

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 1848179-0002-142-WO1	FOR FURTHER ACTION		See item 4 below
International application No. PCT/US2022/033007	International filing date (<i>day/month/year</i>) 10 June 2022 (10.06.2022)	Priority date (<i>day/month/year</i>) 11 June 2021 (11.06.2021)	
International Patent Classification (IPC) or national classification and IPC See relevant information in Form PCT/ISA/237			
Applicant ACCELERON PHARMA INC.			

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a). 2. This REPORT consists of a total of 16 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3. This report contains indications relating to the following items: <table border="0"> <tr> <td>☒</td> <td>Box No. I</td> <td>Basis of the report</td> </tr> <tr> <td>☐</td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td>☒</td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td>☒</td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td>☒</td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td>☐</td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td>☐</td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td>☐</td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table> 4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).	☒	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 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
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	Date of issuance of this report 21 November 2023 (21.11.2023)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Xiaofan Tang e-mail pct.team2@wipo.int

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To: Anita Varma
White & Case LLP
75 State Street
Boston, MA 02109
United States Of America

Date of mailing
(day/month/year)

NOV 22 2022

Applicant's or agent's file reference
1848179-0002-142-WO1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US22/33007

International filing date (day/month/year)

10 June 2022 (10.06.2022)

Priority date (day/month/year)

11 June 2021 (11.06.2021)

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

IPC - INV. A61K 38/17; A61P 9/00; A61P 11/00; C07K 14/475 (2022.01)
ADD.

CPC - INV. A61K 38/17; A61K 38/45; A61P 9/00; A61P 11/00; C07K 14/475; C07K 19/00

ADD.

Applicant ACCELERON PHARMA 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/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Date of completion of this opinion

24 October 2022 (24.10.2022)

Authorized officer

Shane Thomas

PCT Help Desk

Telephone No. 571-272-4300

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US22/33007

Box No. I Basis of this 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 43*bis*.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:

- ☐ 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 13*ter*.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 13*ter*.1(a)).
☐ on paper or in the form of an image file (Rule 13*ter*.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:

An "Invitation to Furnish Nucleotide and/or Amino Acid Sequence Listing and to Pay, Where Applicable, Late Furnishing Fee" (Form PCT/ISA/225), was mailed on 29 June 2022 (29.06.2022), however, a sequence listing was not filed with the ISA/US in response to the Form PCT/ISA/225. Therefore, the international search was carried out only to the extent possible without a sequence listing.

WRITTEN OPINION OF THE
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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. 31-32, 47-198

because:

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

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 31-32, 47-198 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 31-32, 47-198 are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

☐ 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. 31-32, 47-198

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

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

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

☐ See Supplemental Box for further details.

WRITTEN OPINION OF THE
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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has, within the applicable time limit:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest and, where applicable, the protest fee.
 - ☐ paid additional fees under protest but the applicable protest fee was not paid.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☒ not complied with for the following reasons:

-Please See Supplemental Page--

4. Consequently, this opinion has been established in respect of the following parts of the international application:

- ☐ all parts.
- ☒ the parts relating to claims Nos. ***-Please See Supplemental Page-***-

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US22/33007

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

Novelty (N)	Claims	15, 20-21, 25, 33-37, 41-46	YES
	Claims	1-14, 16-19, 22-24, 26-30, 38-40	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-30, 33-46	NO
Industrial applicability (IA)	Claims	1-30, 33-46	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-3, 8-14, 16, 22-24, and 38-40 lack novelty under PCT Article 33(2) as being anticipated by US 10722558 B2 to Acceleron Pharma Inc. (hereinafter "AP'558").

As per claim 1, AP'558 discloses a method of treating pulmonary hypertension associated with lung disease (polypeptides used for (method of) treating pulmonary hypertension associated with lung disease; abstract; column 33, lines 41-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO:1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30), wherein the method reduces the right ventricular systolic pressure "RVSP" by at least 10% (method reduces pulmonary arterial pressure by at least 10%, thereby indicating reduction of the right ventricular systolic pressure or RVSP by at least 10%, since the right ventricle pumps blood into the pulmonary artery; abstract; column 4, lines 1-7).

As per claim 2, AP'558 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with lung disease (method for treating or preventing pulmonary hypertension-associated lung disease, abstract; column 33, lines 41-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 15 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 3, AP'558 discloses the method of claim 2, and AP'558 further discloses wherein the one or more complications of pulmonary hypertension associated with lung disease is selected from the group consisting of persistent cough, productive cough, wheezing, exercise intolerance, respiratory infections, bronchiectasis, chronic infections, nasal polyps, hemoptysis, pneumothorax, respiratory failure, dyspnea, chest pain, hemoptysis, pneumothorax, pulmonary vascular remodeling, pulmonary fibrosis (complications of PH associated with lung disease is idiopathic pulmonary fibrosis; column 5, lines 43-45), pulmonary vascular endothelial dysfunction, hypoxia due to chronic pulmonary injury, hypoxic pulmonary vasoconstriction, inflammation, smooth muscle hypertrophy, and right ventricular hypertrophy.

