v.

PAR PHARMACEUTICAL, INC.

Defendant.

DEFENDANT PAR PHARMACEUTICAL, INC.'S INITIAL INVALIDITY CONTENTIONS

Pursuant to paragraph 1(d) of the Court's Scheduling Order, Defendant Par Pharmaceutical, Inc., ("Par") provides its initial invalidity contentions with respect to claims 1-3 and 7-10 of U.S. Patent No. 5,665,772 ("the '772 patent"), claims 1, 4-8, 10, and 13 of U.S. Patent No. 6,004,973 ("the '973 patent"), and claim 7 of U.S. Patent No. 6,455,518 ("the '518 patent") (collectively, "the Asserted Claims"), presently asserted by Plaintiffs Novartis Pharmaceuticals Corporation and Novartis AG (collectively, "Plaintiffs") as set forth in Plaintiffs' initial infringement contentions served on February 19, 2015.

PRELIMINARY STATEMENT

Par reserves all rights to amend and supplement these initial invalidity contentions in accordance with the Court's orders, local rules, and the Federal Rules of Civil Procedure as appropriate. Discovery is currently ongoing, and Par's searches for, analysis of, and application of relevant prior art are ongoing. For at least these reasons, additional prior art not included in these initial invalidity contentions and/or additional facts, documents, and things, whether known or unknown to Par, may become relevant. Par reserves the right to amend, alter, or supplement these

B.E. Bierer, et al., "Two distinct signal transmission pathways in T lymphocytes are inhibited by complexes formed between an immunophilin and either FK506 or rapamycin," *Proc. Nat'l. Acad. Sci.*, 87:9231-9235 (1990) ("Bierer") qualifies as prior art to the '772, '973, and '518 patents under 35 U.S.C. § 102(b) because it was published in 1990, which is more than one year prior to the earliest claimed U.S. filing dates of the '772 patent of September 24, 1993, of the '973 patent of July 12, 1996, and of the '518 patent of July 29, 1997.

Bierer states that rapamycin and tacrolimus (FK-506) are immunosuppressants that bind to and inhibit the rotamase activity of the immunophilin FKBP. (Bierer, at 9234.)

C. Brookhaven Databank Entry

The Brookhaven National Laboratories Protein Databank Entry for the FKBP-12/Rapamycin complex referenced in Van Duyne I ("Protein Databank Entry") qualifies as prior art to the '772, '973, and '518 patents under 35 U.S.C. § 102(b) because it was deposited into the databank in July 1992, which is more than one year prior to the earliest claimed U.S. filing dates of the '772 patent of September 24, 1993, of the '973 patent of July 12, 1996, and of the '518 patent of July 29, 1997.

The Protein Databank Entry contains the three-dimensional structure of the FKBP-12/rapamycin complex referenced in Van Duyne I, as determined by an X-ray diffraction technique. (*See generally* Brookhaven Databank Entry.)

D. Vézina

C. Vézina, et al., "Rapamycin (AY-22,989), A New Antifungal Antibiotic," *J. Antibiotics*,

receptor in the T cell." (*Id.*)

H. Van Duyne I

G.D. Van Duyne, et al., "Atomic Structure of the Rapamycin Human Immunophilin FKBP-12 Complex," *J. Am. Chem. Soc.*, 113:7433-7434 (1991) ("Van Duyne I") qualifies as prior art to the '772, '973, and '518 patents under 35 U.S.C. § 102(b) because it was published in 1991, which is more than one year prior to the earliest claimed U.S. filing dates of the '772 patent of September 24, 1993, of the '973 patent of July 12, 1996, and of the '518 patent of July 29, 1997.

Van Duyne I reports the three-dimensional structure of the binding complex of rapamycin and FKBP-12.

