Major Adverse Cardiovascular Events across the Sotagliflozin Clinical Development Program

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Introduction

- SGLT inhibitors, including sotagliflozin, have been shown to consistently reduce the risk of heart failure (HF) and renal-related events
- Their effects on major adverse cardiovascular events (MACE: myocardial infarction [MI] and stroke) have been variable
- In the SCORED trial, sotagliflozin was the first SGLT inhibitor to demonstrate a significant reduction in both MI and stroke in adults with type 2 diabetes (T2D) and chronic kidney disease (CKD)

Objective

- To evaluate the effect of sotagliflozin on MACE across the sotagliflozin clinical program

Methods

- The Phase 2 and Phase 3 clinical trial program included 20,292 patients with T2D or type 1 diabetes (T1D) (Table 1)

Table 1. Studies contributing to the MACE meta-analysis

Study Cohort (Study Phase)	N	Patient type	Comparator	Primary endpoint (duration)	Prespecified MACE analysis
SCORED[1] (Phase 3)	10,584	T2D, CKD, and CV risk factors	Placebo	CV endpoint *(Median follow-up 16 months)*	Total investigator-reported events
SOLOIST-WHF[2] (Phase 3)	1,222	T2D with WHF event	Placebo	CV endpoint *(Median follow-up 9 months)*	Total investigator-reported events
T2D (Nine Phase 3 trials)	5,100	T2D on diet and exercise alone or various background antihyperglycemic therapies	Placebo, n = 7, empagliflozin (EFC14867), or glimepiride (EFC14838)	Glycemic control (A1C) (Up to 79 weeks)	Adjudicated, time to first event
T1D[3-5] (Four Phase 2 [3 in T1D and 1 in T2D] and Three Phase 3)	3,386	T1D on insulin; T2D (one Phase 2 study) on various antihyperglycemic therapies	Placebo	Glycemic control (A1C) (Up to one year)	Adjudicated, time to first event

T2D = type 2 diabetes, **T1D** = type 1 diabetes, **CV** = cardiovascular, **MACE** = major adverse cardiovascular events, **WHF** = worsening heart failure

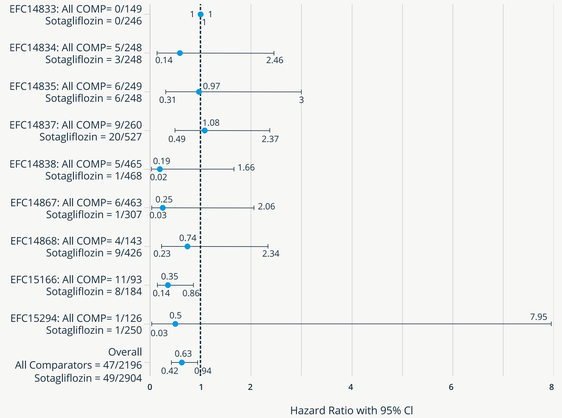
Analysis

- The analysis focused on 3-point MACE (CV death, non-fatal MI, and non-fatal stroke)
- Meta-analysis was performed using a fixed effects model regardless of prespecified MACE analysis. The overall hazards ratio (HR) and 95% confidence interval (CI) based on the fixed effects model method used *inverse variance-weighted* method to combine HRs and 95% CIs from individual analyses. Adjustments of competing events for HR were made at study level.

Results

- Across the nine Phase 3 trials in patients with T2D, trend for lower event rates with sotagliflozin versus all comparators

Figure 1. Forest plot of 3-point MACE by Phase 3 T2D study:



EFC14833 (vs. placebo [PBO] as monotherapy), EFC14834 (vs. PBO as add-on to metformin [MET]), EFC14835 (vs. PBO as add-on to sulfonylurea ± MET), EFC14837 (vs. PBO CKD3 cohort), EFC14838 (vs. PBO or glimepiride as add-on to MET), EFC14867 (vs. PBO or empagliflozin as add-on the DPP4i), EFC14868 (vs. PBO as add-on to basal insulin), EFC15166 (vs. PBO in CKD4 cohort), EFC15294 (vs. PBO in older cohort)

- The effect of sotagliflozin on MACE appeared to occur early with curves separating at approximately 3 months

Figure 2. Total CV death, non-fatal MI, and non-fatal stroke from the SCORED Trial

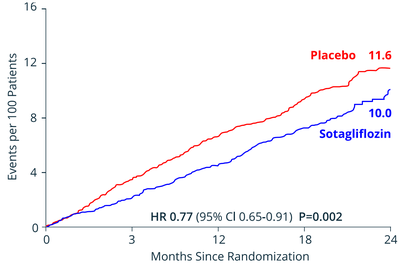


Table 2. Meta-analysis of MACE based on four distinct data sets generated in the sotagliflozin clinical program

Study Cohort (Comparator)	Comparator	Sotagliflozin	HR (95% CI)
SCORED (Placebo) Total events (rate/100PY)*	N = 5,292 442 (6.3)	N = 5,292 343 (4.5)	0.77 (0.65, 0.91)
SOLOIST (Placebo) Total events (rate/100PY)*	N = 614 80 (17.2)	N = 608 83 (17.5)	0.99 (0.72, 1.37)
Phase 3 T2D studies (Placebo, empagliflozin, or glimepiride) n (rate/100 PY)**	N = 2196 47 (2.1)	N = 2904 49 (1.6)	0.63 (0.42, 0.94)
Phase 2 and 3 T1D studies (Placebo) n (rate/100 PY)**	N = 1388 7 (0.87)	N = 1998 9 (0.69)	0.68 (0.25, 1.82)
Meta-analysis			0.79 (0.68, 0.90)

N = number of patients randomized, **n** = number of patients with events, **HR** = Hazard ratio, **CI** = confidence interval, **PY** = patient–years, **T2D** = type 2 diabetes, **T1D** = type 1 diabetes, *Total, investigator-reported events, **Adjudicated events, time to first event

Summary

- MACE results for each dataset significantly or numerically favored sotagliflozin
- SCORED contributed the most events to the analysis (74.1% of events)
- Overall, the composite of 3-point MACE was statistically lower with sotagliflozin compared with comparator (Table 1)

Conclusion

Treatment with sotagliflozin was associated with a statistically significant and clinically meaningful reduction in MACE in patients with T1D and T2D

References

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Disclosures

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