

**Meeting of the FDA's Endocrinologic and Metabolic
Drugs Advisory Committee**

Empagliflozin to Treat Patients with Type 1 Diabetes

**Testimony of Sidney Wolfe, M.D.
Health Research Group of Public Citizen**

November 13, 2019

I have no financial conflicts of interest.

Serious problems preclude FDA approval of empagliflozin, sotagliflozin, dapagliflozin for type 1 diabetes (T1D).

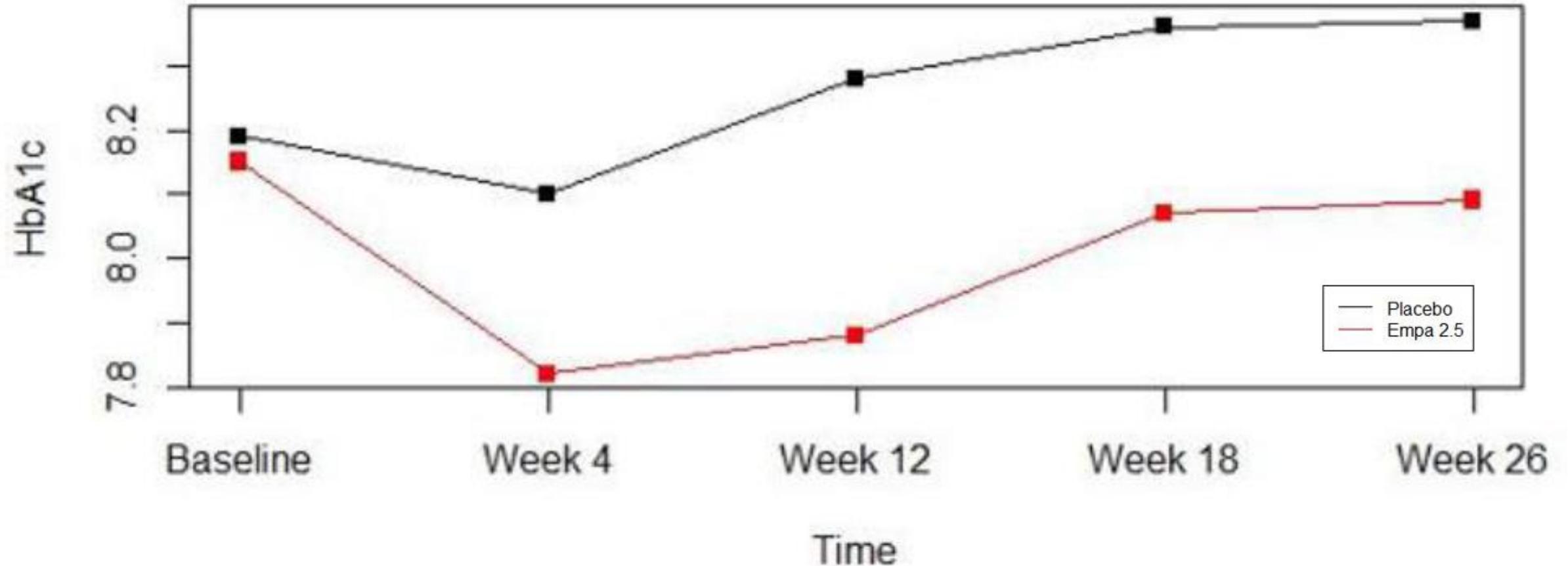
- **The surrogate marker of patient benefit, hemoglobin A1c (HbA_{1c}) improves maximally between 4 to 12 weeks after starting therapy but then starts worsening, continuing to do so for at least one year. No published studies include data for a longer time.**
- **Diabetes ketoacidosis (DKA), the life-threatening harm caused by these drugs can occur less than 3 weeks after therapy begins, continuing to occur throughout the studies.**

Thus, the harm/benefit ratio soon becomes unfavorable for patients, with continued occurrence of life-threatening DKA but decreasing benefit.

