

## 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)

16 DEC 2016

Applicant's or agent's file reference  
025.0012-WO00

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 16/52492

International filing date (day/month/year)

19 September 2016 (19.09.2016)

Priority date (day/month/year)

18 September 2015 (18.09.2015)

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

IPC(8) - A61K 31/675, A61K 31/197 (2016.01)

CPC - A61K 2300/00, A61K 31/198

Applicant THAR PHARMACEUTICALS, 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 or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

## 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/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

11 November 2016

Authorized officer:

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

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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. 14-369 and 399-400

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. 14-369 and 399-400 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. 14-369 and 399-400

☐ 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 13<sup>ter</sup>.1(a) or (b).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

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| Box No. V                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |                                                          |     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|-----|
| <b>1. Statement</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                      |                                                          |     |
| Novelty (N)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Claims                                                                                                                                                               | <u>379-381, 385, 387, and 391-393</u>                    | YES |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Claims                                                                                                                                                               | <u>1-13, 370-378, 382-384, 386, 388-390, and 394-398</u> | NO  |
| Inventive step (IS)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Claims                                                                                                                                                               | <u>None</u>                                              | YES |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Claims                                                                                                                                                               | <u>1-13 and 370-398</u>                                  | NO  |
| Industrial applicability (IA)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Claims                                                                                                                                                               | <u>1-13 and 370-398</u>                                  | YES |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Claims                                                                                                                                                               | <u>None</u>                                              | NO  |
| <p><b>2. Citations and explanations:</b></p> <p>Claims 1-13, 370-378, 382-384, 386, 388-390, and 394-398 lack novelty under PCT Article 33(2) as being anticipated by WO 2011/097269 A9 to Thar Pharmaceuticals, Inc. (hereinafter 'Thar Pharmaceuticals')</p> <p>Regarding claim 1, Thar Pharmaceuticals teaches a composition comprising (pg 5 para 5, composition) comprising at least one API and at least one coformer (pg 5 para 5, an API and at least one coformer).</p> <p>Regarding claim 2, Thar Pharmaceuticals teaches the composition of claim 1, wherein at least one of said at least one coformer is a molecular complex coformer and, wherein the API and the molecular complex coformer form a molecular complex (pg 6 para 3, in one embodiment the additional coformer and the coformer that forms a molecular complex with the API (i.e., the 'molecular complex coformer' are the same).</p> <p>Regarding claim 3, Thar Pharmaceuticals teaches the composition of claim 2, wherein the molecular complex is a salt (pg 5 para 5, molecular complex is a salt).</p> <p>Regarding claim 4, Thar Pharmaceuticals teaches the composition of claim 3, wherein the salt is crystalline (pg 5 para 5, salt is a crystal).</p> <p>Regarding claim 5, Thar Pharmaceuticals teaches the composition of claim 3, wherein the salt is amorphous (pg 6 para 3, coformer is amorphous).</p> <p>Regarding claim 6, Thar Pharmaceuticals teaches the composition of claim 2, wherein the molecular complex is a cocrystal (pg 5 para 5, molecular complex is a cocrystal).</p> <p>Regarding claim 7, Thar Pharmaceuticals teaches the composition of any one of claims 2-4 and 6, wherein the molecular complex is a crystalline two-component molecular complex between the API and a single molecular complex coformer (pg 5 para 5, molecular complex is a crystalline two-component molecular complex between the API and a single coformer).</p> <p>Regarding claim 8, Thar Pharmaceuticals teaches the composition of any one of claims 2-4 and 6, wherein the molecular complex is a crystalline three-component molecular complex comprising the API and at least one molecular complex coformer (pg 5 para 5, molecular complex is a crystalline three-component molecular complex comprising the API and the at least one coformer).</p> <p>Regarding claim 9, Thar Pharmaceuticals teaches the composition of claim 8, wherein the crystalline three-component molecular complex consists of the API, a first molecular complex coformer and a second molecular complex coformer, wherein said first and said molecular complex coformer second molecular complex coformer are not the same (pg 5 para 5, crystalline three-component molecular complex consists of the API, a first coformer and a second (different) coformer).</p> <p>Regarding claim 10, Thar Pharmaceuticals teaches the composition of claim 8, wherein the crystalline three-component molecular complex consists of said API, a molecular complex coformer and a solvent (pg 5 para 5, crystalline three-component molecular complex consists of the API, a coformer and a solvent).</p> <p>Regarding claim 11, Thar Pharmaceuticals teaches the composition of claim 10, wherein said solvent is water or an alcohol (pg 5 para 5, solvent is water).</p> <p>Regarding claim 12, Thar Pharmaceuticals teaches the composition of claim 11, wherein said solvent is water (pg 5 para 5, solvent is water).</p> <p>Regarding claim 13, Thar Pharmaceuticals teaches the composition of claim 11, wherein said solvent is ethanol (pg 39 para 3, molecular complex is a crystalline zoledronic acid, DL-lysine, ethanol, and water complex).</p> <p>-----Continued in Supplemental Box-----</p> |                                                                                                                                                                      |                                                          |     |

