The examination is being carried out on the **following application documents**

Description, Pages

1-99 as originally filed

Claims, Numbers

1-10 as originally filed

Drawings, Sheets

1/15-15/15 as originally filed

1 Independent claim

1. Inhibitor of the activity of DPP3

for use in a method of prevention or treatment of a refractory shock

in a subject that either runs into shock or that has developed shock,

wherein said subject has a level of DPP3 in a sample of bodily fluid of said subject that is above a predetermined threshold when determined by 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 is comprising the steps:
· determining the level of DPP3 in a sample of bodily fluid of said subject, said sample of bodily fluid is selected from the group of whole blood, plasma, and serum.;
· comparing said level of determined DPP3 to a predetermined threshold that is between 25 and 150 ng/ml for plasma DPP3,
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 and,
wherein the inhibitor of the activity of DPP3 is selected from the group comprising anti-DPP3 antibody or anti-DPP3 antibody fragment, and
wherein said anti-DPP3 antibody or anti-DPP3 antibody fragment is binding to an epitope according to SEQ ID NO.: 2, wherein said epitope is comprised in a DPP3

protein or functional derivative thereof and wherein said anti-DPP3 antibody or anti-DPP3 antibody fragment is a monoclonal antibody or a monoclonal antibody fragment thereof.

2 Divisional application (Art. 76(1) EPC)

2.1 The present application has been filed as a divisional application of patent application of patent application EP20764539.9. There appears to be at present no issue of double patenting.

2.2 In the letter dated 28.03.25, the applicant has indicated the basis for the present claims in the PCT application as published. The applicant's attention is drawn to the fact that the basis for the claims needs to be present in the parent application as originally filed (not as published).

2.2.1 Claim 1:

Original parent claim 14 was directed to:

"Inhibitor of the activity of DPP3 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 in a sample of bodily fluid of said subject that is above a predetermined threshold when determined by a method according to any of claims 1 – 11,

wherein the inhibitor of the activity of DPP3 is selected from the group comprising anti-DPP3 antibody or anti-DPP3 antibody fragment or anti-DPP3 non-Ig scaffold".

Original parent claim 1 was directed 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 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,

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.

The passage on page 11, lines 13 to 22 mentions inhibitors of the DPP3 activity for use in a method of prevention or treatment of a refractory shock in a subject that either either runs into shock or that has developed shock.

How this particular embodiment combined with the treatment of shock (not of refractory shock) of original parent claim 14 remains to be determined.

The passage on page 6, lines 32 to 34 indicates that "In another embodiment of said method for predicting or diagnosing a refractory shock in a subject that either runs into shock or that has developed shock, said sample of bodily fluid is selected from the group of whole blood, plasma, and serum". These seem to be the preferred bodily fluid samples to be used.

The passage on page 33, lines 8 to 12 relates to "an angiotensin-receptor-agonist and/ or a precursor thereof for use in the treatment of shock".

The passage page 13, lines 13-15 indicates that "the threshold is within a threshold range for plasma DPP3 that is between 20 and 200 ng/ml, preferably between 25 and 150 ng/ml, even more preferred between 30 and 100 ng/ml, even more preferred between 35 and 75 ng/ml, most 15 preferred a threshold of 50 ng/mL is applied". The threshold of 25 and 150 ng/ml is preferred, but it is not most preferred. this choice represents a selection from one list.

The passage on page 20 lines 15-18 mentions: "Another specific embodiment of the invention relates to an inhibitor of the activity of DPP3 for use in therapy of shock in a subject that either runs into shock or that has developed shock, wherein the inhibitor of the activity of DPP3 is selected from the group comprising anti-DPP3 antibody or anti-DPP3 antibody fragment or anti-DPP3 non-Ig scaffold". The choice of an anti-DPP3 antibody or anti-DPP3 antibody fragment represents a selection from a second list.

