INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15112968
	Filing Date	2016-07-20
	First Named Inventor	Hamdy AHMED
	Art Unit	1618
	Examiner Name	Micah Paul Young
	Attorney Docket Number	055112-5004-US

	31	Byrd et al., "Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia", N Engl J Med, Vol. 374, No. 5, pp. 323-332 (2016)	
	32	International Search Report for PCT/IB2015/000645, dated August 31, 2015	
	33	Written Opinion for PCT/IB2015/000645	
	34	International Search Report for PCT/IB2015/002140, dated February 28, 2016	
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CERTIFICATION STATEMENT

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That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Deping Chai/	Date (YYYY-MM-DD)	2017-08-02
Name/Print	Deping Chai	Registration Number	63187

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Application Number:	15112968
International Application Number:	
Confirmation Number:	1000
Title of Invention:	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor
First Named Inventor/Applicant Name:	Hamdy Ahmed
Customer Number:	28977
Filer:	Deping Chai
Filer Authorized By:	
Attorney Docket Number:	055112-5004-US
Receipt Date:	03-AUG-2017
Filing Date:	20-JUL-2016
Time Stamp:	14:50:50
Application Type:	U.S. National Stage under 35 USC 371

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First Named Inventor	Hamdy AHMED
Art Unit	1618
Examiner Name	Micah Paul Young
Attorney Docket Number	055112-5004-US

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	1	7459554		2008-12-02	Dong et al.	
	2	7825118		2010-11-02	Honigberg et al.	
	3	7960396		2011-06-14	Honigberg et al.	
	4	8377946		2013-02-19	Chen et al.	
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	1	20060084654		2006-04-20	Beck et al.	
	2	20080076921		2008-03-27	Honigberg et al.	
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	5	20120095026		2012-04-19	Honigberg et al.	
	6	20120129821		2012-05-24	Honigberg et al.	
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	12	20140206681		2014-07-24	Kim et al.			
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	2	2010126960	WO		2010-11-04	Locus Pharmaceuticals, Inc.		
	3	2011095556	WO		2011-08-11	Organon NV		
	4	2548877	EP		2013-01-23	MSD Oss B.V.		
	5	2001019828	WO		2001-03-22	BASF Aktiengesellschaft		
	6	2002080926	WO		2002-10-17	Abbott GmbH & Co. KG		
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	8	2005037836	WO		2005-04-28	OSI Pharmaceuticals, Inc.		
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	11	20070648	WO		2007-06-07	Bayer Pharmaceuticals Corp.		
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	14	2009076170	WO		2009-06-18	Novartis AG		
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	19	2013003629	WO		2013-01-03	Pharmacylics, Inc.		
	20	2013010380	WO		2013-01-24	Merck Sharp & Dohme Corp.		
	21	2013010868	WO		2013-01-24	MSD Oss B.V.		
	22	2013010869	WO		2013-01-24	MSD Oss B.V.		
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	24	2014143807	WO		2014-09-18	Stromatt, Scott		
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	30	2015083008	WO	A1	2015-06-11	Acerta Pharma B.V.		

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	1	Berge et al. "Pharmaceutical salts" 66(1) J. Pharm. Sci. 1-19 (1977)	
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	9	Gould "Salt selection for basic drugs" 33 Int'l J. Pharmaceutics 201-217 (1986)	
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	11	Harder et al., "Gain- and Loss-of-Function Lyn Mutant Mice Define a Critical Inhibitory Role for Lyn in the Myeloid Lineage" 15 immunity 603-15 (2001)	
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	18	Lowell et al., "Deficiency of the Hck and Src Tyrosine Kinases Results In Extreme Levels of Extramedullary Hematopoiesis," 87(5) Blood 1780-92 (1996)	
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	20	Mukalyama et al., "Synthesis and c-Src inhibitory activity of imidazo[1,5-a]pyrazine derivatives as an agent for treatment of acute ischemic stroke," 15 Bloom. & Med. Chem. 868-85 (2007).	
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	28	van Tonder et al., "Preparation and Physicochemical Characterization of 5 Niclosamide Solvates and 1 Hemisolvate", 5(1) AAPS PharmSclTech Article 12 (2004)	
	29	Written Opinion mailed 2016-08-10 relating to PCT/IB2016/053988	
	30	International Search Report mailed 2016-08-10 relating to PCT/1B2016/053988	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15112968
	Filing Date	2016-07-20
	First Named Inventor	Hamdy AHMED
	Art Unit	1618
	Examiner Name	Micah Paul Young
	Attorney Docket Number	055112-5004-US

	31	Byrd et al., "Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia", N Engl J Med, Vol. 374, No. 5, pp. 323-332 (2016)	
	32	International Search Report for PCT/IB2015/000645, dated August 31, 2015	
	33	Written Opinion for PCT/IB2015/000645	
	34	International Search Report for PCT/IB2015/002140, dated February 28, 2016	
	35	Written Opinion for PCT/IB2015/002140	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15112968
	Filing Date	2016-07-20
	First Named Inventor	Hamdy AHMED
	Art Unit	1618
	Examiner Name	Micah Paul Young
	Attorney Docket Number	055112-5004-US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Deping Chai/	Date (YYYY-MM-DD)	2017-08-02
Name/Print	Deping Chai	Registration Number	63187

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT COOPERATION TREATY

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WRITTEN OPINION OF THE
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(PCT Rule 43*bis*.1)

Date of mailing
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Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2016/053988	01.07.2016	02.07.2015

International Patent Classification (IPC) or both national classification and IPC
INV. C07D487/04 A61K31/4985 A61P35/00

Applicant
ACERTA PHARMA B.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Sarakinos, Georgios Telephone No. +49 89 2399-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-20
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application relates to a composition comprising a crystalline form of (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base. In addition, processes for the preparation of various crystalline forms of said compound are disclosed as well as the uses in methods of treatment of said crystalline forms.

2. Reference is made to the following document:

D1 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

3. Novelty [Art 33(2) PCT]

(S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base was disclosed in document D1 (Example 6 therein) but no mention of its physical form is made in document D1 or anywhere else in the prior art. Therefore, a composition comprising a crystalline form of (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base is novel and by consequence all claims 1-20 meet the requirements of Novelty [Art 33(2) PCT].

4. Inventive step [Art 33(3) PCT]

(S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base is known from document D1 (Example 6) as a Btk inhibitor for use in the treatment of proliferative and other disorders. The physical form of said compound is not disclosed in document D1 or anywhere else in the prior art for that matter. Starting from document D1 the objective technical problem to be solved by the present application may be viewed as the provision of a form of (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base with improved properties. The applicant provides crystalline (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base of claim 1 as a solution to the objective technical problem. Furthermore, in claims 2-11 the crystalline form relates to the so-called Form I.

In document D1, page 27, lines 1-3, the following is stated: *The 8-amino-imidazo[1,5-a]pyrazine and 4-amino-imidazo[1,5-f][1,2,4]triazine derivatives of the present invention also exist as amorphous forms. Multiple crystalline forms are also possible. All the physical forms are included within the scope of the present invention.* This applies to the compound of Example 6 which is the compound of the present application, namely (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base. Therefore, already in document D1 there is a pointer to the person skilled in the art that crystalline forms of the compounds of document D1 (including the compound of Example 6) exist.

The fact that the Applicant has investigated the crystallization behaviour of said compound and has produced various crystalline forms of it as well as its amorphous form and also crystalline forms of pharmaceutically acceptable salts of said compounds does not involve and inventive step and neither does the determination of the thermodynamically most stable of said crystalline forms. The person skilled in the art interested in coming up with the solid form of a drug-candidate, said solid form being preferable the thermodynamically most stable of all such forms will routinely embark on a research programme that with the aid of automation (i.e. crystallization apparatus) will investigate the formation of crystalline forms of said drug-candidate under a variety of conditions (solvents, antisolvents, concentration, temperature of crystallization, etc). That in the end of such a research programme, one crystalline form is selected as the most suitable one for further development on the basis of its physical properties (its medicinal properties are known already from document D1 in this case and are independent of the crystalline form) is not surprising. There is

therefore nothing surprising for the person skilled in the art starting from document D1 that crystalline forms of (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide free base exist and that among them, one is the most suitable one. Therefore, inventive step is not acknowledged for any of claims 1-20 [Art 33(3) PCT].

5. Method of Treatment

Claims 17-20 relate to subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv) PCT. The patentability can be dependent upon the formulation of the claim. The EPO, for example, does not recognize as patentable claims to the use of a compound in medical treatment, but may allow claims to a product in particular substances or compositions for use in a first or further medical treatment.

Re Item VIII

Certain observations on the international application

The type and source of radiation missing from claims 2-4 is necessary in order to render the claims clear.

Claims 5, 8 and 11 contain the unclear term *substantially* and also refer to Figures. Claim 5, 8 and 11 are thus not clear.

The term *about* in claim 15 is not clear as there is no generally acceptable notion of what *about* means in said context.

PATENT COOPERATION TREATY

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International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2015/000645	21.01.2015	21.01.2014

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/517 A61K31/519 A61K31/52 A61K45/06 A61P35/00 A61P35/02 A61P35/04 A61P43/00

Applicant
ACERTA PHARMA B.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Taylor, Mark Telephone No. +31 70 340-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

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5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Cited Prior Art

D1	WO 2013/010868	D4	WO 2014/130856
D2	WO 2015/083008	D5	WO 2015/057992
D3	WO 2011/153514		

Item V

1 Claims 1-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. Patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

The patentability, in particular novelty and inventive step, of claims 1-22 has thus been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

2 Having regard to the cited prior art the subject-matter of claims 1-22 meets the requirements of Art. 33(2) PCT but not those of Art. 33(3) PCT.

2.1 D1 discloses the use of Btk inhibitors in the treatment of Btk-mediated disorders (abstract). D1 discloses an extensive list of specific Btk inhibitors (page 10, line 19*ff.*; claim 12) of which the compound of present claims 1 and 9 is one example (page 10, line 30; Example 6).

D1 also discloses an extensive list of Btk-mediated disorders, including proliferative disorders (page 22, lines 15-20). Specific examples of these include B cel chronic lymphocytic leukaemia.

In order to arrive at the teachings of present claims 1 and 9, the skilled person must make two independent selections from D1; the subject-matter of present claims 1-22 can therefore be seen as being novel.

2.2 Nevertheless, the selection from D1 of the compound of present claims 1 and 9, and the diseases of present claims 1 and 9, would not appear to involve any inventive merit. Moreover, since the present application does not appear to demonstrate any surprising or unexpected effect arising from this selection, the subject-matter of claims 1 and 9 cannot be seen as meeting the requirements of Art. 33(3) PCT.

The subject-matter of claims 2-8 and 10-22 would appear to represent work of a routine nature to the skilled person and hence also cannot be seen as involving an intentive step.

3 The requirements of Art. 33(3) PCT are furthermore not met because the underlying technical problem is not solved over the whole scope of the claimed subject-matter.

Table 1 of the present description (page 83) shows that the compound of present claims 1 and 9 is inactive against Itk, EGFR, Blk and JAK-3. Since IL-2-inducible T-cell kinase (Itk), Epidermal Growth Factor Receptor (EGFR), B-lymphoid kinase (Blk) and Janus Kinase-3 (JAK-3) are all implicated in cancer, especially haematological cancers and lymphomas, it would appear that the use of the compound of present claims 1 and 9 would not be effective in at least those cancers by which these 3F-Cys kinases are governed.

Moreover, even in the case of the remaining 3F-Cys kinases disclosed in Table 1 against which the compound (II) is active, it would appear to be significantly less active (two orders of magnitude in the case of Bmx, Txk and ErbB2) than Ibrutinib in all examples except that of Tec protein tyrosine kinase (Tec).

Thus, there would only appear to be any plausibly useful effect demonstrated against cancers in which Tec is implicated.

Item VI

4 D2, D4 and D5 are cited under Rules 64.3 and 70.10 PCT.

Item VIII

5 Claims 4, 6, 12 and 20 do not meet the requirements of Art. 6 PCT.

5.1 The subject-matter of claims 4, 6, 12 and 20 is unclear in respect of the following vague and indefinite terms:

'*about*'; '*biosimilars thereof*'.

5.2 Claims 4 and 12 are also unclear because they refer to Formula (II) yet this is not defined in the claims. Although this is defined in the description at page 47, claims should not refer to the description.

5.3 The subject-matter of claims 4 and 12 is furthermore unclear because it attempts to define subject-matter in terms of a result to be achieved, *viz.*

'*wherein the CLL increases monocytes and NK cells in peripheral blood after treatment with Formula (II) from a period ...*'.

PATENT COOPERATION TREATY

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(PCT Rule 43*bis*.1)

Date of mailing
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Applicant's or agent's file reference
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FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2015/002140	17.06.2015	21.01.2015

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4985 A61K31/519 A61K45/06 A61P35/00 A61P35/02 A61P35/04 A61P43/00

Applicant
ACERTA PHARMA B.V.

1. This opinion contains indications relating to the following items:

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For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	Taylor, Mark Telephone No. +31 70 340-0

Form PCT/ISA/237 (Cover Sheet) (January 2015)

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☒ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10-13, 30-32
	No:	Claims	1-9, 14-29
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Cited Prior Art

D1	WO 2013/010868	**D4**	WO 2011/153514
D2	WO 2014/130856	**D5**	WO 2015/057992
D3	WO 2015/083008	**D6**	Byrd *et al.*, *New. Engl. J. Med.* 2015, XP055245199

Item V

1 Claims 1-32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv) / 67.1(iv) PCT. Patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

The patentability, in particular novelty and inventive step, of claims 1-32 has thus been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

2 The subject-matter of claims 1-9 and 14-29 does not meets the requirements of Art. 33(2) PCT.

D1 discloses the use of compounds according to the present claims 1-9 and 14-29 (see, in particular, Examples 1, 3, 6, 35 and 36) in the treatment of Btk-mediated disorders, including the proliferative diseases non-Hodgkin lymphoma, large B-cell lymphoma, mantle cell lymphoma, B cell chronic lymphocytic leukaemia, acute lymphoblastic leukaemia with mature B cell and B cell lymphomas in general (see page 22, lines 15-20).

D2 discloses the use of compounds according to the present claims 1-9 and 14-29 (see, in particular, [0005]-[0011]) in the treatment of proliferative diseases such as Hodgkin and non-Hodgkin lymphoma, chronic lymphocytic leukaemia, large B-cell lymphoma, prolymphocytic leukaemia, Waldenström macroglubulinaemia, myeloma, follicular lymphoma, mantle cell lymphoma and diffuse large B cell lymphoma (see [0053]).

3 The subject-matter of claims 1-32 does not meet the requirements of Art. 33 (3) PCT.

3.1 Not being novel, the subject-matter of claims 1-9 and 14-29 cannot be seen as being inventive.

3.2 The combination of Btk inhibitors according to D1 or D2 with other Btk inhibitors to arrive at a treatment for the same diseases would not appear to involve any inventive merit. The subject-matter of claims 10-13 and 30-32 therefore lacks inventive step.

4 The requirements of Art. 33(3) PCT are furthermore not met because the underlying technical problem is not solved over the whole scope of the claimed subject-matter.

4.1 Table 1 of the present description (page 88) shows that the compounds (II) ot the present application (aka ACP-196 or Acalabrutinib) is inactive against Itk, EGFR, Blk and JAK-3. Since IL-2-inducible T-cell kinase (Itk), Epidermal Growth Factor Receptor (EGFR), B-lymphoid kinase (Blk) and Janus Kinase-3 (JAK-3) are all implicated in cancer, especially haematological cancers and lymphomas, it would appear that the use of the compound of present application would not be effective in at least those cancers by which these 3F-Cys kinases are governed.

Moreover, even in the case of the remaining 3F-Cys kinases disclosed in Table 1 against which the compound (II) is active, it would appear to be significantly less active (two orders of magnitude in the case of Bmx, Txk and ErbB2) than Ibrutinib in all examples except that of Tec protein tyrosine kinase (Tec).

Thus, there would only appear to be any plausibly useful effect demonstrated against cancers in which Tec is implicated.

4.2 The present application provides examples of only one compound (ACP-196, *i.e.* Formula (II)) used alone or in combination with one other Btk inhibitor, namely Ibrutinib. Nevertheless, the claims seek protection for a vast range of compounds, either alone or in combination with another large range of Btk inhibitors.

This does not provide adequate support to demonstrate that the underlying technical problem is solved over the whole scope of the claims, in particular in view of the observations made under §4.1 (above) that ACP-196 is inactive or poorly active against certain lines of 3F-Cys kinases.

Item VI

5 **D3** and **D4** are cited under Rules 64.3 and 70.10 PCT.

Item VIII

6 Claims 9, 11, 12, 22, 30 and 32 do not meet the requirements of Art. 6 PCT.

6.1 The subject-matter of claims 9, 11, 12, 22, 30 and 32 is unclear in respect of the following vague and indefinite terms:

'*about*'; '*biosimilars thereof*'; 'fragments'; derivatives'; 'conjugates'; 'variants'; 'extended-release dipyridamole'; 'low molecular weight'.

6.2 Claims 9 and 22 are also unclear because they refer to Formula (II) yet this is not defined in the claims. Although this is defined in the description at page 52, claims should not refer to the description.

6.3 The subject-matter of claims 9 and 22 is furthermore unclear because it attempts to define subject-matter in terms of a result to be achieved, *viz.*

'*wherein the CLL increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from ...*'.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 055112-5010	**FOR FURTHER ACTION** see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/IB2016/053988	International filing date *(day/month/year)* 1 July 2016 (01-07-2016)	(Earliest) Priority Date *(day/month/year)* 2 July 2015 (02-07-2015)
Applicant ACERTA PHARMA B.V.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. [ ] **Certain claims were found unsearchable** (See Box No. II)
3. [ ] **Unity of invention is lacking** (see Box No III)
4. With regard to the **title,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established by this Authority to read as follows:

   SOLID FORMS AND FORMULATIONS OF
   (S)-4-(8-AMINO-3-(1-(BUT-2-YNOYL)PYRROLIDIN-2-YL)IMIDAZO[1,5-A]PYRAZIN-1-YL)-N-(
   PYRIDIN-2-YL)BENZAMIDE

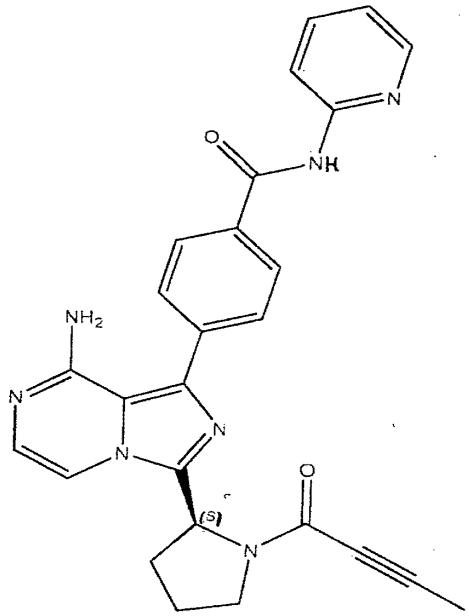
5. With regard to the **abstract,**
   [ ] the text is approved as submitted by the applicant
   [X] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority
6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      [X] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

Form PCT/ISA/210 (first sheet) (January 2015)

Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

ABSTRACT

[00363] In some embodiments, the invention relates to crystalline solid forms, including polymorphs, hydrates, and salt forms, of (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide. In some embodiments, the invention also relates to pharmaceutical compositions containing the crystalline solid forms, and methods for treating conditions or disorders by administering to a subject a pharmaceutical composition that includes the forms, including pharmaceutical compositions and methods for overcoming the effects of acid reducing agents.



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/053988

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04 A61K31/4985 A61P35/00
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)
C07D 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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	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 page 21, line 19 - page 22, line 20 page 27, line 1 - page 27, line 3 example 6 example 134 -----	1-20

☐ 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	Date of mailing of the international search report
28 July 2016	10/08/2016

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	Sarakinos, Georgios

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/053988

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
		AU 2016203837 A1	30-06-2016
		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
		NZ 620085 A	27-05-2016
		PE 16812014 A1	14-11-2014
		US 2014155385 A1	05-06-2014
		US 2016151364 A1	02-06-2016
		US 2016159810 A1	09-06-2016
		WO 2013010868 A1	24-01-2013

Form PCT/ISA/210 (patent family annex) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/000645

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/517 A61K31/519 A61K31/52 A61K45/06 A61P35/00
A61P35/02 A61P35/04 A61P43/00
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, WPI Data, CHEM ABS Data, MEDLINE, 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	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 abstract page 1, line 6 - line 9 page 2, line 35 - page 4, line 28 page 21, line 5 - line 24 page 22, line 15 - line 20 example 6 page 105, line 12 - line 13 claims 13-17 -----	1-22
E	WO 2015/083008 A1 (ACERTA PHARMA B V [NL]) 11 June 2015 (2015-06-11) abstract claims 1-38 -----	1-22

-/--

[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
19 August 2015	31/08/2015

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	Taylor, Mark

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/000645

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 2011/153514 A2 (PHARMACYCLICS INC [US]; BUGGY JOSEPH J [US]; ELIAS LAURENCE [US]; FYFE) 8 December 2011 (2011-12-08) abstract paragraph [0004] - paragraph [0006] paragraph [0309] paragraph [0322] - paragraph [0323] claims 46-48, 82-84, 117 -----	1-22
A,P	WO 2014/130856 A2 (ROTHBAUM WAYNE [US]; BEGLEY GLENN [US]) 28 August 2014 (2014-08-28) paragraph [0053] - paragraph [0054] abstract paragraph [0011] claims 1-34 -----	1-22
E	WO 2015/057992 A1 (IZUMI RAQUEL [US]; SALVA FRANCISCO [US]; HAMDY AHMED [US]) 23 April 2015 (2015-04-23) abstract claims 1-22 -----	1-22

1

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/000645

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 2014520870 A	25-08-2014
		KR 20140036324 A	25-03-2014
		MA 35348 B1	01-08-2014
		PE 16812014 A1	14-11-2014
		US 2014155385 A1	05-06-2014
		WO 2013010868 A1	24-01-2013
WO 2015083008 A1	11-06-2015	NONE	
WO 2011153514 A2	08-12-2011	AU 2011261185 A1	10-01-2013
		CA 2800913 A1	08-12-2011
		CL 2012003381 A1	22-03-2013
		CN 103153311 A	12-06-2013
		EA 201270793 A2	30-08-2013
		EP 2575818 A2	10-04-2013
		JP 2013527249 A	27-06-2013
		KR 20130086957 A	05-08-2013
		NZ 604040 A	27-02-2015
		SG 186077 A1	30-01-2013
		US 2012087915 A1	12-04-2012
		US 2012100138 A1	26-04-2012
		US 2012183535 A1	19-07-2012
		US 2013195852 A1	01-08-2013
		US 2013202611 A1	08-08-2013
		US 2013273030 A1	17-10-2013
		US 2013310402 A1	21-11-2013
		US 2014194446 A1	10-07-2014
		US 2015031710 A1	29-01-2015
		US 2015031711 A1	29-01-2015
		WO 2011153514 A2	08-12-2011
WO 2014130856 A2	28-08-2014	US 2014357636 A1	04-12-2014
		WO 2014130856 A2	28-08-2014
WO 2015057992 A1	23-04-2015	NONE	

Form PCT/ISA/210 (patent family annex) (April 2005)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference A16376-WO/NH	**FOR FURTHER ACTION** see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/IB2015/002140	International filing date *(day/month/year)* 17 June 2015 (17-06-2015)	(Earliest) Priority Date *(day/month/year)* 21 January 2015 (21-01-2015)
Applicant ACERTA PHARMA B.V.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [X] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.
2. [ ] **Certain claims were found unsearchable** (See Box No. II)
3. [ ] **Unity of invention is lacking** (see Box No III)
4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:
5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority
6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

Form PCT/ISA/210 (first sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/002140

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, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [X] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of 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/IB2015/002140

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4985 A61K31/519 A61K45/06 A61P35/00 A61P35/02
A61P35/04 A61P43/00
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, WPI Data, CHEM ABS Data, MEDLINE, 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	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 abstract page 1, line 6 - line 9 page 2, line 35 - page 4, line 28 page 21, line 5 - line 24 page 22, line 15 - line 20 examples 1,3,6,35,36 claims 1-17 ----- -/--	1-32

[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
28 January 2016	03/02/2016
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 Taylor, Mark

2

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/002140

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 2014/130856 A2 (ROTHBAUM WAYNE [US]; BEGLEY GLENN [US]) 28 August 2014 (2014-08-28) paragraph [0053] - paragraph [0054] abstract paragraph [0011] claims 1-34 -----	1-32
X,P	WO 2015/083008 A1 (ACERTA PHARMA B V [NL]) 11 June 2015 (2015-06-11) abstract paragraph [0011] - paragraph [0031] claims 1-38 -----	1-32
X,P	WO 2015/057992 A1 (IZUMI RAQUEL [US]; SALVA FRANCISCO [US]; HAMDY AHMED [US]) 23 April 2015 (2015-04-23) abstract claims 1-23 paragraph [0005] - paragraph [0023] Table A, compounds 1, 3, 6, 35, 36 and 127 claims 1-79 -----	1-32
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2

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/002140

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Form PCT/ISA/210 (patent family annex) (April 2005)

Electronic Acknowledgement Receipt

EFS ID:	29957660
Application Number:	15112968
International Application Number:	
Confirmation Number:	1000
Title of Invention:	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor
First Named Inventor/Applicant Name:	Hamdy Ahmed
Customer Number:	28977
Filer:	Deping Chai
Filer Authorized By:	
Attorney Docket Number:	055112-5004-US
Receipt Date:	03-AUG-2017
Filing Date:	20-JUL-2016
Time Stamp:	14:48:07
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	0551125004US_IDS.pdf	1039034 6b27f389c7e1c2e58599fde0315888e7c109ac57	no	11

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Electronic Patent Application Fee Transmittal

Application Number:	15112968
Filing Date:	20-Jul-2016
Title of Invention:	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor
First Named Inventor/Applicant Name:	Hamdy Ahmed
Filer:	Deping Chai
Attorney Docket Number:	055112-5004-US

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	30011823
Application Number:	15112968
International Application Number:	
Confirmation Number:	1000
Title of Invention:	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor
First Named Inventor/Applicant Name:	Hamdy Ahmed
Customer Number:	28977
Filer:	Deping Chai
Filer Authorized By:	
Attorney Docket Number:	055112-5004-US
Receipt Date:	08-AUG-2017
Filing Date:	20-JUL-2016
Time Stamp:	09:58:28
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$180
RAM confirmation Number	080817INTEFSW00008987500310
Deposit Account	
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
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Warnings:

Information:

Total Files Size (in bytes):	30336

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Attorney Docket 055112-5004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: A. Hamdy et al.	:	
	:	Confirmation No. 1000
Application No. 15/112,968	:	
	:	Art Unit: 1618
For: Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	:	Examiner: M. Young

AMENDMENT UNDER 37 C.F.R. 1.111

In response to the Office Action dated July 25, 2017 please consider the following amendments and remarks. Applicants hereby petition for a three month extension of time by payment of the accompanying fee.

Amendments to the Claims begin on page 2 of this paper.

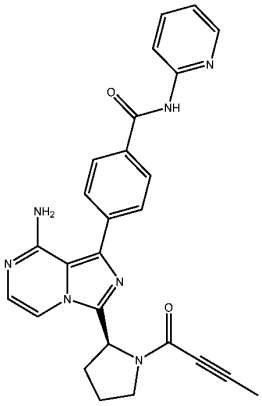
Remarks begin on page 7 of this paper.

DB1/ 94862280.1

Amendments to the claims

Please amend the claims as follows:

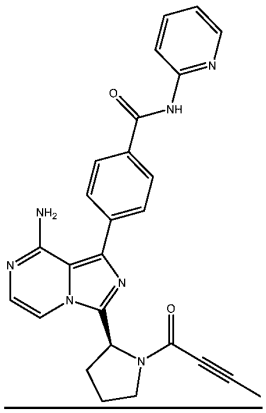
1. (Currently amended) A method of treating chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) in a human subject suffering therefrom, comprising the step of orally administering, to ~~a~~ the human ~~in need thereof~~ subject, ~~the~~ a dose of 100 mg twice daily of a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

2. (Currently amended) The method of claim 1, wherein the BTK inhibitor is a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

3. (Canceled)

4. (Currently amended) The method of Claim ~~1~~ 2, wherein ~~the CLL increases monocytes and NK cells in peripheral blood after treatment with Formula (II)~~ the BTK inhibitor is administered to the human subject for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days.

5. (Currently amended) The method of Claim ~~1~~ 2, wherein the CLL is selected from the group consisting of IgV_H mutation negative CLL, ZAP-70 positive CLL, ZAP-70 methylated at CpG3 CLL, CD38 positive CLL, CLL with a 17p13.1 (17p) deletion, CLL with a 11q22.3 (11q) deletion, CLL in a human sensitive to platelet-mediated thrombosis, CLL in a human presently suffering from platelet-mediated thrombosis, CLL in a human previously suffering from platelet-mediated thrombosis, and combinations thereof.

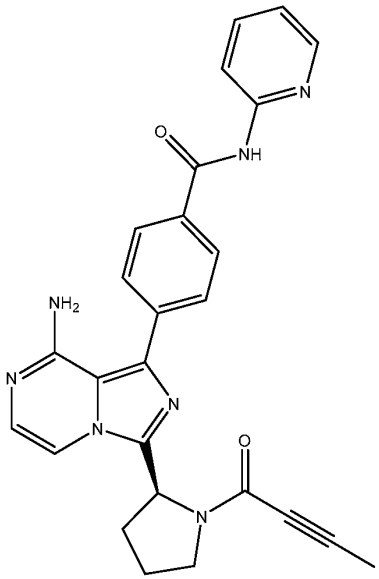
6. (Original) The method of Claim 1, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

7. (Currently amended) The method of Claim ~~1 or Claim 6~~ 2, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

8. (Original) The method of Claim 7, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium,

ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

9. (Currently amended) A method of treating a ~~hematological malignancy~~ mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject, a ~~therapeutically effective dose~~ dose of 100 mg twice daily of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II):



or a pharmaceutically-acceptable salt, hydrate, or solvate thereof~~, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, and myelofibrosis~~.