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 16/52492

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

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**Box No. VIII Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 393 contains an error in the preamble. The claim currently reads, "The process of claim 375...". Claim 375 is an independent claim describing an 'enteric coated oral dosage.' However, independent claim 392 describes a 'process for producing an enteric coated tablet.' For the purposes of this evaluation, Claim 393 is interpreted as "The process of claim 392..."

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**Supplemental Box**

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

Continuation of:

Box V.2 - Citations and Explanations:

Regarding claim 370, Thar Pharmaceuticals teaches a pharmaceutical composition or unit dose thereof, comprising any one composition of Table 11 (pg 160 Table 11, unit dose pharmaceutical composition; ibandronic acid, glycine, > 2g).

Regarding claim 371, Thar Pharmaceuticals teaches a pharmaceutical composition or unit dose thereof, comprising any one composition of Table 12 (pg 164 Table 12, compositions of the present invention; tiludronic acid, free acid, glycine).

Regarding claim 372, Thar Pharmaceuticals teaches a pharmaceutical composition or unit dose thereof, comprising any one composition of Table 13 (pg 168 Table 13, compositions of the present invention; zoledronic acid, free acid, glycine, >5000:1).

Regarding claim 373, Thar Pharmaceuticals teaches a pharmaceutical composition or unit dose thereof, comprising any one composition of Table 14 (pg 184 Table 14, compositions of the present invention; zoledronic acid and glycine complex characterized by an X-ray powder diffraction pattern comprising peaks at about 10.2, 17.8, 19.9, 22.9, and 28.1 +0.2 degrees two-theta, glycine, >5000:1).

Regarding claim 374, Thar Pharmaceuticals teaches a pharmaceutical composition or unit dose thereof, comprising any one composition of Table 15 (pg 188 Table 15, unit doses of a pharmaceutical composition; zoledronic acid, glycine, >10g).

Regarding claim 375, Thar Pharmaceuticals teaches a pharmaceutical enteric coated oral dosage form comprising (pg 20 para 3, compositions of the present invention are particularly advantageous for oral dosage forms; pg 59 para 2, the pharmaceutical composition is an enterically coated dosage form):

a. a zoledronic acid molecular complex (pg 5 para 3, molecular complexes of APIs (e.g., zoledronic acid)), and  
b. a pharmaceutical acceptable excipient (pg 11 para 4, at least one pharmaceutically acceptable excipient), where in, said composition is suitable for oral administration and has an improved safety profile over the corresponding oral dosage form without an enteric coating (pg 28 para 2, present invention includes new forms and formulations of bisphosphonic acids including zoledronic acid, with improved physicochemical properties, such as improved, safety).

Regarding claim 376, Thar Pharmaceuticals teaches the enteric coated oral dosage form of claim 375, wherein said enteric coated oral dosage form comprises an amino acid selected from glycine or lysine (pg 26 para 3, comprising zoledronic acid and an amino acid; the amino acid is lysine or glycine).

Regarding claim 377, Thar Pharmaceuticals teaches the enteric coated oral dosage form of claim 375, wherein said enteric coated oral dosage form comprises at least 10 mg of said zoledronic acid molecular complex (pg 56 para 1, unit dose is between about 10 mg to about 50 mg).

Regarding claim 378, Thar Pharmaceuticals teaches the enteric coated oral dosage form of claim 376, wherein said zoledronic acid molecular complex is a crystalline zoledronic acid molecular complex (pg 184 Table 14, crystalline molecular complex (left column)) selected from the group consisting of:

