UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

HELSINN HEALTHCARE S.A. and ROCHE PALO ALTO LLC, Plaintiffs, v. DR. REDDY'S LABORATORIES, LTD., *et al.*, Defendants.	**Civil Action No. 11-3962 (MLC)(DEA)** **Civil Action No. 13-5815 (MLC) (DEA)** **(Consolidated)** **Hon. Mary L. Cooper, U.S.D.J.** **Hon. Douglas E. Arpert, U.S.M.J.**

REBUTTAL EXPERT REPORT OF TANIOS BEKAII-SAAB, M.D.
WITH RESPECT TO U.S. PATENT NO. 8,598,219

30. Therefore, even assuming that a POSA would have selected "doses falling within the 0.3-90 µg/kg" range disclosed in the Piraccini abstracts for a Phase 2 dose-finding study, a POSA would have been inclined to test doses in the 30-90 µg/kg (2.1-6.3 mg) portion of the 0.3-90 µg/kg range, not the doses below 30 µg/kg. Consistent with the Piraccini abstracts where "[n]o dose-related increase in the incidence or severity of [adverse events] was seen," the Tang 1998 data also showed no appreciable difference in adverse events between the 1 µg/kg, 3 µg/kg, and 30 µg/kg doses. (Exh. 1, at 466; *see also* Candiotti 10/25/13 Report at ¶ 25, n.7.) That the Piraccini abstracts disclosed a 90 µg/kg (6.3 mg), which is more than 25 times larger than the claimed 0.25 mg dose, with no indication of toxicity[18], would have indicated to a POSA that doses higher than 30 µg/kg (2.1 mg) should be tested for further development.[19, 20]

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seek a dose that would treat the entire intended patient population, including those studied in Tang 1998. And, once again, a POSA seeking to develop a single-use, unit-dose antiemetic for treating CINV would know that generally even higher doses are required to treat that patient population.

[18] The most common adverse events were headache and constipation, generally mild to moderate. (*See, e.g.* Exh. 4, at 400a; Exh. 5, at TEVA-0089206; Exh. 6, at 292.)

[19] Dr. Fruehauf states that a Phase 2 antiemetic trial "includes finding the minimum effective dose of the drug." (Fruehauf at ¶ 23.) I disagree. In support of this point, Dr. Fruehauf cites a document describing Phase II design for anticancer drug development. First, I am unaware of any regulation or practice requiring a drug manufacturer to find "the minimum effective dose of the drug." Moreover, as a general matter, the main outcome for most dose-finding designs for oncology trials is toxicity, and thus dose escalation is guided by ethical considerations. The main outcome in non-oncology trials (which would include those relating to an antiemetic), on the other hand, is potential efficacy, and dose escalation is not constrained by ethical considerations. Particularly where no difference in toxicity/safety was observed for the highest doses compared to lower doses, as was reported in the Piraccini abstracts and would have been consistent with Tang 1998, a POSA would pursue a dose that was safe and had maximum potential effectiveness.

[20] The interpretation of Tang 1998 by others as demonstrating palonosetron with "inferior" efficacy to available 5-HT_3 antagonists at the time is consistent with my opinion. (P. Loewen, *Anti-emetics in Development*, 11(6) Expert Opin. Investig. Drugs, 801, 803 (2002) (citing Tang 1998 in support of palonosetron having "inferior" efficacy compared to available 5-HT_3

31. The ’333 patent disclosure does not change my opinion that there would not have been a reasonable expectation of success that a formulation with a low palonosetron dose such as 0.25 mg could treat emesis. Dr. Fruehauf and Dr. Markman cite the following statements in the ’333 patent: “one of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of compound of Formula I for a given disease,” and “a therapeutically effective amount for a 70 kg human may range from 70 ng/day to 70 mg/day.” (Fruehauf Report at ¶ 36, Markman Report at ¶¶ 31, 49 n.11.) A POSA in the relevant time frame would not have conducted a dose-finding study based on such an enormous range of doses, particularly in view of more applicable information that was available in Tang 1998 disclosing that doses less than 2 mg should not be tested. Moreover, the only IV formulation disclosed in the ’333 patent contained between 10-100 mg of palonosetron, which is 40 to 400 times higher than a 0.25 mg palonosetron dose. (Exh. 19, ’333 patent at col. 29:2-11.) Thus, a POSA would not have had reason to test a 0.25 mg dose in a Phase 2 trial based on the disclosure in the ’333 patent.[21]

32. I disagree with Dr. Markman and Dr. Fruehauf that a POSA would consider the Helsinn Press Releases in designing clinical studies. (*See generally* Exhs. 7-10.) I further disagree that the disclosures in the Helsinn Press Releases, combined with the broad dose range disclosed in the Piraccini abstracts, would somehow provide a POSA with “specific knowledge

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antagonists, while itasetron was found to have “similar” efficacy based on different clinical data) (attached as Exh. 18).)

[21] I understand that Dr. DeLuca is of the opinion that 0.25 mg dose would be obvious in view of Tang 1998 and the ’333 patent. (DeLuca at ¶¶ 28-29.) For the reasons discussed, I disagree.

concerning how to design routine palonosetron clinical studies to determine an effective dose" for several reasons. (Markman at ¶¶ 47, 49; *see also* Fruehauf ¶ 46.)

33. First, the Helsinn Press Releases are marketing tools that a POSA would not have considered in designing clinical studies.[22] Helsinn's 9/14/00 News Release announcing the enrollment of patients for Phase 3 clinical trials demonstrates this point: "Helsinn is seeking marketing partners for this patented product in different territories." (Exh. 7, Helsinn's 9/14/00 Press Release, at 1; *see also* Exh. 9, Helsinn's 10/3/01 Press Release, at HELSN0376723 ("HELSINN is the worldwide licensor of palonosetron . . . . [P]alonosetron will compete in the CINV treatment market, which is rapidly approaching $1 billion in North America. HELSINN's negotiations with potential European licensing partners are ongoing, and out-licensing activities for remaining markets will commence next year.").) Second, the Helsinn Press Releases provided no guidance on doses or the specific formulations used in any of the clinical trials. (*See generally* Exhs. 7-10.)

34. Moreover, the discrete pieces of information in the Helsinn Press Releases, such as a "double-blinded, randomized" study design, "intravenous (IV) palonosetron," and "1,800 cancer patients receiving either highly- or moderately-emetogenic chemotherapy" (*see* Markman at ¶¶ 39, 51), would not provide "specific knowledge" to a POSA on "how to design routine

[22] To the extent defendants' experts rely on the Piraccini abstracts (coauthored by Helsinn individuals) and the Helsinn Press Releases to assert that a POSA would have been motivated to focus on palonosetron for commercial development, I disagree. These documents do not report information relevant to a POSA in drug development, such as how and when the drug was administered or the formulation used. Further, the Helsinn Press Releases did not include scientific data that a POSA would have evaluated for potential development. Finally, because Helsinn was an unknown company in the relevant time period, a POSA would not have made commercial drug development decisions requiring significant investment based on the company's own news releases, especially given the context of "seeking marketing partners" for palonosetron.

51. In footnote 75 of ¶ 59, Dr. Fruehauf notes that Phase 3 Study PALO-99-04 was completed on December 27, 2001, and Phase 3 Study PALO-99-05 was completed on December 31, 2001. The respective unblinding dates for these studies were February 28, 2002, and March 19, 2002. (Exh. 25, at HELSN0043702; Exh. 26, at HELSN0049834.) Thus, Helsinn would not have known of the results of these studies before January 30, 2002, let alone completed a full analysis of the data.

Date: September 15, 2014

Tanios Bekaii-Saab, M.D.