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Submitted via email to Janet.Woodcock@fda.hhs.gov and Jean-Marc.Guettier@fda.hhs.gov

Re: Supplemental new drug application for liraglutide (VICTOZA) injection (NDA 022341)

Dear Drs. Woodcock and Guettier,

Public Citizen, a consumer advocacy organization with more than 400,000 members and supporters nationwide, urges the Food and Drug Administration (FDA) to reject the supplemental new drug application (sNDA) for liraglutide (VICTOZA)[1] for the additional indication to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk because the sole clinical trial conducted in support of the sNDA failed to show any benefit for the proposed indication in the very U.S. patients for whom it would be approved.

The LEADER trial

As you know, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was the sole clinical trial conducted in support of the sNDA

[1] All references to liraglutide in this document concern only the Victoza brand-name formulation, at the proposed daily dose of 1.8 mg used in the LEADER trial.

for liraglutide "as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and high cardiovascular risk."[2]

LEADER was a randomized, double-blind, placebo-controlled trial in 9,340 subjects with type 2 diabetes and increased cardiovascular risk. Subjects were randomized to receive liraglutide at a dose of 1.8 mg daily or placebo, in addition to physician-determined standard-of-care treatment for both type 2 diabetes and cardiovascular risk factors.[3] The trial ended after all subjects had a minimum treatment period of 3.5 years plus a follow-up period of 30 days,[4] with subjects taking liraglutide exposed to treatment for a median of 3.5 years and a mean of 3.1 years.[5] The primary outcome was time to first major cardiovascular event (MACE; a composite of cardiovascular death, non-fatal stroke, and non-fatal myocardial infarction).[6]

LEADER was a global trial, with subjects screened for participation in 32 countries.[7] The 2,514 U.S. subjects comprised 27% of the total trial population.[8]

No confirmatory trial

The FDA noted in its briefing document that it typically requires two clinical trials to demonstrate safety and efficacy for a new drug or new indication. The criteria for accepting a single trial as a basis for an NDA or sNDA approval also was noted by the FDA:

> Although the evidentiary standard to support a new efficacy claim has typically relied on two or more adequate and well controlled clinical studies, the FDA has previously relied on a single, adequate and well controlled trial in circumstances where a single trial has provided "highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds."[9]

As we detail in this letter, the LEADER trial did not provide "highly reliable and statistically strong evidence" of benefit in U.S. patients, the only population of patients for whom liraglutide would be approved by the FDA for cardiovascular risk reduction. It is interesting to speculate how the FDA and the advisory committee members would have reacted were the U.S. and non-U.S. subjects studied in separate trials rather than a single trial. It is unlikely that either the

[2] Food and Drug Administration. June 20, 2017 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting. Briefing document. PDF pp. 1 and 6. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM563334.pdf. Accessed July 16, 2017. **Hereafter referred to as "FDA Briefing Document".**
[3] FDA Briefing Document, PDF pp. 6 and 23.
[4] FDA Briefing Document, PDF p. 6.
[5] FDA Briefing Document, PDF p. 34.
[6] FDA Briefing Document, PDF p. 6.
[7] FDA Briefing Document, PDF p. 23.
[8] FDA Briefing Document, PDF p. 44.
[9] FDA Briefing Document, PDF pp. 6-7.

agency or the advisory committee members would favor approval of the drug in U.S. patients in such a circumstance unless another, larger trial were conducted in U.S. subjects.

No benefit in U.S. subjects

In the LEADER trial, the overall reduction in risk of MACE, cardiovascular death, and overall death with liraglutide was entirely due to outcomes at clinical sites outside of the U.S. The FDA conducted a subgroup analysis comparing the outcomes for MACE, cardiovascular death, and all-cause death of U.S. subjects with those of non-U.S. subjects and found no benefit for U.S. subjects on any of these three outcomes (see Table 14 from the FDA Briefing Document, excepted below).