As per claim 8, AP'558 discloses a method of treating pulmonary hypertension associated with restrictive lung disease (administration (method) of polypeptide to treat interstitial lung disease which is classified as a restrictive lung disease according to page 4, lines 32-33 of the instant PCT application; column 5, lines 29-31; column 33, lines 41-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 9, AP'558 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with restrictive lung disease (administration (method) of polypeptide to treat interstitial lung disease which is classified as a restrictive lung disease according to page 4, lines 32-33 of the instant PCT application; column 5, lines 29-31; column 33, lines 41-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

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WRITTEN OPINION OF THE
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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

-Continued From Box IV (ii): Lack of unity of invention--

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-30, 33-46, and amino acid 21 (beginning amino acid), amino acid 110 (ending amino acid) of SEQ ID NO: 1 are directed towards a polypeptide and methods associated therewith.

The polypeptide and methods of Claims 1-30 (each in-part), 33-46 (each in-part) are believed to encompass the first named invention of Groups I+ and are the claims that will be searched without fee to the extent that they encompass amino acid 21 (first exemplary beginning amino acid of SEQ ID NO: 1), amino acid 110 (first exemplary ending amino acid of SEQ ID NO: 1). This first named invention of Group I+ has been selected to encompass the first species of each of the genus found in claims 1-2, 4-5, 8-9, 12, 22-23, 26-27, 33-36, 38-39, 41-42, and 45-46 based on the guidance set forth in section 10.54 of the PCT International Search and Preliminary Examination Guidelines.

Applicant is invited to elect additional beginning and ending amino acid(s) of a specified amino acid sequence to be searched. Additional beginning and ending amino acid(s) of a specified amino acid sequence will be searched upon the payment of additional fees. Applicants must specify the searchable claims that encompass any additionally elected beginning and ending amino acid(s) of a specified amino acid sequence. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. Exemplary elections would be amino acid 22 (beginning amino acid of SEQ ID NO: 1), amino acid 111 (ending amino acid of SEQ ID NO: 1).

Groups I+ were considered to share the technical features including: a method of treating, pulmonary hypertension associated with lung disease, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with lung disease, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence, wherein the method reduces the right ventricular systolic pressure or RVSP by at least 10%; a method of treating pulmonary hypertension associated with obstructive lung disease, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with obstructive lung disease comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with restrictive lung disease, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with restrictive lung disease comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with combined obstructive and restrictive lung disease, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with interstitial lung disease or ILD, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with ILD, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with chronic obstructive pulmonary disease or COPD, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with COPD, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with combined pulmonary fibrosis and emphysema or CPFE, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with CPFE, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia or IIP, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with fibrotic IIP, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with idiopathic pulmonary fibrosis or IPF, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with IPF, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with non-idiopathic pulmonary fibrosis interstitial lung disease or non-IPF ILD, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with non-IPF ILD, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%,

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WRITTEN OPINION OF THE
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Supplemental Box

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Continuation of:

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93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; a method of treating pulmonary hypertension associated with nonspecific interstitial pneumonia or NSIP, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with NSIP, comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; these shared technical features are previously disclosed by US 2020/0397865 A1 to Acceleron Pharma Inc. (hereinafter "Acceleron'865"), WO 2021/092079 A1 to Acceleron Pharma Inc. (hereinafter "Acceleron'079"), as further evidenced by the publication entitled "Idiopathic interstitial pneumonias: review of the latest American Thoracic Society/European Respiratory Society classification" by Oliviera, et al. (hereinafter "Oliviera"), and US 2018/0179279 A1 to Allakos Inc. (hereinafter "Allakos"), as further evidenced by the publication entitled "Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome" by Cottin, et al. ("Cottin").

Acceleron'865 discloses a method of treating pulmonary hypertension associated with lung disease, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with lung disease (methods of using a polypeptide to treat (method of treating), prevent, or reduce the progression rate and/or severity of one or more complications of pulmonary hypertension associated with lung disease; abstract; paragraphs [0007], [0008], [0281], [0282]), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (treating pulmonary arterial hypertension comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%-100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; paragraph [0008]), wherein the method reduces the right ventricular systolic pressure or RVSP by at least 10% (method reduces pulmonary arterial pressure by at least 10%, thereby indicating reduction of the right ventricular systolic pressure or RVSP by at least 10%, since the right ventricle pumps blood into the pulmonary artery; abstract; paragraph [0008]); a method of treating pulmonary hypertension associated with obstructive lung disease, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with obstructive lung disease (method of treating pulmonary hypertension associated with lymphangiomatosis (obstructive lung disease), and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with lymphangiomatosis; abstract; paragraphs [0007], [0008], [0281], [0282]) comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (treating pulmonary arterial hypertension comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%-100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; paragraph [0008]); a method of treating pulmonary hypertension associated with restrictive lung disease, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with restrictive lung disease (method of treating pulmonary hypertension patients associated with sarcoidosis (restrictive lung disease) and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with sarcoidosis; abstract; paragraphs [0007], [0008], [0281], [0282]) comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (treating pulmonary arterial hypertension comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%-100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; paragraph [0008]); a method of treating pulmonary hypertension associated with combined obstructive and restrictive lung disease (method of treating pulmonary hypertension patients associated with sarcoidosis (combined obstructive and restrictive lung disease) and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with sarcoidosis; abstract; paragraphs [0007], [0008], [0281], [0282]), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (treating pulmonary arterial hypertension comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%-100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; paragraph [0008]); a method of treating pulmonary hypertension associated with interstitial lung disease or ILD, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with ILD (methods of using a polypeptide to treat (method of treating), prevent, or reduce the progression rate and/or severity of one or more complications of pulmonary hypertension associated with lung disease, such as interstitial lung disease; abstract; paragraphs [0007], [0008], [0010], [0281], [0282], [0287]), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (treating pulmonary arterial hypertension comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%-100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; paragraph [0008]), wherein the method reduces the right ventricular systolic pressure or RVSP by at least 10% (method reduces pulmonary arterial pressure by at least 10%, thereby indicating reduction of the right ventricular systolic pressure or RVSP by at least 10%, since the right ventricle pumps blood into the pulmonary artery; abstract; paragraph [0008]); a method of treating pulmonary hypertension associated with idiopathic pulmonary fibrosis or IPF, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with IPF (method of treating pulmonary hypertension associated with interstitial lung disease, such as IPF, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with IPF; abstract; paragraphs [0007], [0008], [0010], [0281], [0282], [0287]), comprising administering to a patient in need thereof an

