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Application No.	Ref.	Date
20 764 639.9 - 1109	T75093WOEP	06.11.2024
Applicant: 4TEEN4 Pharmaceuticals GmbH		

Summons to attend oral proceedings pursuant to Rule 115(1) EPC

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent application.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2906).

The oral proceedings, which will not be public, will take place before the Examining Division

on 08.05.2025 at 09:00 hrs (CET), as a videoconference.

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 2009, 68). If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC, see also OJ EPO 2008, 471).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and the decision of the President of the EPO dated 8 July 2024 on the signing and filing of authorisations (OJ EPO 2024, A75).

The final date for making written submissions and/or amendments (R. 116 EPC) is 07.03.2025.

IMPORTANT:
Please provide us as soon as possible with the name and telephone number of a person we can contact about the oral proceedings and an email address to which we can send the details for connecting to the videoconference.

Please inform us immediately if you have not received the details for connecting to the videoconference at least ten days before the scheduled date of the oral proceedings.

You can find out more about the technical requirements and supported systems for videoconferences, making test calls and our data protection policy at www.epo.org.

Registered Letter

Examining Division:

Chairperson:	**Habedanck, Robert**
2nd Examiner:	**Merckling-Ruiz, Virginie**
1st Examiner:	**Fayos, Cecile**

Annexes: Applicants not using the Mailbox can access patent literature via Espacenet
10 page/s reasons (EPO Form 2906)

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

Description, Pages

1-99	as published

Claims, Numbers

1-18	filed in electronic form on	19-09-2024

Drawings, Sheets

1/15-15/15	as published

Having considered the arguments brought by the applicant with his letter of 19.09.2024 and 17.10.2022, as well as the newly filed claims, the objections raised in the previous communication are maintained and oral proceedings are considered expedient.

Since the applicant has requested oral proceedings, a summons is dispatched with this communication.

The topics of the oral proceedings to be held will be the following:

- Added subject matter (Art. 123(2) EPC)
- Clarity and Support (Art. 84 EPC)
- Sufficiency of disclosure (Art. 83 EPC)
- Novelty (Art. 54 EPC)
- Inventive step (Art. 56 EPC)

as outlined below.

The applicant's attention is drawn to the fact that no submissions should be made later than two months prior to the date set for the oral proceedings.

The examining division will exert its discretion in deciding whether to allow or not further amendments according to Rule 137(3) EPC.

The present application is based on the identification of a relation between the plasma concentration of DPP3 in shock patients (septic, cardiogenic) and the development of refractory shock. The effect of inhibition of DPP3 by means of AK1967; "Procizumab" in septic shock-induced heart failure was studied. An improvement was observed.

Based on these findings, the claims relate to a method for predicting or diagnosing a refractory shock in a subject, an inhibitor of the activity of DPP3 for use in therapy of refractory shock and a method for prognosing an outcome and/or the risk of an adverse event in a subject that has developed refractory shock, as detailed below.

The present application seems to demonstrate 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. While this does not seem to have been suggested in the prior art, the claims, as presently worded, fail to reflect this finding.

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.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.

18.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 Added subject matter (Art. 123(2) EPC)

2.1 Claims 1-12 remain unchanged. These claims are based on original claims 1-12.

2.2 Former claims 13, 18, 20 have been deleted.

2.3 Claim 13 is based on original claim 14.

2.4 Claim 14 is based on original claim 15, amended to provide a definition of the "precursor". According to the paragraph bridging pages 31 and 32 (not 30 and 31) of the originally filed application, "The term "prodrug" refers to any precursor compound which is able to generate or to release the above mentioned peptide under physiological conditions". Importantly, this paragraph refers to "An angiotensin II, angiotensin III, or angiotensin IV therapeutic" and not to any Angiotensin receptor agonist peptide and hence does not refer to a precursor of any possible angiotensin receptor agonist peptide.