Table 14. Subgroup Analyses of MACE, CV Death, All-Cause Death

Group	Category	N	MACE HR (95% CI)	CV DEATH HR (95% CI)	ALL-CAUSE DEATH HR (95% CI)
Age	Under Age 60	2321	0.78 (0.62, 0.98)	0.60 (0.42, 0.87)	0.71 (0.52, 0.97)
	60 and Older	7019	0.90 (0.79, 1.02)	0.85 (0.69, 1.04)	0.89 (0.76, 1.04)
Sex	Female	3337	0.88 (0.72, 1.08)	0.81 (0.60, 1.10)	0.83 (0.66, 1.06)
	Male	6003	0.86 (0.76, 0.98)	0.77 (0.62, 0.95)	0.85 (0.72, 1.01)
Country	Outside USA	6826	0.81 (0.71, 0.92)	0.70 (0.57, 0.86)	0.77 (0.65, 0.90)
	USA	2514	1.03 (0.84, 1.25)	1.04 (0.75, 1.46)	1.09 (0.84, 1.40)
Race	White	7238	0.90 (0.80, 1.02)	0.84 (0.68, 1.03)	0.91 (0.77, 1.06)
	Black or African American	777	0.87 (0.59, 1.27)	0.78 (0.44, 1.39)	0.78 (0.50, 1.23)
	Asian	936	0.70 (0.46, 1.05)	0.60 (0.31, 1.16)	0.69 (0.42, 1.13)
	Other	389	0.60 (0.37, 1.00)	0.47 (0.23. 0.93)	0.49 (0.27, 0.89)
HbA1c	<= 8.3	4768	0.89(0.76, 1.05)	0.86 (0.66, 1.13)	0.87 (0.71, 1.07)
	> 8.3%	4572	0.84 (0.72, 0.98)	0.71 (0.57, 0.91)	0.82 (0.68, 0.98)

Source: Statistical Reviewer's analysis
HR < 1.0 indicates treatment benefit of liraglutide

The hazard ratios (HRs) for U.S. subjects were as follows:

- MACE HR 1.03 (95% confidence interval [CI]: 0.84 – 1.25)
- cardiovascular death HR 1.04 (95% CI: 0.75 – 1.46)
- all-cause death HR 1.09 (95% CI: 0.84 – 1.40)

By contrast, the corresponding values for non-U.S. subjects were all significant:

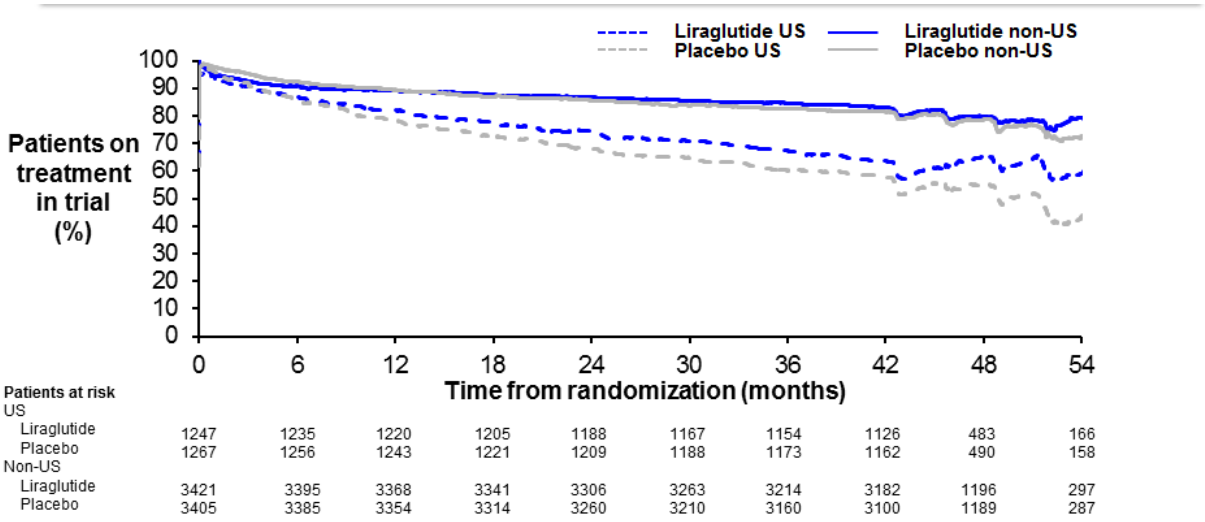
- MACE HR 0.81 (95% CI: 0.71 – 0.92)
- cardiovascular death HR 0.70 (95% CI: 0.57 – 0.86)
- all-cause death HR 0.77 (95% CI: 0.65 – 0.90)

