METHODS FOR TREATING CONDITIONS ASSOCIATED WITH MASP-2 DEPENDENT COMPLEMENT ACTIVATION

Abstract: In one aspect, the invention provides methods of inhibiting the effects of MASP-2-dependent complement activation in a living subject. The methods comprise the step of administering, to a subject in need thereof, an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation. In some embodiments, the MASP-2 inhibitory agent inhibits cellular injury associated with MASP-2-mediated alternative complement pathway activation, while leaving the classical (Clq-dependent) pathway component of the immune system intact. In another aspect, the invention provides compositions for inhibiting the effects of lectin-dependent complement activation, comprising a therapeutically effective amount of a MASP-2 inhibitory agent and a pharmaceutically acceptable carrier.

Survival of STX/LPS induced HUS

Fig.45.
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
— with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:

29 November 2012
A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 39/395; C12N 15/11 (201.201)
USPC - 424/130.1; 424/146.1; 514/44A

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 424/130.1; 146.1; 514/44A

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/7.1; 436/86; 530/387.9; 388.26 (text search, see terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubMed(PGPI,USPT,EPA,PAB); Google Scholar (text search, see terms below)
Search Terms: MBL-associated serine protease 2, MBL-associated protease 2, MASp-2, uremic, uraemic, aHUS, HUS, TTP, PNH, paroxysmal, thrombocytopenia, eculizumab, hemoglobin, platelet, reticulocyte, bilirubin, antibody, anti-MASp-2, humanized, recombinant

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>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 2005/0191298 A1 (BELL et al.) 01 September 2005 (01.09.2005); Claim 93, paras [0011], [0013], [0048], [0050]-[0052], [0060], [0082], [0091]</td>
<td>1, 2, 4-9, 11, 12</td>
</tr>
<tr>
<td>Y</td>
<td>US 7,919,094 B2 (SCHAWELE et al.) 05 April 2011 (05.04.2011); Abstract, (col 3, In 30-46), (col 6, In 12-17), (col 7, In 25-41), (col 8, In 22-33), (col 22, In 33-35), (col 23, In 14-28), (col 36, In 2-6), (col 40, In 4-10), (col 45, In 35-36), (col 56, In 17-20), (col 57, In 37-52), (col 59, In 8-9), (col 79, In 4-7), (col 80, In 45-58), (col 82, In 41-51), (col 101, In 43-51)</td>
<td>3, 10</td>
</tr>
<tr>
<td>Y</td>
<td>Wagner et al. &quot;Therapeutic potential of complement modulation&quot; Nature Reviews; 2010; Vol. 9; pp 43-56; Figure 1, Table 1, (page 43, col 1, para 1), (page 43, col 2, para 2) - page 44, col 2, para 3), (page 48, col 1, para 1), (page 48, sidebar entitled &quot;Atypical haemolytic uraemic syndrome&quot;), (page 54, col 1, para 2)</td>
<td>13-36</td>
</tr>
<tr>
<td>Y</td>
<td>US 2006/0240476 A1 (SOEJIMA et al.) 26 October 2006 (26.10.2006); Claims 8 and 9, paras [0006], [0014], [0015]</td>
<td>57, 59</td>
</tr>
<tr>
<td>Y</td>
<td>US 201 1/0002931 A1 (TAMBURINI) 06 January 2011 (06.01.2011); para [0135]</td>
<td>22-24, 26-29</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

Further documents listed in the continuation of Box C.

Date of the actual completion of the international search
10 September 2012 (10.09.2012)

Date of mailing of the international search report
01 OCT 2012

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. 571-273-3201

Form PCT/ISA/210 (second sheet) (July 2009)
**DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
</table>
## 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.: 44, 45
   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:

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 1: claims 1-12, directed to a method of inhibiting MASP-2-dependent complement activation in a subject suffering from paroxysmal nocturnal hemoglobinuria (PNH), comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation.

- Please see extra sheet for continuation -

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.: 1-43 and 46-70

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.:

### 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.

Form PCT/ISA/2.10 (continuation of first sheet (2)) (July 2009)
INTERNATIONAL SEARCH REPORT

Continuation of Box III: Lack of Unity of Invention

Group II: claims 13-17, directed to a method of inhibiting MASP-2-dependent complement activation in a subject suffering from or at risk for developing non-Factor H-dependent atypical hemolytic uremic syndrome (aHUS), comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation.

