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

Description, Pages

1-99 as published

Claims, Numbers

1-21 filed in electronic form on 17-10-2022

Drawings, Sheets

1/15-15/15 as published

A new Examining Division has been appointed. The previously expressed opinion is maintained. The arguments provided by the applicant in the latest submissions have been duly considered. Additional comments are provided below.

1 Independent claims

1. 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.

13.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 in a sample of bodily fluid of said subject that is below a predetermined threshold,

when determined by a method according to any of claims 1 - 11.

14.Inhibitor of the activity of DPP3

for use in therapy of 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 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.

21.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,
• 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.

2 Clarity, support (Art. 84 EPC), sufficiency of disclosure (Art. 83 EPC)

2.1 It is maintained that claim 1 is not clear, contrary to the requirements of Art. 84 EPC.

Claim 1 refers to a "predetermined threshold" which is not defined. The claims must be clear as such and must define all technical features necessary for achieving the claimed technical effect. This is not the case here, contrary to the requirements of Art. 84 EPC. In fact, the method of claim 1 relies on a comparison of a level of DPP3 in a sample with a predetermined threshold which is not defined in the claims. The subject matter of claim 1 cannot be reproduced by the skilled person without undue burden, contrary to the requirements of Art. 83 EPC.

It is maintained that the claims are more an invitation to perform a research program in order to determine the DPP3 levels which are indicative of a refractory shock. This would require a clinical study and would represent an undue burden for a skilled person.

In that sense, claim 1 is found to contravene both Art. 84 EPC and Art. 83 EPC.

The same applies to all claims, as none of the claims define the referred "predetermined threshold".

2.2 The terms "inhibitors of the DPP3 activity" or "inhibitor of the activity of DPP3" employed throughout the claims are not clear, contrary to the requirements of Art. 84 EPC.

It is noted that "inhibitors of the DPP3 activity" or "inhibitor of the activity of DPP3" are not part of the common general knowledge and the functionality is not accepted in the prior art to have a clear technical meaning. In fact, 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". In addition, the only inhibitor of DPP3 provided in the present application is an anti-DPP3 antibody, namely AK1967.

The subject matter of claims 7, 9, 10, 12, 14-19 is found to contravene both Art. 84 EPC and Art. 83 EPC.

2.3 As indicated in the former communication, claim 18 seems to be dependent of claim 13 but refers to treatment with Angiotensin receptor agonists or DPP3 inhibitors whereas claim 13 is directed to vasopressors. This inconsistency renders the scope of the claim unclear, contrary to the requirements of Art. 84 EPC.

2.4 It is not clear which compounds fall within the scope of the terms "precursor of Angiotensin receptor agonists in claims 15-16 and 18. Said claims lack clarity (Art. 84 EPC).

3 **In view of the above objections, it is not at present possible to perform a complete assessment as to the novelty and inventive step of the subject matter claimed in the present application. The applicant is hereby given one more opportunity to provide amended claims which overcome the above objections before oral proceedings are summoned, as requested.**

3.1 **The following comments are made for the sake of completeness and procedural efficiency in view of the documents at hand and the arguments and evidence provided by the applicant. These comments should be taken into account for further prosecution.**

3.2 The following documents have been cited in the international search report

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 LINDA REHFELD ET AL: "Novel Methods for the Quantification of Dipeptidyl Peptidase 3 (DPP3) Concentration and Activity in Human Blood Samples", THE JOURNAL OF APPLIED LABORATORY MEDICINE, vol. 3, no. 6, 1 May 2019 (2019-05-01), pages 943-953, XP055681701, ISSN: 2576-9456, DOI: 10.1373/jalm.2018.027995

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

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

3.4 The cited documents disclose the following:

3.4.1 Document D1 discloses that circulating DPP3 is increased in patients with refractory cardiogenic shock despite vasopressor treatment, compared to patients having non-refractory shock.

3.4.2 Document D2 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.

3.4.3 Document D3 relates to the treatment of refractory shock. The use of vasopressors for treating shock is well established.

3.4.4 Document D4 discloses the assessment of pro-adrenomedullin fragment for determining the outcome of the treatment with anti-adrenomedullin antibody or antibody-fragment.

3.4.5 Document D5 discloses the use of angiotensin II in the treatment of septic shock.

3.5 In the letter dated 18.03.24, the applicant has indicated that the patient group of D3 was not identical to the patient group as claimed in the present application. The applicant argued that claim 13 was directed to a vasopressor for treating a patient with shock who had a DPP3 value below a threshold value.

The Examining Division notes that since the "threshold value" is not defined in the claims, it cannot serve to delimit or define a group of patients.

According to the applicant, these patients do not have a refractory (= vasopressor-resistant) shock according to claim 1 (have or develop it).

Again, it is noted that no group of patients is defined in the claims. In that sense, D3, which discloses the use of vasopressors e.g. arginine vasopressin for the treatment of refractory shock, anticipates the subject matter of at least claim 13.

According tot he applicant, 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).

Again, the Examining Division cannot agree with this assessment. There is no group of patients defined in claim 13.

The objection is maintained.

3.6 Regarding inventive step, the applicant has indicated that it was known in the prior art that DPP3 is generally increased in septic as well as cardiogenic shock.

According to the applicant, it could not deduced therefrom that a distinction could be made between patients having refractory and non-refractory shock. The applicant noted that this distinction gave 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.

In this respect, the Examining Division notes that the claims, as presently worded do not enable a predicting or diagnosing a refractory shock based on DPP3 levels.

The Examining Division also notes that the use of angiotensin II in the event of refractory shock is known (see D6 below, for example).

The use of vasopressors in the case of non-refractory shock is also well established (see D3).

In that sense, the group of patients treated is not different from that of the prior art. The contribution by the applicant lies in the determination of certain DPP3 levels and their correlation with refractory shock prediction. The therapeutic treatments for refractory or for non-refractory shock are already known.

3.7 The additional data submitted by the applicant and showing in an animal model that refractory septic shock can be successfully treated using the monoclonal antibody Procizumab, which binds and inhibits circulating DPP3 activity has been duly considered.

3.8 It is however maintained that in view of D2 it would be obvious for a skilled person to determine the level of DPP3 in order to assess the risk of refractory shock the outcome of a treatment.

3.9 The following documents are cited by the Examiner for the sake of completeness. A copy of the documents is annexed to the communication and the numbering will be adhered to in the rest of the procedure.

D6 Rachel Bussard ET AL: "Angiotensin II: a new therapeutic option for vasodilatory shock",
THERAPEUTICS AND CLINICAL RISK MANAGEMENT,
vol. 14, 26 July 2018 (2018-07-26), pages 1287-1298, XP055770997,
NZ
ISSN: 1176-6336, DOI: 10.2147/TCRM.S150434

D7 WO 2019/081595 A2 (SPHINGOTEC THERAPEUTICS GMBH [DE]) 2 May 2019 (2019-05-02)

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

D6 suggests the use of Ang II in the treatment of refractory shock.

D7 discloses the use of the DPP3 inhibitory antibody AK1967 in the treatment of septic shock.

D9 is at least relevant pursuant to Art. 54(3) EPC. It discloses the use of Angiotensin-Receptor- Agonist in the treatment of hypotension and shock (claim 1), alone or in combination with an inhibitor of DPP3. Refractory shock does not seem to be mentioned.