

(51) International Patent Classification:
C07K 16/24 (2006.01)

(21) International Application Number:

PCT/EP2012/064129

(22) International Filing Date:

19 July 2012 (19.07.2012)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

1112429.4

19 July 2011 (19.07.2011)

GB

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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, 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.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

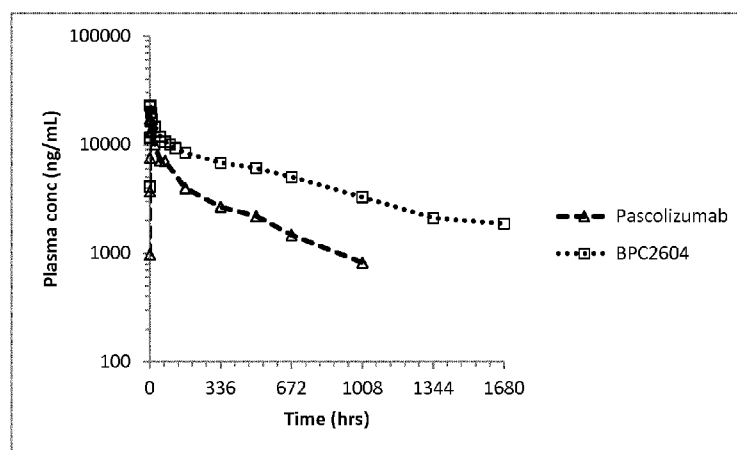
Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

[Continued on next page]

(54) Title: TNF -ALPHA ANTIGEN- BINDING PROTEINS WITH INCREASED FCERN BINDING

Figure 6



(57) Abstract: The present invention provides antigen binding proteins which bind specifically to TNF-alpha. For example novel variants of anti-TNF antibodies such as adalimumab which show increased binding to the FcRn receptor or increased half life compared to adalimumab. Also provided are compositions comprising the antigen binding proteins and uses of such compositions in treatment of disorders and disease.



- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- *of inventorship (Rule 4.17(iv))*
- *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))*

Published:

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

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

4 April 2013

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/064129

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/24
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)
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, BIOSIS, Sequence Search, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/163699 A1 (CHAMBERLAIN AARON KEITH [US] ET AL) 25 June 2009 (2009-06-25)	1-35
A	the whole document in particular abstract paragraphs [0014] - [0021], [0126] - [0132] claims 1-19; figures 1-23; examples 1-7; sequences 23, 24 ----- -/--	36-44



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

15 January 2013

Date of mailing of the international search report

25/01/2013

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/064129

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PAUL R HINTON ET AL: "An engineered human IgG1 antibody with longer serum half-life", THE JOURNAL OF IMMUNOLOGY, THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, US, vol. 176, no. 1, 1 January 2006 (2006-01-01), pages 346-356, XP002484005, ISSN: 0022-1767 the whole document -----	1-44
A	HINTON PAUL R ET AL: "Engineered human IgG antibodies with longer serum half-lives in primates", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 279, no. 8, 20 February 2004 (2004-02-20), pages 6213-6216, XP002482523, ISSN: 0021-9258, DOI: 10.1074/JBC.C300470200 the whole document -----	1-44
A	A. DATTA-MANNAN ET AL: "Monoclonal Antibody Clearance: IMPACT OF MODULATING THE INTERACTION OF IgG WITH THE NEONATAL Fc RECEPTOR", JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 282, no. 3, 1 January 2007 (2007-01-01), pages 1709-1717, XP55043665, ISSN: 0021-9258, DOI: 10.1074/jbc.M607161200 the whole document -----	1-44
A	DATTA-MANNAN AMITA ET AL: "HUMANIZED IGG1 VARIANTS WITH DIFFERENTIAL BINDING PROPERTIES TO THE NEONATAL FC RECEPTOR: RELATIONSHIP TO PHARMACOKINETICS IN MICE AND PRIMATES", DRUG METABOLISM AND DISPOSITION, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 35, no. 1, 1 January 2007 (2007-01-01), pages 86-94, XP009077715, ISSN: 0090-9556, DOI: 10.1124/DMD.106.011734 the whole document ----- -/--	1-44

