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) 28 DEC 2015

Applicant's or agent's file reference
01235-36031.PCT

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US 15/47556

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Priority date (day/month/year) 28 August 2014 (28.08.2014)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/568; A61K 9/48 (2015.01)
CPC - A61K 31/56; A61K 31/568; A61K 9/4858

Applicant LIPOCINE 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
24 November 2015 (24.11.2015)

Authorized officer:
Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (January 2015)
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:
<table>
<thead>
<tr>
<th>Box No. V</th>
<th>Reasoned statement under Rule 43(b)(1)(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Statement</td>
<td></td>
</tr>
<tr>
<td><strong>Novelty (N)</strong></td>
<td>Claims 1-35: YES Claims none: NO</td>
</tr>
<tr>
<td><strong>Inventive step (IS)</strong></td>
<td>Claims none: YES Claims 1-35: NO</td>
</tr>
<tr>
<td><strong>Industrial applicability (IA)</strong></td>
<td>Claims 1-35: YES Claims none: NO</td>
</tr>
</tbody>
</table>

2. Citations and explanations:

Claims 1-21, 24-26, 28-35 lack an inventive step under PCT article 33(3) as being obvious over US 2013/0225544 A1 to Nachaegari et al. (hereinafter 'Nachaegari').

Regarding claim 1, Nachaegari teaches an oral pharmaceutical composition (para [0090]), oral pharmaceutical compositions or the dosage forms...includes a T13 or T14 testosterone ester and a pharmaceutically acceptable carrier...comprising: (a) a (BR,RS,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl testosterone tridecanoate or (BR,SS,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl (testosterone) tetradecanoate active pharmaceutical ingredient (API) (para [0090]), oral pharmaceutical compositions or the dosage forms...includes a T13 or T14 testosterone ester...para [0144], testosterone ester-containing compositions were prepared including the testosterone ester having the structure...R is at least one selected from the groups - C13H25O (Testosterone tridecanoate (triacyclic), T13 testosterone ester) and - C14H27O (Testosterone tetradecanoate (tetradecanoate), T14 testosterone ester))

in an amount ranging from 10-50% w/w in a liquid pharmaceutical carrier (para [0090]), oral pharmaceutical compositions or the dosage forms...includes a T13 or T14 testosterone ester and a pharmaceutically acceptable carrier...wherein the T13 or T14 testosterone ester comprises about 0.5 wt percent to about 50 wt percent of the composition or dosage form; para [0099],...T13 or T14 testosterone...the ester is present in the liquid carrier...the solubility of the API is greater than 5 mg/ml (para [0100]),...pharmaceutically acceptable carrier (e.g. lipophilic additive...). Fig 1; para [0185], solubility of testosterone esters (tridecanoate and tetradecanoate (tetradecanoate) is determined in various lipophilic additives such as...long chain fatty acid (e.g. oleic acid)...solubility in oleic acid is...presented in Fig 3, 1...the Fig 1, shown solubility of API in oleic acid is greater than 5 mg/ml) and (b) one or more additives that allow for loading of API at levels greater than the solubility of the API in the pharmaceutical carrier (para [0107]),...oral pharmaceutical compositions and/or capsule dosage forms...include...pharmaceutically acceptable additive...polyethylene glycols...para [0103], oral pharmaceutical compositions and capsule dosage forms...include at least 10 wt percent of an alcohol...alcohols that can be used as solubilizers include...polyethylene glycol).

Nachaegari does not expressly teach producing a composition without substantially compromising bioavailability, release profile or release profile stability. To a person of ordinary skill in the art it would have been obvious through routine experimentation to include (b) one or more additives or stabilizing agents that allow for loading of API at levels greater than the solubility of the API in the pharmaceutical carrier without substantially compromising bioavailability, release profile or release profile stability in the teaching of Nachaegari, because Nachaegari teaches (b) one or more additives that allow for loading of API at levels greater than the solubility of the API in the pharmaceutical carrier (para [0107]), in order to produce an improved oral pharmaceutical composition comprising testosterone tridecanoate or testosterone tetradecanoate.

Regarding claim 2, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.

Nachaegari further teaches the API is present in an amount ranging from 23-32% w/w (para [0090]),...oral pharmaceutical compositions or the dosage forms...includes a T13 or T14 testosterone ester...the T13 or T14 testosterone ester comprises about 0.5 wt percent to about 50 wt percent of the composition or dosage form...).

