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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

PAR PHARMACEUTICAL, INC.,
BRECKENRIDGE PHARMACEUTICAL, INC. AND
ROXANE LABORATORIES, INC.
Petitioners,

v.

NOVARTIS AG,
Patent Owner

Case IPR2016-00084[1]
U.S. Patent 5,665,772

PATENT OWNER'S MOTION FOR OBSERVATIONS ON CROSS-EXAMINATION OF MARK J. RATAIN, M.D.

[1] Breckenridge Pharmaceutical, Inc. was joined as a party to this proceeding via a Motion for Joinder in IPR2016-01023; Roxane Laboratories, Inc. was joined as a party via a Motion for Joinder in IPR2016-01102.

I. A POSA Would Not Have Reasonably Expected Everolimus's Observed Antitumor Activity

In Ex. 2223, page 11, lines 15-24, Dr. Ratain testified that his "opinions relate only to secondary considerations." Dr. Ratain also admitted that he "can't come up with any independent firsthand opinions related to the chemical modifications and the impact of such" because he is "not a chemist." Ex. 2223 at 14:19-15:6. This testimony is relevant because Dr. Jorgensen did not address whether a POSA would have reasonably expected everolimus's antitumor activity; thus, Drs. Burris's and Roush's opinions that a POSA would not have reasonably predicted what effect the difference in structure between rapamycin and everolimus would have on antitumor activity are unrebutted. Ex. 2095, Burris ¶¶ 86-89; Ex. 2093, Roush ¶ 156.

In Ex. 2223, page 18, line 9 to page 19, line 23, Dr. Ratain testified that all of the references he cited in support of his opinions in Ex. 1119, Ratain ¶¶ 101-106 were published after 1992. Dr. Ratain also admitted that mTOR "had not yet been identified" in 1992. Ex. 2223 at 21:18-20; Ex. 1102, p.527 ("mTOR was identified in 1994"). This testimony is relevant because it confirms that Petitioners improperly rely on post-invention date information to try to rebut Patent Owner's evidence that a POSA would not have had a reasonable expectation that everolimus would have its observed antitumor activity. Paper No. 46 ("Reply") at 17-18 FN 6.

II. Petitioners Have Failed To Establish That Co-Administration Of Everolimus And Cyclosporine, And Everolimus's Half-Life Do Not Provide Unexpected Clinical Benefits

At Ex. 2223, page 204, line 20 to page 205, line 21, Dr. Ratain admitted that he is not an immunologist or a transplant nephrologist and has not prescribed immunosuppressants to transplant patients to induce immunosuppression. This testimony is relevant because it undermines the credibility and weight of Dr. Ratain's opinions, especially when compared to those of Dr. Stefan Tullius—Petitioners' transplant and immunosuppression expert in the related District Court litigation—who admitted that co-administration increases the likelihood that patients will adhere to an immunosuppressive drug regimen and provides clinical benefits. Paper No. 27 ("Response") at 57; Ex. 2132, Tullius Trial 1205:11-23, 1308:8-17.

At Ex. 2223, page 206, line 22 to page 207, line 5, Dr. Ratain admitted that he did not know the recommended dosing regimen for cyclosporine in renal transplant patients. This testimony is relevant because it undermines the credibility and weight of Dr. Ratain's opinions regarding whether physicians would prefer to prescribe everolimus to be taken once a day, or twice a day on the same schedule as cyclosporine, and medication adherence in transplant patients taking either rapamycin or everolimus with cyclosporin. Reply at 25-26 (citing Ex. 1118, Jorgensen ¶¶ 49-50).

At Ex. 2223, page 205, line 22 to page 206, line 17, Dr. Ratain admitted that the Rapamune (rapamycin) label (Ex. 2053) at page 5, section 2.1, recommends that "Rapamune be taken 4 hours after administration of cyclosporine." This testimony is relevant because it contradicts Petitioners' assertion that there is no evidence that rapamycin and cyclosporine cannot be co-administered. Reply at 25.

At Ex. 2223, page 212, line 25 to page 215, line 8, Dr. Ratain admitted that none of the references cited in Ex. 1119, Ratain ¶ 47 disclosed the half-lives of rapamycin analogs, and that a POSA would not have reasonably predicted the effect of chemical modification on rapamycin's half-life or whether the half-life of any derivative would be shorter or longer, rather its half-life would have to be determined experimentally. This testimony is relevant because it contradicts Petitioners' assertion that everolimus's half-life, which is significantly shorter than that of rapamycin, would not have been unexpected. Reply at 25-26. There is no evidence of what a POSA would have reasonably expected everolimus' half-life to be, or that a POSA would have reasonably expected chemical modification to rapamycin to result in a half-life that provides clinical benefits.

At Ex. 2223, page 207, lines 6-22, Dr. Ratain admitted that Ex. 1055 "was not looking at the medical adherence in patients taking cyclosporine

with either everolimus or rapamycin." At Ex. 2223, page 211, lines 8 to page 212, line 24, Dr. Ratain further admitted that the clinical trial reported in Ex. 1057 was not completed and results for the trial were not reported. At Ex. 2223, page 207, lines 10 to page 211, line 7, Dr. Ratain also admitted that Ex. 1056 stated that in a study comparing mycophenolate mofetil (MMF) twice-daily and *rapamycin* once-daily adherence rates, "there was no statistically significant difference between once-daily and twice-daily dosing." This testimony is relevant because it demonstrates that none of the cited references support Dr. Ratain's assertion that rapamycin's longer half-life allows for once-daily dosing, which leads to improved adherence and clinical outcomes. Ex. 1119, Ratain ¶¶ 49-50; Reply at 26.

III. Compelling Objective Indicia Further Support Non-Obviousness

In Ex. 2223, page 12, line 11 to page 13, line 2, Dr. Ratain admitted that he has not offered any opinions regarding failure of others, industry praise, or commercial success. This is relevant because it confirms that Dr. Burris's following opinions are unrebutted: (a) prior to 1992, numerous other therapies had failed for both advanced RCC and breast cancer (Response at 62-63), (b) numerous physicians have praised everolimus (Response at 66), and (c) Afinitor® has achieved significant commercial success due to its active ingredient, everolimus (Response at 66). Likewise, Patent Owner's

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