The passage on page 44 line 32 to page 45 line 2 mentions "Thus, the anti-DPP3 antibody or anti-DPP3 antibody fragment in accordance with the invention may have the formats known in the art. Examples are human antibodies, monoclonal antibodies, humanized antibodies, chimeric antibodies, CDR-grafted antibodies or antibody fragments thereof, but not limited to".

The choice of the anti-DPP3 antibody or anti-DPP3 antibody fragment being a monoclonal antibody is singled out on page 45, lines 4 to 5 "In a specific embodiment of the invention the anti-DPP3 antibody is a monoclonal antibody or a fragment thereof". In addition, the passage on page 46, lines 29 to 32 indicates that "In a specific embodiment of the invention said anti-DPP3 antibody or anti-DPP3 antibody fragment binding to an epitope according to SEQ ID NO.: 2, wherein said epitope is comprised in a DPP3 protein or functional derivative thereof is a monoclonal antibody or a monoclonal antibody fragment thereof".

There appears to be added subject matter. The originally filed application seems to provide basis for the features of claim 1 individually but not in combination. In other words, the combination of features which is presently the subject matter of claim 1 is not clearly and unambiguously derivable from the originally filed parent application.

2.2.2 Claim 2:

The passage on page 45, lines 4 to 8 indicates that "In a specific embodiment of the invention the anti-DPP3 antibody is a monoclonal antibody or 5 a fragment thereof. In one embodiment of the invention the anti-DPP3 antibody or the anti-DPP3 antibody fragment is a human or humanized antibody or derived therefrom. In one specific embodiment one or more (murine) CDR's are grafted into a human antibody or antibody fragment".

This passage does not provide a clear and unambiguous indication that the anti-DPP3 antibody or anti-DPP3 antibody fragment binding to an epitope according to SEQ ID NO.: 2, wherein said epitope is comprised in a DPP3 protein or functional derivative thereof is a monoclonal antibody or a monoclonal antibody fragment thereof and is a human or humanized antibody or derived therefrom or humanized antibody fragment or derived therefrom.

There appears to be added subject matter. There is no clear and unambiguous disclosure of the combination of features which is the subject of claim 2 in the originally filed parent application.

2.2.3 Claim 3:

The passage on page 47, lines 4 to 5 indicates that "In one specific embodiment one or more (murine) CDR's are grafted into a human antibody or antibody fragment". Even if the term "specific embodiment" could be interpreted as a subgroup of the embodiment described in the previous sentence (see claim 2), there is no basis for the combination with any or all of the features which are the subject of claim 1.

There appears to be added subject matter. There is no clear and unambiguous disclosure of the combination of features which is the subject of claim 3 in the originally filed parent application.

The passage on page 82, lines 11 to 14 relates to example 5 and more specifically to Procizumab and does not provide a basis for generalisation to any or all of the possible antibodies potentially encompassed by claim 3.

2.2.4 Claim 4:

The passage on page 44, line 4 to 19 does not provide a bais for the subject matter of claim 4.

The passage on page 82, lines 1 to 20 relates to example 5 and more specifically to Procizumab and does not provide a basis for generalisation to any or all of the possible antibodies potentially encompassed by claim 4.

There appears to be added subject matter. There is no clear and unambiguous disclosure of the combination of features which is the subject of claim 4 in the originally filed parent application.

The objection applies to the subject matter of claim 5, *mutatis mutandis.*

2.2.5 Claim 6:

The passage on page 4, lines 4 to 7 indicates: "In another specific embodiment of said method for predicting or diagnosing a refractory shock in a subject that either runs into shock or that has developed shock, said shock is selected from the group comprising shock due to hypovolemia, cardiogenic shock, obstructive shock and distributive shock, in particular cardiogenic or septic shock". This passage does not provide a basis for treating or preventing shock, wherein said shock is selected from the group comprising shock due to hypovolemia, cardiogenic shock, obstructive shock and distributive shock, in particular cardiogenic or septic shock.

There appears to be added subject matter. There is no clear and unambiguous disclosure of the combination of features which is the subject of claim 6 in the originally filed parent application.

