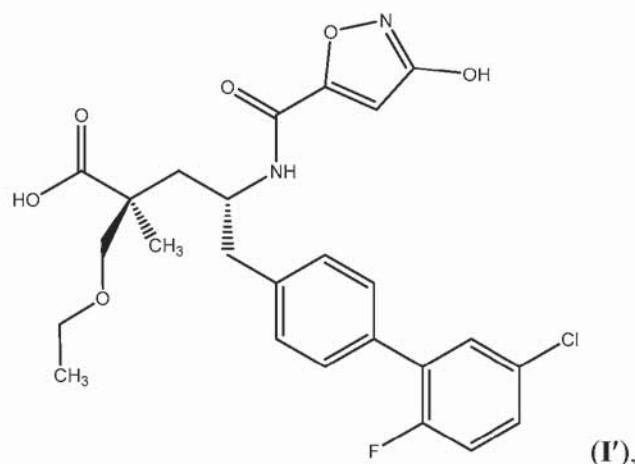


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- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report (Art. 21(3))

(54) Title: CRYSTALLINE(2S,4R)-5-(5'-CHLORO-2'-FLUORO-[1,1'-BIPHENYL]-4-YL)-2-(ETHOXYMETHYL)-4-(3-HYDROXYISOXAZOLE-5-CARBOXAMIDO)-2-METHYLPENTANOIC ACID AND USES THEREOF



(57) Abstract: In one aspect, the invention relates to a crystalline form of the structure: or a pharmaceutically acceptable salt thereof, having neprilysin inhibition activity. In another aspect, the invention relates to pharmaceutical compositions comprising this crystalline form; methods of using this crystalline form and its soluble form (I); and processes for preparing soluble (I) and crystalline (I') forms.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

HAGENAH, Jeffrey A.
Theravance Biopharma US INC.
901 Gateway Boulevard
South San Francisco CA 94080
ETATS-UNIS D'AMERIQUE

RECEIVED

JUL 20 2018

THERAVANCE BIOPHARMA US, INC.
PATENT DEPARTMENT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

06.07.2018

Applicant's or agent's file reference

P-324-PCT

IMPORTANT NOTIFICATION

International application No.

PCTUS2017/021172

International filing date (day/month/year)

07.03.2017

Priority date (day/month/year)

08.03.2016

Applicant

Theravance Biopharma R&D IP, LLC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
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Authorized Officer

Pfitzner, Gabriele

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P-324-PCT		FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2017/021172	International filing date (day/month/year) 07.03.2017	Priority date (day/month/year) 08.03.2016	
International Patent Classification (IPC) or national classification and IPC INV. C07D261/18			
Applicant Theravance Biopharma R&D IP, LLC			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ (sent to the applicant and to the International Bureau) a total of <u>9</u> sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and/or sheets containing rectifications authorized by this Authority, unless those sheets were superseded or cancelled, and any accompanying letters (see Rules 46.5, 66.8, 70.16, 91.2, and Section 607 of the Administrative Instructions). ☐ sheets containing rectifications, where the decision was made by this Authority not to take them into account because they were not authorized by or notified to this Authority at the time when this Authority began to draw up this report, and any accompanying letters (Rules 66.4bis, 70.2(e), 70.16 and 91.2). ☐ superseded sheets and any accompanying letters, where this Authority either considers that the superseding sheets contain an amendment that goes beyond the disclosure in the international application as filed, or the superseding sheets were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in item 4 of Box No. I and the Supplemental Box (see Rule 70.16(b)). b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in the form of an Annex C/ST.25 text file, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3ter of Annex C of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ 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 Article 35(2) with regard to novelty, inventive step or 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			
Date of submission of the demand 26.10.2017		Date of completion of this report 06.07.2018	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465		Authorized officer Wolf, Claudia Telephone No. +49 89 2399-8285	



**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/US2017/021172

Box No. I Basis of the report

1. With regard to the **language**, this report is based on
- ☒ 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 (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a) and (b))
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-78 as originally filed

Claims, Numbers

1-36 filed with telefax on 26-10-2017

Drawings, Sheets

1/6-5/6 as originally filed

6/6 filed with telefax on 26-10-2017

- ☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☒ the claims, Nos. 37-39
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since either they are considered to go beyond the disclosure as filed, or they were not accompanied by a letter indicating the basis for the amendments in the application as filed, as indicated in the Supplemental Box (Rules 70.2(c) and (c-bis)):
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
5. ☐ This report has been established:
- ☐ taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rules 66.1(d-bis) and 70.2(e)).
 - ☐ without taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91(Rules 66.4bis and 70.2(e)).

