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Enibarcimab for the treatment of septic shock in patients selected by a combination of the biomarkers bio-ADM and DPP3: A prespecified subgroup analysis of the AdrenOSS-2 trial

Dear Editor,

Sepsis, characterized by a dysregulated host response to infection leading to organ dysfunction, is a life-threatening condition. When sepsis progresses to septic shock, both vascular tone and vascular integrity are compromised, significantly increasing the risk of mortality [1]. Adrenomedullin (ADM) is a vasoactive peptide involved in maintaining vascular integrity and endothelial function. During sepsis, multiple processes stimulate ADM release, and increased ADM plasma levels were found to be associated with sepsis severity, hemodynamic instability, development of organ dysfunction, and mortality in patients. Based on these findings, ADM has emerged both as biomarker and potential therapeutic target for the treatment of sepsis and septic shock [2]. Enibarcimab is a humanized non-neutralizing monoclonal antibody directed against the N-terminus of ADM and binding to ADM leads to increased levels of active ADM (bio-ADM) in the bloodstream. Previously described preclinical studies [3,4] suggest that ADM present in the circulation counteracts—albeit insufficiently—sepsis-induced vascular leakage through its effects on endothelial cells, while excess interstitial ADM may lead to vasodilation and septic shock through direct effects on vascular smooth muscle cells. As enibarcimab does not freely diffuse from the circulation into the interstitial space it complexes and retains ADM in the circulation, where active ADM exerts its beneficial effect on the vascular endothelium (4).

The AdrenOSS-2 trial was the first double-blind, placebo-controlled, randomized, multicenter, biomarker-guided proof of concept trial, investigating the safety, tolerability, efficacy and pharmacokinetics of enibarcimab in patients with early septic shock and elevated levels of bio-ADM (>70 pg/mL), indicating a septic shock pathophysiology related to endothelial damage. Primary analysis results and further details on the trial setting and design were reported earlier [5]. Recently, another pathophysiological mechanism contributing to septic shock mortality has been identified. Dipeptidyl peptidase 3 (DPP3), a cytosolic protease, can be released into the bloodstream under pathological conditions, leading to degradation of circulating peptide hormone substrates, such as angiotensin II (the primary effector peptide of the renin-angiotensin system). As angiotensin II is an endogenous vasopressor, essential for maintaining organ function, this may lead to further organ dysfunction and mortality. So, the biomarkers ADM and DPP3 represent different pathways that are both independently involved in the development and progression of septic shock. Clinically, patients with elevated levels of DPP3 are suffering from a different septic shock pathology, that cannot be addressed by treatment with the ADM-antibody enibarcimab [6]. Apart from elevated bioADM as an inclusion criterion, exclusion of patients with elevated DPP3 results in further enrichment of patients that likely benefit from treatment with enibarcimab. In this AdrenOSS-1 cohort a DPP3 level of 70 was associated with increased mortality [7]. Therefore, subgroup analyses excluding patients with elevated levels of DPP3 >70 ng/mL have been prespecified in the statistical analysis plan for the efficacy endpoints 28-day all-cause mortality and SOFA score prior to the unblinding of the trial. Elevated levels of DPP3 above 40 ng/mL have been found to be associated with increased (cardiovascular) mortality in patients with septic shock [7]. The cut-off level of 70 ng/mL in the AdrenOSS-2 trial was prospectively chosen to only exclude patients with a clearly elevated risk of DPP3 related mortality. While exploratory analyses on the use of DPP3 for defining a target population of enibarcimab have been published previously [8], the results of the original pre-specified analysis have not yet been reported and are presented here.

