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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, 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).

[Continued on next page]

(54) Title: COMBINATION OF A PI3K INHIBITOR WITH A BCL-2 INHIBITOR FOR USE IN THE TREATMENT OF CANCER

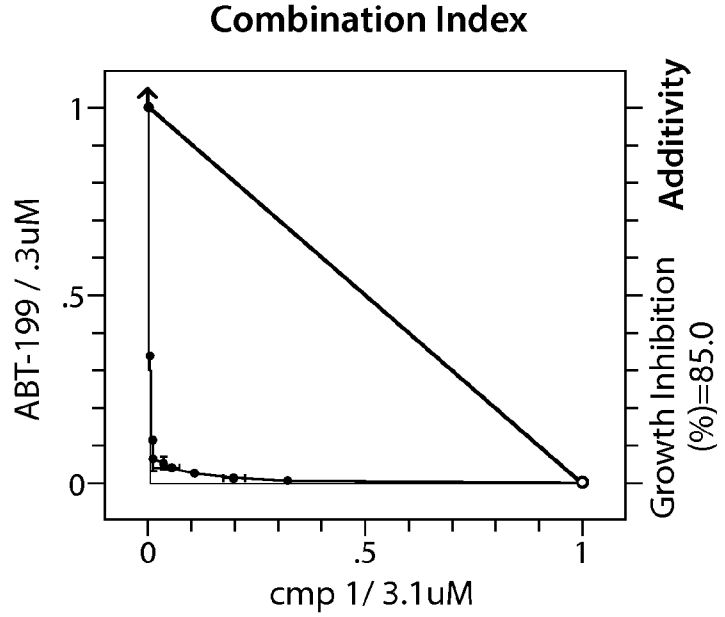

FIG. 1

(57) Abstract: Provided herein are pharmaceutical compositions comprising a phosphatidylinositol 3-kinase inhibitor or a pharmaceutically acceptable form thereof, and a Bcl-2 inhibitor or a pharmaceutically acceptable form thereof. Also provided herein are methods for treating cancer comprising administration the compositions, and uses of the compositions, e.g., for the treatment of cancer.

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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))*

(88) Date of publication of the international search report:
10 December 2015

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/026008

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/52 A61P35/00 A61K31/437 A61K31/496
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)
EPO-Internal, BIOSIS, WPI Data, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DOROTHÉE BUET ET AL: "Cotargeting signaling pathways driving survival and cell cycle circumvents resistance to Kit inhibitors in leukemia", BLOOD, AMERICAN SOCIETY OF HEMATOLOGY, UNITED STATES, vol. 119, no. 18, 3 May 2012 (2012-05-03), pages 4228-4241, XP002678292, ISSN: 1528-0020, DOI: 10.1182/BLOOD-2011-07-368316 [retrieved on 2012-03-20]	1-13, 15-57, 63,64, 69-86
Y	abstract	1-13, 15-58, 60,61, 63,64, 69-86

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[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
9 October 2015	29/10/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kuijper, Rudy

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/026008

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAHMANI MOHAMED ET AL: "Dual Inhibition of Bcl-2 and Bcl-xL Strikingly Enhances PI3K Inhibition-Induced Apoptosis in Human Myeloid Leukemia Cells through a GSK3- and Bim-Dependent Mechanism", CANCER RESEARCH, vol. 73, no. 4, February 2013 (2013-02), pages 1340-1351, XP002740726,	1-13, 15-57, 63,64, 69-86
Y	abstract	1-13, 15-58, 60,61, 63,64, 69-86

X	DATABASE BIOSIS, [Online] 19 November 2010 (2010-11-19), JIN LINHUA ET AL: "Efficacy and Mechanisms of Apoptosis Induction by Simultaneous Inhibition of PI3K with GDC-0941 and Blockade of Bcl-2 (ABT-737) or FLT3 (Sorafenib) In AML Cells In the Hypoxic Bone Marrow Microenvironment", XP002678287, retrieved from BIOSIS Database accession no. PREV201100423323	1-13, 15-57, 63,64, 69-86
Y	abstract	1-13, 15-58, 60,61, 63,64, 69-86