**INTERNATIONAL PRELIMINARY REPORT
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6. ☒ With regard to top-up searches (Rules 66.1 *ter* and 70.2(f)):
- ☒ A top-up search was carried out by this Authority on 24.05.2018 (all discovered documents are listed in the Supplemental Box Relating to Top-up Search).
 - ☐ Additional relevant documents have been discovered during the top-up search.
 - ☐ No top-up search was carried out by this Authority because it would serve no useful purpose.
7. ☐ Supplementary international search report(s) from Authority(ies) has/have been received and taken into account in establishing this report (Rule 45bis.8(b) and (c)).

* If item 4 applies, some or all of those sheets may be marked "superseded".

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-16, 22, 23, 25-36</u>
	No: Claims	<u>17-21, 24</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-36</u>
Industrial applicability (IA)	Yes: Claims	<u>1-36</u>
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box 5

1 The amended set of claims meets Article 19 (2) PCT. Claim 2 as originally filed has been incorporated in to claim 1 as originally filed to build new claim 1, new claim 2 is based on claim 3, new claim 3 on claim 4, new claim 4 on claim 6, new claim 5 on claim 8 as originally filed, new claims 6-36 are based on originally filed claims 9-39 (renumbered).

2 Reference is made to the following document:

D1 US 2014/045906 A1 (FLEURY MELISSA [US] ET AL) 13
February 2014 (2014-02-13)

3 Novelty (Article 33(2) PCT)

Claims 1-16 all refer to new crystalline form (I') which is novel over D1 (compound 6N on page 63).

Claims 17-21 and 24 refer to a method of treating hypertension, heart failure or renal disease comprising administering compound (I) which is compound 6N of D1 and embodiments thereof. In paragraph [0029] of D1 it is stated that compounds of D1 are useful in treating hypertension, heart failure or renal disease. Claims 17-21 and 24 are thus not novel in the light of D1.

Claims 22 and 23 refer to a method of increasing ANP or cGMP levels. The therapeutic application of the products is functionally defined by a mechanism of action, which does not allow any practical application in the form of a defined, real treatment of a pathological condition (no diseases are indicated in the claims). Formally they are novel since D1 does not teach such application for compound (I).

The fact that claims 17-24 also refer to novel compounds of formula (I') does not render such claims novel.

Claims 25-28 refer to a new process of preparing compounds (I) due to the protection and deprotection step but as already indicated in the written opinion these claims have been searched but will be indicated as not unitary with the claims 1-24 and 29-36 since the only common technical feature is the compound (I) which is not novel and thus cannot be an inventive concept in common of all claims on file.

Claims 29-36 refer to a process for producing novel compounds (I') and are thus novel over D1.

4 Inventive step (Article 33(3) PCT)

Claims 1-16 and claims 25-36 are novel.

The technical problem underlying the present application in the light of D1 as closest prior art may be seen in the provision of further compounds having a superior effect over the closest prior art compound 6N of D1 (only the crystalline form (I') instead of the known compound (I) is the differing technical feature).

In the light of the Applicant's arguments an inventive step of the new compounds (I') over the known compound (I) (6N of D1) could not be demonstrated since both compounds appear to have the same pharmacological effect (compound (I') has no surprising effect over known compound (I)). From example 6 the Applicant referred to it appears that compound (I) was also achieved in crystalline form "...small crystals of the free acid of Compound I..." Example 6 appears to be a stability study of compound (I') alone not in comparison with compound (I). The solution to the given technical problem appears to be obvious over the teaching of D1.

The same applies to the process claims 29-36 for preparing compounds (I') since these claims refer to dissolving known compound 6N at an elevated temperature and cooling down the solution to achieve the desired crystalline product (I') and are thus common technical knowledge steps a skilled person would perform to arrive at new polymorphs of a known compound.

