Testimony Before the FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting Regarding Omecamtiv Mecarbil

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I am Nina Zeldes, a Health Researcher at Public Citizen's Health Research Group. I have no financial conflicts of interest.

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Public Citizen strongly opposes FDA approval of omecamtiv mecarbil (OM) to reduce the risk of cardiovascular death and heart failure events in adults with symptomatic chronic heart failure with reduced ejection fraction over two main concerns:

1) The minimal benefits demonstrated in this single trial do not outweigh the significant risks, especially for some heart failure patients.
2) The evidence for the proposed benefits of omecamtiv are not accompanied by confirmatory evidence.

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Although the clinical trial met its primary endpoint, the observed treatment effect was small and not clinically meaningful for patients.[1] For instance, the relative reduction in risk for patients taking omecamtiv was 8% compared to placebo (Hazard ratio [HR] 0.92; 95% confidence interval [CI], 0.86, 0.99).[2] However, the reduction of absolute risk was only 2% or 2 per 100 patient years (PY) (95% CI, 0.3, 3.8 per 100 PY).[3] Moreover, none of the secondary endpoints were met.

At the same time, patients taking omecamtiv had a 7.4% incidence rate of myocardial ischemia events compared to the patients in the placebo group with 6.6%.[4] And although the rate of cardiovascular deaths was similar between the groups with a HR of 1.01 (95%

[1] Food and Drug Administration. FDA briefing document, NDA 216401, drug name: omecamtiv mecarbil; Cardiovascular and Renal Drugs Advisory Committee Meeting. December 13, 2022. https://www.fda.gov/media/163821/download. Accessed December 13, 2022.
[2] *Id.* PDF p. 10.
[3] *Ibid.*
[4] *Id*. PDF. P 32.

CI, 0.9, 1.1),[5] the relative risk of patients with atrial fibrillation or atrial flutter (AFF) at screening was increased by 26% (HR 1.26, 95% CI, 1.1, 1.5) compared to placebo.[6]

We thus agree with FDA that "it is not certain whether the benefit of OM outweighs the risk."[7]

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The efficacy and safety of this drug are based on only one trial. And as FDA stated in the briefing materials, the information from the Phase 2 trial may not be reliable to serve as confirmatory evidence. Given that the observed benefits of this drug were minimal, this is of particular concern.

This lack of reliable data and the limitations of post hoc analyses also make it difficult to evaluate potential benefits or additional risks in different subgroups. For instance, we agree with FDA that there is "no scientific basis"[8] for the observed benefit in patients whose left ventricular ejection fraction (LVEF) at baseline was lower than 28%.[9]

Similarly, using post hoc analyses, it is not possible to establish the sponsor's claim that the increased risk for cardiovascular death seen in AFF patients was mainly concentrated in the subset of this patient group that was treated with digoxin. In addition, it is important to keep in mind that although the post hoc analyses seemed to indicate that the risk was particularly high for this subset, AFF patients not treated with digoxin also had a higher risk for cardiovascular death with omecamtiv compared to placebo.[10]

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In conclusion, the evidence for efficacy and safety of this drug is based on one single trial; no additional, reliable confirmatory evidence was provided. The minimal absolute risk reduction of only 2% cannot be considered a clinically meaningful improvement for patients.

We also agree with FDA that "given the limitations inherent in post hoc analyses, one cannot be certain about differential risk in patient subgroups, thus impacting regulatory decision-making." [11]

We therefore urge the committee to vote "No" on the voting question and strongly recommend that FDA not approve omecamtiv mecarbil.

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[5] *Id.* PDF p. 25.
[6] *Id*. PDF p. 42.
[7] *Id*. PDF p.44.
[8] *Id*. PDF p. 44.
[9] *Id*. PDF p. 11.
[10] *Id*. PDF p. 37.
[11] *Id*. PDF p. 42.