Precision medicine in septic shock with enibarcimab – biomarker guided definition of target population

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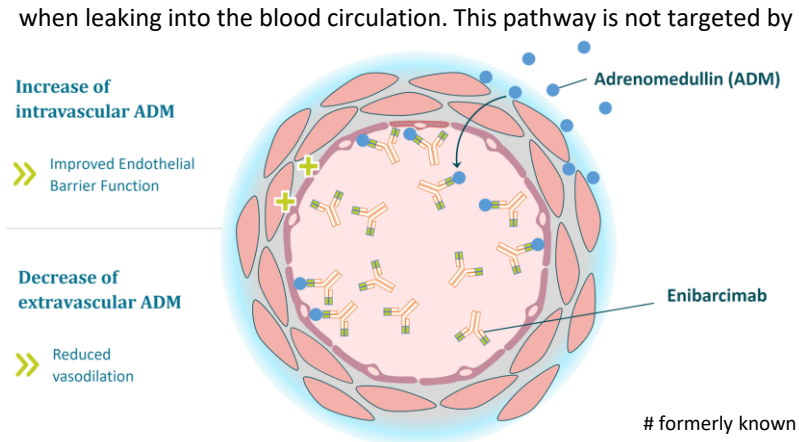
INTRODUCTION

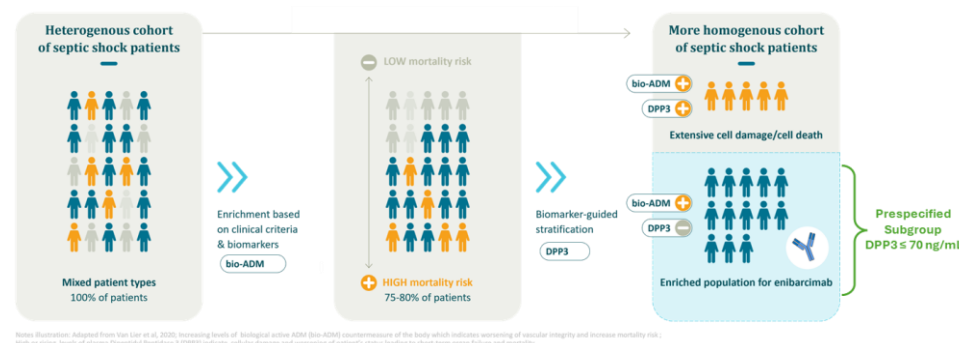
- Sepsis/septic shock patients are a highly heterogenous cohort.
- Enibarcimab[#] is a non-neutralizing monoclonal anti-adrenomedullin (ADM) antibody improving endothelial barrier function in septic shock (1-3).
- Bio-ADM and cDPP3 are both involved in vascular function and have been shown to be independently associated with organ failure and mortality in septic shock (4).
- DPP3 is a cytosolic protease which can degrade signaling molecules like angiotensin II, when leaking into the blood circulation. This pathway is not targeted by enibarcimab.