There is also no clear and unambiguous disclosure of a precursor of an angiotensin-receptor agonist being "pegylated forms of angiotensin-agonist peptides". Pegylated forms of the peptides or conjugates as disclosed in US Patent Publication 2011/0081371 are mentioned page 31. this is not what is claimed.

The feature "Larger peptides comprising Angiotensin-Receptor-Agonist peptides, which upon selective cleaving form the Angiotensin-Receptor-Agonist peptide" seems to be based on page 31 last line and page 32 first line.

Basis for "angiotensinogen, angiotensin I, or its homologues that may result in angiotensin II by the action of certain endogenous or exogenous enzymes" is to be found on page 32 lines 2-4. This is however not what is claimed.

Page 32 lines 6-9 indicates that "Suitable protecting groups for amino groups include the benzyloxycarbonyl, tbutyloxycarbonyl (BOC), fluorenylmethyloxycarbonyl (FMOC), formyl, and acetyl **or** acyl group. Suitable protecting groups for the carboxylic acid group include esters such as benzyl esters or t-butyl esters". These are all alternatives. There is no basis for the term "and" ("and/or").

Finally, page 32 lines 9-14 refers to precursors of angiotensin II, angiotensin III, angiotensin IV (not any possible angiotensin receptor agonist peptide) "having amino acid substitutions, deletions, additions, the substitutions and additions including the standard D and L amino acids and modified amino acids, such as, for example, amidated and acetylated amino acids, wherein the therapeutic activity of the base peptide sequence is maintained at a pharmacologically useful level".

The subject matter of claim 14 is not clearly and unambiguously derivable from the originally filed application and the requirements of Art. 123(2) EPC are not found to be met.

2.5 Claim 15 is based on original claim 16 amended to specify "refractory shock", based on based on page 1, lines 3-7 and page 13, lines 1-11 wherein the treatment of refractory shock is envisaged.

2.6 Claim 16 is based on original claim 20, amended to specify "refractory shock", based on page 1, lines 3-7 and page 13, lines 1-11 wherein the treatment of refractory shock is envisaged.

2.7 Claim 17 is based on original claim 22.

2.8 Claim 18 is based on original claim 25.

2.9 There is added subject matter, the requirements of Art. 123(2) EPC.

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

3.1 The arguments provided by the applicants in the latest submission have been duly considered. All objections are nevertheless maintained. The reasons are as follows.

3.2 Regarding the feature "predetermined threshold", the applicant has argued that it was common practice for a medical practitioner to choose different thresholds in order to include or exclude patients based on these thresholds and that different medical practitioners may chose different threshold values for the

same medical indication based on individual judgment and experience. According to the applicant, the decision on how the patients are divided into risk groups is taken by the medical practitioner.

The Examining Division is of the opinion that either a clear threshold value or an indication as to how such a predetermined threshold value is to be determined for comparison are necessary.

The data presented in Figure 13 indicate that DPP3 is related to refractory shock and that high DPP3 concentrations in plasma of cardiogenic shock patients are related with a higher risk to develop refractory cardiogenic shock compared to patients that have DPP3 plasma concentrations below a certain threshold.

As pointed out by the applicant, Examples 9 and 11 indicate that, the absolute cutoffs are 59.1 ng/ml in the cardiogenic shock patients and 48.4 ng/mL in septic shock patients respectively.

Yet this is not what is claimed. Not only the predetermined threshold valued is not defined, but also the skilled person is left with the burden to determine, in each case and for each different patient what such a predetermined threshold value would be.

The applicant has further argued that a medical practitioner may choose the threshold depending on whether more false-positive or false-negative results are considered tolerable. The medical practitioner would initiate medical treatment based on the division of the patients into the respective risk group. The specific value of a threshold value could thus vary for good reasons. While this might well be the case, the claims, which define the subject matter for which protection is sought in terms of technical features, must be clear, as such. In the absence of a predetermined threshold value or of an indication as to how it is to be determined, the level of DPP3 in a sample of bodily fluid cannot be compared.

