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Endocrinologic and Metabolic Drugs Advisory Committee

Saxagliptin: April 14, 2015

(I have no financial conflict of interest)

2008 FDA Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

- "how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk"

- [pre-approval, the sponsor should] "show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8"

- "[a] postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated **risk ratio is less than1.3**. This can be achieved by conducting a single trial that is **adequately powered**..."[Emphasis added]

"unacceptable increase in cardiovascular risk" Are there such findings in the SAVOR study?

Prespecified outcomes in SAVOR*

- "The primary end point was a composite of cardiovascular death, myocardial infarction, or ischemic stroke. The secondary end point included the primary composite end point together with hospitalization for heart failure, coronary revascularization, or unstable angina."

*16,492 diabetic patients with increased cardiovascular risk, randomized to saxagliptin or placebo-- *Circulation*. 2014;130:1579-1588

(Data from Table 2, Leiter et al: *Diabetes Care*, March 10, 2015, online)

End point	<75 years (placebo *n* = 7,051; saxagliptin *n* = 7,111) KM event rate % Placebo	Saxagliptin	HR (95% CI)	*P* value
Primary* Interaction *P* value 0.67	6.6	6.9	1.01 (0.89, 1.15)	0.840
Secondary* Interaction *P* value 0.57	11.9	12.2	1.01 (0.92, 1.11)	0.857
MI	3.3	3.0	0.9 (0.75, 1.09)	0.289
CV mortality	2.4	2.8	1.10 (0.90, 1.35)	0.344
Non-CV mortality	1.1	1.4	1.21 (0.91, 1.61)	0.191
All-cause mortality	3.4	4.2	1.14 (0.96, 1.34)	0.127
Nonfatal ischemic stroke	1.5	1.7	1.12 (0.86, 1.45)	0.414
Hospitalization for/due to				
Coronary revascularization	5.7	5.2	0.90 (0.78, 1.04)	0.167
Heart failure	2.4	3.0	1.21 (0.99, 1.48)	0.064
Hypoglycemia	0.5	0.6	1.12 (0.72, 1.77)	0.607
Unstable angina	1.0	1.3	1.23 (0.90, 1.68)	0.192
Doubling of creatinine level, initiation of dialysis, renal transplantation, or creatinine >6.0 mg/dL (530 mmol/L)	1.8	2.1	1.13 (0.90, 1.41)	0.288

FDA HF analysis to adjust for CV competing risks

Table 12: Hospitalization for Heart Failure (hHF) in Exploratory Composite Endpoints (Primary MACE, CV-death, or All-Cause Death) (ITT)

	Total N=16492	Saxagliptin N= 8280	Placebo N= 8212	Hazard Ratio* (95% CI)
	n (%)			
hHF or primary MACE	1529 (9.3%)	784 (9.5%)	745 (9.1%)	1.05 (0.95, 1.16)
hHF or CV Death	925 (5.6%)	493 (6.0%)	432 (5.3%)	1.14 (1.00, 1.30)
hHF or all-cause Death	1180 (7.2%)	633 (7.6%)	547 (6.7%)	1.16 (1.03, 1.30)

*All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories using an on-study analysis.

Source: FDA analysis using adtte.xpt.

FDA concluded that **" the composite of hHF with either CV death or all-cause death results in confidence lower bounds that equal or exceed 1. These exploratory analyses do not allay concerns regarding the excess hHF events in the saxgliptin arm."**

Table 22: Sensitivity Analyses for All-cause Mortality Endpoint (mITT-FDA)

	Saxagliptin N=8240	Placebo N=8173	Hazard Ratio* (95.1% CI)
On-study Deaths	416 (5.1%)	376 (4.6%)	1.10 (0.96, 1.27)
On-treatment† + 30 days Deaths	297 (3.1%)	248 (2.5%)	1.18‡ (0.99, 1.39)
On-treatment† + 7 days Deaths	256 (3.1%)	204 (2.5%)	1.23 (1.02, 1.48)

† Events were censored at last dose + 30/7 days as appropriate.

* All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories.

Source: FDA analysis using adth xpt. Also available partly in Figure 16 of Clinical Study Report (page 127/15624).

FDA's conclusion from this analysis was that "Overall, there is a general trend of increasing hazard ratio estimates as follow-up for all-cause mortality is censored closer to treatment exposure."

Table 25: Exploratory Analyses of CV Death (ITT and mITT-FDA)

	Saxagliptin	Placebo	Hazard Ratio* (95.1% CI)
ITT, On-study	269/8280 (3.2%)	260/8212 (3.2%)	1.03 (0.87, 1.23)
mITT-FDA, On-study	266/8240 (3.2%)	258/8173 (3.1%)	1.03 (0.86, 1.22)
mITT-FDA, On-treatment +30 days	216/8240 (2.6%)	182/8173 (2.2%)	1.17 (0.96, 1.42)
mITT-FDA, On-treatment+7 days	196/8240 (2.4%)	164/8173 (2.0%)	1.18 (0.95, 1.45)

* All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories.

Source: FDA analysis using adth xpt.

This analysis, similar to that just shown for all-cause mortality, also demonstrated "a general trend of increasing hazard ratio estimates as follow-up for CV-mortality is censored closer to treatment exposure."

Acute, Definite, Adjudicated Pancreatitis

Table 39: Adjudicated Adverse Events of Pancreatitis (ITT)

Adverse Events	Saxagliptin (N=8280)	Placebo (N=8212)
PANCREATITIS	24 (0.3)	21 (0.3)
Definite acute pancreatitis	17 (0.2)	9 (0.1)
Typical abdominal pain	17	9
Acute pancreatitis enzymes	17	8
Pancreatitis abnormal imaging	6	3
Possible acute pancreatitis	6 (<0.1)	7 (<0.1)
Enzymes	4	4
Abnormal imaging	1	1
Past history	1	4
Chronic pancreatitis	2 (<0.1)	6 (<0.1)

Source: Modified from the Applicant's Clinical Study Report (page 1581 of 12468, labeled as Table 11.3.6.8.1.1).
Note: Since pancreatitis AEs were prespecified and adjudicated, the results from the ITT population are presented in this table.

Although FDA stated the applicant found confirmed cases were "similar" between arms, the agency found, as seen in this slide, that the excess with saxagliptin was clearest among the definite acute pancreatitis cases.

Would your vote be different if:

- Saxagliptin was being considered for approval, the decision now enriched by this unprecedented amount of new, worrisome safety information
- Knowing what you know now, would you prescribe saxagliptin and, if so, to whom?

The first scenario involves your important public health role on this committee. The second, a variant of first, do no [avoidable] harm.

What should be done?

Which action do you recommend FDA take regarding the totality of the safety information (Cardiovascular and other) obtained in SAVOR?.

- **A. No change to labeling (i.e., no new safety information needs to be added to the label)**
- **B. Change labeling to add new safety information**
- **C. Change labeling to add new safety information and restrict distribution**
- **D. Withdraw saxagliptin from the market**

Large increase in post-approval trials to assess cardiovascular risk in diabetes drugs since the 2008 FDA Guidance

"at least 16 cardiovascular outcome trials (that will report by 2020) [are] ongoing in more than 150 000 patients with type 2 diabetes …more cardiovascular outcome trials in type 2 diabetes have been commenced in the past 10 years…Trial sample sizes have also substantially increased from median 1116 to 6000."

The sizes of these 16 trials vary from 2000 to 17,000 with four of them having fewer than 5000 total patients listed.