10. (Cancelled)

11. (Cancelled)

12. (Currently amended) The method of Claim 9, wherein the ~~hematological malignancy~~ Mantle Cell Lymphoma (MCL) increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days.

13. (Cancelled)

14. (Cancelled)

15. (Original) The method of Claim 9, wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.

16. (Cancelled)

17. (Cancelled)

18. (Cancelled)

19. (Cancelled)

20. (Original) The method of Claim 9, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

21. (Previously presented) The method of Claim 9, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

22. (Original) The method of Claim 21, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

23. (New) The method of Claim 2, the method comprising treating chronic lymphocytic leukemia

(CLL) in a human subject suffering from CLL.

24. (New) The method of Claim 3, the method comprising treating small lymphocytic leukemia (SLL) in a human subject suffering from SLL.

25. (New) The method of Claim 1, wherein the free form of the compound of Formula (II) is administered to the human subject.

26. (New) The method of Claim 1, wherein the pharmaceutically acceptable salt of the compound of Formula (II) is administered to the human subject.

27. (New) The method of Claim 9, wherein the free form of the compound of Formula (II) is administered to the human subject.

28. (New) The method of Claim 9, wherein the pharmaceutically acceptable salt of the compound of Formula (II) is administered to the human subject.

REMARKS

I. Status of the Claims

Claims 1-22 are pending. The Office has rejected Claims 1-22. Without acquiescing to the merits of the rejection, Applicant has amended or cancelled certain claims. Specifically, the present response: (a) cancels Claims 3, 10-11, 13-14 & 16-19; (b) amends Claims 1-2, 4-5, 7 & 9; and (c) adds new Claims 23-28.

II. FDA Approval of CALQUENCE® (Acalabrutinib)

On October 31, 2017, the U.S. Food and Drug Administration (FDA) approved the drug product CALQUENCE® for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. The compound of Formula (II) as specified in independent Claims 1 and 9 is the active ingredient in CALQUENCE® and is also known by the International Nonproprietary Name (IAN) of acalabrutinib. In accordance with its duty of disclosure to the Office, Applicant is submitting with the present response a Supplemental Information Disclosure Statement providing the Office with the approved label for the CALQUENCE® as Citation No. 1 in the Non-Patent Literature Section.

The approved label for CALQUENCE® contains further information on acalabrutinib including dosing, clinical pharmacology, and clinical studies. Among the statements in the approved label are those in the following excerpt from the "Highlights of Prescribing Information":

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CALQUENCE safely and effectively. See full prescribing information for CALQUENCE.

CALQUENCE® (acalabrutinib) capsules, for oral use
Initial U.S. Approval: 2017

---------- **INDICATIONS AND USAGE** ----------

CALQUENCE is a kinase inhibitor indicated for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. (1)

This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1, 14)

---------- **DOSAGE AND ADMINISTRATION** ----------

- Recommended dose is 100 mg orally approximately every twelve hours; swallow whole with water and with or without food. (2.1)
- Advise patients not to break, open, or chew capsules. (2.1)
- Manage toxicities using treatment interruption, dose reduction, or discontinuation. (2.2)

---------- **DOSAGE FORMS AND STRENGTHS** ----------

Capsules: 100 mg. (3)

As discussed further below, amended independent Claim 9 now specifies a method of treating mantle cell lymphoma (MCL) in a human subject by orally administering 100 mg of acalabrutinib twice daily to the subject (i.e., the dosing regimen specified in the approved label for CALQUENCE®). In addition, amended independent Claim 1 now specifies a method of treating chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) in a human subject by orally administering 100 mg of acalabrutinib twice daily to the subject. Clinical studies involving this dosing regimen for the treatment of chronic lymphocytic leukemia (CLL) are ongoing with positive clinical results as discussed further below.

III. Claim Amendments

Claim 1 has been amended to incorporate the 100 mg BID dosing regimen specified in Claim 3. Additional written support for the amendments to Claim 1 can be found throughout the specification as filed, including paragraph [008] which provides:

> **[008]** In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the BTK inhibitor is administered twice daily at a dose of 100 mg.

Claim 2 has been amended to further specify that the BTK inhibitor is a compound of Formula II (i.e., the free form of acalabrutinib) or a pharmaceutically acceptable salt thereof.

Claim 3 has been canceled in view of the amendments to Claim 1.

Claim 4 has been amended to further clarify the Markush language.

Claim 9 has been amended to further specify that the hematological malignancy is mantle cell lymphoma and to incorporate the 100 mg BID dosing originally specified in dependent Claim 11. Additional written support for the amendments to Claim 9 can be found throughout the specification as filed, including paragraphs [0016] and [0020] which provide:

> **[0016]** In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenstrom's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, wherein the BTK inhibitor is administered twice daily at a dose of 100 mg.
>
> * * *
>
> **[0020]** In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (S)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-a]pyrazin-1-yl)-N-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is mantle cell lymphoma (MCL), wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.

New Claim 23 depends from Claim 2 and further specifies the treatment of chronic lymphocytic leukemia.

New Claim 24 depends from Claim 2 and further specifies the treatment of small lymphocytic leukemia.

New Claims 25 and 27 depend from Claims 2 and 9 respectively, and further specify that the BTK inhibitor is a compound of Formula II (i.e., the free form of acalabrutinib).

New Claims 26 and 28 depend from Claims 2 and 9 respectively, and further specifies that the BTK inhibitor is a pharmaceutically acceptable salt of the compound of Formula II.

Applicants submit that no new matter has been added by way of this Amendment.

IV. <u>Rejection under 35 U.S.C. §103</u>

The Office rejected all claims under 35 U.S.C. §103 as allegedly being obvious over US2013/0338172 (the "'172 application") in view of WO2013/010868 (the "'868 application"). Specifically, the Office alleged:

> The 172 discloses a method of treating various conditions including cancers like lymphoma [abstract]. The disorders include inflammatory and autoimmune disorders [0192-0203]. The compounds are BTK inhibitors similar to those recited in the instant claims a formula

(II) [0302]. The BTK inhibitor is useful in treating chronic lymphocytic leukemia including ZAP 70+ CLL [0262]. The formulation is oral and can be administered with an additional compounds such as rituximab and anagrelide [0509, 0520]. The formulation can be used to treat various disorders such as NHL, DLBCL-ABC, Burkitt's lymphoma, multiple myeloma, MCL such as mantel zone, and pre-B cell B-ALL [0236-0237, 0242-0246, 0251, 0283, and 0295]. The dosage form is delivered orally at a concentration from 300 to 1000 mg per day as much as 2 to 4 times a day [0486-0489 and 0496].

While the formulation of the 172 discloses a BTK inhibitor useful in methods of treating various disorders including various cancers. The compound is similar to the compound of the instant claims and is used to treat similar disorders. The use of similar compounds for the treatment of various using BTK inhibitors is known in the art as seen in the 868 patent.

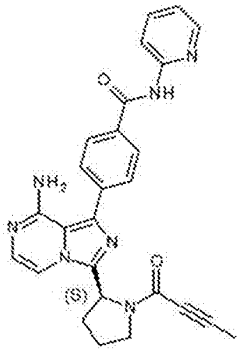
The 868 patent discloses a BTK inhibitor compounds useful in treating various inflammatory conditions including cancers including lymphomas [abstract, page 2]. The compound of example 1 is identical to that of the instant claimed formula (II). [Example 1]. The compounds are similar in that they have the same core structures and are useful in treating the same cancers in similar forms. It would have been obvious to include the compound of the 868 into the formulation of the 172 as the compound have the same cores and treat the same conditions.

With these aspects in mind it would have been obvious to combine the prior art in order to provide a method of treating a variety of cancer conditions with a BTK inhibitor. It would have been obvious to combine the specific compound of the 868 into the method of treatment of the 172 in order to treat a variety of cancer conditions with an oral multiple day formulation.

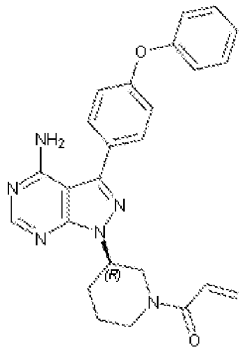
As an initial matter, the compound of Formula (II) specified in the pending claims is not identical to the compound of Example 1 of the '868 application. Applicant notes for the record, however, that the compound of Formula (II) is disclosed as Example 6 on page 30 of the '868 application.

Applicant also does not agree that the compound disclosed in the '172 application and the compounds disclosed in the '868 application have the same core or are similar compounds. Although the compounds have activity as BTK inhibitors, they are not structurally similar and, therefore, have distinct pharmacological properties. The compound disclosed in the '172 application has a phenyl ether group, a pyrazolopyrimidine group, a piperidine group and an acrylate group. The compound in the '868 application has a 2-N-benzoylpyridine group, an imadazopyrazine group, a pyrrolidine group and a propiolate group. These differences in structure are apparent from a comparison of the structures of the

compound disclosed in the '172 application and the compound of Example 6 disclosed in the '868 application (i.e., the compound of Formula (II) of the pending claims):



'172 Application Compound



'868 Application Compound.

Further, although the Office comments that the '172 application discloses that "[t]he dosage form is delivered orally at a concentration from 300 to 1000 mg per day as much as 2 to 4 times a day" the Examiner fails to consider the entirety of the relevant prior art. The '172 application primarily focuses on crystalline forms of the disclosed compound and only incidentally comments on dosing regimens for that compound. The compound of the '172 application is known by the International Nonproprietary Name of ibrutinib and is the active ingredient in the drug product IMBRUVICA® (which was first approved by FDA in 2013). As of the priority date of the pending application (January 21, 2014), IMBRUVICA® was conditionally approved for the treatment of mantle cell lymphoma in non-responsive or refractory patients. As of the convention year filing date of the pending application (January 21, 2015), IMBRUVICA® was approved for both the treatment of mantle cell lymphoma and the treatment of chronic lymphocytic leukemia. The approved dosing regimens are reflected in the following excerpts from the "Highlights of Prescribing Information" from the November 13, 2013 approved label for IMBRUVICA®:

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMBRUVICA safely and effectively. See full prescribing information for IMBRUVICA.

IMBRUVICA™ (ibrutinib) capsules, for oral use

Initial U.S. Approval: 2013

----------INDICATIONS AND USAGE----------

IMBRUVICA is a kinase inhibitor indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy (1).

This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established (14.1).

----------DOSAGE AND ADMINISTRATION----------

560 mg taken orally once daily (four 140 mg capsules once daily) (2.2).

Capsules should be taken orally with a glass of water. Do not open, break, or chew the capsules (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

Capsule: 140 mg (3)

and the February 12, 2014 approved label for IMBRUVICA®:

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use IMBRUVICA safely and effectively. See full prescribing information for IMBRUVICA.

IMBRUVICA™ (ibrutinib) capsules, for oral use

Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2)	1/14
Dosage and Administration (2.2, 2.3)	1/14
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, and 5.5)	1/14

----------INDICATIONS AND USAGE----------

IMBRUVICA is a kinase inhibitor indicated for the treatment of patients with:

- Mantle cell lymphoma (MCL) who have received at least one prior therapy (1.1).
- Chronic lymphocytic leukemia (CLL) who have received at least one prior therapy (1.2).

These indications are based on overall response rate. Improvements in survival or disease-related symptoms have not been established (14.1, 14.2).

----------DOSAGE AND ADMINISTRATION----------

MCL: 560 mg taken orally once daily (four 140 mg capsules once daily) (2.2).

CLL: 420 mg taken orally once daily (three 140 mg capsules once daily) (2.2).

Capsules should be taken orally with a glass of water. Do not open, break, or chew the capsules (2.1).

----------DOSAGE FORMS AND STRENGTHS----------

Capsule: 140 mg (3)

These labels collectively reflect the understanding in the medical community that relatively large, once daily dosing of IMBRUVICA® is required for treatment of both mantle cell lymphoma (560 mg once daily) and chronic lymphocytic leukemia (420 mg once daily). Complete copies of the two IMBRUVICA® labels referenced above have been included with the Supplementary Information Disclosure Statement as Citations No. 2 and 3 in the Non-Patent Literature Section.

As previously noted, amended independent Claim 1 now specifies a method of treating chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) in a human subject by orally administering 100 mg of acalabrutinib twice daily to the subject and amended independent Claim 9 now specifies a method of treating mantle cell lymphoma (MCL) in a human subject by orally administering

100 mg of acalabrutinib twice daily to the subject. Given the materially different structures of ibrutinib and acalabrutinib, and the recognized dosing regimen required for IMBRUVICA®, the '172 application does not teach or suggest the claimed lower dose, twice daily dosing regimen for acalabrutinib. Further, the '868 application does not provide the missing teaching or suggestion, either alone or in combination with the '172 application. The '868 application simply reports the following information on dosing the compounds of that application (see page 20):

> In general parenteral administration requires lower dosages than other methods of administration which are more dependent upon absorption. However, a dosage for humans preferably contains 0.0001-25 mg per kg body weight. The desired dose may be presented as one dose or as multiple subdoses administered at appropriate intervals throughout the day, or, in case of female recipients, as doses to be administered at appropriate daily intervals throughout the menstrual cycle. The dosage as well as the regimen of administration may differ between a female and a male recipient.

Accordingly, the specific 100 mg acalabrutinib BID dosing regimen for the treatment of chronic lymphocytic leukemia, small lymphocytic leukemia, or mantle cell lymphoma as provided in the pending claims is neither taught nor suggested by the '172 application in view of the '868 application. Further, one of skill in the art would not have had a reasonable expectation of success that such a dosing regimen would provide a safe, efficacious treatment for those conditions, particularly in view of the difference in compound structures and the larger dose, once daily treatment for IMBRUVICA® approved by the FDA.

Example 2 of the pending application further illustrates the material difference in the pharmacodynamic properties of acalabrutinib and ibrutinib, particularly with respect to the target occupancy of the target BTK enzyme. Example 2 describes a clinical study of the use of acalabrutinb to treat chronic lymphocytic leukemia and small lymphocytic leukemia and reports the following regarding the measured BTK occupancy:

> **[00318]** BTK target occupany was measured for relapsed/refractory CLL patients with the results shown in FIG. 8. For 200 mg QD dosing of the BTK inhibitor of Formula (II), approximately 94% - 99% BTK occupancy was observed, with superior 24 hour coverage and less inter-patient variability also observed. For 420 mg and 840 mg QD of the BTK inhibitor ibrutinib, 80% - 90% BTK occupancy was observed, with more inter-patient variability and capped occupancy. These results indicate that the BTK inhibitor of Formula (II) achieves superior BTK occupancy in CLL patients than ibrutinib.

These results show that acalabrutinib provides greater BTK occupancy, superior 24-hour coverage, and less inter-patient variability at a significantly lower dose (200mg QD) than ibrutinib (420mg and 840 QD) in patients being treated for chronic lymphocytic leukemia.

A clinical study published in the New England Journal of Medicine further supports the uniqueness of the claimed acalabrutinib 100 mg BID dosing regimen:

> In this uncontrolled, phase 1–2, multicenter study, we administered oral acalabrutinib to 61 patients who had relapsed CLL to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of acalabrutinib. Patients were treated with acalabrutinib at a dose of 100 to 400 mg once daily in the dose-escalation (phase 1) portion of the study and 100 mg twice daily in the expansion (phase 2) portion.
>
> * * *
>
> . . . Patients were successively enrolled in cohorts that were to receive oral acalabrutinib at a dose of 100 mg, 175 mg, 250 mg, or 400 mg once daily as part of the dose-escalation (phase 1) portion of the study or 100 mg twice daily as part of the expansion (phase 2) portion. BTK) by acalabrutinib was measured in peripheral-blood mononuclear cells with the aid of a biotin-tagged analogue probe at baseline, 4 hours after administration of acalabrutinib on days 1, 8, and 28, and before administration of acalabrutinib on days 2, 8, and 28 . . .
>
> * * *
>
> . . . Starting with the dose of 100 mg once daily, BTK occupancy was complete (99 to 100%) 4 hours after dosing and ranged from 87 to 95% before dose administration with once-daily dosing. Because acalabrutinib has no plasma accumulation, we explored the feasibility and safety of a dosing regimen of 100 mg twice daily. Figure 1C shows improved BTK occupancy of 99% 4 hours after dose administration and 97% before dose administration on days 8 and 28 . . .
>
> * * *
>
> . . . The short half-life and selective properties of acalabrutinib allow twice-daily dosing with virtually complete and continuous BTK inhibition without increased toxic effects. Thus far, twice-daily dosing of ibrutinib has not been pursued and may not be possible owing to the potential for drug accumulation given the ibrutinib half-life of 4 to 13 hours.

Byrd et al. (2016) Acabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia, N. Engl. J. Med. 374, pp. 323-332. A copy of this article is attached to the present response and also included with the Supplementary Information Disclosure Statement as Citation No. 4 in the Non-Patent Literature Section.

Accordingly, the '172 application does not, either alone or in combination with the '868 application, render obvious the presently claimed methods of treatment which specify an acalabrutinib dosing regimen of 100 mg BID. The medical community recognizes that effective treatment of chronic lymphocytic leukemia and mantle cell lymphoma with ibrutinib requires a large, once daily dose of Ibrutinib (420 mg once daily and 580 mg once daily, respectively). It was unexpected that acalabrutinib could be orally administered twice daily at a significantly lower dose (100 mg BID) than ibrutinib and provide continuous and improved BTK target occupancy (greater than 95% over a period of 24 hours) relative to ibrutinib, particularly since acalabrutinib has limited or no plasma accumulation at lower doses. One skilled in the art when considering the '172 application would not have expected the lower amount BID dosing of acalabrutinib to be sufficient to provide for full BTK occupancy by acalabrutinib over the selected dosing period. The '868 application does not specifically address BTK target occupancy over time and thus does not cure the deficiencies of the '172 application.

In view of the claim amendments and above remarks, Applicant submits that the rejection is overcome and requests that the rejection be withdrawn.

Conclusion

In view of the foregoing, Applicant requests reconsideration and the timely allowance of the pending claims. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the Applicant's undersigned representative to expedite prosecution.

Respectfully submitted,

/robert smyth/

Dated: Jan. 25, 2018

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15112968
Filing Date	2016-07-20
First Named Inventor	A. Hamdy
Art Unit	1618
Examiner Name	M. Young
Attorney Docket Number	055112-5004

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)	Application Number	15112968
	Filing Date	2016-07-20
	First Named Inventor	A. Hamdy
	Art Unit	1618
	Examiner Name	M. Young
	Attorney Docket Number	055112-5004

	1	CALQUENCE Prescribing Information dated October 2017	
	2	IMBRUVICA Prescribing Information dated November 2013	
	3	IMBRUVICA Prescribing Information dated February 2014	
	4	Byrd et al. (2016) N. Engl. J. Med. 374, 323-332	

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	15112968
	Filing Date	2016-07-20
	First Named Inventor	A. Hamdy
	Art Unit	1618
	Examiner Name	M. Young
	Attorney Docket Number	055112-5004

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/robert smyth/	Date (YYYY-MM-DD)	2018-25-01
Name/Print	Robert Smyth, PhD	Registration Number	50801

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal

Application Number:	15112968
Filing Date:	20-Jul-2016
Title of Invention:	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor
First Named Inventor/Applicant Name:	Hamdy Ahmed
Filer:	Robert John Smyth
Attorney Docket Number:	055112-5004-US

Filed as Large Entity

Filing Fees for U.S. National Stage under 35 USC 371

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension - 3 months with $0 paid	1253	1	1400	1400
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	240	240
		Total in USD ($)		**1640**

Electronic Acknowledgement Receipt

EFS ID:	31609565
Application Number:	15112968
International Application Number:	
Confirmation Number:	1000
Title of Invention:	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor
First Named Inventor/Applicant Name:	Hamdy Ahmed
Customer Number:	28977
Filer:	Robert John Smyth
Filer Authorized By:	
Attorney Docket Number:	055112-5004-US
Receipt Date:	25-JAN-2018
Filing Date:	20-JUL-2016
Time Stamp:	17:21:16
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1640
RAM confirmation Number	012618INTEFSW00008623500310
Deposit Account	500310
Authorized User	Robert Smyth

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		055112-5004OAR12518.pdf	332960 d81af5a3249ba3ef73503538bf8c0440bf185e25	yes	15

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment/Req. Reconsideration-After Non-Final Reject	1	1
Claims	2	6
Applicant Arguments/Remarks Made in an Amendment	7	15

Warnings:

Information:

2	Information Disclosure Statement (IDS) Form (SB08)	055112-5004ids12518.pdf	612073 7bd31a0b7aef2ea15f62e70ab4d2fa78a7fe9b99	no	4

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

3	Non Patent Literature	2017CalquenceLabel.PDF	397742 2d427f41c13b74b495445870dab0eaf8774b52a9	no	17

Warnings:

Information:

4	Non Patent Literature	2013ImbruvicaLabel.pdf	288211 ae47f2c75fef7a4d9f0c425c7fe9504ba48c6144	no	15

Warnings:

Information:

5	Non Patent Literature	2014ImbruvicaLabel.pdf	374974 2e0bf135debc66d60c11e5a1bb84e821fbdffc45	no	19
Warnings:					
Information:					
6	Non Patent Literature	Byrd2016NEJM.PDF	217996 cda0b1fa6efca9e0d263e774bf5dfa3c7b201b46	no	10
Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	32511 acb02f3d6eccfe967f8a56e1b6b7a8b8440eefa8	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2256467	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

VIA ELECTRONIC FILING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: A. Hamdy	:
	: Confirmation No. 1000
Serial No. 15/112,968	:
	: Attorney Docket 055112-5004-US
Filed: July 20, 2016	:
	:

For: Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia using a BTK Inhibitor

REQUEST FOR CORRECTED FILING RECEIPT

Applicant requests a corrected filing receipt to reflect the change for Inventor 1 from Hamdy, Ahmed to Ahmed Hamdy in this application. Attached, in support of this request is a marked up Application Data Sheet reflecting the change.

Respectfully submitted,

Dated: 3/13/2018

By: /Deping Chai/

Deping Chai
Registration Number 63,187
MORGAN, LEWIS & BOCKIUS LLP
1701 Market Street
Philadelphia, PA 19103-2921
Telephone: 215.963.5747
Facsimile: 215.963.5001

DB1/ 96340808.1

PTO/AIA/14 (11-15)
Approved for use through 04/30/2017. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	~~Hamdy~~ Ahmed		~~Ahmed~~ Hamdy	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	Santa Cruz	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	640 Henry Cowell Drive		
Address 2			
City	Santa Cruz	State/Province	CA
Postal Code	95060	Country i	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Wayne		Rothbaum	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	New York	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	101 Central Park West, PHC		
Address 2			
City	New York	State/Province	NY
Postal Code	10023	Country i	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Raquel		Izumi	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

City	San Carlos	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	3437 Brittan Avenue		
Address 2			
City	San Carlos	State/Province	CA
Postal Code	94070	Country i	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Brian		Lannutti	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	Solana Beach	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	627 Glencrest Place		
Address 2			
City	Solana Beach	State/Province	CA
Postal Code	92075	Country i	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Todd		Covey	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	San Carlos	State/Province	CA	Country of Residence i	US

Mailing Address of Inventor:

Address 1	3437 Brittan Avenue		
Address 2			
City	San Carlos	State/Province	CA
Postal Code	94070	Country i	US

Inventor 6 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Roger		Ulrich	

Residence Information (Select One) ◉ US Residency Non US Residency Active US Military Service

City	Sammamish	State/Province	WA	Country of Residence i	US

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

Mailing Address of Inventor:

Address 1	22525 SE 46th Place		
Address 2			
City	Sammamish	State/Province	WA
Postal Code	98075	Country i	US

Inventor 7 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Dave		Johnson	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Aptos	State/Province	CA	Country of Residence	US

Mailing Address of Inventor:

Address 1	694 St. Andrew Circle		
Address 2			
City	Aptos	State/Province	CA
Postal Code	95033	Country i	US

Inventor 8 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Tjeerd		Barf	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Ravenstein	Country of Residence i	NL

Mailing Address of Inventor:

Address 1	St. Luciastraat 7		
Address 2			
City	Ravenstein	State/Province	
Postal Code	5371 AS	Country i	NL

Inventor 9 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Allard		Kaptein	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

City	Zaltbommel	Country of Residence i	NL

Mailing Address of Inventor:

Address 1	Marten van Rossemsingel 51		
Address 2			
City	Zaltbommel	State/Province	
Postal Code	5301 HB	Country i	NL

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	28977		
Email Address	phpatentcorrespondence@morganlewis.com	Add Email	Remove Email

Application Information:

Title of the Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor		
Attorney Docket Number	055112-5004-US	Small Entity Status Claimed	☐
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	28	Suggested Figure for Publication (if any)	1

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	● Customer Number	US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	28977		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	a 371 of international	PCT/IB2015/000645	2015-01-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/IB2015/000645	Claims benefit of provisional	61929742	2014-01-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/IB2015/000645	Claims benefit of provisional	61974665	2014-04-03

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/IB2015/000645	Claims benefit of provisional	62035777	2014-08-11
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name	Acerta Pharma B.V.		
Mailing Address Information For Applicant:			
Address 1	RK 4210		
Address 2	Industrielaan 63		
City	Oss	**State/Province**	
Country	NL	Postal Code	5349 AE
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	Given Name	Middle Name	Family Name	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	~~/Frederick G. Vogt/~~ /Deping Chai/			Date (YYYY-MM-DD)	~~2016-07-20~~ 2018-03-09
First Name	~~Frederick G.~~ Deping	Last Name	~~Vogt~~ Chai	Registration Number	~~70115~~ 63,187

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	055112-5004-US
	Application Number	15/112,968
Title of Invention	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

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2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

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5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

EFS Web 2.2.12

Electronic Acknowledgement Receipt

EFS ID:	32032244
Application Number:	15112968
International Application Number:	
Confirmation Number:	1000
Title of Invention:	Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor
First Named Inventor/Applicant Name:	Hamdy Ahmed
Customer Number:	28977
Filer:	Deping Chai
Filer Authorized By:	
Attorney Docket Number:	055112-5004-US
Receipt Date:	13-MAR-2018
Filing Date:	20-JUL-2016
Time Stamp:	10:06:26
Application Type:	U.S. National Stage under 35 USC 371

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	0551125004US_Request_CorrectedOFR.pdf	99649 bbc0f2e7495f6223284fecd9138522819d220e52	no	1

Warnings:

Information:					
2	Application Data Sheet	Scan.pdf	15075031 f85427af7cb9ad2cbacdb397334d56f9c98ac4e7	no	11
Warnings:					
Information:					
This is not an USPTO supplied ADS fillable form					
			Total Files Size (in bytes):	15174680	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Document code: WFEE

United States Patent and Trademark Office
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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
15/112,968	07/20/2016	1618	2580	055112-5004-US	22	1

CONFIRMATION NO. 1000

REPLACEMENT FILING RECEIPT

28977
MORGAN, LEWIS & BOCKIUS LLP (PH)
1701 MARKET STREET
PHILADELPHIA, PA 19103-2921

OC000000098250306

Date Mailed: 03/23/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Hamdy Ahmed, Santa Cruz, CA;
Wayne Rothbaum, New York, NY;
Raquel Izumi, San Carlos, CA;
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Todd Covey, San Carlos, CA;
Roger Ulrich, Sammamish, WA;
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Applicant(s)

ACERTA PHARMA B.V., Oss, NETHERLANDS;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/IB2015/000645 01/21/2015
which claims benefit of 62/035,777 08/11/2014
and claims benefit of 61/929,742 01/21/2014
and claims benefit of 61/974,665 04/03/2014

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 08/15/2016

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 15/112,968**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/112,968	07/20/2016	Hamdy Ahmed	055112-5004-US	1000

28977 7590 05/03/2018
MORGAN, LEWIS & BOCKIUS LLP (PH)
1701 MARKET STREET
PHILADELPHIA, PENNSYLVANIA 19103-2921
UNITED STATES OF AMERICA

EXAMINER
YOUNG, MICAH PAUL

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
05/03/2018	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 15/112,968	Applicant(s) Ahmed et al.	
	Examiner MICAH PAUL YOUNG	Art Unit 1618	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☑ This action is **FINAL.** 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-2,4-9,12,15 and 20-28 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-2,4-9,12,15 and 20-28 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 8/3/17, 1/25/18.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED CORRESPONDENCE

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/3/17 was filed in a timely manner. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1, 2, 4-9, 12, 15 and 20-28 is/are rejected under 35 U.S.C. 103 as being unpatentable over the combined disclosures of Smyth et al (US 2013/0338172 hereafter Smyth) in view of Johannes et al (WO 2013/010868 hereafter Johannes) and Evarts et al (US 2014/0179673 hereafter Evarts).

The Smyth patent discloses a method of treating various conditions including cancers like lymphoma [abstract]. The disorders include inflammatory and autoimmune disorders [0192-0203]. The compounds are BTK inhibitors similar to those recited in the instant claims a formula (II) [0302]. The BTK inhibitor is useful in treating chronic lymphocytic leukemia including ZAP 70+CLL [0262]. The formulation is oral and can be administered with an additional compounds such as rituximab and anagrelide [0509, 0520]. The formulation can be used to treat various disorders such as NHL, DLBCL-ABC, Burkitt's lymphoma, multiple myeloma, MCL such as mantel zone, and pre-B cell B-ALL [0236-0237, 0242-0246, 0251, 0283, and 0295]. The dosage form is delivered orally at a concentration from 300 to 1000 mg per day as much as 2 to 4 times a day [0486-0489 and 0496].

