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

This refers to the Communication pursuant to Rules 161(1) and 162 EPC dated April 7, 2022

Enclosed herewith is an amended set of 21 claims (marked-up and clean copy respectively) addressing the objections raised by the Examiner. It is requested that the enclosed amended documents be taken as basis for the future examination of this application.

1. AMENDMENTS TO THE CLAIMS

a) Claim 14 has been amended by changing the term "shock" to "refractory shock".

The basis for this amendment can be found, e.g., on page 1, lines 3-7 and page 13, lines 1-11.

b) Claim 6 has been amended by changing the term "a treatment is initiated and/or maintained and/or withheld and/ or terminated" to "a treatment is to be initiated and/or maintained and/or withheld and/ or terminated".

Claims 9 to 12 have been amended analogously.

This subject matter is supported at least by claim 5 and the disclosure in the first paragraph on page 11 of the present description, which reads (emphasis added):

> *[A further embodiment of the present invention relates to a] method for predicting or diagnosing a refractory shock in a subject that either runs into shock or that has developed shock according to the present invention, wherein said method is used for initiation and/or termination and/ or stratification and/or guidance of treatment.*

It is clearly stated that the method of the present invention may be used for stratification and/or guidance of treatment. With respect to treatment, stratification means in essence, based on the outcome of the determination of a biomarker in a patient, assigning said patient either into the group that is to receive a treatment or not, or in other words, instructing the physician whether for said patient treatment is to be initiated and/or maintained and/or withheld and/or terminated.

c) Previous claims 20 to 23 (present claims 17 to 20) have been reworded into purpose-related-product format in accordance with Art. 54(5) EPC. Consequently, the back-references have been adapted from the previous method of treatment claims to the corresponding purpose-related-product claims.

d) Previous claims 17-19 and 24 have been deleted.

e) The numbering of the remaining claims and any back-references therein has been adapted in accordance with the above amendments.

As laid out above, all amendments are in accordance with Art 123(2) EPC.

2. NOVELTY

a) Claims 1-12 and 25 were considered not novel in view of D2.

Present claim 1 relates to a specific method for predicting or diagnosing refractory shock in a subject that either runs into shock or that has developed shock.

D2 fails to establish the link between the risk of *refractory* shock in a subject that either runs into shock or that has developed shock and the level of DPP3. D2 merely refers to the link between DPP3 level and sepsis (see D2, "Results", second to last sentence: "*Septic patients show significantly increased DPP3 plasma activity at hospital admission.*"). D2 is in fact focused on the development of a novel method of measuring DPP3 activity and concentration (see D2, "Background", last sentence).

Hence, D2 does not disclose all features of present claim 1 and the subject matter of present claim 1 and dependent claims 2-12 is novel in view of D2.

The above arguments apply, mutatis mutandis, to present claim 21 (previous claim 25).

b) Claims 13 and 17 were considered not novel in view of D3.

D3 concerns a review of therapeutic strategies for high-dose vasopressor-dependent shock (title). The clinical use of vasopressors such as arginine vasopressin for the treatment of refractory shock (see p. 4, under headline "Arginine Vasopressin"), as well as of other vasopressors for said purpose, is described.

Present claim 13 relates to a vasopressor for use in therapy of shock in a subject that either runs into shock or that has developed shock, wherein said subject has a level of DPP3 [...] that is below a predetermined threshold [...] (and conversely, vasopressor treatment is withheld when DPP3 is above said threshold). This amounts to a stratification of the patients into a) patients that receive vasopressor treatment and b) patients that do not receive such treatment.

D3 does not describe a vasopressor for the aforementioned use, let alone for use in patients that have been stratified in dependance of DPP3 levels. In fact, DPP3 is not mentioned at all in D3. Hence, D3 does not disclose all features of present claim 13 and the subject matter of present claim 13 and dependent claims 14-16 is novel in view of D3.

The objection over previous claim 17 is moot in view of its deletion.

3. INVENTIVE STEP

a) Present claim 1 relates to a specific method for predicting or diagnosing refractory shock in a subject that either runs into shock or that has developed shock.

