



(51) International Patent Classification:

A61K 31/4985 (2006.01) A61K 45/06 (2006.01)
A61K 31/506 (2006.01) A61P 35/00 (2006.01)
A61K 31/519 (2006.01) A61P 35/02 (2006.01)

(21) International Application Number:

PCT/IB2015/001811

(22) International Filing Date:

17 June 2015 (17.06.2015)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/013,506 17 June 2014 (17.06.2014) US
62/035,785 11 August 2014 (11.08.2014) US
62/087,975 5 December 2014 (05.12.2014) US
62/115,493 12 February 2015 (12.02.2015) US

(71) Applicant: ACERTA PHARMA B.V. [NL/NL]; Pivot Park, Room RK 2111, Molenweg 79, NL-5349 AC Oss (NL).

(72) Inventors: **HAMDY, Ahmed**; 640 Henry Cowell Drive, Santa Cruz, CA 95060 (US). **ROTHBAUM, Wayne**; 101 Central Park West, PHC, New York, NY 10023 (US). **IZUMI, Raquel**; 3437 Brittan Avenue, San Carlos, CA 94070 (US). **LANNUTTI, Brian**; 627 Glencrest Place, Solana Beach, CA 92075 (US). **COVEY, Todd**; 3437 Brittan Avenue, San Carlos, CA 94070 (US). **ULRICH, Roger**; 22525 SE 46th Place, Sammamish, WA 98075 (US). **JOHNSON, Dave**; 4442 54th Avenue SW, Seattle, WA 98116 (US). **BARF, Tjeerd**; St. Luciastraat 7, NL-5371 AS Ravenstein (NL). **KAPTEIN, Allard**; Nonnenstraat 14, NL-5301 BJ Zaltmommel (NL).

(74) Agent: MAIWALD PATENTANWALTS GMBH; Elisenhof, Elisenstrasse 3, 80335 München (DE).

(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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, 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, SA, 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, ST, 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, KM, ML, MR, NE, SN, TD, TG).

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:

4 August 2016

(15) Information about Correction:

Previous Correction:

see Notice of 21 April 2016

(54) Title: THERAPEUTIC COMBINATIONS OF A BTK INHIBITOR, A PI3K INHIBITOR AND/OR A JAK-2 INHIBITOR

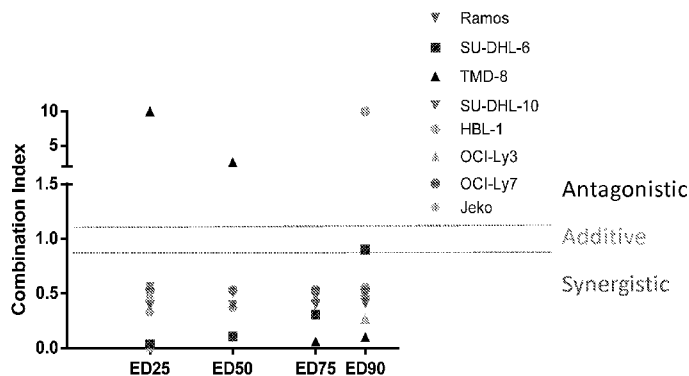


FIG. 86

(57) Abstract: Therapeutic combinations of a Janus kinase-2 (JAK-2) inhibitor, a Bruton's tyrosine kinase (BTK) inhibitor, and/or a phosphoinositide 3-kinase (PI3K) inhibitor, including PI3K inhibitors selective for the γ - and δ -isoforms and selective for both γ - and δ -isoforms, are described. In some embodiments, the invention provides pharmaceutical compositions comprising combinations of (1) a PI3K- δ inhibitor and a BTK inhibitor, (2) a JAK-2 inhibitor and a BTK inhibitor, or (3) a JAK-2 inhibitor, PI3K- δ inhibitor, and BTK inhibitor, and methods of using the pharmaceutical compositions for treating a disease, in particular a cancer.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/001811

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4985 A61K31/506 A61K31/519 A61K45/06 A61P35/00
A61P35/02

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 A61P

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)

EP0-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COSTANZA BOGANI ET AL: "mTOR Inhibitors Alone and in Combination with JAK2 Inhibitors Effectively Inhibit Cells of Myeloproliferative Neoplasms", PLOS ONE, vol. 8, no. 1, 31 January 2013 (2013-01-31), page e54826, XP055139435, DOI: 10.1371/journal.pone.0054826 page 2, column 2	1-68
Y	WO 2013/010868 A1 (MSD OSS BV [NL]; BARF TJEERD A [NL]; JANS CHRISTIAAN GERARDUS JOHANNES) 24 January 2013 (2013-01-24) cited in the application claims ----- -/--	1-68



