PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	FEB 26 2024

Applicant's or agent's file reference	FOR FURTHER ACTION
MET10638P00651PC	See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US23/30689	21 August 2023 (21.08.2023)	19 August 2022 (19.08.2022)

International Patent Classification (IPC) or both national classification and IPC
IPC - INV. A61K 31/33; A61K 9/20; A61K 45/06 (2023.01)
ADD. A61P 35/00 (2023.01)
CPC - INV. A61K 31/33; A61K 9/0053; A61K 9/20; A61K 45/06
ADD. A61P 35/00

Applicant MIRATI THERAPEUTICS, 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 43*bis*.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 66.1*bis*(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/	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	29 October 2023 (29.10.2023)	Shane Thomas PCT Help Desk 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 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.

   b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.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. 13-22, 24-36

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. 13-22, 24-36 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 13-22, 24-36 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. 13-22, 24-36

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

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

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

☐ See Supplemental Box for further details.

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

1. Statement

Novelty (N)	Claims	1-12, 23	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	1-12, 23	YES
	Claims	NONE	NO
Industrial applicability (IA)	Claims	1-12, 23	YES
	Claims	NONE	NO

2. Citations and explanations:
Claims 1-12 and 23 meet the criteria set out in PCT Article 33(2) (3).

Claim 1 meets the criteria set out in PCT Article 33(2) (3), because the prior art does not teach or fairly suggests a solid composition comprising adagrasib constituting about 30-67% percent of the composition.

US 2010/0310651 A1 to Mittal. B (hereinafter "MITTAL") discloses a solid pharmaceutical composition (a solid pharmaceutical composition; abstract), comprising: 1) an active ingredient constituting about 30-67% percent of the composition (an active ingredient comprising about 1 % w/w to about 60% w/w; paragraph [0097]); 2) microcrystalline cellulose constituting about 20-55% of the composition (comprising microcrystalline cellulose present in the amount from about 27% to about 53% w/w; paragraphs [0043], [0091]); 3) mannitol (mannitol; paragraphs [0043], [0101]); 4) crospovidone constituting about 2% to about 5% of the composition (a disintegrant comprising crospovidone; the disintegrant is present in an amount from about 0% w/w to about 20% w/w; paragraphs [0116], [0117]; [0119]); 5) colloidal silicon dioxide constituting up to about 0.5-2% of the composition (the glidant is colloidal silicon dioxide, and about 0% w/w to about 5% w/w of a glidant; paragraphs [0048], [0097]); and 6) magnesium stearate constituting about 1-3% of the composition (lubricants comprising magnesium stearate; and the lubricant is present in an amount from about 0% w/w to about 5% w/w; paragraphs [0122], [0123]); wherein all percentages are percentages by weight and wherein the total weight is 100% (wherein all percentages are percentages by weight and wherein the total weight is 100%; paragraph [0016]). However, MITTAL fails to disclose adagrasib constituting about 30-67% percent of the composition, mannitol constituting about 0-10% of the composition.

US 2019/0224175 A1 to Salix Pharmaceuticals, Ltd, (hereinafter "SALIX") discloses a solid pharmaceutical composition (a solid pharmaceutical composition; abstract; paragraph [0014]), comprising: 1) an active ingredient constituting about 30-67% percent of the composition (an active ingredient comprising 47 %w/w of the composition; table 2); 2) microcrystalline cellulose constituting about 20-55% of the composition (microcrystalline cellulose constituting about 1- wt % to 19 wt %; paragraph [0031]; claim 1); 5) colloidal silicon dioxide constituting up to about 0.5-2% of the composition (from about 0.15 wt% to about 0.25 wt% of colloidal silicon dioxide; paragraph [0043]); and 6) magnesium stearate constituting about 1-3% of the composition (from about 0.45 wt % to about 0.55 wt % of magnesium stearate; claim 1); wherein all percentages are percentages by weight and wherein the total weight is 100% (wherein all percentages are percentages by weight and wherein the total weight is 100%; claim 1). However, SALIX fails to disclose adagrasib constituting about 30-67% percent of the composition, 3) mannitol constituting about 0-10% of the composition; 4) crospovidone constituting about 2% to about 5% of the composition.

