
</tbody>
</table>
## Phase 2 / 3 T1DM Studies: Summary of Characteristics of TEAE of GMI – Sex and Severity

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo N=1,324</th>
<th>Sotagliflozin 200 mg N=559</th>
<th>Sotagliflozin 400 mg N=1,321</th>
</tr>
</thead>
<tbody>
<tr>
<td>All GMI Events (subject, %, event)</td>
<td>30 (2.2) 45</td>
<td>49 (8.8) 61</td>
<td>111 (8.4) 173</td>
</tr>
<tr>
<td>Severe events</td>
<td>0</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Male (subject, %, event)</td>
<td>5 (0.8) 6</td>
<td>8 (2.8) 9</td>
<td>23 (3.5) 29</td>
</tr>
<tr>
<td>Severe events</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Female (subject, %, event)</td>
<td>25 (3.7) 39</td>
<td>41 (15.0) 52</td>
<td>88 (13.3) 144</td>
</tr>
<tr>
<td>Severe events</td>
<td>0</td>
<td>1 (0.4)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
## Absolute Risk of DKA: Consistent Rates of DKA Among SGLT Inhibitors in T1D Clinical Trials and Real World Data

<table>
<thead>
<tr>
<th></th>
<th>Approximate Events per 100 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1D Clinical Trials</td>
</tr>
<tr>
<td><strong>Sotagliflozin</strong></td>
<td>3.6</td>
</tr>
<tr>
<td><strong>Empagliflozin(^1)</strong></td>
<td>5.5</td>
</tr>
<tr>
<td><strong>Dapagliflozin(^2)</strong></td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Canagliflozin</strong></td>
<td>N/A</td>
</tr>
</tbody>
</table>

1. Diabetes Care, 2018 Oct; dc181749 (empagliflozin clinical trial); 2. Diabetes Care, 2018 Oct; dc181087 (dapagliflozin clinical trials); 3. Figure 32 FDA Briefing Doc
### Total Hospitalizations – Severe Hypoglycemia and DKA

<table>
<thead>
<tr>
<th></th>
<th>Placebo Events / Patients</th>
<th>All Sotagliflozin Events / Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Hospitalizations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(All Phase 3)</td>
<td>62 / 1,229</td>
<td>126 / 1,748</td>
</tr>
<tr>
<td><strong>SH Hospitalizations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(All Phase 3)</td>
<td>8 / 1,229</td>
<td>6 / 1,748</td>
</tr>
<tr>
<td><strong>DKA Hospitalizations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(All Phase 2/3)</td>
<td>5 / 1,307</td>
<td>54 / 1,896</td>
</tr>
</tbody>
</table>

- Most severe hypoglycemia episodes occur outside of hospital
- Most DKA events require hospitalization
**Pooled 309 / 310 (mITT): Placebo-Corrected UACR Percent Changes in Micro/Macroalbuminuria (≥ 30 mg/g)**

---

**Macro/Microalbuminuria (UACR ≥ 30 mg/g)**

- **SOTA 200 mg**
- **SOTA 400 mg**

Weeks: 0 12 24 52

- Placebo, n: 63 60 59 45
- SOTA 200 mg, n: 74 72 69 57
- SOTA 400 mg, n: 59 59 58 47

\[ p = 0.30 \]
\[ p = 0.18 \]
\[ p = 0.020 \]
\[ p = 0.054 \]
\[ p = 0.16 \]
\[ p = 0.0032 \]

*Geometric mean was estimated from MMRM model.*
### Phase 2 / 3 T1D and T2D Studies: Positively Adjudicated MACE

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Sotagliflozin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n / N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>7 / 1388 (0.50%)</td>
<td>0.68</td>
<td>(0.251, 1.822)</td>
</tr>
<tr>
<td>CV death</td>
<td>2 / 1388 (0.1%)</td>
<td>&lt; 0.01</td>
<td>(0 , - )</td>
</tr>
<tr>
<td>Non-fatal MI including silent MI</td>
<td>4 / 1388 (0.28%)</td>
<td>1.07</td>
<td>(0.321, 3.577)</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>2 / 1388 (0.14%)</td>
<td>0.25</td>
<td>(0.023, 2.798)</td>
</tr>
</tbody>
</table>

Includes data from 7 completed T1D and T2D studies
Study 309: Enrollment Flow Diagram

Excluded* n=267
- Inclusion criteria not met n=149
- Exclusion criteria met n=68
- Patient decision n=39
- Consent withdrawn n=7
- Physician decision n=2
- Noncompliance n=2
- Sponsor decision n=1

Screened N=1,099

Single-blind Placebo Run-in n=832

Discontinued* n=39
- Patient decision n=14
- Exclusion criteria met n=10
- Inclusion criteria not met n=6
- Noncompliance n=5
- Physician decision n=2
- Consent withdrawn n=2
- Lost to follow-up n=1

*patients could be included more than once
## Improvement in DTSQs Individual Items