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

19 February 2016

Date of mailing of the international search report

13/06/2016

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

Büttner, Ulf

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2015/001811

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	ANTHONY D. WILLIAM ET AL: "Discovery of the Macrocyclic 11-(2-Pyrrolidin-1-yl-ethoxy)-14,19-dioxo-5,7,26-triaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacos-1(25),2(26),3,5,8,10,12(27),16,21,23-decaene (SB1518), a Potent Janus Kinase 2/Fms-Like Tyrosine Kinase-3 (JAK2/FLT3) Inhibitor for the Treatment of Myelofibrosis and Lympho", JOURNAL OF MEDICINAL CHEMISTRY, vol. 54, no. 13, 14 July 2011 (2011-07-14), pages 4638-4658, XP055163145, ISSN: 0022-2623, DOI: 10.1021/jm200326p page 4649; figure 6	1-68
Y	----- LIM JONGWON ET AL: "Discovery of 1-Amino-5H-pyrido[4,3-b]indol-4-carboxamide Inhibitors of Janus Kinase 2 (JAK2) for the Treatment of Myeloproliferative Disorders", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 54, no. 20, 1 January 2011 (2011-01-01), pages 7334-7349, XP002738677, ISSN: 0022-2623, DOI: 10.1021/JM200909U tables 7,8 page 7334	1-68
Y	----- US 2009/312319 A1 (REN PINGDA [US] ET AL) 17 December 2009 (2009-12-17) cited in the application claims	1-68
X,P	----- WO 2014/168975 A1 (PHARMACYCLICS INC [US]; JANSSEN PHARMACEUTICA NV [BE]; CHANG BETTY [US]) 16 October 2014 (2014-10-16) paragraph [0191]	1-4,15, 19, 32-34, 42,59-68
E	----- WO 2015/127234 A1 (UNIV TEXAS [US]) 27 August 2015 (2015-08-27) claims 1,13,22	1,7,16, 19,23, 32-34, 37,43, 46,47, 50,59-68

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/001811

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.:

1-58, 62-68(completely); 59-61(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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-58, 62-68(completely); 59-61(partially)

A pharmaceutical composition comprising a JAK-2 inhibitor in combination with a BTK inhibitor.

2. claims: 59-61(partially)

A pharmaceutical composition comprising a JAK-2 inhibitor in combination with a PI3K inhibitor.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2015/001811

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013010868	A1	24-01-2013	
		AU 2012285987 A1	06-02-2014
		CA 2841886 A1	24-01-2013
		CL 2014000130 A1	22-08-2014
		CN 103889987 A	25-06-2014
		CO 6940411 A2	09-05-2014
		CR 20140030 A	03-06-2014
		DO P2014000008 A	30-04-2014
		EA 201490300 A1	30-05-2014
		EC SP14013217 A	31-03-2015
		EP 2734522 A1	28-05-2014
		JP 5826931 B2	02-12-2015
		JP 2014520870 A	25-08-2014
		JP 2016034968 A	17-03-2016
		KR 20140036324 A	25-03-2014
		MA 35348 B1	01-08-2014
		PE 16812014 A1	14-11-2014
		US 2014155385 A1	05-06-2014
		US 2016151364 A1	02-06-2016
		WO 2013010868 A1	24-01-2013

US 2009312319	A1	17-12-2009	
		AU 2010274075 A1	09-02-2012
		CA 2768307 A1	20-01-2011
		CN 102711767 A	03-10-2012
		DK 2456444 T3	11-05-2015
		EP 2456444 A1	30-05-2012
		EP 2918589 A1	16-09-2015
		ES 2538853 T3	24-06-2015
		HK 1170491 A1	16-10-2015
		HR P20150586 T1	03-07-2015
		JP 2012533541 A	27-12-2012
		KR 20120097479 A	04-09-2012
		NZ 597595 A	29-08-2014
		NZ 619727 A	29-05-2015
		PT 2456444 E	09-06-2015
		RU 2012105071 A	20-08-2013
		SG 177641 A1	28-02-2012
		SG 10201503886W A	29-06-2015
		SI 2456444 T1	31-07-2015
		SM T201500141 B	07-09-2015
		UA 109878 C2	26-10-2015
		US 2009312319 A1	17-12-2009
		US 2012149701 A1	14-06-2012
		US 2012245169 A1	27-09-2012
		US 2013345216 A1	26-12-2013
		US 2014341894 A1	20-11-2014
		US 2016031886 A1	04-02-2016
		WO 2011008302 A1	20-01-2011

WO 2014168975	A1	16-10-2014	
		AU 2014251028 A1	05-11-2015
		CA 2908375 A1	16-10-2014
		CN 105263496 A	20-01-2016
		EA 201591656 A1	31-05-2016
		EP 2983670 A1	17-02-2016
		KR 20150141971 A	21-12-2015
		PH 12015502337 A1	22-02-2016
		WO 2014168975 A1	16-10-2014

WO 2015127234	A1	27-08-2015	NONE

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2015/001811

Patent document cited in search report	Publication date	Patent family member(s)	Publication date