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- (81) **Designated States** (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,
BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM,
DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR,
KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ,
OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC,
SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN,
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TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
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WO 2013/189606 A3

(54) **Title:** INTERVAL THERAPY FOR THE TREATMENT OF LOSS OF EYESIGHT IN HUMANS WITH GLAUCOMA AND OTHER DEGENERATIVE EYE DISEASES

(57) **Abstract:** Methods for the prevention and treatment of ocular disorders, in particular glaucoma, through blocking the toxic effects of β -amyloid ($A\beta$) derivatives, pharmaceutical compositions for effecting such prevention and interval treatment thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/001832

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/05 A61P27/02 A61K38/02
ADD.
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)
A61K
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)
EPO-Internal, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/024346 A2 (MERZ PHARMA GMBH & CO KGAA [DE]; RUSS HERMANN [DE]) 26 February 2009 (2009-02-26) the whole document -----	1-20,28
Y	WO 2008/148564 A1 (MERZ PHARMA GMBH & CO KGAA [DE]; HANSCHMANN ANGELIKA [DE]; STOEFFLER A) 11 December 2008 (2008-12-11) paragraphs [0020] - [0028] paragraph [0064]; claims 16,17 -----	1-20,28
Y	US 2011/200531 A1 (TAN ZHIQUN [US]) 18 August 2011 (2011-08-18) paragraphs [0011], [0013] - [0016], [0098] -----	1-20,28
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 30 April 2014	Date of mailing of the international search report 15/05/2014
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Engl, Brigitte
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/47193 A2 (KAROLINSKA INNOVATIONS AB [SE]; CAO YIHAI [SE]) 17 August 2000 (2000-08-17) abstract; claim 1 -----	1-20,28
A	ZHANG B; SAFA R; RUSCIANO D; OSBORNE N N: "Epigallocatechin gallate, an active ingredient from green tea, attenuates damaging influences to the retina caused by ischemia/reperfusion", BRAIN RESEARCH, vol. 1159, July 2007 (2007-07), pages 40-53, XP022156863, ISSN: 0006-8993, DOI: DOI:10.1016/J.BRAINRES.2007.05.029 the whole document -----	1-20,28
A	WO 2012/066549 A1 (UNIV RAMOT [IL]; MERZ PHARMA GMBH & CO KGAA [DE]; GAZIT EHUD [IL]; AMI) 24 May 2012 (2012-05-24) page 8, line 30 - page 9, line 1 page 10, line 10 - page 11, line 16 page 25, lines 30-32 -----	1-20,28
A	US 2006/148905 A1 (KIM DARRICK S H [US] KIM DARRICK S H L [US]) 6 July 2006 (2006-07-06) paragraphs [0019], [0020] -----	1-20,28
A	YUN A J ET AL: "Paradoxical strategy for treating chronic diseases where the therapeutic effect is derived from compensatory response rather than drug effect", MEDICAL HYPOTHESES, EDEN PRESS, PENRITH, US, vol. 64, no. 5, 1 January 2005 (2005-01-01), pages 1050-1059, XP004952012, ISSN: 0306-9877, DOI: 10.1016/J.MEHY.2004.09.007 page 1052, left-hand column, lines 24-27 page 1053, right-hand column, lines 3-12 -----	1-20,28
Y	US 2005/119187 A1 (HAMMER ROBERT P [US] ET AL) 2 June 2005 (2005-06-02) paragraphs [0025], [0042], [0044], [0068] -----	24-27
Y	US 7 781 396 B2 (GAZIT EHUD [IL]) 24 August 2010 (2010-08-24) examples 48-50 -----	24-27
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2013/001832

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	<p>US 2010/093648 A1 (CRUZ ANTONIO [CA]) 15 April 2010 (2010-04-15) the whole document</p> <p>-----</p>	24-27
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/001832

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	LUNA C ET AL: "Resveratrol prevents the expression of glaucoma markers induced by chronic oxidative stress in trabecular meshwork cells", FOOD AND CHEMICAL TOXICOLOGY, PERGAMON, GB, vol. 47, no. 1, 1 January 2009 (2009-01-01), pages 198-204, XP025769233, ISSN: 0278-6915, DOI: 10.1016/J.FCT.2008.10.029 [retrieved on 2008-11-06] the whole document	24-27
Y	FRADINGER ERICA A ET AL: "C-terminal peptides coassemble into A beta 42 oligomers and protect neurons against A beta 42-induced neurotoxicity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 105, no. 37, September 2008 (2008-09), pages 14175-14180, XP002723831, ISSN: 0027-8424, DOI: 10.1073/PNAS.0807163105 the whole document	24-27
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Y	GUO LI ET AL: "Targeting amyloid-beta in glaucoma treatment", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, NATIONAL ACADEMY OF SCIENCES, US, vol. 104, no. 33, 1 August 2007 (2007-08-01), pages 13444-13449, XP002471873, ISSN: 0027-8424, DOI: 10.1073/PNAS.0703707104 the whole document	24-27

INTERNATIONAL SEARCH REPORT

International application No.
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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.: 24-27 (partially)
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:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
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:

see additional sheet

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 an 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.:
1-20, 24-28

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-20, 28

Dipeptide comprising an aromatic amino acid and another amino acid for use in treating an ophthalmic condition associated with beta-amyloid toxicity, wherein the dosage of the dipeptide is reduced or discontinued after an initial treatment period.

2. claims: 21-23

Various substances, such as e.g. (-)-epigallocatechin-3-gallate or QSHYRHISPAQV, for use in treating an ophthalmic condition associated with beta-amyloid toxicity, wherein the dosage of the substance is reduced or discontinued after an initial treatment period.

3. claims: 24-27

Bulky non-toxic beta-amyloid protein aggregate for use in treating an ophthalmic condition associated with beta-amyloid toxicity.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: 24-27(partially)

Claims 24 to 27 are to "bulky non-toxic β -amyloid (A β) protein aggregates".

The indication found in claims 25 and 26, viz. that the claimed aggregates are induced by administering an A β modulator to a subject, would mean that not an aggregate as claimed, but an A β modulator is used for treating the envisaged condition, which causes lack of clarity and leaves the claimed aggregates completely undefined.

Claim 27

describes the preparation of the aggregates by adding an A β modulator to a conditioned medium of A β producing cells, followed by isolating and washing the aggregates, but equally fails to define the chemical structure of the claimed aggregates. It is noted that the precise conditions of preparation of the aggregates do not appear to be described in the specification in a reproducible manner.

Thus, the "bulky non-toxic β -amyloid (A β) protein aggregates" claimed in claims 24 to 27 are not characterised by any feature that would allow to determine and verify their constitution or structural identity, and their preparation is not disclosed in any detail. The said claims are therefore considered to contravene Articles 5 and 6 PCT.

The search has been carried out based on the general principle derivable from pharmacological Example 2 given in the specification.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guidelines C-IV, 7.2), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/001832

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