While the formulation of the Smyth discloses a BTK inhibitor useful in methods of treating various disorders including various cancers. The compound is similar to the compound of the instant claims and is used to treat similar disorders. The use of similar compounds for the treatment of various using BTK inhibitors is known in the art as seen in the Johannes patent.

The Johannes patent discloses a BTK inhibitor compounds useful in treating various inflammatory conditions including cancers including lymphomas [abstract, page 2]. The compound of example 1 is identical to that of the instant claimed formula (II). [Example 1]. The compounds are similar in that they have the same core structures and are useful in treating the same cancers in similar forms. It would have been obvious to include the compound of the Johannes into the formulation of the Smyth patent as the compound have the same cores and treat the same conditions.

The combination, while disclosing a method of treating various leukemia disorders with a compound as recited in the instant claims, the combination is silent to the specific dosage form and

amount. The use of specific dosage amounts for the treatment of various cancers is known in the art as seen in Evarts.

Evarts discloses a method of treating a variety of cancers such including leukemia like Mantle Cell Leukemia with BTK inhibitor compounds [abstract, 0258, claims]. The dosage form comprises from 100-150 mg of the active agents and can be administered in combination with other known chemotherapeutic compounds [0264, 0270]. The dosages form can be administered twice daily [0288]. The dosage form can be administered orally [0276]. It would have been obvious to follow these administration disclosures in order to provide an optimal treatment regimen.

With these aspects in mind it would have been obvious to combine the prior art in order to provide a method of teaching a variety of cancer conditions with a BTK inhibitor. It would have been obvious to combine the specific compound of the Johannes into the method of treatment of the Smyth in order to treat a variety of cancer conditions with an oral multiple day formulation. It would have been obvious to follow the treatment regimen of the Evarts patent in order to optimize the treatment of leukemia.

Response to Arguments

Applicant's arguments with respect to claims 1, 2, 4-9, 12, 15 and 20-28 have been considered but are moot because the arguments do not apply to any of the references being used in the current rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICAH PAUL YOUNG whose telephone number is (571)272-0608. The examiner can normally be reached on Monday through Friday, 9:00 am to 5:30 pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 5712720616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MICAH PAUL YOUNG/
Primary Examiner, Art Unit 1618

Notice of References Cited	Application/Control No. 15/112,968	Applicant(s)/Patent Under Reexamination Ahmed et al.	
	Examiner MICAH PAUL YOUNG	Art Unit 1618	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-20130338172-A1	12-2013	Smyth; Mark	C07D487/04	514/262.1
*	B	US-20140179673-A1	06-2014	EVARTS; Jerry	C07D471/08	514/210.21
	C					
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
*	N	WO-2013010868-A1	01-2013	WO	WIJKMANS JACOBUS C H M	C07D487/04
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/112,968	Ahmed et al.
	Examiner	**Art Unit**
	MICAH PAUL YOUNG	1618

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/23/2017	04/30/2018							
	1	✓	✓							
	2	✓	✓							
	3	✓	-							
	4	✓	✓							
	5	✓	✓							
	6	✓	✓							
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	16	✓	-							
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	28		✓							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	15/112,968	Ahmed et al.
	Examiner	**Art Unit**
	MICAH PAUL YOUNG	1618

CPC - Searched*		
Symbol	**Date**	**Examiner**

CPC Combination Sets - Searched*		
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US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**

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Search Notes		
Search Notes	**Date**	**Examiner**
see notes	7/21/17	MPY

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**

/MICAH-PAUL YOUNG/ Primary Examiner.Art Unit 1618	

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(Not for submission under 37 CFR 1.99)

Application Number	15112968
Filing Date	2016-07-20
First Named Inventor	A. Hamdy
Art Unit	1618
Examiner Name	M. Young
Attorney Docket Number	055112-5004

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	Examiner Name	M. Young
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/M.Y/	1	CALQUENCE Prescribing Information dated October 2017	
/M.Y/	2	IMBRUVICA Prescribing Information dated November 2013	
/M.Y/	3	IMBRUVICA Prescribing Information dated February 2014	
/M.Y/	4	Byrd et al. (2016) N. Engl. J. Med. 374, 323-332	

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Signature	/robert smyth/	Date (YYYY-MM-DD)	2018-25-01
Name/Print	Robert Smyth, PhD	Registration Number	50801

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Filing Date	2016-07-20
First Named Inventor	Hamdy AHMED
Art Unit	1618
Examiner Name	Micah Paul Young
Attorney Docket Number	055112-5004-US

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	7459554		2008-12-02	Dong et al.	
	2	7825118		2010-11-02	Honigberg et al.	
	3	7960396		2011-06-14	Honigberg et al.	
	4	8377946		2013-02-19	Chen et al.	
	5	8658794		2014-02-25	deMan et al.	
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	First Named Inventor	Hamdy AHMED
	Art Unit	1618
	Examiner Name	Micah Paul Young
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	1	20060084654		2006-04-20	Beck et al.	
	2	20080076921		2008-03-27	Honigberg et al.	
	3	20110257203		2011-10-20	Honigberg et al.	
	4	20120053189		2012-03-01	Loury	
	5	20120095026		2012-04-19	Honigberg et al.	
	6	20120129821		2012-05-24	Honigberg et al.	
	7	20120135944		2012-05-31	Honigberg et al.	
	8	20120165328		2012-06-28	Honigberg et al.	
	9	20130018032		2013-01-17	Chen et al.	
	10	20130079327		2013-03-28	Yamamoto et al.	
	11	20140073593		2014-03-13	Conklin et al.	

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	12	20140206681		2014-07-24	Kim et al.		
	13	20140212425		2014-07-31	Chang et al.		

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	1	2008121742	WO		2008-10-09	Pharmacylics, Inc.		
	2	2010126960	WO		2010-11-04	Locus Pharmaceuticals, Inc.		
	3	2011095556	WO		2011-08-11	Organon NV		
	4	2548877	EP		2013-01-23	MSD Oss B.V.		
	5	2001019828	WO		2001-03-22	BASF Aktiengesellschaft		
	6	2002080926	WO		2002-10-17	Abbott GmbH & Co. KG		
	7	2003065995	WO		2003-08-14	Supergen, Inc.		

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	8	2005037836	WO		2005-04-28	OSI Pharmaceuticals, Inc.		
	9	2005097800	WO		2005-10-20	OSI Pharmaceuticals, Inc.		
	10	2007061737	WO		2007-05-31	OSI Pharmaceuticals, Inc.		
	11	20070648	WO		2007-06-07	Bayer Pharmaceuticals Corp.		
	12	2007064993	WO		2001-06-07	OSI Pharmaceuticals, Inc.		
	13	2007106503	WO		2007-09-20	OSI Pharmaceuticals, Inc.		
	14	2009076170	WO		2009-06-18	Novartis AG		
	15	2011119663	WO		2011-09-29	Glaxosmithkline LLC		
	16	2011152351	WO		2011-12-08	Ono Pharmaceutical Co., Ltd.		
	17	2011153514	WO		2011-12-08	Pharmacylics, Inc.		
	18	2012158843	WO		2012-11-22	Univ. California		

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	19	2013003629	WO		2013-01-03	Pharmacylics, Inc.		
	20	2013010380	WO		2013-01-24	Merck Sharp & Dohme Corp.		
	21	2013010868	WO		2013-01-24	MSD Oss B.V.		
	22	2013010869	WO		2013-01-24	MSD Oss B.V.		
	23	2013059738	WO		2013-04-25	Pharmacylics, Inc.		
	24	2014143807	WO		2014-09-18	Stromatt, Scott		
	25	2014159745	WO		2014-10-02	Pharmacylics, Inc.		
	26	2014159745	WO		2014-10-16	Pharmacylics, Inc.		
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	28	2014130856	WO	A2	2014-08-28	Rothbaum et al.		
	29	2015057992	WO	A1	2014-04-23	Izumi et al.		

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	Examiner Name	Micah Paul Young
	Attorney Docket Number	055112-5004-US

	30	2015083008	WO	A1	2015-06-11	Acerta Pharma B.V.		

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	1	Berge et al. "Pharmaceutical salts" 66(1) J. Pharm. Sci. 1-19 (1977)	
	2	Bingham et al., "Over one hundred solvates ofsulfathlazole" Chem. Commun. 603-04 (2001)	
	3	Caira et al., "Preparation and Crystal Characterization of a Polymorph, a Monohydrate, and an Ethyl Acetate Solvate of the Antifungal Fluconazole," 93(3) J. Pharma. Sci. 601-11 (2004)	
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	5	Dhar et al., "Synthesis and SAR of p38a MAP kinase inhibitors based on heterobicyclic scaffolds," 17 Bioorg. & Med. Chem. Lett. 5019-24 (2007)	
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	8	Gilfillan et al., "The tyrosine kinase network regulating mast cell activation," 288 Immun. Rev. 149-69 (2009)	

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	9	Gould "Salt selection for basic drugs" 33 Int'l J. Pharmaceutics 201-217 (1986)	
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	11	Harder et al., "Gain- and Loss-of-Function Lyn Mutant Mice Define a Critical Inhibitory Role for Lyn in the Myeloid Lineage" 15 immunity 603-15 (2001)	
	12	Hartz et al., "Synthesis and Evaluation of imidazo[1,5·a]pyrazines as Corticotrophin Releasing Hormone Receptor Ligands," 12 Bioorg. & Med. Chem. Lett. 291-94 (2002)	
	13	Higuchi et al. (eds.), Pro-drugs as Novel Delivery Systems. 14 A.C.S. Symposium Series (1975)	
	14	Ji et al., ""A novel, potent, and selective insulin-like growth factor-I receptor kinase inhibitor blocks insulin-like growth factor-I receptor signaling in vitro and inhibits insulin-like growth factor-Ireceptor-dependent tumor growth in vivo,"" 6(8) Mol. Cancer Ther. 2158-67 (2007)"	
	15	King et al., "Nucleofugallty effects in the pyridine promoted formation of esters from 2-substituted ethanesulfonyl chlorides," 66 Can. J. Chem. 1109-16 (1988)	
	16	Klinghoffer et al., "Src family kinases are required for integrin but not PDGFR signal transduction," 18(9) EMBO J. 2459-71 (1999)	
	17	Lim et al., "Anti-CD20 monoclonal antibodies: historical and future perspectives," 95(1) Hematological 135-43 (2010)	
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	20	Mukalyama et al., "Synthesis and c-Src inhibitory activity of imidazo[1,5-a]pyrazine derivatives as an agent for treatment of acute ischemic stroke," 15 Bloom. & Med. Chem. 868-85 (2007).	
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	29	Written Opinion mailed 2016-08-10 relating to PCT/IB2016/053988	
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	31	Byrd et al., "Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia", N Engl J Med, Vol. 374, No. 5, pp. 323-332 (2016)	
	32	International Search Report for PCT/IB2015/000645, dated August 31, 2015	
	33	Written Opinion for PCT/IB2015/000645	
	34	International Search Report for PCT/IB2015/002140, dated February 28, 2016	
	35	Written Opinion for PCT/IB2015/002140	

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Signature	/Deping Chai/	Date (YYYY-MM-DD)	2017-08-02
Name/Print	Deping Chai	Registration Number	63187

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	15112968
Filing Date	2016-07-20
First Named Inventor	Hamdy AHMED
Art Unit	1618
Examiner Name	Micah Paul Young
Attorney Docket Number	055112-5004-US

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	1	7459554		2008-12-02	Dong et al.	
	2	7825118		2010-11-02	Honigberg et al.	
	3	7960396		2011-06-14	Honigberg et al.	
	4	8377946		2013-02-19	Chen et al.	
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	1	20060084654		2006-04-20	Beck et al.	
	2	20080076921		2008-03-27	Honigberg et al.	
	3	20110257203		2011-10-20	Honigberg et al.	
	4	20120053189		2012-03-01	Loury	
	5	20120095026		2012-04-19	Honigberg et al.	
	6	20120129821		2012-05-24	Honigberg et al.	
	7	20120135944		2012-05-31	Honigberg et al.	
	8	20120165328		2012-06-28	Honigberg et al.	
	9	20130018032		2013-01-17	Chen et al.	
	10	20130079327		2013-03-28	Yamamoto et al.	
	11	20140073593		2014-03-13	Conklin et al.	

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	Examiner Name	Micah Paul Young
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	12	20140206681		2014-07-24	Kim et al.		
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	1	2008121742	WO		2008-10-09	Pharmacylics, Inc.		
	2	2010126960	WO		2010-11-04	Locus Pharmaceuticals, Inc.		
	3	2011095556	WO		2011-08-11	Organon NV		
	4	2548877	EP		2013-01-23	MSD Oss B.V.		
	5	2001019828	WO		2001-03-22	BASF Aktiengesellschaft		
	6	2002080926	WO		2002-10-17	Abbott GmbH & Co. KG		
	7	2003065995	WO		2003-08-14	Supergen, Inc.		

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	8	2005037836	WO		2005-04-28	OSI Pharmaceuticals, Inc.		
	9	2005097800	WO		2005-10-20	OSI Pharmaceuticals, Inc.		
	10	2007061737	WO		2007-05-31	OSI Pharmaceuticals, Inc.		
	11	20070648	WO		2007-06-07	Bayer Pharmaceuticals Corp.		
	12	2007064993	WO		2001-06-07	OSI Pharmaceuticals, Inc.		
	13	2007106503	WO		2007-09-20	OSI Pharmaceuticals, Inc.		
	14	2009076170	WO		2009-06-18	Novartis AG		
	15	2011119663	WO		2011-09-29	Glaxosmithkline LLC		
	16	2011152351	WO		2011-12-08	Ono Pharmaceutical Co., Ltd.		
	17	2011153514	WO		2011-12-08	Pharmacylics, Inc.		
	18	2012158843	WO		2012-11-22	Univ. California		

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	19	2013003629	WO		2013-01-03	Pharmacylics, Inc.		
	20	2013010380	WO		2013-01-24	Merck Sharp & Dohme Corp.		
	21	2013010868	WO		2013-01-24	MSD Oss B.V.		
	22	2013010869	WO		2013-01-24	MSD Oss B.V.		
	23	2013059738	WO		2013-04-25	Pharmacylics, Inc.		
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	29	2015057992	WO	A1	2014-04-23	Izumi et al.		

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	30	2015083008	WO	A1	2015-06-11	Acerta Pharma B.V.		

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	1	Berge et al. "Pharmaceutical salts" 66(1) J. Pharm. Sci. 1-19 (1977)	
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	9	Gould "Salt selection for basic drugs" 33 Int'l J. Pharmaceutics 201-217 (1986)	
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	31	Byrd et al., "Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia", N Engl J Med, Vol. 374, No. 5, pp. 323-332 (2016)	
	32	International Search Report for PCT/IB2015/000645, dated August 31, 2015	
	33	Written Opinion for PCT/IB2015/000645	
	34	International Search Report for PCT/IB2015/002140, dated February 28, 2016	
	35	Written Opinion for PCT/IB2015/002140	

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Examiner Signature	/MICAH PAUL YOUNG/	Date Considered	04/30/2018

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	First Named Inventor	Hamdy AHMED
	Art Unit	1618
	Examiner Name	Micah Paul Young
	Attorney Docket Number	055112-5004-US

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

See attached certification statement.

The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Deping Chai/	Date (YYYY-MM-DD)	2017-08-02
Name/Print	Deping Chai	Registration Number	63187

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	15112968	Filing Date	2016-07-20	Docket Number (if applicable)	055112-5004-US	Art Unit	1618
First Named Inventor	Ahmed Hamdy			Examiner Name	Micah Paul Young		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

- ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
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MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

☒ **The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.**
The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to
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SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

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Signature	/Deping Chai/	Date (YYYY-MM-DD)	2018-11-05
Name	Deping Chai	Registration Number	63187

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: H. Ahmed et al.	:
	: Confirmation No. 1000
Serial No. 15/112,968	:
	: Attorney Docket No. 055112-5004 US
Filed: July 20, 2016	:
	:
For: Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor	

Response under 37 C.F.R. 1.114

This paper is in response to the Final Office Action dated May 3, 2018. Applicant petitions for a three-month extension of time by the payment of the accompanying fee, extending the deadline to November 3, 2018. This response is being filed concurrently with a Request for Continued Examination (RCE). This paper is being filed under the next business day rule as the due date for responding fell on a Saturday.

Amendments to Specification begin on page 2 of this paper.

Amendments to the Claims begin on page 3 of this paper.

Remarks begin on page 8 of this paper.

DB1/ 99938848.6

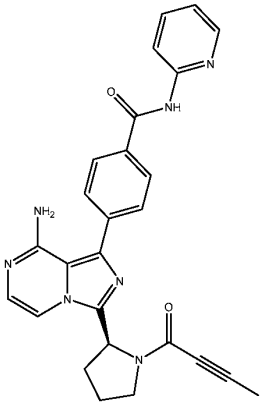
Amendments to Specification

Please enter the attached substitute specification and drawings.

Amendments to the claims

This listing of the claims will replace all prior versions.

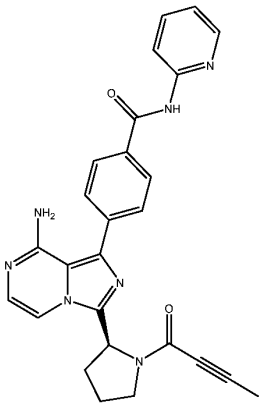
1. (Previously presented) A method of treating chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL) in a human subject suffering therefrom, comprising the step of orally administering, to the human subject, a dose of 100 mg twice daily of a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

2. (Previously presented) The method of claim 1, wherein the BTK inhibitor is a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

3. (Cancelled)

4. (Previously presented) The method of Claim 2, wherein the BTK inhibitor is administered to the human subject for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days.

5. (Previously presented) The method of Claim 2, wherein the CLL is selected from the group consisting of IgV_H mutation negative CLL, ZAP-70 positive CLL, ZAP-70 methylated at CpG3 CLL, CD38 positive CLL, CLL with a 17p13.1 (17p) deletion, CLL with a 11q22.3 (11q) deletion, CLL in a human sensitive to platelet-mediated thrombosis, CLL in a human presently suffering from platelet-mediated thrombosis, CLL in a human previously suffering from platelet-mediated thrombosis, and combinations thereof.

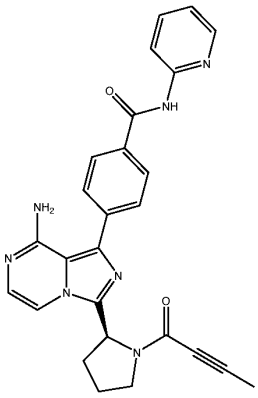
6. (Currently Amended) The method of ~~Claim 1~~ Claim 2, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

7. (Previously presented) The method of Claim 2, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

8. (Original) The method of Claim 7, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin,

ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

9. (Previously presented) A method of treating a mantle cell lymphoma (MCL) in a human subject suffering therefrom comprising the step of orally administering, to the human subject, a dose of 100 mg twice daily of a BTK inhibitor, wherein the BTK inhibitor is a compound of Formula (II):



or a pharmaceutically-acceptable salt, hydrate, or solvate thereof.

10. (Cancelled)

11. (Cancelled)

12. (Currently amended) The method of ~~Claim 9~~ Claim 29, wherein the Mantle Cell Lymphoma (MCL) increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, and about 56 days.

13. (Cancelled)

14. (Cancelled)

15. (Currently amended) The method of ~~Claim 9~~ Claim 29, wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.

16. (Cancelled)

17. (Cancelled)

18. (Cancelled)

19. (Cancelled)

20. (Currently amended) The method of ~~Claim 9~~ Claim 29, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

21. (Currently amended) The method of ~~Claim 9~~ Claim 29, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

22. (Original) The method of Claim 21, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

23. (Previously presented) The method of Claim 2, the method comprising treating chronic lymphocytic leukemia (CLL) in a human subject suffering from CLL.

24. (Currently amended) The method of ~~Claim 3~~ Claim 2, the method comprising treating small lymphocytic leukemia (SLL) in a human subject suffering from SLL.

25. (Currently amended) The method of ~~Claim 1~~ Claim 2, wherein the free form of the compound of

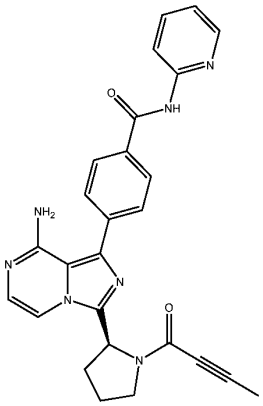
Formula (II) is administered to the human subject.

26. (Currently amended) The method of ~~Claim 1~~ Claim 2, wherein the pharmaceutically acceptable salt of the compound of Formula (II) is administered to the human subject.

27. (Currently amended) The method of ~~Claim 9~~ Claim 29, wherein the free form of the compound of Formula (II) is administered to the human subject.

28. (Currently amended) The method of ~~Claim 9~~ Claim 29, wherein the pharmaceutically acceptable salt of the compound of Formula (II) is administered to the human subject.

29. (New) The method of claim 9, wherein the BTK inhibitor is a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof.

Remarks

Claims 1, 2, 4-9, 12, 15 and 20-29 are pending upon entry of this amendment. New claim 29 has been added and claims 6, 12, 15, 20, 21, and 24-28 have been amended to revise their dependencies. Written support for new claim 29 and the amendments to claims 6, 12, 15, 20, 21, and 24-28 can be found in the specification and original claims.

In filing this response, the specification and drawings are being amended to remove certain experimental data in the Examples and Figures as set forth in the attached mark-up of the specification and drawings. Specifically, Figures 15, 17, and 18 have been deleted along with subject matter related to these Figures. The figure numbers in the Figure Legend section have been renumbered in view of the deleted subject matter. As the amendments to the Figures are simple deletion rather than revision, no markup of the drawings is provided. The replacement sheets of the drawings provided herein simply renumber the figure number in view of the deletion of certain figures.

With regard to deletion of the Figures and the related subject matter thereof, the subject matter of the present application was included in a retrospective review conducted by the Applicant as part of an assessment of research activities. Applicant attempted to establish the source of data that contributed to the information in the deleted Figures. No source of the data could be identified, however, to support the experimental data in Figures 15, 17, and 18. As the source of these data cannot be located, Applicant concluded that these data are not reliable and requests entry of this amendment to delete the aforementioned Figures from the drawings and related subject matter from the specification.

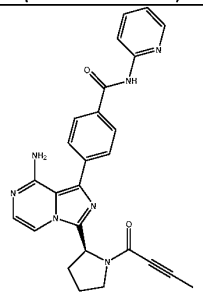
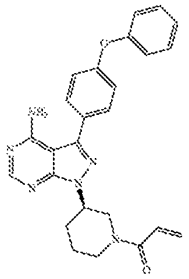
Applicant submits that no new matter has been added. Entry of the foregoing amendments is requested.

Applicant thanks the Examiner for the courtesies extended and the helpful assistance provided during the interview of October 9, 2018. The substance discussed during this interview is incorporated into the remarks as set forth below.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1, 2, 4-9, 12, 15 and 20-28 as being obvious over the combined disclosures of Smyth in view of Johannes et al and Evarts et al as set forth on pages 2-4 of the office action.

Smyth reports crystalline forms of one specific compound and pharmaceutical formulations comprising that specific compound. For clarity, the compound reported in Smyth and the compound of Formula (II) specified in the pending claims are shown in the table below:

Compound of Formula (II) (Acalabrutinib)	Smyth Compound (Ibrutinib)
	

Applicants do not agree with the statement in the office action that the Smyth compound and the compound of Formula (II) "are similar in that they have the same core structure" (see office action at page 3). As can be seen from the comparison above, the two compounds have different and distinct chemical cores and structures. Further, in the Examiner interview with Applicant on October 9, 2018, the examiner also stated that the structures of these compounds are different and the rejection could not be maintained in view of this.

Supplementing Smyth with the disclosure of Johannes and Evarts does not cure the deficiency of the rejection. The office action specifically acknowledged that "the combination of Smyth and Johannes is silent to the specific dosage form and amount of the claimed methods of treatment" (see pages 3-4 of office action).

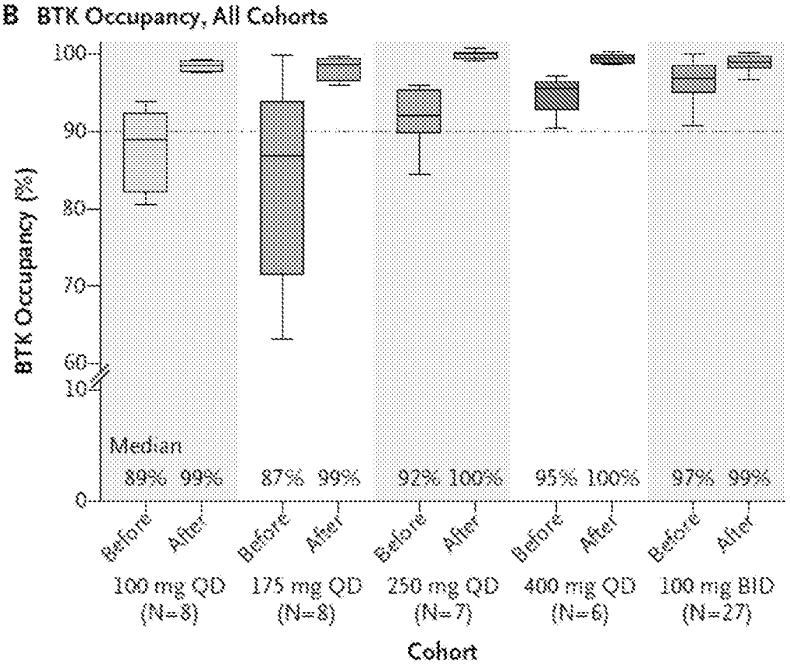
Clinical study findings for the compound of Formula (II) (acalabrutinib) further support the patentability of the claimed inventions. It was unexpected that acalabrutinib could be orally administered twice daily (BID) and at a significantly lower dose (100 mg BID) than the Smyth compound (ibrutinib) and provide continuous and improved Bruton Tyrosine Kinase (BTK) target occupancy (greater than 95% over the treatment interval) relative to ibrutinib, particularly since acalabrutinib has limited or no plasma accumulation at a 100 mg dose. See, for example, the results reported in The New England Journal of Medicine for a phase 1-2 study assessing the safety, efficacy, pharmacokinetics, and pharmacodynamics of acalabrutinib when orally administered to patients with relapsed chronic

lymphocytic leukemia (CLL). Byrd (2016) Acalabrutinib (ACP-196) in Relapsed Chronic Lymphocytic Leukemia, N. Engl. J. Med. 374, pp. 323-332 (the Byrd Publication). The Byrd publication was submitted May 3, 2018 via IDS.

In this clinical study, patients received an acalabrutinib dose of 100 to 400 mg once daily in the dose-escalation (phase 1) portion of the study and 100 mg twice daily in the expansion (phase 2) portion. The Byrd publication commented on the clinical trial findings as follows:

> The short half-life and selective properties of acalabrutinib allow twice-daily dosing with virtually complete and continuous BTK inhibition without increase toxic effects. Thus far, twice-daily dosing of ibrutinib has not been pursued and may not be possible owing to the potential for drug accumulation given the ibrutinib half-life of 4 to 13 hours.

Figure 1 of the Byrd publication provides an overview of the specific pharmacokinetic and pharmacodynamic findings. Panel A of Figure 1 shows the mean plasma concentration of acalabrutinib over time in the once-daily (QD) and twice-daily (BID) cohorts. The pharmacokinetic profile for acalabrutinib displays a rapid absorption and a rapid clearance, with linear dose exposure. Panel B of Figure 1 shows the BTK target occupancy in each cohort before and 4 hours after dosing on day 8 (steady-state). For the BID cohort, BTK target occupancy was evaluated for the morning dose only. Panel B of Figure 1 is reproduced below. Panel C of Figure 1 further shows BTK occupancy over time in the 100-mg BID cohort.



All cohorts exhibited similar BTK target occupancy at four hours following dosing, but the once-daily cohorts exhibited a lower median BTK target occupancy and more variance compared to the 100 mg twice-daily cohort immediately prior to administration of the next dose (Panel B). Although BTK target occupancy was complete (99 to 100%) four hours after dosing for all cohorts, median BTK target occupancy ranged from 87 to 95% immediately before administration of the next dose (at trough) for the once-daily dosing cohorts. Only the BTK target occupancy for 400 mg once-daily dose cohort approached the trough value seen with the 100 mg BID cohort. Further, BTK target occupancy for the 100 mg BID dosing regimen was maintained over time with a measured BTK target occupancy of 99% at four hours after dose administration and 97% before dose administration on days 8 and 28 (Panel C). The unexpected benefit of the claimed 100 mg BID dosing regimen relative to the other dosing regimens evaluated could not have been predicted in view of the cited references and are a result of the pharmacokinetic and pharmacodynamic properties of acalabrutinib.

In view of the above remarks, Applicant submits that the rejection is moot and should be withdrawn.

Conclusion

In view of the foregoing, Applicant requests reconsideration and the timely allowance of the pending claims. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the Applicant's undersigned representative to expedite prosecution.

Respectfully submitted,

Date: November 5, 2018

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METHODS OF TREATING CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LEUKEMIA USING A BTK INHIBITOR

FIELD OF THE INVENTION

[001] Therapeutic methods of treating chronic lymphocytic leukemia using a Bruton's tyrosine kinase (BTK) inhibitor are disclosed herein.

BACKGROUND OF THE INVENTION

[002] Bruton's Tyrosine Kinase (BTK or Btk) is a TEC family non-receptor protein kinase expressed in B cells and myeloid cells. The function of BTK in signaling pathways activated by the engagement of the B cell receptor (BCR) and FCER1 on mast cells is well established. Functional mutations in BTK in humans result in a primary immunodeficiency disease characterized by a defect in B cell development with a block between pro- and pre-B cell stages. The result is an almost complete absence of B lymphocytes, causing a pronounced reduction of serum immunoglobulin of all classes. These findings support a key role for BTK in the regulation of the production of auto-antibodies in autoimmune diseases.