As even the company that produces liraglutide implicitly acknowledged in its attempt to explain away the findings through a post-hoc analysis (see next section), it is unlikely that these subgroup findings are due to chance, for several reasons. First, the U.S. subgroup was large, with 8,799 subject-years of follow-up time (2,514 subjects[10] followed for a minimum of 3.5 years, as with all subjects[11]). Second, the absence of a significant benefit with use of liraglutide for U.S. subjects was seen across multiple different outcomes. Finally, there was an absence of even a trend in favor of liraglutide for U.S. subjects across these different outcomes.

Company's post-hoc explanation of the lack of benefit in U.S. subjects

The regional subgroup comparison demonstrating a complete lack of efficacy of liraglutide for MACE, cardiovascular death, and overall death in U.S. subjects was a pre-specified per-protocol analysis. By contrast, the company attempted to explain away this striking disparity between the U.S. and non-U.S. subjects through a post-hoc analysis. The company's explanation rested entirely on the fact that U.S. subjects were treated for significantly less time than were non-U.S. subjects (**Figure 1**). Notably, no explanation was provided, in either the company's or the FDA's briefing materials, of the reasons (e.g., adverse events, intolerability, or simple attrition) for the higher discontinuation rates in U.S. subjects.

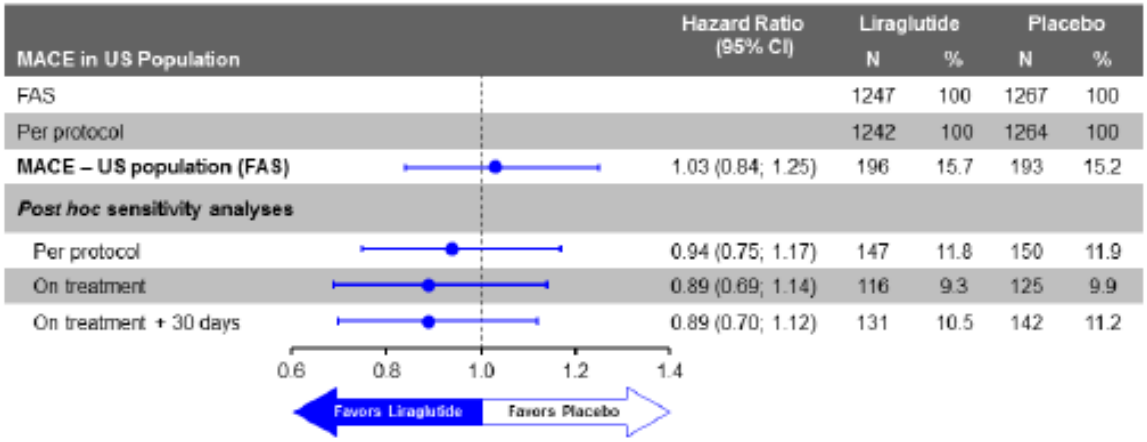
Figure 1. Percentage of patients on treatment over time for U.S. and non-U.S. populations (copied from Novo Nordisk Briefing Document, PDF p. 47).[12]



[10] FDA Briefing Document, PDF p. 44.
[11] FDA Briefing Document, PDF p. 6.
[12] Novo Nordisk. June 20, 2017 FDA Endocrinologic and Metabolic Drugs Advisory Committee meeting. Victoza® (liraglutide) injection. LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results. NDA 22341 S-027. Briefing Document. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM563335.pdf. Accessed July 16, 2017. PDF p. 47. **Hereafter referred to as "Novo Nordisk Briefing Document".**

Based on this finding, the company then conducted post-hoc analyses measuring HRs for MACE for U.S. subjects during treatment and during treatment plus 30 days post-treatment, both of which showed a non-significant trend in favor of liraglutide (**Figure 2**).

Figure 2. Forest plot of treatment contrasts for time to first EAC-confirmed MACE in the US population (taken as-is from Novo Nordisk Briefing Document, PDF p. 48).[13]



The company therefore concluded that the reason that liraglutide was not efficacious in the U.S. subgroup was that the U.S. subjects were not exposed to liraglutide for a sufficient period of time to experience the drug's purported cardiovascular benefits.