Regarding claim 3, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.

Nachaegari further teaches API is (BR,RS,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-1,2,6,7,8,9,11,12,14,15,16,17-dodecahydrocyclopenta[a]phenanthren-17-yl testosterone tridecanoate (para [0144]), testosterone ester-containing compositions were prepared including the testosterone ester having the structure, wherein R is at least one selected from the groups - C13H25O (testosterone tridecanoate (triacyclic), T13 testosterone ester).

Regarding claim 4, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.

Nachaegari further teaches liquid pharmaceutically acceptable carrier is present in an amount ranging from 30% to 70% w/w (Table 1; para [0145], Tables 1...show the typical components and their relative proportions that can be utilized in the compositions...)

Table 1

<table>
<thead>
<tr>
<th>Component</th>
<th>Composition (weight percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone tridecanoate, (T13)</td>
<td>10–30</td>
</tr>
<tr>
<td>Testosterone tetradecanoate, (T14)</td>
<td>0–30</td>
</tr>
<tr>
<td>Carrier</td>
<td>50–90, 50–90</td>
</tr>
</tbody>
</table>

- Please see Supplemental Box -

Form PCT/ISA/237 (Box No. V) (January 2015)
Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V. No 2: Citations and Explanations:

Regarding claim 5, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further teaches additive is present in an amount ranging from 1-30% w/w (para [0094]); T3 or T4 testosterone ester comprises about 5 to 50 wt % of the composition or the dosage form, and...includes...0 wt % to about 50 wt % of hydrophilic additive...hydrophilic additive can be hydrophilic surfactant... (para [0995]); hydrophilic surfactant can comprise at least about 20 wt % of the composition).

Regarding claim 6, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further teaches composition comprising (BZ)-octade-9-enolic acid (oleic acid) (para [0094]); dosage forms...includes...T3 or T4 testosterone ester...includes...lipophilic additive...; para [0168], such lipophilic additives can includes...fatty acids (fatty acids of CS-C22, like oleic acid,...)).

Regarding claim 7, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further teaches composition comprising (BZ)-octade-9-enolic acid (oleic acid) present in an amount ranging from about 30% to about 75% (para [0094]); dosage forms...includes...T3 or T4 testosterone ester comprises about 5 to 50 wt % of the composition or the dosage form...includes about 50 to 100 wt % of lipophilic additive...; para [0168], such lipophilic additives can include...fatty acids (fatty acids of CS-C22, like oleic acid,...)).

Regarding claim 8, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further teaches the oral pharmaceutical composition is a non-liquid at room temperature (para para [0107],...oral pharmaceutical compositions and/or capsule dosage forms...pharmaceutical composition can be a solid at about 20 degrees centigrade...).

Regarding claim 9, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further teaches the oral pharmaceutical composition is a semi-solid at room temperature (para [0107],...oral pharmaceutical compositions and/or capsule dosage forms, namely the capsule fill...pharmaceutical compositions...at temperatures around room temperature...composition and capsule fill can be semi-solid at standard temperature and pressure...).

Nacheagari does not teach the oral pharmaceutical composition is a non-solid at room temperature.
To a person of ordinary skill in the art it would have been obvious through routine experimentation to include the oral pharmaceutical composition is a non-solid at room temperature in the teaching of Nacheagari, because Nacheagari teaches the oral pharmaceutical composition is a semi-solid at room temperature (para [0107]), and because this may lead to a superior oral pharmaceutical composition comprising testosterone tridecanoate OR testosterone tetradecanoate or a liquid pharmaceutical carrier.

Regarding claim 10, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further teaches composition comprises 5 to 2000 mg (para [0107],...oral pharmaceutical compositions...can be formulated as a hard gel capsule or a soft gel capsule...; para [0109],...oral dosage form can be a capsule having a pharmaceutical composition...both soft and hard gelatin and non-gelatin capsules can be used...).