US 2015/0196493 A1 to McNeil-PPC, Inc., (hereinafter "MCNEIL") discloses a solid pharmaceutical composition (process for making a tablet (solid pharmaceutical composition); abstract), comprising: 1) an active agent constituting about 30-67% percent of the composition (an active agent comprising about 20% to about 70% of the composition; paragraph [0013]); 2) microcrystalline cellulose (microcrystalline cellulose; paragraph [0031]); 3) mannitol constituting about 0-10% of the composition (mannitol at a concentration of 0.6% w/w; paragraph [0106]); 5) colloidal silicon dioxide (colloidal silicon dioxide; paragraph [0018]); wherein all percentages are percentages by weight and wherein the total weight is 100% (wherein all percentages are percentages by weight and wherein the total weight is 100%; paragraph [0014]). However, MCNEIL fails to disclose adagrasib constituting about 30-67% percent of the composition, microcrystalline cellulose constituting about 20-55% of the composition; 4) crospovidone constituting about 2% to about 5% of the composition; colloidal silicon dioxide constituting up to about 0.5-2% of the composition; and 6) magnesium stearate constituting about 1-3% of the composition.

MITTAL, SALIX, MCNEIL, either alone or in combination fail to disclose a solid composition comprising adagrasib constituting about 30-67% percent of the composition. While, MITTAL, SALIX and MCNEIL discloses a process for making a solid composition; the composition comprising an active ingredient, a diluent, disintegrants, a glidant and a lubricant. However, It would not have been obvious to one of ordinary skill in the art before the relevant date to have modified the active ingredients disclosed by MITTAL, SALIX and MCNEIL to incorporate adagrasib, as there is no apparent motivation to combine them, and a person of ordinary skill in the art, at the time of invention, would not have had any reason to infer that such a combination would be plausible and beneficial without the benefit of impermissible hindsight.

Claims 2-6, 8-11, 12/1-6, 12/8-11 meet the criteria set out in PCT Article 33(2)-(3), because of their dependency on claim 1.

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

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

Claims 1and 4 are objected to under PCT Rule 66.2(a)(iii) as containing the following defect in the form or contents thereof: in claim 1 and 4, line 7, the phrase "% of the composition." is interpreted as being a typographical error, and for the purposes of this opinion, the period at the end of the sentence will be replaced by a semicolon, and will be interpreted as "% of the composition;".

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
-***-Continued From Box V. 2: Citations and Explanations-***-

Claim 7 meets the criteria set out in PCT Article 33(2) (3), because the prior art does not teach or fairly suggests an oral solid composition comprising adagrasib constituting about 33.3% percent of the composition, and mannitol constituting about 10.0% of the composition.

MITTAL discloses an oral solid pharmaceutical composition in the form of a tablet (oral solid pharmaceutical compositions in the form of a tablet; abstract; paragraph [0016]) comprising: 1) an active ingredient constituting about 33.3% percent of the composition (an active ingredient comprising about 1 % w/w to about 60% w/w; paragraph [0097]); 2) microcrystalline cellulose constituting about 51.2% of the composition (comprising microcrystalline cellulose present in the amount from about 27% to about 53% w/w; paragraphs [0043], [0091]); 3) mannitol (mannitol; paragraphs [0043], [0101]); 4) crospovidone constituting about 3.0% of the composition (a disintegrant comprising crospovidone; the disintegrant is present in an amount from about 0% w/w to about 20% w/w; paragraphs [0116], [0117]; [0119]); 5) colloidal silicon dioxide constituting about 1.0% of the composition (the glidant is colloidal silicon dioxide, and about 0% w/w to about 5% w/w of a glidant; paragraphs [0048], [0097]); and 6) magnesium stearate constituting about 1.5% of the composition (lubricants comprising magnesium stearate; and the lubricant is present in an amount from about 0% w/w to about 5% w/w; paragraphs [0122], [0123]), wherein all percentages are percentages by weight and wherein the total weight is 100.0% (wherein all percentages are percentages by weight and wherein the total weight is 100%; paragraph [0016]), and wherein the solid pharmaceutical composition further comprises a film coat (the solid pharmaceutical composition further comprises a film coat; paragraphs [0030], [0171]). But MITTAL fails to disclose adagrasib constituting about 33.3% percent of the composition; mannitol constituting about 10.0% of the composition.

SALIX discloses an oral solid pharmaceutical composition (a solid pharmaceutical composition; abstract; paragraph [0014]) in the form of a tablet (in the form of a tablet; paragraph [0058]) comprising: 1) an active ingredient constituting about 33.3% percent of the composition (an active ingredient comprising 47 %w/w of the composition; table 2); 2) microcrystalline cellulose (microcrystalline cellulose constituting about 1- wt % to 19 wt %; paragraph [0031]; claim 1); 5) colloidal silicon dioxide (of colloidal silicon dioxide; paragraph [0043]); and 6) magnesium stearate (magnesium stearate; claim 1), wherein all percentages are percentages by weight and wherein the total weight is 100.0% (wherein all percentages are percentages by weight and wherein the total weight is 100%; claim 1), and wherein the solid pharmaceutical composition further comprises a film coat (the pharmaceutical compositions described herein are film coated; paragraph [0060]). But SALIX fail to disclose adagrasib constituting about 33.3% percent of the composition, 2) microcrystalline cellulose constituting about 51.2% of the composition; 3) mannitol constituting about 10.0% of the composition; 4) crospovidone constituting about 3.0% of the composition; 5) colloidal silicon dioxide constituting about 1.0% of the composition; and 6) magnesium stearate constituting about 1.5% of the composition.