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effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (treating pulmonary arterial hypertension comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%-100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; paragraph [0008]).

Acceleron'079 discloses a method of treating pulmonary hypertension associated with chronic obstructive pulmonary disease or COPD, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with COPD (method of treating (one or more complications of) pulmonary hypertension associated with COPD; abstract; page 99, lines 3-5; page 162, lines 4-16), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 80% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; abstract; page 20, lines 16-21; page 162, lines 4-16); a method of treating pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia or IIP, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with fibrotic IIP (a method of treating (one or more complications of) pulmonary hypertension associated with usual interstitial pneumonia, which is the same as fibrotic idiopathic interstitial pneumonia, shown by the Oliveira evidentiary reference (IIPs, such as IPF (fibrotic IIP), are characterized histologically by the usual interstitial pneumonia pattern; page 322, 1st column, 2nd paragraph); abstract; page 6, lines 18-19; page 99, lines 3-5; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 80% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; abstract; page 20, lines 16-21; page 162, lines 4-16); a method of treating pulmonary hypertension associated with non-idiopathic pulmonary fibrosis interstitial lung disease or non-IPF ILD, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with non-IPF ILD (a method of treating pulmonary hypertension associated with SSC-ILD (non-IPF ILD); abstract; page 99, lines 3-5; page 138, lines 19-22; page 139, lines 3-14; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 80% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; abstract; page 20, lines 16-21; page 162, lines 4-16); a method of treating pulmonary hypertension associated with nonspecific interstitial pneumonia or NSIP, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with NSIP (method of treating (one or more complications of) pulmonary hypertension associated with NSIP; abstract; page 6, lines 17-18; page 99, lines 3-5; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 80% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence; abstract; page 20, lines 16-21; page 162, lines 4-16).

Allakos discloses a method of treating pulmonary hypertension associated with combined pulmonary fibrosis and emphysema or CPFE, and treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with CPFE (methods for the prevention or treatment (of one or more complications of) of fibrotic diseases, such as CPFE, which would intrinsically involve treating pulmonary hypertension associated with CPFE, as shown by the Cottin evidentiary reference (pulmonary hypertension is frequent in patients with CPFE; page 105, 2nd column, 2nd paragraph); abstract; paragraph [0092]), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence (comprising administering to an individual (patient in need thereof) an effective amount of a truncated antibody (a polypeptide comprising an amino acid sequence that is at least 70%-100% identical to an amino acid sequence that begins and ends at specific amino acid positions of an amino acid sequence); abstract; paragraphs [0009], [0210]).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Acceleron'865, Acceleron'079, and Allakos references, unity of invention is lacking.

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Groups I+, Claims 1-30, 33-46, and amino acid 21 (beginning amino acid of a specified amino acid sequence), amino acid 110 (ending amino acid of a specified amino acid sequence).

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As per claim 10, AP'558 discloses the method of claims 8-9, and AP'558 further discloses wherein the restrictive lung disease is selected from the group consisting of pulmonary fibrosis, interstitial lung disease (administration of polypeptide to treat interstitial lung disease which is classified as a restrictive lung disease according to page 4, lines 32-33 of the instant PCT application; column 5, lines 29-31; column 33, lines 41-45), sarcoidosis, idiopathic pulmonary fibrosis, pneumoconiosis, obesity, scoliosis, myasthenia gravis, and pleural effusion.

As per claim 11, AP'558 discloses the method of claim 9, and AP'558 further discloses wherein the one or more complications of pulmonary hypertension associated with restrictive lung disease is selected from the group consisting of shortness of breath with exertion, shortness of breath during rest, shortness of breath with minimal activity (pulmonary hypertension associated with lung disease leads to patients suffering from extreme shortness of breath, which would intrinsically be either during rest or with minimal activity; column 111, lines 4-13), cough, dry cough, productive cough, chronic cough, fatigue, weight loss, anxiety, depression, and fibrosis.

As per claim 12, AP'558 discloses a method of treating pulmonary hypertension associated with combined obstructive and restrictive lung disease (method of treating pulmonary hypertension patients associated with sarcoidosis, which is a combined obstructive and restrictive lung disease according to page 5, lines 14-16 of the instant PCT application specification; abstract; column 33, lines 41-45; column 110, lines 1-2), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21, of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO: 1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 13, AP'558 discloses the method of claim 12, and AP'558 further discloses wherein the combined obstructive and restrictive lung disease is a pulmonary parenchymal disorder (method of treating pulmonary hypertension patients associated with sarcoidosis, which is a combined obstructive and restrictive lung disease and a pulmonary parenchymal disorder according to page 5, lines 14-16 of the instant PCT application specification; abstract; column 33, lines 41-45; column 110, lines 1-2).

