UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

ASTRAZENECA AB,
Patent Owner.

Case: IPR2015-01340
U.S. Patent No. RE44,186

DECLARATION OF JEFFREY ROBL, PH.D.

I, Jeffrey Robl, declare as follows:

I. Introduction

1. All facts in this declaration are based on my personal knowledge unless otherwise stated.

2. I am one of the co-inventors of U.S. Patent No. RE44,186 (Ex. 1001).

3. I completed and successfully defended my Ph.D. thesis in 1987, joined Squibb as a full time employee in 1987, and received a Ph.D. degree in 1988. Since 1987, I have worked at Bristol-Myers Squibb Co. ("BMS") and its predecessor.

4. In 1998, I was an Associate Director in the Metabolic Diseases department within BMS. In late-1998, I proposed to one of the biology leaders in the Metabolic Diseases department the idea of synthesizing dipeptidyl peptidase ("DPP-IV") inhibitors to treat diabetes, and presented the idea at the November 20, 1998 Metabolic Diseases New Target Evaluation meeting. Around that time, I prepared a document that identifies potential starting points for a medicinal chemistry program. *See* Ex. 2169.

5. I initially proposed a variety of unknown chemical structures with constrained rings as potential DPP-IV inhibitors. For instance, I proposed the constrained ring structures identified as "Aliphatic Bicyclics," "Benzo-Fused

Bicyclics," "Non-Bicyclics," and other constrained "Miscellaneous" compounds. *Id.*

6. I also identified two compounds as "Literature Standards." *Id.* I identified these compounds because they were the most prominently highlighted reversible DPP- IV inhibitors in the literature, and I wanted them to serve as benchmarks for our program. Probiodrug developed the compound on the left, and Ferring developed the compound on the right. Both "Literature Standards" included a sulfur in its pyrrolidine ring.

7. In January 1999, BMS's DPP-IV research group began actively working on generating constrained compounds, and the first new compounds were synthesized in February 1999.

8. The initial constrained ring structures that we tested were essentially inactive against DPP-IV. *See, e.g.,* Ex. 2183 at 1. Our group experimented by generating analogs with different ring sizes, but we began to understand that the constrained analogs did not exhibit promising inhibition of DPP- IV, and our group gradually shifted our focus away from those analogs.

9. We also began exploring one of my initial ideas of fusing a cyclopropyl group to the cyanopyrrolidine ring and first highlighted our work in the Chemistry Significant Events report around August 1999. *See* Ex. 2184 at 1-2;

see also Ex. 2169 ("Non-Bicyclics" including a cyclopropyl group fused to a pyrrolidine ring). The group knew that the pyrrolidine at the P1 position did not tolerate many modifications, but I thought that it may be worthwhile to introduce a cyclopropyl group there. To do so, we needed to identify scientific literature that provided a synthetic scheme for generating cyclopropyl pyrrolidines. Such literature did not exist. Instead, we found an article by Hanessian et al., *Probing the Importance of Spacial and Conformational Domains in Captopril Analogs for Angiotensin Converting Enzyme Activity*, 8 BIOORGANIC & MED. CHEM. LETTERS 2123 (1998) (Ex. 2028), which disclosed a scheme for cyclopropanating proline groups. We used this scheme to synthesize our first cyclopropyl compound, BMS-356379.

10. BMS-356379 had a nitrile at the 2-position and a cyclopropyl group at the 4,5-position. Ex. 2184 at 1-2. With a K_i of 28 nM, BMS-356379 represented the first breakthrough by the group. Based on this breakthrough, we conducted extensive structure-activity-relationship ("SAR") studies on the cyclopropyl series. That SAR indicated that, depending on the location and stereochemistry of the cyclopropyl group, there was a dramatic and unpredictable effect on potency. Ex. 2185. For instance, some compounds with the cyclopropyl group at the 2,3-position did not exhibit significant inhibitor activity, while some,

but not all, of the compounds with the cyclopropyl group at the 3,4-position did. *See, e.g.,* Ex. 2186 at 2 (compare to BMS-378736 to BMS-383680).

11. We also discovered an unexpected increase in potency from the combination of a *cis*-4,5-cyclopropyl-pyrrolidine in the P1 position and a tert-butyl group in the P2 position. Ex. 2182. Positive data from the tert-butyl compound led us to propose and test a series of beta-branched derivatives, including adamantyl. Ex. 2187; Ex. 2182. We found that not all beta-branched groups gave potent DPP-IV inhibitors. Ex. 2175 at 2.

12. In the cyclopropyl series, we observed interesting properties related to one of our *cis*-4,5-cyclopropyl compounds with a cyclopentyl group in the P2 position. That compound, BMS-431285, exhibited exceptionally good *in vivo* inhibitor activity, (*see* Ex. 2188 at 1), but had an unusual disconnect between its pharmacokinetic ("PK") and pharmacodynamic ("PD") profile, showing low bioavailablity and a short half-life, yet a prolonged PD effect (*id.* at 3). When the group searched for the administered compound in plasma, it found that the compound was not present for a very long time and was not present at a high concentration. The team hypothesized that the PD effect was due to an active metabolite formed *in vivo*.

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