MCNEIL discloses an oral solid pharmaceutical composition in the form of a tablet (process for making a tablet (solid pharmaceutical composition); abstract) comprising: 1) an active agent constituting about 33.3% percent of the composition (an active agent comprising about 20% to about 70% of the composition; paragraph [0013]); 2) microcrystalline cellulose (microcrystalline cellulose; paragraph [0031]); 3) mannitol constituting about 10.0% of the composition (mannitol at a concentration of 0.6% w/w; paragraph [0106]); 5) colloidal silicon dioxide constituting about 1.0% of the composition (colloidal silicon dioxide; paragraph [0018]); wherein all percentages are percentages by weight and wherein the total weight is 100.0% (wherein all percentages are percentages by weight and wherein the total weight is 100%; paragraph [0014]), and wherein the solid pharmaceutical composition further comprises a film coat (wherein the solid pharmaceutical composition further comprises a film coat; paragraph [0068]). But MCNEIL fails to disclose adagrasib constituting about 33% percent of the composition, microcrystalline cellulose constituting about 51,2% of the composition; 4) crospovidone constituting about 3% of the composition; colloidal silicon dioxide constituting 1% of the composition; and 6) magnesium stearate constituting about 1,5 % of the composition.

MITTAL, SALIX, MCNEIL, either alone or in combination fail to disclose a solid composition comprising adagrasib constituting about 33,3 % percent of the composition, and mannitol constituting about 10.0 % of the composition. While, MITTAL, SALIX and MCNEIL disclose a process for making a solid composition in the form of a tablet; said composition comprising an active ingredient, a diluent, disintegrants, a glidant and a lubricant. However, It would not have been obvious to one of ordinary skill in the art before the relevant date to have modified the active ingredients disclosed by MITTAL, SALIX and MCNEIL to incorporate adagrasib, as there is no apparent motivation to combine them, and a person of ordinary skill in the art, at the time of invention, would not have had any reason to infer that such a combination would be plausible and beneficial without the benefit of impermissible hindsight.

Claim 12/7 meets the criteria set out in PCT Article 33(2)-(3), because of their dependency on claim 7.

Claim 23 meets the criteria set out in PCT Article 33(2) (3), because the prior art does not teach or fairly suggests a solid pharmaceutical composition comprising adagrasib prepared by a process which comprises the steps of a) pre-blending, wherein a diluent, a glidant, and adagrasib are blended together; c) blending the components of step "b" with a disintegrant, and a glidant e) performing a dry granulation of the components of step "d" using a roller compactor.

MITTAL discloses a solid pharmaceutical composition (a solid pharmaceutical composition; abstract) comprising an active ingredient prepared by a process which comprises the steps of: a) pre-blending, a diluent and an active ingredient are blended together (mixing one active ingredient, a suitable solvent and an excipient, paragraph [0024], claim 1); b) de-lumping the components of step "a" using a screening mill (milling the granules of step "a" using a screening mill (de-lumping); paragraphs [0026], [0037]); d) lubricating by adding a lubricant to the components of step "c" (blending the granules of step "b" with a disintegrant, a glidant and a lubricant; paragraph [0027]; claim 1); producing a granulated blend (producing a granulated blend; paragraphs [0024]-[0027]); f) blending a diluent, a disintegrant and a glidant with the granulated blend of step "e"(blending the granules with a buffer, a disintegrant and a glidant can be performed as consecutive blending steps; paragraphs [0027], [0032]); g) lubricating by adding a lubricant to the components of step "f" to produce a lubricated blend (one or more lubricants may be added after all the other pharmaceutically acceptable excipients have been added thereby producing a lubricated blend; paragraph [0032]; h) performing compression by charging the lubricated blend of step "g" to a rotary tablet press and compressing the lubricated blend into tablet cores (loading the blended granules (lubricated blend) into a piccolo 10 station tablet

-***-Continued Within the Next Supplemental Box-***-

Supplemental Box

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-***-Continued from previous Supplemental Box-***-

press (rotary tablet press) and compressing the granules to manufacture tablet cores; paragraphs [0025], [0032], [0041], [0171]; claim 3); and i) performing film coating by charging the core tablets of step "h" into a pan coater and adding a film coating agent (and film coating the resulting tablets using a pan coater; and adding a film coating agent; paragraphs [0030], [0171]). But MITTAL fails to disclose a solid pharmaceutical composition comprising adagrasib prepared by a process which comprises the steps of a) pre-blending, wherein a diluent, a glidant, and adagrasib are blended together; c) blending the components of step "b" with a disintegrant, and a glidant e) performing a dry granulation of the components of step "d" using a roller compactor.