The subject matter of claim 1 cannot be reproduced by the skilled person without undue burden, contrary to the requirements of Art. 83 EPC.

The objection as to lack of clarity is maintained (Art. 84 EPC).

The objection as to lack of sufficient disclosure is also maintained (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. Relying on the individual expertise and assessment of a clinical practitioner in the assessment of each individual patient further highlights the lack of reproducibility.

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".

The objection applies *mutatis mutandis* to the subject matter of claim 11.

3.3 Regarding the features "inhibitors of the DPP3 activity" or "inhibitor of the activity of DPP3", the applicant argued that “DPP3 activity” or “activity of DPP3" referred to the enzymatic activity. This is however not what is claimed. Even if this was specified in the claims (which is not the case), it is maintained 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. The only inhibitor of DPP3 provided in the present application is an anti-DPP3 antibody, namely AK1967.

There is thus lack of clarity, as the inhibitor is not defined and lack of technical support, as only one specific such inhibitor has been used in the examples and shown to have an effect (Art. 84 EPC). In addition, there is also lack of sufficient disclosure as it has not been rendered plausible that any or all possible "inhibitors of the DPP3 activity" or "inhibitor of the activity of DPP3" would be suitable, let alone effective for achieving a therapeutic effect.

In addition, it is maintained that 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 also applies to claims 13-17 (which indicate that "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") as the antibody or antibody fragment is not defined and the activity which is to be inhibited is also not defined.

3.4 It is noted that that claim 1 indicates "determining the level of DPP3 in a sample of bodily fluid of said subject". The bodily fluid is not specified. Claim 1 is thus not supported by the technical contents description as required by Article 84 EPC, as its scope is broader than justified by the description and examples, which solely refer to level of DPP3 in whole blood, plasma, and serum. Bodily

fluids include for example saliva, tears, urine, among others. The objection applies to all claims, which are found to contravene Art. 84 EPC for that reason also.

3.5 Claim 6 indicates that "a treatment is to be initiated and/or maintained and/or withheld and/ or terminated if said determined level of DPP3 is above said predetermined threshold". Claim 6 is not clear as such as it envisages both initiating and terminating at the same time, for example ("and/or"). Claim 7, which is dependent from claim 6 specifies that "said treatment is selected from the group of vasopressors, Angiotensin-Receptor-Agonists and/or precursors thereof, inhibitors of the DPP3 activity and anti-adrenomedullin antibodies or anti-adrenomedullin antibody fragments" and lacks clarity (Art. 84 EPC) when read in conjunction with claim 6 which for the same therapeutic agent, and the same level of DPP3 ("above said predetermined threshold") envisages any of initiating, maintaining, withholding or terminating the treatment or their combination. The same situation encompasses contradicting embodiments.

The objection applies *mutatis mutandis* to the subject matter of claim 9 " wherein a treatment with Angiotensin-Receptor-Agonists and/ or precursors thereof and/or inhibitors of the DPP3 activity is to be initiated and/or continued when the level of DPP3 in said sample is above a certain threshold and/or wherein a treatment with vasopressors is to be withheld and/ or terminated if said determined level of DPP3 is above said predetermined threshold" and of claim 10 "wherein a treatment with vasopressors is to be initiated and/or continued when the level of DPP3 in said sample is below a certain threshold and/or wherein a treatment with Angiotensin-Receptor-Agonists and/ or precursors thereof and/or inhibitors of the DPP3 activity is to be withheld and/ or terminated if the said determined level of DPP3 is below said predetermined threshold", as contradicting actions are to be taken under equivalent circumstances.

4 **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. Novelty and Inventive step will be assessed once claims are available which meet the requirements of Art. 123(2) EPC, Art. 84 EPC and Art. 83 EPC.**

4.1 **Preliminary comments are detailed below 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.**

5 Cited documents

5.1 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

5.2 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)

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

5.4 The cited documents disclose the following:

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

5.4.2 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.

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

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

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

5.4.6 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.

5.5 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 be 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).

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.

5.6 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.