

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

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155 Seaport Boulevard
Boston, MA 02210-2600
United States of America**

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

30 May 2023

Applicant's or agent's file reference

RPH-00125

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2023/012487

International filing date (day/month/year)

07 February 2023

Priority date (day/month/year)

07 February 2022

International Patent Classification (IPC) or both national classification and IPC

**C07D 498/04(2023.01)i; C07D 498/14(2023.01)i; A61K 31/553(2023.01)i; A61P 9/10(2023.01)i;
A61P 9/12(2023.01)i; A61P 29/00(2023.01)i; A61P 31/00(2023.01)i; A61P 37/00(2023.01)i;
A61P 37/06(2023.01)i**

CPC C07D 498/04; C07D 498/14; A61K 31/553; A61P 9/10; A61P 9/12; A61P 29/00; A61P 31/00; A61P 37/00; A61P 37/06

Applicant

RIPARIAN PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/IL

**Israel Patent Office
Technology Park, Bldg.5, Malcha,
Jerusalem, 9695101, Israel
Israel**

Date of completion of this opinion

30 May 2023

Authorized officer

SOMECH Erez

Telephone No. **972-73-3927252**

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INTERNATIONAL SEARCHING AUTHORITY**

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Box No. I

Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(b)).
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 44,45

because:

☒ the said international application, or the said claims Nos. 44,45 relate to the following subject matter which does not require an international search (*specify*):

Claims 44-45 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) PCT. Consequently, no opinion will be given on the question of whether the subject matter of these claims is industrially applicable (Article 17(2)(a)(i)).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a).

☐ See Supplemental Box for further details.

