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(74) Agent: **GRAFF, Alan**; Novartis Pharma AG, Patent Department, CH-4002 Basel (CH).

(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, 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, KM, 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, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- 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:

27 September 2012

(54) Title: METHODS OF TREATING RHEUMATOID ARTHRITIS USING IL-17 ANTAGONISTS

(57) Abstract: The disclosure relates to novel regimens for treating an inflammatory arthritis, e.g., rheumatoid arthritis (RA) patients, e.g., high risk RA patients, which employ a therapeutically effective amount of an IL-17 antagonist, e.g., IL-17 binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof, e.g., secukinumab) or IL-17 receptor binding molecule (e.g., IL-17 antibody or antigen binding fragment thereof).



WO 2012/059598 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP2011/069476

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. (means)
 - on paper
 - in electronic form
 - b. (time)
 - in the international application as filed
 - together with the international application in electronic form
 - subsequently to this Authority for the purpose of search
2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2011/069476

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.:
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.:

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.:

1-68, 74-82(completely); 70-73, 83-85(partially)

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/069476

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 C07K16/24 A61K31/519
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 C07K

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, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARK GENOVESE ET AL: "Secukinumab (AIN457), a novel monoclonal antibody targeting IL-17A demonstrates efficacy in active rheumatoid arthritis patients despite stable methotrexate treatment: Results of a phase IIb study", ARTHRITIS & RHEUMATISM; ABSTRACTS OF THE AMERICAN COLLEGE OF RHEUMATOLOGY & ASSOCIATION OF RHEUMATOLOGY HEALTH PROFESSIONALS, ANNUAL SCIENTIFIC MEETING, JOHN WILEY & SONS, INC, US; ATLANTA, GEORGIA, USA, vol. 62, no. Suppl. 10, 1 October 2010 (2010-10-01), XP008147986, ISSN: 0004-3591, DOI: 10.1002/ART.30166 [retrieved on 2010-12-28] the whole document ----- -/--	1-23, 25-28, 30-52, 54-68, 70-76, 79,83-85

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search 9 February 2012	Date of mailing of the international search report 10/08/2012
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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 Bumb, Peter
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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/069476

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HUEBER WOLFGANG ET AL: "Effects of AIN457, a Fully Human Antibody to Interleukin-17A, on Psoriasis, Rheumatoid Arthritis, and Uveitis", SCIENCE TRANSLATION MEDICINE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE, US, vol. 2, no. 52 / Article No.: 52ra72, 1 October 2010 (2010-10-01), pages 1-9, XP009155660, ISSN: 1946-6234 table 1 figure 4 page 7, right-hand column -----	1,2,5, 12-16, 23-25, 27,28, 30,31, 34, 41-45, 52-54, 57-62, 74-79, 83-85
X	GENOVESE M C ET AL: "LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: A phase I randomized, double-blind, placebo-controlled, proof-of-concept study.", ARTHRITIS AND RHEUMATISM APR 2010 LNKD-PUBMED:20131262, vol. 62, no. 4, April 2010 (2010-04), pages 929-939, XP002669154, ISSN: 1529-0131 the whole document -----	1,2,5, 12-16, 23-25, 28,30, 31,34, 41-45, 52-54, 56-61, 74-79,83
A	WO 2006/013107 A1 (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; DI PADOVA FRANCO E [CH];) 9 February 2006 (2006-02-09) page 42, column 43 sequences 7-10 -----	1-68, 70-85
X	US 5 250 442 A (CABEZAS ORESTES [US]) 5 October 1993 (1993-10-05) claim 1 column 2, line 35 - line 43 -----	80-82
X	MACHOLD K P ET AL: "Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease.", RHEUMATOLOGY (OXFORD, ENGLAND) FEB 2007 LNKD- PUBMED:16899498, vol. 46, no. 2, February 2007 (2007-02), pages 342-349, XP002669155, ISSN: 1462-0324 the whole document -----	29,82
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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/069476

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>YOSHIDA MINORU ET AL: "Methotrexate suppresses inflammatory agonist induced interleukin 6 synthesis in osteoblasts", JOURNAL OF RHEUMATOLOGY, JOURNAL OF RHEUMATOLOGY PUBLISHING COMPANY, CA, vol. 32, no. 5, 1 May 2005 (2005-05-01), pages 787-795, XP008147990, ISSN: 0315-162X page 794, left-hand column, line 10 - line 12</p> <p style="text-align: center;">-----</p>	1-85
A,P	<p>HOU WEI-KUN ET AL: "Methotrexate ameliorates pristane-induced arthritis by decreasing IFN-[gamma] and IL-17A expressions.", JOURNAL OF ZHEJIANG UNIVERSITY. SCIENCE. B JAN 2011 LNKD- PUBMED:21194185, vol. 12, no. 1, January 2011 (2011-01), pages 40-46, XP002669156, ISSN: 1862-1783 figure 2B page 44, right-hand column, line 28 - line 31</p> <p style="text-align: center;">-----</p>	1-85

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/069476

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006013107	A1	09-02-2006	AR 050200 A1 04-10-2006
			AT 517924 T 15-08-2011
			AU 2005268857 A1 09-02-2006
			AU 2010201689 A1 20-05-2010
			BR PI0513078 A 22-04-2008
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			DK 1776142 T3 31-10-2011
			EC SP077198 A 28-02-2007
			EP 1776142 A1 25-04-2007
			EP 2364729 A2 14-09-2011
			EP 2366405 A2 21-09-2011
			ES 2367440 T3 03-11-2011
			HR P20110758 T1 30-11-2011
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			US 2009280131 A1 12-11-2009
			US 2010215666 A1 26-08-2010
			WO 2006013107 A1 09-02-2006
			ZA 200700242 A 27-08-2008

US 5250442	A	05-10-1993	NONE

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-68, 74-82(completely); 70-73, 83-85(partially)

Treating/assaying RA-patients

- 1.1. claims: 1-62, 68, 74-79(completely); 70-73, 83-85(partially)

A method of treating high risk RA patients using an IL-17 antagonist or IL-17 binding molecule, e.g. wherein "high risk" is characterized by (i) RF and/or ACPA and (ii) ESR and/or CRP. I.e. focusing treatment on a particular patient subgroup.

- 1.2. claims: 63-67

A method of treating an RA-patient with a particular dosing regime of an IL-17 binding molecule providing specific pharmacokinetics, namely at least (a) a C_{max} of about 360 ug/ml and (b) either an average steady-state through level of about 8-30 ug/ml or an AUC tau of about 331-1323 (mg*day)/L is achieved. I.e. focusing treatment on a particular dosing regimen.

- 1.3. claims: 80-82

A method comprising assaying a sample of the patient for at least two factors, namely (a) RF and/or ACPA and (b) CRP and/or ESR, and basing patient-selection or transmission of information thereon. I.e. focusing a detection/diagnosis/prognosis assay on two disease-markers.

2. claims: 69(completely); 70-73, 83-85(partially)

A method of treating a psoriasis-patient with a particular dosing regime of an IL-17 binding molecule providing specific pharmacokinetics, namely at least (a) a C_{max} of about 401 ?g/ml and (b) either an average steady-state through level of about 9.4-3130 ?g/ml or an AUC tau of about 314-1256 (mg*day)/L is achieved.