As per claim 14, AP'558 discloses the method of claim 13, and AP'558 further discloses wherein the pulmonary parenchymal disorder is selected from the group consisting of: a. sarcoidosis, b. chronic obstructive pulmonary disease "COPD" and interstitial lung disease "ILD", c. COPD and idiopathic pulmonary fibrosis, d. pneumoconiosis, e. ILD (treatment of interstitial lung disease complications such as pulmonary hypertension associated with connective tissue disease; column 4, lines 43-44; column 33, lines 41-45), f. Langerhans cell histiocytosis, g. idiopathic pulmonary fibrosis "IPF" (obstructive and restrictive lung disease associated with pulmonary hypertension which is treated and also a pulmonary parenchymal disorder is idiopathic pulmonary fibrosis; column 33, lines 41-45; column 110, lines 1-6), h. pulmonary alveolar proteinosis, i. lymphangioleiomyomatosis, j. bronchiolitis obliterans syndrome.

As per claim 16, AP'558 discloses the method of claim 14, AP'558 further discloses wherein the ILD is associated with systemic lupus erythematosus, rheumatoid arthritis, connective tissue disease (treatment of interstitial lung disease complications such as pulmonary hypertension associated with connective tissue disease; column 4, lines 43-44; column 33, lines 41-45), interstitial pneumonitis, constrictive bronchiolitis, or cryptogenic organizing pneumonia.

As per claim 22, AP'558 discloses a method of treating pulmonary hypertension associated with interstitial lung disease "ILD" (administration (method) of polypeptide to treat interstitial lung disease; column 5, lines 29-31; column 33, lines 41-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO: 1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30), wherein the method reduces the right ventricular systolic pressure "RVSP" by at least 10% (method reduces pulmonary arterial pressure by at least 10%, thereby indicating reduction of the right ventricular systolic pressure or RVSP by at least 10%, since the right ventricle pumps blood into the pulmonary artery; abstract; column 4, lines 1-7).

As per claim 23, AP'558 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with interstitial lung disease "ILD" (administration of polypeptide to treat interstitial lung disease; column 5, lines 29-31; column 33, lines 41-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO: 1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 24, AP'558 discloses the method of claims 16 and 23, and AP'558 further discloses wherein the ILD is associated with a condition selected from the group consisting of a connective tissue disease (treatment of interstitial lung disease complications such as pulmonary hypertension associated with connective tissue disease; column 4, lines 43-44; column 33, lines 41-45), sarcoidosis, vascular destruction due to progressive parenchymal fibrosis, vascular inflammation, perivascular fibrosis, thrombotic angiopathy, and endothelial dysfunction.

As per claim 38, AP'558 discloses a method of treating pulmonary hypertension (treatment for pulmonary hypertension complications with

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antagonists; column 3, lines 5-7; column 33, lines 41-45) associated with idiopathic pulmonary fibrosis "IPF" (the interstitial lung disease associated with hypertension and treated with polypeptide can be idiopathic pulmonary fibrosis; column 5, lines 43-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 39, AP'558 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension (treatment for pulmonary hypertension complications with antagonists; column 3, lines 5-7; column 33, lines 41-45) associated with idiopathic pulmonary fibrosis "IPF" (the interstitial lung disease associated with hypertension and treated with polypeptide can be idiopathic pulmonary fibrosis; column 5, lines 43-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 40, AP'558 discloses the method of claim 39, and AP'558 further discloses wherein the one or more complications of pulmonary hypertension associated with IPF is selected from the group consisting of increased need for supplemental oxygen (treating pulmonary hypertension associated with IPF, which leads to patients suffering from shortness of breath and would result in an increased need for supplemental oxygen; column 33, lines 41-46; column 111, lines 4-13; column 115, lines 29-30), reduced mobility, and decreased survival.

Claims 4-7, 17-19, and 26-30 lack novelty under PCT Article 33(2) as being anticipated by AP'558, as further evidenced by the publication entitled "Chronic Obstructive Pulmonary Disease and the Cardiovascular System: Vascular Repair and Regeneration as a Therapeutic Target" by Karnati, et al. (hereinafter "Karnati").

As per claim 4, AP'558 discloses a method of treating pulmonary hypertension associated with obstructive lung disease (method of treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD (obstructive lung disease), as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2); column 111, lines 31-34), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 5, AP'558 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with obstructive lung disease (method of treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD (obstructive lung disease), as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2); column 111, lines 31-34), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 6, AP'558 discloses the method of claim 4 or 5, and AP'558 further discloses wherein the obstructive lung disease is selected from the group consisting of chronic obstructive pulmonary disease "COPD" (method of treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD (obstructive lung disease), as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2); column 111, lines 31-34), cystic fibrosis, asthma, emphysema, lymphangioleiomyomatosis, and chronic bronchitis.

As per claim 7, AP'558 discloses the method of claim 6, and AP'558 further discloses wherein the one or more complications of pulmonary hypertension associated with obstructive lung disease is selected from the group consisting of increased need for supplemental oxygen (treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD (obstructive lung disease), as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2), and which leads to patients suffering from shortness of breath and would result in an increased need for supplemental oxygen; column 111, lines 4-34; column 115, lines 29-30), reduced mobility, and decreased survival.

