BOEHMERT & BOEHMERT Pettenkoferstraße 22 80336 München Germany

Online Filing

Europäisches Patentamt
80298 München

Ihr Zeichen / your ref.
20764639.9

Ihre Nachricht / your letter

Unser Zeichen / our ref.
T75093WOEP

München
05.03.2025

Dr. Ute Kilger
Pettenkoferstraße 22
80336 München
Germany

T +49-89 559680
F +49-89-559685090
kilger@boehmert.de
www.boehmert.de

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

This refers to the Summons to attend oral proceedings pursuant to Rule 115(1) EPC dated November 6, 2024:

I. Added Subject Matter Art 123(2) EPC

Pending claim 1 (corresponding to claim 1 as originally filed) was amended by introducing the wordings "said sample of bodily fluid is selected from the group of whole blood, plasma, and serum" and "that is between 25 and 150 ng/ml for plasma DPP3."

Basis for this amendment can be found on page 6, lines 32 to 34 of the PCT application as published and on page 13, line 13 of the PCT application as published.

Pending claims 2 to 5 correspond to claims 2 to 5 as originally filed.
Pending claim 6 (corresponding to claim 6 as originally filed) was amended by replacing the wording "wherein a treatment is initiated and/or maintained and/or withheld and/ or terminated if said determined level of DPP3 is above said predetermined threshold" by the wording "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 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 or wherein a treatment with vasopressors is 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 withheld and/ or terminated if the said determined level of DPP3 is below said predetermined threshold."

Basis for this amendment can be found on page 9, line 21 to page 10, line 14 of the PCT application as published.

Pending claim 7 (corresponding to claim 7 as originally filed) was cancelled.

Pending claim 8 is now pending claim 7.

Pending claims 9 and 10 were cancelled.

Pending claims 11 and 12 (now pending claims 8 and 9) correspond to claims 11 and 12 as originally filed.

Pending claims 13 to 17 (corresponding to claims 14 to 16, 19, 20 and 22 as originally filed) were cancelled.

Pending claim 18 (now pending claim 12, corresponding to claim 25 as originally filed) was amended by introducing the wordings "said sample of bodily fluid is selected from the group of whole blood, plasma, and serum" and "that is between 25 and 150 ng/ml for plasma DPP3."

Basis for this amendment can be found on page 6, lines 32 to 34 of the PCT application as published and on page 13, line 13 of the PCT application as published.

All amendments are in accordance with Article 123(2) EPC.

II. <u>Clarity, Support (Art 84 EPC), Sufficiency of Disclosure (Art 83 EPC).</u>

II.1 Thresholds, re 3.2

Thresholds in diagnostic methods arise from statistical methods based on study data. In a diagnostic company, teams of experts work together wherein a statistician is a member of the team and the statistician is the one who determines thresholds and/or threshold ranges based on study data. The statistician is a mathematician in most cases.

We herewith, respectfully, ask to include a mathematician or statistician into the Examining Division.

We, respectfully, submit that a mathematician or statistician would understand that based on the disclosure of the present application it is a routine procedure to choose a threshold value. It is neither a burden for the practitioner nor would it require another clinical study, nor would it be an invitation for a research project.
On the other hand, if the applicant was forced to include a specific value as e.g. 59,1 ng/ml or 48,4 ng/ml as this Examining Division seems to suggest, this would render the scope of protection absolutely worthless as the claims could be easily circumvented by any copycat. Any competitor could then sell a diagnostic assay for predicting or diagnosing a refractory shock in as subject that either runs into shock or that has developed shock and circumvent the claims by recommending a threshold value of e.g. 30 ng/ml or 40 ng/ml or 50 ng/ml or 60 ng/ml etc. and in either case the practitioner would obtain a valid result for everyone tested with the only difference that specificity and sensitivity of said test differs.
We asked the statistician of the applicant to illustrate the before-mentioned statement, and you will see that that the choice of either of the before-mentioned threshold leads to meaningful results for the tested individual. The expert declaration as attached to this brief.

The summary of the expert declaration is the following:

1. From mathematical point of view, it would be unjustified and it is not required to be limited to a specific threshold value.

2. Albeit the explained statistics may sound difficult for someone who is not a person skilled in the art, the opposite is true. Once the correlation between – in this example – concentration of a biomarker to the risk of acquiring a condition is known it is a routine procedure to choose a threshold. There is no undue burden to choose a threshold.

3. Thirdly, if the applicants were forced to introduce a specific threshold value into the claims such claims could be circumvented easily. It is not only easy to choose another threshold that results in essentially the same performance of the same diagnostic method, but the infringer could also easily change the numerical values by changing the calibrators and the calibration of the test.

<u>Patents before Examining Divisions with physicists, mathematicians or statisticians In Examining</u>

In divisions with physicists, mathematicians or statisticians it has never been objected if a threshold was mentioned in a claim without mentioning a specific value for said threshold.

It is e.g. common practice in motion correction in MR imaging to cite "predetermined threshold" in a claim without mentioning a specific value: e.g. in EP3500869 (B1), EP3123191 (B1), EP2986340.

It is e.g. common practice in image processing in diagnostic imaging to cite. a "predetermined threshold" in claims without mentioning a specific value: EP3735776 (B1), EP3948777B1, EP3817665B1.

