FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting
Tommy Douglas Conference Center
10000 New Hampshire Ave, Silver Spring, Maryland
October 18, 2017

DRAFT QUESTIONS

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1. **DISCUSSION:** The applicant has proposed that semaglutide be indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Discuss the efficacy of semaglutide with respect to glycemic control.

2. **DISCUSSION:** Semaglutide once weekly injection has been studied in seven phase 3 studies and a two-year cardiovascular outcomes trial (SUSTAIN-6). Excluding issues related to diabetic retinopathy and CV risk, which will be considered subsequently, discuss any safety concerns you have related to semaglutide, if any.

3. **DISCUSSION:** In SUSTAIN-6 (CVOT), a pre-specified secondary safety endpoint was time from randomization to the first occurrence of either a need for retinal photocoagulation, vitreous hemorrhage, treatment with intravitreal agents, or diabetes-related blindness. The results for this composite endpoint showed an increased risk with semaglutide (HR: 1.76 [95% CI: 1.11, 2.78]).

    a. Discuss the strengths and limitations of this assessment (e.g., endpoint definitions, methods of ascertainment, adjudication, trial design, and any other considerations relevant to interpretation of the results).

    b. One hypothesis regarding this finding is that rapid and larger reductions in HbA1c can be expected to increase the short-term risk of diabetic retinopathy complications. Discuss the extent to which you are convinced that a reduction in blood glucose/HbA1c is the mediator of the observed increase in diabetic retinopathy complications in SUSTAIN-6.

    c. Improving glycemic control should be expected to reduce the risk of retinopathy over the long term. Discuss whether the increase in diabetic retinopathy complications in this two-year controlled trial affects your assessment of the clinical benefits expected from long-term use of semaglutide for glycemic control.

    d. In SUSTAIN-6, the increase in absolute risk of diabetic retinopathy complications was greater among those with diabetic retinopathy at baseline (8.2% semaglutide, 5.2% placebo) compared to those without diabetic retinopathy at baseline (0.7% semaglutide, 0.4% placebo), although the relative risk increases were similar. Patients with diabetic retinopathy are often among those most in need of improved glycemic control. Discuss whether you would have any concerns about the use of semaglutide among patients with diabetic retinopathy, if approved.

e. Taking into account the discussion above, comment on your level of concern related to the observed increased risk in diabetic retinopathy complications observed in SUSTAIN-6.

4. **DISCUSSION:** In SUSTAIN-6, a total of 254 first major adverse cardiovascular events (MACE) occurred during a median 2-year follow-up. The estimated hazard ratio of MACE and the components of MACE for semaglutide vs. placebo (ITT) are shown below:

	Semaglutide N=1648 PY=3408.2	**Placebo** N=1649 PY=3401.1	**Hazard Ratio (95% CI)**
MACE	**108 [3.2]**	**146 [4.3]**	**0.74 (0.58, 0.95)**
Cardiovascular death	44	46	0.98 (0.65, 1.48)
Non-fatal MI	47	64	0.74 (0.51, 1.08)
Non-fatal Stroke	27	44	0.61 (0.38, 0.99)
MI (fatal+nonfatal)	54	67	0.81 (0.57, 1.16)
Stroke (fatal+nonfatal)	30	46	0.65 (0.41, 1.03)

PY: person-years; [] indicates incidence rate per 100 PY
Numbers for components of MACE

a. Discuss these results and comment whether these data are adequate to characterize the CV safety of semaglutide.

5. **VOTE:** Do the available efficacy and safety data support approval of semaglutide 0.5 mg and 1 mg, administered subcutaneously once weekly, as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus?

a. If yes, please explain your rationale and comment on whether any additional studies should be required after approval.

b. If no, please describe what further studies you believe the applicant must conduct to establish favorable benefit/risk to support approval.