UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN LABORATORIES LIMITED
Petitioner,
v.
AVENTIS PHARMA S.A.
Patent Owner.

Case IPR2016-00712
U.S. Patent No. 8,927,592

REPLY DECLARATION OF ALTON OLIVER SARTOR, M.D.

Aventis Exhibit 2259

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I. Qualifications and Scope

1. I am the same Dr. Sartor who previously submitted declarations filed on June 24, 2016 ("First Declaration," Exh. 2001) and December 23, 2016 ("Second Declaration," Exh. 2176) in IPR2016-00712.

2. I understand that Dr. Rahul Seth submitted declarations on March 15, 2016 ("Petition Declaration," Exh. 1002) addressing the validity of the claims of U.S. Patent No. 8,927,592 ("the '592 patent") and on March 14, 2017 ("Reply Declaration," Exh. 1043) addressing the validity of the current claims of the '592 patent and substitute Claims 31-34 from Patent Owner's Motion to Amend. I have been asked by counsel for Aventis Pharma S.A. ("Aventis") to respond to Dr. Seth's opinions regarding only Claims 31-34.

II. "increasing survival"

3. Dr. Seth argues that because it is impossible to know whether a drug will or has resulted in an increase in survival of a patient, "a method of increasing survival" means "administration of cabazitaxel with the intention of increasing survival of the patient, regardless of whether the intended survival actually results." Exh. 1043 at ¶¶36-40.

4. I disagree with Dr. Seth that it is impossible to know whether a drug will or has resulted in an increase in survival in a patient. As discussed in my Second Declaration, overall survival is a key endpoint for clinical studies in prostate cancer

that is measured by a randomized and controlled clinical study. Exh. 2176 at ¶231; Ramiah *et al.*,*Clinical Endpoints for Drug Development in Prostate Cancer*, 18 Curr. Opin. Urol. 303-08 (2008) (Exh. 2030) at 306; Armstrong & George, *New Drug Development in Metastatic Prostate Cancer*, 26 Urologic Oncology: Seminars & Original Investigations 430-37 (2008) (Exh. 2005) at 431 (discussing power necessary to detect an overall survival advantage); Pazdur, *Endpoints for Assessing Drug Activity in Clinical Trials*, 13 (suppl. 2) The Oncologist 19-21 (2008) (Exh. 2080) at 19-20.

5. The purpose of measuring overall survival in clinical studies is to determine whether that regimen prolongs the life of individual patients. Once a study shows a statistically significant increase in overall survival as compared to no therapy or palliative therapy, a POSA can reasonably conclude that another patient with the same characteristics as in the clinical study has an increased life expectancy when given the study drug, and can treat the patient with the studied regimen with the intent to increase the survival of that patient.

6. The TROPIC study described in Example 1 of the ’592 patent is an example of such a clinical trial designed to determine whether cabazitaxel plus prednisone would result in an increase in overall survival as compared to mitoxantrone plus prednisone. The TROPIC study randomized 755 patients with mCRPC that had progressed during or after a docetaxel-containing regimen. Exh.

1001 at Example 1. The results of the study showed that the cabazitaxel plus prednisone arm had statistically significantly longer overall survival as compared to the mitoxantrone plus prednisone arm, with a p-value of <0.0001. *Id.* Based on the results of TROPIC, another mCRPC patient that has progressed during or after docetaxel has an increased life expectancy when he receives cabazitaxel plus prednisone therapy as compared to mitoxantrone plus prednisone therapy.

7. A POSA would understand that in an ideal world an experimental medication could be compared to no therapy to determine whether the experimental medication prolongs life. However, such a clinical trial could be considered unethical for mCRPC patients who are very sick. Accordingly, instead of no therapy, an appropriate comparator is palliative therapy, such as the mitoxantrone plus prednisone arm of the TROPIC study described in the '592 patent. The palliative mitoxantrone therapy is essentially a surrogate for no therapy with respect to survival because an increase in survival as compared to mitoxantrone is necessarily an increase in survival as compared to no therapy.

8. Dr. Seth also asserts that the investigators of the TROPIC study intended to prolong the lives of their patients and that patients entering phase III studies intend themselves to live longer. Exh. 1043 at ¶39. I disagree. Patients in the TROPIC study were randomized to receive either cabazitaxel and prednisone or mitoxantrone and prednisone. Mitoxantrone had not been shown to prolong life.

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