formerly known as adrecizumab

METHODS

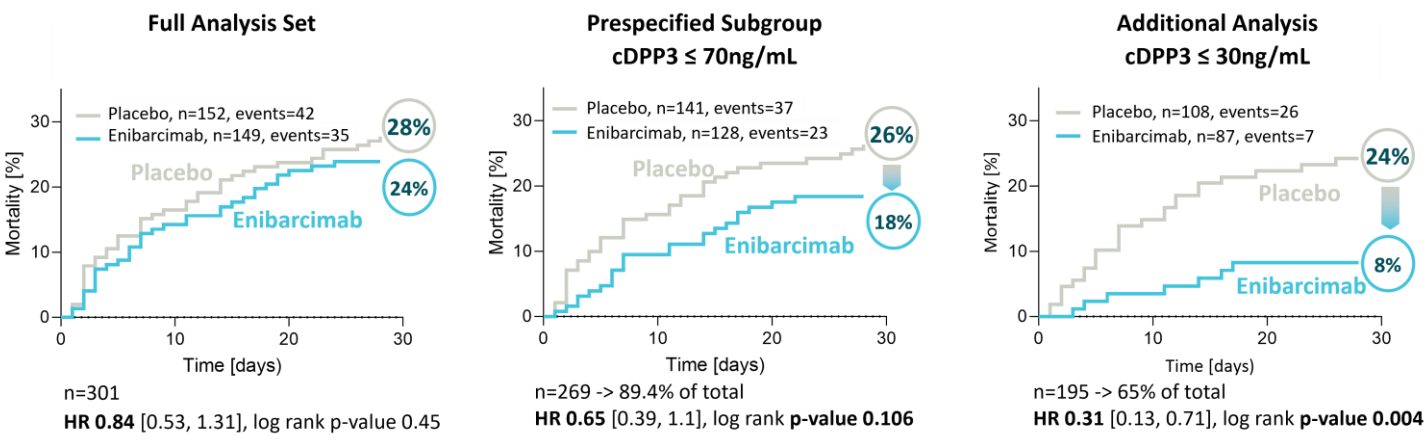
- AdrenOSS-2 was a double-blind, randomized, placebo-controlled, biomarker-guided, phase II trial of enibarcimab in septic shock patients (5).
- Elevated bio-ADM plasma concentration at baseline (>70pg/mL) was required for inclusion.
- Circulating dipeptidyl-peptidase 3 (cDPP3) was used to exclude patients from the analysis that were unlikely to respond to enibarcimab treatment. Omission of patients with cDPP3 >70ng/mL at baseline was a prespecified subgroup in the statistical analysis plan for the assessment of 28-day mortality.



RESULTS

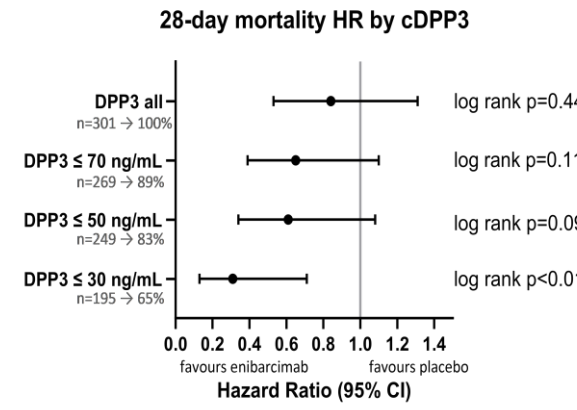
28-day all cause mortality

→ Efficacy of enibarcimab on 28-day all cause mortality improves with lower cDPP3 cut-off



Kaplan-Meier plots: Presented Hazard Ratio and 95% CI intervals are derived from univariate Cox proportional hazard modeling.