However, the post-hoc analyses restricted to time-on-treatment and time-on-treatment plus 30 days post-treatment were based on exceedingly small numbers of MACE events (116 in the liraglutide group vs. 125 in the placebo group and 131 liraglutide vs. 142 placebo, respectively). Such sparse data render impossible any reliable conclusions.

The fact that the company's explanation was post-hoc further decreases confidence in its conclusions. The FDA has historically, and correctly, based drug approval decisions on intention-to-treat analyses because these are the closest approximation to real-world conditions, taking into account discontinuation and non-adherence. Liraglutide had no cardiovascular or mortality benefit for U.S. subjects in the intention-to-treat analysis. That such a lack of efficacy was seen in a clinical trial setting in which subjects were followed and assisted carefully during treatment makes it highly likely that U.S. patients, in a real-world setting, will experience a similar lack of cardiovascular benefit.

As previously explained, it is unlikely that the difference in the U.S. and non-U.S. subgroup findings was due to chance. In such a scenario, there are two possible interpretations of the U.S. data. If the lack of benefit in U.S. subjects is not generalizable to the U.S. target population, then there are no data on which to base approval of liraglutide for cardiovascular risk reduction in U.S. patients. If the data are generalizable, then liraglutide has been proven ineffective on an intention-to-treat basis in U.S. patients.

[13] Novo Nordisk Briefing Document, PDF p. 48.

More intensive cardiovascular-risk-reducing treatment may explain lack of incremental benefit in U.S. subjects

During the advisory committee meeting, the company presented a slide (CO-42) stating that analyses controlling for the following covariates did not account for the disparate efficacy results between U.S. and non-U.S. subjects (list taken verbatim from company slide):[14]

- Baseline demographics
- Disease characteristics
- Concomitant [cardiovascular] or diabetes medications
- HbA1c
- Body weight
- Systolic blood pressure

However, this non-specific covariate analysis does not preclude the possibility that baseline or post-randomization use of cardiovascular-risk-reducing medications accounted for the lack of incremental cardiovascular benefit from liraglutide in U.S. subjects. For one, "'concomitant [cardiovascular]' medications" is a vague category with no further breakdown by those medications that have been proven to reduce MACE or cardiovascular death. Secondly, where this breakdown was provided in a limited fashion (with no covariate analyses) by the company in its briefing materials, the categories were equally vague in some cases.[15] For example, the category "lipid-lowering drugs" does not distinguish between cardiovascular-risk-reducing statins and unproven, non-statin lipid-lowering drugs. Furthermore, the company did not present data on the dose of or cumulative duration of treatment for any of these drugs in U.S. and non-U.S. subjects.

Because this subdivision within lipid-lowering drugs was not provided, we conducted Fisher's Exact tests of the prevalence of baseline plus exclusively post-randomization use of lipid-lowering drugs in U.S. and non-U.S. subjects in the liraglutide- and placebo-treated groups (**Figure 3**). We found a significant difference in the prevalence of use of lipid-lowering drugs in U.S. subjects compared with non-U.S. subjects by treatment group.

[14] Novo Nordisk. Victoza (liraglutide) Injection Evaluation of Cardiovascular Outcome Results from LEADER. June 20, 2017 Endocrinologic and Metabolic Drugs Advisory Committee. Slide CO-42. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM566063.pdf. Accessed July 16, 2017.
[15] Novo Nordisk Briefing Document, PDF p. 127.

Figure 3. Fisher's Exact test of the prevalence of use of lipid-lowering drugs (LLD; baseline + exclusively post-randomization initiation), using data provided by the company in its briefing materials (PDF p. 127).[16]

Liraglutide group

Subgroup	LLD	No LLD	
U.S.	1186	61	**1247**
Non-U.S.	3031	390	**3421**
Total	**4217**	**451**	**4668**

The two-tailed P value is less than 0.0001.

Placebo group

Subgroup	LLD	No LLD	
U.S.	1180	87	**1267**
Non-U.S.	3065	340	**3405**
Total	**4245**	**427**	**4672**

The two-tailed P value is less than 0.001.