As per claim 17, AP'558 discloses the method of claim 12, and AP'558 further discloses wherein the combined obstructive and restrictive lung disease is a combination of pulmonary parenchymal disorder and a non-pulmonary disease (method of treating pulmonary hypertension patients that have pulmonary hypertension with left heart disease (non-pulmonary disease), wherein the pulmonary hypertension is associated obstruction of the vascular lumen which causes COPD (obstructive pulmonary parenchymal disorder), as shown

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by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2); abstract; column 110, lines 61-62; column 111, lines 31-34).

As per claim 18, AP'558 discloses the method of claim 17, and AP'558 further discloses wherein the combination of pulmonary parenchymal disorder and non-pulmonary disease is selected from the group consisting of: a. chronic obstructive pulmonary disease or COPD and other non-parenchymal diseases (method of treating pulmonary hypertension patients that have pulmonary hypertension with left heart disease (non-pulmonary non-parenchymal disease), wherein the pulmonary hypertension is associated obstruction of the vascular lumen which causes COPD (obstructive pulmonary parenchymal disorder), as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2); abstract; column 110, lines 61-62; column 111, lines 31-34); b. congestive heart failure or CHF and other non-pulmonary diseases; c. asthma and other disorder; d. interstitial lung disease or ILD and obesity; e. ILD and CHF; and f. lung hypoplasia and scoliosis.

As per claim 19, AP'558 discloses the method of claim 18, and AP'558 further discloses wherein the COPD and other non-parenchymal disease is selected from the group consisting of: a. COPD and congestive heart failure or CHF (method of treating pulmonary hypertension patients that have pulmonary hypertension with left heart disease (CHF), wherein the pulmonary hypertension is associated obstruction of the vascular lumen which causes COPD (obstructive pulmonary parenchymal disorder), as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2); abstract; column 110, lines 61-62; column 111, lines 31-34); b. COPD and obesity; c. COPD and thoracic surgery; d. COPD and diaphragm paralysis; e. COPD and scoliosis; and f. COPD and pleurodesis.

As per claim 26, AP'558 discloses a method of treating pulmonary hypertension associated with chronic obstructive pulmonary disease or COPD (method of treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD, as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2); column 111, lines 31-34), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acids 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 27, AP'558 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with chronic obstructive pulmonary disease or COPD (method of treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD, as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2); column 111, lines 31-34), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30).

As per claim 28, AP'558 discloses the method of claim 27, and AP'558 further discloses wherein the one or more complications of pulmonary hypertension associated with COPD is selected from the group consisting of wheezing, productive cough, frequent cough, tightness in the chest, shortness of breath without physical activity, shortness of breath with physical activity (treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD, as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2), and which leads to patients suffering from extreme shortness of breath which would intrinsically be either with or without physical activity; column 111, lines 4-34; column 115, lines 29-30), respiratory infection, weight loss, weakness in the muscles of the lower extremities, swelling in the lower extremities, and heart disease.

As per claim 29, AP'558 discloses the method of claims 26-28, and AP'558 further discloses wherein the patient has COPD with Gold grade 1, Gold grade 2, Gold grade 3, or Gold grade 4 as recognized by the Global Initiative for Chronic Obstructive Lung Disease (treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD, as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2), wherein the COPD would intrinsically be classified as one of four GOLD stages, and wherein the PAH is advanced, thereby indicating an advanced stage COPD, such as GOLD stage 3 or 4, as per page 58, lines 25-30 of the specification of the instant PCT application; column 111, lines 4-34; column 115, lines 29-30).

As per claim 30, AP'558 discloses the method of claims 26-28, and AP'558 further discloses wherein the patient has Group A COPD, Group B COPD, Group C COPD, or Group D COPD (treating pulmonary hypertension associated obstruction of the vascular lumen which causes COPD, as shown by the Karnati evidentiary reference (patients with end-stage COPD have thickened walls or vascular occlusion, reducing the vascular lumen; page 4, column 1, paragraph 2), wherein the COPD would intrinsically be classified as one of four Group stages, and wherein the PAH is advanced, thereby indicating an advanced stage COPD, such as Group C or Group D COPD; column 111, lines 4-34; column 115, lines 29-30).

Claim 15 lacks an inventive step under PCT Article 33(3) as being obvious over AP'558 in view of the publication entitled "Upregulation of activin-B and follistatin in pulmonary fibrosis -- a translational study using human biopsies and a specific inhibitor in mouse fibrosis models"

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by Myllarniemi M. et al. (hereinafter "Myllarniemi").

As per claim 15, AP'558 discloses the method of claim 14, AP'558 does not disclose wherein the pneumoconiosis is selected from the group consisting of silicosis, coal worker's lung, and berylliosis. Myllarniemi discloses a peptide inhibiting activin signaling to treat pneumoconiosis, such as silicosis (activin levels were elevated in mice exposed to silica dioxide (pneumoconiosis, such as silicosis), following which they were treated with ActRIIB polypeptide to inhibit activin signaling; abstract; page 3, column 2, paragraph 3). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'558 to include discloses a peptide inhibiting activin signaling to treat pneumoconiosis, such as silicosis, as taught by Myllarniemi, because that would provide the capability of treating pneumoconiosis, such as silicosis, with elevated activin levels, and therefore increased activin signaling, by inhibiting activin signaling using the ActRII polypeptide, thereby providing an improved and efficacious treatment method for silicosis.