Process claims 25-28 refer to the preparation of known compounds (I), the compounds (I') are not mentioned (see point 2 above).

- 5 Claims 17-24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the patentability of the subject-matter of these claims (Article 34(4)(a)(I) PCT) in their present formulation but only on the alleged effect of the compounds as claimed.

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.

Attorney's Docket No.: P-324-PCT

**INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY
IN THE EUROPEAN PATENT OFFICE**

In re Patent Application of: Theravance Biopharma R&D IP, LLC
International Application No.: PCT/US2017/021172
International Filing Date: 07 March 2017
For: **CRYSTALLINE (2*S*,4*R*)-5-(5'-CHLORO-2'-FLUORO-
[1,1'-BIPHENYL]-4-YL)-2-(ETHOXYMETHYL)-4-(3-
HYDROXYISOXAZOLE-5-CARBOXAMIDO)-2-
METHYLPENTANOIC ACID AND USES THEREOF**

WRITTEN REPLY IN RESPONSE TO WRITTEN OPINION

European Patent Office
Attn: IPEA
D-80298 Munich
GERMANY

Sir:

In response to the Written Opinion of the International Searching Authority under PCT Rule 43*bis*.1¹, Applicant respectfully requests entry of the following amendments and consideration for the following remarks.

REMARKS

Applicant has proposed amendment to Figure 10, which is discussed below. Pursuant to the requirements of PCT Rule 66.8(a), also submitted herewith is a replacement sheet, numbered Figure 6/6, to replace original Figure 6/6 of the Figures that were filed with the International Application.

Amended Figure 10

Replacement Figure 6/6 is submitted herewith. The 10 mg data set (bar on graph) is missing the dotted hashtags. This was an inadvertent error made when preparing formal figures to be filed in this application.

Comments on Item V(3) - Novelty

D1 (US 2014/045906) teaches compound 6N on page 63. It is asserted that original Claims 1 and 8-27 lack novelty because it is not clear from D1 if the compound noted is crystalline or not and Claim 1 of the present invention is directed to a crystalline form without giving the powder x-ray diffraction pattern. The observation is that Claim 1 may encompass the compound 6N of D1. According to the observations, Claims 8-27 as far as they refer back to

¹ Note that the *Notification of Transmittal of the International Search Report and the Written Opinion of the International Searching Authority or the Declaration* has not yet been received by Applicant as of October 26, 2017. Applicant inquired and received email confirmation from EPO on September 26, 2017 (attached) that the International Searching Authority was made aware of this issue and that the search report and opinion with a new time limit was being mailed to Applicant. This has not yet been communicated. The International Search Report and Written Opinion of the International Searching Authority was published on 14 September 2017.

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Attorney's Docket No.: P-324-PCT

claim 1 lack novelty in light of D1. Claims 2-7 (crystalline form I') however appear to be novel due to the data given in the claims.

In response, Applicant directs attention to the amended claims filed under Article 19 amendment on October 6, 2017 and recorded on October 13, 2017 in the WIPO electronic file. See footnote on page 1. A copy of the Article 19 amended claims are included herewith.

Applicant has amended Claim 1 to include the powder x-ray diffraction pattern of original Claim 2, with the remaining claims being renumbered after cancellation of original Claims 2, 5, and 7. Thus, original Claims 1-27 (now Claims 1-24) meet the novelty criteria.

Additionally, with regard to original Claims 20-27 (now Claims 17-24), the observation is that these claims refer to compound (I) which is known from D1 (compound 6N) and these claims are not novel and they are unclear (see item VIII). Response to this is discussed below in section entitled "Comments on Item VIII."

With regard to the process claims, please note that former Claims 37-39 (now Claims 34-36) are directed to steps to make compound (I'). There was a typographical error in the dependency of the original claims that was corrected in the Article 19 amendment. Thus former Claims 32-39 (now Claims 29-36) are directed to making compound (I'), whereas former Claims 28-31 (now Claims 25-28) are directed to making compound (I) by a new process prior to the crystallization process.

