

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

ACERTA PHARMA B.V., et al.,

Plaintiffs,

v.

ALEMBIC PHARMACEUTICALS
LIMITED, et al.,

Defendants.

C.A. No. 22-00154-RGA (consolidated)

DEFENDANTS’ JOINT INITIAL INVALIDITY CONTENTIONS

Pursuant to the Scheduling Order (D.I. 30, 69), Defendants Alembic Pharmaceuticals Limited (“Alembic”), Cipla Limited and Cipla USA, Inc. (collectively, “Cipla”), MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited (collectively, “MSN”), Natco Pharma, Ltd. and Natco Pharma, Inc. (collectively, “Natco”), and Sandoz Inc. (“Sandoz”) (collectively, “Defendants”) submit the following initial invalidity contentions to Plaintiffs Acerta Pharma B.V., Astrazeneca UK Limited, Astrazeneca Pharmaceuticals LP, Astrazeneca AB, and Merck Sharp & Dohme B.V. (collectively, “Plaintiffs”) concerning the asserted claims of U.S. Patent Nos. 9,290,504 (“the ’504 patent”), 9,758,524 (“the ’524 patent”), 10,239,883 (“the ’883 patent”), 9,796,721 (“the ’721 patent”), 10,167,291 (“the ’291 patent”), 10,272,083 (“the ’083 patent”) (collectively, “the Patents-in-Suit”).

As identified in Plaintiffs’ Initial Infringement Contentions dated September 26, 2022, Plaintiffs assert the following claims of the Patents-in-Suit (“the Asserted Claims”) against each Defendant:

Exhibit C

**DEFENDANTS' INITIAL INVALIDITY CONTENTIONS REGARDING
U.S. PATENT NO. 10,272,083**

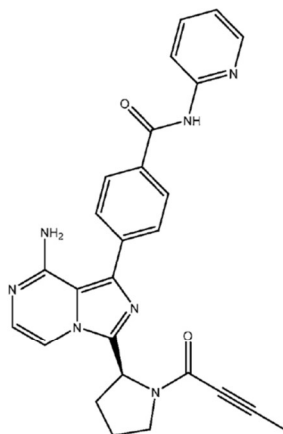
I. U.S. PATENT NO. 10,272,083

The '083 patent, entitled "Methods of Treating Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia Using a BTK Inhibitor," issued on April 30, 2019 to inventors Ahmed Hamdy, Wayne Rothbaum, Raquel Izumi, Brian Lannutti, Todd Covey, Roger Ulrich, Dave Johnson, Tjeerd Barf, and Allard Kaptein. The '083 patent issued from U.S. Application No. 15/112,968, which is the U.S. counterpart to International Patent Application No. PCT/IB2015/000645, filed on January 21, 2015. The '083 patent claims priority to U.S. Provisional Application No. 62/035,777, filed on August 11, 2014, and U.S. Provisional Application No. 61/974,665, filed on April 3, 2014, and U.S. Provisional Application No. 61/929,742, filed on January 21, 2014. The earliest potential priority date for the '083 patent is January 21, 2014. The named assignee on the face of the '083 patent is Acerta Pharma B.V.

A. The '083 Patent Claims & Specification

The '083 patent issued with 20 claims. The asserted claims of the '083 patent are 1–5, 8–12, 15–17, and 19 and recite:

1. 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):



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, ~~or~~ and myelofibrosis

In an Office Action dated July 25, 2017, the Examiner rejected all claims for obviousness over Smyth et al. (US 2013/0338172; "WO '172" or "Smyth") in view of Johannes et al. (WO 2013/010868; "WO '868" or "Johannes"). Office Action dated July 25, 2017 at 2. The Examiner noted that Smyth discloses a method of treatment using BTK inhibitors similar to that of the claimed compound of Formula II (acalabrutinib), which inhibitors are useful for treating CLL and MCL and are formulated into oral dosage forms at a concentration of 300 to 1000 mg per day, administered as much as 2 times a day. *Id.* at 2–3. The Examiner further noted that Johannes discloses the use of BTK inhibitor compounds for treating lymphomas, including specifically with the compound acalabrutinib. *Id.* at 3. According to the Examiner, a skilled artisan would have included acalabrutinib as disclosed in Johannes into the formulations disclosed in Smyth and used it to treat the conditions disclosed in Smyth with an oral multiple day formulation, since the compounds disclosed in the references have structural similarity, including the same core structures. *Id.*

C. The '777 Application

The '777 application does not provide adequate written description support for any of the asserted claims of the '083 patent for several reasons, similar to those reasons as discussed for the '665 application. The '777 application is directed to combination therapy with a PI3K inhibitor and a BTK inhibitor. The '777 application similarly lacks disclosures relating to methods of treatment of CLL, SLL, or MCL with single agent acalabrutinib. Additionally, the '777 application lacks disclosures relating to dosing of a single agent acalabrutinib.

III. THE SCOPE AND CONTENT OF THE PRIOR ART

In addition to the prior art cited in Exhibits A–C and Appendices A–F, below is a summary of the prior art to the '083 patent. To the extent that Exhibits A–C discuss the same references as listed below, any descriptions of such references are incorporated herein. Some of the references listed below have already been produced by Plaintiffs in the certified file wrapper of the '083 patent (ACAZA-0000962–12196); the beginning bates numbers of such references are denoted in the charts.