As detailed above, D2 is silent on refractory shock and fails to establish the link between the risk of refractory shock in a subject that either runs into shock or that has developed shock and the level of DPP3.

Accordingly, the skilled person could not have obtained any indication of the presently claimed subject matter relating to refractory shock, from D2, and the subject matter of present claim 1 is consequently non-obvious, i.e., inventive in view of D2.

Claims 2-12 are directly dependent on claim 1. Claims 13-20 are directed to medical uses of vasopressors or inhibitors of the activity of DPP3, wherein the administration of the respective medication depends at least on the DPP3 level, determined by a method according to present claims 1-11 being in a certain relation to a predetermined threshold.

Consequently, the subject matter of present claim 2-20 is inventive in view of the prior art as well.

b) Present claim 21 concerns a method for prognosing an outcome and/or the risk of an adverse event in a subject that has developed refractory shock, wherein said method is comprising the steps: determining the level of DPP3 in a sample of bodily fluid of said subject; comparing said level of determined DPP3 to a predetermined threshold, and correlating said level of DPP3 with said risk of an adverse event in said subject, wherein an elevated level above a certain threshold is predictive for an enhanced risk of said adverse events or, correlating said level of DPP3 with success of a therapy or intervention in said subject, wherein a level below a certain threshold is predictive for a success of therapy or intervention.

As detailed above for present claim 1, the prior art is silent on the relation between refractory shock and DPP3 levels. Consequently, the above arguments apply, mutatis mutandis, to the subject matter of claim 21 (previous claim 25), which is inventive in view of the prior art.

c) The objections raised in points 4.2 and 4.3 of the WO-ISA against Claims 14 and 18, and Claims 11-12 and 22-24, respectively, are moot in view of the above.

4. CLARITY

a) According to the WO-ISA, it is not possible to assess the scope of claims 1, 6-14 and 20-25 because the value of the predetermined threshold is not defined.

Applicant respectfully disagrees. Present claim 1 relates to a method for predicting or diagnosing a refractory shock in a subject that either runs into shock or that has developed shock, wherein said method comprises the steps of

- determining the level of DPP3 in a sample of bodily fluid of said subject;
- comparing said level of determined DPP3 to a predetermined threshold,

wherein said subject is predicted to run into refractory shock or is diagnosed as having refractory shock if said determined level of DPP3 is above said predetermined threshold.

Firstly, one should consider how a threshold value can be established. For example, the level of DPP3 at baseline can be determined from bodily fluid samples that were taken from participants in a study. As a result, a distribution of DPP3 levels over the analyzed study population is obtained. This population can be divided in percentiles, quintiles or quartiles or terciles, etc. For arguments sake, take the case of quartiles, meaning the subjects are grouped into four groups, each comprising the same number of individuals. Each of these groups has an upper and a lower level of DPP3 as determined in the individuals of the at the extremes (the "ends") of the respective quartile. Each of the separating levels may be used as a threshold value. In the case of quartiles, three thresholds are thus obtained.

Each of the four groups will have subjects who end up with refractory shock and subjects who do not. If the correlation between the increased risk and the level of DPP3 is significant, then there are significantly more individuals in the group with the highest DPP3 levels (the fourth quartile) who end up with refractory shock than in the group with the lowest DPP3 levels (the first quartile).

In any case, even in the first quartile, there will still be some subjects who end up with refractory shock. These individuals are false negatives, because they would be grouped as (likely) not ending up with refractory shock, while in reality they do. Vice versa, even in the fourth quartile, there are individuals who will not end up with refractory shock, i.e. false positives.

Adjusting the threshold value and separating different groups, would change the number of false positives and false negatives, but never get rid of either one, or even both occurring. (The only way of avoiding false positives or false negatives would be to either designate all subjects as "ends up with refractory shock", or designate all subjects as "does not end up with refractory shock", which is of course renders the grouping meaningless.)