[003] Other diseases with an important role for dysfunctional B cells are B cell malignancies. The reported role for BTK in the regulation of proliferation and apoptosis of B cells indicates the potential for BTK inhibitors in the treatment of B cell lymphomas. BTK inhibitors have thus been developed as potential therapies, as described in O. J. D'Cruz and F. M. Uckun, *OncoTargets and Therapy* **2013,** *6,* 161-176.

[004] B cell chronic lymphocytic leukemia (CLL) is one of the most prevalent B cell malignancies in adults. CLL is characterized by an expansion of monoclonal mature B cells. CLL patients who relapsed after standard treatments generally experience poor outcomes. Although survival has been improved by the addition of immunotherapies such as rituximab to standard chemotherapies such as fludarabine and cyclophosphamide, as described in M. Hallek, *et al.*, *Lancet,* **2010,** *76,* 1164-74, many standard treatments are associated with toxicities and immunosuppression. There is therefore a significant need to identify less toxic and highly efficacious treatments for CLL. Small lymphocytic leukemia (SLL) is closely related to CLL, and differs only in that a lower level of monoclonal lymphocytes is observed in blood than in

CLL, along with an enlarged spleen or lymph nodes. There is also a significant need to identify less toxic and highly efficacious treatments for SLL.

[005] CLL (and SLL) cells rapidly accumulate and are resistant to apoptosis *in vivo*, but are known to die rapidly *in vitro*. M. Buchner, *et al.*, *Blood* **2010,** *115,* 4497-506. One cause of this effect is from nonmalignant accessory cells in the tumor microenvironment, such as stromal cell contact mediated cell survival. Stromal cells in the bone marrow and lymph nodes are known to have an antiapoptotic and protective effect on CLL cells, protecting them from both chemotherapeutic and spontaneous apoptosis. R. E. Mudry, *et al.*, *Blood* **2000,** *96,* 1926-32. The chemokine SDF1α (CXCL12) directs homing of CLL cells towards protective niches. M. Burger, *et al.*, *Blood* **2005,** *106,* 1824-30. Existing drugs that target the BCR pathway in B cell malignancies can lead to some lymphocytosis, *i.e.* lymphocyte egress from nodal compartments, through disruption of CXCR4-SDF1α signaling and other adhesion factors in bone marrow and the resulting mobilization of cells. However, existing therapies may not eradicate residual malignent B cell populations in the microenvironment of the bone marrow and lymph nodes, where protective stromal cells prevent apoptosis. There is thus an urgent need for treatments that reduce or overcome the protective effect of the microenvironment on CLL cells to enable superior clinical responses in patients.

SUMMARY OF THE INVENTION

[006] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof.

[007] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the

BTK inhibitor is administered once daily at a dose selected from the group consisting of 100 mg, 175 mg, 250 mg, and 400 mg.

[008] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the BTK inhibitor is administered twice daily at a dose of 100 mg.

[009] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the CLL increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, or about 56 days.

[0010] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, wherein the CLL is selected from the group consisting of IgVH mutation negative CLL, ZAP-70 positive CLL, ZAP-70 methylated at CpG3 CLL, CD38 positive CLL, CLL with a 17p13.1 (17p) deletion, CLL with a 11q22.3 (11q) deletion, CLL in a human sensitive to platelet-mediated thrombosis, CLL in a human presently suffering from platelet-mediated thrombosis, CLL in a human previously suffering from platelet-mediated thrombosis, or combinations thereof.

[0011] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a

pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

[0012] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

[0013] In an embodiment, the invention includes a method of treating CLL and/or SLL, comprising the step of orally administering, to a human in need thereof, a Bruton's tyrosine kinase (BTK) inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban

hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

[0014] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis.

[0015] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, wherein the BTK inhibitor is administered once daily at a dose selected from the group consisting of 100 mg, 175 mg, 250 mg, and 400 mg.

[0016] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's

macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, wherein the BTK inhibitor is administered twice daily at a dose of 100 mg.

[0017] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, wherein the hematological malignancy increases monocytes and NK cells in peripheral blood after treatment with Formula (II) for a period selected from the group consisting of about 14 days, about 28 days, or about 56 days.

[0018] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is non-Hodgkin's lymphoma (NHL), wherein the NHL is selected from the group consisting of indolent NHL and aggressive NHL.

[0019] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is diffuse large B cell lymphoma (DLBCL), wherein the DLBCL is selected from the group consisting of activated B-cell like diffuse large B-cell lymphoma (DLBCL-ABC) and germinal center B-cell like diffuse large B-cell lymphoma (DLBCL-GCB).

[0020] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is mantle cell lymphoma (MCL), wherein the MCL is selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL.

[0021] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is B cell acute lymphoblastic leukemia (B-ALL), wherein the B-ALL is selected from the group consisting of early pre-B cell B-ALL, pre-B cell B-ALL, and mature B cell B-ALL.

[0022] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is Burkitt's lymphoma, wherein the Burkitt's lymphoma is selected from the group consisting of sporadic Burkitt's lymphoma, endemic Burkitt's lymphoma, and human immunodeficiency virus-associated Burkitt's lymphoma.

[0023] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is multiple myeloma, wherein the multiple myeloma is selected from the group consisting of hyperdiploid multiple myeloma and non-hyperdiploid multiple myeloma.

[0024] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is myelofibrosis, wherein the myelofibrosis is selected from the group consisting of primary myelofibrosis, myelofibrosis secondary to polycythemia vera, and myelofibrosis secondary to essential thrombocythaemia.

[0025] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, further comprising the step of administering a therapeutically effective dose of an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, ibritumomab, and fragments, derivatives, conjugates, variants, radioisotope-labeled complexes, and biosimilars thereof.

[0026] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, further

comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

[0027] In an embodiment, the invention includes a method of treating a hematological malignancy in a human comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Burkitt's lymphoma, Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, and combinations thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] The foregoing summary, as well as the following detailed description of the invention, will be better understood when read in conjunction with the appended drawings.

[0029] FIG. 1 illustrates *in vivo* potency of Formula (II) (labeled "BTK inhibitor") and ibrutinib. Mice were gavaged at increasing drug concentration and sacrificed at one time point (3 h post-dose). BCR is stimulated with IgM and the expression of activation markers CD69 and CD86 are monitored by flow cytometry to determine EC_{50}'s. The results show that Formula (II) is more potent at inhibiting expression of activation makers than ibrutinib.

[0030] FIG. 2 illustrates the results of the clinical study of Formula (II) (labeled "BTK inhibitor") in CLL, which are shown in comparison to the results reported for ibrutinib in Figure 1A of J.C. Byrd, et al., *N. Engl. J. Med.* **2013,** *369,* 32-42. The results show that the BTK inhibitor of Formula (II) causes a much smaller relative increase and much faster decrease in absolute lymphocyte count (ALC) relative to the BTK inhibitor ibrutinib. The sum of the product of greatest diameters (SPD) also decreases more rapidly during treatment with the BTK inhibitor than with the BTK inhibitor ibrutinib.

[0031] FIG. 3 shows overall response data shown by SPD of enlarged lymph nodes in CLL patients as a function of dose of the BTK inhibitor of Formula (II).

[0032] FIG. 4 shows a comparison of progression-free survival (PFS) in CLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). The ibrutinib data is taken from J.C. Byrd, et al., *N. Engl. J. Med.* **2013,** *369,* 32-42. CLL patients treated with Formula (II) for at least 8 days are included.

[0033] FIG. 5 shows a comparison of number of patients at risk in CLL patients treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). CLL patients treated with Formula (II) for at least 8 days are included.

[0034] FIG. 6 shows a comparison of progression-free survival (PFS) in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II). The ibrutinib data is taken from J.C. Byrd, et al., *N. Engl. J. Med.* **2013,** *369,* 32-42.

[0035] FIG. 7 shows a comparison of number of patients at risk in CLL patients exhibiting the 17p deletion and treated with the BTK inhibitor ibrutinib or the BTK inhibitor of Formula (II).

The ibrutinib data is taken from J.C. Byrd, et al., *N. Engl. J. Med.* **2013,** *369,* 32-42. CLL patients treated with Formula (II) for at least 8 days are included.

[0036] FIG. 8 shows improved BTK target occupancy of Formula (II) at lower dosage versus ibrutinib in relapsed/refractory CLL patients.

[0037] FIG. 9 shows the % change in myeloid-derived suppressor cell (MDSC) (monocytic) level over 28 days versus % ALC change at Cycle 1, day 28 (C1D28) with trendlines.

[0038] FIG. 10 shows the % change in MDSC (monocytic) level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

[0039] FIG. 11 shows the % change in natural killer (NK) cell level over 28 days versus % ALC change at Cycle 1, day 28 (C2D28) with trendlines.

[0040] FIG. 12 shows the % change in NK cell level over 28 days versus % ALC change at Cycle 2, day 28 (C2D28) with trendlines.

[0041] FIG. 13 compares the % change in MDSC (monocytic) level and % change in NK cell level over 28 days versus % ALC change with the % change in level of $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+/CD8^+$ T cell ratio, NK-T cells, PD-1^+ $CD4^+$ T cells, and PD-1^+ $CD8^+$ T cells, also versus % ALC change, at Cycle 1 day 28 (C1D28). Trendlines are shown for % change in MDSC (monocytic) level and % change in NK cell level.

[0042] FIG. 14 compares the % change in MDSC (monocytic) level and % change in NK cell level over 28 days versus % ALC change with the % change in level of $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+/CD8^+$ T cell ratio, NK-T cells, PD-1^+ $CD4^+$ T cells, and PD-1^+ $CD8^+$ T cells, also versus % ALC change, at Cycle 2 day 28 (C2D28). Trendlines are shown for % change in MDSC (monocytic) level and % change in NK cell level.

~~[0043] FIG. 15 illustrates representative photomicrographs and comparison of maximal thrombus size in laser injured arterioles of VWF HA1 mutant mice infused with human platelets in the absence or presence of various BTK inhibitors. Representative photomicrographs are given as a comparison of maximal thrombus size in laser-injured arterioles (1 μM concentrations shown).~~

~~[0044]~~[0043] ~~-~~FIG. ~~16~~ 15 illustrates a quantitative comparison obtained by *in vivo* analysis of early thrombus dynamics in a humanized mouse laser injury model using three BTK inhibitors at a concentration of 1 μM.

~~[0045] FIG. 17 illustrates the effect of the tested BTK inhibitors on thrombus formation. The conditions used were N=4, 3 mice per drug; anti-clotting agents < 2000 μM[2]. In studies with ibrutinib, 48% MCL bleeding events were observed with 560 mg QD and 63% CLL bleeding events were observed with 420 mg QD, where bleeding event is defined as subdural hematoma, ecchymoses, GI bleeding, or hematuria.~~

~~[0046] FIG. 18 illustrates the effect of the concentration of the tested BTK inhibitors on thrombus formation.~~

~~[0047]~~[0044] ~~-~~FIG. ~~19~~ 16 illustrates the results of platelet collagen receptor glycoprotein VI (GPVI) platelet aggregation studies of Formula (II) (IC_{50} = 1.15 μM) and ibrutinib (IC_{50} = 0.13 μM).

~~[0048]~~[0045] FIG. ~~20~~ 17 illustrates the results of GPVI platelet aggregation studies of Formula (II) and ibrutinib.

~~[0049]~~[0046] FIG. ~~21~~ 18 shows *in vitro* analysis of antibody-dependent NK cell–mediated INF-γ release with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with 0.1 or 1 μM of ibrutinib or 1 μM of Formula (II) for 4 hours together with rituximab-coated (10 μg/mL) lymphoma cells, DHL4, or trastuzumab-coated (10 μg/mL) HER2+ breast cancer cells, HER18, and supernatant was harvested and analyzed by enzyme-linked immunosorbent assay for interferon-γ (IFN-γ). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.018, **p = 0.002, ***p = 0.001.

~~[0050]~~[0047] FIG. ~~22~~ 19 shows *in vitro* analysis of antibody-dependent NK cell–mediated degranulation with BTK inhibitors. To evaluate NK cell function, purified NK cells were isolated from healthy peripheral blood mononuclear cells and cultured with 0.1 or 1 μM of ibrutinib or 1 μM of Formula (II) for 4 hours together with rituximab-coated (10 μg/mL) lymphoma cells, DHL4, or trastuzumab-coated (10 μg/mL) HER2+ breast cancer cells, HER18, and NK cells isolated and analyzed for degranulation by flow cytometry for CD107a

mobilization. All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.01, **p = 0.002, ***p = 0.003, ****p = 0.0005.

~~[0051]~~[0048] FIG. ~~23~~ 20 shows that ibrutinib antagonizes antibody-dependent NK cell–mediated cytotoxicity in primary CLL cells. NK cell cytotoxicity as percent lysis of tumor cells was analyzed in chromium release assays with purified NK cells incubated with chromium-labeled Raji for 4 hours at variable rituximab concentrations at a constant effector:target ratio of 25:1 and ibrutinib (1 μM), Formula (II) (1 μM), or other ITK sparing BTK inhibitors CGI-1746, inhibA (1 μM) and BGB-3111 (1 μM). All *in vitro* experiments were performed in triplicate. Labels are defined as follows: *p = 0.001.

~~[0052]~~[0049] FIG. ~~24~~ 21 shows a summary of the results given in FIG. ~~24~~ 20 at the highest concentration of rituximab ("Ab") (10 μg/mL).

~~[0053]~~[0050] FIG. ~~25~~ 22 shows that ibrutinib antagonizes antibody-dependent NK cell–mediated cytotoxicity, as in FIG. ~~23~~ 20, using the Raji cell line.

~~[0054]~~[0051] FIG. ~~26~~ 23 shows the effects of BTK inhibition on generalized NK cell mediated cytotoxicity.

~~[0055]~~[0052] FIG. ~~27~~ 24 shows that Formula (II) has no adverse effect on T helper 17 (Th17) cells, which are a subset of T helper cells that produce interleukin 17 (IL17), while ibrutinib strongly inhibits Th17 cells.

~~[0056]~~[0053] FIG. ~~28~~ 25 shows that Formula (II) has no effect on regulatory T cell (Treg) development, while ibrutinib strongly increases Treg development.

BRIEF DESCRIPTION OF THE SEQUENCE LISTINGS

~~[0057]~~[0054] SEQ ID NO:1 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

~~[0058]~~[0055] SEQ ID NO:2 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody rituximab.

~~[0059]~~[0056] SEQ ID NO:3 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody obinutuzumab.

~~[0060]~~[0057] SEQ ID NO:4 is the light chain amino acid sequence of the anti-CD20

monoclonal antibody obinutuzumab.

~~[0061]~~[0058] SEQ ID NO:5 is the variable heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

~~[0062]~~[0059] SEQ ID NO:6 is the variable light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

~~[0063]~~[0060] SEQ ID NO:7 is the Fab fragment heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

~~[0064]~~[0061] SEQ ID NO:8 is the Fab fragment light chain amino acid sequence of the anti-CD20 monoclonal antibody ofatumumab.

~~[0065]~~[0062] SEQ ID NO:9 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

~~[0066]~~[0063] SEQ ID NO:10 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody veltuzumab.

~~[0067]~~[0064] SEQ ID NO:11 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

~~[0068]~~[0065] SEQ ID NO:12 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody tositumomab.

~~[0069]~~[0066] SEQ ID NO:13 is the heavy chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

~~[0070]~~[0067] SEQ ID NO:14 is the light chain amino acid sequence of the anti-CD20 monoclonal antibody ibritumomab.

DETAILED DESCRIPTION OF THE INVENTION

~~[0071]~~[0068] While preferred embodiments of the invention are shown and described herein, such embodiments are provided by way of example only and are not intended to otherwise limit the scope of the invention. Various alternatives to the described embodiments of the invention may be employed in practicing the invention.

~~[0072]~~[0069] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

~~[0073]~~[0070] The terms “co-administration” and “administered in combination with” as used herein, encompass administration of two or more active pharmaceutical ingredients to a subject so that both agents and/or their metabolites are present in the subject at the same time. Co-administration includes simultaneous administration in separate compositions, administration at different times in separate compositions, or administration in a composition in which two or more agents are present.

~~[0074]~~[0071] The term “*in vivo*” refers to an event that takes place in a subject's body.

~~[0075]~~[0072] The term “*in vitro*” refers to an event that takes places outside of a subject's body. *In vitro* assays encompass cell-based assays in which cells alive or dead are employed and may also encompass a cell-free assay in which no intact cells are employed.

~~[0076]~~[0073] The term “IC_{50}” refers to the half maximal inhibitory concentration, *i.e.* inhibition of 50% of the desired activity. The term “EC_{50}” refers to the drug concentration at which one-half the maximum response is achieved.

~~[0077]~~[0074] The term “effective amount” or “therapeutically effective amount” refers to that amount of an active pharmaceutical ingredient or combination of active pharmaceutical ingredients as described herein that is sufficient to effect the intended application including, but not limited to, disease treatment. A therapeutically effective amount may vary depending upon the intended application (*in vitro* or *in vivo*), or the subject and disease condition being treated (*e.g.*, the weight, age and gender of the subject), the severity of the disease condition, the manner of administration, and other factors which can readily be determined by one of ordinary skill in the art. The term also applies to a dose that will induce a particular response in target cells, (*e.g.*, the reduction of platelet adhesion and/or cell migration). The specific dose will vary depending on the particular compounds chosen, the dosing regimen to be followed, whether the compound is administered in combination with other compounds, timing of administration, the tissue to which it is administered, and the physical delivery system in which the compound is carried.

~~[0078]~~[0075] A "therapeutic effect" as that term is used herein, encompasses a therapeutic benefit and/or a prophylactic benefit as described above. A prophylactic effect includes delaying or eliminating the appearance of a disease or condition, delaying or eliminating the onset of symptoms of a disease or condition, slowing, halting, or reversing the progression of a disease or condition, or any combination thereof.

~~[0079]~~[0076] The terms "QD," "qd," or "q.d." means *quaque die*, once a day, or once daily. The terms "BID," "bid," or "b.i.d." mean *bis in die*, twice a day, or twice daily. The terms "TID," "tid," or "t.i.d." mean *ter in die*, three times a day, or three times daily. The terms "QID," "qid," or "q.i.d." mean *quater in die*, four times a day, or four times daily.

~~[0080]~~[0077] The term "pharmaceutically acceptable salt" refers to salts derived from a variety of organic and inorganic counter ions known in the art. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins. Specific examples include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In selected embodiments, the pharmaceutically acceptable base addition salt is chosen from ammonium, potassium, sodium, calcium, and magnesium salts. The term "cocrystal" refers to a molecular complex derived from a number of cocrystal formers known in the art. Unlike a salt, a cocrystal typically does not involve proton transfer between the cocrystal and the drug, and instead involves intermolecular interactions, such as hydrogen bonding, aromatic ring stacking, or dispersive forces, between the cocrystal former and the drug in the crystal structure.

~~[0084]~~[0078] "Pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic, and absorption delaying agents. The use of such media and agents for active pharmaceutical ingredients is well known in the art. Except insofar as any conventional media or agent is incompatible with the active pharmaceutical ingredient, its use in the therapeutic compositions of the invention is contemplated. Supplementary active ingredients can also be incorporated into the described compositions.

~~[0085]~~[0079] "Prodrug" is intended to describe a substance that may be converted under physiological conditions or by solvolysis to a biologically active pharmaceutical ingredient described herein. Thus, the term "prodrug" refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active pharmaceutical ingredient, for example, by hydrolysis. The prodrug compound often offers the advantages of solubility, tissue compatibility or delayed release in a mammalian organism (see, *e.g.*, H. Bundgaard, *Design of Prodrugs*, Elsevier, Amsterdam (1985)). The term "prodrug" is also intended to include any covalently bonded carriers, which release the active pharmaceutical ingredient *in vivo* when administered to a subject. Prodrugs of an active pharmaceutical ingredient, as described herein, may be prepared by modifying functional groups present in the active pharmaceutical ingredient in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to yield the active pharmaceutical ingredient. Prodrugs include, for example, compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active pharmaceutical ingredient is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetates, formates and benzoate derivatives of an alcohol, various ester derivatives of a carboxylic acid, or acetamide, formamide and benzamide derivatives of an amine functional group in the active pharmaceutical ingredient.

~~[0086]~~[0080] When ranges are used herein to describe, for example, physical or chemical properties such as molecular weight or chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. Use of the term "about" when referring to a number or a numerical range means that the number or

numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") includes those embodiments such as, for example, an embodiment of any composition of matter, method or process that "consist of" or "consist essentially of" the described features.

~~[0084]~~[0081] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to ten carbon atoms (*e.g.*, C_1-C_{10} alkyl). Whenever it appears herein, a numerical range such as "1 to 10" refers to each integer in the given range - *e.g.*, "1 to 10 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the definition is also intended to cover the occurrence of the term "alkyl" where no numerical range is specifically designated. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl isobutyl, tertiary butyl, pentyl, isopentyl, neopentyl, hexyl, septyl, octyl, nonyl and decyl. The alkyl moiety may be attached to the rest of the molecule by a single bond, such as for example, methyl (Me), ethyl (Et), *n*-propyl (Pr), 1-methylethyl (isopropyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl) and 3-methylhexyl. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$ where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[0085]~~[0082] "Alkylaryl" refers to an -(alkyl)aryl radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

~~[0086]~~[0083] "Alkylhetaryl" refers to an -(alkyl)hetaryl radical where hetaryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

~~[0087]~~[0084] "Alkylheterocycloalkyl" refers to an -(alkyl) heterocycyl radical where alkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heterocycloalkyl and alkyl respectively.

~~[0088]~~[0085] An "alkene" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon double bond, and an "alkyne" moiety refers to a group consisting of at least two carbon atoms and at least one carbon-carbon triple bond. The alkyl moiety, whether saturated or unsaturated, may be branched, straight chain, or cyclic.

~~[0089]~~[0086] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double bond, and having from two to ten carbon atoms (*i.e.*, C_2-C_{10} alkenyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkenyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkenyl moiety may be attached to the rest of the molecule by a single bond, such as for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl and penta-1,4-dienyl. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -$N(R^a)_2$, -C(O)R^a, -C(O)OR^a, -OC(O)$N(R^a)_2$, -C(O)$N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[0090]~~[0087] "Alkenyl-cycloalkyl" refers to an -(alkenyl)cycloalkyl radical where alkenyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkenyl and cycloalkyl respectively.

~~[0091]~~[0088] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to ten carbon atoms (i.e. C_2-C_{10} alkynyl). Whenever it appears herein, a numerical range such as "2 to 10" refers to each integer in the given range - *e.g.*, "2 to 10 carbon atoms" means that the alkynyl group may consist of 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. The alkynyl may be attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl and hexynyl. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[0092]~~[0089] "Alkynyl-cycloalkyl" refers to an -(alkynyl)cycloalkyl radical where alkynyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for alkynyl and cycloalkyl respectively.

~~[0093]~~[0090] "Carboxaldehyde" refers to a -(C=O)H radical.

~~[0094]~~[0091] "Carboxyl" refers to a -(C=O)OH radical.

~~[0095]~~[0092] "Cyano" refers to a -CN radical.

~~[0096]~~[0093] "Cycloalkyl" refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen, and may be saturated, or partially unsaturated. Cycloalkyl groups include groups having from 3 to 10 ring atoms (i.e. C_2-C_{10} cycloalkyl). Whenever it appears herein, a numerical range such as "3 to 10" refers to each integer in the given range - *e.g.*, "3 to 10 carbon atoms" means that the cycloalkyl group may consist of 3 carbon atoms, *etc.*, up to and including 10 carbon atoms. Illustrative examples of cycloalkyl groups include, but are not limited to the following moieties: cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl,

cyclohexenyl, cycloseptyl, cyclooctyl, cyclononyl, cyclodecyl, norbornyl, and the like. Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[0097]~~[0094] "Cycloalkyl-alkenyl" refers to a -(cycloalkyl)alkenyl radical where cycloalkyl and alkenyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and alkenyl, respectively.

~~[0098]~~[0095] "Cycloalkyl-heterocycloalkyl" refers to a -(cycloalkyl)heterocycloalkyl radical where cycloalkyl and heterocycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heterocycloalkyl, respectively.

~~[0099]~~[0096] "Cycloalkyl-heteroaryl" refers to a -(cycloalkyl)heteroaryl radical where cycloalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for cycloalkyl and heteroaryl, respectively.

~~[00100]~~[0097] The term "alkoxy" refers to the group -O-alkyl, including from 1 to 8 carbon atoms of a straight, branched, cyclic configuration and combinations thereof attached to the parent structure through an oxygen. Examples include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy and cyclohexyloxy. "Lower alkoxy" refers to alkoxy groups containing one to six carbons.

~~[00101]~~[0098] The term "substituted alkoxy" refers to alkoxy wherein the alkyl constituent is substituted (*i.e.*, -O-(substituted alkyl)). Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxy group is optionally substituted by one or more

substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00103]~~[00099] The term "alkoxycarbonyl" refers to a group of the formula (alkoxy)(C=O)- attached through the carbonyl carbon wherein the alkoxy group has the indicated number of carbon atoms. Thus a C_1-C_6 alkoxycarbonyl group is an alkoxy group having from 1 to 6 carbon atoms attached through its oxygen to a carbonyl linker. "Lower alkoxycarbonyl" refers to an alkoxycarbonyl group wherein the alkoxy group is a lower alkoxy group.

~~[00103]~~[001000] The term "substituted alkoxycarbonyl" refers to the group (substituted alkyl)-O-C(O)- wherein the group is attached to the parent structure through the carbonyl functionality. Unless stated otherwise specifically in the specification, the alkyl moiety of an alkoxycarbonyl group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00104]~~[001011] "Acyl" refers to the groups (alkyl)-C(O)-, (aryl)-C(O)-, (heteroaryl)-C(O)-, (heteroalkyl)-C(O)- and (heterocycloalkyl)-C(O)-, wherein the group is attached to the parent structure through the carbonyl functionality. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the alkyl, aryl or heteroaryl moiety of the acyl group is optionally substituted by one or more substituents which are independently alkyl,

heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -$N(R^a)_2$, -C(O)R^a, -C(O)OR^a, -OC(O)$N(R^a)_2$, -C(O)$N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00105]~~[001102] "Acyloxy" refers to a R(C=O)O- radical wherein R is alkyl, aryl, heteroaryl, heteroalkyl or heterocycloalkyl, which are as described herein. If the R radical is heteroaryl or heterocycloalkyl, the hetero ring or chain atoms contribute to the total number of chain or ring atoms. Unless stated otherwise specifically in the specification, the R of an acyloxy group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -$N(R^a)_2$, -C(O)R^a, -C(O)OR^a, -OC(O)$N(R^a)_2$, -C(O)$N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00106]~~[001103] "Amino" or "amine" refers to a -$N(R^a)_2$ radical group, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl, unless stated otherwise specifically in the specification. When a -$N(R^a)_2$ group has two R^a substituents other than hydrogen, they can be combined with the nitrogen atom to form a 4-, 5-, 6- or 7-membered ring. For example, -$N(R^a)_2$ is intended to include, but is not limited to, 1-pyrrolidinyl and 4-morpholinyl. Unless stated otherwise specifically in the specification, an amino group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, -OR^a, -SR^a, -OC(O)-R^a, -$N(R^a)_2$, -C(O)R^a, -C(O)OR^a, -OC(O)$N(R^a)_2$, -C(O)$N(R^a)_2$, -$N(R^a)C(O)OR^a$, -

$N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00103]~~[001104] The term "substituted amino" also refers to *N*-oxides of the groups $-NHR^d$, and NR^dR^d each as described above. *N*-oxides can be prepared by treatment of the corresponding amino group with, for example, hydrogen peroxide or m-chloroperoxybenzoic acid.

~~[00108]~~[001105] "Amide" or "amido" refers to a chemical moiety with formula $-C(O)N(R)_2$ or -NHC(O)R, where R is selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), each of which moiety may itself be optionally substituted. The R_2 of $-N(R)_2$ of the amide may optionally be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. Unless stated otherwise specifically in the specification, an amido group is optionally substituted independently by one or more of the substituents as described herein for alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl. An amide may be an amino acid or a peptide molecule attached to a compound of Formula (I), thereby forming a prodrug. The procedures and specific groups to make such amides are known to those of skill in the art and can readily be found in seminal sources such as T. H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis,* 3rd Ed., John Wiley & Sons, New York (1999).

~~[00109]~~[001106] "Aromatic" or "aryl" or "Ar" refers to an aromatic radical with six to ten ring atoms (*e.g.*, C_6-C_{10} aromatic or C_6-C_{10} aryl) which has at least one ring having a conjugated pi electron system which is carbocyclic (*e.g.*, phenyl, fluorenyl, and naphthyl). Bivalent radicals formed from substituted benzene derivatives and having the free valences at ring atoms are named as substituted phenylene radicals. Bivalent radicals derived from univalent polycyclic hydrocarbon radicals whose names end in "-yl" by removal of one hydrogen atom from the carbon atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical, *e.g.*, a naphthyl group with two points of attachment is termed naphthylidene. Whenever it appears herein, a numerical range such as "6 to 10" refers to each integer in the given range; *e.g.*, "6 to 10 ring atoms" means that the aryl group may consist of 6

ring atoms, 7 ring atoms, *etc.*, up to and including 10 ring atoms. The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Unless stated otherwise specifically in the specification, an aryl moiety is optionally substituted by one or more substituents which are independently alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00114]~~[001107] "Aralkyl" or "arylalkyl" refers to an (aryl)alkyl-radical where aryl and alkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for aryl and alkyl respectively.

~~[00114]~~[001108] "Ester" refers to a chemical radical of formula -COOR, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The procedures and specific groups to make esters are known to those of skill in the art and can readily be found in seminal sources such as T. H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis,* 3rd Ed., John Wiley & Sons, New York (1999). Unless stated otherwise specifically in the specification, an ester group is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, trifluoromethyl, trifluoromethoxy, nitro, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00113]~~[001109] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl,

difluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. The alkyl part of the fluoroalkyl radical may be optionally substituted as defined above for an alkyl group.

