

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

MAY 16 2024

Applicant's or agent's file reference
1848179-0002-169-WO1

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 24/13378

International filing date (day/month/year)

29 January 2024 (29.01.2024)

Priority date (day/month/year)

09 March 2023 (09.03.2023)

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

IPC - INV. A61K 38/17, A61K 38/18, C07K 14/71, C07K 19/00 (2024.01)

ADD.

CPC - INV. A61K 38/179, A61K 38/17, C07K 14/71

ADD. C07K 2319/00, C07K 2319/30

Applicant **MERCK SHARP & DOHME LLC**

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

12 April 2024 (12.04.2024)

Authorized officer

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Telephone No. 571-272-4300

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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 43bis.1(b)).
3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☒ forming part of the international application as filed.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13ter.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

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

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

☐ the entire international application.

☒ claims Nos. 10-32, 36-37, 42-46

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. 10-32, 36-37, 42-46 are so unclear that no meaningful opinion could be formed (*specify*):

because they 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. 10-32, 36-37, 42-46

☐ 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.

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

1. Statement

Novelty (N)	Claims	1-9, 33-35, 38-41	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-9, 33-35, 38-41	NO
Industrial applicability (IA)	Claims	1-9, 33-35, 38-41	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-2 lack an inventive step under PCT Article 33(3) as being obvious over US 2022/0204588 A1 to Acceleron Pharma Inc. (hereinafter "API'588"), in view of US 2007/0249022 A1 to Knopf et al. (hereinafter "Knopf").

Regarding claim 1, API'588 teaches a pharmaceutical formulation comprising a human ActRIIa fusion protein (para [0009]; para [0012] "An activin-binding ActRII polypeptide may be a fusion protein that has, as one domain, an ActRII polypeptide, (e.g., a ligand-binding portion of an ActRIIa or ActRIIb) and one or more additional domains that provide a desirable property, such as improved pharmacokinetics, easier purification, targeting to particular tissues, etc. For example, a domain of a fusion protein may enhance one or more of in vivo stability, in vivo half life, uptake/administration, tissue localization or distribution, formation of protein complexes, multimerization of the fusion protein, and/or purification. An activin-binding ActRII fusion protein may include an immunoglobulin Fc domain"), a buffer, a surfactant (para [0123] "Typically, activin-ActRII antagonists will be administered parenterally. Pharmaceutical compositions suitable for parenteral administration may comprise one or more ActRII polypeptides in combination with one or more pharmaceutically acceptable... buffers... Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants."; para [0127] "the pharmaceutical compositions may also comprise buffering agents") and a stabilizer (para [0126] "In certain embodiments, methods of the invention can be administered for orally, e.g., in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose"; instant application claim 35 identifies sucrose as a stabilizer), yet does not specifically teach the ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO: 32 or SEQ ID NO:41. Knopf teaches a sequence for ActRIIa comprising SEQ ID NO: 32 (para [0011] "An activin-binding ActRIIa polypeptide for use in such a preparation may be any of those disclosed herein, such as a polypeptide having an amino acid sequence selected from SEQ ID NOs: 2, 3, 7 or 12"; SEQ ID NO: 7 has 100% identity to SEQ ID NO: 32). It would have been obvious to an artisan of ordinary skill in the art to utilize a known ActRIIa sequence for the ActRIIa, such as the sequence taught by Knopf, in the creation of the ActRIIa fusion protein taught by API'588.

Regarding claim 2, the combination of API'588 and Knopf makes obvious the pharmaceutical formulation of claim 1, and API'588 further teaches wherein the buffer is selected from the group consisting of sodium citrate (para [0127] "In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), one or more therapeutic compounds of the present invention may be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate").

Claims 3-6 and 8-9 lack an inventive step under PCT Article 33(3) as being obvious over API'588, in view of Knopf, and US 2006/0093598 A1 to Chen et al. (hereinafter "Chen").

Regarding claim 3, the combination of API'588 and Knopf makes obvious the pharmaceutical formulation of claims 1 and 2, however fail to teach wherein the buffer is present in an amount of between 4 mM and 50 mM.

Chen teaches wherein it is a benefit to create liquid polypeptide containing pharmaceutical composition comprising a physiological stabilizing buffer, wherein the buffer is present in an amount of between 4 mM and 50 mM (para [0005] "there is a need for additional pharmaceutical compositions comprising physiologically compatible stabilizers that promote stability of polypeptide components, thereby maintaining their therapeutic effectiveness."; para [0106] "When the concentration of arginine is increased to 230 mM with addition of arginine HCl and pH is adjusted to 5.8 with 10 mM succinic acid and sodium succinate buffer, the half-life at 50° C"). Given that Chen teaches buffering the pharmaceutical composition to be at a physiological compatible pH, it would have been obvious to an artisan of ordinary skill in the art to consider the buffering solution taught by Chen, including 10 mM of succinic acid.