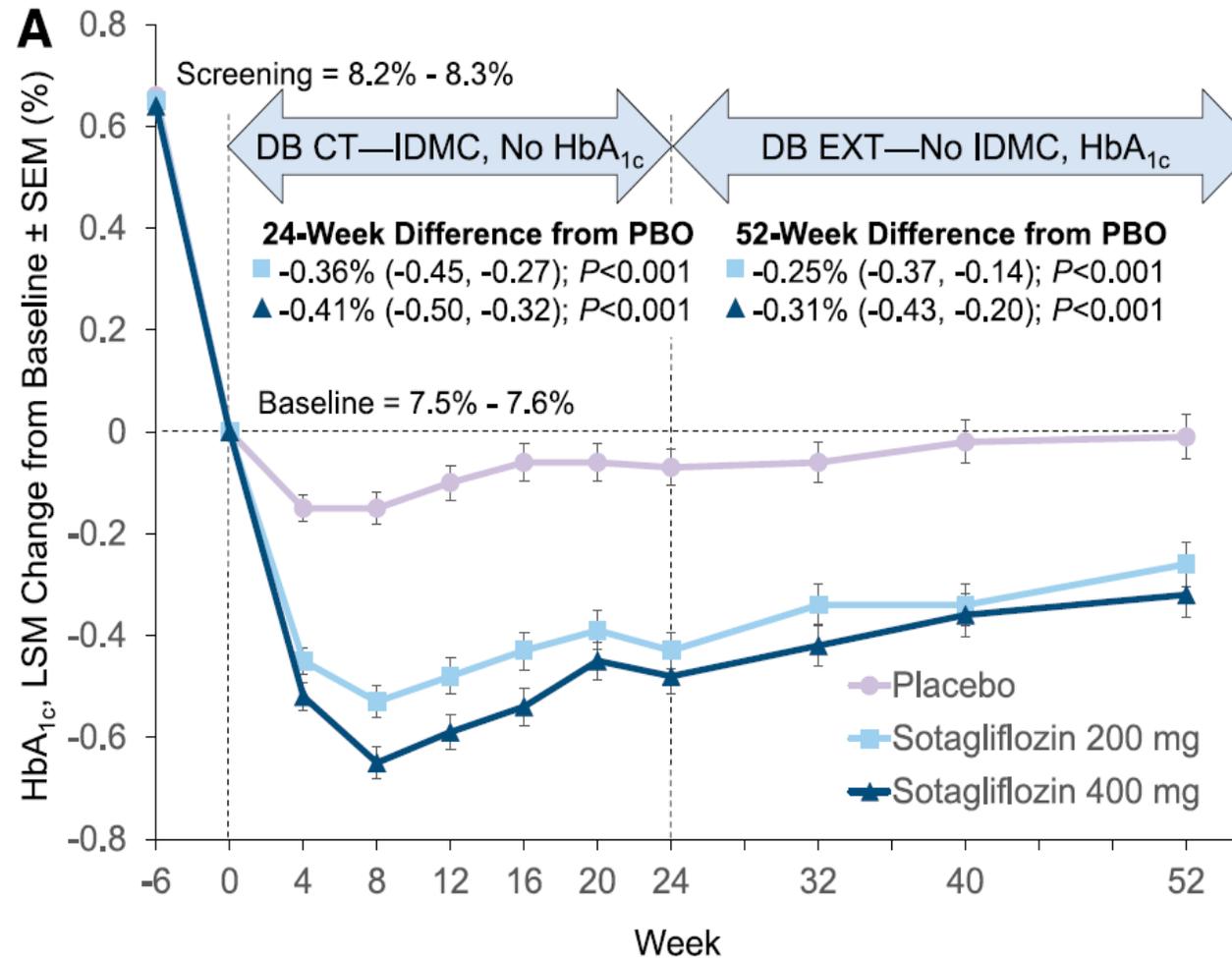
- **The belief—by industry and many physicians — that the unacceptably increased harm of DKA can ever be lessened — by using harm-mitigations strategies more stringent than used in the clinical trials — is dangerously false, lacking evidence.**