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/064129

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DALL'ACQUA W F ET AL: "Properties of human IgG1s engineered for enhanced binding to the neonatal Fc receptor (FcRn)", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 281, no. 33, 21 June 2006 (2006-06-21), pages 23514-23524, XP002404904, ISSN: 0021-9258, DOI: 10.1074/JBC.M604292200 the whole document	1-44
A	ROBERT L SHIELDS ET AL: "High resolution mapping of the binding site on human IgG1 for Fc gamma RI, Fc gamma RII, Fc gamma RIII and FcRn and design of IgG1 variants with improved binding to the Fc gamma R", JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, US, vol. 276, no. 9, 2 March 2001 (2001-03-02), pages 6591-6604, XP002638208, ISSN: 0021-9258, DOI: 10.1074/JBC.M009483200 [retrieved on 2000-11-28] cited in the application the whole document	1-44
A	WO 2010/097385 A1 (GLAXO GROUP LTD [GB]; HAMBLIN PAUL ANDREW [GB]; PARMAR RADHA SHAH [GB]) 2 September 2010 (2010-09-02) the whole document	1-44
A	WO 2010/136492 A2 (GLAXO GROUP LTD [GB]; ADAMSON PETER [GB]; ERTL PETER FRANZ [GB]; GERMA) 2 December 2010 (2010-12-02) the whole document	1-44
A	WO 2009/068649 A2 (GLAXO GROUP LTD [GB]; ASHMAN CLAIRE [GB]; BATUWANGALA THIL [GB]; BURDE) 4 June 2009 (2009-06-04) the whole document	1-44
	----- -/--	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2012/064129

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/102251 A2 (ABBOTT LAB [US]; HSIEH CHUNG-MING [US]; HUGUNIN MARGARET; MURTAZA ANWA) 10 September 2010 (2010-09-10)	36-44
A	the whole document in particular abstract page 3, line 1 - page 32, line 26 page 35, line 24 - page 36, line 26 page 84, line 23 - page 86, line 18 page 131, line 19 - page 132, line 5 claims 1-201; examples 1-6 -----	1-35
X	WO 2008/057240 A2 (ABBOTT BIOTECH LTD [GB]; BORHANI DAVID W [US]; FRAUNHOFER WOLFGANG [US] 15 May 2008 (2008-05-15)	36-44
A	the whole document in particular abstract page 6, line 15 - page 13, line 20 page 19, line 14 - page 20, line 22 claims 1-41; figures 1-7; examples 1-47 -----	1-35
X	WO 2009/073805 A2 (VERDEZYNE INC [US]; KITTLE JOSEPH D [US]) 11 June 2009 (2009-06-11)	36-44
A	the whole document in particular abstract paragraphs [0005] - [0029], [0102] claims 1-16; figures 1-18; examples 1-6 -----	1-35
X	WO 2009/083246 A1 (BAYER SCHERING PHARMA AG [DE]; VOTSMEIER CHRISTIAN [DE]; GRITZAN UWE []) 9 July 2009 (2009-07-09)	36-44
A	the whole document in particular abstract paragraphs [0003] - [0009], [0075] claims 1-16; figures 1-34; examples -----	1-35

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.:
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.:

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: 1-35

Subject-matter of claims 1-35 which relates to an antigen binding protein (e.g. an antibody) which specifically binds to TNF-alpha comprising

(i) CDRH1 (SEQ ID No. 27), CDRH2 (SEQ ID No. 28), CDRH3 (SEQ ID No. 29), CDRL1 (SEQ ID No. 30), CDRL2 (SEQ ID No. 31) and CDRL3 (SEQ ID No 32) or a CDR variant thereof which contains 1, 2, 3 or 4 amino acid substitutions, insertions or deletions as compared to CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 or CDRL3 and

(ii) a neonatal Fc receptor (FcRn) binding portion of a human IgG1 constant domain comprising one of more amino acid substitutions relative to the human IgG1 constant domain, wherein the antigen binding protein has an increased FcRn binding affinity at pH 6 and/or increased half-life as compared to an IgG comprising the light chain (VL) sequence of SEQ ID No. 2 and the heavy chain (VH) sequence of SEQ ID No. 12.