*****Continued in Supplemental Box*****

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Box No. VI **Certain documents cited**

1. Certain published documents (Rules 43bis.1 and 70.10)

Application No.
Patent No.

Publication date
(day/month/year)

Filing date
(day/month/year)

Priority date (valid claim)
(day/month/year)

2. Non-written disclosures (Rules 43bis.1 and 70.9)

Kind of non-written disclosure

Date of non-written disclosure
(day/month/year)

Date of written disclosure
referring to non-written disclosure
(day/month/year)

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Supplemental Box

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

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Box V(2) Citations and Explanations:

Regarding claim 4, the combination of API'588 and Knopf makes obvious the pharmaceutical formulation of claims 1-2, however fail to teach wherein the buffer is present in an amount of about 10 mM.
Chen teaches wherein it is a benefit to create pharmaceutical composition comprising a physiological stabilizing buffer, wherein the buffer is present in an amount of about 10 mM (para [0005]; para [0106]). Given that Chen teaches buffering the pharmaceutical composition to be at a physiological compatible pH, it would have been obvious to an artisan of ordinary skill in the art to consider the buffering solution taught by Chen, including 10 mM of succinic acid.

Regarding claim 5, the combination of API'588 and Knopf makes obvious the pharmaceutical formulation of claims 1 and 2, however fails to teach wherein the buffer is a citrate buffer at a pH from about 5.5 to about pH 6.5.
Chen teaches wherein it is a benefit to create pharmaceutical composition comprising a physiological stabilizing buffer that adjusts the pH to 5.8, wherein said buffering agent comprises sodium citrate (para [0005]; para [0106]; Claim 24 "The composition of claim 1, wherein said buffering agent comprises sodium citrate"). Given that Chen teaches buffering the pharmaceutical composition to be at a physiological compatible pH of 5.8, wherein the buffering agent may comprise citrate, it would have been obvious to an artisan of ordinary skill in the art to consider the buffering solution taught by Chen.

Regarding claim 6, the combination of API'588 and Knopf makes obvious the pharmaceutical formulation of claims 1 and 2, however fail to teach wherein the buffer is a succinate buffer at a pH from about 5.5 to about pH 6.5.
Chen teaches wherein it is a benefit to create pharmaceutical composition comprising a physiological stabilizing buffer that adjusts the pH to 5.8, wherein the buffer is a succinate buffer (para [0005]; para [0031] "when succinic acid is used to buffer arginine base added to a liquid formulation comprising the protein interleukin-2 (IL-2) and having a pH optimum for that protein (pH 5.8)"; para [0106]). Given that Chen teaches buffering the pharmaceutical composition to be at a physiological compatible pH of 5.8, it would have been obvious to an artisan of ordinary skill in the art to consider the buffering solution taught by Chen.

Regarding claim 8, the combination of API'588 and Knopf makes obvious the pharmaceutical formulation of claims 1 and 2, however fail to teach wherein the buffer is a citrate buffer at a pH 5.8.
Chen teaches wherein it is a benefit to create pharmaceutical composition comprising a physiological stabilizing buffer that adjusts the pH to 5.8, wherein said buffering agent comprises sodium citrate (para [0005]; para [0106]; Claim 24). Given that Chen teaches buffering the pharmaceutical composition to be at a physiological compatible pH of 5.8, wherein the buffering agent may comprise citrate, it would have been obvious to an artisan of ordinary skill in the art to consider the buffering solution taught by Chen.

Regarding claim 9, the combination of API'588 and Knopf makes obvious the pharmaceutical formulation of claims 1 and 2, however fail to teach wherein the buffer is a succinate buffer at a pH of 5.8.
Chen teaches wherein it is a benefit to create pharmaceutical composition comprising a physiological stabilizing buffer that adjusts the pH to 5.8, wherein the buffer is a succinate buffer (para [0005]; para [0106]). Given that Chen teaches buffering the pharmaceutical composition to be at a physiological compatible pH of 5.8, it would have been obvious to an artisan of ordinary skill in the art to consider the buffering solution taught by Chen.

Claim 7 lacks an inventive step under PCT Article 33(3) as being obvious over API'588, in view of Knopf, and US 2008/0095806 A1 to Bathurst et al. (hereinafter "Bathurst").