~~[0013]~~[001101] "Halo," "halide," or, alternatively, "halogen" is intended to mean fluoro, chloro, bromo or iodo. The terms "haloalkyl," "haloalkenyl," "haloalkynyl" and "haloalkoxy" include alkyl, alkenyl, alkynyl and alkoxy structures that are substituted with one or more halo groups or with combinations thereof. For example, the terms "fluoroalkyl" and "fluoroalkoxy" include haloalkyl and haloalkoxy groups, respectively, in which the halo is fluorine.

~~[0014]~~[001111] "Heteroalkyl," "heteroalkenyl," and "heteroalkynyl" include optionally substituted alkyl, alkenyl and alkynyl radicals and which have one or more skeletal chain atoms selected from an atom other than carbon, *e.g.*, oxygen, nitrogen, sulfur, phosphorus or combinations thereof. A numerical range may be given - *e.g.*, C_1-C_4 heteroalkyl which refers to the chain length in total, which in this example is 4 atoms long. A heteroalkyl group may be substituted with one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[0015]~~[001112] "Heteroalkylaryl" refers to an -(heteroalkyl)aryl radical where heteroalkyl and aryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and aryl, respectively.

~~[0016]~~[001113] "Heteroalkylheteroaryl" refers to an -(heteroalkyl)heteroaryl radical where heteroalkyl and heteroaryl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heteroaryl, respectively.

~~[0017]~~[001114] "Heteroalkylheterocycloalkyl" refers to an -(heteroalkyl)heterocycloalkyl radical where heteroalkyl and heterocycloalkyl are as disclosed herein and which are optionally

substituted by one or more of the substituents described as suitable substituents for heteroalkyl and heterocycloalkyl, respectively.

~~[0018]~~[0015] "Heteroalkylcycloalkyl" refers to an -(heteroalkyl)cycloalkyl radical where heteroalkyl and cycloalkyl are as disclosed herein and which are optionally substituted by one or more of the substituents described as suitable substituents for heteroalkyl and cycloalkyl, respectively.

~~[0019]~~[0016] "Heteroaryl" or "heteroaromatic" or "HetAr" refers to a 5- to 18-membered aromatic radical (*e.g.*, C_5-C_{13} heteroaryl) that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur, and which may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system. Whenever it appears herein, a numerical range such as "5 to 18" refers to each integer in the given range - *e.g.*, "5 to 18 ring atoms" means that the heteroaryl group may consist of 5 ring atoms, 6 ring atoms, etc., up to and including 18 ring atoms. Bivalent radicals derived from univalent heteroaryl radicals whose names end in "-yl" by removal of one hydrogen atom from the atom with the free valence are named by adding "-idene" to the name of the corresponding univalent radical - *e.g.*, a pyridyl group with two points of attachment is a pyridylidene. A *N*-containing "heteroaromatic" or "heteroaryl" moiety refers to an aromatic group in which at least one of the skeletal atoms of the ring is a nitrogen atom. The polycyclic heteroaryl group may be fused or non-fused. The heteroatom(s) in the heteroaryl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl may be attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[*d*]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[*b*][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzoxazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzofurazanyl, benzothiazolyl, benzothienyl(benzothiophenyl), benzothieno[3,2-*d*]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[*d*]pyrimidinyl, 6,7-dihydro-5*H*-cyclopenta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6-dihydrobenzo[*h*]quinazolinyl, 5,6-dihydrobenzo[*h*]cinnolinyl, 6,7-dihydro-5*H*-benzo[6,7]cyclohepta[1,2-*c*]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furazanyl, furanonyl, furo[3,2-*c*]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyrimidinyl, 5,6,7,8,9,10-

hexahydrocycloocta[*d*]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[*d*]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyranyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-*d*]pyrimidinyl, pyrido[3,4-*d*]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5*H*-cyclohepta[4,5]thieno[2,3-*d*]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-*c*]pyridazinyl, thiazolyl, thiadiazolyl, thiapyranyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-*d*]pyrimidinyl, thieno[3,2-*d*]pyrimidinyl, thieno[2,3-*c*]pyridinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl moiety is optionally substituted by one or more substituents which are independently: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-OC(O)N(R^a)_2$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-N(R^a)C(O)R^a$, $-N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00120]~~[001171] Substituted heteroaryl also includes ring systems substituted with one or more oxide (-O-) substituents, such as, for example, pyridinyl *N*-oxides.

~~[00121]~~[001181] "Heteroarylalkyl" refers to a moiety having an aryl moiety, as described herein, connected to an alkylene moiety, as described herein, wherein the connection to the remainder of the molecule is through the alkylene group.

~~[00122]~~[001191] "Heterocycloalkyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Whenever it appears herein, a numerical range such as "3 to 18" refers to each integer in the given range - *e.g.*, "3 to 18 ring atoms" means that the

heterocycloalkyl group may consist of 3 ring atoms, 4 ring atoms, *etc*., up to and including 18 ring atoms. Unless stated otherwise specifically in the specification, the heterocycloalkyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. The heteroatoms in the heterocycloalkyl radical may be optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocycloalkyl radical is partially or fully saturated. The heterocycloalkyl may be attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocycloalkyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, a heterocycloalkyl moiety is optionally substituted by one or more substituents which independently are: alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, hydroxy, halo, cyano, nitro, oxo, thioxo, trimethylsilanyl, -OR^a, -SR^a, -$OC(O)$-R^a, -$N(R^a)_2$, -$C(O)R^a$, -$C(O)OR^a$, -$OC(O)N(R^a)_2$, -$C(O)N(R^a)_2$, -$N(R^a)C(O)OR^a$, -$N(R^a)C(O)R^a$, -$N(R^a)C(O)N(R^a)_2$, $N(R^a)C(NR^a)N(R^a)_2$, -$N(R^a)S(O)_tR^a$ (where t is 1 or 2), -$S(O)_tOR^a$ (where t is 1 or 2), -$S(O)_tN(R^a)_2$ (where t is 1 or 2), or $PO_3(R^a)_2$, where each R^a is independently hydrogen, alkyl, fluoroalkyl, carbocyclyl, carbocyclylalkyl, aryl, aralkyl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl or heteroarylalkyl.

~~[00123]~~[001201] "Heterocycloalkyl" also includes bicyclic ring systems wherein one non-aromatic ring, usually with 3 to 7 ring atoms, contains at least 2 carbon atoms in addition to 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen, as well as combinations comprising at least one of the foregoing heteroatoms; and the other ring, usually with 3 to 7 ring atoms, optionally contains 1-3 heteroatoms independently selected from oxygen, sulfur, and nitrogen and is not aromatic.

~~[00124]~~[001211] "Isomers" are different compounds that have the same molecular formula. "Stereoisomers" are isomers that differ only in the way the atoms are arranged in space - *i.e.*, having a different stereochemical configuration. "Enantiomers" are a pair of stereoisomers that

are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon can be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and can thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that can be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. The present chemical entities, pharmaceutical compositions and methods are meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)-isomers can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers.

~~[0043]~~[001221] "Enantiomeric purity" as used herein refers to the relative amounts, expressed as a percentage, of the presence of a specific enantiomer relative to the other enantiomer. For example, if a compound, which may potentially have an (*R*)- or an (*S*)-isomeric configuration, is present as a racemic mixture, the enantiomeric purity is about 50% with respect to either the (*R*)- or (*S*)-isomer. If that compound has one isomeric form predominant over the other, for example, 80% (*S*)- and 20% (*R*)-, the enantiomeric purity of the compound with respect to the (*S*)-isomeric form is 80%. The enantiomeric purity of a compound can be determined in a number of ways known in the art, including but not limited to chromatography using a chiral support, polarimetric measurement of the rotation of polarized light, nuclear magnetic resonance spectroscopy using chiral shift reagents which include but are not limited to lanthanide containing chiral complexes or the Pirkle alcohol, or derivatization of a compounds using a chiral compound such as Mosher's acid followed by chromatography or nuclear magnetic resonance spectroscopy.

~~[00126]~~[00123] "Moiety" refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

~~[00127]~~[00124] "Nitro" refers to the $-NO_2$ radical.

~~[00128]~~[00125] "Oxa" refers to the -O- radical.

~~[00129]~~[00126] "Oxo" refers to the =O radical.

~~[00130]~~[00127] "Tautomers" are structurally distinct isomers that interconvert by tautomerization. "Tautomerization" is a form of isomerization and includes prototropic or proton-shift tautomerization, which is considered a subset of acid-base chemistry. "Prototropic tautomerization" or "proton-shift tautomerization" involves the migration of a proton accompanied by changes in bond order, often the interchange of a single bond with an adjacent double bond. Where tautomerization is possible (e.g. in solution), a chemical equilibrium of tautomers can be reached. An example of tautomerization is keto-enol tautomerization. A specific example of keto-enol tautomerization is the interconversion of pentane-2,4-dione and 4-hydroxypent-3-en-2-one tautomers. Another example of tautomerization is phenol-keto tautomerization. A specific example of phenol-keto tautomerization is the interconversion of pyridin-4-ol and pyridin-4(1*H*)-one tautomers.

~~[00131]~~[00128] The terms "enantiomerically enriched," "enantiomerically pure," and "non-racemic," as used herein, refer to compositions in which the percent by weight of one enantiomer is greater than the amount of that one enantiomer in a control mixture of the racemic composition (e.g., greater than 1:1 by weight). For example, an enantiomerically enriched preparation of the (S)-enantiomer, means a preparation of the compound having greater than 50% by weight of the (S)-enantiomer relative to the (*R*)-enantiomer, such as at least 75% by weight, such as at least 80% by weight. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially enantiomerically enriched," "substantially enantiomerically pure," or a "substantially non-racemic" preparation, which refers to preparations of compositions which have at least 85% by weight of one enantiomer relative to the other enantiomer, such as at least 90% by weight, and such as at least 95% by weight. The terms "diastereomerically enriched" and "diastereomerically pure," as used herein, refer to

compositions in which the percent by weight of one diastereomer is greater than the amount of that one diastereomer in a control mixture of diastereomers. In some embodiments, the enrichment can be significantly greater than 80% by weight, providing a "substantially diastereomerically enriched" or "substantially diastereomerically pure" preparation, which refers to preparations of compositions which have at least 85% by weight of one diastereomer relative to other diastereomers, such as at least 90% by weight, and such as at least 95% by weight.

~~[00132]~~[001291] In preferred embodiments, the enantiomerically enriched composition has a higher potency with respect to therapeutic utility per unit mass than does the racemic mixture of that composition. Enantiomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred enantiomers can be prepared by asymmetric syntheses. See, for example, Jacques, *et al.*, *Enantiomers, Racemates and Resolutions*, Wiley Interscience, New York (1981); E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York (1994).

~~[00133]~~[001301] A "leaving group or atom" is any group or atom that will, under selected reaction conditions, cleave from the starting material, thus promoting reaction at a specified site. Examples of such groups, unless otherwise specified, include halogen atoms and mesyloxy, p-nitrobenzensulphonyloxy and tosyloxy groups.

~~[00134]~~[001311] "Protecting group" is intended to mean a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site and the group can then be readily removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T. H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley & Sons, New York (1999).

~~[00135]~~[001321] "Solvate" refers to a compound in physical association with one or more molecules of a pharmaceutically acceptable solvent.

~~[00136]~~[001331] "Substituted" means that the referenced group may have attached one or more additional moieties individually and independently selected from, for example, acyl, alkyl, alkylaryl, cycloalkyl, aralkyl, aryl, carbohydrate, carbonate, heteroaryl, heterocycloalkyl,

hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, ester, thiocarbonyl, isocyanato, thiocyanato, isothiocyanato, nitro, oxo, perhaloalkyl, perfluoroalkyl, phosphate, silyl, sulfinyl, sulfonyl, sulfonamidyl, sulfoxyl, sulfonate, urea, and amino, including mono- and di-substituted amino groups, and protected derivatives thereof. The substituents themselves may be substituted, for example, a cycloalkyl substituent may itself have a halide substituent at one or more of its ring carbons.

~~[00137]~~[00134] "Sulfanyl" refers to groups that include -S-(optionally substituted alkyl), -S-(optionally substituted aryl), -S-(optionally substituted heteroaryl) and -S-(optionally substituted heterocycloalkyl).

~~[00138]~~[00135] "Sulfinyl" refers to groups that include -S(O)-H, -S(O)-(optionally substituted alkyl), -S(O)-(optionally substituted amino), -S(O)-(optionally substituted aryl), -S(O)-(optionally substituted heteroaryl) and -S(O)-(optionally substituted heterocycloalkyl).

~~[00139]~~[00136] "Sulfonyl" refers to groups that include $-S(O_2)-H$, $-S(O_2)-$(optionally substituted alkyl), $-S(O_2)-$(optionally substituted amino), $-S(O_2)-$(optionally substituted aryl), $-S(O_2)-$(optionally substituted heteroaryl), and $-S(O_2)-$(optionally substituted heterocycloalkyl).

~~[00140]~~[00137] "Sulfonamidyl" or "sulfonamido" refers to a $-S(=O)_2-NRR$ radical, where each R is selected independently from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). The R groups in -NRR of the $-S(=O)_2-NRR$ radical may be taken together with the nitrogen to which it is attached to form a 4-, 5-, 6- or 7-membered ring. A sulfonamido group is optionally substituted by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

~~[00141]~~[00138] "Sulfoxyl" refers to a $-S(=O)_2OH$ radical.

~~[00142]~~[00139] "Sulfonate" refers to a $-S(=O)_2-OR$ radical, where R is selected from the group consisting of alkyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon). A sulfonate group is optionally substituted on R by one or more of the substituents described for alkyl, cycloalkyl, aryl, heteroaryl, respectively.

~~[001 43]~~[00140] Compounds of the invention also include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. "Crystalline form" and "polymorph" are intended to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to.

~~[001 44]~~[00141] Compounds of the invention also include antibodies. The terms "antibody" and its plural form "antibodies" refer to whole immunoglobulins and any antigen-binding fragment ("antigen-binding portion") or single chains thereof. An "antibody" further refers to a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, or an antigen-binding portion thereof. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as V_H) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as V_L) and a light chain constant region. The light chain constant region is comprised of one domain, C_L. The V_H and V_L regions of an antibody may be further subdivided into regions of hypervariability, which are referred to as complementarity determining regions (CDR) or hypervariable regions (HVR), and which can be interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen epitope or epitopes. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system.

~~[001 45]~~[00142] The terms "monoclonal antibody," "mAb," "monoclonal antibody composition," or their plural forms refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding

specificity and affinity for a particular epitope. Monoclonal antibodies specific to CD20 can be made using knowledge and skill in the art of injecting test subjects with CD20 antigen and then isolating hybridomas expressing antibodies having the desired sequence or functional characteristics. DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the monoclonal antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Recombinant production of antibodies will be described in more detail below.

~~[00146]~~[001431] The terms "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen such as CD20. It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the V_L, V_H, C_L and CH1 domains; (ii) a F(ab′)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the V_H and CH1 domains; (iv) a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody, (v) a domain antibody (dAb) fragment (Ward *et al.*, *Nature,* **1989,** *341,* 544-546), which may consist of a V_H or a V_L domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, V_L and V_H, are coded for by separate genes, they can be joined, using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the V_L and V_H regions pair to form monovalent molecules known as single chain Fv (scFv); see, for example, Bird *et al.*, *Science* **1988,** *242,* 423-426; and Huston *et al.*, *Proc. Natl. Acad. Sci. USA* **1988,** *85,* 5879-5883). Such scFv chain antibodies are also intended to be encompassed within the terms "antigen-binding portion" or "antigen-binding fragment" of an antibody. These antibody fragments are obtained using conventional techniques known to those with skill in the art, and the fragments are

screened for utility in the same manner as are intact antibodies.

~~[00147]~~[001444] The term "human antibody," as used herein, is intended to include antibodies having variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. Furthermore, if the antibody contains a constant region, the constant region also is derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*). The term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

~~[00148]~~[001445] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human germline immunoglobulin sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

~~[00149]~~[001446] The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as (a) antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom (described further below), (b) antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, (c) antibodies isolated from a recombinant, combinatorial human antibody library, and (d) antibodies prepared, expressed, created or isolated by any other means that involve splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while

derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

~~[00150]~~[001471] As used herein, "isotype" refers to the antibody class (e.g., IgM or IgG1) that is encoded by the heavy chain constant region genes.

~~[00151]~~[001481] The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen."

~~[00152]~~[001491] The term "human antibody derivatives" refers to any modified form of the human antibody, e.g., a conjugate of the antibody and another agent or antibody. The term "conjugate" or "immunoconjugate" refers to an antibody, or a fragment thereof, conjugated to a therapeutic moiety, such as a bacterial toxin, a cytotoxic drug or a radionuclide-containing toxin. Toxic moieties can be conjugated to antibodies of the invention using methods available in the art.

~~[00153]~~[001501] The terms "humanized antibody," "humanized antibodies," and "humanized" are intended to refer to antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Additional framework region modifications may be made within the human framework sequences. Humanized forms of non-human (for example, murine) antibodies are chimeric antibodies that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a 15 hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or nonhuman primate having the desired specificity, affinity, and capacity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human

immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones *et al.*, *Nature* **1986,** *321,* 522-525; Riechmann *et al.*, *Nature* **1988,** *332,* 323-329; and Presta, *Curr. Op. Struct. Biol.* **1992,** *2,* 593-596.

~~[00154]~~[001511] The term "chimeric antibody" is intended to refer to antibodies in which the variable region sequences are derived from one species and the constant region sequences are derived from another species, such as an antibody in which the variable region sequences are derived from a mouse antibody and the constant region sequences are derived from a human antibody.

~~[00155]~~[001521] A "diabody" is a small antibody fragment with two antigen-binding sites. The fragment comprises a heavy chain variable domain (V_H) connected to a light chain variable domain (V_L) in the same polypeptide chain (V_H-V_L or V_L-V_H). By using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, *e.g.*, European Patent No. EP 404,097, International Patent Publication No.WO 93/11161; and Bolliger *et al.*, *Proc. Natl. Acad. Sci. USA* **1993,** *90,* 6444-6448.

~~[00156]~~[001531] The term "glycosylation" refers to a modified derivative of an antibody. An aglycoslated antibody lacks glycosylation. Glycosylation can be altered to, for example, increase the affinity of the antibody for antigen. Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Aglycosylation may increase the affinity of the antibody for antigen, as described in U.S. Patent Nos. 5,714,350 and 6,350,861. Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered

glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, the cell lines Ms704, Ms705, and Ms709 lack the fucosyltransferase gene, FUT8 (alpha (1,6) fucosyltransferase), such that antibodies expressed in the Ms704, Ms705, and Ms709 cell lines lack fucose on their carbohydrates. The Ms704, Ms705, and Ms709 FUT8−/− cell lines were created by the targeted disruption of the FUT8 gene in CHO/DG44 cells using two replacement vectors (see e.g. U.S. Patent Publication No. 2004/0110704 or Yamane-Ohnuki, *et al.*, *Biotechnol. Bioeng.*, **2004,** *87,* 614-622). As another example, European Patent No. EP 1,176,195 describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation by reducing or eliminating the alpha 1,6 bond-related enzyme, and also describes cell lines which have a low enzyme activity for adding fucose to the N-acetylglucosamine that binds to the Fc region of the antibody or does not have the enzyme activity, for example the rat myeloma cell line YB2/0 (ATCC CRL 1662). International Patent Publication WO 03/035835 describes a variant CHO cell line, Lec 13 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, *et al.*, *J. Biol. Chem.* **2002,** *277,* 26733-26740. International Patent Publication WO 99/54342 describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)-N-acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana, *et al.*, *Nat. Biotech.* **1999,** *17*, 176-180). Alternatively, the fucose residues of the antibody may be cleaved off using a fucosidase enzyme. For example, the fucosidase alpha-L-fucosidase removes fucosyl residues from antibodies as described in Tarentino, *et al., Biochem.* **1975,** *14,* 5516-5523.

~~[001537]~~[001541] "Pegylation" refers to a modified antibody, or a fragment thereof, that typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. Pegylation may, for example, increase the biological (e.g., serum) half life of the antibody. Preferably, the pegylation is carried out via an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the

forms of PEG that have been used to derivatize other proteins, such as mono (C_1-C_{10}) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. The antibody to be pegylated may be an aglycosylated antibody. Methods for pegylation are known in the art and can be applied to the antibodies of the invention. See, for example, European Patent Nos. EP 0154316 and EP 0401384.

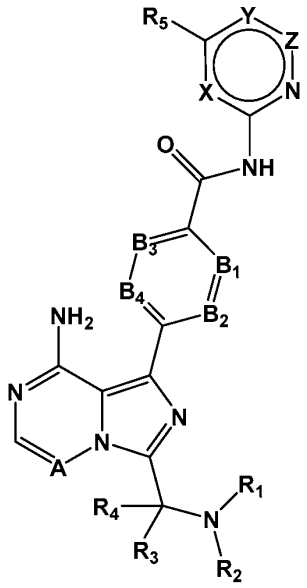
~~[00158]~~[00155] As used herein, an antibody that "specifically binds to human CD20" is intended to refer to an antibody that binds to human CD20 with a K_D of 1×10^{-7} M or less, more preferably 5×10^{-8} M or less, more preferably 1×10^{-8} M or less, more preferably 5×10^{-9} M or less.

~~[00159]~~[00156] The term "radioisotope-labeled complex" refers to both non-covalent and covalent attachment of a radioactive isotope, such as ^{90}Y, ^{111}In, or ^{131}I, to an antibody.

~~[00160]~~[00157] The term "biosimilar" means a biological product that is highly similar to a U.S. licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. Furthermore, a similar biological or "biosimilar" medicine is a biological medicine that is similar to another biological medicine that has already been authorized for use by the European Medicines Agency. The term "biosimilar" is also used synonymously by other national and regional regulatory agencies. Biological products or biological medicines are medicines that are made by or derived from a biological source, such as a bacterium or yeast. They can consist of relatively small molecules such as human insulin or erythropoietin, or complex molecules such as monoclonal antibodies. For example, if the reference anti-CD20 monoclonal antibody is rituximab, an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to rituximab is a "biosimilar to" rituximab or is a "biosimilar thereof" rituximab.

BTK Inhibitors

~~[00161]~~[00158] In an embodiment, the BTK inhibitor is a compound of Formula (I):



Formula (I)

or a pharmaceutically acceptable salt thereof,

wherein:

X is CH, N, O or S;

Y is $C(R_6)$, N, O or S;

Z is CH, N or bond;

A is CH or N;

B_1 is N or $C(R_7)$;

B_2 is N or $C(R_8)$;

B_3 is N or $C(R_9)$;

B_4 is N or $C(R_{10})$;

R_1 is $R_{11}C(=O)$, $R_{12}S(=O)$, $R_{13}S(=O)_2$ or (C_{1-6})alkyl optionally substituted with R_{14};

R_2 is H, (C_{1-3})alkyl or (C_{3-7})cycloalkyl;

R_3 is H, (C_{1-6})alkyl or (C_{3-7})cycloalkyl); or

R_2 and R_3 form, together with the N and C atom they are attached to, a (C_{3-7})heterocycloalkyl optionally substituted with one or more fluorine, hydroxyl, (C_{1-3})alkyl, (C_{1-3})alkoxy or oxo;

R_4 is H or (C_{1-3})alkyl;

R_5 is H, halogen, cyano, (C_{1-4})alkyl, (C_{1-3})alkoxy, (C_{3-6})cycloalkyl, any alkyl group of which is optionally substituted with one or more halogen; or R_5 is (C_{6-10})aryl or (C_{2-6})heterocycloalkyl;

R_6 is H or (C_{1-3})alkyl; or

R_5 and R_6 together may form a (C_{3-7})cycloalkenyl or (C_{2-6})heterocycloalkenyl, each optionally substituted with (C_{1-3})alkyl or one or more halogens;

R_7 is H, halogen, CF_3, (C_{1-3})alkyl or (C_{1-3})alkoxy;

R_8 is H, halogen, CF_3, (C_{1-3})alkyl or (C_{1-3})alkoxy; or

R_7 and R_8 together with the carbon atoms they are attached to, form (C_{6-10})aryl or (C_{1-9})heteroaryl;

R_9 is H, halogen, (C_{1-3})alkyl or (C_{1-3})alkoxy;

R_{10} is H, halogen, (C_{1-3})alkyl or (C_{1-3})alkoxy;

R_{11} is independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl and (C_{2-6})alkynyl, where each alkyl, alkenyl or alkynyl is optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, $[(C_{1-4})$alkyl]amino, di$[(C_{1-4})$alkyl]amino, (C_{1-3})alkoxy, (C_{3-7})cycloalkoxy, (C_{6-10})aryl and (C_{3-7})heterocycloalkyl; or R_{11} is (C_{1-3})alkyl-C(O)-S-(C_{1-3})alkyl; or

R_{11} is (C_{1-5})heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen or cyano;

R_{12} and R_{13} are independently selected from the group consisting of (C_{2-6})alkenyl or (C_{2-6})alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, $[(C_{1-4})$alkyl]amino, di$[(C_{1-4})$alkyl]amino, (C_{1-3})alkoxy, (C_{3-7})cycloalkoxy, (C_{6-10})aryl and (C_{3-7})heterocycloalkyl; or a (C_{1-5})heteroaryl optionally substituted with one or more substituents selected from the group consisting of halogen and cyano; and

R_{14} is independently selected from the group consisting of halogen, cyano, (C_{2-6})alkenyl and (C_{2-6})alkynyl, both optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, (C_{1-4})alkylamino, di$[(C_{1-4})$alkyl]amino, (C_{1-3})alkoxy, (C_{3-7})cycloalkoxy, (C_{6-10})aryl, (C_{1-5})heteroaryl and (C_{3-7})heterocycloalkyl;

with the proviso that:

0 to 2 atoms of X, Y, Z can simultaneously be a heteroatom;

when one atom selected from X, Y is O or S, then Z is a bond and the other atom selected from X, Y can not be O or S;

when Z is C or N then Y is $C(R_6)$ or N and X is C or N;

0 to 2 atoms of B_1, B_2, B_3, and B_4 are N;

with the terms used having the following meanings:

(C_{1-2})alkyl means an alkyl group having 1 to 2 carbon atoms, being methyl or ethyl,

(C_{1-3})alkyl means a branched or unbranched alkyl group having 1-3 carbon atoms, being methyl, ethyl, propyl or isopropyl;

(C_{1-4})alkyl means a branched or unbranched alkyl group having 1-4 carbon atoms, being methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl and *tert*-butyl, (C_{1-3})alkyl groups being preferred;

(C_{1-5})alkyl means a branched or unbranched alkyl group having 1-5 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl and isopentyl, (C_{1-4})alkyl groups being preferred. (C_{1-6})Alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, *n*-pentyl and *n*-hexyl. (C_{1-5})alkyl groups are preferred, (C_{1-4})alkyl being most preferred;

(C_{1-2})alkoxy means an alkoxy group having 1-2 carbon atoms, the alkyl moiety having the same meaning as previously defined;

(C_{1-3})alkoxy means an alkoxy group having 1-3 carbon atoms, the alkyl moiety having the same meaning as previously defined. (C_{1-2})alkoxy groups are preferred;

(C_{1-4})alkoxy means an alkoxy group having 1-4 carbon atoms, the alkyl moiety having the same meaning as previously defined. (C_{1-3})alkoxy groups are preferred, (C_{1-2})alkoxy groups being most preferred;

(C_{2-4})alkenyl means a branched or unbranched alkenyl group having 2-4 carbon atoms, such as ethenyl, 2-propenyl, isobutenyl or 2-butenyl;

(C_{2-6})alkenyl means a branched or unbranched alkenyl group having 2-6 carbon atoms, such as ethenyl, 2-butenyl, and *n*-pentenyl, (C_{2-4})alkenyl groups being most preferred;

(C_{2-4})alkynyl means a branched or unbranched alkynyl group having 2-4 carbon atoms, such as ethynyl, 2-propynyl or 2-butynyl;

(C_{2-6})alkynyl means a branched or unbranched alkynyl group having 2-6 carbon atoms, such as ethynyl, propynyl, *n*-butynyl, *n*-pentynyl, isopentynyl, isohexynyl or *n*-hexynyl. (C_{2-4})alkynyl

groups are preferred; (C_{3-6})cycloalkyl means a cycloalkyl group having 3-6 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl;

(C_{3-7})cycloalkyl means a cycloalkyl group having 3-7 carbon atoms, being cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl;

(C_{2-6})heterocycloalkyl means a heterocycloalkyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S, which may be attached via a heteroatom if feasible, or a carbon atom; preferred heteroatoms are N or O; also preferred are piperidine, morpholine, pyrrolidine and piperazine; with the most preferred (C_{2-6})heterocycloalkyl being pyrrolidine; the heterocycloalkyl group may be attached via a heteroatom if feasible;

(C_{3-7})heterocycloalkyl means a heterocycloalkyl group having 3-7 carbon atoms, preferably 3-5 carbon atoms, and one or two heteroatoms selected from N, O and/or S. Preferred heteroatoms are N or O; preferred (C_{3-7}) heterocycloalkyl groups are azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl or morpholinyl; more preferred (C_{3-7})heterocycloalkyl groups are piperidine, morpholine and pyrrolidine; and the heterocycloalkyl group may be attached via a heteroatom if feasible;

(C_{3-7})cycloalkoxy means a cycloalkyl group having 3-7 carbon atoms, with the same meaning as previously defined, attached via a ring carbon atom to an exocyclic oxygen atom;

(C_{6-10})aryl means an aromatic hydrocarbon group having 6-10 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl or indenyl; the preferred (C_{6-10})aryl group is phenyl;

(C_{1-5})heteroaryl means a substituted or unsubstituted aromatic group having 1-5 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (C_{1-5})heteroaryl may optionally be substituted; preferred (C_{1-5})heteroaryl groups are tetrazolyl, imidazolyl, thiadiazolyl, pyridyl, pyrimidyl, triazinyl, thienyl or furyl, a more preferred (C_{1-5})heteroaryl is pyrimidyl;

(C_{1-9})heteroaryl means a substituted or unsubstituted aromatic group having 1-9 carbon atoms and 1-4 heteroatoms selected from N, O and/or S; the (C_{1-9})heteroaryl may optionally be substituted; preferred (C_{1-9})heteroaryl groups are quinoline, isoquinoline and indole;

[(C_{1-4})alkyl]amino means an amino group, monosubstituted with an alkyl group containing 1-4 carbon atoms having the same meaning as previously defined; preferred [(C_{1-4})alkyl]amino group is methylamino;

di[(C_{1-4})alkyl]amino means an amino group, disubstituted with alkyl group(s), each containing 1-4 carbon atoms and having the same meaning as previously defined; preferred di[(C_{1-4})alkyl]amino group is dimethylamino;

halogen means fluorine, chlorine, bromine or iodine;

(C_{1-3})alkyl-C(O)-S-(C_{1-3})alkyl means an alkyl-carbonyl-thio-alkyl group, each of the alkyl groups having 1 to 3 carbon atoms with the same meaning as previously defined;

(C_{3-7})cycloalkenyl means a cycloalkenyl group having 3-7 carbon atoms, preferably 5-7 carbon atoms; preferred (C_{3-7})cycloalkenyl groups are cyclopentenyl or cyclohexenyl; cyclohexenyl groups are most preferred;

(C_{2-6})heterocycloalkenyl means a heterocycloalkenyl group having 2-6 carbon atoms, preferably 3-5 carbon atoms; and 1 heteroatom selected from N, O and/or S; preferred (C_{2-6})heterocycloalkenyl groups are oxycyclohexenyl and azacyclohexenyl group.