Claim 25 lacks an inventive step under PCT Article 33(3) as being obvious over AP'558 in view of WO 2021/092079 A1 to Acceleron Pharma Inc. (hereinafter "AP'079").

As per claim 25, AP'558 discloses the method of claim 24, AP'558 does not disclose wherein the connective tissue disease is selected from the group consisting of systemic sclerosis, rheumatoid arthritis, polymyositis, dermatomyositis, and Sjogren syndrome. AP'079 discloses an ActRII antagonist to treat a connective tissue disease, such as systemic sclerosis (systemic sclerosis treated with ActRII antagonist polypeptide; page 2, lines 3-4; page 161, lines 21-24). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'558 to include an ActRII antagonist to treat a connective tissue disease, such as systemic sclerosis, as taught by AP'079, because that would provide the capability to treat PH associated with connective tissue disease, such as systemic sclerosis, using an ActRII polypeptide that inhibits ActRII signaling, thereby providing an improved and efficacious treatment for PH associated with systemic sclerosis.

Claims 33-34 lack an inventive step under PCT Article 33(3) as being obvious over AP'558 in view of the publication entitled "TGF-beta Signaling in Lung Health and Disease" by Saito, et al. (hereinafter "Saito").

As per claim 33, AP'558 discloses a method of treating pulmonary hypertension (polypeptides used for (method of) treating pulmonary hypertension associated with lung disease; abstract; column 33, lines 41-45) comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO: 1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30), wherein the polypeptide binds to TGF-beta ligands (ActRII polypeptide binds to TGF-beta ligands; column 59, lines 16-34; column 123, lines 7-18). AP'558 does not disclose specifically disclose treating pulmonary hypertension associated with combined pulmonary fibrosis and emphysema or CPFE. Saito discloses pulmonary hypertension associated with combined pulmonary fibrosis and emphysema or CPFE caused by upregulation of TGF-beta ligands (upregulation of TGF-beta ligands is observed in CPFE with pulmonary hypertension; page 8, paragraph 1; fig. 3). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by AP'558, for the integration of pulmonary hypertension associated with combined pulmonary fibrosis and emphysema or CPFE caused by upregulation of TGF-beta ligands, based on the teachings of Saito, as this modification would provide the capability of treating PH associated with CPFE, caused by upregulated TGF-beta ligands, using an ActRII polypeptide that acts by binding to TGF-beta ligands, thereby providing an efficacious approach for treating PH associated with CPFE.

As per claim 34, AP'558 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension (polypeptides used for (method of) treating pulmonary hypertension associated with lung disease; abstract; column 33, lines 41-45), comprising administering to a patient in need thereof an effective amount of a polypeptide (therapeutic amount of polypeptide administered to patient in need; column 3, lines 18-21) comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical to an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (the therapeutic polypeptide comprises the sequence set forth in amino acids 21 to 110 of SEQ ID NO: 1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; column 3, lines 18-30), wherein the polypeptide binds to TGF-beta ligands (ActRII polypeptide binds to TGF-beta ligands; column 59, lines 16-34; column 123, lines 7-18). AP'558 does not disclose specifically disclose treating pulmonary hypertension associated with combined pulmonary fibrosis and emphysema or CPFE. Saito discloses pulmonary hypertension associated with combined pulmonary fibrosis and emphysema or CPFE caused by upregulation of TGF-beta ligands (upregulation of TGF-beta ligands is observed in CPFE with pulmonary hypertension; page 8, paragraph 1; fig. 3). It would have been obvious to a person of ordinary skill in the art, at the time of the invention, to have modified the method, as previously disclosed by AP'558, for the integration of pulmonary hypertension associated with combined pulmonary fibrosis and emphysema or CPFE caused by upregulation of TGF-beta ligands, based on the teachings of Saito, as this modification would provide the capability of treating PH associated with CPFE, caused by upregulated TGF-beta ligands, using an ActRII polypeptide that acts by binding to TGF-beta ligands, thereby providing an efficacious approach for treating PH associated with CPFE.

Claims 41-46 lack an inventive step under PCT Article 33(3) as being obvious over AP'079 in view of AP'558.

As per claim 41, AP'079 discloses a method of treating pulmonary hypertension associated with non-idiopathic pulmonary fibrosis interstitial lung disease "non-IPF ILD" (a method of treating pulmonary hypertension associated with SSc-ILD (non-IPF ILD); abstract; page 2, lines 3-13; page 99, lines 3-5; page 138, lines 19-22; page 139, lines 3-14; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide (treating SSc-ILD by administering to a patient in need thereof an

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effective amount of an ActRII antagonist polypeptide; abstract; page 2, lines 3-13; page 161, lines 21-24; page 162, lines 4-16). AP'079 does not disclose an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1. AP'558 discloses treating pulmonary hypertension comprising administering to a patient in need thereof an effective amount of an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (treating PAH by administering to a subject in need, a therapeutic ActRII polypeptide comprising the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; abstract; column 3, lines 18-30). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'079 to include an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1, as taught by AP'558, because that would provide the capability of treating pulmonary hypertension associated with non-IPF ILD by inhibiting ActRII signaling using an ActRII polypeptide of a well-defined amino acid sequence, thereby providing an improved and efficacious approach for the treatment of PH associated with non-IPF ILD.