X	ZHU SHUDONG ET AL: "PI3K inhibition potentiates Bcl-2-dependent apoptosis in renal carcinoma cells", JOURNAL OF CELLULAR AND MOLECULAR MEDICINE, vol. 17, no. 3, March 2013 (2013-03), pages 377-385, XP002740727,	1-13, 15-57, 63,64, 69-86
Y	abstract	1-13, 15-58, 60,61, 63,64, 69-86

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/026008

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JASON G HARB ET AL: "Combined Pharmacologic Inhibition of Bcl-Xl/Bcl-2 and mTORC1/2 Survival Signals Trigger Apoptosis in BCR-ABL1(+) in Vitro Models of Blast Crisis Chronic Myelogenous Leukemia (CML-BC), and Primary CD34(+)/CD38(-) Stem and CD34(+) progenitor Cells From CML-BC Patients", BLOOD; 53RD ASH ANNUAL MEETING AND EXPOSITION OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY,SAN DIEGO, CA, USA; DECEMBER 10-13, 2011, AMERICAN SOCIETY OF HEMATOLOGY, US , vol. 118, no. 21 1 November 2011 (2011-11-01), pages 1177-1178, XP002678288, ISSN: 0006-4971 Retrieved from the Internet: URL:https://ash.confex.com/ash/2011/webprogram/Paper44381.html	1-13, 15-57, 63,64, 69-86
Y	the whole document	1-13, 15-58, 60,61, 63,64, 69-86

X	US 2012/184568 A1 (REN PINGDA [US] ET AL) 19 July 2012 (2012-07-19) cited in the application	1-13, 15-57, 63,64, 69-86
Y	page 1, paragraph 9 page 63, paragraph 511 - page 64, paragraph 513 page 70, paragraph 566	1-13, 15-58, 60,61, 63,64, 69-86

Y	KLAUS OKKENHAUG: "Two Birds with One Stone: Dual p110[delta] and p110[gamma] Inhibition", CHEMISTRY & BIOLOGY, vol. 20, no. 11, 1 November 2013 (2013-11-01), pages 1309-1310, XP055095287, ISSN: 1074-5521, DOI: 10.1016/j.chembiol.2013.11.002 the whole document figure 1	1-13, 15-58, 60,61, 63,64, 69-86

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/026008

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; November 2013 (2013-11), FLINN IAN ET AL: "Preliminary Safety and Efficacy Of IPI-145, a Potent Inhibitor Of Phosphoinositide-3-Kinase-delta,gamma, In Patients With Chronic Lymphocytic Leukemia", XP002740728, Database accession no. PREV201400359822 abstract & BLOOD, vol. 122, no. 21, November 2013 (2013-11), page 677, 55TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 07 -10, 2013 ISSN: 0006-4971(print) the whole document -----	1-13, 15-58, 60,61, 63,64, 69-86
Y	"Infinity Reports Preclinical Data at ASH Annual Meeting in Diffuse Large B-Cell Lymphoma and T-Cell Acute Lymphoblastic Leukemia Suggesting Broad Potential of IPI-145 in Blood Cancers", http://businesswire.com , 7 December 2013 (2013-12-07), XP002740590, Retrieved from the Internet: URL:http://www.businesswire.com/news/home/20131207005015/en/Infinity-Reports-Preclinical-Data-ASH-Annual-Meeting#.VXWFrGNELjN [retrieved on 2015-06-08] the whole document -----	1-13, 15-58, 60,61, 63,64, 69-86
Y	LETAI A ET AL: "Antiapoptotic BCL-2 is required for maintenance of a model leukemia", CANCER CELL, CELL PRESS, US, vol. 6, no. 3, 1 September 2004 (2004-09-01), pages 241-249, XP002684777, ISSN: 1535-6108, DOI: 10.1016/J.CCR.2004.07.011 abstract ----- -/--	1-13, 15-58, 60,61, 63,64, 69-86

