IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Jerome B. Zeldis	Group Art Unit: 1629
Serial No.: 12/621,502	Confirmation No.: 2588
Filed: November 19, 2009	Examiner: Anderson, James D.
For: METHODS USING 3-(4-AMINO-1-OXO-1,3-DIHYDRO-ISOINDOL-2-YL)-PIPERIDINE-2,6-DIONE FOR TREATMENT OF MANTLE CELL LYMPHOMAS	Attorney Docket No.: 9516-904-999

DECLARATION BY LEI ZHANG, M.D. UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Lei Zhang, M.D., declare and state that:

1. I received my M.D. degree from the Capital Medical University in Beijing, China, and a M.S. degree in biochemistry at Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia.

2. Following completion of my medical degree, I was trained as a staff physician in internal medicine, including the diagnosis and treatment of hematologic malignancies. I later worked at several major pharmaceutical companies in their clinical development and regulatory submission divisions, with an emphasis on oncology drugs. I joined Celgene Corporation, Summit, New Jersey in 2008. I am presently a Executive Director and Clinical Research Physician of Celgene Corporation, and I am responsible for its oncology clinical research and development in the lymphoma program. I have been the lead physician in Celgene Corporation's global regulatory submission team in Mantle Cell Lymphoma ("MCL") registration program. I have overseen the clinical and scientific activities in key global registration studies of lenalidomide in MCL treatment. A copy of my curriculum vitae is enclosed herewith.

3. I am familiar with the disclosure and claims of the above-identified patent application ("the '502 application"). I understand that the pending claims are directed to, *inter alia*, methods of treating MCL with about 5 mg to 25 mg per day of 3-(4-amino-1-oxo-1,3-dihydro-isoindol-2-yl)-piperidine-2,6-dione (*i.e.*, lenalidomide) or its salt or hydrate. The compound lenalidomide is administered for a period of time followed by a period of rest. I also understand that in an Office Action issued on September 19, 2013 by the Patent Office, the pending claims are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Zeldis (U.S. Publication No. 2004/0029832 A1) in view of secondary references Damaj *et al.* (*Leukemia*, 2003, vol. 17, pages 1914-1915; "Damaj"), Wilson *et al.* (*British J. of Haematology*, 2002, vol. 119, pages 128-130; "Wilson"), and Kaufmann *et al.* (*Blood*, 2004, vol. 104, no. 8, pages 2269-2271; "Kaufmann").

4. I have reviewed the cited references including Damaj, Wilson and Kaufmann. It is my opinion that one of ordinary skill in the art would not have concluded based on the disclosure of these references that the compound thalidomide would be therapeutically effective in treating MCL. Damaj reported two individual MCL patients treated with thalidomide. Wilson reported the case of a single MCL patient. To determine whether an agent is therapeutically effective in treating a certain disease, one of ordinary skill in the art would have needed a statistically significant amount of evidence, including preclinical safety and toxicity information. The evidence presented in Damaj and Wilson is limited to three individual patients and is clearly insufficient. While Kaufmann evaluated a combination strategy using thalidomide and rituximab in 16 patients and reported that 13 patients achieved objective responses, only 3 of these patients were previously treated with rituximab, an agent that was known to inhibit MCL at the time of Kaufmann's study. As such, it cannot be ascertained whether the response observed in the 13 patients was induced by rituximab, thalidomide, or their combination. Therefore, it is my opinion that one of ordinary skill in the art would not have concluded that thalidomide is therapeutically effective in treating MCL based on these three references. Additionally, I am not aware of any large-scale clinical study of thalidomide in treating MCL that was conducted following the publication of these references.

5. There is a significant unmet need in therapeutic options for MCL patients, in particular those with relapsed, refractory, or relapsed and refractory MCL. In spite of improved

treatment options for MCL patients, MCL continues to have the poorest prognosis among non-Hodgkin's lymphoma (NHL) subtypes. With each successive relapse, MCL patients experience chemo-resistance and shorter duration of response. The overall survival for relapsed or refractory MCL is estimated to be only 1-2 years. Prior to June 2013, bortezomib (Velcade®) was the only drug approved by the U.S. Food and Drug Administration ("FDA") for patients with relapsed or refractory MCL. Once the patients relapse after or fail the bortezomib treatment, no clear treatment option is available.

6. I was the lead clinician in the Phase II study of lenalidomide in MCL treatment. I am familiar with both the compound lenalidomide and its therapeutic effects in MCL patients. All patients enrolled in this study were heavily pretreated for MCL (median number of prior treatments is 4) and 93% of the patients had stage III-IV MCL. In addition, all patients had received prior treatment with bortezomib. Lenalidomide, when administered as described in the claims, achieved an overall response rate of 28% (central review)/32% (investigator review), including a complete response rate of 7.5% (central review)/16% (investigator review). The median duration of response is 16.6 months (central review)/18.5 months (investigator review). The median duration of response for complete response is 16.6 months (central review)/26.7 months (investigator review). Also significantly, with a median follow-up of 9.9 months, median overall survival is 19.0 months. The results of the Phase II study are described in the Goy *et al.* (2013) article enclosed herewith. The safety profile of lenalidomide in these patients was also manageable.

7. It is my opinion that the efficacy of lenalidomide in relapsed, refractory, or relapsed and refractory MCL demonstrated in this study would have been unexpected and surprising at the time the claimed invention was made, particularly in view of the unfavorable prognosis of the patients. The FDA granted fast track designation to lenalidomide based on its activity and tolerability in heavily pretreatment relapsed or refractory MCL patients who received prior bortezomib therapy, and approved lenalidomide for this indication based on the Phase II study results.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Dated: Oct 15, 2013

Lei Zhang, M.D.

Exhibit A

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