UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

NEPTUNE GENERICS, LLC
Petitioner

v.

CORCEPT THERAPEUTICS, INC.
Patent Owner

Patent No. 8,921,348
Issued: December 30, 2014
Filed: October 29, 2013
Inventor: Joseph K. Belanoff
Title: "Optimizing mifepristone levels in plasma serum of patients suffering from mental disorders treatable with glucocorticoid receptor antagonists"

Inter Partes Review No.—not yet assigned

DECLARATION OF MIKKO A. OSKARI HEIKINHEIMO, M.D., Ph.D.

I, Mikko A. Oskari Heikinheimo, M.D., Ph.D., declare as follows:

1. I received an M.D. degree from the University of Helsinki in 1989, and my M.D. and Ph.D. as a Doctor of Medicine and Surgery from the University of Helsinki in 1990. Subsequently, I completed a post-doctoral fellowship at the Jones Institute for Reproductive Medicine at the Eastern Virginia Medical School in Norfolk, Virginia from 1992-1994, and my specialist training in obstetrics and gynecology at the University of Helsinki, Finland, in 2000.

2. Since 2009, I have been the Physician-in-chief at the Kätilöopisto Hospital Department of Obstetrics and gynecology (part of Helsinki University Hospital), and since 2014 also a Professor in the Department of Obstetrics and Gynecology at the University of Helsinki.

3. I have more than 130 original publications in scientific journals. Six (6) of them are discussed in this declaration and the Petition it accompanies. A more thorough summary of my education, experience, publications, awards, honors and presentations is provided in my curriculum vitae, a copy of which is attached to this declaration as Exhibit A.

4. Mifepristone is the active ingredient in Corcept's Korlym product (previously referred to as Corlux) and is also known as RU-486, a key component in medical abortion (in combination with synthetic prostaglandin), and the active

ingredient in the "early option" birth control pill, first marketed as Mifegyne® (by Exelgyn, Paris, France) and marketed as Mifeprex (first FDA-approved in 2000) in the US.

5. A POSA (person of skill in the art) may have collaborated with others having expertise in, for example, methods of treating diseases and administering medicines.

6. The arguments that Applicant proffered to rebut the assertions of the Examiner for the '114 application were based on partial and incomplete information of what was known in the prior art at the time of the invention.

7. There were many studies available at the time of filing of the application that became the '348 Patent that used detection methods capable of distinguishing mifepristone from its metabolites. These same studies have indicated clearly that the oral administration of mifepristone doses of greater than or equal to 200mg would indeed result in blood serum levels at the levels claimed. Documents teaching the detection of mifepristone (and differentiation of its metabolites) as well as the pharmacokinetics of administration include at least:

"Quantitation of RU486 in human plasma by HPLC and RIA after column chromatography." Heikinheimo *et al.*	Contraception 1986; 34: 613-624.
"Clinical Pharmacokinetics of Mifepristone" Heikinheimo	Clin. Pharmacokinet. 1997 July, 33 (I): 7-17 (Ex. 1011)

"Plasma concentrations and receptor binding of RU 486 and its metabolites in humans." Heikinheimo, *et al.*	J. Steroid Biochem Vol. 26: 279-284, 1987 (Ex. 1012)
"Pharmacokinetics of the Antiporgesterone RU 486 in Women During Multiple Dose Administration" Heikinheimo, *et al.*	J. Steroid Biochem. Vol. 32, No. 1A, pp. 21-25, 1989. (Ex. 1013)
"Pharmacokinetics of Mifepristone After Low Oral Doses" Kekkonen, *et al.*	Contraception 1996; 54:229-234. (Ex. 1014)
"A Study of the Effect of Mifepristone (Antiprogesterone) Followed by Prostaglandin on Uterine Activity and Fetal Heart Rate in Patients Having a Termination of Pregnancy" Pulkkinen, *et al.*	Arch Gynecol Obstet (1989) 244:75-78 (Ex. 1015)
"Pharmacokinetic study of RU 486 and its metabolites after oral administration of single doses to pregnant and non-pregnant women" Shi, *et al.*	Contraception August 1993:48, 133-149 (Ex. 1016)
Alterations in the pituitary-thyroid and pituitary-adrenal axis - Consequences of long-term mifepristone treatment. Heikinheimo *et al.*	Metabolism, 1997; 46: 292-296.

8. Because of its clinical use as an effective abortifacient beginning more than 25 years before the priority date of the '348 Patent, the pharmacokinetics of mifepristone were extremely well studied and understood (see references above). Dosing from ranges of less than a milligram to 1200 mg daily or more had been investigated and studied in both single dose administrations and prolonged administrations for years prior to the filing of the '348 Patent application. For example, Belanoff 2002 (Ex. 1007) reports daily dosing of both 600 mg and 1200 mg.

9. The FDA-approved dose of Korlym is between 300mg and 1200mg oral mifepristone daily.

10. Under the broadest reasonable interpretation of the claim, the term "adjusting the daily dose of the patient" should be construed to mean "changing the daily dose of the patient."

11. The '348 specification describes "plasma collection devices" as those well known in clinical labs, such as "vacutainers". However, "vacutainers" are not "suitable for *detecting* mifepristone serum levels." (In every example in the '348 specification, the device that is used to collect the plasma (*e.g.*, vacutainer) is different than the device used to detect the mifepristone level)

12. A "suitable" device "for detecting mifepristone" is one that is capable of actually sensing or identifying mifepristone in a serum sample. A "vacutainer" is only a blood collection device, not a device for sensing or detecting components in blood. Accordingly "a plasma sampling collection device suitable for detecting mifepristone serum levels" must be a device capable of identifying or revealing mifepristone in a blood serum sample. Such devices include instruments like mass spectrometers and chromatography such as high pressure liquid chromatography (HPLC). In addition, techniques based on radioimmunoassay, preceded by separation of mifepristone from its metabolites have been employed. Before such analytical methods or instruments can be applied, mifepristone must be separated from other components of

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