- a. a crystalline zoledronic acid, sodium zoledronate and water molecular complex characterized by an X-ray powder diffraction pattern having peaks at about 8.1, 13.3, 21.5, 24.6, and 25.6 +/- 0.2 degrees two-theta (Table 14, pg 169);
- b. a crystalline ammonium zoledronic acid salt and water molecular complex characterized by an X-ray powder diffraction pattern having strong peaks at about 11.0, 14.6, 15.4, 19.9, and 29.4 +/- 0.2 degrees two-theta (Table 14, pg 169);
- c. a crystalline zoledronic diammonia water molecular complex characterized by an X-ray powder diffraction pattern having strong peaks at about 12.2, 13.0, 14.1, 17.1, and 19.3 +/- 0.2 degrees two-theta (Table 14, pg 169);
- d. a crystalline zoledronic acid, L-lysine, and water molecular complex characterized by an X-ray powder diffraction pattern comprising peaks at about 9.0, 14.4, 18.1, 26.0, and 29.6 +/- 0.2 degrees two-theta (Table 14, pg 169);
- e. a crystalline zoledronic acid, L-lysine, and water molecular complex characterized by an X-ray powder diffraction pattern comprising peaks at about 9.6, 10.7, 14.3, 21.4, 23.5 +/- 0.2 degrees two-theta (Table 14, pg 169);
- f. a crystalline zoledronic acid DL-lysine and water molecular complex characterized by an X-ray powder diffraction pattern comprising peaks at about 8.3, 11.8, 12.3, 15.8, and 20.8 +/- 0.2 degrees two-theta (Table 14, pg 169);
- g. a crystalline zoledronic acid, DL-lysine, and water molecular complex characterized by an X-ray powder diffraction pattern comprising peaks at about 9.1, 14.7, 18.0, 21.2, and 26.0 +/- 0.2 degrees two-theta (Table 14, pg 169);
- h. a crystalline zoledronic acid, DL-lysine, and water molecular complex characterized by an X-ray powder diffraction pattern comprising peaks at about 9.7, 10.8, 14.4, 18.9, 21.4 +/- 0.2 degrees two-theta (Table 14, pg 169);
- i. a crystalline zoledronic acid, zoledronic, DL-lysine, ethanol, and water complex characterized by an X-ray powder diffraction pattern comprising peaks at about 8.8, 9.7, 17.6, 23.1, and 26.5 +/- 0.2 degrees two-theta (Table 14, pg 169);
- j. a crystalline zoledronic acid, adenine, and water molecular complex characterized by an X-ray powder diffraction pattern comprising peaks at about 13.6, 15.9, 19.7, 27.9, and 29.5 +/- 0.2 degrees two-theta (Table 14, pg 169);
- k. a crystalline zoledronic acid, nicotinamide, and water molecular complex characterized by an X-ray powder diffraction pattern comprising peaks at about 13.1, 15.2, 21.0, 23.9, and 26.5 +/- 0.2 degrees two-theta (Table 14, pg 169); and
- l. a crystalline zoledronic acid and glycine molecular complex characterized by an X-ray powder diffraction pattern comprising peaks at about 10.2, 17.8, 19.9, 22.9, and 28.1 +/- 0.2 degrees two-theta (Table 14, pg 169-170).

Regarding claim 382, Thar Pharmaceuticals teaches the enteric coated oral dosage form of claim 376, comprising between about 10 mg to about 150 mg of said zoledronic acid molecular complex (pg 56 para 1, unit dose is between about 10 mg to about 400 mg) and about 400 mg to about 1400 mg of said amino acid (pg 42 para 1, unit dose comprises between about 50 to about 5000mg of amino acid).

-----Continued in next Supplemental Box-----

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**Supplemental Box**

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

Continuation of:  
Supplemental Box - Box V.2 - Citations and Explanations:

Regarding claim 383, Thar Pharmaceuticals teaches the enteric coated oral dosage form of claim 375, wherein said oral dosage form is a tablet (pg 55 para 3, pharmaceutical composition of the invention may be in any pharmaceutical form, for example, a tablet).

Regarding claim 384, Thar Pharmaceuticals teaches the enteric coated oral dosage form of claim 375, wherein said oral dosage form is a capsule (pg 55 para 3, pharmaceutical composition of the invention may be in any pharmaceutical form, for example... capsule).

Regarding claim 386, Thar Pharmaceuticals teaches the enteric coated solid oral dosage form of claim 375, wherein said significantly improved safety profile comprises a significant reduction in an adverse event selected from the group consisting of: abdominal pain (pg 26 para 1, lower dose of bisphosphonic acid should result in reduced esophageal and GI irritation or ulceration and thus, increased safety to the patient; pg 28 para 2, bisphosphonic acids including zoledronic acid), nausea, diarrhea, and loose stool.