Of the 301 patients randomized, 3 patients had no baseline DPP3 measurements available; of the remaining 298 patients, 269 patients (89 %) had baseline DPP3 levels ≤70 ng/mL and were included in the analysis of the prespecified subgroup (low DPP3 subgroup). Treatment groups (enibarcimab and placebo) were comparable regarding demographic and baseline characteristics in the overall trial population, as well as in the prespecified subset of patients with baseline DPP3 level of ≤70 ng/mL. When comparing baseline and demographic characteristics of patients in the low and high DPP3 groups, they were comparable in terms of age, sex, body mass index (BMI), Acute Physiology And Chronic Health Evaluation II (APACHE II) Score, body temperature, mean arterial blood pressure (MAP) and time to trial treatment. The parameters SOFA score, heart rate, norepinephrine given, interleukin (IL)-6 values, procalcitonin (PCT), lactate levels and fluid input were higher in patients with elevated DPP3 values >70 ng/mL. As previously reported [9], in the overall trial population 35 of 149 patients (24 %) in the enibarcimab group and 42 of 152 patients (28 %) in the placebo group of had died by day 28 ($p = 0.4$). In the prespecified subgroup of patients with baseline DPP3 values ≤70 ng/mL, the mortality rate in the enibarcimab group was 6 % lower (18 %, 23 of 128 patients), whereas it was similar (2 % lower) in the placebo group (26 %, 37 of 141 patients) (Fig. 1). Consequently, the estimated hazard ratio was lower in the prespecified subgroup (0.65 [95 % CI 0.39–1.1] in favor of enibarcimab) than in the overall trial population (0.84 [95 % CI 0.53–1.31]. 90-day mortality, showed a similar effect: a HR of 0.82 [95 % CI 0.54–1.26] in favor of enibarcimab in the prespecified low DPP3 subgroup compared to 0.94 [95 % CI 0.64–1.39] in the overall trial population. There was no evidence for an increased mortality in the treatment group of patients with DPP3 levels >70 ng/mL. It should be noted, that this subgroup consisted of 32 patients only, limiting the statistical power.

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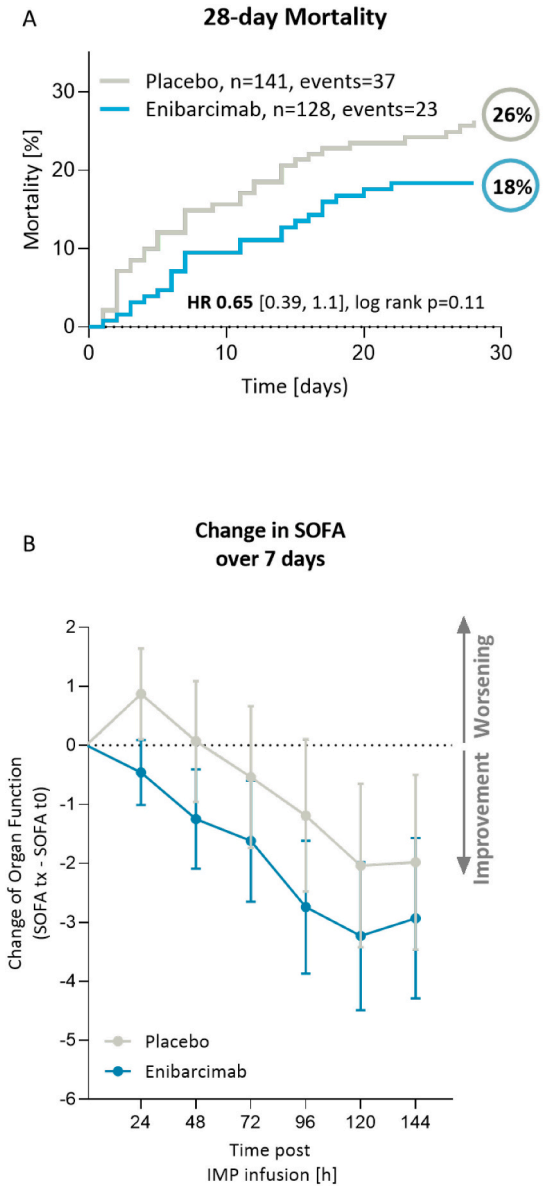

Fig. 1. (A) Kaplan–Meier plot for 28-day all-cause mortality after enibarcimab infusion for the prespecified subgroup of DPP3 with baseline DPP3 values ≤70 ng/mL. Hazard Ratios (enibarcimab vs placebo) and their 95 %CI were calculated based on Cox proportional hazard model. (B) SOFA Mean Change from baseline to day 7 in the prespecified subgroup of DPP3 with baseline DPP3 values ≤70 ng/mL. Change was calculated when patients had a value at both baseline and that time point. t0 = baseline defined as the most recent assessment prior to treatment start; tx = time indicated on the x-axis. * $p < 0.05$ student's *t*-test; enibarcimab dose groups are combined and placebo.