In the above definitions with multifunctional groups, the attachment point is at the last group.

When, in the definition of a substituent, is indicated that "all of the alkyl groups" of said substituent are optionally substituted, this also includes the alkyl moiety of an alkoxy group.

A circle in a ring of Formula (I) indicates that the ring is aromatic.

Depending on the ring formed, the nitrogen, if present in X or Y, may carry a hydrogen.

The term "substituted" means that one or more hydrogens on the designated atom/atoms is/are replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. "Stable compound" or "stable structure" is defined as a compound or structure that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into a drug product containing an efficacious active pharmaceutical ingredient.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

~~[00162]~~[001591] In an embodiment of Formula (I), B_1 is $C(R_7)$; B_2 is $C(R_8)$; B_3 is $C(R_9)$; B_4 is $C(R_{10})$; R_7, R_9, and R_{10} are each H; and R_8 is hydrogen or methyl.

~~[00163]~~[00160] In an embodiment of Formula (I), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl, pyridazyl, triazinyl, thiazolyl, oxazolyl and isoxazolyl.

~~[00164]~~[00161] In an embodiment of Formula (I), the ring containing X, Y and Z is selected from the group consisting of pyridyl, pyrimidyl and pyridazyl.

~~[00165]~~[00162] In an embodiment of Formula (I), the ring containing X, Y and Z is selected from the group consisting of pyridyl and pyrimidyl.

~~[00166]~~[00163] In an embodiment of Formula (I), the ring containing X, Y and Z is pyridyl.

~~[00167]~~[00164] In an embodiment of Formula (I), R_5 is selected from the group consisting of hydrogen, fluorine, methyl, methoxy and trifluoromethyl.

~~[00168]~~[00165] In an embodiment of Formula (I), R_5 is hydrogen.

~~[00169]~~[00166] In an embodiment of Formula (I), R_2 and R_3 together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl, piperidinyl, homopiperidinyl and morpholinyl, optionally substituted with one or more of fluoro, hydroxyl, (C_{1-3})alkyl and (C_{1-3})alkoxy.

~~[00170]~~[00167] In an embodiment of Formula (I), R_2 and R_3 together form a heterocycloalkyl ring selected from the group consisting of azetidinyl, pyrrolidinyl and piperidinyl.

~~[00171]~~[00168] In an embodiment of Formula (I), R_2 and R_3 together form a pyrrolidinyl ring.

~~[00172]~~[00169] In an embodiment of Formula (I), R_1 is independently selected from the group consisting of (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{2-6})alkynyl, each optionally substituted with one or more substituents selected from the group consisting of hydroxyl, (C_{1-4})alkyl, (C_{3-7})cycloalkyl, [(C_{1-4})alkyl]amino, di[(C_{1-4})alkyl] amino, (C_{1-3})alkoxy, (C_{3-7})cycloalkoxy, (C_{6-10})aryl and (C_{3-7})heterocycloalkyl.

~~[00173]~~[00170] In an embodiment of Formula (I), B_1, B_2, B_3 and B_4 are CH; X is N; Y and Z are CH; R_5 is CH_3; A is N; R_2, R_3 and R_4 are H; and R_1 is CO-CH_3.

~~[00174]~~[00171] In an embodiment of Formula (I), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is N; R_2, R_3 and R_4 are H; and R_1 is CO-CH_3.

~~[00175]~~[00172] In an embodiment of Formula (I), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a piperidinyl ring; R_4 is H; and R_1 is CO-ethenyl.

~~[00176]~~[00173] In an embodiment of Formula (I), B_1, B_2, B_3 and B_4 are CH; X, Y and Z are CH; R_5 is H; A is CH; R_2 and R_3 together form a pyrrolidinyl ring; R_4 is H; and R_1 is CO-propynyl.

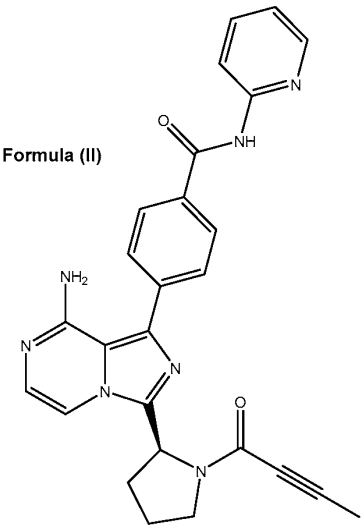
~~[00177]~~[00174] In an embodiment of Formula (I), B_1, B_2, B_3 and B_4 are CH; X, Y and Z are CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a piperidinyl ring; R_4 is H; and R_1 is CO-propynyl.

~~[00178]~~[00175] In an embodiment of Formula (I), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is H; A is CH; R_2 and R_3 together form a morpholinyl ring; R_4 is H; and R_1 is CO-ethenyl.

~~[00179]~~[00176] In an embodiment of Formula (I), B_1, B_2, B_3 and B_4 are CH; X and Y are N; Z is CH; R_5 is CH_3; A is CH; R_2 and R_3 together form a morpholinyl ring; R_4 is H; and R_1 is CO-propynyl.

~~[00180]~~[00177] In a preferred embodiment, the BTK inhibitor is a compound of Formula (II):

Formula (II)



or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The compound of Formula (II) is also known as (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide. In an embodiment, the BTK inhibitor is (*S*)-4-(8-amino-3-(1-(but-2-ynoyl)pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide or a pharmaceutically acceptable salt, solvate, hydrate, cocrystal, or prodrug thereof. The preparation of this compound is described at Example 6 of U.S. Patent Application Publication No. US 2014/0155385 A1, the disclosure of which is incorporated herein by reference. Briefly, the preparation of Formula (II) can be accomplished by the following procedure. 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (also known as HATU, *N*-[(Dimethylamino)-1*H*-1,2,3-triazolo-[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide, and *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate) (18.75 mg, 0.049 mmol) was added to a solution of (*S*)-4-(8-amino-3-(pyrrolidin-2-yl)imidazo[1,5-*a*]pyrazin-1-yl)-*N*-(pyridin-2-yl)benzamide (19.7 mg, 0.049 mmol), triethylamine (20 mg, 0.197 mmol, 0.027 mL) and 2-butynoic acid in dichloromethane (2 mL). The mixture was stirred for 30 minutes at room temperature. The mixture was washed with water dried over magnesium sulfate and concentrated under vacuum. The residue was purified by preparative liquid chromatography. Fractions containing product were collected and reduced to dryness to afford 10.5 mg of Formula (II) (18.0% yield).

Pharmaceutical Compositions

~~[00181]~~[001178] In selected embodiments, the invention provides pharmaceutical compositions for treating lymphoma and leukemia, including CLL and SLL.

~~[00182]~~[001179] The pharmaceutical compositions are typically formulated to provide a therapeutically effective amount of a BTK inhibitor, including the BTK inhibitors of Formula (I) or Formula (II), or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. Where desired, the pharmaceutical compositions contain a pharmaceutically acceptable salt and/or coordination complex thereof, and one or more pharmaceutically acceptable excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Where desired, other active ingredients in addition to a BTK inhibitor of Formula (I) or Formula (II) may be mixed into a preparation or both components may be formulated into separate preparations for use in combination separately or at the same time.

~~[00183]~~[001801] In selected embodiments, the concentration of the BTK inhibitors of Formula (I) or Formula (II) provided in the pharmaceutical compositions of the invention is less than, for example, 100%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v or v/v.

~~[00184]~~[001811] In selected embodiments, the concentration of the BTK inhibitors of Formula (I) or Formula (II) provided in the pharmaceutical compositions of the invention is independently greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25% 19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%, 16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%, 13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%, 10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%, 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%, 4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%, 1.75%, 1.50%, 125%, 1%, 0.5%, 0.4%, 0.3%, 0.2%,

0.1%, 0.09%, 0.08%, 0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002% or 0.0001% w/w, w/v, or v/v.

~~[00185]~~[001182] In selected embodiments, the concentration of the BTK inhibitors of Formula (I) or Formula (II) is independently in the range from approximately 0.0001% to approximately 50%, approximately 0.001% to approximately 40%, approximately 0.01% to approximately 30%, approximately 0.02% to approximately 29%, approximately 0.03% to approximately 28%, approximately 0.04% to approximately 27%, approximately 0.05% to approximately 26%, approximately 0.06% to approximately 25%, approximately 0.07% to approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09% to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2% to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4% to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6% to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8% to approximately 14%, approximately 0.9% to approximately 12% or approximately 1% to approximately 10% w/w, w/v or v/v.

~~[00186]~~[001183] In selected embodiments, the concentration of the BTK inhibitors of Formula (I) or Formula (II) is independently in the range from approximately 0.001% to approximately 10%, approximately 0.01% to approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03% to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

~~[00187]~~[001184] In selected embodiments, the amount of the BTK inhibitors of Formula (I) or Formula (II) is independently equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007

g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g or 0.0001 g.

~~[00188]~~[001885] In selected embodiments, the amount of the BTK inhibitors of Formula (I) or Formula (II) is independently more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, 0.15 g, 0.2 g, 0.25 g, 0.3 g, 0.35 g, 0.4 g, 0.45 g, 0.5 g, 0.55 g, 0.6 g, 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5 g, 7 g, 7.5 g, 8 g, 8.5 g, 9 g, 9.5 g or 10 g.

~~[00189]~~[001886] The BTK inhibitors of Formula (I) or Formula (II) are effective over a wide dosage range. For example, in the treatment of adult humans, dosages independently ranging from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that may be used. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the gender and age of the subject to be treated, the body weight of the subject to be treated, and the preference and experience of the attending physician.

~~[00190]~~[001887] Described below are non-limiting exemplary pharmaceutical compositions and methods for preparing the same.

Pharmaceutical Compositions for Oral Administration

~~[00191]~~[001888] In selected embodiments, the invention provides a pharmaceutical composition for oral administration containing a BTK inhibitor of Formula (I) or Formula (II), and a pharmaceutical excipient suitable for oral administration.

~~[00192]~~[001889] In selected embodiments, the invention provides a solid pharmaceutical composition for oral administration containing: (i) an effective amount of a BTK inhibitor of Formula (I) or Formula (II), in combination and (ii) a pharmaceutical excipient suitable for oral administration. In selected embodiments, the composition further contains (iii) an effective amount of at least one additional active ingredient.

~~[00193]~~[001910] In selected embodiments, the pharmaceutical composition may be a liquid pharmaceutical composition suitable for oral consumption. Pharmaceutical compositions of the invention suitable for oral administration can be presented as discrete dosage forms, such as capsules, cachets, or tablets, or liquids or aerosol sprays each containing a predetermined amount of an active ingredient as a powder or in granules, a solution, or a suspension in an aqueous or non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such dosage forms can be prepared by any of the methods of pharmacy, but all methods include the step of bringing the active ingredient(s) into association with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient(s) with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet can be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with an excipient such as, but not limited to, a binder, a lubricant, an inert diluent, and/or a surface active or dispersing agent. Molded tablets can be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

~~[00194]~~[001911] The invention further encompasses anhydrous pharmaceutical compositions and dosage forms since water can facilitate the degradation of some compounds. For example, water may be added (*e.g.*, 5%) in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms of the invention which contain lactose can be made anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected. An anhydrous pharmaceutical composition may be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions may be packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastic or the like, unit dose containers, blister packs, and strip packs.

~~[00195]~~[00192] The BTK inhibitors of Formula (I) or Formula (II) can be combined in an intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier can take a wide variety of forms depending on the form of preparation desired for administration. In preparing the compositions for an oral dosage form, any of the usual pharmaceutical media can be employed as carriers, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as suspensions, solutions, and elixirs) or aerosols; or carriers such as starches, sugars, micro-crystalline cellulose, diluents, granulating agents, lubricants, binders, and disintegrating agents can be used in the case of oral solid preparations, in some embodiments without employing the use of lactose. For example, suitable carriers include powders, capsules, and tablets, with the solid oral preparations. If desired, tablets can be coated by standard aqueous or nonaqueous techniques.

~~[00196]~~[00193] Binders suitable for use in pharmaceutical compositions and dosage forms include, but are not limited to, corn starch, potato starch, or other starches, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, pre-gelatinized starch, hydroxypropyl methyl cellulose, microcrystalline cellulose, and mixtures thereof.

~~[00197]~~[00194] Examples of suitable fillers for use in the pharmaceutical compositions and dosage forms disclosed herein include, but are not limited to, talc, calcium carbonate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof.

~~[00198]~~[00195] Disintegrants may be used in the compositions of the invention to provide tablets that disintegrate when exposed to an aqueous environment. Too much of a disintegrant may produce tablets which disintegrate in the bottle. Too little may be insufficient for disintegration to occur, thus altering the rate and extent of release of the active ingredients from the dosage form. Thus, a sufficient amount of disintegrant that is neither too little nor too much to detrimentally alter the release of the active ingredient(s) may be used to form the dosage forms of the compounds disclosed herein. The amount of disintegrant used may vary based upon the

type of formulation and mode of administration, and may be readily discernible to those of ordinary skill in the art. About 0.5 to about 15 weight percent of disintegrant, or about 1 to about 5 weight percent of disintegrant, may be used in the pharmaceutical composition. Disintegrants that can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums or mixtures thereof.

~~[00199]~~[001196] Lubricants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethylaureate, agar, or mixtures thereof. Additional lubricants include, for example, a syloid silica gel, a coagulated aerosol of synthetic silica, or mixtures thereof. A lubricant can optionally be added, in an amount of less than about 1 weight percent of the pharmaceutical composition.

~~[00200]~~[001197] When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various combinations thereof.

~~[00201]~~[001198] The tablets can be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

~~[00202]~~[001199] Surfactants which can be used to form pharmaceutical compositions and dosage forms of the invention include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. That is, a mixture of hydrophilic surfactants may be employed, a mixture of lipophilic surfactants may be employed, or a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant may be employed.

~~[00203]~~[001200] A suitable hydrophilic surfactant may generally have an HLB value of at least 10, while suitable lipophilic surfactants may generally have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (*i.e.*, hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. However, HLB value of a surfactant is merely a rough guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

~~[00204]~~[002011] Hydrophilic surfactants may be either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

~~[00205]~~[002021] Within the aforementioned group, ionic surfactants include, by way of example: lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acylactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides;

succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

~~[00206]~~[00203] Ionic surfactants may be the ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

~~[00207]~~[00204] Hydrophilic non-ionic surfactants may include, but not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. The polyol may be glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

~~[00208]~~[00205] Other hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400

oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25 glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

~~[00209]~~[002206] Suitable lipophilic surfactants include, by way of example only: fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, preferred lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

~~[00210]~~[002207] In an embodiment, the composition may include a solubilizer to ensure good solubilization and/or dissolution of the compound of the present invention and to minimize precipitation of the compound of the present invention. This can be especially important for compositions for non-oral use, such as for compositions for injection. A solubilizer may also be

added to increase the solubility of the hydrophilic drug and/or other components, such as surfactants, or to maintain the composition as a stable or homogeneous solution or dispersion.

~~[00214]~~[002208] Examples of suitable solubilizers include, but are not limited to, the following: alcohols and polyols, such as ethanol, isopropanol, butanol, benzyl alcohol, ethylene glycol, propylene glycol, butanediols and isomers thereof, glycerol, pentaerythritol, sorbitol, mannitol, transcutol, dimethyl isosorbide, polyethylene glycol, polypropylene glycol, polyvinylalcohol, hydroxypropyl methylcellulose and other cellulose derivatives, cyclodextrins and cyclodextrin derivatives; ethers of polyethylene glycols having an average molecular weight of about 200 to about 6000, such as tetrahydrofurfuryl alcohol PEG ether (glycofurol) or methoxy PEG; amides and other nitrogen-containing compounds such as 2-pyrrolidone, 2-piperidone, Ɛ-caprolactam, *N*-alkylpyrrolidone, *N*-hydroxyalkylpyrrolidone, *N*-alkylpiperidone, *N*-alkylcaprolactam, dimethylacetamide and polyvinylpyrrolidone; esters such as ethyl propionate, tributylcitrate, acetyl triethylcitrate, acetyl tributyl citrate, triethylcitrate, ethyl oleate, ethyl caprylate, ethyl butyrate, triacetin, propylene glycol monoacetate, propylene glycol diacetate, .epsilon.-caprolactone and isomers thereof, δ-valerolactone and isomers thereof, β-butyrolactone and isomers thereof; and other solubilizers known in the art, such as dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidones, monooctanoin, diethylene glycol monoethyl ether, and water.

~~[00215]~~[002209] Mixtures of solubilizers may also be used. Examples include, but not limited to, triacetin, triethylcitrate, ethyl oleate, ethyl caprylate, dimethylacetamide, N-methylpyrrolidone, N-hydroxyethylpyrrolidone, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cyclodextrins, ethanol, polyethylene glycol 200-100, glycofurol, transcutol, propylene glycol, and dimethyl isosorbide. Particularly preferred solubilizers include sorbitol, glycerol, triacetin, ethyl alcohol, PEG-400, glycofurol and propylene glycol.

~~[00216]~~[002210] The amount of solubilizer that can be included is not particularly limited. The amount of a given solubilizer may be limited to a bioacceptable amount, which may be readily determined by one of skill in the art. In some circumstances, it may be advantageous to include amounts of solubilizers far in excess of bioacceptable amounts, for example to maximize the concentration of the drug, with excess solubilizer removed prior to providing the composition to a patient using conventional techniques, such as distillation or evaporation. Thus, if present,

the solubilizer can be in a weight ratio of 10%, 25%, 50%, 100%, or up to about 200% by weight, based on the combined weight of the drug, and other excipients. If desired, very small amounts of solubilizer may also be used, such as 5%, 2%, 1% or even less. Typically, the solubilizer may be present in an amount of about 1% to about 100%, more typically about 5% to about 25% by weight.

~~[00214]~~[002111] The composition can further include one or more pharmaceutically acceptable additives and excipients. Such additives and excipients include, without limitation, detackifiers, anti-foaming agents, buffering agents, polymers, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, flavorants, colorants, odorants, opacifiers, suspending agents, binders, fillers, plasticizers, lubricants, and mixtures thereof.

~~[00215]~~[002112] In addition, an acid or a base may be incorporated into the composition to facilitate processing, to enhance stability, or for other reasons. Examples of pharmaceutically acceptable bases include amino acids, amino acid esters, ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium aluminum silicate, synthetic aluminum silicate, synthetic hydrocalcite, magnesium aluminum hydroxide, diisopropylethylamine, ethanolamine, ethylenediamine, triethanolamine, triethylamine, triisopropanolamine, trimethylamine, tris(hydroxymethyl)aminomethane (TRIS) and the like. Also suitable are bases that are salts of a pharmaceutically acceptable acid, such as acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acid, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, *p*-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid, uric acid, and the like. Salts of polyprotic acids, such as sodium phosphate, disodium hydrogen phosphate, and sodium dihydrogen phosphate can also be used. When the base is a salt, the cation can be any convenient and pharmaceutically acceptable cation, such as ammonium, alkali metals and alkaline earth metals. Examples may include, but are not limited to, sodium, potassium, lithium, magnesium, calcium and ammonium.

~~[00216]~~[002113] Suitable acids are pharmaceutically acceptable organic or inorganic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, hydriodic

acid, sulfuric acid, nitric acid, boric acid, phosphoric acid, and the like. Examples of suitable organic acids include acetic acid, acrylic acid, adipic acid, alginic acid, alkanesulfonic acids, amino acids, ascorbic acid, benzoic acid, boric acid, butyric acid, carbonic acid, citric acid, fatty acids, formic acid, fumaric acid, gluconic acid, hydroquinosulfonic acid, isoascorbic acid, lactic acid, maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic acid, *p*-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, thioglycolic acid, toluenesulfonic acid and uric acid.

Pharmaceutical Compositions for Injection

~~[00217]~~[00214] In selected embodiments, the invention provides a pharmaceutical composition for injection containing a BTK inhibitor of Formula (I) or Formula (II), and a pharmaceutical excipient suitable for injection. Components and amounts of agents in the compositions are as described herein.

~~[00218]~~[00215] The forms in which the compositions of the present invention may be incorporated for administration by injection include aqueous or oil suspensions, or emulsions, with sesame oil, corn oil, cottonseed oil, or peanut oil, as well as elixirs, mannitol, dextrose, or a sterile aqueous solution, and similar pharmaceutical vehicles.

~~[00219]~~[00216] Aqueous solutions in saline are also conventionally used for injection. Ethanol, glycerol, propylene glycol and liquid polyethylene glycol (and suitable mixtures thereof), cyclodextrin derivatives, and vegetable oils may also be employed. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, for the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid and thimerosal.

~~[00220]~~[00217] Sterile injectable solutions are prepared by incorporating a a BTK inhibitor of Formula (I) or Formula (II) in the required amounts in the appropriate solvent with various other ingredients as enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile

injectable solutions, certain desirable methods of preparation are vacuum-drying and freeze-drying techniques which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical Compositions for Topical Delivery

~~[00221]~~[002218] In some embodiments, the invention provides a pharmaceutical composition for transdermal delivery containing the BTK inhibitors of Formula (I) or Formula (II) and a pharmaceutical excipient suitable for transdermal delivery.

~~[00222]~~[002219] Compositions of the present invention can be formulated into preparations in solid, semi-solid, or liquid forms suitable for local or topical administration, such as gels, water soluble jellies, creams, lotions, suspensions, foams, powders, slurries, ointments, solutions, oils, pastes, suppositories, sprays, emulsions, saline solutions, dimethylsulfoxide (DMSO)-based solutions. In general, carriers with higher densities are capable of providing an area with a prolonged exposure to the active ingredients. In contrast, a solution formulation may provide more immediate exposure of the active ingredient to the chosen area.

~~[00223]~~[002220] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients, which are compounds that allow increased penetration of, or assist in the delivery of, therapeutic molecules across the stratum corneum permeability barrier of the skin. There are many of these penetration-enhancing molecules known to those trained in the art of topical formulation. Examples of such carriers and excipients include, but are not limited to, humectants (*e.g.*, urea), glycols (*e.g.*, propylene glycol), alcohols (*e.g.*, ethanol), fatty acids (*e.g.*, oleic acid), surfactants (*e.g.*, isopropyl myristate and sodium lauryl sulfate), pyrrolidones, glycerol monolaurate, sulfoxides, terpenes (*e.g.*, menthol), amines, amides, alkanes, alkanols, water, calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

~~[00224]~~[002221] Another exemplary formulation for use in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the BTK inhibitors of Formula (I) or Formula (II) in controlled amounts, either with or without another active pharmaceutical ingredient.

~~[00225]~~[00222] The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, *e.g.*, U.S. Patent Nos. 5,023,252; 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Other Pharmaceutical Compositions

~~[00226]~~[00223] Pharmaceutical compositions may also be prepared from compositions described herein and one or more pharmaceutically acceptable excipients suitable for sublingual, buccal, rectal, intraosseous, intraocular, intranasal, epidural, or intraspinal administration. Preparations for such pharmaceutical compositions are well-known in the art. See, *e.g.*, Anderson, et al. eds., *Handbook of Clinical Drug Data*, Tenth Edition, McGraw-Hill, 2002; and Pratt and Taylor, eds., *Principles of Drug Action*, Third Edition, Churchill Livingston, N.Y., 1990.

~~[00227]~~[00224] Administration of the BTK inhibitors of Formula (I) or Formula (II) or pharmaceutical composition of these compounds can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral routes, intraduodenal routes, parenteral injection (including intravenous, intraarterial, subcutaneous, intramuscular, intravascular, intraperitoneal or infusion), topical (*e.g.*, transdermal application), rectal administration, via local delivery by catheter or stent or through inhalation. The combination of compounds can also be administered intraadiposally or intrathecally.

~~[00228]~~[00225] Exemplary parenteral administration forms include solutions or suspensions of active compound in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

~~[00229]~~[00226] The invention also provides kits. The kits include the BTK inhibitors of Formula (I) or Formula (II), either alone or in combination in suitable packaging, and written material that can include instructions for use, discussion of clinical studies and listing of side effects. Such kits may also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care

provider. Such information may be based on the results of various studies, for example, studies using experimental animals involving *in vivo* models and studies based on human clinical trials. The kit may further contain another active pharmaceutical ingredient. Suitable packaging and additional articles for use (*e.g.*, measuring cup for liquid preparations, foil wrapping to minimize exposure to air, and the like) are known in the art and may be included in the kit. Kits described herein can be provided, marketed and/or promoted to health providers, including physicians, nurses, pharmacists, formulary officials, and the like. Kits may also, in selected embodiments, be marketed directly to the consumer. In an embodiment, the invention provides a kit comprising a BTK inhibitor of Formula (I) or Formula (II) for use in the treatment of CLL or SLL, hematological malignancies, or any of the other cancers described herein.

Dosages and Dosing Regimens

~~[00230]~~[00227] The amounts of BTK inhibitors administered will be dependent on the mammal being treated, the severity of the disorder or condition, the rate of administration, the disposition of the compounds and the discretion of the prescribing physician. However, an effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, such as about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to about 0.05 to 7 g/day, such as about 0.05 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect - *e.g.*, by dividing such larger doses into several small doses for administration throughout the day.

~~[00231]~~[00228] In some embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered in a single dose. Typically, such administration will be by injection - *e.g.*, intravenous injection, in order to introduce the agents quickly. However, other routes may be used as appropriate. A single dose of a BTK inhibitor of Formula (I) or Formula (II) may also be used for treatment of an acute condition.

~~[00232]~~[00229] In some embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered in multiple doses. Dosing may be once, twice, three times, four times, five times, six times, or more than six times per day. Dosing may be once a month, once every two weeks, once a week, or once every other day. In other embodiments, a BTK inhibitor of Formula (I) or

Formula (II) is administered about once per day to about 6 times per day. In some embodiments a BTK inhibitor of Formula (I) or Formula (II) is administered once daily, while in other embodiments a BTK inhibitor of Formula (I) or Formula (II) is administered twice daily, and in other embodiments a BTK inhibitor of Formula (I) or Formula (II) is administered three times daily.

~~[00233]~~[00230] Administration of the BTK inhibitor of Formula (I) or Formula (II) may continue as long as necessary. In some embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, the the BTK inhibitor of Formula (I) or Formula (II) is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered chronically on an ongoing basis - *e.g.*, for the treatment of chronic effects. In another embodiment the administration of a BTK inhibitor of Formula (I) or Formula (II) continues for less than about 7 days. In yet another embodiment the administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some embodiments, continuous dosing is achieved and maintained as long as necessary.

~~[00234]~~[00231] In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is in the range of about 1 mg to about 500 mg, about 10 mg to about 300 mg, about 20 mg to about 250 mg, about 25 mg to about 200 mg, about 10 mg to about 200 mg, about 20 mg to about 150 mg, about 30 mg to about 120 mg, about 10 mg to about 90 mg, about 20 mg to about 80 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 45 mg to about 55 mg, about 48 mg to about 52 mg, about 50 mg to about 150 mg, about 60 mg to about 140 mg, about 70 mg to about 130 mg, about 80 mg to about 120 mg, about 90 mg to about 110 mg, about 95 mg to about 105 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, about 195 mg to about 205 mg, or about 198 to about 202 mg. In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is about 25 mg, about 50 mg, about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, or about 500 mg. In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is 25 mg, 50

mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475 mg, or 500 mg.