Regarding claim 388, Thar Pharmaceuticals teaches a method of treating or preventing a disease for which zoledronic acid is indicated, said method comprising the step of administering to a patient in need thereof, said enteric coated solid oral dosage form of claim 375 (pg 53 para 2-pg 54 para 1, a method of treating or preventing a disease for which a bisphosphonic acid is indicated, the method comprising the step of administering to a patient in need of the bisphosphonic acid a therapeutically effective amount of a pharmaceutical composition of the present invention; pg 28 para 2, bisphosphonic acids including zoledronic acid).

Regarding claim 389, Thar Pharmaceuticals teaches the method of claim 388, wherein said enteric coated solid oral dosage form has a significant reduction in an adverse event, as compared to an equivalent form without an enteric coating, wherein said adverse event is selected from the group consisting of: abdominal pain (pg 26 para 1, lower dose of bisphosphonic acid should result in reduced esophageal and GI irritation or ulceration and thus, increased safety to the patient; pg 28 para 2, bisphosphonic acids including zoledronic acid), nausea, diarrhea, and loose stool.

Regarding claim 390, Thar Pharmaceuticals teaches the method of claim 389, wherein said disease is selected from the group consisting of: osteoporosis (pg 54 para 1), hypercalcemia (pg 54 para 1), cancer induced bone metastasis (pg 54 para 1), tumor induced hypercalcemia (TIH), Paget's disease (pg 54 para 1), adjuvant cancer therapy (pg 54 para 1), neoadjuvant cancer therapy (pg 54 para 1) and an amplified musculoskeletal pain syndrome (AMPS).

Regarding claim 394, Thar Pharmaceuticals teaches an oral dosage form (pg 20 para 3, compositions of the present invention are particularly advantageous for oral dosage forms) comprising a form of a bisphosphonic acid (pg 24 para 3, new crystalline forms and compositions of bisphosphonic acids) and a pharmaceutically acceptable excipient (pg 11 para 4, at least one pharmaceutically acceptable excipient) and an enteric coating (pg 59 para 2, the pharmaceutical composition is an enterically coated dosage form).

Regarding claim 395, Thar Pharmaceuticals teaches an oral dosage form according to claim 394 wherein the form of the bisphosphonic acid is selected from the group consisting of a bisphosphonic acid, a salt of a bisphosphonic acid, or a molecular complex of a bisphosphonic acid and a coformer (pg 28 para 4, molecular complex comprises a bisphosphonic acid or salt thereof and at least one coformer).

Regarding claim 396, Thar Pharmaceuticals teaches an oral dosage form according to claim 395 further comprising a coformer (pg 28 para 4 at least one coformer).

Regarding claim 397, Thar Pharmaceuticals teaches an oral dosage form according to claim 396 having excess coformer present (pg 29 para 1, coformer is in molar excess).

Regarding claim 398, Thar Pharmaceuticals teaches an oral dosage form according to one of claims 394-397, wherein the oral dosage form is an enterically coated tablet (pg 59 para 2, the enterically coated dosage form is an enterically coated tablet).

Claims 385, 387, and 392-393 lack an inventive step under PCT Article 33(3) as being obvious over Thar Pharmaceuticals.

Regarding claim 385, Thar Pharmaceuticals teaches the enteric coated oral dosage form of claim 376, wherein said oral dosage form is a tablet (pg 58 para 1, tablets of the present invention may be uncoated or coated by known techniques) comprising:

a. a core comprising said zoledronic acid molecular complex and said amino acid (pg 63 para 4, the API and matrix-forming material are combined and compressed to form a sustained release core, and the excess coformer is blended with one or more coating agents and coated); Thar Pharmaceuticals does not explicitly teach:

b. a first coating comprising a pharmaceutically acceptable polymer; and

c. a second coating, wherein said second coating is an enteric coating.

However, Thar Pharmaceuticals teaches the coating of multiparticulates or hydrophilic matrix tablets with pH-dependent coating polymers, or coating with combinations of pH dependent coating polymers and extended release barrier membrane systems (pg 58 para 5-pg 59 para 1). It would have been obvious to a person of ordinary skill in the art to formulate, through routine experimentation, a tablet with an API core and coatings of acceptable polymer and enteric compounds such that a preferable release profile can be achieved.

Regarding claim 387, Thar Pharmaceuticals teaches the enteric coated solid oral dosage form of claim 375, but does not explicitly teach said significantly improved safety profile is an improved dose safety margin selected from the group consisting of: at least 4 fold, at least 6 fold, and at least 8 fold. However, Thar Pharmaceuticals teaches that the ability to achieve such high levels of oral bioavailability has the distinct advantage of being able to lower the dose of the drug, thereby increasing safety to the patient (pg 25 para 4). It would have been obvious to a person of ordinary skill in the art to formulate the dosage as necessary through coatings or excipients to improve the dose safety margin as necessary.