The change in SOFA score from baseline over 7 days for the prespecified subgroup with DPP3 values at baseline ≤70 ng/mL (Fig. 1) showed the time course as in the overall trial population [9]. In the overall population, the SOFA score in the enibarcimab group remained stable over the first 24 h after trial drug administration before showing continued improvement over the remainder of the time and through 7 days after administration, while it worsened initially in the placebo group, before starting to improve then also. In the low DPP3 subgroup, the same trend was observed, however, the SOFA score in the enibarcimab group started to improve directly after trial drug administration, without the 24 h lag time as in the overall trial population. A statistically significant difference in SOFA score to the advantage of enibarcimab treatment compared to placebo, measured as change from baseline in SOFA scores, was shown in the overall trial population, including patients with elevated baseline DPP3, at 24 h but not at other time points. In the low DPP3 subgroup, the benefit of enibarcimab over placebo was more pronounced, as indicated by a between-group difference of 1.33 SOFA score points ($p = 0.006$), vs 1.01 ($p = 0.005$) in the overall trial population. All organ subscores contributed to the overall effect.

In the overall trial population, Adverse Events (AEs) were evenly distributed between patients treated with enibarcimab (142 AEs (95 %)) and placebo (142 AEs (93 %), see supplementary data). In the low DPP3 subgroup, the proportions of patients experiencing any AE was similar to the overall trial population (enibarcimab 121 AE (95 %); placebo 131 AEs (93 %)). The SOC populated with the highest proportion of patients was 'Infections and Infestations', with the most common term being septic shock (worsening of the pre-existing septic shock as per protocol defined adverse event criteria). The second most populated SOC was 'Metabolism and Nutrition Disorders' with the most common terms hypokalemia, hypernatremia, hypophosphatemia, and hyperglycemia. Summary statistics of AEs by system organ class (SOC) and preferred term are provided as supplementary material for the overall trial population as well as the low DPP3 subgroup.

Previous sepsis trials failed to show therapeutic efficacy which can be partially explained by considerable patient heterogeneity caused by interindividual differences in comorbidities, comedication, source of infection, causative pathogens and most likely due to multiple signaling pathways that are involved in sepsis and septic shock development, reinforcing the fact that sepsis represents a highly heterogeneous syndrome. The analysis of the prespecified low DPP3 subgroup of patients with baseline DPP3 ≤ 70 ng/mL from the AdrenOSS-2 trial shows that introducing DPP3 as a second biomarker to exclude patients with elevated DPP3 improves the enrichment and efficacy outcomes in patients with septic shock treated with enibarcimab, as in the prespecified subgroup baseline demographics and patient's characteristics were comparable between both treatment groups and compared to full study population. Also, the safety profile remained unchanged in the prespecified subgroup. The observed trend towards improved organ dysfunction and reduced mortality in this prespecified subgroup provides a proof-of-principle for the selection of patients with this dual biomarker strategy. Indeed, earlier exploratory analyses showed a significant interaction between DPP3 levels and enibarcimab therapeutic efficacy for the treatment of septic shock. They showed that lower DPP3 cut-off values resulted in improved clinical benefit and illustrated this by employing a tighter cut-off value of 50 ng/mL which reduced day 28 all-cause mortality from 25 % in the placebo group to 16 in the enibarcimab treated group (Hazard Ratio 0.61; 95 %CI 0.34–1.08; $p = 0.085$) [8]. These so far unpublished results from the prespecified subgroup analysis of the AdrenOSS-2 trial form the basis for future trials to further investigate the efficacy and safety of enibarcimab for the treatment of septic shock. Based on these and previous findings on even lower DPP3 values a cut-off for DPP3 in the range of 30–50 ng/mL is proposed. This would be in line with the upper limit of the normal range for DPP3, which is approximately 40 ng/mL [7].

CRediT authorship contribution statement

Claudia Knothe: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Stephan Witte:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Andreas Bergmann:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Alexandre Mebazaa:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Pierre-Francois Laterre:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Peter Pickkers:** Writing – original draft, Supervision, Resources, Methodology, Investigation, Conceptualization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2025.155077.

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