METHODS OF TREATING TRANSTHYRETIN (TTR) MEDIATED AMYLOIDOSIS

Disclosed herein are methods for reducing or arresting an increase in a Neuropathy Impairment Score (NIS) or a modified NIS (mNIS+7) in a human subject by administering an effective amount of a transthyretin (TTR)-inhibiting composition.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61P 25/02, 25/28; C12N 15/00 (2016.01)
CPC - C12N 15/1137, 15/1138

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): A61P 25/02, 25/28, 1/12, 13/12, 25/28, 9/04; C12N 15/00 (2016.01)
CPC: C12N 15/1137, 15/1138; A61K 31/7088, 31/71 15, 31/713

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data); Google Scholar; Pubmed; EBSCO; "neuropathy impairment score;" "NIS;" "mNIS+7;" "TTR;" transthyretin decrease, reduce, levels; dos;" adjust;" 'sirNA; ' antisense, patisran, revusiran, determin', , measur, amyloid"

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
</tr>
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</table>

Further documents are listed in the continuation of Box C.

Date of the actual completion of the international search

15 January 2016 (15.01.2016)

Date of mailing of the international search report

09 FEB 2016

Name and mailing address of the ISA/

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## INTERNATIONAL SEARCH REPORT

### Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.:
   - because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos.:
   - because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos. 4-15
   - because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

> "Please see Supplemental Page.".

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

   Group 1 Claims 1-3

**Remark on Protest**

- □ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
- □ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- □ No protest accompanied the payment of additional search fees.
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-3 are directed toward a method for reducing a Neuropathy Impairment Score (NIS) or a modified NIS (mNIS+7) or arresting an increase in a NIS or a mNIS+7 in a human subject having a TTR related disorder, and adjusting dosage of a TTR-inhibiting composition for reducing or arresting an increase NIS or mNIS+7 in a human subject having a TTR related disorder.

Group II: Claims 16, 17 and 19-38 are directed toward a method for reducing a Neuropathy Impairment Score (NIS) or a modified NIS (mNIS+7) in a human subject having a TTR related disorder comprising administering to the human subject 0.3 mg/kg of patisiran as described in Table 1; compositions comprising patisiran for said method; and a kit comprising said compositions.

Group III: Claim 18 is directed toward a method for reducing or arresting an increase in a Neuropathy Impairment Score (NIS) or a modified NIS (mNIS+7) in a human subject having a TTR related disorder, wherein the effective amount results in a mean serum TTR AUC of 9000 to 18000 after 6 months of treatment.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the special technical features of Group I include adjusting a dosage, which is not present in either of Groups II or III, the special technical features of Group II including patisiran, as described in Table 1, which is not present in either of Groups I or III, the special technical features of Group III include a mean serum TTR AUC of 9000 to 18000 after 6 months of treatment, which not present in either of Groups I or II.

Groups I-II share the technical features including: a method for reducing or arresting an increase in a Neuropathy Impairment Score (NIS) or a modified NIS (mNIS+7) in a human subject having a TTR related disorder, comprising administering to the human subject an effective amount of a transthyretin (TTR)-inhibiting composition. Groups I and II share the technical features including: wherein the effective amount reduces a concentration of serum TTR protein to below 50 microg/ml or by at least 80%.

However, these shared technical features are previously disclosed by the publication entitled 'Recent Progress in The Understanding And Treatment Of Transthyretin Amyloidosis' by Sekijima (hereinafter 'Sekijima').

Sekijima discloses a method for arresting an increase in a Neuropathy Impairment Score (NIS) (a method of producing a treatment response of a less than 2 point increase (arresting and increase) in a Neuropathy Impairment Score; page 229, column 1, paragraph 2) in a human subject having a TTR related disorder (in a multicenter phase III/III clinical trial of FAP stage I patients (in a human subject having a TTR-related disorder); page 229, column 1, paragraph 2); a method comprising administering to the human subject an effective amount of a transthyretin (TTR)-inhibiting composition (comprising administering to a human subject a TTR-inhibiting siRNA (a method comprising administering to the human subject an effective amount of a transthyretin (TTR)-inhibiting composition); page 229, column 2, paragraph 3; page 229, column 2, paragraph 6 to page 230, column 1, paragraph 1); and wherein the effective amount reduces a concentration of serum TTR protein by at least 80% (page 229, column 2, paragraph 6 to page 230, column 1, paragraph 1).

Since none of the special technical features of the Groups I-III inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Sekijima reference, utility of invuullll is lacking.