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On Behalf Of:

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NOVEN PHARMACEUTICALS INC.
AND MYLAN PHARMACEUTICALS INC.,
Petitioners

v.

NOVARTIS AG AND LTS LOHMANN THERAPIE-SYSTEME AG,
Patent Owners

Inter Partes Review No. 2014-00550[1]
U.S. Patent 6,335,031

[redacted]

PATENT OWNERS' MOTION FOR OBSERVATIONS ON CROSS-EXAMINATION OF AGIS KYDONIEUS, Ph.D.

[1] Case IPR2015-00268 has been joined with this proceeding.

I. The Prior Art Taught That Rivastigmine Has Greater Chemical Stability *In Vitro*

At Ex. 1049, page 69, lines 6 to 20, Dr. Kydonieus agreed that "one reference from the Weinstock Group can aid in the interpretation of other references from the same scientific group."[2] This testimony is relevant to Dr. Kydonieus's erroneous opinion that a POSA would have understood that the antioxidant was added to RA7 in Elmalem to prevent its oxidation in ¶ 57 of Ex. 1031. The testimony is relevant because, in a subsequent paper—Weinstock 1994—the Weinstock Group did not add an antioxidant to rivastigmine. (Ex. 2012 at ¶¶ 47, 72; Ex. 2027.) A POSA reading Elmalem in light of Weinstock 1994 and the art as a whole would have concluded that rivastigmine did not require an antioxidant. (Ex. 2012 at ¶¶ 72, 74.)

At Ex. 1049, page 206, line 16 to page 208, line 18, Dr. Kydonieus admitted that "chemical stability" refers mostly to *in vitro* stability. This testimony is relevant to Enz 1991 and Weinstock 1994, which both report that rivastigmine has greater "chemical stability" than physostigmine in Ex. 2026 at 272 and Ex. 2027 at 219, and Dr. Kydonieus's assertion in ¶¶ 68-70 of Ex. 1031 that Dr. Klibanov

[2] At Ex. 1049, page 6, line 20 to page 7, line 14, Dr. Kydonieus testified that, unless he indicated otherwise, the opinions he expressed during cross-examination applied to both the '031 and '023 Patents.

mischaracterized these references as relating to *in vitro* stability. This testimony is relevant because it confirms that Enz 1991 and Weinstock 1994 disclose that rivastigmine has greater "chemical stability" *in vitro* than physostigmine and that Dr. Klibanov did not mischaracterize these references. (*See* Ex. 2012 at ¶ 47.)

At Ex. 1049, page 100, line 10 to page 101, line 12 and page 102, line 6 to page 103, line 2, Dr. Kydonieus admitted that Rosin states that physostigmine was chemically unstable *in vitro* and there was a need for new carbamate derivatives with greater chemical stability *in vitro* than physostigmine. This testimony is relevant to Dr. Kydonieus's erroneous opinion that the statement in Rosin that the greater *in vivo* potency of RA7 over physostigmine may be due to "greater chemical stability" relates to *in vivo*, not *in vitro*, stability in Ex. 1049, page 104, line 22 to page 105, line 2. This testimony is relevant because it demonstrates that when Rosin discusses "chemical stability" it relates to *in vitro*, not *in vivo*, stability.

At Ex. 1049, page 110, line 24 to page 111, line 14, Dr. Kydonieus admitted that, if a drug is stable to hydrolysis inside the body, it would be expected to be stable to hydrolysis outside the body. This testimony is relevant to Dr. Kydonieus's erroneous opinion that the statement in Rosin that the greater *in vivo* potency of RA7 over physostigmine may be due to "greater chemical stability" relates to *in vivo*, not *in vitro*, stability in Ex. 1049, page 104, line 22 to page 105,

line 2. Physostigmine was known to degrade *in vitro* by hydrolysis. (Ex. 2012 at ¶ 78.) This testimony is relevant because it demonstrates that, even under Dr. Kydonieus's incorrect interpretation of Rosin, a POSA would have understood that greater chemical stability *in vivo* also means greater chemical stability *in vitro*.

At Ex. 1049, page 103, line 3 to page 104, line 11, Dr. Kydonieus admitted that "metabolic degradation" refers to degradation inside the body, *e.g.*, by enzymes, and "excretion" refers to elimination from the body, *e.g.*, by the liver or kidneys. This testimony is relevant to Dr. Kydonieus's erroneous opinion that the statement in Rosin that the greater *in vivo* potency of RA7 over physostigmine may be due to "greater chemical stability" relates to *in vivo*, not *in vitro*, stability in Ex. 1049, page 104, line 22 to page 105, line 2. This testimony is relevant because Dr. Kydonieus further admitted that "slower metabolic degradation or/and excretion," which refers to *in vivo* degradation or elimination, is a different reason from "greater chemical stability" for the greater *in vivo* potency of RA7 over physostigmine reported in Rosin. (Ex. 1049, page 104, lines 12 to 21.)

At Ex. 1049, page 9, line 13 to page 10, line 16, Dr. Kydonieus confirmed that if a drug degrades, the potency of the drug is reduced. This testimony is relevant to Dr. Kydonieus's opinion in ¶ 46 of Ex. 1031 that Dr. Klibanov did not assert that there is a link between *in vivo* potency and greater oxidative stability under pharmaceutically relevant conditions. This testimony is relevant because it

demonstrates that there is a link between *in vivo* potency and greater oxidative stability under pharmaceutically relevant conditions.

II. A POSA Would Not Reasonably Have Predicted That Rivastigmine Would Oxidatively Degrade Absent Testing

At Ex. 1049, page 43, lines 2 to 17, Dr. Kydonieus admitted that "oxidation is formulation-dependent." This testimony is relevant to Dr. Kydonieus's opinion that "a POSA would have understood . . . that rivastigmine was likely to undergo oxidative degradation in any given pharmaceutical formulation" in ¶ 8 of Ex. 1031. This testimony is relevant because it contradicts that erroneous opinion. It further confirms that "a POSA would conduct testing to confirm to what extent, if any, the drug in the formulation oxidatively degrades." (Ex. 1031 at ¶ 10.)

At Ex. 1049, page 154, line 11 to page 155, line 3, Dr. Kydonieus asserted that a POSA should "expect" to see degradation of rivastigmine in any formulation. This testimony is relevant to that opinion. This testimony is relevant because it is contradicted by Dr. Kydonieus's opinion that oxidative degradation is formulation specific and "a POSA would conduct testing to confirm to what extent, if any, the drug in the formulation oxidatively degrades." (Ex. 1031 at ¶ 10.)

III. A POSA Would Not Reasonably Have Predicted That Rivastigmine Would Oxidatively Degrade Based On Structure

At Ex. 1049, page 92, line 21 to page 94, line 5, Dr. Kydonieus admitted that just because a drug is formulated as a salt "doesn't mean that it will not degrade."

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