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Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement																										
1. Statement	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 30%; vertical-align: top;">Novelty (N)</td> <td style="width: 30%; vertical-align: top;">Claims</td> <td style="width: 30%; border-bottom: 1px solid black; vertical-align: bottom;">3,10-13,19-27,29-36,40,42,44,45</td> <td style="width: 10%; vertical-align: bottom; text-align: center;">YES</td> </tr> <tr> <td></td> <td style="vertical-align: top;">Claims</td> <td style="border-bottom: 1px solid black; vertical-align: bottom;">1,2,4-9,14-18,28,37-39,41,43</td> <td style="vertical-align: bottom; text-align: center;">NO</td> </tr> <tr> <td style="vertical-align: top;">Inventive step (IS)</td> <td style="vertical-align: top;">Claims</td> <td style="border-bottom: 1px solid black; vertical-align: bottom;">3,10-13,19-27,29-36,40,42,44,45</td> <td style="vertical-align: bottom; text-align: center;">YES</td> </tr> <tr> <td></td> <td style="vertical-align: top;">Claims</td> <td style="border-bottom: 1px solid black; vertical-align: bottom;">1,2,4-9,14-18,28,37-39,41,43</td> <td style="vertical-align: bottom; text-align: center;">NO</td> </tr> <tr> <td style="vertical-align: top;">Industrial applicability (IA)</td> <td style="vertical-align: top;">Claims</td> <td style="border-bottom: 1px solid black; vertical-align: bottom;">1-43</td> <td style="vertical-align: bottom; text-align: center;">YES</td> </tr> <tr> <td></td> <td style="vertical-align: top;">Claims</td> <td style="border-bottom: 1px solid black; vertical-align: bottom;"></td> <td style="vertical-align: bottom; text-align: center;">NO</td> </tr> </table>			Novelty (N)	Claims	3,10-13,19-27,29-36,40,42,44,45	YES		Claims	1,2,4-9,14-18,28,37-39,41,43	NO	Inventive step (IS)	Claims	3,10-13,19-27,29-36,40,42,44,45	YES		Claims	1,2,4-9,14-18,28,37-39,41,43	NO	Industrial applicability (IA)	Claims	1-43	YES		Claims		NO
Novelty (N)	Claims	3,10-13,19-27,29-36,40,42,44,45	YES																								
	Claims	1,2,4-9,14-18,28,37-39,41,43	NO																								
Inventive step (IS)	Claims	3,10-13,19-27,29-36,40,42,44,45	YES																								
	Claims	1,2,4-9,14-18,28,37-39,41,43	NO																								
Industrial applicability (IA)	Claims	1-43	YES																								
	Claims		NO																								
2. Citations and explanations:	[0001] &lt;body xmlns=&quot;http://www.w3.org/1999/xhtml&quot; xfa:APIVersion=&quot;Acroform:2.7.0.0&quot; xfa:spec=&quot;2.1&quot; xmlns:xfa=&quot;http:// www.xfa.org/schema/xfa-data/1.0/&quot;&gt;&lt;p dir=&quot;ltr&quot; style=&quot;line- height:13.8pt;font-family:&apos;Times New Roman&apos;;font-size:11pt;font-weight:bold;text- decoration:underline&quot;&gt;&lt;span style=&quot;xfa-spacerun:yes&quot;&gt;&lt;/span&gt;&lt;/ p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;line-height:13.8pt;font-family:&apos;Times New Roman&apos;;font-size:11pt;font-weight:bold;text-decoration:underline&quot;&gt;2.1. Reference is made to the following documents:&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin- left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:&apos;Times New Roman&apos;;font- size:11pt;font-weight:bold;text-decoration:none&quot;&gt;D1:&lt;span style=&quot;font- weight:normal&quot;&gt; CAS Registry Number: 1215615-88-5; CA Index Name: Benzofuro[2,3-f]-1,4- oxazepine-3-carboxamide, 4-(3,5-dimethylphenyl)-2,3,4,5-tetrahydro-N-[(4-methoxyphenyl)methyl]-3- methyl-5-oxo-; Entered STN: 02 April 2010. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals.&lt;/span&gt;&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin- left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:&apos;Times New Roman&apos;;font- size:4pt;text-decoration:none&quot;&gt;&lt;span style=&quot;xfa-spacerun:yes&quot;&gt;&lt;/span&gt;&lt;/ span&gt;&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin-left:21.3pt;text-indent:-14.15pt;line- height:13.8pt;font-family:&apos;Times New Roman&apos;;font-size:11pt;font-weight:bold;text- decoration:none&quot;&gt;D2:&lt;span style=&quot;font-weight:normal&quot;&gt; CAS Registry Number: 1189959-66-7; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, N-[(4- chlorophenyl)methyl]-2,3,4,5-tetrahydro-3-methyl-5-oxo-4-phenyl; Entered STN: 25 October 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals.&lt;/span&gt;&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font- family:&apos;Times New Roman&apos;;font-size:4pt;text-decoration:none&quot;&gt;&lt;span style=&quot;xfa-spacerun:yes&quot;&gt;&lt;/span&gt;&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:&apos;Times New Roman&apos;;font-size:11pt;font-weight:bold;text-decoration:none&quot;&gt;D3:&lt;span style=&quot;font-weight:normal&quot;&gt; CAS Registry Number: 1189706-00-0; CA Index Name: Benzofuro[2,3-f]-1,4-oxazepine-3-carboxamide, 2,3,4,5-tetrahydro-3-methyl-5-oxo-4- phenyl-N-(phenylmethyl)-; Entered STN: 23 October 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals.&lt;/span&gt;&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:&apos;Times New Roman&apos;;font-size:4pt;text-decoration:none&quot;&gt;&lt;span style=&quot;xfa- spacerun:yes&quot;&gt;&lt;/span&gt;&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin- left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:&apos;Times New Roman&apos;;font- size:11pt;font-weight:bold;text-decoration:none&quot;&gt;D4:&lt;span style=&quot;font- weight:normal&quot;&gt; CAS Registry Number: 1185009-90-8; CA Index Name: Benzofuro[2,3- f]-1,4-oxazepine-3-carboxamide, 4-butyl-2,3,4,5-tetrahydro-N-[(4-methoxyphenyl)methyl]-3- methyl-5-oxo-; Entered STN: 16 September 2009. Source of Registration: Chemical Library, Supplier: Aurora Fine Chemicals.&lt;/span&gt;&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:&apos;Times New Roman&apos;;font-size:4pt;text-decoration:none&quot;&gt;&lt;span style=&quot;xfa-spacerun:yes&quot;&gt;&lt;/span&gt;&lt;/ span&gt;&lt;/p&gt;&lt;p dir=&quot;ltr&quot; style=&quot;margin-left:21.3pt;text-indent:-14.15pt;line-																										