Regarding claim 11, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further teaches composition comprises the formula: H-(O-(CH2CH2)n)-OH where n is an integer from 5 to 2000 mg (para [0107],...oral pharmaceutical compositions...can be formulated as a hard gel capsule...). (para [0112],...oral pharmaceutical composition can be formulated as dosage (e.g. capsule or tablet) form to be administered to provide a daily T3 or T4 testosterone ester dose of about 420 mg to about 1250 mg based on single unit or multiple unit dosing...the subject has to consume two, three, four or more unit dosages per administration) to a hypogonadal male provides Cavg serum testosterone levels of greater than 300 ng/dL (para [0015],...T3 and T4 testosterone esters each have a unique daily dose range for which, upon daily administration to each subject in a group...). (para [0112],...provides a serum testosterone Cavg of 300 ng/dL to 1100 ng/dL in at least 75 percent of the hypogonadal males in the group).

Regarding claim 12, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further comprising a compound of formula: H-(O-(CH2CH2)n)OH where n is an integer from 9 to 500 mg (para [0107],...oral pharmaceutical compositions...can include a solidifying agent...examples of solidifying agents can be used include polyethylene glycols (H-(O-(CH2CH2)n)-OH)...polyethylene glycol (PEG) having molecular weight from about 1000 (n = 23) to about 20,000 (n = 454),...

Regarding claim 13, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further comprising 0.1% to 20% of a compound of formula: H-(O-(CH2CH2)n)-OH where n is an integer from 9 to 500 mg (para [0107],...oral pharmaceutical compositions...can include a solidifying agent...examples of solidifying agents that can be used include polyethylene glycols (H-(O-(CH2CH2)n)-OH)...polyethylene glycol (PEG) having molecular weight from about 1000 (n = 23) to about 20,000 (n = 454),...).

Regarding claim 14, Nacheagari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nacheagari further comprising 1% to 10% of a compound of formula: H-(O-(CH2CH2)n)-OH where n is an integer from 10 to 300 mg (para [0107],...oral pharmaceutical compositions...can include a solidifying agent...solidifying agent can comprise from 0.1 wt % to 25 wt % of the pharmaceutical composition...examples of solidifying agents that can be used include polyethylene glycols (H-(O-(CH2CH2)n)-OH)...polyethylene glycol (PEG) having molecular weight from about 1000 (n = 23) to about 20,000 (n = 454),...).

Please see next Supplemental Box --
In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Prior Supplemental Box:

Regarding claim 15, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nachaegari teaches further comprising (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol (para [0085],...lipophilic additive can include a lipophilic surfactant...various lipophilic surfactants can be used including...menthol ((1R,2S,5R)-2-isopropyl-5-methylcyclohexanol)...).

Regarding claim 16, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nachaegari teaches further comprising (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol which is present in an amount ranging from 50% to about 100% (w/w) (para [0093],...lipophilic additive can include a lipophilic surfactant...various lipophilic surfactants can be used including...menthol ((1R,2S,5R)-2-isopropyl-5-methylcyclohexanol)...: para [0094],...dosage forms...T13 or T14 testosterone ester...composition includes about 50 wt percent to about 100 wt percent of lipophilic additive...).
Nachaegari does not teach (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol is present in an amount ranging from 5% to about 40% (w/w).
To a person of ordinary skill in the art it would have been obvious through routine experimentation to include (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol in an amount ranging from 5% to about 40% (w/w) in the teaching of Nachaegari, because Nachaegari teaches (1R,2S,5R)-2-isopropyl-5-methylcyclohexanol which is present in an amount ranging from 50% to about 100% (w/w) (para [0085], [0094]), in order to improve the bioabsorption of a testosterone tridecanoate OR testosterone tetradecanoate.

Regarding claim 17, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nachaegari teaches further comprising a polyoxyethylated hydrogenated castor oil (para [0094],...dosage forms...includes...T13 or T14 testosterone ester...includes about 50 to 100 wt percent of lipophilic additive...: para [0085],...lipophilic additive can include...hydrogenated oils such as PEG-6 hydrogenated castor oil, PEG-7 hydrogenated castor oil, PEG-9 hydrogenated castor oil...).

Regarding claim 18, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nachaegari teaches further comprising a polyoxyethylated hydrogenated castor oil in an amount ranging from 50% to about 100% w/w (para [0094],...dosage forms...includes...T13 or T14 testosterone ester...includes about 50 to 100 wt percent of lipophilic additive...: para [0085],...lipophilic additive can include...hydrogenated oils such as PEG-5 hydrogenated castor oil...).
Nachaegari does not teach in an amount ranging from 0% to about 25% w/w.
To a person of ordinary skill in the art it would have been obvious through routine experimentation to include a polyoxyethylated hydrogenated castor oil in an amount ranging from 0% to about 25% w/w in the teaching of Nachaegari, because Nachaegari teaches a polyoxyethylated hydrogenated castor oil in an amount ranging from 50% to about 100% w/w (para [0094], [0085]), in order to improve the bioabsorption of a testosterone tridecanoate OR testosterone tetradecanoate.