Comments on Item V(4) – Inventive Step

The observations under section V(4) regarding inventive step are directed to unexpected effects exhibited by form (I') in light of compound 6N of D1. Applicant directs attention to Example 6, which describes in part the inventive nature of the crystalline form (I').

Comments on Item VII

With regard to the observations noted in Item VII, Applicant has deleted Claims 5 and 7.

Comments on Item VIII

With regard to the observations noted in Item VIII, Applicant has amended former Claims 20-27 (now Claims 17-24) to reference both compound (I) and (I'). It will be appreciated that whether crystalline or non-crystalline form of (2S,4R)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid is administered to a subject, it is the dissolved compound that inhibits neprilysin. In the disclosure of the application, both forms were tested in subjects. Compound (I) was tested in animal species, e.g., rat, dog and monkey, and compound (I') was tested in human subjects. Although the oral bioavailability was higher in human subjects receiving compound (I') versus animal species receiving compound (I), all species showed very low renal elimination compared to standard treatment, which is eliminated largely through the kidneys. This can be a huge benefit for patients who already have compromised heart, lung and kidney function. This was an unexpected result based on prior art teaching.

Another surprising and unexpected result was the duration of target engagement from trough to 24 hours. Among other things, this allows for once-daily dosing of the compound in subjects. The standard of treatment did not show this result but instead it demonstrated efficacy with a twice-daily administration.

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For the reasons discussed above, the method of treatment claims highlighting the new and unexpected results, e.g., once-daily dosing, elevated ANP or cGMP levels over 24-hours after administration, and treatment of renally impaired patients as well as heart failure and hypertensive patients, meet novelty and inventive step under Articles 33(2) and (3).

SUMMARY

The above discussion and amendment to Figure 10 are submitted for the purpose of clarifying the subject matter being claimed and for addressing the issues raised in the Written Opinion. Applicant respectfully requests the Authorized Officer to consider these remarks and amendments in preparing the International Preliminary Examination Report.

If in the opinion of the Authorized Officer, a telephone conference would expedite the review and consideration of this Written Reply, the Authorized Officer is invited to call the undersigned.

Respectfully submitted,
THERAVANCE BIOPHARMA R&D IP, LLC

Date: October 26, 2017

By: /Wendy Petka/
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Encls. Email confirmation from EPO dated September 26, 2017; and Article 19 amended claims

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CLAIMS

WHAT IS CLAIMED IS:

1. A crystalline free acid form of (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid (I'), wherein the crystalline form is characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2 θ values of 6.51 $\pm$ 0.20, 11.62 $\pm$ 0.20, 13.05 $\pm$ 0.20, 15.07 $\pm$ 0.20, and 23.28 $\pm$ 0.20.
2. The crystalline form of Claim 1, wherein the crystalline form is characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2 θ values of 6.51 $\pm$ 0.20, 11.62 $\pm$ 0.20, 13.05 $\pm$ 0.20, 15.07 $\pm$ 0.20, 17.12 $\pm$ 0.20, 23.28 $\pm$ 0.20, and 26.19 $\pm$ 0.20.
3. The crystalline form of Claim 1, wherein the crystalline form is characterized by having one or more additional diffraction peaks at 2 θ values selected from 6.51 $\pm$ 0.20, 11.62 $\pm$ 0.20, 13.05 $\pm$ 0.20, 15.07 $\pm$ 0.20, 15.72 $\pm$ 0.20, 17.12 $\pm$ 0.20, 20.79 $\pm$ 0.20, 21.10 $\pm$ 0.20, 23.28 $\pm$ 0.20, 24.48 $\pm$ 0.20, 25.81 $\pm$ 0.20, and 26.19 $\pm$ 0.20.
4. The crystalline form of Claim 1, wherein the crystalline form is characterized by a differential scanning calorimetry trace recorded at a heating rate of 10 °C per minute which shows a maximum in endothermic heat flow at a temperature between about 214 °C and about 218 °C.
5. A pharmaceutical composition comprising the crystalline form of any one of Claims 1 to 4 and a pharmaceutically acceptable carrier.
6. The pharmaceutical composition of Claim 5, wherein the pharmaceutically acceptable carrier is magnesium stearate.
7. A pharmaceutical composition comprising the crystalline form of any one of Claims 1 to 4 and an AT₁ receptor antagonist, a phosphodiesterase inhibitor, a renin inhibitor, a soluble guanylate cyclase inhibitor, a mineralocorticoid-receptor antagonist, a diuretic, or combinations

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thereof.