Related Patent Literature

Abbreviation	Patent/Publication No.	Country	Issue/Publication Date
	WO 2015/110923 ACAZA-0001691	PCT	July 30, 2015

Prior Art Patent Literature

Abbreviation	Patent/Publication No.	Country	Issue/Publication Date
'868 publication or WO '868	WO 2013/010868	PCT	January 24, 2013
'883 patent	U.S. Patent No. 10,239,883	United States	March 26, 2019
'524 patent	U.S. Patent No. 9,758,524	United States	September 12, 2017

Prior Art Non-Patent Literature

Abbreviation	Title	Publication Date	Author	Publisher/Source
Advani 2013	R. Advani et al., Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) has Significant Activity in Patients with Relapsed/Refractory B-Cell Malignance	2013	R. Advani, et al.	J. CLIN. ONCOLOGY
Akinleye 2013	Ibrutinib and Novel BTK Inhibitors in Clinical Development	2013	A. Akinleye, et al.	J. HEMATOLOGY & ONCOLOGY
Arnason 2014	B cell receptor pathway in chronic lymphocytic leukemia: specific role of CC-292	2014	J. Arnason & J. Brown	IMMUNOTARGETS & THERAPY
Barf 2012	Irreversible Protein Kinase Inhibitors: Balancing the Benefits and Risks	2012	T. Barf & A.Kaptein	J. MED. CHEM.
Brown 2013	PCI-32765, the First BTK (Bruton's Tyrosine Kinase) Inhibitor in Clinical Trials	2013	J. Brown	CURR. HEMATOL. MALIG. REP.
Chavez 2013	Ibrutinib: An Evidence-Based Review of Its Potential in the Treatment of Advanced Chronic Lymphocytic Leukemia	2013	J. Chavez, et al.	CORE EVID.
Cheng 2014	BTK Inhibition Targets in vivo CLL Proliferation Through its Effects on B-cell Receptor Signaling Activity	2013	S. Cheng, et al.	LEUKEMIA
Cheson 2013	The Potential for Eliminating Chemotherapy in Indolent Non-Hodgkin Lymphoma	2013	B. Cheson	CLIN. ADV. IN HEMATOLOGY & ONCOLOGY

Prior Art Non-Patent Literature

Abbreviation	Title	Publication Date	Author	Publisher/Source
2013 FDA Good Review Practice	Good Review Practice: Clinical Review of Investigational New Drug Applications	2013	U.S. Food and Drug Administration	U.S. Food and Drug Administration
Fowler	The Btk Inhibitor, PCI-32765, Induces Durable Responses with Minimal Toxicity In Patients with Relapsed/Refractory B-Cell Malignancies: Results from a Phase I Study	2010	Fowler et al.	BLOOD
Gardner 2014	Abstract 1744: ACP-196: A Second Generation Btk Inhibitor Demonstrates Biologic Activity in a Canine Model of B-Cell non-Hodgkin Lymphoma	2014	H. Gardner, et al.	CANCER RES.
Goy 2013	Mantle Cell Lymphoma: The Changing Landscape	2013	A. Goy	CLIN. ADV. IN HEMATOLOGY & ONCOLOGY
Gribben 2013	B-Cell Receptor Pathway Inhibitors- Rationale and Potential	2013	J. Gribben	CLIN. ADV. IN HEMATOLOGY & ONCOLOGY
Hantschel	The Btk tyrosine kinase is a major target of the Bcr-Abl inhibitor dasatinib	2008	Hantschel et al.	PNAS
Harb 2013	Phase 1 Study of Single Agent CC-292, a Highly Selective Bruton's Tyrosine Kinase (BTK) Inhibitor, in Relapsed/Refractory Chronic Lymphocytic Leukemia (CLL)	2013	J. Brown et al.	BLOOD

Prior Art Non-Patent Literature

Abbreviation	Title	Publication Date	Author	Publisher/Source
Niemann 2014	Abstract 2624: The Novel Bruton's Tyrosine Kinase Inhibitor ACP-196 Shows In Vivo Efficacy Against Human Chronic Lymphocytic Leukemia Cells Xenografted to the NSG Mouse Model	2014	C. Niemann et al.	CANCER RES.
Noel 2012	Novel Agents in Mantle Cell Lymphoma	2012	M. Noel et al.	BEST PRACT. RES. CLIN. HEMATOL.
O'Brien 2008	CHRONIC LYMPHOCYTIC LEUKEMIA	2008	Susan O'Brien ed.	Informa Healthcare USA, Inc.
O'Brien 2011	The Bruton's Tyrosine Kinase (BTK) Inhibitor CI-32765 Induces Durable Responses in Relapsed or Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Follow-up of a Phase Ib/II Study	2011	S. O'Brien	BLOOD
O'Brien 2013	The Changing Landscape in CLL	2013	S. O'Brien	CLIN. ADV. IN HEMATOLOGY & ONCOLOGY
Paolo 2012	Specific Btk Inhibition Suppresses B Cell- and Myeloid Cell-Mediated Arthritis	2010	J. Paolo et al.	NATURE CHEM. BIOLOGY
Pierce 2013	Target Engagement, Pathway Inhibition, and Efficacy of the Bruton's Tyrosine Kinase (Btk) Inhibitor CC-292	2013	D. Pierce et al.	BLOOD