Testimony to the FDA Endocrinologic and Metabolic Drugs Advisory Committee

Liraglutide (Victoza) for Cardiovascular Risk Reduction

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(We have no financial conflicts of interest)

U.S. vs. non-U.S. sites

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 overall reduction in risk of MACE, CV death, and overall death with Victoza was due **entirely** to outcomes at clinical sites outside of the U.S.

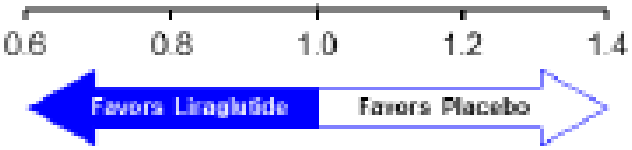
Disturbingly, in its briefing package, the FDA offered no explanation for this startling lack of efficacy in U.S. subjects nor did it even weigh in on the validity of the company's attempted explanation through a post-hoc analysis.

HRs in opposite direction: Significant outside U.S., Not significant in U.S.

- MACE:
  - Outside U.S. HR 0.81 (0.71, 0.92)
  - U.S. HR 1.03 (0.84, 1.25)
- CV Death:
  - Outside U.S. HR 0.70 (0.57, 0.86)
  - U.S. HR 1.04 (0.75, 1.46)
- All-cause Death:
  - Outside U.S. HR 0.77 (0.65, 0.90)
  - U.S. HR 1.09 (0.84, 1.40)

Company's post-hoc explanation

MACE in US Population	Hazard Ratio (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
FAS		1247	100	1267	100
Per protocol		1242	100	1264	100
MACE – US population (FAS)	1.03 (0.84; 1.25)	196	15.7	193	15.2
***Post hoc* sensitivity analyses**					
Per protocol	0.94 (0.75; 1.17)	147	11.8	150	11.9
On treatment	0.89 (0.69; 1.14)	116	9.3	125	9.9
On treatment + 30 days	0.89 (0.70; 1.12)	131	10.5	142	11.2



Company's post-hoc explanation

The regional subgroup comparison demonstrating a complete lack of efficacy of Victoza for MACE, CV death, and overall death in U.S. subjects was a pre-specified per-protocol analysis. By contrast, the company attempts to explain away this striking disparity through a post-hoc analysis.

The company's explanation rested entirely on the fact that U.S. subjects were on-treatment for significantly less time than were non-U.S. subjects.

Company's post-hoc explanation

Victoza had no CV or mortality benefit for U.S. subjects in the more appropriate (for real-world use) intention-to-treat analysis. 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 Victoza for CV risk reduction in U.S. patients. If the data are generalizable, then Victoza has been proven ineffective, on an intention-to-treat basis, in U.S. patients.

That such a lack of efficacy was seen in a clinical trial setting, in which subjects were carefully followed and assisted in their treatment makes it highly likely that American patients, in a real-world setting, will experience a similar lack of cardiovascular benefit.

Conclusion

Victoza has not been proven effective for CV risk reduction in the U.S. population in which it was studied. The absence of any evidence for a benefit in favor of Victoza on MACE, CV death, or overall death raises serious doubts about the real-world effectiveness of Victoza for reducing CV 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.