Regarding claim 7, the combination of API'588 and Knopf makes obvious the pharmaceutical formulation of claims 1 and 2, however fail to teach wherein the buffer is a histidine buffer at a pH from about 5.5 to about pH 6.0.
Bathurst teaches wherein it is a benefit to create a peptide containing pharmaceutical composition comprising a physiological stabilizing buffer that adjusts the pH to a compatible level, comprising a histidine buffer (para [0015] "A protease inhibitor composition and methods of making and using the composition are described herein. The composition is a pharmaceutical composition containing an effective amount of a protease inhibitor in a pharmaceutically acceptable carrier or diluent."; para [0018] "The physiological buffer in the pharmaceutical composition described herein includes buffers such as tris, histidine... The pH range of the physiological buffer used in the pharmaceutical composition is preferably from about pH 6 to about 9 "). Given that Bathurst teaches stabilizing the composition with a histidine buffer at pH around 6, it would have been obvious to an artisan of ordinary skill in the art to consider using a histidine buffer to create a physiologically stabilizing pharmaceutical composition.

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Claims 38 and 41 lack an inventive step under PCT Article 33(3) as being obvious over API'588, in view of US 2016/0152683 A1 to Amgen Inc. (hereinafter "Amgen"), and Knopf.

Regarding claim 38, API'588 teaches a pharmaceutical formulation comprising a human ActRIIa fusion protein (para [0012]), citrate (para [0127]) "one or more therapeutic compounds of the present invention may be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate", and sucrose (para [0126]). API'588 fails to teach the pharmaceutical formulation further lyophilized, comprising polysorbate 80, wherein the ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41. Amgen teaches lyophilizing and reconstituting a pharmaceutical composition comprising an ActRIIb protein, potentially with polysorbate 80 (para [0010]; para [0056]-[0057]) "the therapeutic composition may be formulated as a lyophilizate"; para [0063]-[0064] "lyophilization and reconstitution"; para [0054] "Pharmaceutical compositions containing the ActRIIb5 polypeptides and proteins of the present invention are also provided. Such compositions comprise a therapeutically or prophylactically effective amount of the polypeptide in admixture with pharmaceutically acceptable materials, and physiologically acceptable formulation materials... surfactants or wetting agents (such as... polysorbate 80)". Given that ActRIIb fusion proteins can be lyophilized for storage and then reconstituted, it would have been obvious to an artisan of ordinary skill in the art to considered lyophilizing and reconstituting the ActRIIa fusion proteins taught by API'588 in a similar manner, with polysorbate 80, to increase shelf life. Knopf teaches a sequence for ActRIIa comprising SEQ ID NO: 32 (para [0011]; SEQ ID NO: 7 is 100% homologous to SEQ ID NO: 32). Given that Knopf teaches a known sequence for ActRIIa, it would have been obvious to an artisan of ordinary skill in the art to utilize a known ActRIIa sequence for the ActRIIa, such as the sequence taught by Knopf, in the creation of the fusion protein taught by API'588.

Regarding claim 41, API'588 teaches a reconstituted pharmaceutical formulation comprising ActRIIa (para [0123]) "Typically, activin-ActRII antagonists will be administered parenterally. Pharmaceutical compositions suitable for parenteral administration may comprise one or more ActRII polypeptides in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions", citrate (para [0127]), and sucrose (para [0126]).

API'588 fails to teach wherein the formulation further comprises 50 mg/mL of a human ActRIIa fusion protein, 10 mM citrate, 0.2 mg/ml polysorbate 80, and 80 mg/ml sucrose at pH 5.8, wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41.

Amgen teaches an ActRIIb protein as part of a pharmaceutical composition, comprising polysorbate 80 (para [0054]) "Pharmaceutical compositions containing the ActRIIb5 polypeptides and proteins...in admixture with pharmaceutically acceptable materials, and physiologically acceptable formulation materials... surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80)". Given that ActRIIb proteins can be lyophilized for storage and then reconstituted, it would have been obvious to an artisan of ordinary skill in the art to have considered lyophilizing and reconstituting the ActRIIa fusion proteins taught by API'588 in a similar manner, including with polysorbate 80, to increase shelf life.

Knopf teaches a sequence for ActRIIa comprising SEQ ID NO: 32 (para [0011]; amino acids 1-344 of SEQ ID NO: 7 are 100% homologous to SEQ ID NO: 32). Given that Knopf teaches a known sequence for ActRIIa, it would have been obvious to an artisan of ordinary skill in the art to utilize a known ActRIIa sequence for the ActRIIa, such as the sequence taught by Knopf, in the creation of the fusion protein taught by API'588.