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.
Y	OLTERSDORF T ET AL: "an inhibitor of BCL-2 family proteins induces regression of solid tumours", NATURE, NATURE PUBLISHING GROUP, UNITED KINGDOM, vol. 435, 2 June 2005 (2005-06-02), pages 677-681, XP002491257, ISSN: 0028-0836, DOI: 10.1038/NATURE03579 abstract -----	1-13, 15-58, 60,61, 63,64, 69-86
Y	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; November 2013 (2013-11), SEYMOUR JOHN F ET AL: "Bcl-2 Inhibitor ABT-199 (GDC-0199) Monotherapy Shows Anti-Tumor Activity Including Complete Remissions In High-Risk Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)", XP002740729, Database accession no. PREV201400360012 abstract & BLOOD, vol. 122, no. 21, November 2013 (2013-11), page 872, 55TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 07 -10, 2013 ISSN: 0006-4971(print) the whole document -----	1-13, 15-58, 60,61, 63,64, 69-86
Y	ROBERTS ANDREW W ET AL: "Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease.", JOURNAL OF CLINICAL ONCOLOGY : OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY 10 FEB 2012, vol. 30, no. 5, 10 February 2012 (2012-02-10), pages 488-496, XP002740730, ISSN: 1527-7755 abstract page 495, column 1, paragraph 2 -----	1-13, 15-58, 60,61, 63,64, 69-86

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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.
X	J. SCHWAMB ET AL: "B-cell receptor triggers drug sensitivity of primary CLL cells by controlling glucosylation of ceramides", BLOOD, vol. 120, no. 19, 8 November 2012 (2012-11-08), pages 3978-3985, XP055218383, US ISSN: 0006-4971, DOI: 10.1182/blood-2012-05-431783 the whole document	58,60, 61,64, 68-71, 82,85,86
X	J. QIAN ET AL: "Synergy between phosphatidylinositol 3-kinase/Akt pathway and Bcl-xL in the control of apoptosis in adenocarcinoma cells of the lung", MOLECULAR CANCER THERAPEUTICS, vol. 8, no. 1, 1 January 2009 (2009-01-01) , pages 101-109, XP055218643, US ISSN: 1535-7163, DOI: 10.1158/1535-7163.MCT-08-0973 abstract page 103, column 2, paragraph 2 page 106	58,60, 61,64, 68,85,86
Y	TARU MURANEN ET AL: "Inhibition of PI3K/mTOR Leads to Adaptive Resistance in Matrix-Attached Cancer Cells", CANCER CELL, CELL PRESS, US, vol. 21, no. 2, 20 December 2011 (2011-12-20), pages 227-239, XP028456386, ISSN: 1535-6108, DOI: 10.1016/J.CCR.2011.12.024 [retrieved on 2012-01-04] the whole document	1-13, 15-58, 60,61, 63,64, 69-86
Y	ALice Goodman: "Encouraging Early Results With Novel Agents in CLL", ASCO Post , 1 March 2014 (2014-03-01), XP002745555, Retrieved from the Internet: URL:http://www.ascopost.com/issues/march-1 ,-2014/encouraging-early-results-with-nove l-agents-in-cll.aspx [retrieved on 2015-10-06] the whole document	1-13, 15-58, 60,61, 63,64, 69-86

