Testimony Before the FDA's Cardiovascular and Renal Drugs Advisory Committee Meeting:

Daprodustat Offers No Clinical Benefits But Increases Risks For CKD Patients

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I have no financial conflicts of interest.

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Introduction

Public Citizen strongly opposes FDA approval of daprodustat for the treatment of anemia due to CKD, both in adults not on dialysis and those on dialysis.

This drug offers no additional benefits compared to current treatment options, while putting patients at substantial additional safety risks. We agree with the FDA review that a further increase in risks "beyond that seen with the ESAs is concerning."

No Evidence for Additional Clinical Benefit

In the pivotal trials in both non-dialysis and dialysis subjects, daprodustat was noninferior to ESAs regarding the change in the hemoglobin level from baseline, with similar continued need for RBC transfusions or rescue therapy.

As stated by the FDA “there were no other benefits demonstrated on how patients feel, function, or survive.”

Substantial Safety Concerns

Safety issues found in <u>both trials</u>:

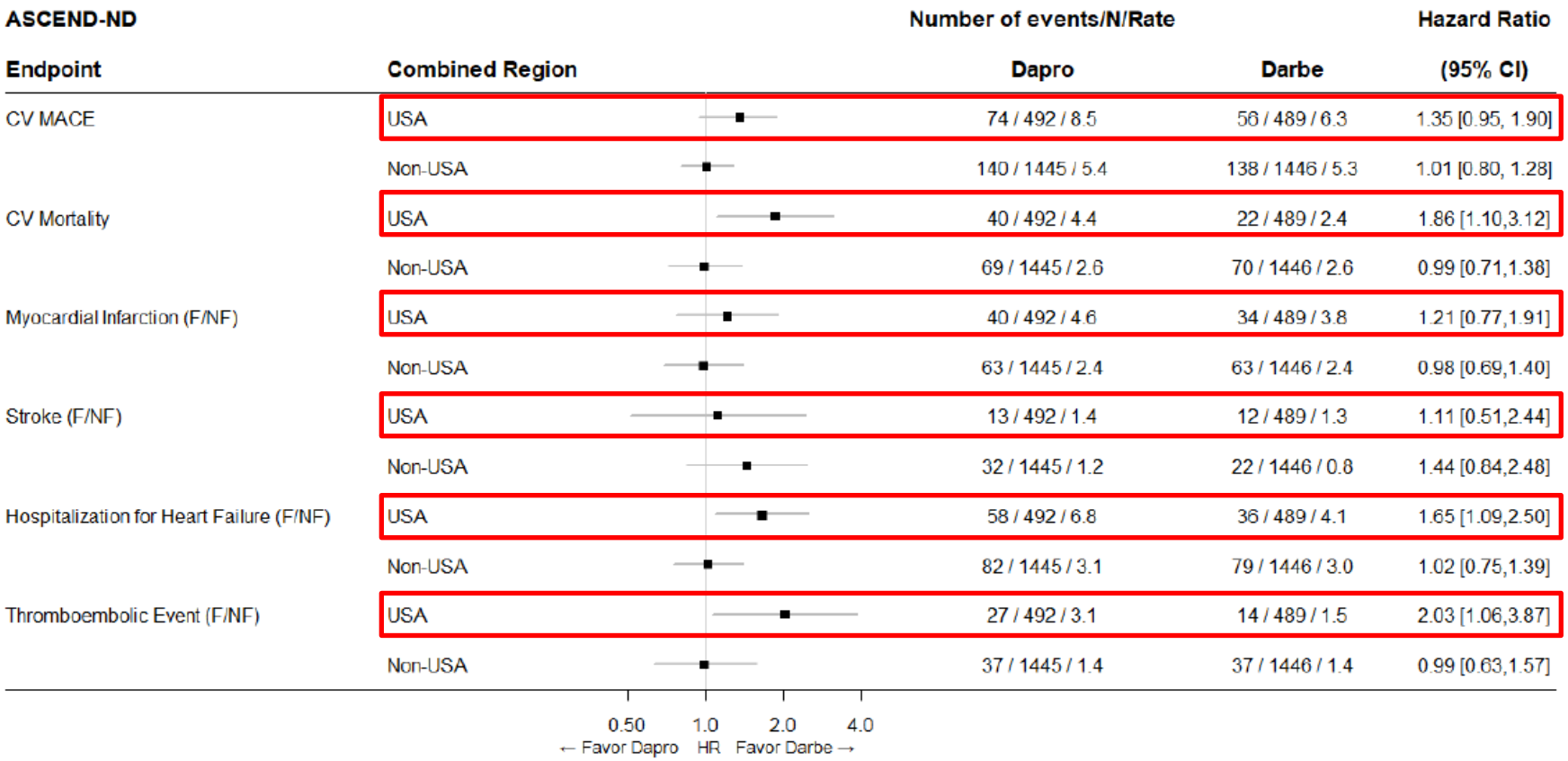
- Higher incidence of hospitalization for heart failure
- Higher incidence of gastrointestinal erosions and bleeding

Additional safety issues for patients <u>not on dialysis</u>:

- Higher incidence for cardiovascular mortality, myocardial infarction, stroke, thromboembolic disease, and vascular access thrombosis
- Higher incidence of some CV risks in the USA subgroup
- Elevated hazard ratios for MACE on some analyses
- Potential increased risk of acute kidney injury

Substantial Safety Concerns ND

Figure 5. Combined Region (USA, non-USA) Subgroup Analyses for All Adjudicated CV Endpoints, ASCEND-ND (On-Study Analysis)

