IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PHARMACYCLICS LLC and JANSSEN BIOTECH, INC.,	)	
	)	C.A. No. 18-192 (CFC)
Plaintiffs,	)	CONSOLIDATED
v.	)	**CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**
FRESENIUS KABI USA, LLC, et al.,	)	
Defendants.	)	

PLAINTIFFS' FIRST SUPPLEMENTAL RESPONSES TO DEFENDANTS' FIRST SET OF JOINT INTERROGATORIES (NOS. 1–4)

Pursuant to Rules 26 and 34 of the Federal Rules of Civil Procedure, Plaintiffs Pharmacyclics LLC ("Pharmacyclics" or "PCYC") and Janssen Biotech, Inc. ("Janssen") (collectively, "Plaintiffs") hereby provide their first supplemental responses to Defendants' First Set of Joint Interrogatories (Nos. 1–4), served by Defendants Fresenius Kabi USA, LLC and Fresenius Kabi Oncology Limited (collectively, "Fresenius Kabi"); Zydus Worldwide DMCC and Cadila Healthcare Limited (collectively, "Zydus"); Sun Pharma Global FZE and Sun Pharmaceutical Industries LTD (collectively, "Sun"); and Cipla Limited and Cipla USA Inc. (collectively, "Cipla"), on September 7, 2018. On September 18, 2018, Sandoz Inc. and Lek Pharmaceuticals D.D. (collectively, "Sandoz") joined as well. *See* C.A. No. 18-275 (CFC) (D.I. 67) (D. Del. Sept. 18, 2018). Fresenius Kabi, Zydus, Sun, Cipla, and Sandoz are collectively referred to as "Defendants" herein.

IV. The Method Patents Are Valid

Pursuant to Fed. R. Civ. P. 33(d), and subject to and without waiver of the foregoing objections, Plaintiffs refer Defendants to the following documents[1]:

- U.S. Patent No. 8,754,090 ("the '090 Patent")
- U.S. Patent No. 9,125,889 ("the '889 Patent")
- U.S. Patent No. 8,999,999 ("the '999 Patent")
- U.S. Patent No. 9,801,881 ("the '881 Patent")
- U.S. Patent No. 9,801,883 ("the '883 Patent")
- U.S. Patent No. 10,000,746 ("the '746 Patent")
- U.S. Patent No. 9,795,604 ("the '604 Patent")

Plaintiffs further refer Defendants to the prosecution histories of these patents:

- '090 Patent File History
- '889 Patent File History
- '999 Patent File History
- '881 Patent File History
- '883 Patent File History
- '746 Patent File History
- '604 Patent File History

The asserted claims of the '090, '889, '999, '881, '883, '746, and '604 Patents (collectively, the "Method Patents") are presumed valid. In considering obviousness, the Court must assess (1) the scope and content of the prior art, (2) the differences between the claimed invention and the prior art, (3) the level of ordinary skill in the art, and (4) objective indicia of non-obviousness. To prove an invention is invalid for obviousness, defendants must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). Defendants have not and will not be able to meet that burden. Their Invalidity Contentions fail to adequately disclose Defendants'

[1] U.S. Patent No. 9,814,721 is no longer at issue in the litigation.

obviousness theories, let alone establish obviousness by the requisite clear and convincing evidence. The asserted claims of the Method Patents would not have been obvious to a person of ordinary skill in the art ("POSA").

1. Response To Defendants' Position On The Level Of Ordinary Skill In The Art

Issues of obviousness are viewed from the perspective of the hypothetical POSA as of the time of invention. Defendants' Invalidity Contentions do not identify a purported POSA for the asserted claims of the Method Patents. Defendants reference such a person throughout their contentions, but have not specified the level of ordinary skill on which their Invalidity Contentions are based. They simply state that "a POSA would generally include individuals, either alone or collectively, having experience in and/or an understanding of the treatment of cancer patients and other disorders associated with treating cancer patients." Defendants' contentions are therefore deficient. In any event, under any appropriate definition of a POSA the asserted claims of the Method Patents would not have been obvious as of their priority date.

