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European Patent Application 20764639.9
THERAPY GUIDANCE AND/OR THERAPY MONITORING FOR TREATMENT OF SHOCK
4TEEN4 Pharmaceuticals GmbH

This is in response to Communication pursuant to Article 94(3) EPC dated November 20, 2023:

Novelty

The Examining Division alleges that the patient group of D3 is identical to the patient group as claimed in the present application. Applicants submits that such an allegation does not suffice in order to reject claim 13.

Claim 13 is directed to a vasopressor for treating a patient with shock who has a DPP3 value below a threshold value (according to one of the previous claims), i.e. these are the patients who do not have a refractory (= vasopressor-resistant) shock according to claim 1 (have or develop it). In D3 there is an overview of therapeutic strategies in patients with high-dose vasopressor-dependent/refractory shock. No statements are made here about DPP3 levels.

With the help of the determination of DPP3, the medical practitioner can better control the administration of vasopressors, i.e. the medical practitioner would not give vasopressors to patients who would only respond to this therapy to a limited extent or no longer at all (which can be determined by high DPP3 levels).

In contrast patient which have a DPP3 level below a threshold indicating that the patient is not in/going into refractory shock, shall be treated with vasopressors.

In the embodiments of the application (here 16) we described this again as a "method of treatment". In fact, some of the patients mentioned in D3 would be treated with vasopressors, but some (namely those with refractory shock) would not be treated with vasopressors. These would be treated with therapies targeting DPP3 in the form of DPP3 inhibitors and/or angiotensin II agonists.

Thus, claim 13 is novel.

Inventive step

With regard to the lack of inventive step of claims 1 and 21 as well as 14 and 17, we would like to comment that it is known in the prior art that DPP3 is generally increased in septic as well as cardiogenic shock.

However, it cannot in any way be deduced therefrom that a distinction can be made between patients having refractory and non-refractory shock.

Furthermore, this distinction gives rise to different treatment consequence, namely stopping vasopressors and giving DPP3 inhibitors/ angiotensin II agonists in the event of refractory shock. In the case of non-refractory shock, additional vasopressors would be given.

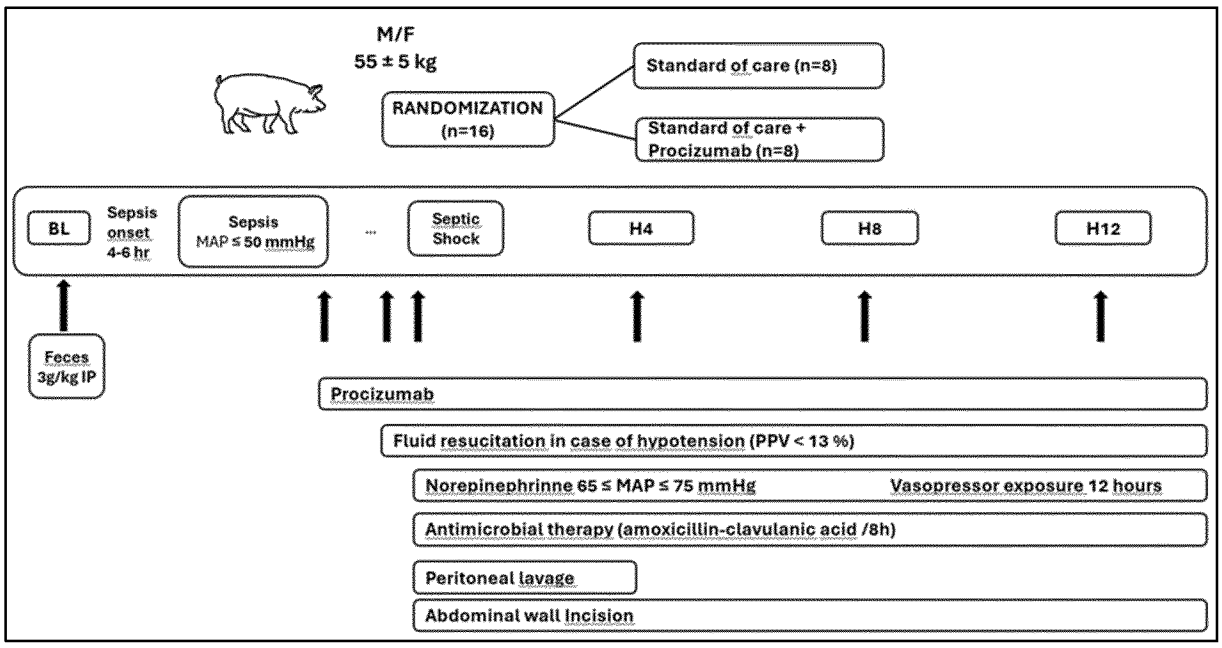
Therefore, applicants submit that the present claims are inventive.