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/026008

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	MORRISON CHRIS: "First PI3k inhibitor launches into crowded hematology markets.", NATURE BIOTECHNOLOGY OCT 2014, vol. 32, no. 10, October 2014 (2014-10), pages 963-964, XP002745556, ISSN: 1546-1696 the whole document	1-13, 15-58, 60,61, 63,64, 69-86
X,P	CHOUDHARY G S ET AL: "MCL-1 and BCL-xL-dependent resistance to the BCL-2 inhibitor ABT-199 can be overcome by preventing PI3K/AKT/mTOR activation in lymphoid malignancies.", CELL DEATH & DISEASE 2015, vol. 6, E1593, 2015, pages 1-12, XP002745557, ISSN: 2041-4889 the whole document	58,60, 61,64, 68-71, 82,85,86
X,P	YANG CAO ET AL.: "The BCL2 antagonist ABT-199 triggers apoptosis, and augments ibrutinib and idelalisib mediated cytotoxicity in CXCR4Wild-type and CXCR4WHIM mutated Waldenstrom macroglobulinaemia cells", BRISTISH JOURNAL OF HAEMATOLOGY, vol. 170, 12 January 2015 (2015-01-12), pages 134-138, XP002745558, the whole document	58,60, 61,64, 68-71, 82,85,86
X,P	VACHHANI PANKIT ET AL: "Rational combination of dual PI3K/mTOR blockade and Bcl-2/-xL inhibition in AML.", PHYSIOLOGICAL GENOMICS 1 JUL 2014, vol. 46, no. 13, 1 July 2014 (2014-07-01), pages 448-456, XP002745559, ISSN: 1531-2267 the whole document	1-13, 15-58, 60,61, 63,64, 69-86
X,P	WO 2014/071109 A1 (INFINITY PHARMACEUTICALS INC [US]) 8 May 2014 (2014-05-08) page 3, paragraph 13 page 90, paragraph 335 page 137, paragraph 511 page 151, paragraph 573 - page 152 page 195; compound 292 claims 48-49	1-13, 15-58, 60,61, 63,64, 68-86

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.:

13, 54-58(completely); 1-12, 15-53, 60, 61, 63, 64, 68-86(partially)

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: 13, 54-57(completely); 1-12, 15-53, 63, 64, 69-86(partially)

   (S)-3-(1-((9H-purin-6-yl)amino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one (IPI-145) in combination with a Bcl-2 inhibitor together with its use in the treatment of cancer

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2. claims: 14(completely); 1-12, 15-53, 63, 64, 69-86(partially)

   (S)-2-(1-(9H-purin-6-ylamino)propyl)-5-fluoro-3-phenylquinazolin-4(3H)-one (GS1101 or Idelalisib) in combination with a Bcl-2 inhibitor together with its use in the treatment of cancer

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3. claims: 58, 60, 61, 64, 68-86(all partially)

   The PI3K inhibitor IPI-145 followed by a combination of the PI3K inhibitor IPI-145 with a Bcl-2 inhibitor for use in a method of reducing the likelihood for a subject to develop resistance to the PI3K inhibitor IPI-145 treatment

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4. claims: 59, 62, 65(completely); 60, 61, 64, 68-86(partially)

   a PI3K inhibitor in combination with a Bcl-2 inhibitor for use in delaying or decreasing resistance of a subject having a cancer, for reducing the level of minimal residual disease (MRD) compared to a reference value in a subject having a cancer or for treating cancer

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5. claims: 66, 87(completely); 68-86(partially)

   a method of evaluating the responsiveness of a cancer or tumor, or a subject having a cancer or tumor, to a treatment that includes a PI3K inhibitor

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6. claims: 67(completely); 68-86(partially)

   a method of monitoring a subject receiving a treatment that includes a PI3K inhibitor

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7. claims: 58, 60, 61, 64, 68-86(all partially)

   A PI3K inhibitor (as selected from the 39 PI3K inhibitors as defined on page 10, paragraph [0042]) followed by a combination of said PI3K inhibitor with a Bcl-2 inhibitor for use in a method of reducing the likelihood for a subject

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

to develop resistance to this PI3K inhibitor : this additional invention is in itself non-unitary and comprises 39 sub-inventions, see WO-ISA)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/026008

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012184568 A1	19-07-2012	AR 084824 A1	26-06-2013
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