US 2005/0051922 A1 to Nangia, A et al., (hereinafter "NANGIA") discloses a solid pharmaceutical composition prepared by a process (process for preparing a tablet; abstract; paragraphs [0017]-[0024]) which comprises the steps of: a) pre-blending, wherein a diluent and an active ingredient are blended together (mixing the drug, a diluent; paragraph [0035]); lubricating by adding a lubricant (blending a drug with a lubricant; paragraph [0044]); e) performing a dry granulation of the components of step "d", producing a granulated blend (the core may also be formed by dry granulating a drug and a binder followed by blending the granules with an absorption/ compression enhancer and a lubricant; paragraph [0044]); g) lubricating by adding a lubricant to the components of step (f) to produce a lubricated blend (producing a lubricated blend by adding a lubricant to the blend; paragraph [0044]); h) performing compression by charging the lubricated blend of step "g" to a rotary tablet press and compressing the lubricated blend into tablet cores (charging the lubricated blend to a 32-station tablet press and compressing the blend into tablet cores; paragraphs [0044], [0058], [0079]); and i) performing film coating by charging the core tablets of step (h) into a pan coater and adding a film coating agent (the tablets are film coated in a 36" coating pan with an OPADRY® White suspension; paragraphs [0060], [0077]). But NANGIA fails to disclose a composition comprising adagrasib, and the steps of: a) pre-blending, wherein a diluent, a glidant, and adagrasib are blended together; b) de-lumping the components of step "a" using a screening mill; c) blending the components of step "b" with a disintegrant, and a glidant; performing a dry granulation using a roller compactor; f) blending a diluent, a disintegrant and a glidant with the granulated blend of step "e".

SALIX discloses a solid pharmaceutical composition prepared by a process (process for making a tablet comprising at least one pharmaceutically active agent; abstract) which comprises the steps of: c) blending the components of step "b" with a disintegrant, and a glidant (mixing the active ingredient with silica (glidant) and polyvinylpyrrolidone; paragraphs [0017], [0063]); h) performing compression by charging the blend of step "g" to a rotary tablet press and compressing the blend into tablet cores (the tablet shape may be made using a rotary compression module including a fill zone, insertion zone, compression zone, ejection zone, and purge zone in a single apparatus; paragraph [0078]); and i) performing film coating (adding a film coating; paragraph [0068]). But SALIX fails to disclose a composition comprising adagrasib which comprises the steps of: a) pre-blending, wherein a diluent, a glidant, and adagrasib are blended together; b) de-lumping the components of step "a" using a screening mill by charging the core tablets of step "h" into a pan coater and adding a film coating agent; lubricating by adding a lubricant to the components of step "c"; e) performing a dry granulation of the components of step (d) using a roller compactor, producing a granulated blend; f) blending a diluent, a disintegrant and a glidant with the granulated blend of step "e"; g) lubricating by adding a lubricant to the components of step (f) to produce a lubricated blend.

MITTAL, NANGIA and SALIX, either alone or in combination fail to disclose a solid pharmaceutical composition comprising adagrasib prepared by a process which comprises the steps of a) pre-blending, wherein a diluent, a glidant, and adagrasib are blended together; c) blending the components of step "b" with a disintegrant, and a glidant e) performing a dry granulation of the components of step "d" using a roller compactor. While MITTAL, NANGIA and SALIX disclose a process for making a solid composition in the form of a tablet that is coated with a film coat; said composition comprises an active ingredient, a diluent, disintegrants, a glidant and a lubricant. However, It would not have been obvious to one of ordinary skill in the art before the relevant date to have modified the active ingredients disclosed by MITTAL, NANGIA and SALIX to incorporate adagrasib, as there is no apparent motivation to combine them, and a person of ordinary skill in the art, at the time of invention, would not have had any reason to infer that such a combination would be plausible and beneficial without the benefit of impermissible hindsight.

Claims 1-12 and 23 have industrial applicability under PCT Article 33(4) because they can be made or used in industry.