Regarding claim 19, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.
In regard to Nachaegari teaches API is present in an amount ranging from 150 mg to about 400 mg per unit dosage form (para [0007],...a capsule dosage form for oral administration of a testosterone ester is provided. The capsule dosage form can include about 100 mg to about 400 mg of at least one testosterone ester and a lipophilic additive. The testosterone ester can have the structure: wherein R is -C13H25SO or -C14H27O and one or both esters can be present in the dosage form).

Regarding claim 20, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nachaegari further teaches a unit dosage form that when tested with a USP type 2 paddle apparatus having 1000 mL of 8% octoxynol-9 (Triton-100) in water at 37 C (~0.5) (para [0114],...dosage forms...T13 testosterone ester...dissolution testing using USP type 2 apparatus in about 1000 mL aqueous medium...: para [0117],...aqueous medium...release testing medium...including about 4 percent to 8 percent (w/v), of Triton X100 (octoxynol-9) solution in water...: para [0036],...amount of the T13 or T14 testosterone ester dissolved...at about 37 C (a) releases 80% or more of the active pharmaceutical ingredient at 4, 3, 2 hours (para [0114],...dosage forms...T13 testosterone ester...dissolution testing using USP type 2 apparatus in about 1000 mL aqueous medium...substantially all (~90 percent) of the T13 testosterone ester amount present in the composition is released in about 2 to about 4 hours (b) releases less than 100% at 4, 3, 2 hours (para [0114]).

Regarding claim 21, Nachaegari teaches an oral pharmaceutical composition of claim 1 as discussed above.
Nachaegari further teaches a unit dosage form that when tested with a USP type 2 paddle apparatus having 1000 mL of 8% octoxynol-9 (Triton-100) in water at 37 C (~0.5) (para [0114],...dosage forms...T13 testosterone ester...dissolution testing using USP type 2 apparatus in about 1000 mL aqueous medium...: para [0117],...aqueous medium...release testing medium...including about 8 percent (w/v), of Triton X100 (octoxynol-9) solution in water...: para [0036],...amount of the T13 or T14 testosterone ester dissolved...at about 37 deg C), releases 80% or more of the active pharmaceutical ingredient at 4 hours (para [0114],...T13 testosterone ester releases substantially all (~90 percent) of the T13 testosterone ester amount comprised therein, in about 4 hours).

Regarding claim 24, Nachaegari teaches a pharmaceutical composition of claim 22 as discussed above.
Nachaegari further teaches carrier is liquid solvent at 25 C and the API has a solubility of greater than 20 mg/g and less than 300 mg/g (para [0100],...physically acceptable carrier (e.g. lipophilic additive...:...Fig 1; para [0185], solubility of testosterone esters...tridecanoate (tridecanoate)...was determined in various lipophilic additives such as oleic acid (melting point: 13-14 deg C, liquid at 25 deg C)...solubility in oleic acid...is presented in FIGS. 1...In FIG 1, shown solubility of testosterone tridecanoate in oleic acid is greater than 100 mg/g and less than 150 mg/g).

Regarding claim 25, Nachaegari teaches a pharmaceutical composition of claim 22 as discussed above.
Nachaegari further teaches additive is at room temperature (para [0107],...oral pharmaceutical compositions...include a solidifying agent. A solidifying agent is a pharmaceutically acceptable additive that is in a solid physical state at 20 deg C...).
In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Prior Supplemental Box:

Regarding claim 26, Nakaegari teaches a pharmaceutical composition of claim 22 as discussed above.

Nakaegari further teaches additive is polyethylene glycol, stearic acid, glycerol palmitostearate (para [0107]), oral pharmaceutical compositions...include a solidifying agent. A solidifying agent is a pharmaceutically acceptable additive...polyethylene glycol...stearic acid...glycerol palmitostearate...).

Regarding claim 28, Nakaegari teaches a pharmaceutical composition of claim 22 as discussed above.