<table>
<thead>
<tr>
<th>Individual DTSQs Items</th>
<th>Study 309</th>
<th></th>
<th>Study 310</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=268</td>
<td>200 mg N=263</td>
<td>400 mg N=262</td>
<td>Placebo N=258</td>
</tr>
<tr>
<td>How satisfied are you with your current treatment?</td>
<td>0.0 (1.39)</td>
<td>0.4 (1.24)</td>
<td>0.4 (1.14)</td>
<td>0.0 (1.21)</td>
</tr>
<tr>
<td>How often have you felt that your blood sugars have been unacceptably high recently?</td>
<td>0.1 (1.57)</td>
<td>-0.7 (1.53)</td>
<td>-0.7 (1.69)</td>
<td>0.0 (1.40)</td>
</tr>
<tr>
<td>How often have you felt that your blood sugars have been unacceptably low recently?</td>
<td>0.2 (1.54)</td>
<td>-0.2 (1.65)</td>
<td>-0.2 (1.42)</td>
<td>-0.1 (1.49)</td>
</tr>
<tr>
<td>How convenient have you been finding your treatment to be recently?</td>
<td>0.1 (1.40)</td>
<td>0.7 (1.23)</td>
<td>0.6 (1.25)</td>
<td>0.1 (1.20)</td>
</tr>
<tr>
<td>How flexible have you been finding your treatment to be recently?</td>
<td>0.2 (1.52)</td>
<td>0.6 (1.43)</td>
<td>0.4 (1.34)</td>
<td>0.1 (1.17)</td>
</tr>
<tr>
<td>How satisfied are you with your understanding of your diabetes?</td>
<td>0.0 (0.88)</td>
<td>0.3 (0.89)</td>
<td>0.3 (0.90)</td>
<td>0.0 (0.93)</td>
</tr>
<tr>
<td>Would you recommend this form of treatment to someone else with your kind of diabetes?</td>
<td>-0.4 (1.29)</td>
<td>0.2 (1.09)</td>
<td>0.2 (1.09)</td>
<td>-0.1 (1.02)</td>
</tr>
<tr>
<td>How satisfied would you be to continue with your present form of treatment?</td>
<td>-0.3 (1.26)</td>
<td>0.3 (1.15)</td>
<td>0.3 (1.08)</td>
<td>-0.2 (1.08)</td>
</tr>
</tbody>
</table>

Mean (SD) change from baseline to week 24; no p-values reported for single item change scores
## A1c Effect on Microvascular Disease Risk and Sotagliflozin Effect on Death due to SH and DKA

<table>
<thead>
<tr>
<th>Morbid Complications</th>
<th>Incidence per 10,000 PY</th>
<th>Potential % Reduction</th>
<th>Event Difference per 10,000 PY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microvascular complications</strong>¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>225</td>
<td>20%</td>
<td>-45</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>412</td>
<td>20%</td>
<td>-82</td>
</tr>
<tr>
<td>Renal disease*</td>
<td>233</td>
<td>20%</td>
<td>-47</td>
</tr>
<tr>
<td><strong>Decrease in Severe Hypoglycemia Death</strong>²</td>
<td>3 to 6</td>
<td>24 to 41%</td>
<td>-1 to -2</td>
</tr>
<tr>
<td><strong>Increase in DKA Death</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>0 to +1</td>
</tr>
</tbody>
</table>

*Persistent albuminuria ≥ 40 mg per 24 hours
1. DCCT
2. Swedish and Norwegian National Registry
Pooled 309 / 310 CGM Sub-Study: Dose Related Improvements in Glucose Variability

**CGM Standard Deviation**

- Placebo: N=93, LS Mean Change from Baseline = -1.4 (p = 0.042)
- Sotagliflozin 200 mg: N=89, LS Mean Change from Baseline = -6.0 (p = 0.002)
- Sotagliflozin 400 mg: N=96, LS Mean Change from Baseline = -8.2 (p < 0.001)

**Mean Amplitude Glycemic Excursion**

- Placebo: N=93, LS Mean Change from Baseline = -3.0 (p = 0.022)
- Sotagliflozin 200 mg: N=89, LS Mean Change from Baseline = -15.7 (p = 0.022)
- Sotagliflozin 400 mg: N=96, LS Mean Change from Baseline = -25.1 (p < 0.001)

*p-value vs placebo*
## Pooled 309 / 310: Documented Hypoglycemia by Time of Day

<table>
<thead>
<tr>
<th>Documented Hypoglycemia Event Rate (events/patient/year)</th>
<th>Placebo N=526</th>
<th>Sotagliflozin 200 mg N=524</th>
<th>Sotagliflozin 400 mg N=525</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Documented Hypoglycemia ≤ 70 mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Event Rate</td>
<td>95.6</td>
<td>81.3</td>
<td>83.7</td>
</tr>
<tr>
<td>Diurnal Event Rate</td>
<td>83.9</td>
<td>70.6</td>
<td>72.9</td>
</tr>
<tr>
<td>Nocturnal Event Rate</td>
<td>12.2</td>
<td>11.0</td>
<td>11.1</td>
</tr>
<tr>
<td><strong>Documented Hypoglycemia ≤ 55 mg/dl</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Event Rate</td>
<td>19.0</td>
<td>14.9</td>
<td>15.0</td>
</tr>
<tr>
<td>Diurnal Event Rate</td>
<td>16.3</td>
<td>12.6</td>
<td>12.7</td>
</tr>
<tr>
<td>Nocturnal Event Rate</td>
<td>2.7</td>
<td>2.3</td>
<td>2.3</td>
</tr>
</tbody>
</table>