As per claim 42, AP'079 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with non-idiopathic pulmonary fibrosis interstitial lung disease "non-IPF ILD" (a method of treating pulmonary hypertension associated with SSc-ILD (non-IPF ILD); abstract; page 2, lines 3-13; page 99, lines 3-5; page 138, lines 19-22; page 139, lines 3-14; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide (treating SSc-ILD by administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide; abstract; page 2, lines 3-13; page 161, lines 21-24; page 162, lines 4-16). AP'079 does not disclose an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1. AP'558 discloses treating pulmonary hypertension comprising administering to a patient in need thereof an effective amount of an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (treating PAH by administering to a subject in need, a therapeutic ActRII polypeptide comprising the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; abstract; column 3, lines 18-30). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'079 to include an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1, as taught by AP'558, because that would provide the capability of treating pulmonary hypertension associated with non-IPF ILD by inhibiting ActRII signaling using an ActRII polypeptide of a well-defined amino acid sequence, thereby providing an improved and efficacious approach for the treatment of PH associated with non-IPF ILD.

As per claim 43, AP'079 and AP'558, in combination, disclose the method of claims 41-42, and AP'079 further discloses wherein the non-IPF ILD is selected from the group consisting of smoking-related ILD, hypersensitivity pneumonitis related ILD (non-IPF ILD can be hypersensitivity pneumonitis related ILD; page 2, lines 3-13; page 99, lines 3-5; page 120, lines 12-13; page 138, lines 19-22; page 139, lines 3-14; page 162, lines 8-16), connective tissue-related ILD, occupation-related ILD, and medication-induced ILD.

As per claim 44, AP'079 and AP'558, in combination, disclose the method of claim 42, and AP'079 further discloses wherein the one or more complications of pulmonary hypertension associated with non-idiopathic pulmonary fibrosis interstitial lung disease "non-IPF ILD" is selected from the group consisting of increased need for supplemental oxygen, reduced mobility, and decreased survival (levels of IL-6 are elevated in subjects with SSc-ILD (non-IPF ILD) and associated with decreased survival, page 134, lines 11-17).

As per claim 45, AP'079 discloses a method of treating pulmonary hypertension associated with nonspecific interstitial pneumonia "NSIP" (method of treating (one or more complications of) pulmonary hypertension associated with NSIP; abstract; page 6, lines 17-18; page 99, lines 3-5; page 121, lines 1-4; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide (treating SSc-ILD manifestations, such as PAH and NSIP, by administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide; abstract; page 2, lines 3-13; page 6, lines 17-18; page 99, lines 3-5; page 121, lines 1-4; page 161, lines 21-24; page 162, lines 4-16). AP'079 does not disclose an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1. AP'558 discloses treating pulmonary hypertension comprising administering to a patient in need thereof an effective amount of an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (treating PAH by administering to a subject in need, a therapeutic ActRII polypeptide comprising the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; abstract; column 3, lines 18-30). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'079 to include an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1, as taught by AP'558, because that would provide the capability of treating pulmonary hypertension associated with NSIP by inhibiting ActRII signaling using an ActRII polypeptide of a well-defined amino acid sequence, thereby providing an improved and efficacious approach for the treatment of PH associated with NSIP.

As per claim 46, AP'079 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with nonspecific interstitial pneumonia "NSIP" (method of treating (one or more complications of) pulmonary hypertension associated with NSIP; abstract; page 6, lines 17-18; page 99, lines 3-5; page 121, lines 1-4; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 15 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical (treating SSc-ILD manifestations, such as PAH and NSIP, by administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide; abstract; page 2, lines 3-13; page 6, lines 17-18; page 99, lines 3-5; page 121, lines 1-4; page 161, lines 21-24; page 162, lines 4-16). AP'079 does not disclose an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1. AP'558 discloses treating pulmonary hypertension comprising administering to a patient in need thereof an effective amount of an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (treating PAH by administering to a subject in need, a

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therapeutic ActRII polypeptide comprising the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; abstract; column 3, lines 18-30). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'079 to include an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1, as taught by AP'558, because that would provide the capability of treating pulmonary hypertension associated with NSIP by inhibiting ActRII signaling using an ActRII polypeptide of a well-defined amino acid sequence, thereby providing an improved and efficacious approach for the treatment of PH associated with NSIP.

Claims 20-21 lack an inventive step under PCT Article 33(3) as being obvious over AP'558, as evidenced by Karnati, in view of US 2019/0365844 A1 to Acceleron Pharma Inc. (hereinafter "AP'844").

As per claim 20, AP'558 discloses the method of claim 18, AP'558 does not disclose wherein the CHF and other non-pulmonary disease is selected from the group consisting of: a. CHF and scoliosis; b. CHF and lung resection; and c. CHF and obesity. AP'844 discloses a peptide inhibiting ActRII signaling to treat CHF and another non-pulmonary disease, obesity (congestive heart disease and obesity are two diseases which can be treated by ActRII binding protein and reduced ActRII signaling; paragraphs [0007], [0038], [0361], [0368]). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'558 to include CHF and additional non-pulmonary disease, such as obesity, as taught by AP'844, because that would provide the capability of simultaneously treating CHF and obesity with an ActRII signaling antagonist, such as the ActRII polypeptide, thereby providing an improved and efficacious treatment method for CHF and obesity.