2.2.6 Claim 7:

The passage on page 21, lines 12 to 21 provides basis for the wording "said Inhibitor is administered in combination with an Angiotensin-Receptor-Agonist and/or precursor thereof , and wherein said Angiotensin-Receptor-Agonist and/ or precursor thereof that is selected from the group comprising angiotensin I, angiotensin II, angiotensin III, angiotensin IV, in particular angiotensin II".

The passage on page 31, line 29 to page 32, line 14 has been considered but fails to provide a basis for each feature and each combination of features which is the subject of claim 7, let alone in combination with the claims from which it depends.

There is added subject matter.

2.2.7 Claim 8:

The passage on page 21, lines 17 to 21 provides basis for the wording of claim 8, but not for the combination of features resulting from its dependency from claim 7.

2.2.8 Claim 9:

The passage on page 9, lines 21 to 26 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 a treatment with Angiotensin-Receptor-Agonists and/ or precursors thereof and/or inhibitors of the DPP3 activity is initiated and/or continued when the level of DPP3 in said sample is above 25 a certain threshold and/or wherein a treatment with vasopressors is withheld and/ or terminated if said determined level of DPP3 is above said predetermined threshold", not to the treatment or prevention of refractory shock by means of an inhibitor of activity of DPP3.

There appears to be added subject matter. There is no clear and unambiguous disclosure of the combination of features which is the subject of claim 9 in the originally filed parent application.

The objection applies to the subject matter of claim 12, *mutatis mutandis* (see page 12, lines 12 to 23).

2.3 Whereas the original parent application seems to provide literal basis for most features of the claims taken individually, this is not the case for their combination, as presently claimed. The requirements of Art. 76(1) EPC are not met.

3 **In view of the identified non-compliances with the requirements of Art. 76(1) EPC, it is not at present possible to perform a complete assessment as to the further patentability requirements in accordance with the EPC. Comments are made below for the sake of completeness and procedural efficiency in view of the evidence at hand. These comments can be taken into account for further prosecution. The applicant can file new claims which take into account all objections and comments made in the present communication. In this respect, it is noted that in line with the requirements of Rule 137(4) EPC, the applicant shall identify any amendment and indicate the basis for them in the application as filed. Listing passages of the application where to find the features of the**

claims is not sufficient, in particular, when the amendments to the claims are extensive, giving rise to new combinations of features. The requirement to indicate the basis for amendments amendments is to be understood as an opportunity for the applicant to provide convincing arguments to the division as to why the amendments (each feature and each combination of features of each claim) are directly and unambiguously derivable from the application as filed (Guidelines H-III 2.1).

4 Comments on clarity, support (Art. 84 EPC) and sufficiency of disclosure (Art. 83 EPC)

4.1 Claim 1 is directed to certain compounds ("inhibitor of the activity of DPP3") for use in a method of medical treatment ("prevention or treatment of a refractory shock"), wherein said compounds are defined only in terms of their functional activity, namely by their ability to somehow inhibit an activity of DPP3. Neither the activity which is to be inhibited nor the inhibitor are defined.

In such a situation, a function definition of the compounds can only be allowed if the following conditions are met (cf. Guidelines F-III, 1 and F-IV, 2.1; and T 68/85):

1) the compounds showing the desired functionality are part of the common general knowledge and the functionality is accepted in the prior art to have a clear technical meaning,

2) the functionality can be verified using tests or procedures adequately specified in the description of known to the skilled person and which do not require undue experimentation, and

3) the disclosure of the invention unambiguously shows that the functional activity defined in the claim(s) is the essential feature of the invention, regardless of the structure of the compound(s).

In the present case, however, none of these conditions /are not fulfilled, because inhibitors of the activity of DPP3 are not part of the common general knowledge, there are no tests to verify a functionality which is not defined (there is no indication that it is the enzymatic activity of DPP3 which is to be inhibited) and only one such inhibitor is provided in the present application, namely Procizumab.

Therefore, the requirements of Article 83 and Article 84 EPC are not met.