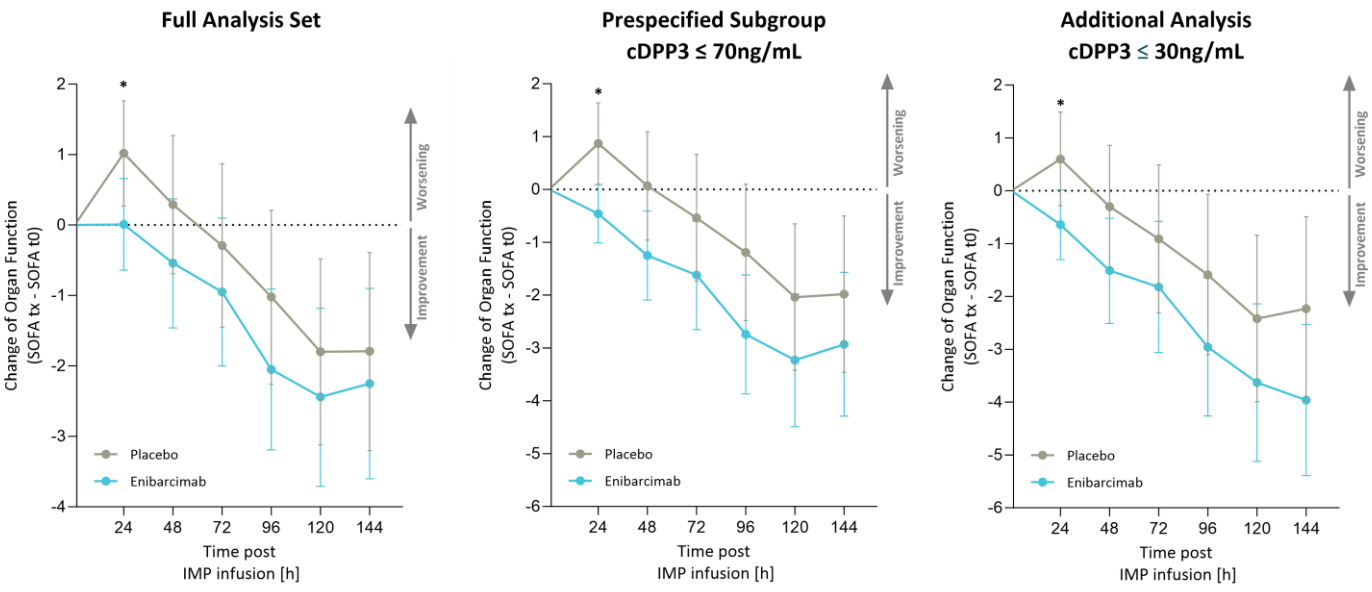
Forest Plot HR



Forest Plot of Hazard Ratio and 95% CI for 28-day mortality by baseline cDPP3 level and bio-ADM<70pg/mL.

Organ Dysfunction – Change in SOFA from baseline

→ SOFA scores in the enibarcimab group improved immediately after treatment and even more pronounced in cDPP3 subgroups



Change in SOFA after 24h from baseline

	FAS	cDPP3 ≤ 70ng/mL	cDPP3 ≤ 30ng/mL
Enibarcimab	0.01	-0.46	-0.64
Placebo	1.02	0.87	0.60
Δ Treatment Group	1.01	1.33	1.24
Student t-test	0.005	0.006	0.027

Safety

→ Safety profile in cDPP3 subgroups was similar to FAS population.

Considerably fewer patients treated with enibarcimab than placebo experienced serious/severe TEAEs and TEAEs leading to death, most prominently in the subgroup with the lowest DPP3 threshold.

	FAS		cDPP3 ≤ 70 ng/mL		cDPP3 ≤ 30 ng/mL	
Number of patients with at least one	Enibarcimab (N=149) n (%)	Placebo (N=152) n (%)	Enibarcimab (N=128) n (%)	Placebo (N=141) n (%)	Enibarcimab (N=87) n (%)	Placebo (N=108) n (%)
Total number of TEAEs (calculated average number per patient)	1029 (6.9)	940 (6.2)	890 (7.0)	890 (6.3)	624 (7.2)	712 (6.6)
Serious TEAE	87 (58.4)	94 (61.8)	71 (55.5)	87 (61.7)	42 (48.3)	68 (63.0)
TEAE leading to death	49 (32.9)	52 (34.2)	37 (28.9)	48 (34.0)	16 (18.4)	35 (32.4)

CONCLUSION

- **These unpublished data from the prespecified subgroup of the AdrenOSS-2 trial show that a precision medicine approach using bio-ADM and cDPP3 for patient selection can overcome patient heterogeneity in septic shock, resulting in a more pronounced treatment effect of enibarcimab.**
- **The use of enibarcimab in combination with the two biomarkers bio-ADM and cDPP3 does have the potential to become the first effective targeted treatment of septic shock.**

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REFERENCES

ABBREVIATION: biologically active adrenomedullin (bio-ADM), cytosolic dipeptidyl peptidase 3 (cDPP3)

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