Claim 1 of EP3735776 (B1) for instance reads:

1. An apparatus for generating an image data bitstream, the apparatus comprising a store (201) for storing a set of image parts and associated depth data representing a scene from different view poses; a predictability processor (203) for generating predictability measures for image parts of the set of image parts for view poses of the scene, a predictability measure for a first image part for a first view pose being indicative of an estimate of a prediction quality for a prediction of at least part of an image for a viewport of the first view pose from a first subset of image parts of the set of image parts not including the first image part;
a selector (205) for selecting a second subset of image parts of the set of image parts in response to the predictability measures; and
a bitstream generator (207) for generating the image bitstream comprising image data and depth data from the second subset of image parts;
characterized in that the selector (205) is arranged to select a plurality of contiguous image parts .....having a predictability measure **below a first threshold** for an interior part of the region and a predictability measure **above a second threshold** for a border part of the region

In these patents there is general support in the description as to how to determine a threshold as it is the case in the present applications as well. There are no objections by the ED's in these cases, apparently no need to be convinced by extensive examples, apparently no undue burden, rather common workshop practice and calibration to system and individual circumstances. It would be unduly, if the Examining Division would require other standards for the present application. If required we can more extensively elaborate on these and further patents that were granted before Examining Divisions with physicists, mathematicians or statisticians and the term "predetermined" threshold has never been objected to!

Patents in the Life Science Area

Further, patents have been granted in the life science area which are based on biochemical and/or biological inventions in which the term "predetermined threshold" has been accepted.

EP granted patents with 'threshold' in claims		**IPC=G01N33/574**
publication number	*claim including threshold*	*primary examiner*
EP 3 079 772 B1	1	G. Jenkins
EP 2 864 501 B1	1	J. Botz
EP 2 619 576 B1	1	C. van Bohemen
EP 1 996 940 B1	1	Van Montfort
EP 1 861 509 B1	1	C. Bigot
EP 2 387 717 B1	1	C. Bigot
EP 3 193 927 B1	1	P. Lunter

It would be unduly and unjustified, if the Examining Division would require other standards for the present application.

Patents claiming to diagnostic methods prosecuted by Boehmert&Boehmert

It is further common practice of the EPO to allow a wording like: "Level above a certain threshold" or "pre-determined threshold" for inventions very, very similar to the present case: for instance: EP2904403B1 (B75021WOEP); EP3201631B1 (S75037WOEP); EP 2904398B1 (B75022WOEP); EP 2943792B1 (B75025WOEP); EP 2823313B1 (B75032WOEP); EP 2976646B1 (B75036WOEP), EP 3262421B1 (S75040WOEP), EP 3482208B1 (S75092WOEP).

See e.g. granted claim 1 of EP 2904403B1 (emphasize added):

1. A method for (a) diagnosing or monitoring kidney function in a subject or (b) diagnosing kidney dysfunction in a subject or (c) predicting or monitoring the risk of an adverse event in a diseased subject wherein said adverse event is

selected from the group comprising worsening of kidney dysfunction including kidney failure, loss of kidney function and end-stage kidney disease or death due to kidney dysfunction including kidney failure, loss of kidney function and end-stage kidney disease or (d) predicting or monitoring the success of a therapy or intervention comprising

• determining the level of Pro-Enkephalin or fragments thereof of at least 5 amino acids in a bodily fluid obtained from said subject; and

(a) correlating said level of Pro-Enkephalin or fragments thereof with kidney function in a subject or

(b) correlating said level of Pro-Enkephalin or fragments thereof with kidney dysfunction **wherein an elevated level above a certain threshold is predictive or diagnostic for kidney dysfunction in said subject or**

(c) correlating said level of Pro-Enkephalin or fragments thereof with said risk of an adverse event in a diseased subject, **wherein an elevated level above a certain threshold** is predictive for an enhanced risk of said adverse events or

(d) correlating said level of Pro-Enkephalin or fragments thereof with success of a therapy or intervention in a diseased subject, wherein **a level below a certain threshold** is predictive for a success of therapy or intervention, wherein said therapy or intervention may be renal replacement therapy or may be treatment with hyaluronic acid in patients having received renal replacement or predicting or monitoring the success of therapy or intervention may be prediction or monitoring recovery of renal function in patients with impaired renal function prior to and after renal replacement therapy and/or pharmaceutical interventions,

wherein said Pro-Enkephalin or fragment is selected from the group comprising SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10 and SEQ ID No. 11.

There is no reason to treat the present application differently than all the others above-mentioned applications/patents. It would be unduly and unjustified, if the Examining Division would require other standards for the present application.

In summary, applicants do not see any reason so whatsoever to specify the predetermined threshold in the claims. The claims are clear, supported and enabled without specifying a predetermined threshold in the claims. For the sake of expediting this application applicants have introduced a range for the thresholds to be chosen,

namely "...a predetermined threshold that is between 25 and 150 ng/ml for plasma DPP3...".

II.2 Inhibitors of the DPP3 activity, re 3.3

Claims directed to Inhibitors of DPP3 activity has been deleted from the present application.

II.3 Bodily Fluid, re 3.4

Present claim 1 cites that "said sample of bodily fluid is selected from the group of whole blood, plasma, and serum". The objection should have been addressed by this amendment.

II.4 "Treatment is to be initiated...", re 3.5

Claim 6 has been amended in order to overcome the respective objections.

III. Requests

The applicant requests that a patent is granted on basis of the present claims. The applicant submits that the present claims meet the requirements of Art 123(2) EPC, Art. 84 EPC and Art. 83 EPC as well as Art 54 and 56 EPC.

As an auxiliary request the applicant requests that the Examining Division performs a complete assessment as to novelty and inventive step of the subject matter claimed in the written procedure and that the oral proceedings are cancelled in this case. It would be an undue burden to discuss novelty and inventive step during oral proceedings before the Examination Division sees itself in the position to assess novelty and inventive step completely in the written procedure.

If none of the before-mentioned requests will be granted applicants will participate in the schedule oral proceedings.

BOEHMERT & BOEHMERT

Dr. Ute Kilger
Patent Attorney

Enclosures:
- Amended claims (marked-up and clean version)
- Expert declaration biostatistician