It is not clear what is intended by "the DPP3 activity". In fact, while DPP3 is a metallopeptidase, as acknowledged in the present application, "the exact biological function of DPP3 in cellular physiology is not understood". The activity is by no means limited to the enzymatic activity as metallopeptidase.

The objection applies to all claims.

4.2 In addition, and whereas in order for a further medical use claim to be deemed sufficiently disclosed, it is not necessary for a therapeutic effect to have been demonstrated clinically, the effect shown in the application (examples) must directly and unambiguously reflect the claimed therapeutic applications. This is however not the case here.

Only procizumab is used in the examples (see examples 5-7) and shown to be potentially effective in the treatment of septic shock induced heart failure (example 6). It is also shown that application of Procizumab to isoproterenol-induced heart failure mice restores heart function within the first hour after administration. Kidney function of sick mice shows significant improvement at 6 hours post Procizumab injection and is comparable to the kidney function of sham animals at 24 hours.

Nothing is shown regarding the treatment or the prevention of refractory shock.

Attaining a therapeutic effect in the medical indication recited in a purpose-related product claim is a functional feature of such a claim. If an invention lacks reproducibility because its desired technical effect as expressed in the claim is not achieved, this results in lack of sufficient disclosure, contrary to the requirements of Art. 83 EPC.

The effect shown in the application are not disputed.

What is has not been rendered credible, is that any or all of the possible inhibitors of any possible DPP3 activity would be suitable, let alone effective in treating or preventing refractory shock in a subject that either runs into shock or that has developed shock, wherein said subject has a level of DPP3 as determined in a sample of whole blood, plasma, and serum which is above a predetermined threshold that is between 25 and 150 ng/ml for plasma DPP3.

The requirements of Art. 83 EPC are not met. The objection applies to all claims.

5 Cited documents and priority

5.1 Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D1 KOJI TAKAGI ET AL: "Circulating dipeptidyl peptidase 3 and alteration in haemodynamics in cardiogenic shock: results from the OptimaCC trial", EUROPEAN JOURNAL OF HEART FAILURE, vol. 22, no. 2, 31 August 2019 (2019-08-31), pages 279-286, XP055681198, NL ISSN: 1388-9842, DOI: 10.1002/ejhf.1600

D2 BENJAMIN DENIAU ET AL: "Circulating dipeptidyl peptidase 3 is a myocardial depressant factor: dipeptidyl peptidase 3 inhibition rapidly and sustainably improves haemodynamics", EUROPEAN JOURNAL OF HEART FAILURE, vol. 22, no. 2, 31 August 2019 (2019-08-31), pages 290-299, XP055681384, NL ISSN: 1388-9842, DOI: 10.1002/ejhf.1601

D3 ESTEVÃO BASSI ET AL: "Therapeutic Strategies for High-Dose Vasopressor-Dependent Shock", CRITICAL CARE RESEARCH AND PRACTICE, vol. 2013, 1 January 2013 (2013-01-01), pages 1-10, XP055681557, ISSN: 2090-1305, DOI: 10.1155/2013/654708

D4 WO 2019/077082 A1 (ADRENOMED AG [DE]) 25 April 2019 (2019-04-25)

D5 JADHAV AMAR P ET AL: "Angiotensin II in septic shock", AMERICAN JOURNAL OF EMERGENCY MEDICINE, vol. 37, no. 6, 19 March 2019 (2019-03-19), pages 1169-1174, XP085707434, ISSN: 0735-6757, DOI: 10.1016/J.AJEM.2019.03.026

D6 WO 2019/081595 A2 (SPHINGOTEC THERAPEUTICS GMBH [DE]) 2 May 2019 (2019-05-02)

D7 WO 2021/185786 A1 (4TEEN4 PHARMACEUTICALS GMBH [DE]) 23 September 2021 (2021-09-23)

D8 WO 2020/128039 A2 (4TEEN4 PHARMACEUTICALS GMBH [DE]) 25 June 2020 (2020-06-25)

5.2 The most relevant passages are indicated in the seach report unless otherwise specified.

5.3 The present application claims priority from

EP 19 194 729.0 (30-08-2019)

EP 19 201 098.1 (02-10-2019)

The priorities claimed appear to be valid. The priority documents seem to disclose the same subject matter as the parent application as originally filed.

