

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2020/042028

International filing date (day/month/year)
15.07.2020

Priority date (day/month/year)
16.07.2019

International Patent Classification (IPC) or both national classification and IPC
INV. C07D413/14 A61P9/04 A61K31/454

Applicant
MYOKARDIA, 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 usually 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:



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Date of completion of
this opinion

see form
PCT/ISA/210

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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(a))
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:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-121</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-121</u>
Industrial applicability (IA)	Yes: Claims	<u>1-121</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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:

see separate sheet

Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Claims 74-92 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

1. PRIOR ART

Reference is made to the following documents:

- D1 WO 2016/118774 A1
- D2 MINO R CAIRA ED - MONTCHAMP JEAN-LUC: "Crystalline Polymorphism of Organic Compounds", TOPICS IN CURRENT CHEMISTRY; [TOPICS IN CURRENT CHEMISTRY], SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP008166276,
- D3 STEPHEN BYRN ET AL: "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations", PHARMACEUTICAL RESEARCH, vol. 12, no. 7, 1 January 1995 (1995-01-01), pages 945-954,

2. NOVELTY

The subject-matter of the claims is considered to be novel (Article 33(2) PCT). D1 discloses a generic formula in claim 1 that encompasses the presently claimed compound I-491 (as defined in paragraph [0037] of the application). Furthermore, D1 discloses 312 specific compounds, the compound of formula I-491 corresponds to compound 20 disclosed on pages 73/74 of D1. Therefore, the compound I-491 represents a selection from the list 312 of compounds of D1. However, D1 does not refer to any crystalline form of the compound. Compound 20 in D1 was merely described as obtained from column chromatography (MeOH/DCM) as a white solid.

3. INVENTIVE STEP

The subject-matter of the claims does not fulfil the requirements of Article 33(3) PCT.

The closest state of the art for the present application is represented by D1. D1 discloses the compound I-491 as compound 20 out of 312 tested compounds for the treatment of heart failure, merely the specific crystalline forms are not mentioned. In the present application, this specification/selection is alleged to lead to alternative derivatives with the same qualitative activity/properties as those described in D1. The problem underlying the present application can, however, not be seen in the provision of further novel derivatives, because the proposed solution would be seen as obvious. In view of the mere selection of the compound from D1 it is considered that the man skilled in the art would regard the new polymorphs of this application as being obvious alternatives to the known compounds. It is obvious for the skilled person to further investigate the most active compounds of D1, one of which is I-491 (cf. D1, Table 2, compound 20). With regard to the specific crystalline forms, it is considered routine investigation for the skilled person in the pharmaceutical field.

The claimed polymorphs A and B differ from compound 20 of D1 through its crystalline form. In the light of the application, a particular technical effect due to this difference is at present not evident. Starting from D1 the problem to be solved is thus seen in providing a further compound for the same therapeutic application. The biological activity of a compound depends primarily on its molecular structure. To reach its target it will be at some point in solution, e.g. in body fluids, where all differences among polymorphs disappear. The skilled person would thus expect that all polymorphs of compound I-491 possess activity against heart failure, at least to a certain extend.

From common general knowledge it is known that the systematic investigation of a compound to determine whether it is prone to polymorphism is routine practice in the pharmaceutical industry. It is also known that most substances when investigated for a sufficiently long time will reveal more than one polymorph (cf. D2, paragraph bridging pages 165-166). Furthermore, the methods to screen for polymorphs are well known in the art (cf. D2, chapter 3.1).

The skilled person being interested in the therapeutic application of compound I-491 would thus routinely screen for polymorphs of compound I-491. If such routine work yields one or more polymorphs, e.g. the present polymorphs A and B, then the provision is an obvious solution of the problem as defined above. In the absence of any substantiated unexpected property (D3, page 952, right column, line 13ff) of the claimed polymorphs, which is relevant for its technical application, in comparison with the closest related compound/form (compound 20 of D1), no inventive step would be acknowledged for polymorphs A and B and subject-matter referring to it.

Item VIII

Certain observations on the international application

1. In several claims the polymorph is not clearly defined and the requirements of Article 6 PCT are violated. Form A, B and D as such are not clearly defined in the absence of characterising parameters or other definitions. This applies in particular to independent claims 1, 23, 24, 29, 34, 58, 59, 65, 73, 113 and 121, however, also Form D, as in claim 21, needs to be defined.
2. At least claims 9, 10, 17, 43, 44 and 52 contain a reference to the drawings. According to Rule 6.2(a) PCT, claims should not contain such references except where absolutely necessary, which is not the case here.
3. Claims 1, 23, 24, 29, 65, 73 and 101 relate to compositions comprising form A, claims 34, 58, 59, 113 and 121 relate to compositions comprising form B and claims 94, 97 and 103 relate to polymorph form B as such. All these claims are formulated as independent claims, however, only one independent claim should be present for each subject-matter (compositions comprising form A; compositions comprising form B; polymorph form B as such). Several of the above mentioned claims should contain a reference to claim 1 or claim 34 as they comprise all features of the other claim and need to be formulated as dependent claims (cf. i.a. claim 65 and 74 should clearly depend on claim 1). The set of claims lacks clarity (Article 6 PCT).
4. In claim 93 the term "slow" is relative and unclear (Article 6 PCT).
5. In claims 20-22 and 55-57 the term "substantially" is relative and unclear (Article 6 PCT).
6. I.a. claim 74 makes reference to claims which have a higher number, the order of the claims should be reversed.
7. Claim 93, 94 and 97 are product-by-process claims.