Increasing HbA_{1c} during clinical trials: empagliflozin

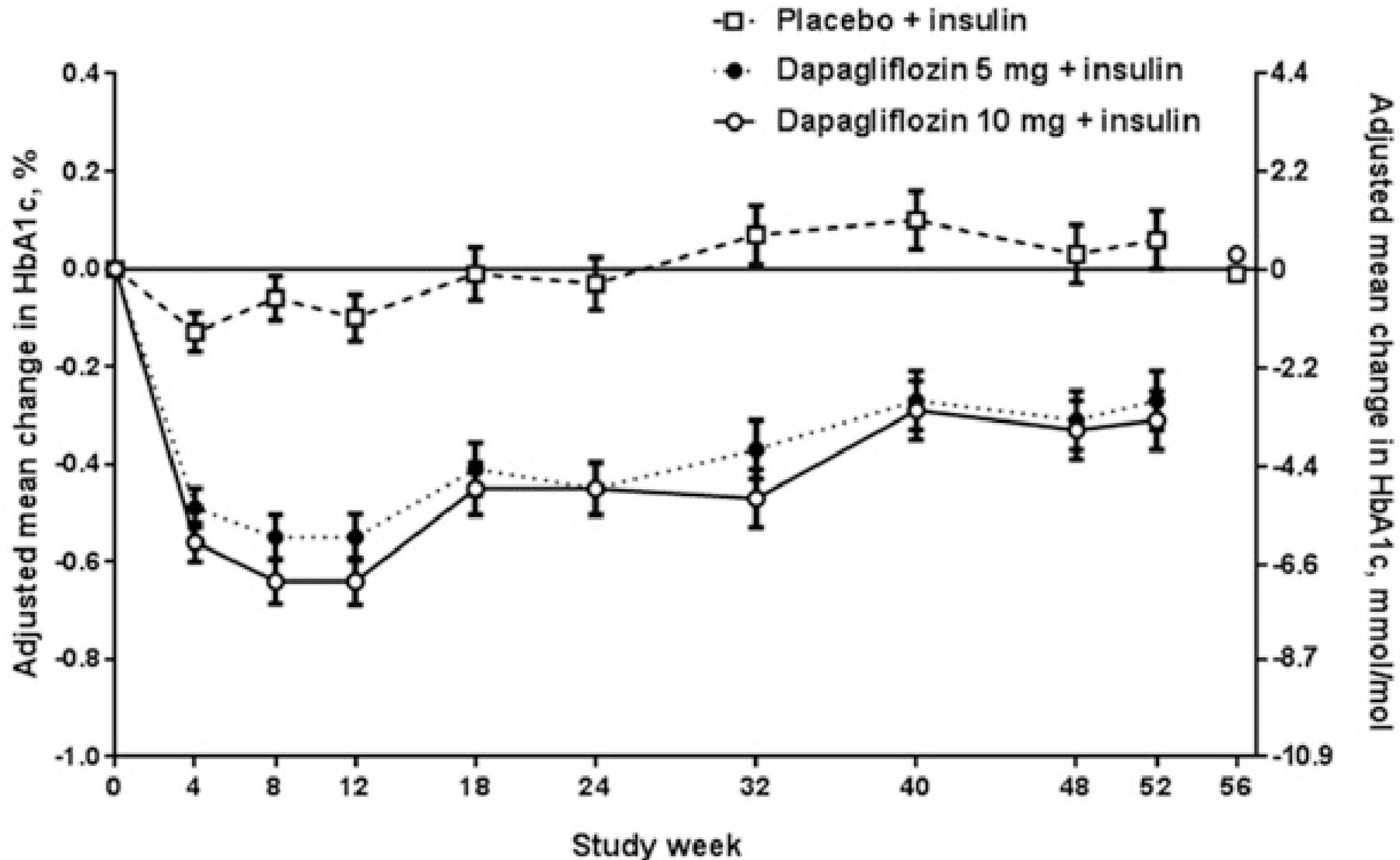
Figure 8: HbA_{1c} and total insulin over time: EASE-3