8. The pharmaceutical composition of Claim 7, further comprising a pharmaceutical acceptable carrier.

9. An oral dosage form comprising the crystalline form of any one of Claims 1 to 4 in a capsule, tablet, or suspension.

10. The oral dosage form of Claim 9, wherein a release of the crystalline form in a subject is an immediate, controlled or delayed release.

11. The oral dosage form of Claim 9, wherein the capsule material is gelatin, polysaccharide, chitosan or synthetic polymers.

12. The oral dosage form of Claim 9, wherein the hard capsule comprises gelatin, polysaccharides, or synthetic polymers.

13. The oral dosage form of Claim 9, wherein the capsule comprises hydroxypropyl methylcellulose.

14. A crystalline form according to any one of Claims 1 to 4 for use in therapy.

15. A crystalline form as claimed in Claim 14, for use in treating hypertension, heart failure, or renal disease.

16. The use of a compound according to any one of Claims 1 to 4, for the manufacture of a medicament for treating hypertension, heart failure, or renal disease.

17. A method for treating hypertension, heart failure, or renal disease, the method comprising administering (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid (I) or its crystalline form (I'), for

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AMENDED SHEET

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example the compound of any one of Claims 1 to 4, to a patient once-daily.

18. The method according to Claim 17, wherein hypertension is primary hypertension, pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension, or hypertension with renal artery stenosis.

19. The method according to Claim 17, wherein renal disease is diabetic nephropathy, chronic kidney disease, proteinuria, acute kidney injury, nephrotic syndrome, focal segmental glomerulosclerosis or polycystic kidney disease.

20. A method of treating hypertension, heart failure, or renal disease in a renally-impaired patient, the method comprising administering a therapeutically effective amount of the (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid (I) or its crystalline form (I'), for example the compound of any one of Claims 1 to 4, to the patient once-daily.

21. The method according to claim 20, wherein the renally-impaired patient has chronic kidney disease with an estimated glomerular filtration rate (eGFR) between 60 mL/min/1.73 m² and 15 mL/min/1.73 m².

22. A method of increasing atrial natriuretic peptide (ANP) or cyclic guanosine monophosphate (cGMP) levels in a human for at least 24 hours, the method comprising administering to the human an ANP or cGMP-increasing amount of (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid (I) or its crystalline form (I'), for example the compound of any one of Claims 1 to 4, once-daily.

23. The method according to Claim 22, wherein levels of ANP and cGMP are measured in either urine or plasma or both in the human.

24. The method according to any one of Claims 17, 20 or 22, wherein (2*S*,4*R*)-5-(5'-

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chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid (I) or its crystalline form (I'), for example the compound of any one of Claims 1 to 4, is administered parenterally.

25. A process for preparing (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid (I), the process comprising:

(a) coupling benzyl (2*S*,4*R*)-4-amino-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-2-methylpentanoate hydrochloride with 3-((4-methoxybenzyl)oxy)isoxazole-5-carboxylic acid in a solvent in approximately a 1:1 molar ratio to give benzyl (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-((4-methoxybenzyl)oxy)isoxazole-5-carboxamido)-2-methylpentanoate; and

(b) deprotecting benzyl (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-((4-methoxybenzyl)oxy)isoxazole-5-carboxamido)-2-methylpentanoate to form (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid (I).

26. The process of Claim 25, where step (a) further comprises a peptide coupling agent and a base in approximately a 1:3:1:1 molar ratio of coupling agent to base to benzyl (2*S*,4*R*)-4-amino-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-2-methylpentanoate hydrochloride to 3-((4-methoxybenzyl)oxy)isoxazole-5-carboxylic acid.

27. The process of Claim 26, where the coupling agent is 2-(6-chloro-1*H*-benzo[d][1,2,3]triazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(V) and the base is *N,N*-diisopropylethylamine.

