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

On the communication pursuant to Art. 94(3) EPC dated May 27, 2024:

It is requested to proceed with the examination on the basis of new claims 1 to 18 replacing the claims on file and the remaining documents as currently on file.

I. Amendments

Claims 13, 18 and 20 have been deleted.

Present claim 14 (previous claim 15) has been amended by including a definition of the term "precursor", based on the disclosure in the paragraphs bridging pages 31 and 32 of the WO publication.

The numbering of the remaining claims and back-references have been adapted to the above amendments as necessary.

No matter going beyond what was in the application documents as filed has been added by the amendment. Thus, all amendments meet the requirements of Art. 123(2) EPC.

II. Clarity

1) In section 2.1 of the official communication, it is objected that the term "predetermined threshold" it is not defined.

Applicant respectfully disagrees and submits that it is neither helpful nor justified to limit the claims to specific thresholds or values.

It is common practice for a medical practitioner to choose different thresholds in order to include or exclude patients based on these thresholds. Depending on how the selected thresholds are set, certain numbers of false positive and false negative patients are included. Here, the medical practitioner must weigh the risk in order to decide to which extent the selected threshold values affect the number of false-positive and false-negative patients for a specific medical question.

However, it cannot be excluded that different medical practitioners choose different threshold values for the same medical indication and are influenced by their individual judgement and experience. In medical practice, a further medical treatment is arranged by the medical practitioner based on the concentration of the biomarker determined by the laboratory. This results in, for example, that the medical practitioner has to decide whether the administration of a certain treatment is sufficient or whether other medical treatments have to be initiated. The decision on how the patients are divided into risk groups is taken by the medical practitioner: For example he could divide the patients into three different categories based on the risk: High-risk patients, and low-risk patients. The medical practitioner then sets, for example, a threshold value, which is based on the percentile of the statistical calculations. However, he could also define several risk groups of the patients and set two or three threshold values, e.g. to distinguish high, medium and low risk groups.

Present examples 9 and 11 show that within the group of patients with cardiogenic shock and septic shock, respectively, patients with DPP3 levels in the 3rd quartile have a significantly higher occurrence of refractory shock than patients with lower DPP3 levels (also see Figs. 13 and 15). The absolute cutoffs are 59.1 ng/ml in the cardiogenic shock patients and 48.4 ng/mL in septic shock patients respectively.

Moreover, a medical practitioner may choose the threshold depending on whether more false-positive or false-negative results are considered tolerable. The medical practitioner will initiate medical treatment based on the division of

the patients into the respective risk group. This leads to the conclusion that the specific value of a threshold value can vary for good reasons.

It is also emphasized that fixing the threshold to an absolute number would unduly restrict the scope of the claims, which could then be easily circumvented. A suspected infringer could, by choosing a slightly different threshold, draw similar conclusions regarding the number of false positives or false negatives and thus circumvent the present invention. The applicant therefore kindly argues that the term "predetermined threshold" is sufficiently clear for the medical practitioner as a specialist to use the present invention and his experience to choose a suitable threshold and initiate appropriate treatment.

Finally, it is a principle well established by case law that claims must be clear for the sake of legal certainty, as their purpose is to enable the protection conferred by the patent to be determined. In the case of the present claims, the skilled person can determine the protection conferred by claim 1 without undue burden. Incidentally, it has also been accepted in a number of similar patents that the threshold need not be defined to have a specific value. Please, see in this regard e.g. granted patents EP2943792, EP2976646 and EP2823316. These are a small selection of granted patents where the language like "... wherein a level above a threshold is ..." has been accepted by the EPO without demanding the limitation of such a claim to a specific threshold which would make the scope of protection worthless. There is no apparent reason to decide otherwise in the present case.

2) The terms "inhibitors of the DPP3 activity" or "inhibitor of the activity of DPP3" were considered not clear.

Applicant respectfully disagrees. According to long-standing case law of the Boards of Appeal, the claims are to be interpreted from the viewpoint of the skilled person, who reads the claims with the mind willing to understand, not a mind desirous of misunderstanding (see e.g. section 6.1 of the present issue of the case law of the Boards of Appeal).

It is clear in view of the terms plain meaning, and in particular in view of the application as filed (see e.g. the description of activity measurement of DPP3 and determination of how said activity is inhibited by inhibitors under the present invention) that "DPP3 activity" or "activity of DPP3" refers to the enzymatic activity, not to a known or (partially) unknown physiological role, as seems to be insinuated by the Examining Division.

The skilled person also knows how to determine said activity and its inhibition, and is provided with additional information in the present application.

The term is therefore clear in the meaning of Article 84 EPC.

3) The objection over previous claims 13 and 18 is moot in view of their deletion.

4) In section 2.4 of the official communication, it is objected that it is not clear which compounds fall within the scope of the term "precursor of Angiotensin receptor agonists" in previous claims 15-16 and 18.

Corresponding present claims 14 and 15 have been amended as detailed above to further define the "precursor of Angiotensin receptor agonists", thus overcoming the objection.

The objection over previous claim 18 is moot in view of its deletion.

III. Novelty

The objection brought forward in item 3.5 of the Office Action, and Item 3 of the Office Action dated 20.11.2023 respectively, is moot in view of the deletion of claim 13.

Thus, the claimed subject matter is new.

IV. Inventive Step

D2 is considered as closest prior art.

While D2 shows that DPP3 is elevated in septic shock, there is no indication regarding refractory shock. Thus, the technical feature distinguishing the present invention from D2 is predicting or diagnosing specifically refractory shock with DPP3, or treating the same with a DPP3 inhibitor.

Even if a certain biomarker is known to be elevated in shock, this is no indication that said biomarker can differentiate between refractory and non-refractory shock within a certain shock group.

For instance, present examples 9 and 11 demonstrate that within the group of patients with cardiogenic shock and septic shock, respectively, patients with DPP3 levels in the 3rd quartile have a significantly higher occurrence of refractory shock than patients with lower DPP3 levels (also see Figs. 13 and 15).

None of the cited prior art documents disclose the connection between DPP3 and refractory shock. The present invention demonstrates for the first time that DPP3 is higher in patients with refractory shock than in shock patients without refractory shock and demonstrates the correlation with organ failure. This was simply not foreseeable from the prior art.

Thus, even if the skilled person would not arrive at the solution provided by claim 1 from the teaching of any of the cited prior art documents taken alone or in combination, which is therefore based on an inventive step.

The same considerations apply *mutatis mutandis* to claims 14 and 18, which are therefore likewise based on an inventive step.

V. Conclusion

In view of the amendments made and the above explanations, it is believed that the application is now in a state acceptable for grant. Should the Examining Division, nevertheless, still see deficiencies in the documents on file, it is kindly asked to give the applicant the opportunity to file further arguments and, if necessary, amendments. Minor issues could be discussed by telephone.

Only as a measure of precaution,

Oral Proceedings

are herewith requested.

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Dr. Ute Kilger
Patent Attorney

Enclosures:
- New claims 1 to 18 (clean copy)
- New claims 1 to 18 (marked-up copy)