UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LUPIN LTD. and LUPIN PHARMACEUTICALS INC.

Petitioners,

v.

HORIZON THERAPEUTICS, LLC

Patent Owner.

IPR2017-00829
U.S. Patent No. 9,095,559

PETITIONERS' REPLY

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1. **Horizon Mischaracterizes Both the Claims and State of the Prior Art**

Patent Owner Horizon greatly overstates the scope of the claimed subject matter, mischaracterizing it as "an ingenious solution" to the "problem" of "how to treat a patient suffering from a nitrogen retention disorder," while referencing "accumulation of potentially fatal levels of ammonia." (POR at 1.) Methods of using glyceryl tri-[4-phenylbutyrate] to lower plasma ammonia levels were known long before the '559 patent, and Horizon did not solve the problem of how to lower fatal ammonia levels. Indeed, the '559 patent claims are not even related to treating acute hyperammonemia. They are instead narrowly directed to fine-tuning or optimizing drug dosage in patients who already have normal fasting plasma ammonia levels, based on comparing the patient's fasting plasma ammonia levels to the ULN for plasma ammonia. The use of ammonia as a biomarker for evaluating drug dosages was well known; fine-tuning drug dosage was well within the ordinary skill of physicians; and the effect of carrying out the claimed methods would be to routinely maintain normal plasma ammonia levels—a goal that was fully reported in the prior art. Because the challenged claims are to nothing more than "the predictable use of prior art elements according to their established functions," *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007), they should be cancelled as obvious.

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(a) **POSAs Used Ammonia Levels to Adjust Drug Dosage**

In arguing that plasma ammonia levels "were not a basis upon which to increase the dosage of a drug" (POR at 46), Horizon directly contradicts the prior art. For example, the '857 Publication—which shares an inventor with the '559 patent—clearly teaches using ammonia levels to determine whether to adjust drug dosage. (*See* Petition at 22-23.)

Horizon lists several purported drawbacks of using ammonia as a biomarker, none of which change the fact that POSAs used ammonia levels when adjusting drug dosage. And the claimed methods fail to address these purported drawbacks in any event. For example, citing Ex. 2015, Horizon contends that inherent difficulties with the interpretation of blood ammonia levels "undermined its usefulness as a diagnostic tool." (POR at 12, 49.) This argument misses the mark. Ex. 2015 discusses the difficulty in diagnosing a specific UCD based on the specific numerical level of ammonia (Ex. 2015 at 75), but the '559 claims do not cover using a specific numerical value of ammonia to diagnose diseases. Thus Horizon did not solve this purported problem.

Nor have the '559 patent claims solved any of the other purported problems with ammonia that Horizon raised, including diurnal fluctuation; artificially high levels if a patient is catabolic due to fasting, exercise, surgery, an infection, or pregnancy; and lack of correlation of ammonia levels with clinical status. (POR at

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12, 48-50.) The prior art disclosed all of these issues with ammonia, yet POSAs still used ammonia levels to adjust drug dosage. (*See, e.g.*, Ex. 1007 at [0232] ("[D]ose adjustment would be based on repeated measurement of urinary PAGN as well as assessment of dietary protein and plasma ammonia.").)

(b) **A POSA Would Have Been Motivated to Adjust Drug Levels in Patients Near the ULN Because the Prior Art Taught POSAs to Maintain Stable Plasma Ammonia Levels**

In trying to undercut a motivation to combine, Horizon disputes that a goal of nitrogen scavenging therapy is to maintain a "stable" plasma ammonia level. (POR at 33-34.) Once again, Horizon ignores the express teachings of the prior art, which make clear that maintenance of plasma ammonia levels within normal limits, and below the ULN, is one of the objectives of drug therapy. *See, e.g.*, Ex. 1007 at [0046] (noting desire to "maintain a stable level of plasma ammonia"); [0182] (noting that HPN-100-treated subjects will typically "achieve and maintain normal plasma ammonia levels"); [0209] (discussing consistent reduction of ammonia to below about 40 μmol/L); Ex. 1020 at 3327 (noting that plasma ammonia "should be maintained within normal limits"). Horizon further asserts that due to the known variability in plasma ammonia levels, a stable level cannot be achieved. (POR at 34.) But that is exactly Petitioners' point: because ammonia levels were known to vary, a POSA would have been motivated to keep the baseline ammonia levels low, such that despite transient fluctuations, *e.g.* in

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