Increasing HbA1c during clinical trials: Sotagliflozin



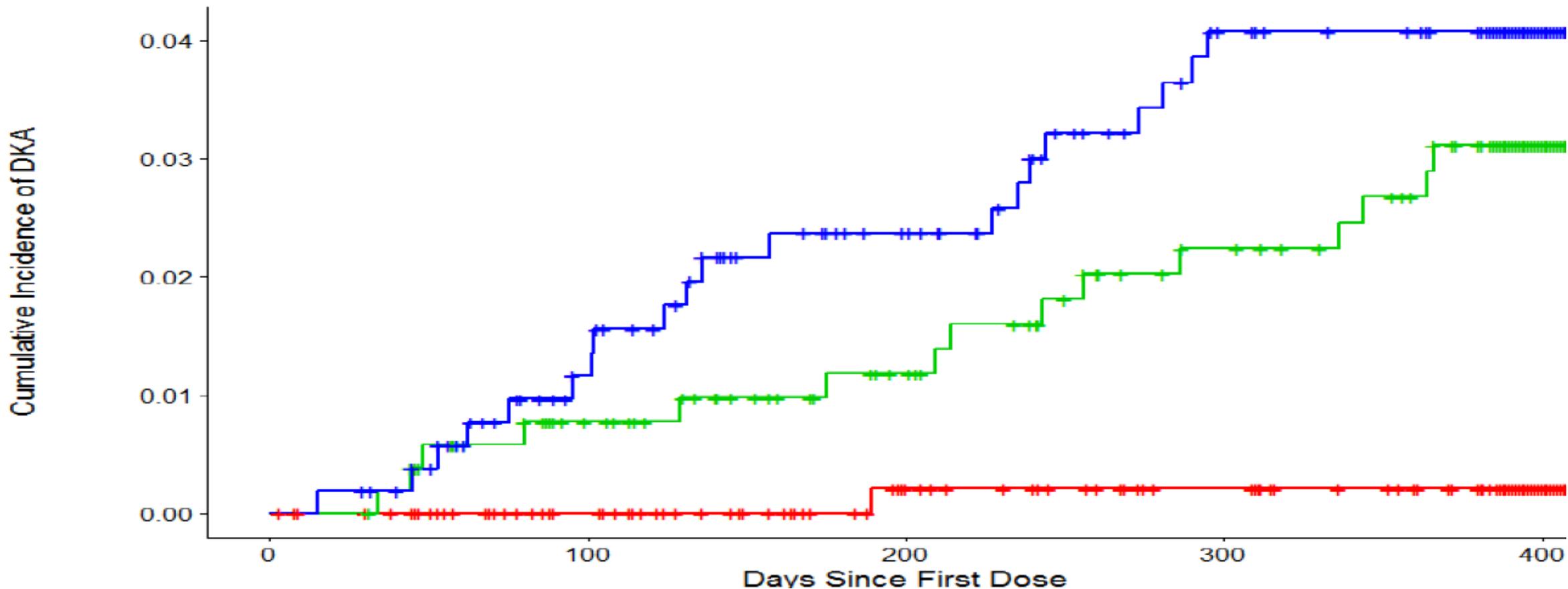
Increasing HbA_{1c} during clinical trials: dapagliflozin