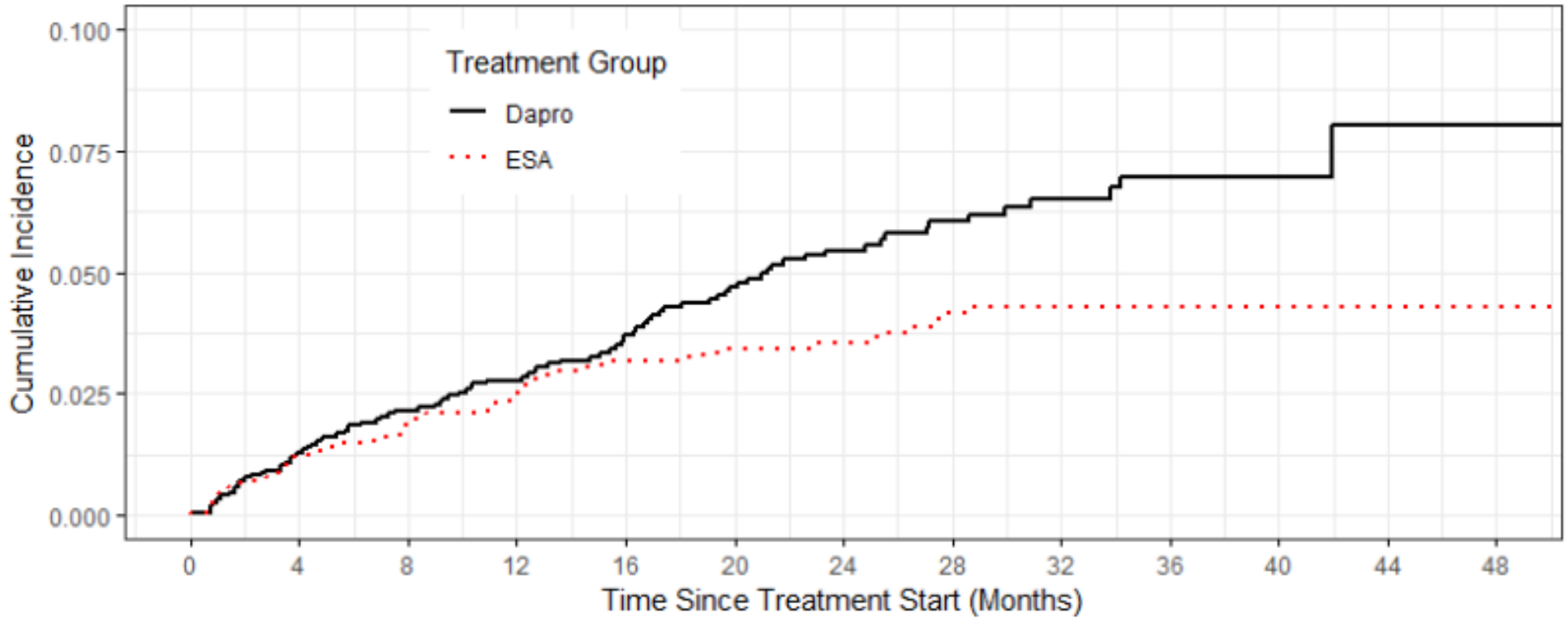


ASCEND-ND		Number of events/N/Rate		Hazard Ratio
Endpoint	**Combined Region**	**Dapro**	**Darbe**	**(95% CI)**
CV MACE	USA	74 / 492 / 8.5	56 / 489 / 6.3	1.35 [0.95, 1.90]
	Non-USA	140 / 1445 / 5.4	138 / 1446 / 5.3	1.01 [0.80, 1.28]
CV Mortality	USA	40 / 492 / 4.4	22 / 489 / 2.4	1.86 [1.10,3.12]
	Non-USA	69 / 1445 / 2.6	70 / 1446 / 2.6	0.99 [0.71,1.38]
Myocardial Infarction (F/NF)	USA	40 / 492 / 4.6	34 / 489 / 3.8	1.21 [0.77,1.91]
	Non-USA	63 / 1445 / 2.4	63 / 1446 / 2.4	0.98 [0.69,1.40]
Stroke (F/NF)	USA	13 / 492 / 1.4	12 / 489 / 1.3	1.11 [0.51,2.44]
	Non-USA	32 / 1445 / 1.2	22 / 1446 / 0.8	1.44 [0.84,2.48]
Hospitalization for Heart Failure (F/NF)	USA	58 / 492 / 6.8	36 / 489 / 4.1	1.65 [1.09,2.50]
	Non-USA	82 / 1445 / 3.1	79 / 1446 / 3.0	1.02 [0.75,1.39]
Thromboembolic Event (F/NF)	USA	27 / 492 / 3.1	14 / 489 / 1.5	2.03 [1.06,3.87]
	Non-USA	37 / 1445 / 1.4	37 / 1446 / 1.4	0.99 [0.63,1.57]

Source: FDA analysis.

Substantial Safety Concerns ND (cont.)

Figure 8. Time to First TESAE of Acute Kidney Injury (Narrow FMQ), (On-Study Analysis)



Conclusions

- **Serious additional safety risks for patients, particularly those not on dialysis**
- **No additional clinical benefit for patients**
- **Instead of offering convenience, the oral route may cause more harm**

We therefore urge the committee to vote “No” on the two voting questions and recommend that the FDA not approve daprodustat.