2. claims: 36-44

Subject-matter of claims 36-44 which relates to a liquid formulation comprising a TNF-alpha antigen binding protein and an acetate buffer.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/064129

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009163699 A1	25-06-2009	US 2009163699 A1	25-06-2009
		US 2010204454 A1	12-08-2010
		US 2010234571 A1	16-09-2010
		US 2010234572 A1	16-09-2010
		US 2010234573 A1	16-09-2010
		US 2010234574 A1	16-09-2010
		US 2010234575 A1	16-09-2010
		US 2011110928 A1	12-05-2011
		US 2012088905 A1	12-04-2012
WO 2010097385 A1	02-09-2010	CA 2753287 A1	02-09-2010
		EP 2401298 A1	04-01-2012
		JP 2012518398 A	16-08-2012
		US 2011305692 A1	15-12-2011
		WO 2010097385 A1	02-09-2010
WO 2010136492 A2	02-12-2010	AR 076796 A1	06-07-2011
		AU 2010251966 A1	22-12-2011
		CA 2763469 A1	02-12-2010
		CN 102458471 A	16-05-2012
		EA 201190273 A1	28-12-2012
		EP 2435075 A2	04-04-2012
		JP 2012528112 A	12-11-2012
		SG 176202 A1	29-12-2011
		TW 201106963 A	01-03-2011
		US 2012076787 A1	29-03-2012
		UY 32665 A	31-12-2010
		WO 2010136492 A2	02-12-2010
WO 2009068649 A2	04-06-2009	AR 069495 A1	27-01-2010
		AU 2008328726 A1	04-06-2009
		CA 2706419 A1	04-06-2009
		CN 101932608 A	29-12-2010
		CO 6280497 A2	20-05-2011
		DE 112008003232 T5	24-02-2011
		EA 201000704 A1	30-12-2010
		EP 2222709 A2	01-09-2010
		GB 2468232 A	01-09-2010
		JP 2011504742 A	17-02-2011
		KR 20100097720 A	03-09-2010
		MA 31940 B1	01-12-2010
		PE 12342009 A1	07-09-2009
		TW 200944231 A	01-11-2009
		US 2009148905 A1	11-06-2009
		US 2011008345 A1	13-01-2011
		UY 31504 A1	17-07-2009
		WO 2009068649 A2	04-06-2009
WO 2010102251 A2	10-09-2010	AR 075798 A1	27-04-2011
		AU 2010221166 A1	08-09-2011
		CA 2752648 A1	10-09-2010
		CN 102781470 A	14-11-2012
		CO 6410314 A2	30-03-2012
		DO P2011000274 A	31-10-2011
		EP 2403531 A2	11-01-2012
		JP 2012519708 A	30-08-2012
		KR 20110128909 A	30-11-2011
		PE 10942012 A1	13-09-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/064129

Patent document cited in search report	Publication date	Patent family member(s)	Publication date	
		SG 173705 A1	29-09-2011	
		TW 201043241 A	16-12-2010	
		US 2010266531 A1	21-10-2010	
		UY 32477 A	30-06-2010	
		WO 2010102251 A2	10-09-2010	

WO 2008057240	A2	15-05-2008	AR 063429 A1	28-01-2009
			AU 2007318120 A1	15-05-2008
			CA 2667655 A1	15-05-2008
			CL 30942007 A1	16-05-2008
			CN 101616932 A	30-12-2009
			EP 2089428 A2	19-08-2009
			JP 2010507670 A	11-03-2010
			KR 20090101893 A	29-09-2009
			NZ 576133 A	26-10-2012
			PE 06632012 A1	01-06-2012
			PE 12582008 A1	04-09-2008
			RU 2009119988 A	10-12-2010
			SG 176427 A1	29-12-2011
			TW 200835699 A	01-09-2008
			US 2010034823 A1	11-02-2010
			US 2012251550 A1	04-10-2012
			UY 30662 A1	31-05-2008
			WO 2008057240 A2	15-05-2008

WO 2009073805	A2	11-06-2009	NONE	

WO 2009083246	A1	09-07-2009	CA 2710779 A1	09-07-2009
			EP 2225276 A1	08-09-2010
			JP 2011508597 A	17-03-2011
			US 2010297700 A1	25-11-2010
			WO 2009083246 A1	09-07-2009