5.3.1 D1, published on 31.08.2019, is not part of the prior art for the present assessment.

5.3.2 D7, published on 23.09.2021, filed on 15.03.2021 and claiming priority from 16.02.2020, 24.04.2020 and 12.06.2020, is not part of the prior art for the present assessment.

5.3.3 D8 was published on 25.06.2020 and was filed on 20.12.2019. It claims priority from EP18215656.2 (21.12.2018) and EP19194769 (30.08.2019).

It has been supplied to the European Patent Office in one of its official languages according to Article 153(3) and (4) EPC and the filing fee provided for in Rule 159(1)(c) EPC or Article 39(1) PCT has been paid. The requirements of Rule 165 EPC are thus fulfilled. Its content as filed is therefore considered to be comprised in the state of the art relevant to the question of novelty, pursuant to Article 54(3) EPC.

D8 is from the same applicant as the present application. Hence, and only insofar as it discloses the same subject matter as claimed in the present application (if applicable), the priority date claimed for the present application would not be valid, since the subject matter disclosed therein has already been filed by the same applicant. This is at present not the case since D8 does not seem to mention the treatment or prevention of refractory shock.

6 Comments on novelty (Art. 54 EPC) and Inventive step (Art. 56 EPC)

6.1 The cited prior art documents disclose the following:

6.1.1 Document D2 (XP055681384) discloses a method for assessing circulatory DPP3 in patients with severe sepsis and septic shock and shows that DPP3 levels increase with the severity and the mortality risk. cDPP3 inhibition by Procizumab, a specific antibody directed against cDPP3, promptly normalized

cardiac function and kidney haemodynamics in an acute heart failure mouse model, with a marked reduction in oxidative stress and inflammatory signalling (see Figures 1 and 3).

It is indicated that high levels of cDPP3 in cardiogenic shock patients, after acute myocardial infarction,are associated with low cardiac index and high occurrence of refractory shock and impaired kidney function.

D2 does not mention the treatment or prevention of refractory shock.

6.1.2 Document D3 (XP055681557) relates to the treatment of refractory shock. The use of vasopressors for treating shock is well established.

6.1.3 Document D4 (WO2019077082) discloses the assessment of pro-adrenomedullin fragment for determining the outcome of the treatment with anti-adrenomedullin antibody or antibody-fragment.

6.1.4 Document D5 (XP085707434) discloses the use of angiotensin II in the treatment of septic shock.

6.1.5 Document D6 (WO2019081595) discloses the use of an hDPP3 binding antibody (AK1967) in the treatment of septic shock (example 3).

D6 does not mention the treatment or prevention of refractory shock.

6.1.6 Document D8 (WO2020/128039) discloses the combined use of an angiotensin receptor agonist and an inhibitor of DPP3 (anti-DPP3 antibody procizumab) for use in the treatment of shock.

D8 does not mention the treatment or prevention of refractory shock.

6.2 None of the presently available prior art documents seem to mention the treatment or prevention of refractory shock.

6.3 Problem /Solution approach

6.3.1 Closest prior art: D6

6.3.2 Difference: D6 fails to mention the treatment or prevention of refractory shock

6.3.3 No technical effect linked to the specific treatment or prevention of refractory shock has been shown in the present application.

6.3.4 The objective technical problem can be formulated as the provision of alternative uses for AK1967.

6.3.5 The solution proposed is the treatment or prevention of refractory shock.

6.3.6 Starting from D6 and looking for further uses of AK1967, the skilled person would have considered its use in the treatment or prevention of refractory shock. It would have been at least obvious to try AK1967 so as to inhibit DPP3 in the context of refractory shock. Claim 1 lacks inventive step.

No technical effect linked to the other features of claim 1 or of any of claims 2-10 can be identified. These claims are also found to lack inventive step.