~~[00235]~~[00232] In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is in the range of about 0.01 mg/kg to about 4.3 mg/kg, about 0.15 mg/kg to about 3.6 mg/kg, about 0.3 mg/kg to about 3.2 mg/kg, about 0.35 mg/kg to about 2.85 mg/kg, about 0.15 mg/kg to about 2.85 mg/kg, about 0.3 mg to about 2.15 mg/kg, about 0.45 mg/kg to about 1.7 mg/kg, about 0.15 mg/kg to about 1.3 mg/kg, about 0.3 mg/kg to about 1.15 mg/kg, about 0.45 mg/kg to about 1 mg/kg, about 0.55 mg/kg to about 0.85 mg/kg, about 0.65 mg/kg to about 0.8 mg/kg, about 0.7 mg/kg to about 0.75 mg/kg, about 0.7 mg/kg to about 2.15 mg/kg, about 0.85 mg/kg to about 2 mg/kg, about 1 mg/kg to about 1.85 mg/kg, about 1.15 mg/kg to about 1.7 mg/kg, about 1.3 mg/kg mg to about 1.6 mg/kg, about 1.35 mg/kg to about 1.5 mg/kg, about 2.15 mg/kg to about 3.6 mg/kg, about 2.3 mg/kg to about 3.4 mg/kg, about 2.4 mg/kg to about 3.3 mg/kg, about 2.6 mg/kg to about 3.15 mg/kg, about 2.7 mg/kg to about 3 mg/kg, about 2.8 mg/kg to about 3 mg/kg, or about 2.85 mg/kg to about 2.95 mg/kg. In some embodiments, an effective dosage of a BTK inhibitor of Formula (I) or Formula (II) is about 0.35 mg/kg, about 0.7 mg/kg, about 1 mg/kg, about 1.4 mg/kg, about 1.8 mg/kg, about 2.1 mg/kg, about 2.5 mg/kg, about 2.85 mg/kg, about 3.2 mg/kg, or about 3.6 mg/kg.

~~[00236]~~[00233] In some embodiments, a BTK inhibitor of Formula (I) or Formula (II) is adminstered at a dosage of 10 to 400 mg BID, including a dosage of 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, and 400 mg BID.

~~[00237]~~[00234] An effective amount of the combination of the BTK inhibitor of Formula (I) or Formula (II) may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, including rectal, buccal, sublingual, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, or as an inhalant.

Methods of Treating Hematological Malignancies, Cancers, and Other Diseases

~~[00238]~~[00235] In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a therapeutically effective amount

of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~[00239]~~[002361] In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in a dosing regimen selected from the group consisting of 100 mg QD, 175 mg QD, 250 mg QD, 400 mg QD, and 100 mg BID. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in a dosing regimen selected from the group consisting of 100 mg QD, 175 mg QD, 250 mg QD, 400 mg QD, and 100 mg BID.

~~[00240]~~[002371] In an embodiment, the invention relates to a use of a composition of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating CLL, wherein the treating comprises the step of administering one or more doses of Formula (II) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a use of a composition of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating SLL, wherein the treating comprises the step of administering one or more doses of Formula (II) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a use of a composition of Formula (I), or a

pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating CLL, wherein the treating comprises the step of administering one or more doses of Formula (I) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a use of a composition of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, in the manufacture of a medicament for treating SLL, wherein the treating comprises the step of administering one or more doses of Formula (I) or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~[00241]~~[00238] In an embodiment, the invention relates to a method of treating CLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating CLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the invention relates to a method of treating SLL in a mammal that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (I), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. In an embodiment, the mammal in any of the foregoing embodiments is selected from the group consisting of a human, a canine, a feline, or an equine. In an embodiment, the mammal in any of the foregoing embodiments is a companion animal.

~~[00242]~~[00239] In an embodiment, the invention relates to a method of treating a subtype of CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (I) or Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. A number of subtypes of CLL have been characterized. CLL is often classified for immunoglobulin heavy-chain variable-region (IgV_H) mutational status in leukemic cells. R. N. Damle, *et al.*, *Blood* **1999,** *94,* 1840-47;

T. J. Hamblin, *et al.*, *Blood* **1999**, *94,* 1848-54. Patients with IgV_H mutations generally survive longer than patients without IgV_H mutations. ZAP70 expression (positive or negative) is also used to characterize CLL. L. Z. Rassenti, *et al.*, *N. Engl. J. Med.* **2004,** *351,* 893-901. The methylation of ZAP-70 at CpG3 is also used to characterize CLL, for example by pyrosequencing. R. Claus, *et al.*, *J. Clin. Oncol.* **2012,** *30,* 2483-91; J. A. Woyach, *et al.*, *Blood* **2014,** *123,* 1810-17. CLL is also classfied by stage of disease under the Binet or Rai criteria. J. L. Binet, *et al.*, *Cancer* **1977,** *40,* 855-64; K. R. Rai, T. Han, *Hematol. Oncol. Clin. North Am.* **1990,** *4,* 447-56. Other common mutations, such as 11p deletion, 13q deletion, and 17p deletion can be assessed using well-known techniques such as fluorescence *in situ* hybridization (FISH). In an embodiment, the invention relates to a method of treating a CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the CLL is selected from the group consisting of IgV_H mutation negative CLL, ZAP-70 positive CLL, ZAP-70 methylated at CpG3 CLL, CD38 positive CLL, chronic lymphocytic leukemia characterized by a 17p13.1 (17p) deletion, and CLL characterized by a 11q22.3 (11q) deletion.

~~[00243]~~[002401] In an embodiment, the invention relates to a method of treating a CLL in a human that comprises the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the CLL has undergone a Richter's transformation. Methods of assessing Richter's transformation, which is also known as Richter's syndrome, are described in P. Jain and S. O'Brien, *Oncology*, **2012,** *26,* 1146–52. Richter's transformation is a subtype of CLL that is observed in 5-10% of patients. It involves the development of aggressive lymphoma from CLL and has a generally poor prognosis.

~~[00244]~~[002411] In an embodiment, the invention relates to a method of treating a subtype of CLL in a human, comprising the step of administering to said mammal a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the subtype of CLL is a subtype of CLL that increases monocytes and NK cells in peripheral blood when measured after a period of treatment with Formula (II) selected from the group consisting of about 14 days, about 28 days,

about 56 days, about 1 month, about 2 months, about 3 months, about 6 months, and about 1 year, and wherein the term "about" refers to a measurement interval of +/- 2 days.

~~[00245]~~[002421] In an embodiment, the invention relates to a method of treating chronic lymphocytic leukemia in a patient, wherein the chronic lymphocytic leukemia is chronic lymphocytic leukemia in a patient sensitive to lymphocytosis. In an embodiment, the invention relates to a method of treating chronic lymphocytic leukemia in a patient, wherein the chronic lymphocytic leukemia is chronic lymphocytic leukemia in a patient exhibiting lymphocytosis caused by a disorder selected from the group consisting of a viral infection, a bacterial infection, a protozoal infection, or a post-splenectomy state. In an embodiment, the viral infection in any of the foregoing embodiments is selected from the group consisting of infectious mononucleosis, hepatitis, and cytomegalovirus. In an embodiment, the bacterial infection in any of the foregoing embodiments is selected from the group consisting of pertussis, tuberculosis, and brucellosis.

~~[00246]~~[002431] The methods described above may be used as first-line cancer therapy, or after treatment with conventional chemotherapic active pharmaceutical ingredients, including cyclophosphamide, fludarabine, cyclophosphamide and fludarabine (FC chemotherapy), and chlorambucil. The methods described above may also be supplemented with immunotherapeutic monoclonal antibodies such as the anti-CD52 monoclonal antibody alemtuzumab. In an embodiment, the invention relates to a method of treating CLL in a human that comprises the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt, ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprises the step of administering to said human an active pharmaceutical ingredient selected from the group consisting of cyclophosphamide, fludarabine, cyclophosphamide, chlorambucil, salts, esters, prodrugs, cocrystals, solvates, or hydrates thereof, and combinations thereof, and alemtuzumab, antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof.

~~[00247]~~[002441] In an embodiment, the invention relates to a method of treating hematological malgnancies in a human comprising the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof. Hematological malignancies include CLL and SLL, as well as other cancers of the blood, including B cell

malignancies. In an embodiment, the invention relates to a method of treating a hematological malignancy selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis in a human that comprises the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~[00248]~~[00245] In an embodiment, the invention relates to a method of treating a NHL selected from the group consisting of indolent NHL and aggressive NHL comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~[00249]~~[00246] In an embodiment, the invention relates to a method of treating a DLBCL selected from the group consisting of activated B-cell like diffuse large B-cell lymphoma (DLBCL-ABC) and germinal center B-cell like diffuse large B-cell lymphoma (DLBCL-GCB), comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~[00250]~~[00247] In an embodiment, the invention relates to a method of treating an MCL selected from the group consisting of mantle zone MCL, nodular MCL, diffuse MCL, and blastoid MCL (also known as blastic variant MCL), comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~[00251]~~[00248] In an embodiment, the invention relates to a method of treating a B-ALL selected from the group consisting of early pre-B cell B-ALL, pre-B cell B-ALL, and mature B cell B-ALL (also known as Burkitt's leukemia), comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~[00252]~~[00249] In an embodiment, the invention relates to a method of treating a Burkitt's lymphoma selected from the group consisting of sporadic Burkitt's lymphoma, endemic

Burkitt's lymphoma, and human immunodeficiency virus-associated Burkitt's lymphoma, comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~{00253}~~[00250] In an embodiment, the invention relates to a method of treating a multiple myeloma selected from the group consisting of hyperdiploid multiple myeloma and non-hyperdiploid multiple myeloma, comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~{00254}~~[00251] In an embodiment, the invention relates to a method of treating a myelofibrosis selected from the group consisting of primary myelofibrosis (also known as chronic idiopathic myelofibrosis) and myelofibrosis secondary to polycythemia vera or essential thrombocythaemia, comprising the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~{00255}~~[00252] In an embodiment, the invention relates to a method of treating a subtype of a hematological malignancy in a human, comprising the step of administering to said human a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, wherein the subtype of a hematological malignancy is a subtype of a hematological malignancy that increases monocytes and NK cells in peripheral blood when measured after a period of treatment with Formula (II) selected from the group consisting of about 14 days, about 28 days, about 56 days, about 1 month, about 2 months, about 3 months, about 6 months, and about 1 year, wherein the term "about" refers to a measurement interval of +/- 2 days, and wherein the hematological malignancy is selected from the group consisting of non-Hodgkin's lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), Hodgkin's lymphoma, B cell acute lymphoblastic leukemia (B-ALL), Waldenström's macroglobulinemia (WM), Burkitt's lymphoma, multiple myeloma, or myelofibrosis.

Methods of Treating Cancers in Patients Sensitive to Thrombosis

~~[00256]~~[00253] In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof. In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient.

~~[00257]~~[00254] In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anticoagulant or the antiplatelet active pharmaceutical ingredient are administered sequentially. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anticoagulant or the antiplatelet active pharmaceutical ingredient are administered concomitantly. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered before the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient.

~~[00258]~~[00255] In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), and wherein the cancer is selected from the group consisting of CLL, SLL, NHL, DLBCL, FL, MCL, Hodgkin's lymphoma, B-ALL, WM, Burkitt's lymphoma, multiple myeloma, or myelofibrosis that comprises the step of administering a therapeutically effective amount of a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof.

~~[00259]~~[00256] In selected embodiments, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), and wherein the cancer is selected from the group consisting of acute myeloid leukemia, squamous cell carcinoma including chronic myelocytic leukemia, bladder cancer, head and neck tumor, pancreatic ductal adenocarcinoma (PDA), pancreatic cancer, colon carcinoma, mammary carcinoma, breast cancer, fibrosarcoma, mesothelioma cancer, renal cell carcinoma, lung carcinoma, thyoma, prostate cancer, colorectal cancer, ovarian cancer, thymus cancer, brain cancer, squamous cell cancer, skin cancer, eye cancer, retinoblastoma, melanoma, intraocular melanoma, oral cavity and oropharyngeal cancers, gastric cancer, stomach cancer, cervical cancer, renal cancer, kidney cancer, liver cancer, ovarian cancer, prostate cancer, colorectal cancer, esophageal cancer, testicular cancer, gynecological cancer, thyroid cancer, aquired immune deficiency syndrome (AIDS)-related cancers (e.g., lymphoma and Kaposi's sarcoma), viral-induced cancer, glioblastoma, esophogeal tumors, hematological neoplasms, non-small-cell lung cancer, esophagus tumor, hepatitis C virus infection, hepatocellular carcinoma, metastatic colon cancer, multiple myeloma, ovary tumor, pancreas tumor, renal cell carcinoma, small-cell lung cancer, and stage IV melanoma.

~~[00260]~~[00257] In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (I) or Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, wherein the cancer is a hematogolical malignancy, and wherein the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia, B cell acute lymphoblastic leukemia, and non-Hodgkin's lymphoma.

~~[00261]~~[00258] In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the cancer is a hematological malignancy,

and wherein the hematological malignancy is selected from the group consisting of chronic lymphocytic leukemia, B cell acute lymphoblastic leukemia, and non-Hodgkin's lymphoma.

~~[00263]~~[002591] Preferred anti-platelet and anticoagulant agents for use in the methods of the present invention include, but are not limited to, cyclooxygenase inhibitors (e.g., aspirin), adenosine diphosphate (ADP) receptor inhibitors (e.g., clopidogrel and ticlopidine), phosphodiesterase inhibitors (e.g., cilostazol), glycoprotein IIb/IIIa inhibitors (e.g., abciximab, eptifibatide, and tirofiban), adenosine reuptake inhibitors (e.g., dipyridamole), and acetylsalicylic acid (aspirin). Examples of anti-platelet active pharmaceutical ingredients for use in the methods of the present invention include acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, cocrystals thereof, prodrugs thereof, and combinations thereof.

~~[00263]~~[002601] In an embodiment, the invention provides a method of treating a cancer in a human sensitive to platelet-mediated thrombosis, comprising the step of administering a therapeutically effective dose of a BTK inhibitor, wherein the BTK inhibitor is Formula (II), or a pharmaceutically-acceptable salt, cocrystal, hydrate, solvate, or prodrug thereof, further comprising the step of administering a therapeutically effective dose of an anticoagulant or antiplatelet active pharmaceutical ingredient, wherein the anticoagulant or antiplatelet active pharmaceutical ingredient is selected from the group consisting of acenocoumarol, anagrelide, anagrelide hydrochloride, abciximab, aloxiprin, antithrombin, apixaban, argatroban, aspirin, aspirin with extended-release dipyridamole, beraprost, betrixaban, bivalirudin, carbasalate

calcium, cilostazol, clopidogrel, clopidogrel bisulfate, cloricromen, dabigatran etexilate, darexaban, dalteparin, dalteparin sodium, defibrotide, dicumarol, diphenadione, dipyridamole, ditazole, desirudin, edoxaban, enoxaparin, enoxaparin sodium, eptifibatide, fondaparinux, fondaparinux sodium, heparin, heparin sodium, heparin calcium, idraparinux, idraparinux sodium, iloprost, indobufen, lepirudin, low molecular weight heparin, melagatran, nadroparin, otamixaban, parnaparin, phenindione, phenprocoumon, prasugrel, picotamide, prostacyclin, ramatroban, reviparin, rivaroxaban, sulodexide, terutroban, terutroban sodium, ticagrelor, ticlopidine, ticlopidine hydrochloride, tinzaparin, tinzaparin sodium, tirofiban, tirofiban hydrochloride, treprostinil, treprostinil sodium, triflusal, vorapaxar, warfarin, warfarin sodium, ximelagatran, salts thereof, solvates thereof, hydrates thereof, cocrystals thereof, prodrugs thereof, and combinations thereof.

Combinations of BTK Inhibitors and Anti-CD20 Antibodies

~~[00264]~~[00261] The BTK inhibitors of Formula (I) and Formula (II) may also be safely co-administered with immunotherapeutic antibodies such as the anti-CD20 antibodies rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, and or antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof, which may be given alone or with conventional chemotherapeutic active pharmaceutical ingredients such as those described herein. The CD20 antigen also called human B-lymphocyte-restricted differentiation antigen, Bp35, or B1) is found on the surface of normal “pre-B” and mature B lymphocytes, including malignant B lymphocytes. L. M. Nadler, *et al.*, *J. Clin. Invest.* **1981,** *67,* 134-40; P. Stashenko, *et al.*, *J. Immunol.* **1980,** *139,* 3260-85. The CD20 antigen is a glycosylated integral membrane protein with a molecular weight of approximately 35 kD. T. F. Tedder, *et al.*, *Proc. Natl. Acad. Sci. USA,* **1988,** *85,* 208-12. CD20 is also expressed on most B cell non-Hodgkin's lymphoma cells, but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissues. Anti-CD20 antibodies are currently used as therapies for many hematological malignancies, including indolent NHL, aggressive NHL, and CLL/SLL. S. H. Lim, *et. al., Haematologica* **2010,** *95,* 135-43; S. A. Beers, *et. al.*, *Sem. Hematol.* **2010,** *47,* 107-14; C. Klein, *et al.*, *mAbs* **2013,** *5,* 22-33.

~~[00265]~~[00262] In an embodiment, the invention relates to a method of treating a hematological malignancy in a human comprising the step of administering to said human a BTK

inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is a monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating a hematological malignancy in a human comprising the step of administering to said human a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is an anti-CD20 monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, and wherein the anti-CD20 antibody specifically binds to human CD20 with a K_D selected from the group consisting of 1×10^{-7} M or less, 5×10^{-8} M or less, 1×10^{-8} M or less, and 5×10^{-9} M or less.

~~[00266]~~[002631] In an embodiment, the invention relates to a method of treating CLL or SLL in a human comprising the step of administering to said human a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is a monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the invention relates to a method of treating CLL or SLL in a human comprising the step of administering to said human a BTK inhibitor of Formula (II), or a pharmaceutically acceptable salt or ester, prodrug, cocrystal, solvate or hydrate thereof, and further comprising the step of administering an anti-CD20 antibody, wherein the anti-CD20 antibody is an anti-CD20 monoclonal antibody or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, and wherein the anti-CD20 antibody specifically binds to human CD20 with a K_D selected from the group consisting of 1×10^{-7} M or less, 5×10^{-8} M or less, 1×10^{-8} M or less, and 5×10^{-9} M or less.

~~[00267]~~[002641] In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anti-CD20 monoclonal antibody are administered sequentially. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anti-CD20 monoclonal antibody are administered concomitantly. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered before the anti-CD20 monoclonal antibody. In

selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) is administered after the anticoagulant or the antiplatelet active pharmaceutical ingredient. In selected embodiments, the BTK inhibitor of Formula (I) or Formula (II) and the anti-CD20 monoclonal antibody are administered over the same time period, and the BTK inhibitor administration continues after the anti-CD20 monoclonal antibody administration is completed.

~~[00268]~~[00265] In an embodiment, the anti-CD20 monoclonal antibody is rituximab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Rituximab is a chimeric murine-human monoclonal antibody directed against CD20, and its structure comprises an IgG1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids. The amino acid sequence for the heavy chains of rituximab is set forth in SEQ ID NO:1. The amino acid sequence for the light chains of rituximab is set forth in SEQ ID NO:2. Rituximab is commercially available, and its properties and use in cancer and other diseases is described in more detail in W. Rastetter, *et al.*, *Ann. Rev. Med.* **2004,** *55,* 477-503, and in G. L. Plosker and D. P. Figgett, *Drugs*, **2003,** *63,* 803-43. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to rituximab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:2. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:1. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:2.

~~[00269]~~[00266] In an embodiment, the anti-CD20 monoclonal antibody is obinutuzumab,

or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Obinutuzumab is also known as afutuzumab or GA-101. Obinutuzumab is a humanized monoclonal antibody directed against CD20. The amino acid sequence for the heavy chains of obinutuzumab is set forth in SEQ ID NO:3. The amino acid sequence for the light chains of obinutuzumab is set forth in SEQ ID NO:4. Obinutuzumab is commercially available, and its properties and use in cancer and other diseases is described in more detail in T. Robak, *Curr. Opin. Investig. Drugs* **2009,** *10,* 588-96. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to obinutuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:3. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:4. In an embodiment, the anti-CD20 monoclonal antibody obinutuzumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen B1, Leu-16 or Bp35)), humanized mouse monoclonal obinutuzumab des-CH3107-K-γ1 heavy chain (222-219')-disulfide with humanized mouse monoclonal obinutuzumab κ light chain dimer (228-228":231-231")-bisdisulfide antibody.

~~[00279]~~[002671] In an embodiment, the anti-CD20 monoclonal antibody is ofatumumab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Ofatumumab is described in B. D. Cheson, *J. Clin. Oncol.* **2010,** *28,* 3525-30. The crystal structure of the Fab fragment of ofatumumab has been reported in Protein Data Bank reference 3GIZ and in J. Du, *et al.*, *Mol. Immunol.* **2009,** *46,* 2419-2423. Ofatumumab is commercially available, and its preparation, properties, and use in cancer and other diseases is

described in more detail in U.S. Patent No. 8,529,202 B2, the disclosure of which is incorporated herein by reference. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to ofatumumab. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 90% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 90% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 95% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 95% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 98% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 98% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a variable heavy chain sequence identity of greater than 99% to SEQ ID NO:5. In an embodiment, the anti-CD20 monoclonal antibody has a variable light chain sequence identity of greater than 99% to SEQ ID NO:6. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 90% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 90% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 95% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 95% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 98% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 98% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment heavy chain sequence identity of greater than 99% to SEQ ID NO:7. In an embodiment, the anti-CD20 monoclonal antibody has a Fab fragment light chain sequence identity of greater than 99% to SEQ ID NO:8. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, B-lymphocyte surface antigen B1, Leu-16 or Bp35)); human monoclonal ofatumumab-CD20 γ1 heavy chain (225-214')-disulfide with human monoclonal ofatumumab-

CD20 κ light chain, dimer (231-231":234-234")-bisdisulfide antibody.

~~[00274]~~[00268] In an embodiment, the anti-CD20 monoclonal antibody is veltuzumab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. Veltuzumab is also known as hA20. Veltuzumab is described in D. M. Goldenberg, *et al.*, *Leuk. Lymphoma* **2010,** *51,* 747-55. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to veltuzumab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:9. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:10. In an embodiment, the anti-CD20 monoclonal antibody ofatumumab is an immunoglobulin G1, anti-(human B-lymphocyte antigen CD20 (membrane-spanning 4-domains subfamily A member 1, Leu-16, Bp35)); [218- arginine,360-glutamic acid,362-methionine]humanized mouse monoclonal hA20 γ1 heavy chain (224-213')-disulfide with humanized mouse monoclonal hA20 κ light chain (230-230":233-233")-bisdisulfide dimer

~~[00272]~~[00269] In an embodiment, the anti-CD20 monoclonal antibody is tositumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is ^{131}I-labeled tositumomab. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:12. In an embodiment, the anti-

CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:12. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:11. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:12.

~~[00273]~~[00270] In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof. The active form of ibritumomab used in therapy is ibritumomab tiuxetan. When used with ibritumomab, the chelator tiuxetan (diethylene triamine pentaacetic acid) is complexed with a radioactive isotope such as ^{90}Y or ^{111}In. In an embodiment, the anti-CD20 monoclonal antibody is ibritumomab tiuxetan, or radioisotope-labeled complex thereof. In an embodiment, the anti-CD20 monoclonal antibody is an anti-CD20 biosimilar monoclonal antibody approved by drug regulatory authorities with reference to tositumomab. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 90% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 90% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 95% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 95% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 98% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 98% to SEQ ID NO:14. In an embodiment, the anti-CD20 monoclonal antibody has a heavy chain sequence identity of greater than 99% to SEQ ID NO:13. In an embodiment, the anti-CD20 monoclonal antibody has a light chain sequence identity of greater than 99% to SEQ ID NO:14.

~~[00274]~~[00271] In an embodiment, an anti-CD20 antibody selected from the group consisting of obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, and or

antigen-binding fragments, derivatives, conjugates, variants, and radioisotope-labeled complexes thereof, is administered to a subject by infusion in a dose selected from the group consisting of about 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600 mg, about 700 mg, about 800 mg, about 900 mg, about 1000 mg, about 1100 mg, about 1200 mg, about 1300 mg, about 1400 mg, about 1500 mg, about 1600 mg, about 1700 mg, about 1800 mg, about 1900 mg, and about 2000 mg. In an embodiment, the anti-CD20 antibody is admininstered weekly. In an embodiment, the anti-CD20 antibody is admininstered monthly. In an embodiment, the anti-CD20 antibody is administered at a lower initial dose, which is escalated when administered at subsequent intervals admininstered monthly. For example, the first infusion can deliver 300 mg of anti-CD20 antibody, and subsequent weekly doses could deliver 2,000 mg of anti-CD20 antibody for eight weeks, followed by monthly doses of 2,000 mg of anti-CD20 antibody. During any of the foregoing embodiments, the BTK inhibitors of Formula (I) or Formula (II) may be administered daily, twice daily, or at different intervals as described above, at the dosages described above.

~~[00275]~~[00272] In an embodiment, the invention provides a kit comprising a composition comprising a BTK inhibitor of Formula (I) or Formula (II) and a composition comprising an anti-CD20 antibody selected from the group consisting of rituximab, obinutuzumab, ofatumumab, veltuzumab, tositumomab, and ibritumomab, or an antigen-binding fragment, derivative, conjugate, variant, or radioisotope-labeled complex thereof, for use in the treatment of CLL or SLL, hematological malignancies, B cell malignanciesor, or any of the other diseases described herein. The compositions are typically both pharmaceutical compositions. The kit is for use in co-administration of the anti-CD20 antibody and the BTK inhibitor, either simultaneously or separately, in the treatment of CLL or SLL, hematological malignancies, B cell malignancies, or any of the other diseases described herein.

EXAMPLES

~~[00276]~~[00273] The embodiments encompassed herein are now described with reference to the following examples. These examples are provided for the purpose of illustration only and the disclosure encompassed herein should in no way be construed as being limited to these examples, but rather should be construed to encompass any and all variations which become evident as a result of the teachings provided herein.

Example 1 – Preclinical Study of a Second Generation BTK Inhibitor for Use in CLL/SLL

~~[00277]~~[00274] The BTK inhibitor ibrutinib ((1-[(3*R*)-3-[4-amino-3-(4-phenoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl]piperidin-1-yl]prop-2-en-1-one) is a first-generation BTK inhibitor. In clinical testing as a monotherapy in subjects with hematologic malignancies, ibrutinib was generally well tolerated at dose levels through 840 mg (the highest dose tested). R. H. Advani, *et al.*, *J. Clin. Oncol.* **2013,** *31,* 88-94; J. C. Byrd, *et al.*, *N. Engl. J. Med.* **2013**, *369,* 32-42; M. L. Wang, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 507-16. No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to > 2 years. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with ibrutinib treatment. No drug-related reductions in circulating $CD4^+$ T cells or serum immunoglobulins were noted. Adverse events with an apparent relationship to study drug included diarrhea and rash.

~~[00278]~~[00275] In subjects with heavily pretreated non-Hodgkin lymphoma (NHL), ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in most subjects. Improvements in disease-associated anemia and thrombocytopenia were observed. The pattern of changes in subjects with CLL was notable. Single-agent ibrutinib caused rapid and substantial reductions in lymph node size concomitant with a redistribution of malignant sites into the peripheral blood. An asymptomatic absolute lymphocyte count (ALC) increase was observed that was maximal during the first few months of treatment and generally decreased thereafter but could be persistent in some subjects or could be seen repeatedly in subjects who had interruption and resumption of drug therapy.

~~[00279]~~[00276] Collectively, these data with ibrutinib support the potential benefits of selective BTK inhibition in the treatment of subjects with relapsed lymphoid cancers. However, while highly potent in inhibiting BTK, ibrutinib has also shown *in vitro* activity against other kinases with a cysteine in the same position as Cys481 in BTK to which the drug covalently binds. For example, ibrutinib inhibits epidermal growth factor receptor (EGFR), which may be the cause of ibrutinib-related diarrhea and rash. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5 and 2D6, which increases the possibility of drug-drug interactions. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancer.

~~[00280]~~[00277] The preclinical selectivity and potency characteristics of the second-generation BTK inhibitor of Formula (II) were compared to the first-generation BTK inhibitor ibrutinib. In Table 1, a kinome screen (performed Life Technologies or based on literature data) is shown that compares these compounds.

TABLE 1. Kinome Screen for BTK Inhibitors (IC_{50}, nM)

3F-Cys Kinase	Formula (II)	Ibrutinib
Btk	3.1	0.5
Tec	29	78
Bmx	39	0.80
Itk	>1000	10.7
Txk	291	2.0
EGFR	>1000	5.6
ErbB2	912	9.4
ErbB4	13.2	2.7
Blk	>1000	0.5
JAK-3	>1000	16.1

~~[00281]~~[00278] The results shown in Table 1 are obtained from a 10 point biochemical assay generated from 10 point concentration curves. The BTK inhibitor of Formula (II) shows much greater selectivity for BTK compared to other kinases than ibrutinib.

~~[00282]~~[00279] A comparison of the *in vivo* potency results for the BTK inhibitors of Formula (II) and ibrutinib is shown in FIG. 1. CD86 and CD69 are cell surface proteins that are BCR activation markers. To obtain the *in vivo* potency results, mice were gavaged at increasing drug concentration and sacrificed at one time point (3 h post-dose). BCR was stimulated with IgM and the expression of activation marker CD69 and CD86 are monitored by flow cytometry and to determine EC_{50} values.

~~[00283]~~[00280] Formula (II) is currently being evaluated in an ongoing study of canine spontaneous B-cell lymphoma. Six dogs have been treated with Formula (II) using 2.5 mg/kg once daily oral administration for an average of 22 days (range 14 to 42 days). To date, partial remission (PR), per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma, has been observed in 2 of 6 dogs. D. M. Vali, *et al.*, *Vet. Comp. Oncol.* **8,** 28-37 (2010). No drug-related adverse events have been reported to date in this study.

These findings are preliminary and similar to the clinical responses (*i.e.*, 3 dogs with PR out of 8 dogs treated) observed with ibrutinib in dogs with spontaneous B-cell lymphoma. L. A. Honigberg, *et al.*, *Proc. Nat. Acad. Sci. USA,* **107,** 13075-13080 (2010).