If a physician is very risk adverse and rather prefers to "overtreat" a given subject, he/she might be inclined to choose a lower threshold, e.g., the threshold between the second and third quartile in the above example as the relevant threshold for predicting whether the subject end up with refractory shock. The physician will then "overtreat" quite a number of subjects. On the other hand, the physician might also be of the opinion that only people with very high level should be predicted as high-risk subjects. Accordingly, the physician may choose the higher threshold level between the third and fourth quartile. Under these circumstances, the physician would "overtreat" a smaller number of subjects but might oversee some individuals at risk.

The terms "false positive" and "false negative" may also be expressed as "sensitivity" and "specificity" of the method. Choosing a threshold corresponding to high sensitivity will result in a lot of false positives, while avoiding missing true positives. One the other hand, choosing a threshold corresponding to high specificity will result in the opposite. Specificity and sensitivity of a method are opposing trends. This means, that a physician will choose a threshold that fits the specificity and the sensitivity required for the respective circumstances and medical question. In each setting, the physician has to decide whether or not a number of false negatives or rather false positives are tolerable.

It should also be kept in mind that the decision how many false positives or false negatives are acceptable highly depends not only on the severity of the medical condition to be treated, but also on the consequences of a treatment. As a drastic illustrative example, take an assessment of "has a (high) risk of breast cancer – yes/no". If the consequence of an assessment of "has a risk of cancer" is a surgery or even amputation of the breast, it is certainly preferable to avoid false positives, in order to spare any given subject an unnecessary surgery or amputation. The threshold would thus be set comparably high. If however, the consequence of an assessment of "has a risk of cancer" is that the subject should submit to regular screenings, it would be more important to avoid false negatives, to assure that as few individuals as possible "slip through the cracks" of the screening. The threshold would thus be set comparably low.

This consequence of such an assignment, i.e., what happens after the subject is assigned to either group, and consequently whether the threshold should be higher or lower, is completely out of the control of the Applicant, and it is clear that it would be unreasonable to limit the claims to a specific threshold in the present claims.

In summary, if in the present claims the threshold were to be restricted, e.g., to a specific numerical value, the scope of such claims would be unduly limited and effectively render the claim (and a resulting patent) practically meaningless.

In addition, the results of an assay, i.e., the obtained values, of course may vary depending on the specific conditions the assay is run under, which is also addressed in the description on page 18, line 4 et seqq.

Finally, and importantly, choosing the appropriate threshold for the respective medical question comes down to a routine task involving. The skilled person, who would in this case be a medical statistician or a team comprising a physician and a statistician, can determine the threshold based on the statistical data obtained from

a study population, as mentioned above, and having the medical question in mind. While this may involve a certain amount of practical effort, it is still a routine task.

It is stated for sake of completeness that the above arguments apply to aspects relating to ADM-NH2 levels, and/or to the subject being "diagnosed as having refractory shock", etc., and to claims 6-14 and 20-25, mutatis mutandis.

In view of the aspects detailed above, it is apparent that the present claims define the matter for which protection is sought clearly.

b) Claims 6 to 12 were considered unclear for allegedly being directed to a method of diagnosis of refractory shock wherein the claims also relate to the treatment of a patient.

As detailed above, amended claims 6 to 12 state that the treatment is to be initiated and/or maintained and/or withheld and/or terminated, based on the outcome of the determination of the level of DPP3 or Pro-adrenomedullin or fragments thereof. In other words, based on the outcome of the aforementioned determination, the information is given to the treating physician that treatment is to be initiated and/or maintained and/or withheld and/or terminated. The methods of amended claims 6 to 12 therefore do not comprise treatment steps per se.

The objection has therefore been rendered moot.

5. REQUESTS

With the above explanations the Applicant has met the requirements set forth in the Communication.

If, however, the Examining Division does not agree with the above, it is requested that either a further Communication pursuant to Art. 94(3) EPC or a summons to attend oral proceedings according to Art. 116(1) EPC be issued. If deemed expedient, an informal interview is requested. The undersigned is prepared to discuss minor amendments over the phone.

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Dr. Ute Kilger
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Enclosures:
– Amended claims (marked-up and clean copy)