While the exact amounts of fusion protein, citrate, polysorbate 80, and sucrose is not taught by API'588 or Amgen, API'588 teaches use of a therapeutically effective amount of ActRIIa polypeptide (para [0016]), and it was well known in the art of medicine to determine through routine experimentation the optimal amount of each ingredient in a pharmaceutical composition needed to achieve the desired formulation properties. It would have been obvious to an artisan of ordinary skill in the art to determine through routine experimentation the optimal amount of each ingredient needed to achieve the desired formulation properties.

Claims 33-35 lack an inventive step under PCT Article 33(3) as being obvious over API'588, Amgen, Knopf, and Chen.

Regarding claim 33, API'588 teaches a pharmaceutical formulation comprising a human ActRIIa fusion protein (para [0012]), a buffer, a surfactant (para [0123]-[0127]) and a stabilizer (para [0126]; claim 35), however API'588 fails to teach wherein the pharmaceutical formulation is lyophilized and then reconstituted with Sterile Water for Injection. API'588 further fails to teach wherein the buffer is selected to be physiologically compatible and to maintain a pH of 5.8 and wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41.

Amgen teaches lyophilizing and reconstituting a pharmaceutical composition comprising an ActRIIb fusion protein that can be lyophilized and then reconstituted with Sterile Water for Injection (para [0010]) "a protein comprising human activin receptor IIB5 (designated ActRIIb5) polypeptides."; para [0057] "The formulations can be delivered...by injection...A particularly suitable vehicle for parenteral injection is sterile distilled water in which a polypeptide is formulated as a sterile, isotonic solution, properly preserved."; para [0064] "Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (e.g., lyophilized) requiring reconstitution prior to administration.". Given that ActRIIb fusion proteins can be lyophilized for storage and then reconstituted, it would have been obvious to an artisan of ordinary skill in the art to considered lyophilizing the ActRIIa fusion proteins taught by API'588 in a similar manner.

Knopf teaches a sequence for ActRIIa comprising SEQ ID NO: 32 (para [0011]; amino acids 1-344 of SEQ ID NO: 7 are 100% homologous to SEQ ID NO: 32). Given that Knopf teaches a known sequence for ActRIIa, it would have been obvious to an artisan of ordinary skill in the art to utilize a known ActRIIa sequence for the ActRIIa, such as the sequence taught by Knopf, in the creation of the fusion protein taught by API'588.

Chen teaches wherein it is a benefit to create pharmaceutical composition comprising a physiological stabilizing buffer to maintain a pH of 5.8 (para [0005]; para [0106]). Given that Chen teaches buffering the pharmaceutical composition to be at a physiological compatible pH, such as 5.8, it would have been obvious to an artisan of ordinary skill in the art to consider the buffering solution taught by Chen.

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Supplemental Box

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Regarding claim 34, the combination of API'588, Amgen, Knopf and Chen makes obvious the lyophilized pharmaceutical formulation of claim 33, and Chen further teaches wherein the buffer comprises citrate (para [0005]; para [0106]; Claim 24 "The composition of claim 1, wherein said buffering agent comprises sodium citrate").

Regarding claim 35, the combination of API'588, Amgen, Knopf and Chen makes obvious the lyophilized pharmaceutical formulation of claims 33 and 34, and API'588 further teaches wherein the stabilizer is sucrose (para [0126]-[0127]).

Claims 39-40 lack an inventive step under PCT Article 33(3) as being obvious over API'588, in view of Amgen, WO 2022/271571 A1 to Acceleron Pharma, Inc. (hereinafter "API'571"), and Knopf.

Regarding claim 39, API'588 teaches a pharmaceutical formulation comprising a human ActRIIa fusion protein (para [0012]), and sucrose (para [0126]).

API'588 fails to teach wherein the formulation is lyophilized and comprises: 55.0 mg of a human ActRIIa fusion protein, 0.48 mg of citric acid monohydrate, 2.56 mg tri-sodium citrate dihydrate, 0.22 mg polysorbate 80, 88.0 mg sucrose, and wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41.

Amgen teaches lyophilizing and reconstituting a ActRIIb fusion protein, potentially with polysorbate 80 (para [0010]; para [0057]; para [0064]; para [0054]) "Pharmaceutical compositions containing the ActRIIB5 polypeptides and proteins of the present invention are also provided. Such compositions comprise a therapeutically or prophylactically effective amount of the polypeptide in admixture with pharmaceutically acceptable materials, and physiologically acceptable formulation materials... surfactants or wetting agents (such as pluronics, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80"). Given that ActRIIb fusion proteins can be lyophilized for storage and then reconstituted, it would have been obvious to an artisan of ordinary skill in the art to considered lyophilizing the ActRIIa fusion proteins taught by API'588 in a similar manner.

