**Onglyza**, **Kombiglyze XR**, **Nesina**, **Oseni**, and **Kazano** — FDA Advisory Committee Recommendations

- On April 14, 2015, the FDA held an Advisory Committee Meeting to discuss the results of two cardiovascular outcomes trials (CVOTs) regarding **Onglyza (saxagliptin)**, **Kombiglyze XR (saxagliptin/metformin)**, **Nesina (alogliptin)**, **Oseni (alogliptin/pioglitazone)**, and **Kazano (alogliptin/metformin)**: (1) Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR), and (2) Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE).

- **Onglyza**, **Kombiglyze XR**, **Nesina**, **Oseni**, **Kazano**, **Januvia** (sitagliptin), and **Tradjenta** (linagliptin) contain dipeptidyl peptidase-4 (DPP-4) inhibitors, and are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM).

- **SAVOR** and **EXAMINE** were conducted to demonstrate that the diabetic drugs are not associated with an unacceptable increase in cardiovascular (CV) risk.
  - In **SAVOR**, a 27% increase in the rate to first event of hospitalization for heart failure (HF) was reported in saxagliptin-treated subjects (HR 1.27 [95% CI 1.07, 1.51]). Analysis of all-cause mortality did not reveal significant differences between treatment groups [HR = 1.11 (95.1% CI: 0.96, 1.27)], but sensitivity analyses suggested significant or near-significant increases in all-cause mortality.
  - Results from **EXAMINE** do not suggest an increased risk of mortality (CV mortality or all-cause mortality) with alogliptin. However, an increased risk for hospitalization for HF was observed in the alogliptin arm vs. placebo [HR 1.19 (95% CI 0.90, 1.58)].

- FDA advisory panel recommendations:
  - The panel voted 13-1 that the results of the SAVOR study demonstrated that use of saxagliptin in patients with T2DM has an acceptable CV risk profile.
  - The majority of the committee (14 of 15) recommended that the FDA supplement the Onglyza and Kombiglyze labeling to add new safety information, with one member voting to withdraw saxagliptin from the market.
  - The panel voted 16-0 that the results of the EXAMINE study demonstrated that the use of alogliptin in patients with T2DM has an acceptable CV risk profile.
  - The majority of the committee (13 of 16) recommended that safety information from the EXAMINE study be added to the alogliptin labeling and the other three members voted for no change to the labeling.

- At this time, the FDA has not made any final conclusions regarding CV outcomes or changes to the labeling for any of the saxagliptin and/or alogliptin products.

- Additional CVOTs are ongoing for sitagliptin and linagliptin, with anticipated completion dates in 2015 and 2018, respectively.