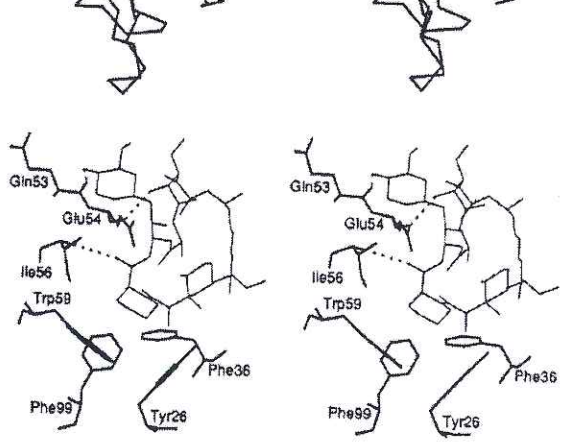

Figure 1. (a, top) A stereoview of the α-carbon tracing of FKBP-12 and rapamycin. The N- and C-terminal α-carbons are labeled. (b, bottom) A stereodrawing of the binding pocket showing all of the bound rapamycin molecule and selected FKBP-12 residues.

(Van Duyne I, at Figure 1.)

Van Duyne I states that the complete refined coordinates of the FKBP-12/rapamycin complex will be deposited in the Brookhaven Protein Databank, and, according to the Databank, such deposit was made in July 1992. (*Id.*, at 7434.)

The protein component of the FKBP-12/rapamycin complex forms a five-stranded antiparallel β-sheet wrapping with a right-handed twist around a short α-helix. (*Id.*, at 7433-34.) Rapamycin binds in a cavity between the β -sheet and α-helix with the pipecolinyl ring deeply buried in the protein. (*Id.*, at 7434.) The protein-ligand interface involves atoms from the pyranose ring through the C-28 hydroxyl, with the remainder, including the C-17 to C-22 triene, exposed. (*Id.*) The C-1 ester, the pipecolinyl ring, the C-8 and C-9 carbonyls, and the pyranose ring adopt the following conformation: three hydrogen bonds between this region and FKBP-12 (Ile-56 NH to C-1 carbonyl, Tyr-82 hydroxyl to C-8 carbonyl, and Asp-37 carboxylate to C-10

interaction of the dipeptide portion of a natural substrate with FKBP-12. (*Id.*) The second hydrogen bond is from Gln-53 main chain carbonyl to the C-40 hydroxyl; the cyclohexyl group (C-35 to C-42) is bound to the protein through this hydrogen bond. (*Id.*, at 7433-34.)

Van Duyne I states that rapamycin has two-fold higher affinity for FKBP-12 than does the structurally-similar tacrolimus (FK-506). (*Id.*, at 7434.) Van Duyne I reports a K_d for rapamycin of 0.2 nM and a K_d for tacrolimus of 0.4 nM. (*Id.*) Van Duyne I states that rapamycin's added anchoring of the cyclohexyl hydroxyl (the C-40 position) via hydrogen bonding to the FKBP-12 could partially explain the higher affinity of rapamycin. (*Id.*)

I. Van Duyne III

G.D. Van Duyne, et al., "Atomic Structures of the Human Immunophilin FKBP-12 Complexes with FK506 and Rapamycin," *J. Mol. Biol.*, 229: 105-124 (1993) ("Van Duyne III") qualifies as prior art to the '772 patent at least under 35 U.S.C. §102(a) because it published in January 1993, which is prior to the earliest date of invention that can be established in the U.S. or a NAFTA country of September 24, 1993. *See* 37 C.F.R. § 1.131 (stating that prior invention may not be established before January 1, 1996 in a WTO member country other than a NAFTA country). Van Duyne III qualifies as prior art to the '973 and '518 patents under 35 U.S.C. § 102(b) because it published in January 1993, which is more than one year prior to the earliest claimed U.S. filing dates of the '973 patent of July 12, 1996 and of the '518 patent of July 29, 1997.

Van Duyne III provides a detailed description of three-dimensional structures of rapamycin

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