-----Continued in next Supplemental Box-----

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**Supplemental Box**

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

Continuation of:  
Supplemental Box - Box V.2 - Citations and Explanations"

Regarding claim 392, Thar Pharmaceuticals teaches a process for producing (pg 5 para 3, disclosure further includes processes of making) an enteric coated tablet (pg 59 para 2, the enterically coated dosage form is an enterically coated tablet) comprising a zoledronic acid molecular complex (pg 5 para 3, molecular complexes of APIs (e.g., zoledronic acid)), said process comprising the steps of:

a. compressing a composition comprising a zoledronic acid molecular complex and a pharmaceutical excipient to form a core tablet (pg 63 para 4, the API and matrix-forming material are combined and compressed to form a sustained release core, and the excess coformer is blended with one or more coating agents and coated); Thar Pharmaceuticals does not explicitly teach:

b. coating said core tablet with a first coating comprising a pharmaceutically acceptable polymer;

c. over coating said first coating with a second coating, wherein said second coating is an enteric coating.

However, Thar Pharmaceuticals teaches the coating of multiparticulates or hydrophilic matrix tablets with pH-dependent coating polymers, or coating with combinations of pH dependent coating polymers and extended release barrier membrane systems (pg 58 para 5-pg 59 para 1). It would have been obvious to a person of ordinary skill in the art to formulate, through routine experimentation, a tablet with an API core and coatings of acceptable polymer and enteric compounds such that a preferable release profile can be achieved.

Regarding claim 393, Thar Pharmaceuticals teaches the process of claim 392, but does not explicitly teach said step a) comprises compressing a composition comprising a zoledronic acid molecular complex, an amino acid selected from lysine and glycine, and a pharmaceutical excipient to form a core tablet. However, Thar Pharmaceuticals teaches the API and matrix-forming material are combined and compressed to form a sustained release core (pg 63 para 4). Further Thar Pharmaceuticals teaches molecular complexes of APIs include zoledronic acid (pg 5 para 3) and the pharmaceutical composition comprises zoledronic acid and an amino acid (pg 26 para 3) where the amino acid is lysine or glycine (pg 26 para 3). It would have been obvious to a person of ordinary skill in the art, based on the teachings of Thar Pharmaceuticals, to formulate a tablet core, through routine experimentation, comprising a zoledronic acid molecular complex, an amino acid selected from lysine and glycine, and a pharmaceutical excipient with enhanced delivery properties.

Claims 379-381 and 391 lack an inventive step under PCT Article 33(3) as being obvious over Thar Pharmaceuticals in view of US 2013/0303488 A1 (Tabuteau).

Regarding claim 379, Thar Pharmaceuticals teaches the enteric coated oral dosage form of claim 375, but does not explicitly teach said zoledronic acid molecular complex is a sodium salt of zoledronic acid. However, Tabuteau teaches the application of oral dosage forms of bisphosphonate compounds, such as Zoledronic acid (abstract), such that the zoledronic acid is administered in a sodium salt form, such as a monosodium salt (para [0041]). It would have been obvious to a person of ordinary skill in the art to combine the salt forms of zoledronic acid taught by Tabuteau with the formulation disclosed by Thar Pharmaceuticals to formulate an enteric coated oral dosage form with improved performance.

Regarding claim 380, Tabuteau teaches the enteric coated oral dosage form of claim 379, wherein said sodium salt of zoledronic acid is disodium zoledronate (para [0041], dosage form comprising a disodium salt form of zoledronic acid).

Regarding claim 381, Tabuteau teaches the enteric coated oral dosage form of claim 379, wherein said sodium salt of zoledronic acid is disodium zoledronate tetrahydrate (para [0084], zoledronic acid was administered in the disodium salt form as disodium zoledronate tetrahydrate).

Regarding claim 391, Thar Pharmaceuticals teaches the method of claim 390, but does not explicitly teach said AMPS is Complex Regional Pain Syndrome (CRPS). However, Tabuteau teaches method of treating complex regional pain syndrome comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof (para [0006]). It would have been obvious to a person of ordinary skill in the art to combine the applications of zoledronic acid disclosed by Tabuteau with the zoledronic acid formulations taught by Thar Pharmaceuticals to administer an enteric coated oral dosage form to a patient with Complex Regional Pain Syndrome.

Claims 1-13 and 370-398 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.