28. The process of Claim 25, where the deprotecting step (b) is performed with a palladium catalyst and hydrogen gas.

29. A process for preparing the crystalline form of Claim 1, the process comprising:

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- (a) forming a solution comprising (2*S*,4*R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-2-(ethoxymethyl)-4-(3-hydroxyisoxazole-5-carboxamido)-2-methylpentanoic acid and a solvent, optionally with a metal scavenger, at an elevated temperature;
- (b) cooling the solution to a temperature between about -20 °C and 5 °C; and
- (c) isolating the resulting solids to yield the crystalline form.

30. The process according to Claim 29, where the solvent in step (a) is a polar solvent.

31. The process according to Claim 30, where the solvent is a mixture of ethyl acetate and water, ethyl acetate, or ethanol.

32. The process according to Claim 29, where the temperature in step (a) is between about 60 °C and 95 °C.

33. The process according to Claim 32, where the temperature is between about 70 °C and 85 °C.

34. The process according to Claim 29, where isolating the solids in step (c) involves filtering, washing with one or more solvents, drying in air or under vacuum, or a combination of these steps.

35. The process according to Claim 34, where the solvent is ethyl acetate and water, ethyl acetate or ethanol.

36. The process according to Claim 34, where drying under vacuum is performed at a temperature between 25 °C and 70 °C.

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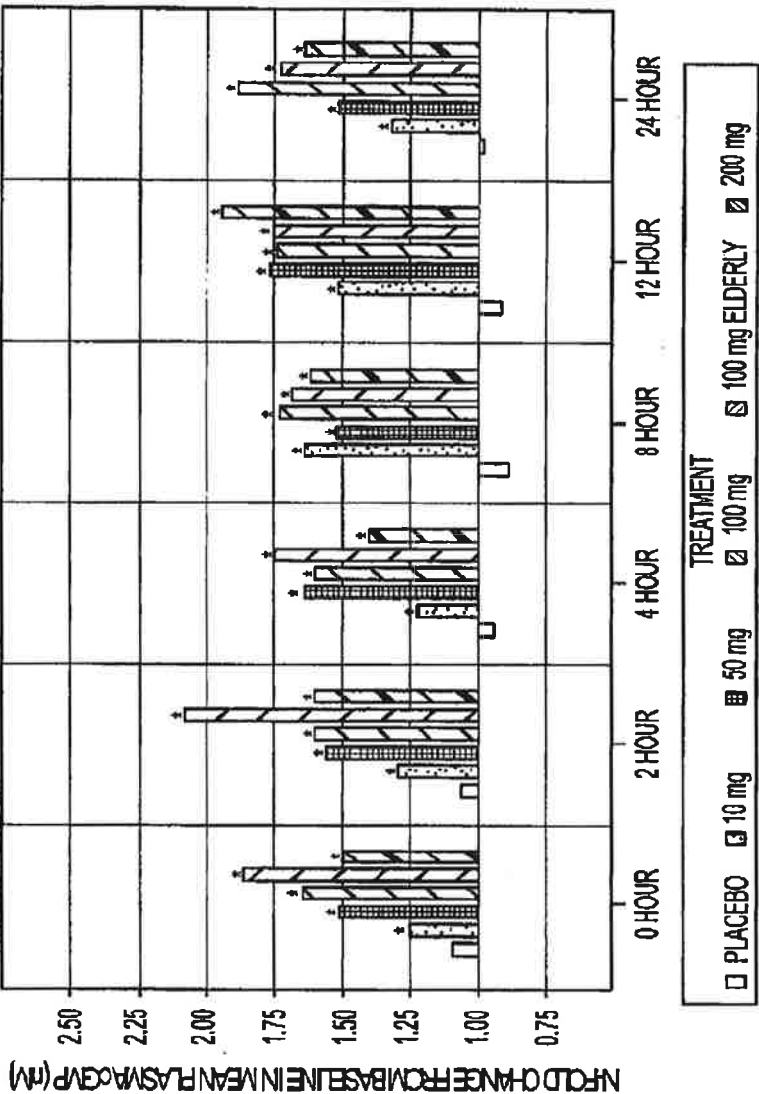


FIG. 10

AMENDED SHEET

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