Nakaegari further teaches disposed of in a hard gel capsule (para [0109]), oral dosage form can be a capsule having a pharmaceutical composition...both soft and hard gelatin...can be used...)

Regarding claim 29, Nakaegari teaches a pharmaceutical composition of claim 22 as discussed above.

Nakaegari further teaches disposed of in a soft gel capsule (para [0109]), oral dosage form can be a capsule having a pharmaceutical composition...both soft and hard gelatin...can be used...)

Regarding claim 30, Nakaegari teaches a pharmaceutical composition of claim 22 as discussed above.

Nakaegari further teaches comprising (92)-octadec-9-enoic acid (oleic acid) (para [0094]), dosage forms...includes...T13 or T14 testosterone ester...includes...lipophilic additive...para [0166], such lipophilic additives can include...fatty acids (fatty acids of C5-C22, like oleic acid...)).

Nakaegari does not teach (92)-octadec-9-enoic acid is about 63%-100% (92)-octadec-9-enoic acid, less than 7% tetradecanoic acid, less than 18% hexadecanoic acid, less than 19% (92)-hexadec-9-enoic acid, less than 8% octadecanoic acid, less than 20% (92, 122)-9,12-octadecadienoic acid, less than 6% linoleic acid and less than 5% fatty acid with chain length greater than 16 carbons.

To a person of ordinary skill in the art it would have been obvious through routine experimentation to include wherein (92)-octadec-9-enoic acid is about 63%-100% (92)-octadec-9-enoic acid, less than 7% tetradecanoic acid, less than 18% hexadecanoic acid, less than 10% (92)-hexadec-9-enoic acid, less than 8% octadecanoic acid, less than 20% (92, 122)-9,12-octadecadienoic acid, less than 6% linoleic acid and less than 5% fatty acid with chain length greater than 16 carbons in the teaching of Nakaegari, in order to improve the bioabsorption of a testosterone tridecanoate OR testosterone tetradecanoate.

Regarding claim 31, Nakaegari teaches a pharmaceutical composition of claim 22 as discussed above.

Nakaegari further teaches comprising (92)-octadec-9-enoic acid (oleic acid) (para [0094]), dosage forms...includes...T13 or T14 testosterone ester...includes...lipophilic additive...para [0166], such lipophilic additives can include...fatty acids (fatty acids of C5-C22, like oleic acid...)).

Nakaegari does not teach (92)-octadec-9-enoic acid is about 75%-95% (92)-octadec-9-enoic acid, less than 4% tetradecanoic acid, less than 14% hexadecanoic acid, less than 6% (92) hexadec-9-enoic acid, less than 4% octadecanoic acid, less than 16% (92, 122)-9,12-octadecadienoic acid, less than 4% linoleic acid and less than 3% fatty acid with chain length greater than 16 carbons.

To a person of ordinary skill in the art it would have been obvious through routine experimentation to include wherein (92)-octadec-9-enoic acid is about 75%-95% (92)-octadec-9-enoic acid, less than 4% tetradecanoic acid, less than 14% hexadecanoic acid, less than 6% (92) hexadec-9-enoic acid, less than 4% octadecanoic acid, less than 16% (92, 122)-9,12-octadecadienoic acid, less than 4% linoleic acid and less than 3% fatty acid with chain length greater than 16 carbons in the teaching of Nakaegari, because this may lead to improved bioabsorption of testosterone tridecanoate OR testosterone tetradecanoate.

Regarding claim 32, Nakaegari teaches a pharmaceutical composition of claim 22 as discussed above.

Nakaegari further teaches comprising (82)-octadec-9-enoic acid (oleic acid) (para [0094]), dosage forms...includes...T13 or T14 testosterone ester...includes...lipophilic additive...para [0166], such lipophilic additives can include...fatty acids (fatty acids of C5-C22, like oleic acid...)).

Nakaegari does not teach (92)-octadec-9-enoic acid is greater than 80% or 85% (92)-octadec-9-enoic acid has one or more of: 0.1%-5% tetradecanoic acid, 0.1-10% hexadecanoic acid, 0.1-8% (92)-hexadec-9-enoic acid, 0.1-6% octadecanoic acid, 0.1-18% (92, 122)-9,12-octadecadienoic acid, 0.1-4% linoleic acid and 0.1-4% fatty acid with chain length greater than 16 carbons.