2. The PTO Considered The Subject Matter Of Many Of Defendants' Cited References

Defendants' obviousness arguments regarding the Method Patents are primarily based on references which were considered by the examiner during prosecution, including at least: the Archive History for NCT00849654, U.S. National Library of Medicine ("the '654 Clinical Trial"); Pollyea et al., *A phase I dose escalation study of the Btk inhibitor PCI-32765 in relapsed and refractory B cell non-Hodgkin lymphoma and use of a novel fluorescent probe pharmacodynamics assay*, 114 BLOOD 3713 (2009) ("Pollyea"); "Pharmacyclics, Inc. Announces Presentation of Interim Results from Phase I Trials of Its First-In-Human Btk Inhibitor PCI-32765," PRNewswire (December 7, 2009) ("PR Newswire"); "Pharmacyclics Initiates Phase 1 Clinical Trial of Novel Oral Btk Inhibitor for Refractory B-cell Non-Hodgkin's Lymphoma,"

PRNewswire (April 13, 2009) ("PR Newswire April 2009"); Advani, *Effect of Btk Inhibitor PCI-32765 monotherapy on responses in patients with relapsed aggressive NHL: Evidence of antitumor activity from a phase I study,* J. CLIN. ONCOLOGY (May 2010) ("Advani"); Archive History for NCT01105247, U.S. National Library of Medicine ("the '247 Clinical Trial"); the API Patents; U.S. Published Patent Application No. 2008/0076921 ("the '921 Publication"); Pan et al., *Discovery of Selective Irreversible Inhibitors for Bruton's Tyrosine Kinase,* 2 CHEMMEDCHEM 58 (2007) ("Pan"); Davis et al., *Chronic Active B Cell Receptor Signaling in Diffuse Large B Cell Lymphoma,* 463 NATURE 88 (2010) ("Davis 2010"); Glassman et al., *The Value of Fluorescence In Situ Hybridization in the Diagnosis and Prognosis of Chronic Lymphocytic Leukemia,* 158 CANCER GENETICS & CYTOGENETICS 88 (2005) ("Glassman"); and Hagemeister, *Rituximab for the Treatment of Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia,* 70 DRUGS 261 (2010) ("Hagemeister").

Patent examiners are presumed to have considered prior art references listed on the face of the patent. *Shire LLC v. Amneal Pharm., LLC,* 802 F.3d 1301, 1307 (Fed. Cir. 2015). Because the PTO considered the subject matter of these references during the prosecution of the Method Patents, Defendants have not met and will not meet "the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job." *Id.* The additional references Defendants cite would not in any way change the conclusion the examiner reached regarding the non-obviousness of the claims.

3. The Asserted Claims Would Not Have Been Obvious To A Person of Ordinary Skill In The Art

The asserted claims of the Method Patents would not have been obvious to a POSA. Defendants' obviousness theories, as disclosed in their Paragraph IV letters and Initial Invalidity Contentions, are hindsight-driven and unsupported. A POSA would have had no reason to focus

narrowly on ibrutinib—ignoring other compounds known at the time of inventions—to develop the claimed methods for once-daily oral administration at the claimed dosages. Moreover, even if a POSA were to focus on ibrutinib, a POSA would not have had a reasonable expectation of success in achieving the claimed methods, particularly in light of at least the difficulty of treating the diseases of the claims.

a) No Motivation To Select Ibrutinib For Treating The Claimed Cancers Of The Method Patents

A POSA would not have been motivated to select ibrutinib for the treatment of any of the specific cancers of the '090 Patent (MCL), the '889 Patent (WM), the '999 Patent (relapsed, refractory CLL/SLL), the '881 Patent (CLL), the '883 Patent (CLL/SLL), and the '746 Patent (CLL/SLL) (the "Claimed Cancers of the Method Patents"). There were various classes of drugs under investigation for the treatment of each of the different cancers in the claims of the Method Patents, and a POSA would have had no reason to limit the scope of compounds that they were considering developing to protein kinase inhibitors. In addition to kinase inhibitors, illustrative examples of drugs under investigation include antibodies, chemotherapies, immunomodulators, small molecule immunopharmaceuticals, and HDAC inhibitors. Many of these compounds were at a more advanced stage of investigation, and thus would have been more attractive to a POSA seeking to develop treatments for the Claimed Cancers of the Method Patents.

Even if a POSA were to focus only on protein kinase inhibitors, and there was no reason to do so, there were different kinase inhibitors being pursued at the time of the invention. Inhibitors of non-tyrosine kinases, such as phosphatidylinositol 3-kinase (PI3kinase), protein kinase D, and checkpoint kinases, were being pursued for the treatment of cancer at the time of the claimed inventions. Even within the genus of tyrosine kinase inhibitors, there were many potential compounds. In fact, the specific kinase to be targeted to inhibit the B-cell receptor

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