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2023/012487

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

height:13.8pt;font-family:'Times New Roman';font-size:11pt;font-weight:bold;text-decoration:none">D5:> RU 2281947 C1 (Obshchestvo s ogranichennoj otvetstvennost'ju "Issledovatel'skij Institut Khimicheskogo Raznoobrazija" [RU]), 20 August 2006.</p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:4pt;text-decoration:none"></p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:11pt;font-weight:bold;text-decoration:none">>D6:> WO 2005/105805 A1 (CHEMICAL DIVERSITY RESEARCH INSTITUTE LTD), 10 November 2005.</p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:4pt;text-decoration:none"></p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:11pt;font-weight:bold;text-decoration:none">>D7:> DABRAVOLSKI, Siarhei A., et al. The role of KLF2 in the regulation of atherosclerosis development and potential use of KLF2-targeted therapy.>Biomedicines>, 2022, 10.2: 254.# Published: 24 January 2022. DOI: <10.3390/biomedicines10020254>. Retrieved from URL: <https://www.mdpi.com/2227-9059/10/2/254></p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:4pt;text-decoration:none"></p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:11pt;font-weight:bold;text-decoration:none">>D8:> WO 2004/091660 A1 (KOWA CO., LTD. [JP]), 28 October 2004.</p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:4pt;text-decoration:none"></p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:11pt;font-weight:bold;text-decoration:none">>D9:> WO 2008/132458 A1 (INION LIMITED [GB]), 06 November 2008.</p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:4pt;text-decoration:none"></p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:11pt;font-weight:bold;text-decoration:none">>D10:> LAHA, Dipranjan; DEB, Moonmoon; DAS, Hiranmoy. KLF2 (kruppel-like factor 2 [lung]) regulates osteoclastogenesis by modulating autophagy.>Autophagy>, 2019, 15.12: 2063-2075.# Accepted author version posted online: 20 March 2019. DOI: <10.1080/15548627.2019.1596491>. Retrieved from URL: <https://www.tandfonline.com/doi/full/10.1080/15548627.2019.1596491></p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:4pt;text-decoration:none"></p><p dir="ltr" style="margin-left:21.3pt;text-indent:-14.15pt;line-height:13.8pt;font-family:'Times New Roman';font-size:11pt;font-weight:bold;text-decoration:none">>D11:> GRACIA-SANCHO, Jorge, et al. Endothelial expression of transcription factor Kruppel-like factor 2 and its vasoprotective target genes in the normal and cirrhotic rat liver.>Gut>, 2011, 60.4: 517-524.# First published 26 November 2010. DOI: <10.1136/

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Form PCT/ISA/237 (Box No. V) (July 2022)

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

style="font-size:13.8pt;font-family:'Times New Roman';font-size:11pt;text-decoration:none">>The compound of R is methyl; X is C-R; R and Z are each H; and Z is 4-chlorophenyl. Hence, claims 1, 2, 4-9, 14-18 and 37-39 are also anticipated by D2 and D3 .

style="font-size:13.8pt;font-family:'Times New Roman';font-size:11pt;text-decoration:none">>The compound of R is methyl; X is C-R; R and Z are each H; and Z is 4-methoxyphenyl. Hence, claims 1, 2, 4-9, 14-18, 28 and 37-39 are anticipated by D4 and D6 (as well as one additional publication, not provided herein) discloses seven of the compounds which were excluded from the scope of claim 1 by a proviso. These compounds are disclosed in D5 and D6 as pharmaceutically active agents. D5 and D6 also disclose the compound 2,3,4,5-tetrahydro-N-[(2-methoxyphenyl)methyl]-3-methyl-4-[2-(2-methylphenyl)ethyl]-5-oxobenzofuro[2,3-b]pyridine-1,4-oxazepine-3-carboxamide, which was not excluded, presumably due to a typographical error (note that the last compound in the proviso is not identical to this compound). In D5 see compound G215-0724 (table 3, ex. 1.11(6), which is the last compound on page 45) and in D6

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Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

span> see compound 10 on table 1.14 (which is the last compound on page 398). Hence, novelty of claims 1, 2, 4-9, 14-18, 37-39, 41 and 43, as currently drafted, is also not acknowledged over any one ofD5 andD6.<p><span style="fa