To a person of ordinary skill in the art it would have been obvious through routine experimentation to include wherein (92)-octadec-9-enoic acid is greater than 80% or 85% (92)-octadec-9-enoic acid has one or more of: 0.1%-5% tetradecanoic acid, 0.1-10% hexadecanoic acid, 0.1-8% (92)-hexadec-9-enoic acid, 0.1-6% octadecanoic acid, 0.1-18% (92, 122)-9,12-octadecadienoic acid, 0.1-4% linoleic acid and 0.1-4% fatty acid with chain length greater than 16 carbons, in the teaching of Nakaegari, because this may lead to improved bioabsorption of testosterone tridecanoate OR testosterone tetradecanoate.

Regarding claim 33, Nakaegari teaches a pharmaceutical composition of claim 1 as discussed above.

Nakaegari further teaches a method of treating a hypogonadal male (para [0015]) said method comprising administering a pharmaceutical composition as recited in claim 1 to said hypogonadal male as 1, 2, 3, 4, 5, or 6 unit dosage forms (para [0015]), T13 and T14 testosterone esters each have a unique daily dose range for which, upon daily administration to each subject in a group (....12 hypogonadal males),...oral pharmaceutical composition can be formulated as dosage (e.g. capsule or tablet) form to be administered to provide a daily T13 or T14 testosterone ester dose of about 420 mg to about 1250 mg based on single unit or multiple unit dosing.....the subject has to consume two, three, four or more unit doses, per administration)

said method providing Cavg serum testosterone levels of greater than 300 ng/dL (para [0015]).... T13 and T14 testosterone esters each have a unique daily dose range for which, upon daily administration to each subject in a group (....12 hypogonadal males).....provides a serum testosterone Cavg of 300 ng/dL to 1100 ng/dL in...the hypogonadal males in the group).

- Please see next Supplemental Box -
In case the space in any of the preceding boxes is not sufficient.

Regarding claim 34, Nachaegari teaches a method of claim 33 as discussed above.
Nachaegari further teaches method is once-a-day administration (para [0113]), oral dosage forms, including...can be formulated for once-a-day administration...).

Regarding claim 35, Nachaegari teaches a method of claim 33 as discussed above.
Nachaegari further teaches method approximates normal gonadal male circadian rhythms for serum testosterone (para [0015]), T13 and T14 testosterone esters each have a unique daily dose range for which, upon daily administration to each subject in a group...12 hypogonadal males)...provides a serum testosterone Cavg of 300 ng/dL to 1100 ng/dL in...hypogonadal males in the group (for normal gonadal male: total testosterone levels range from 300-1000 ng/dL)).

Claims 22-23, 27 lack an inventive step under PCT article 33(3) as being obvious over Nachaegari, in view of US 2012/0244215 A1 to Gililary et al. (hereinafter 'Gililary').

Regarding claim 22, Nachaegari teaches a pharmaceutical composition for oral administration (para [0072]) said composition: (a) comprising at least 23 % w/w (R,95,10R,13S,14S,17S)-10,13-dimethyl-3-oxo 1, 26,7,8,9,11,12,14,15,16,17-dodecachydroxydipenta[α]phenanthren-17-yl (testosterone) tridecanoate (para [0072]),...oral pharmaceutical composition for administration to subjects in need of testosterone is provided. The composition comprises a testosterone ester...testosterone ester can have the structure:
R is -C13H25O...para [0144],...testosterone ester having the structure, wherein R is...-C13H25O (testosterone tridecanoate (tridecanoate), T13 testosterone ester)...para [0090],...T13 testosterone ester comprises about 0.5 wt percent to about 50 wt percent of the composition or dosage form) and a liquid carrier (para [0072],...oral pharmaceutical composition...comprises a testosterone ester and a pharmaceutically acceptable carrier...para [0099]),...T13 or T14 testosterone ester...is present in the liquid carrier...an additive (para [0077],...capsule dosage form can include...testosterone ester and a lipophilic additive...).
(b) releasing 85% or more of the (R,95,10R,13S,14S,17S)-10,13-dimethyl-3-oxo-1,26,7,8,9,11,12,14,15,16,17-dodecachydroxydipenta[α]phenanthren-17-yl (testosterone) tridecanoate in four hours (para [0114],...dosage forms...T13 testosterone ester (testosterone tridecanoate) release testing...substantially all (>90 percent) of the T13 testosterone ester amount present in the composition is released in about 2 to about 4 hours; para [0144],...testosterone ester having the structure, wherein R is...-C13H25O (Testosterone tridecanoate (tridecanoate), T13 testosterone ester)),
when tested with a USP Type II apparatus in 1000 mL water having 8% Triton X100 at 37 deg C (para [0114],...dosage forms...T13 testosterone ester...release testing using USP type II apparatus in about 1000 mL aqueous medium...; para [0117],...aqueous medium...release testing method...including about 4 percent to 8 percent (w/w) of Triton X100 solution in water...; para [0036],...amount of the T13 or T14 testosterone ester dissolved...at about 37 deg C).