Cumulative Incidence of DKA for Sotagliflozin Trials 309/310

Trials 309/310, On-Treatment Analysis (30-Day Window), CEC-Adjudicated DKAs

Strata Placebo Sota 200mg Sota 400mg



First 400 mg case: ~17 days

First 200 mg : ~33 days

First Placebo case: ~187 days

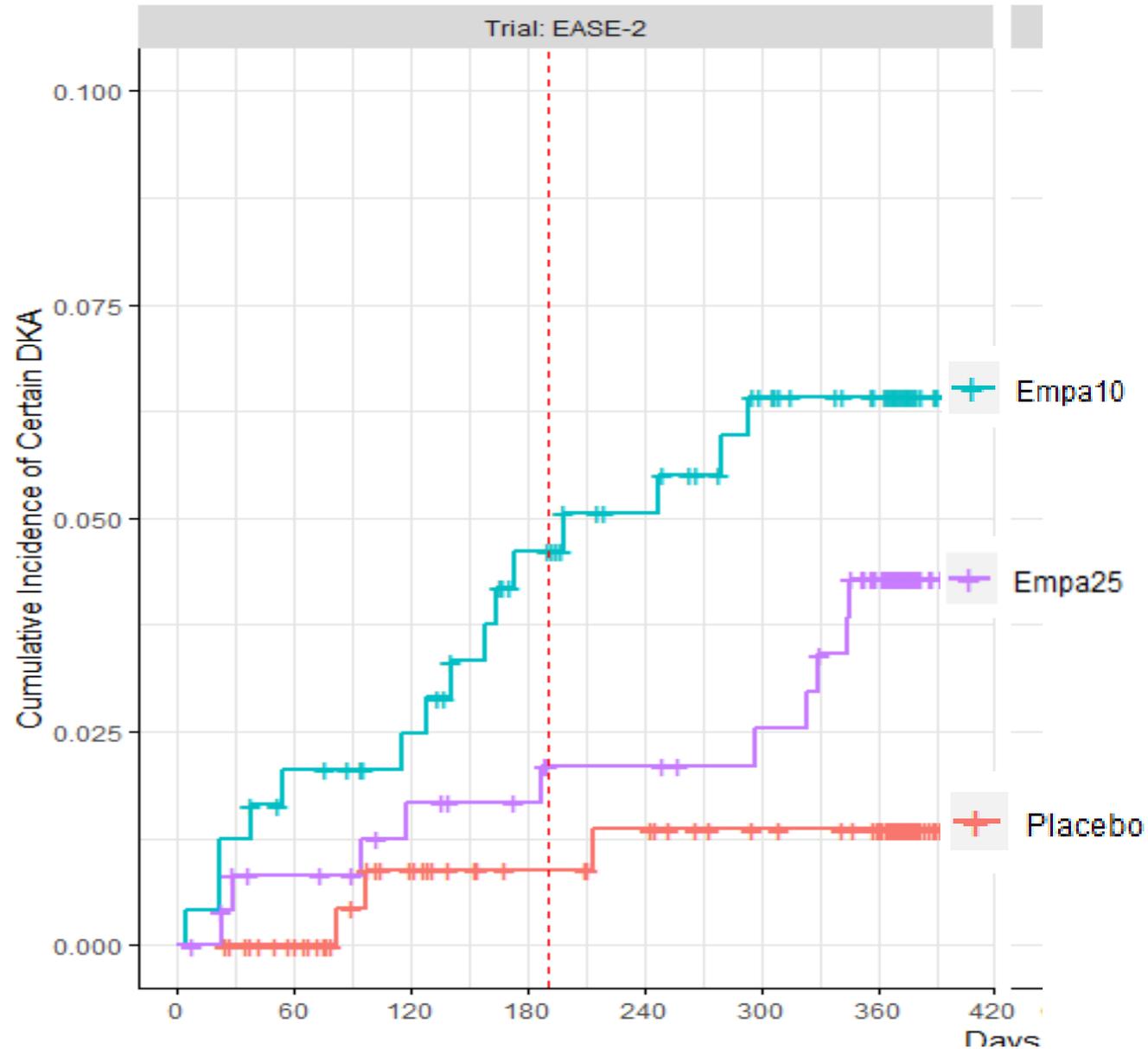
From FDA slide 65, sotagliflozin EMDAC meeting, 1/17/19

Delayed DKA appearance with lower sotagliflozin dose or/placebo

| Times of occurrences | placebo | 200 mg dose | 400 mg dose |
|-----------------------------|----------------|--------------------|--------------------|
| First case | 187 days | 33 days | 17 days |
| Cases, first 26 weeks | no case | 6 cases | 12 cases |
| Cases, rest of study | 1 case | 10 cases | 8 cases |