Group III: claims 18-25, directed to a method for reducing the likelihood that a subject at risk for developing atypical hemolytic uremic syndrome (aHUS) will suffer clinical symptoms associated with aHUS comprising: (a) determining the presence of a genetic marker in the subject known to be associated with aHUS; (b) periodically monitoring the subject to determine the presence or absence of at least one symptom selected from the group consisting of anemia, thrombocytopenia, renal insufficiency and rising creatinine; and (c) administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation upon the determination of the presence of at least one of anemia, thrombocytopenia, renal insufficiency or rising creatinine, wherein the composition is administered in an effective amount and for a sufficient time period to improve said one or more symptoms.

Group IV: claims 26-29, directed to a method of inhibiting MASP-2-dependent complement activation in a subject suffering from, or at risk for developing, atypical hemolytic uremic syndrome (aHUS) secondary to an infection, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 complement activation.

Group V: claims 30-36, directed to a method of treating a subject suffering from atypical hemolytic uremic syndrome (aHUS) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation, wherein the administration of the MASP-2 inhibitory agent is administered via an intravenous catheter or other catheter delivery method.

Group VI: claims 37-43 and 46-47, directed to a method of decreasing the likelihood of developing impaired renal function in a subject at risk for developing hemolytic uremic syndrome (HUS), comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation.

Group VII: claims 48-54, directed to a method of treating a subject suffering from hemolytic uremic syndrome (HUS) comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation, wherein the administration of the MASP-2 inhibitory agent is administered to the subject via an intravenous catheter or other catheter delivery method.

Group VIII: claims 55-65, directed to a method of treating a subject suffering from thrombotic thrombocytopenic purpura (TTP), or exhibiting symptoms consistent with a diagnosis of TTP, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation, wherein the administration of the MASP-2 inhibitory agent is administered to the subject via an intravenous catheter or other catheter delivery method.

Group IX: claims 66-70, directed to a method of treating a subject suffering from refractory thrombotic thrombocytopenic purpura (TTP), comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation.

Group X: claims 71-73, directed to a method of inhibiting MASP-2-dependent complement activation in a subject suffering from cryoglobulinemia, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation.

Group XI: claims 74-76, directed to a method of inhibiting MASP-2-dependent complement activation in a subject suffering from cold agglutinin disease, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation.

Group XII: claims 77-79, directed to a method of inhibiting MASP-2 dependent complement activation in a subject suffering from glaucoma, comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation.

Group XIII: claims 80-85, directed to a method of inhibiting MASP-2 dependent complement activation in a subject at risk for developing, or is suffering from acute radiation syndrome comprising administering to the subject a composition comprising an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation.

The inventions listed as Groups I - XIII 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 the claims of Groups I-XII are indicated in the Group descriptions, above. It should be noted that hemolytic uremic syndrome (HUS) and atypical hemolytic uremic syndrome (aHUS) are distinct conditions (see the article entitled "Complement in glomerular injury" by Berger et al. (hereinafter "Berger"), particularly pg. 380, col 1, para 3).

- Please see next extra sheet for continuation -

Form PCT/ISA/2 16 (extra sheet) (July 2009)
Continuation of First Extra Sheet: Lack of Unity of Invention

The only common technical element shared by the above groups is that they are related to inhibition of MASP-2 dependent complement activation in a subject, comprising administering to the subject in need thereof an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2 dependent complement activation. Groups VI and VII are further related to hemolytic uremic syndrome. Groups VIII and IX are further related to thrombotic thrombocytopenic purpura. Groups II-V, VI and XIII are related to administration to a subject at risk of developing a particular condition. These common technical elements do not represent an improvement over the prior art of US 2006/0002937 A1 to Schwaeble et al., which discloses "methods of inhibiting the effects of MASP-2-dependent complement activation in a living subject. The methods comprise the step of administering, to a subject in need thereof, an amount of a MASP-2 inhibitory agent effective to inhibit MASP-2-dependent complement activation" (abstract), wherein the conditions treated may include HUS and TTP (para [0035]), and wherein the administration may be prophylactically given to subjects at risk (para [0403]).

Groups II-V share the common technical element of being related to atypical hemolytic uremic syndrome. This common technical element does not improve upon the prior art of Schwaeble in view of Berger, as above. In particular, since Berger teaches wherein "the clinical and experimental findings clearly point towards an important role of complement regulation in the pathogenesis of aHUS" (pg. 380, col. 2, para 3), and as Schwaeble teaches treatment of HUS using a MASP-2 complement activation inhibitor (para [0035]), it would have been obvious to a person skilled in the art to similarly treat aHUS or a subject at risk of developing aHUS using a MASP-2 inhibitor, as taught by Schwaeble, in order to compensate for complement pathway defects found in aHUS, as taught by Berger (pg. 308).

Therefore, the inventions of Groups I-XIII lack unity of invention under PCT Rule 13 because they do not share a same or corresponding special technical feature.