Applicant has shown when filing the application, that high DPP3 plasma concentrations are associated with vasopressor-resistant refractory septic shock as well as with the development of refractory shock in patients with cardiogenic shock. In other words, a distinction can be made between patients having or developing refractory shock vs. non-refractory shock. It is therefore plausible that DPP3 inhibitors may be used to treat patients with refractory shock or to prevent refractory shock in shock patients, respectively. We hereby submit additional data showing in an animal model that refractory septic shock can be successfully treated using the monoclonal antibody Procizumab, which binds and inhibits circulating DPP3 acitivity.

Data

A randomized, open-label, controlled study in 16 anesthetized and mechanically ventilated pigs was performed. Septic shock was induced by fecal peritonitis. Resuscitation with fluids, antimicrobial therapy and abdominal drainage was initiated one hour after the onset of septic shock. Septic pigs were randomly allocated to receive Procizumab (on top of standard of care) or standard of care (norepinephrine and fluids) to maintain mean arterial pressure between 65 and 75 mmHg for 12 h (Fig. A). Eight females and eight male pigs were used in the experiment and gender was properly balanced between treatment and standard of care arms.

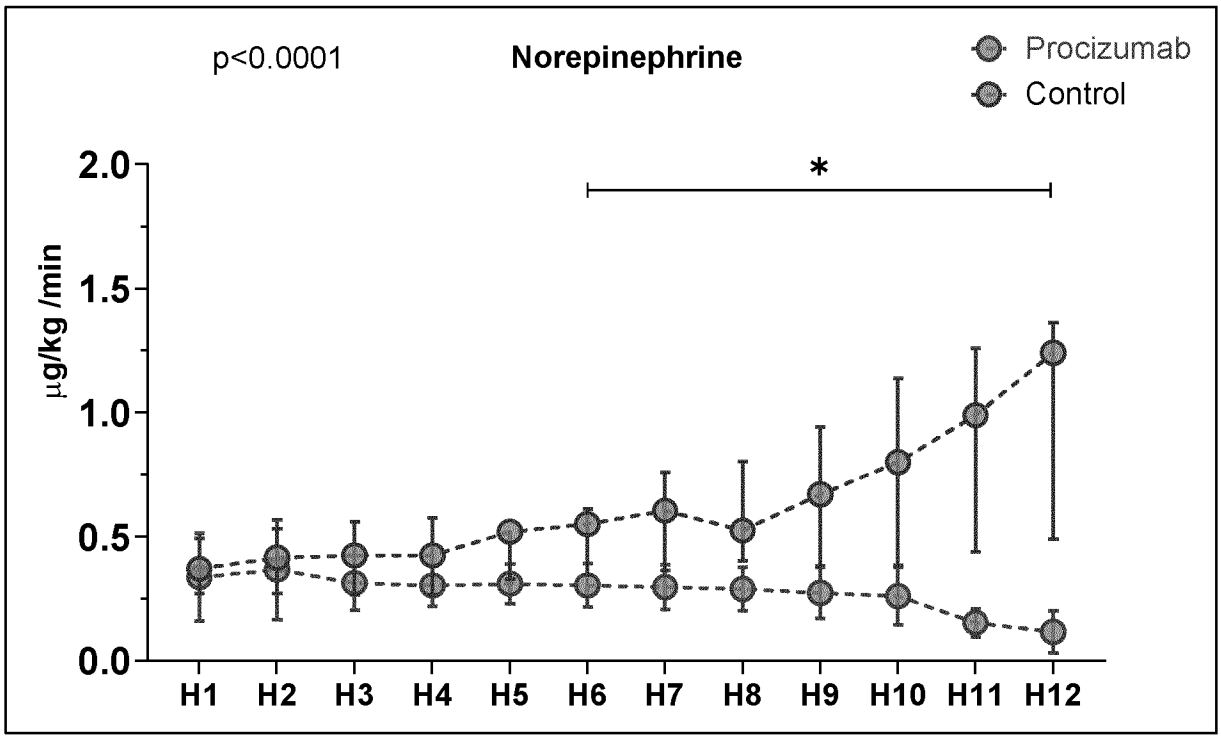
Fig. A



The inclusion criteria for refractory shock were: animals in shock (BP <50 mmHg), vasopressor dose of 0.2µg/kg/min at H1 (defining refractory shock). Three animals were included in the Procizumab-treated arm (n=3) and compared to Placebo (n=6) (Fig. B). Norepinephrine dose in µg/kg/min was recorded every hour from hour 1. While the standard of care arm of animals in refractory shock had a significantly high norepinephrine need, the Procizumab-treated animals were infused with significantly lower norepinephrine doses required to achieve the same target mean arterial pressure of 65 mmHg (Fig. B). The difference between treated and standard of care arms became

significant at H6 and the two arms diverged even more after H10 (10 hours after norepinephrine infusion was started.

Fig. B



These data clearly show, that refractory shock can be treated effectively with the DPP3 inhibitor Procizumab.

Applicants request that a patent is granted on basis of the currently pending claims. As an auxiliary request applicants request oral proceedings in case the Examining Division intends to reject the application. The representative is prepared to discuss minor issues over the phone.

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