Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee

Sotagliflozin to Treat Patients with Type 1 Diabetes

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I have no financial conflicts of interest.

A key issue/criticism in FDA briefing package: The need to re-balance the harm vs benefit evaluation

Manufacturer's pre-specified primary composite end point:

"HbA1c<7% with no episodes of severe hypoglycemia or diabetic ketoacidosis."

"This endpoint attempts to incorporate benefit and risk into a single composite, but we have concerns about the clinical significance of the chosen composite…..such [benefit-risk] assessments must start with a clinically meaningful way to frame both benefits and risks." [FDA briefing materials, page 11]

Why is this *successful** end point clinically meaningless?

Including in this composite the *absence* of patients with diabetic ketoacidosis or severely low blood sugar (severe hypoglycemia) along with the *presence* of patients whose HbA1c was less than 7% meaninglessly, but misleadingly, tilts the harm vs benefit evaluation toward benefit.

(*Deemed successful because, employing it, sotagliflozin met this primary composite benefit and risk endpoint. FDA stated that this successful result "was primarily driven by the HbA1c reduction." [FDA briefing materials, page 24])

FDA questions benefit of HbA1c lowering to < 7%

"[T]he composite uses a responder rate for glycemic efficacy (achieving or not achieving HbA1c <7%), and for example, puts equal weight on a lowering from 7.5% to 6.9% as on a lowering from 9.5% to 6.9%." [FDA briefing materials, page 11]

The latter, larger decrease is of much greater benefit than the former, smaller one, yet the primary composite endpoint looked only at the final achieved HbA1C (<7%).

The dangerous elephant in the room: Diabetic ketoacidosis (DKA)

- In a search of the FDA Adverse Event Reporting System database, the agency identified 444 spontaneously reported (from 2013 or earlier through September 11, 2018) cases of “flozin”-associated DKA in patients with Type 1 diabetes (an off-label use), even though those previously-approved drugs were only indicated for treatment of Type 2 diabetes. [FDA briefing materials, pages 106-107]

- The overall FDA analysis of the three trials (309, 310, and 312) that the company has used to support the approval of sotagliflozin shows the following:

- "Sotagliflozin was associated with an approximately 8-fold increase in DKA risk vs. placebo (95% CI: [3.1, 19.9]). The estimated number needed to harm (NNH) was approximately 26 patient-years of exposure to sotagliflozin to observe 1 additional DKA event (95% CI: [20.1, 38.5])."
- "Subgroup analyses showed a consistently elevated DKA risk associated with sotagliflozin, with estimated hazard ratios ranging from 4 to 11, and NNH ranging from 11 to 37."

The rate of adjudicated DKA cases in the three trials:

Placebo: 5 cases/1229 patients=0.4%

Sotagliflozin:56 cases/1748 patients=3.2%

[FDA briefing materials, pages 24-25 & 71]

Conclusion

Knowing what you know now, would you — if sotagliflozin were approved — prescribe it for a patient?

Refusing to allow the small HbA1c benefits to swamp out the large, dangerous increased risk of DKA *is* clinically meaningful.

The advisory committee should oppose the new approval of sotagliflozin.