API'571 teaches wherein a pharmaceutical comprising an ActRIIa variant polypeptide is lyophilized and wherein the composition comprises citric acid monohydrate and/or trisodium citrate dehydrate as buffering agents (Claim 83 "wherein the ActRIIA variant polypeptide is lyophilized prior to administration."; Pg 14, ln 27-29 "In some embodiments, the pharmaceutically acceptable excipient is selected from a buffering agent [e.g., citric acid (monohydrate) and/or trisodium citrate (dehydrate)]"). Given that API'571 suggests that citric acid monohydrate and tri-sodium citrate dihydrate can be used as buffers in a lyophilized ActRIIa polypeptide for pharmaceutical use, it would have been obvious to an artisan of ordinary skill in the art to consider these buffers in the pharmaceutical compositions taught by API'588.

Knopf teaches a sequence for ActRIIa comprising SEQ ID NO: 32 (para [0011]; amino acids 1-344 of SEQ ID NO: 7 are 100% homologous to SEQ ID NO: 32). Given that Knopf teaches a known sequence for ActRIIa, it would have been obvious to an artisan of ordinary skill in the art to utilize a known ActRIIa sequence for the ActRIIa, such as the sequence taught by Knopf, in the creation of the fusion protein taught by API.

While the exact amounts of fusion protein, citric buffer, polysorbate 80, and sucrose is not taught by API'588, Amgen or API'571, API'588 teaches use of a therapeutically effective amount of ActRIIa polypeptide (para [0016]), and it was well known in the art of medicine to determine through routine experimentation the optimal amount of each ingredient in a pharmaceutical composition needed to achieve the desired formulation properties. It would have been obvious to an artisan of ordinary skill in the art to determine through routine experimentation the optimal amount of each ingredient needed to achieve the desired formulation properties.

Regarding claim 40, API'588 teaches a pharmaceutical formulation comprising a human ActRIIa fusion protein (para [0012]), and sucrose (para [0126]).

API'588 fails to teach wherein the formulation is lyophilized and comprises: 72.5 mg of a human ActRIIa fusion protein, 0.64 mg of citric acid monohydrate, 3.37 mg tri-sodium citrate dihydrate, 0.29 mg polysorbate 80, and 116.0 mg sucrose, and wherein the human ActRIIa fusion protein comprises the amino acid sequence of SEQ ID NO:32 or SEQ ID NO:41.

Amgen teaches lyophilizing and reconstituting a ActRIIb fusion protein, potentially with polysorbate 80 (para [0010]; para [0057]; para [0064]; para [0054]). Given that ActRIIb fusion proteins can be lyophilized for storage and then reconstituted, it would have been obvious to an artisan of ordinary skill in the art to considered lyophilizing the ActRIIa fusion proteins taught by API'588 in a similar manner.

API'571 teaches wherein a pharmaceutical comprising an ActRIIa variant polypeptide is lyophilized and wherein the composition comprises citric acid monohydrate and/or trisodium citrate dehydrate as buffering agents (Claim 83 "wherein the ActRIIA variant polypeptide is lyophilized prior to administration."; Pg 14, ln 27-29 "In some embodiments, the pharmaceutically acceptable excipient is selected from a buffering agent [e.g., citric acid (monohydrate) and/or trisodium citrate (dehydrate)]"). Given that API'571 suggests that citric acid monohydrate and tri-sodium citrate dihydrate can be used as buffers in a lyophilized ActRIIa polypeptide for pharmaceutical use, it would have been obvious to an artisan of ordinary skill in the art to consider these buffers in the pharmaceutical taught by API'588.

Knopf teaches a sequence for ActRIIa comprising SEQ ID NO: 32 (para [0011]; amino acids 1-344 of SEQ ID NO: 7 are 100% homologous to SEQ ID NO: 32). Given that Knopf teaches a known sequence for ActRIIa, it would have been obvious to an artisan of ordinary skill in the art to utilize a known ActRIIa sequence for the ActRIIa, such as the sequence taught by Knopf, in the creation of the fusion protein taught by API.

While the exact amounts of fusion protein, citric buffer, polysorbate 80, and sucrose is not taught by API'588, Amgen or API'571, API'588 teaches use of a therapeutically effective amount of ActRIIa polypeptide (para [0016]), and it was well known in the art of medicine to determine through routine experimentation the optimal amount of each ingredient in a pharmaceutical composition needed to achieve the desired formulation properties. It would have been obvious to an artisan of ordinary skill in the art to determine through routine experimentation the optimal amount of each ingredient needed to achieve the desired formulation properties.

Claims 1-9, 33-35, and 38-41 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.