Further, more comprehensive analyses using patient-level data are necessary to determine whether U.S. subjects were given specific cardiovascular-risk-reducing medications (e.g., statins, beta blockers, and platelet inhibitors) at a higher rate, dose, or cumulative duration, either at baseline or during the trial, than their non-U.S. counterparts. Neither the FDA nor the company has presented such analyses.

Lack of FDA analyses or explanations

Disturbingly, in its briefing package, the FDA did not provide its own interpretation or analyses of the striking lack of a significant benefit in U.S. subjects taking liraglutide. The FDA offered only a table (Table 14 from the FDA Briefing Document) presenting subgroup hazard ratios for MACE, cardiovascular death, and all-cause death that included values for U.S. and non-U.S. subjects, along with the following observation:

[16] Novo Nordisk Briefing Document, PDF p. 127.

> The hazard ratio for the subgroup of USA was greater than 1 across all three endpoints in the table below, although the 95% confidence interval includes 1. This trend is in the opposite direction from the primary analysis.[17]

The agency also offered no opinion on — and did not even make reference to — the company's post-hoc interpretation of this finding. Nor did the FDA include a specific question to advisory committee members to elicit their opinion on the finding.[18] It is shocking that the FDA did not consider the apparent lack of significant benefit in U.S. subjects for a product intended only for U.S. patients relevant enough to expand upon in its briefing materials.

During the advisory committee meeting, FDA officials were asked what they thought of the company's post-hoc, during-treatment analysis comparing the U.S. and non-U.S. subgroup findings and whether the agency had performed its own analyses. FDA officials stated that they were not prepared to endorse the company's analysis as a sufficient explanation for the lack of benefit seen in the U.S. subgroup, nor had the agency conducted its own analyses of the finding. An FDA official stated that such analyses would be "complicated," without elaborating further.[19]

We have the following questions for the FDA (and are making a separate Freedom of Information Act request for documents involving these issues):

1. Did FDA reviewers raise any concerns about the lack of significant benefit in U.S. subjects taking liraglutide? If so, why were these concerns not included in the Briefing Document for advisory committee members to review?
2. Did the FDA request additional documents from Novo Nordisk, including patient-level data that may have included data on treatment with other drugs?
3. Did FDA reviewers conduct any post-hoc analyses, including, crucially, of patient-level data, if the FDA had such data, on the U.S. and non-U.S. subgroup findings? If so, what were the results of these analyses and, again, why were such results not included in the FDA Briefing Document?

We note that the FDA had ample time not only to conduct its own analyses of the U.S. and non-U.S. subgroup efficacy findings, but also to request patient-level data that, if analyzed by the FDA, would have shed light on the possible reasons for the differing results in U.S. subjects. The company submitted the final results of the LEADER study to the FDA on October 25, 2016,[20] approximately eight months before the FDA convened the June 20, 2017, advisory committee meeting to discuss the application.

It is vital that the FDA be confident in the safety and efficacy of a drug product — especially one that, like liraglutide, has serious side effects — for patients in whom the product will be used

[17] FDA Briefing Document, PDF pp.43-44.
[18] Food and Drug Administration. June 20, 2017 Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) meeting. Final questions to committee members. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM566057.pdf. Accessed July 16, 2017.
[19] Paragraph based on recollection of one of the authors of this letter, Sammy Almashat, who was present at the advisory committee meeting.
[20] FDA Briefing Document, PDF p. 15.

following approval. For the agency to ignore a finding as critically important as a lack of efficacy in U.S. subjects raises doubts about the rigor of the FDA's handling of data supporting drug approvals.

Conclusion: No proven efficacy in U.S. subjects

Liraglutide has not been proven effective for cardiovascular risk reduction in the U.S. population in which it was studied. The absence of any evidence that liraglutide prevents MACE, cardiovascular death, or overall death raises serious doubts about the real-world effectiveness of liraglutide for reducing cardiovascular risk in U.S. diabetes patients. Given this lack of evidence of benefit in U.S. patients, voting for approval for a cardiovascular benefit in the same patients is not rational. We therefore strongly urge the FDA to reject this sNDA.

Thank you for taking our comments into consideration.

Sincerely,

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