Data from FDA slide 65, sotagliflozin EMDAC meeting 1/17/19

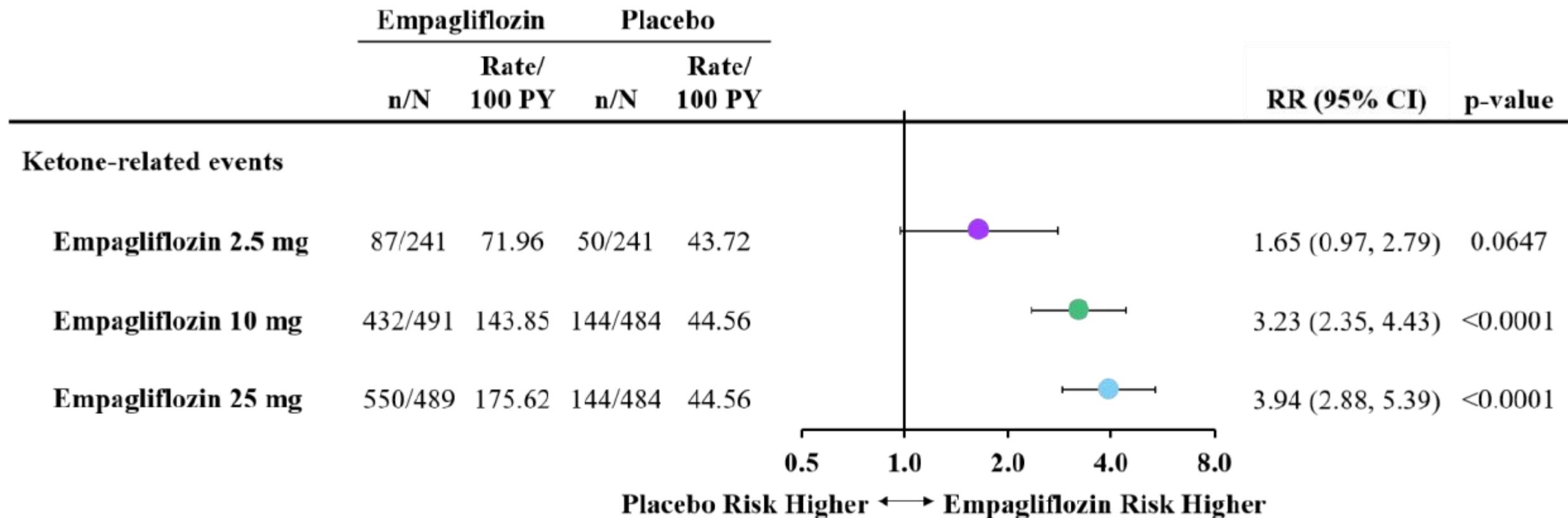
Cumulative Certain DKA Incidence for empagliflozin



Ketone-related events empagliflozin:

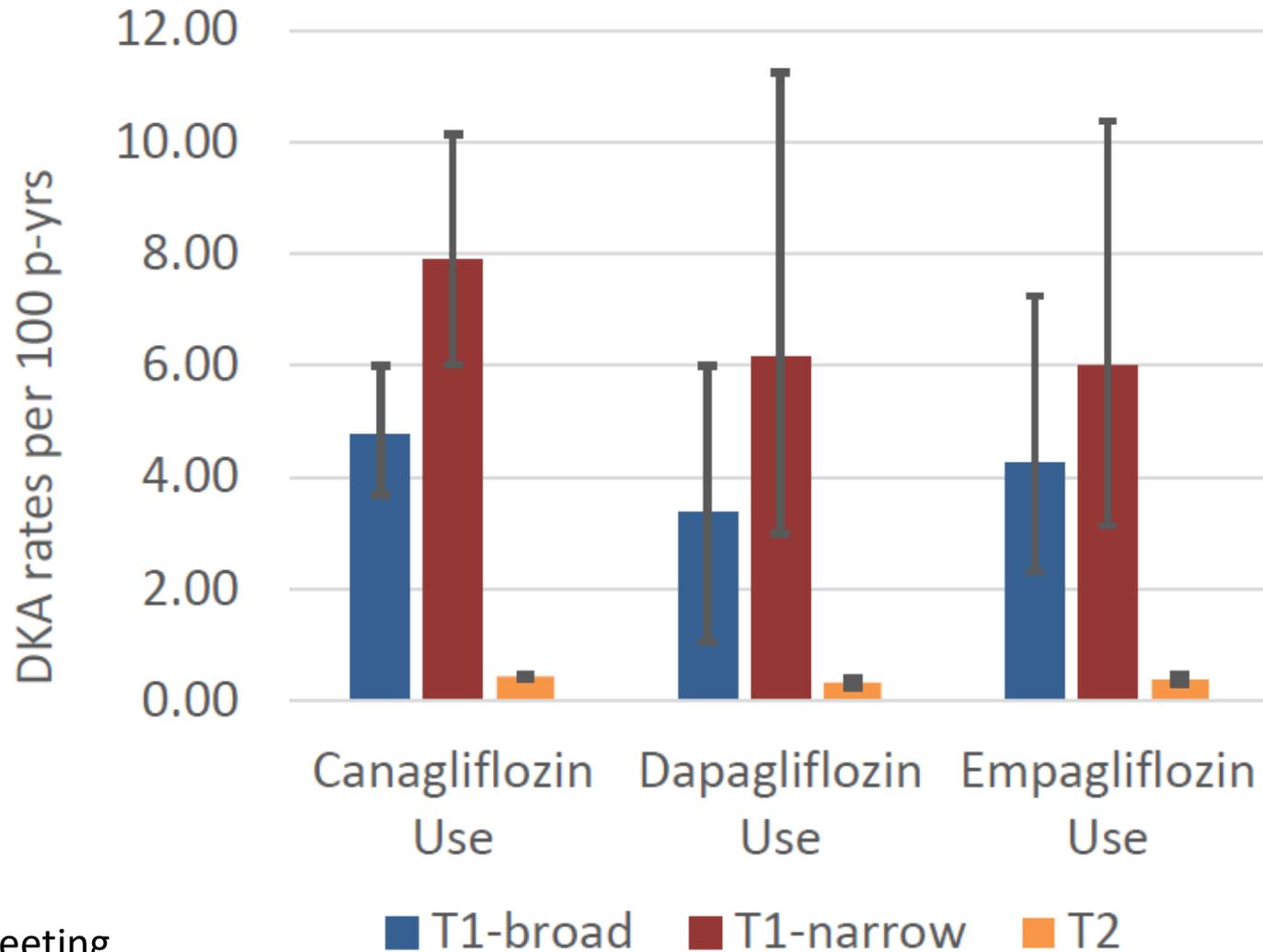
Adjudicated certain or potential DKA, adjudicated ketosis or ketones > 1.5 mm/L

Figure 33 Patients with ketone-related events in EASE-2 and EASE-3



SGLT2 Inhibitor DKA Rates

From FDA Sentinel data



FDA slide 103 1/17/19
sotagliflozin EMDAC meeting

VOTE: Do the available data suggest that the benefits outweigh the risks and support approval of empagliflozin 2.5 mg, administered orally once daily, as an adjunct to insulin to improve glycemic control in adults with type 1 diabetes mellitus? NO

The harm/benefit ratio soon becomes unfavorable for patients, with continued occurrence of life-threatening DKA but decreasing benefit. The single 2.5 mg empagliflozin study was too brief and too underpowered to reach any conclusion that the benefit outweighs the harm. The company's slide showing near statistically significant ketone-related events with this dose compared with a placebo suggests harm.

Given that tens of thousands of T1D patients are being prescribed off-label flozins, with unacceptably high DKA rates, the FDA approval of the 2.5 mg dose, after non-approval of larger doses of empagliflozin, sotagliflozin, and dapagliflozin might well signal a green light for flozin benefits outweighing risks with T1D patients.