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Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

weight:normal"> are not relevant for the assessment of an inventive step, because they merely relate to compounds from a chemical library, and no activity or use is disclosed in these publications.</p><p dir="ltr" style="line-height: 13.8pt;font-family:"Times New Roman";font-size: 11pt;text-decoration:none">Although any one of D5 and D6 discloses derivatives of the present compound of formula I which had to be excluded by a proviso, the activity of these compounds was not explicitly demonstrated in any of these documents (see table 5 in D5, and table 24 in D6). Moreover, the claimed uses (present application, claims 44-45) or the ability to induce KLF2, are not disclosed in D5/D6 which only demonstrate inhibition of cell-proliferation of selected compounds as anti-cancer agents (in D5 see example 2, particularly the ABL-kinase inhibitory activity on page 54 lines 45-47, as well as example 3, table 5; and in D6 see page 11, example 2 in pages 14-15, table 24 and claim 16). Hence, if novelty would be restored over these documents, D5 and D6 would also not be regarded relevant for the assessment of an inventive step of the novel-subject matter of the claims.</p><p dir="ltr" style="line-height: 13.8pt;font-family:"Times New Roman";font-size: 11pt;text-decoration:none">The present application discloses that the compound of formula I may be used to induce KLF2 (present application, pages 150-152). There is no fair teaching in the art that said compounds would be effective inducers of KLF2. D7 is a review article, published two weeks before the priority date of the present application, which discusses the role of KLF2 in the regulation of atherosclerosis development, and the potential use of KLF2-targeted therapy. D7 summarizes known drugs and natural plant-based bioactive compounds that can be used for atherosclerosis treatment, by up-regulating KLF2 expression (D7, figure 2). Additional KLF2 modulators are also provided in D8-D12. The claimed compound of formula I is not-obvious in view of any of the compounds reviewed in D7 or discloses in D8-D12 (or any combination thereof).</p><p dir="ltr" style="line-height: 13.8pt;font-family:"Times New Roman";font-size: 11pt;text-decoration:none">The present application discloses active agents, including benzofurano[2,3-f]-1,4-oxazepine-5-one derivatives, which inhibit leukocyte adherence to vascular endothelium and are effective for treating inflammatory diseases (abstract, formula I and table I). However, there is no teaching or motivation in to use the present compound

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Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

of formula I which further comprises a $\text{-C(O)NHCH}_2\text{-Z}$ group on the 3-position of the fused oxazepine ring. D14 relates to compounds which reduce KLF5 expression, and are suitable for reducing vascular permeability, neovascularisation, angiogenesis, inflammation, cell migration and/or proliferation, which are also structurally distinct from the present compound of formula I (see formula II in D14).

Therefore, any novel scope of formula I (currently claims 3, 10-13, 19-27, 29-36, 40, 42, 44 and 45) is also not obvious in view of the prior art.

INDUSTRIAL APPLICABILITY (Article 33(4) PCT)

Claims 1-43 meet the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for the assessment of claims 44-45 on the question whether they are industrially applicable. The patentability can also be dependent upon the formulation of the claim. The ILPO, for example, does not recognize as industrially applicable the subject-matter of claims relating to a method of medical treatment of the human body, but may allow claims relating to a compound for use in the medical treatment of the human body.

**WRITTEN OPINION OF THE
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International application No.

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. Claims 1-41 (and, therefore, also claims 43-45 which relate thereto) are unclear since they relate to optionally substituted groups, however the claimed substituents are not clearly defined in the claims (ARTICLE 6 PCT). For example: 1.A. The definition of a non-limiting substituent list on group Z (using the abbreviation "e.g.") does not define the claimed scope fully and clearly. 1.B. The groups in R3 also appear to be optionally substituted in an undefined scope. For example see claims 1 and 26 in view of claim 27; claims 1 and 35 in view of claims 34 and 36; etc. 1.C. Similarly see the definitions of R2a-R2d in claims 1 and 10 in view of dependent claims 5 and 11. 2. The dependencies of claims 23 and 24 should be corrected (ARTICLE 6 PCT). 3. The full scope of diseases or disorders covered by the definition "endothelial dysfunction" (claim 44) is unclear (ARTICLE 6 PCT).