~~[00284]~~[002811] *In vitro* and *in vivo* safety pharmacology studies with Formula (II) have demonstrated a favorable nonclinical safety profile. When screened at 10 μM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, Formula (II) shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a IC_{50} of 2.7 μM, suggesting a low clinical risk of off-target effects. Formula (II) at 10 μM showed no inhibition of *in vitro* EGFR phosphorylation in an A431 human epidermoid cancer cell line whereas ibrutinib had an IC_{50} of 66 nM. The *in vitro* effect of Formula (II) on human ether-à-go-go-related gene (hERG) channel activity was investigated *in vitro* in human embryonic kidney cells stably transfected with hERG. Formula (II) inhibited hERG channel activity by 25% at 10 μM, suggesting a low clinical risk that Formula (II) would induce clinical QT prolongation as predicted by this assay. Formula (II) was well tolerated in standard *in vivo* Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of Formula (II) at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT interval) parameters. The results suggest that Formula (II) is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

~~[00285]~~[002821] The drug-drug interaction potential of Formula (II) was also evaluated. *In vitro* experiments evaluating loss of parent drug as catalyzed by CYPs indicated that Formula (II) is metabolized by CYP3A4. *In vitro* metabolism studies using mouse, rat, dog, rabbit, monkey, and human hepatocytes incubated with ^{14}C-labeled Formula (II) indicated two mono-oxidized metabolites and a glutathione conjugate. No unique human metabolite was identified. Preliminary evaluations of metabolism in the plasma, bile, and urine of rats, dogs, and monkeys

indicated metabolic processes of oxidation, glutathione binding, and hydrolysis. It was shown that Formula (II) binds to glutathione but does not deplete glutathione *in vitro*. Nonclinical CYP interaction studies data indicate that Formula (II) is very unlikely to cause clinical drug-drug interactions through alteration of the metabolism of drugs that are substrates for CYP enzymes.

Example 2 – Clinical Study of a Second Generation BTK Inhibitor for Use in CLL/SLL

~~[00286]~~[00283] Clinical studies have shown that targeting the BCR signaling pathway by inhibiting BTK produces significant clinical benefit in patients with non-Hodgkin's lymphoma (NHL). The second generation BTK inhibitor, Formula (II), achieves significant oral bioavailability and potency, and has favorable preclinical characteristics, as described above. The purpose of this study is to evaluate the safety and efficacy of the second generation BTK inhibitor of Formula (II) in treating subjects with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

~~[00287]~~[00284] The design and conduct of this study is supported by an understanding of the history and current therapies for subjects with lymphoid cancers; knowledge of the activity and safety of a first-generation BTK inhibitor, ibrutinib, in subjects with hematologic cancers; and the available nonclinical information regarding Formula (II). The collective data support the following conclusions. BTK expression plays an important role in the biology of lymphoid neoplasms, which represent serious and life-threatening disorders with continuing unmet medical need. Clinical evaluation of Formula (II) as a potential treatment for these disorders has sound scientific rationale based on observations that the compound selectively abrogates BTK activity and shows activity in nonclinical models of lymphoid cancers. These data are supported by clinical documentation that ibrutinib, a first-generation BTK inhibitor, is clinically active in these diseases. Ibrutinib clinical data and Formula (II) nonclinical safety pharmacology and toxicology studies support the safety of testing Formula (II) in subjects with B cell malignancies.

~~[00288]~~[00285] The primary objectives of the clinical study are as follows: (1) establish the safety and the MTD of orally administered Formula (II) in subjects with CLL/SLL; (2) determine pharmacokinetics (PK) of orally administered Formula (II) and identification of its major metabolite(s); and (3) measure pharmacodynamic (PD) parameters including drug occupancy of BTK, the target enzyme, and effect on biologic markers of B cell function.

~~[00289]~~[00286] The secondary objective of the clinical study is to evaluate tumor responses in patients treated with Formula (II).

~~[00290]~~[00287] This study is a multicenter, open-label, nonrandomized, sequential group, dose escalation study. The following dose cohorts will be evaluated:

Cohort 1: 100 mg/day for 28 days (= 1 cycle)

Cohort 2: 175 mg/day for 28 days (= 1 cycle)

Cohort 3: 250 mg/day for 28 days (= 1 cycle)

Cohort 4: 350 mg/day for 28 days (= 1 cycle)

Cohort 5: 450 mg/day for 28 days (= 1 cycle)

Cohort 6: To be determined amount in mg/day for 28 days (= 1 cycle)

~~[00291]~~[00288] Each cohort will be enrolled sequentially with 6 subjects per cohort. If ≤ 1 dose-limiting toxicity (DLT) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Subjects may be enrolled in the next cohort if 4 of the 6 subjects enrolled in the cohort completed Cycle 1 without experiencing a DLT, while the remaining 2 subjects are completing evaluation. If ≥ 2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the MTD will be established as the previous cohort. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1. Dose escalation will end when either the MTD is achieved or at 3 dose levels above full BTK occupancy, whichever occurs first. Full BTK occupancy is defined as Formula (II) active-site occupancy of > 80% (average of all subjects in cohort) at 24 hours postdose. Should escalation to Cohort 6 be necessary, the dose will be determined based on the aggregate data from Cohorts 1 to 5, which includes safety, efficacy, and PK/PD results. The dose for Cohort 6 will not exceed 900 mg/day.

~~[00292]~~[00289] Treatment with Formula (II) may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. Subjects with disease progression will be removed from the study. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another

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cancer therapy within that timeframe. Radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 12 and at investigator discretion. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment. For subjects who remain on study for > 11 months, a mandatory bone marrow aspirate and biopsy is required in Cycle 12 concurrent with the radiologic tumor assessment.

~~[00293]~~[00290] All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) due to the pancreatic findings in the 28-day GLP rat toxicity study. Once dosing commences, all subjects will be evaluated for safety once weekly for the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected during the first week of treatment for PK/PD assessments. ECGs will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6. ECGs are done in triplicate for screening only. Thereafter, single ECG tests are done unless a repeat ECG testing is required.

~~[00294]~~[00291] Dose-limiting toxicity is defined as any of the following events (if not related to disease progression): (1) any Grade ≥ 3 non-hematologic toxicity (except alopecia) persisting despite receipt of a single course of standard outpatient symptomatic therapy (e.g., Grade 3 diarrhea that responds to a single, therapeutic dose of Imodium® would not be considered a DLT); (2) grade ≥ 3 prolongation of the corrected QT interval (QTc), as determined by a central ECG laboratory overread; (3) grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) lasting > 7 days after discontinuation of therapy without growth factors or lasting > 5 days after discontinuation of therapy while on growth factors (i.e., Grade 4 neutropenia not lasting as long as specified will not be considered a DLT), (4) grade 4 thrombocytopenia (platelet count < 20,000/μL) lasting > 7 days after discontinuation of therapy or requiring transfusion (*i.e.*, Grade 4 thrombocytopenia not lasting as long as specified will not be considered a DLT), and (5) dosing delay due to toxicity for > 7 consecutive days.

~~[00295]~~[00292] The efficacy parameters for the study include overall response rate, duration of response, and progression-free survival (PFS). The safety parameters for the study include DLTs and MTD, frequency, severity, and attribution of adverse events (AEs) based on

the Common Terminology Criteria for Adverse Events (CTCAE v4.03) for non-hematologic AEs. M. Hallek, *et al.*, *Blood* **2008,** *111,* 5446-5456.

~~[00296]~~[00293] The schedule of assessments is as follows, with all days stated in the following meaning the given day or +/- 2 days from the given day. A physical examination, including vital signs and weight, are performed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up (after the last dose). The screening physical examination includes, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter. Vital signs (blood pressure, pulse, respiratory rate, and temperature) are assessed after the subject has rested in the sitting position. Eastern Cooperative Oncology Group (ECOG) status is assessed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up, using the published ECOG performance status indications described in M. M. Oken, *et al.*, *Am. J. Clin. Oncol.* **1982,** *5,* 649-655. ECG testing is performed at screening, during cycle 1 at 1, 2, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. The 12-lead ECG test will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be <480 ms for eligibility. On cycle 1, day 1 and cycle 1, day 8, single ECGs are done predose and at 1, 2, 4, and 6 h postdose. The single ECG on Cycle 1 Day 2 is done predose. On cycle 1, day 15, day 22, and day 28, a single ECG is done 2 hours post-dose. Starting with cycle 2, a single ECG is done per visit. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 ms or > 60 ms above baseline require central ECG review. Hematology, including complete blood count with differential and platelet and reticulocyte counts, is assesed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry is assesed at screening, during cycle 1 at 1, 8, 15, 22, and 28 days, during cycle 2 at 15 and 28 days, during cycles 3 to 24 at 28 days, and at follow up. Serum chemistry includes albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Cell counts and serum

immunoglobulin are performed at screening, at cycle 2, day 28, and at every 6 months thereafter until last dose and include T/B/NK/monocyte cell counts (CD3, CD4, CD8, CD14, CD19, CD19, CD16/56, and others as needed) and serum immunoglobulin (IgG, IgM, IgA, and total immunoglobulin). Bone marrow aspirates are performed at cycle 12. Pharmacodynamics samples are drawn during cycle 1 at 1, 2, and 8 days, and at follow up. On days 1 and 8, pharmacodynamic samples are drawn pre-dose and 4 hours (±10 minutes) post-dose, and on day 2, pharmacodynamic samples are drawn pre-dose. Pharmacokinetics samples are drawn during cycle 1 at 1, 2, 8, 15, 22, and 28 days. Pharmacokinetic samples for Cycle 1 Day 1 are drawn pre-dose and at 0.5, 1, 2, 4, 6 and 24 hours (before dose on Day 2) post-dose. Samples for Cycle 1 Day 8 are drawn pre-dose and at 0.5, 1, 2, 4, and 6 hours post-dose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn pre-dose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition, which is 2 hours postdose. Pretreatment radiologic tumor assessments are performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis. In addition, a positron emission tomography (PET) or PET/CT must done for subjects with SLL. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (- 7days), and Cycle 12 (-7 days). Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis is required for subjects with CLL. In addition, a PET/CT is required in subjects with SLL. Bone marrow and radiologic assessments are both required for confirmation of a complete response (CR). Clinical assessments of tumor response should be done at the end of Cycle 6 and every 3 months thereafter. Molecular markers are measured at screening, and include interphase cytogenetics, stimulated karyotype, IgHV mutational status, Zap-70 methylation, and beta-2 microglobulin levels. Urinalysis is performed at screening, and includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Other assessments, including informed consent, eligibility, medical history, and pregnancy test are done at the time of screening.

~~[00297]~~[00294] The investigator rates the subject's response to treatment based on recent guidelines for CLL, as given in M. Hallek, *et al.*, *Blood* **2008,** *111,* 5446-56, and for SLL, as given in B. D. Cheson, *et al., J. Clin. Oncol.* **2007,** *25,* 579-586. The response assessment criteria for CLL are summarized in Table 2.

TABLE 2. Response Assessment Criteria for CLL. Abbreviations: ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission.

Response	Peripheral Blood	Bone Marrow (if performed)	Nodes, Liver, and Spleen[a]
CR	Lymphocytes < 4 x 10^9/L ANC >1.5 x 10^9/L[b] Platelets > 100 x 10^9/L[b] Hemoglobin > 11.0 g/dL (untransfused)[b]	Normocellular <30% lymphocytes No B-lymphoid nodules	Normal (e.g., no lymph nodes >1.5 cm)
CRi	Lymphocytes < 4 x 10^9/L Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity	Hypocellular <30% lymphocytes	Normal (*e.g.*, no lymph nodes >1.5 cm)
PR	Lymphocytes ≥ 50% decrease from baseline ANC > 1.5 x 10^9/L or Platelets > 100 x 10^9/L or 50% improvement over baseline[b] or Hemoglobin > 11.0 g/dL or 50% improvement over baseline (untransfused)[b]	Not assessed	≥50% reduction in lymphadenopathy[c] and/or in spleen or liver enlargement

a. Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation
b. Without need for exogenous growth factors
c. In the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

~~[00298]~~[002951] The response assessment criteria for SLL are summarized in Table 3.

TABLE 3. Response Assessment Criteria for SLL. Abbreviations: CR = complete remission, CT = computed tomography, FDG = [^{18}F]fluorodeoxyglucose, PET = positron-emission

tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters.

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohisto-chemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; ≥ 1 PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or progressive disease	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET (b) Variably FDG avid or PET negative; no change in size of previous lesions on CT		

~~[00299]~~[00296] The PK parameters of the study are as follows. The plasma PK of Formula (II) and a metabolite is characterized using noncompartmental analysis. The following PK parameters are calculated, whenever possible, from plasma concentrations of Formula (II):

$AUC_{(0\text{-}t)}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (Ct),

$AUC_{(0-24)}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation,

$AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + Ct / \lambda z$, where λz is the apparent terminal elimination rate constant,

C_{max}: Maximum observed plasma concentration,

T_{max}: Time of the maximum plasma concentration (obtained without interpolation),

$t_{½}$: Terminal elimination half-life (whenever possible),

λ_z: Terminal elimination rate constant (whenever possible),

Cl/F: Oral clearance.

~~[00300]~~[002297] The PD parameters of the study are as follows. The occupancy of BTK by Formula (II) are measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged Formula (II) analogue probe. The effect of Formula (II) on biologic markers of B cell function will also be evaluated.

~~[00301]~~[002298] The statistical analysis used in the study is as follows. No formal statistical tests of hypotheses are performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) are used to summarize data as appropriate.

~~[00302]~~[002299] The following definitions are used for the safety and efficacy analysis sets: Safety analysis set: All enrolled subjects who receive ≥ 1 dose of study drug; Per-protocol (PP) analysis set: All enrolled subjects who receive ≥ 1 dose of study drug and with ≥ 1 tumor response assessment after treatment. The safety analysis set will be used for evaluating the safety parameters in this study. The PP analysis sets will be analyzed for efficacy parameters in this study.

~~[00303]~~[003000] No imputation of values for missing data is performed except for missing or partial start and end dates for adverse events and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

~~[00304]~~[00301] The safety endpoint analysis was performed as follows. Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent adverse events will be reported in each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event and by relationship to study drug. Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated. Vital signs, ECGs, and physical exams will be tabulated and summarized.

~~[00305]~~[00302] Additional analyses include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

~~[00306]~~[00303] The analysis of efficacy parameters was performed as follows. The point estimate of the overall response rate will be calculated for the PP analysis set. The corresponding 95% confidence interval also will be derived. The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (including the median). Progression-free survival is measured from the time of first study drug administration until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate the event-free curves and corresponding quantiles (including the median).

~~[00307]~~[00304] The study scheme is a seqential cohort escalation. Each cohort consists of six subjects. The sample size of the study is 24 to 36 subjects, depending on dose escalation into subsequent cohorts. Cohort 1 (N = 6) consists of Formula (II), 100 mg QD for 28 days. Cohort 2 (N = 6) consists of Formula (II), 175 mg QD for 28 days. Cohort 3 (N = 6) consists of Formula (II), 250 mg QD for 28 days. Cohort 4 (N = 6) consists of Formula (II), 350 mg QD for 28 days. Cohort 5 (N = 6) consists of Formula (II), 450 mg QD for 28 days. Cohort 6 (N = 6)

consists of Formula (II), at a dose to be determined QD for 28 days. The dose level for Cohort 6 will be determined based on the safety and efficacy of Cohorts 1 to 5, and will not exceed 900 mg/day. Escalation will end with either the MTD cohort or three levels above full BTK occupancy, whichever is observed first. An additional arm of the study will explore 100 mg BID dosing. Treatment with oral Formula (II) may be continued for greater than 28 days until disease progression or an unacceptable drug-related toxicity occurs.

~~[00308]~~[003305] The inclusion criteria for the study are as follows: (1) men and women ≥ 18 years of age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL; however, subjects with 17p deletion are eligible if they have relapsed after, or been refractory to, 1 prior treatment for CLL/SLL; (2) body weight ≥ 60 kg, (3) ECOG performance status of ≤ 2; (4) agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children; (5) willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty; or (6) ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).

~~[00309]~~[003306] The dosage form and strength of Formula (II) used in the clinical study is a hard gelatin capsules prepared using standard pharmaceutical grade excipients (microcrystalline cellulose) and containing 25 mg of Formula (II) each. The color of the capsules is Swedish orange. The route of administration is oral (*per os*, or PO). The dose regimen is once daily or twice daily, as defined by the cohort, on an empty stomach (defined as no food 2 hours before and 30 minutes after dosing).

~~[00310]~~[00307] The baseline characteristics for the patients enrolled in the clinical study are given in Table 4.

TABLE 4. Relapsed/refractory CLL baseline characteristics.

Characteristic	**CLL (N=44)**
Patient Demographics	
Age (years), median (range)	62 (45-84)
Sex, men (%)	33 (75)
Prior therapies, median (range), n	3 (1-10)
≥3 prior therapies, n (%)	26 (59)
Clinical Details	
ECOG performance status ≥1 (%)	28 (63)
Rai stage III/IV	16 (36)
Bulky disease ≥ 5 cm, n (%)	15 (34)
Cytopenia at baseline	33 (75)
Cytogenic Status	
Chromosome 11q22.3 deletion (Del 11q), n (%)	18 (41)
Chromosome 17p13.1 (Del 17p), n (%)	19 (34)
IgV_H status (unmutated), n (%)	28 (64)

~~[00311]~~[00308] The results of the clinical study in relapsed/refractory CLL patients are summarized in Table 5.

TABLE 5. Activity of Formula (II) in relapsed/refractory CLL. (PR = partial response; PR+L = partial response with lymphocytosis; SD = stable disease; PD = progressive disease.)

n (%)	**All Cohorts (N=31)**[†]	**100 mg QD (N=8)**	**175 mg QD (N=8)**	**250 mg QD (N=7)**	**100 mg BID (N=3)**	**400 mg QD (N=5)**
PR	22 (71)	7 (88)	5 (63)	5 (71)	3 (100)	2 (40)
PR+L	7 (23)	0 (0)	3 (37)	2 (29)	0 (0)	2 (40)
SD	2 (6)	1 (12)	0 (0)	0 (0)	0 (0)	1 (20)
PD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Median (range) Cycles						
	7.3 (3.0-10.8)	**10.0 (9.0-10.8)**	**8.6 (3.0-8.8)**	**7.0 (7.0-7.3)**	**5.2 (4.7-5.5)**	**5.0 (4.8-5.5)**

~~[00312]~~[003309] FIG. 2 shows the median % change in ALC and SPD from baseline in the clinical study of Formula (II), plotted in comparison to the results reported for ibrutinib in Figure 1A of J. C. Byrd, *et al*., *N. Engl. J. Med.* **2013,** *369,* 32-42. The results show that Formula (II) leads to a more rapid patient response in CLL than corresponding treatment with ibrutinib. This effect is illustrated, for example, by the median % change in SPD, which achieved the same status in the present study at 7 months of treatment with Formula (II) as compared to 18 months for ibrutinib. The % change in SPD observed in the different cohorts (*i.e.* by dose and dosing regimen) is shown in FIG. 3, and in all cases shows significant responses.

~~[00313]~~[003310] A Kaplan-Meier curve showing PFS from the clinical CLL study of Formula (II) is shown in FIG. 4. A comparison of survival curves was performed using the Log-Rank (Mantle-Cox) test, with a p-value of 0.0206 indicating that the survival curves are different. The number of patients at risk is shown in FIG. 5. Both FIG. 4 and FIG. 5 show the results for Formula (II) in comparison to the results reported for ibrutinib in J. C. Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. An improvement in survival and a reduction in risk are observed in CLL patients treated with Formula (II) in comparison to patients treated with ibrutinib.

~~[00314]~~[003111] Based on the data and comparisons shown in FIG. 2 to FIG. 5, the CLL study with Formula (II) showed that the efficacy of Formula (II) was surprisingly superior to that of ibrutinib.

~~[00315]~~[003112] In the literature study of ibrutinib, increased disease progression was associated with patients with high-risk cytogenetic lesions (17p13.1 deletion or 11q22.3 deletion), as shown in Figure 3A in J. C. Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42, which shows ibrutinib PFS including PFS broken down by genetic abnormality. The 17p and 11q deletions are validated high-risk characteristics of CLL, and the 17p deletion is the highest risk. In FIG. 6, the PFS is shown for Formula (II) in patients with the 17p deletion in comparison to the results obtained for ibrutinib in J. C. Byrd, *et al.*, *N. Engl. J. Med.* **2013,** *369,* 32-42. A p-value of 0.0696 was obtained. In FIG. 7, the number of patients at risk with the 17p deletion is compared. To date, no 17p patients have progressed on Formula (II).

~~[00316]~~[00313] The adverse events observed in the clinical study in relapsed/refractory CLL are given in Table 6. No DLTs were observed. The MTD was not reached. No treatment-related serious adverse events (SAEs) were observed. No prophylactic antivirals or antibiotics were needed.

TABLE 6. Treatment-related adverse events reported in the clinical study of Formula (II) in relapsed/refractory CLL. (Reported in ≥ 5% of patients.)

Adverse Events (Treatment-Related), n (%)	**Grade**	**All (N=44)**
Headache	1/2	7 (16)
Increased tendency to bruise	1	6 (14)
Diarrhea	1	4 (9)
Petechiae	1	3 (7)

~~[00317]~~[00314] The clinical study of Formula (II) thus showed other unexpectedly superior results compared to ibrutinib therapy. A lack of lymphocytosis was observed in the study. Furthermore, only grade 1 AEs were observed, and these AEs were attributable to the high BTK selectivity of Formula (II).

~~[00318]~~[00315] BTK target occupany was measured for relapsed/refractory CLL patients with the results shown in FIG. 8. For 200 mg QD dosing of the BTK inhibitor of Formula (II), approximately 94% - 99% BTK occupancy was observed, with superior 24 hour coverage and less inter-patient variability also observed. For 420 mg and 840 mg QD of the BTK inhibitor ibrutinib, 80% - 90% BTK occupancy was observed, with more inter-patient variability and capped occupancy. These results indicate that the BTK inhibitor of Formula (II) achieves superior BTK occupancy in CLL patients than ibrutinib.

~~[00319]~~[00316] The effects of Formula (II) on cell subset percentages were also evaluated using flow cytometry analysis of peripheral blood, with the results shown in FIG. 9, FIG. 10, FIG. 11, FIG. 12, FIG. 13, and FIG. 14. PBMC samples from CLL patient samples drawn prior to (predose) and after 28 days of dosing with Formula (II) were compared for potential changes in cell subsets. PBMCs were stained with monoclonal antibodies conjugated to fluorescent tags (flourochromes) to identify cell subsets via flow cytometry. Non-viable cells were excluded

from the analysis using the dye 7-aminoactinomycin D (7-AAD). To produce the metric of percent change, the following steps were taken. First, each cell subset was defined by hierarchical flow cytometry gating. Then, the change in frequency (between day 1 and day 28) was calculated for each cell subset. MDSC subsets were measured as a % of all myeloid cells. T cell subsets were measured as a % of all $CD3^+$ cells, and NK cells were measured as a % of all live $CD45^+$ cells. In FIG. 9 and FIG. 10, the results show the % change in MDSC (monocytic) level over 28 days versus % ALC change at cycle 1 day 28 (C1D28) and at cycle 2 day 28 (C2D28). A cycle is 28 days. A trend is observed wherein patients with decreasing ALC % had increasing MDSC (monocytic) %. This may include patients who had quickly resolving lymphocytosis and those with no initial lymphocytosis. This provides evidence that treatment with Formula (II) mobilizes MDSCs and thus affects the CLL tumor microenvironment in marrow and lymph nodes, which is an unexpected indication of superior efficacy. In FIG. 11 and FIG. 12, the results show the % change in NK cell level over 28 days versus % ALC change, measured at C1D28 or C2D28, and similar trends are observed wherein patients with decreasing ALC % had increasing NK cell %. This may include patients who had quickly resolving lymphocytosis and those having no initial lymphocytosis. The effects in FIG. 9 to FIG. 12 are observed in multiple cohorts, at doses including 100 mg BID, 200 mg QD, and 400 mg QD. In FIG. 13 and FIG. 14, the effects on NK cells and MDSC cells are compared to a number of other markers versus % change in ALC at C1D28 and C2D28. These other markers include CD4+ T cells, CD8+ T cells, CD4+/CD8+ T cell ratio, NK-T cells, PD-1+ CD4+ T cells, and PD-1+ CD8+ T cells. The effects on NK cells and MDSC cells are observed to be much more pronounced than on any of these other markers.

~~[00320]~~[003171] These results suggest that after Formula (II) administration, the CLL microenvironment undergoes a change wherein NK cells and monocytic MDSC subsets increase in frequency in the peripheral blood in patients with falling ALC counts, an important clinical parameter in CLL. The NK cell increase may reflect an overall increase in cytolytic activity against B-CLL resulting in the ALC % to drop. The increase in MDSC % in the blood may be due to a movement of these cells out of the lymph nodes, spleen, and bone marrow, which are all possible sites of CLL proliferation. Fewer MDSCs at the CLL proliferation centers would likely result in a reduced immunosuppressive microenvironment leading to an increase in cell-mediated

immunity against the tumor, decreased tumor proliferation, and eventually lower ALC% in the circulation.

~~[00321]~~[00318] Overall, Formula (II) shows superior efficacy as measured by ALC than first generation BTK inhibitors such as ibrutinib, or PI3K-δ inhibitors such as idelalisib. Formula (II) has better target occupancy and better pharmacokinetic and metabolic parameters than ibrutinib, leading to improved B cell apoptosis. Furthermore, unlike treatment with ibrutinib and PI3K-δ inhibitors, treatment with Formula (II) does not affect NK cell function. Finally, treatment with Formula (II) leads to a CLL tumor microenvironmental effect by excluding MDSC cells from the marrow and lymph nodes and reducing their number.

Example 3 – Effects of BTK Inhibitors on Thrombosis

~~[00322]~~[00319] Clinical studies have shown that targeting the BCR signaling pathway by inhibiting BTK produces significant clinical benefit (J. C. Byrd, et al., *N. Engl. J. Med.* **2013**, *369,* 32-42; M. L. Wang, et al., *N. Engl. J. Med.* **2013,** *369,* 507-16). However, in these studies, bleeding has been reported in up to 50% of ibrutinib-treated patients. Most bleeding events were of grade 1-2 (spontaneous bruising or petechiae) but, in 5% of patients, they were of grade 3 or higher after trauma. These results are reflected in the prescribing information for ibrutinib, where bleeding events of any grade, including bruising and petechiae, were reported in approximately half of patients treated with ibrutinib (IMBRUVICA package insert and prescribing information, revised July 2014, U.S. Food and Drug Administration).

~~[00323]~~[00320] Constitutive or aberrant activation of the BCR signaling cascade has been implicated in the propagation and maintenance of a variety of B cell malignancies. Small molecule inhibitors of BTK, a protein early in this cascade and specifically expressed in B cells, have emerged as a new class of targeted agents. There are several BTK inhibitors, including CC-292 and ibrutinib (PCI-32765), in clinical development. CC-292 refers to (*N*-(3-((5-fluoro-2-((4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide, or a pharmaceutically acceptable salt thereof, including a hydrochloride salt or besylate salt thereof. Importantly, early stage clinical trials have found ibrutinib to be particularly active in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), suggesting that this class of inhibitors may play a significant role in various types of cancers (Aalipour and Advani, *Br. J.*

Haematol. **2013,** *163,* 436-43). However, their effects are not limited to leukemia or lymphomas as platelets also rely on the Tec kinases family members BTK and Tec for signal transduction in response to various thrombogenic stimuli (Oda, *et al.*, *Blood* **2000**, *95(5),* 1663-70; Atkinson, et al. *Blood* **2003**, *102(10),* 3592-99). In fact, both Tec and BTK play an important role in the regulation of phospholipase Cγ2 (PLCγ2) downstream of GPVI in human platelets. In addition, BTK is activated and undergoes tyrosine phosphorylation upon challenge of the platelet thrombin receptor, which requires the engagement of αIIbβ3 integrin and PI3K activity (Laffargue, *et al.*, *FEBS Lett.* **1999,** *443(1),* 66-70). It has also been implicated in GPIbα-dependent thrombus stability at sites of vascular injury (Liu, *et al.*, *Blood* **2006**, *108(8),* 2596-603). Thus, BTK and Tec are involved in several processes important in supporting the formation of a stable hemostatic plug, which is critical for preventing significant blood loss in response to vascular injury. Hence, the effects of the BTK inhibitor of Formula (II) and ibrutinib were evaluated on human platelet-mediated thrombosis by utilizing the *in vivo* human thrombus formation in the VWF HA1 mice model described in Chen, et al. *Nat. Biotechnol.* **2008,** *26(1),* 114-19.

~~[00324]~~[00321] Administration of anesthesia, insertion of venous and arterial catheters, fluorescent labeling and administration of human platelets (5 x 10^8/ml), and surgical preparation of the cremaster muscle in mice have been previously described (Chen, *et al.*, *Nat Biotechnol.* **2008,** *26(1),* 114-19). Injury to the vessel wall of arterioles (~40–65 mm diameter) was performed using a pulsed nitrogen dye laser (440 nm, Photonic Instruments) applied through a 20× water-immersion Olympus objective (LUMPlanFl, 0.5 numerical aperture (NA)) of a Zeiss Axiotech vario microscope. Human platelet and wall interactions were visualized by fluorescence microscopy using a system equipped with a Yokogawa CSU-22 spinning disk confocal scanner, iXON EM camera, and 488 nm and 561 nm laser lines to detect BCECF-labeled and rhodamine-labeled platelets, respectively (Revolution XD, Andor Technology). The extent of thrombus formation was assessed for 2 minutes after injury and the area (μm^2) of coverage determined (Image IQ, Andor Technology). For the Formula (II), CC-292, ibrutinib inhibition studies, the BTK inhibitors were added to purified human platelets for 30 minutes before administration.

~~[00325]~~[00322] The *in vivo* thrombus effects of the BTK inhibitors, Formula (II), CC-292,