Nachaegari does not teach release profile stable when stored for at least a month at 25 deg C and 60% relative humidity.
Gililary teaches an oral pharmaceutical composition comprising a testosterone ester (para [0006],...pharmaceutical compositions and oral dosage capsules containing testosterone undecanoate...).

Gililary further teaches release profile stable when stored for at least a month at 25 deg C and 60% relative humidity (Table XII; para [0127], testosterone undecanoate (TU) formulations of Examples 12 through 19 were prepared...formulations were filled into hard gelatin capsules and the testosterone undecanoate release from capsules is measured using a USP Type-II apparatus in about 100 rpm in about 1000 mL of 8% w/w solution of Triton X100 in water...at 37 deg C. The results of the release testing are also shown in Table XII; para [0133],...stability evaluation...was carried out with the compositions of Example 17...filled in hard gelatin capsules...capsules were packed...for stability studies...at 25 deg C /60 % RH...HPLC analysis method after about three months storage and the results shown in Table XVII: TU (testosterone undecanoate) composition Degradant Example 17 0.15%.

To a person of ordinary skill in the art it would have been obvious to include release profile stable when stored for at least a month at 25 deg C and 60% relative humidity as taught by Gililary in the teaching of Nachaegari, because both Nachaegari and Gililary are directed towards an oral pharmaceutical composition comprising a testosterone ester, and because this may lead to a superior oral pharmaceutical composition comprising testosteroder tridecanoate OR testosterone tetradecanoate.

Regarding claim 23, Nachaegari in view of Gililary teach a pharmaceutical composition of claim 22 as discussed above.
Gililary further teach release profile stable when stored for at least a month at 25 deg C and 60% relative humidity (para [0133],...stability evaluation...was carried out with the compositions of Example 17...for stability studies...at 25 deg C /80 % RH...HPLC analysis method after about three months storage and the results shown in Table XVII: TU (testosterone undecanoate) composition Degradant Example 17 0.15%.

Gililary does not teach release profile stable when stored for at least a month at 40 deg C and 75% relative humidity.
To a person of ordinary skill in the art it would have been obvious through routine experimentation to include release profile stable when stored for at least a month at 40 deg C and 75% relative humidity in the teaching of Nachaegari in view of Gililary, because Gililary teaches release profile stable when stored for at least a month at 25 deg C and 60% relative humidity (para [0133]), and because this may lead to a superior oral pharmaceutical composition comprising testosterone tridecanoate OR testosterone tetradecanoate and a liquid pharmaceutical carrier.

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Supplemental Box

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

Continuation of:

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Regarding claim 27, Nachaegari in view of Giliyar teach a pharmaceutical composition of claim 22 as discussed above. Giliyar further teach a pharmaceutical composition is a clear liquid at 50 deg C (para [0134]), testosterone undecanoate-containing compositions (capule fill material) were prepared by weighing all of the components...mixed together at about 50 deg C to about 70 deg C, using a stirrer. The testosterone undecanoate (TU) is added and stirred into the mixture of other components until the testosterone undecanoate dissolves (clear liquid)... Giliyar does not teach a pharmaceutical composition is flowable at 36 deg C. To a person of ordinary skill in the art it would have been obvious through routine experimentation to include a pharmaceutical composition is a clear liquid at 50 deg C and flowable at 36 C in the teaching of Nachaegari in view of Giliyar, because Giliyar teaches a pharmaceutical composition is a clear liquid at 50 deg C (para [0134]), and because this may lead to a superior oral pharmaceutical composition comprising testosterone undecanoate OR testosterone tetradecanoate and a liquid pharmaceutical carrier.

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