As per claim 21, AP'558 discloses the method of claim 18, AP'558 does not disclose wherein the asthma and other disorder are selected from the group consisting of: a. asthma and obesity; b. asthma and lung resection; c. asthma and radiation fibrosis; d. asthma and trapped lung; and e. asthma and CHF. AP'844 discloses a peptide inhibiting ActRII signaling to treat asthma and CHF (congestive heart disease and asthma are two diseases which can be treated by ActRII binding protein and reduced ActRII signaling; paragraphs [0007], [0038], [0346], [0361]). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the combination of pulmonary parenchymal disorder and non-pulmonary disease of AP'558 to include asthma and CHF, as taught by AP'844, because that would provide the capability of simultaneously treating asthma and CHF with an ActRII signaling antagonist, such as the ActRII polypeptide, thereby providing an improved and efficacious treatment method for asthma and CHF.

Claims 35-37 lack an inventive step under PCT Article 33(3) as being obvious over AP'079 as evidenced by publication entitled "Idiopathic interstitial pneumonias: review of the latest American Thoracic Society/European Respiratory Society classification" by Oliviera, et al. (hereinafter "Oliviera"), in view of AP'558.

As per claim 35, AP'079 discloses a method of treating pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia "IIP" (a method of treating pulmonary hypertension associated with usual interstitial pneumonia, which is the same as fibrotic idiopathic interstitial pneumonia, as shown by the Oliviera evidentiary reference (IIPs, such as IPF (fibrotic IIP), are characterized histologically by the usual interstitial pneumonia pattern; page 322, column 1, paragraph 2); abstract; page 6, lines 18-19; page 99, lines 3-5; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide (treating SSC-ILD manifestations, such as PAH and UIP, by administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide; abstract; page 2, lines 3-13; page 6, lines 18-19; page 99, lines 3-5; page 121, lines 1-4; page 161, lines 21-24; page 162, lines 4-16). AP'079 does not disclose an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1. AP'558 discloses treating pulmonary hypertension comprising administering to a patient in need thereof an effective amount of an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (treating PAH by administering to a subject in need, a therapeutic ActRII polypeptide comprising the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; abstract; column 3, lines 18-30). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'079 to include an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1, as taught by AP'558, because that would provide the capability of treating pulmonary hypertension associated with fibrotic IIP by inhibiting ActRII signaling using an ActRII polypeptide of a well-defined amino acid sequence, thereby providing an improved and efficacious approach for the treatment of PH associated with fibrotic IIP.

As per claim 36, AP'079 discloses a method of treating, preventing, or reducing the progression rate and/or severity of one or more complications of pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia "IIP" (a method of treating (one or more complications of) pulmonary hypertension associated with usual interstitial pneumonia, which is the same as fibrotic idiopathic interstitial pneumonia, as shown by the Oliviera evidentiary reference (IIPs, such as IPF (fibrotic IIP), are characterized histologically by the usual interstitial pneumonia pattern; page 322, 1st column, 2nd paragraph); abstract; page 6, lines 18-19; page 99, lines 3-5; page 162, lines 8-16), comprising administering to a patient in need thereof an effective amount of a polypeptide comprising an amino acid sequence that is at least 70%, 75%, 80%, 85%, 86%, 87%, 88%, 89%, 90%, 91 %, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% identical (treating SSC-ILD manifestations, such as PAH and UIP, by administering to a patient in need thereof an effective amount of an ActRII antagonist polypeptide; abstract; page 2, lines 3-13; page 6, lines 18-19; page 99, lines 3-5; page 121, lines 1-4; page 161, lines 21-24; page 162, lines 4-16). AP'079 does not disclose an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1. AP'558 discloses treating pulmonary hypertension comprising administering to a patient in need thereof an effective amount of an ActRII polypeptide comprising an amino acid sequence that begins at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1 (treating PAH by administering to a subject in need, a therapeutic ActRII polypeptide comprising the sequence set forth in amino acids 21 to 110 of SEQ ID NO:1 of the instant PCT application, which is 100% identical to the sequence of amino acids 21 to 110 of SEQ ID NO: 9 of AP'558; abstract; column 3, lines 18-30). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method of AP'079 to include an ActRII polypeptide comprising an amino acid sequence that begins

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at amino acid 21 of SEQ ID NO: 1 and ends at amino acid 110 of SEQ ID NO: 1, as taught by AP'558, because that would provide the capability of treating pulmonary hypertension associated with fibrotic IIP by inhibiting ActRII signaling using an ActRII polypeptide of a well-defined amino acid sequence, thereby providing an improved and efficacious approach for the treatment of PH associated with fibrotic IIP.

As per claim 37, AP'079 and AP'558, in combination, disclose the method of claims 35-36, and AP'079 further discloses wherein the patient has one or more diagnostic parameters selected from the group consisting of a high fibrotic score and a low diffusing capacity for carbon monoxide "DLco" prior to treatment (subjects with SSc-ILD associated with PAH and UIP have low DLCO scores, which would intrinsically be prior to treatment; abstract; page 6, lines 18-19; page 12, lines 17-23; page 99, lines 3-5; page 162, lines 8-16).

Claims 1-30 and 33-46 have industry applicability as defined by PCT article 33(4) because the subject matter can be made or used in industry.