IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Brian AULT *et al.*	Group Art Unit: To Be Assigned
Serial No.: 14/593,212	Examiner: To Be Assigned
Filing Date: January 9, 2015	Attorney Docket No.: POZN.P0027US.C1
Title: METHOD FOR TREATING A PATIENT AT RISK FOR DEVELOPING AN NSAID-ASSOCIATED ULCER	Confirmation No.: 2930

DECLARATION UNDER 37 C.F.R. §1.132 BY LEE S. SIMON, MD, FACP, FACR

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

I, Lee S. Simon, MD, FACP, FACR, declare as follows:

1. I have been a clinical Rheumatologist for 25 years. I am American Board of Internal Medicine (ABIM) certified in Internal Medicine and Rheumatology. I am a fellow of the American College of Physicians (1991) and the American College of Rheumatology (1986). I served as the Division Director of Analgesic, Anti-inflammatory and Ophthalmologic Drug Products (DAAODP) (2001–2003), within the Center for Drug Evaluation and Research (CDER), FDA. I served on and was the Acting Chair (1999) of the Arthritis Advisory Committee of the DAAODP (1993–2001). I also served on the advisory committees for the Division of Over the Counter Drugs (1996), Center for Devices (1995), and for the Division of Hematologic and Gastroenterologic Drug Products (1996).

2. I have had extensive experience in drug development in the US, and have served on consulting advisory boards for many different companies. This experience includes drugs and

other therapeutics used for pain, anti-inflammatory effects, alteration of bone turnover, as well as modifying inflammatory disease states.

3. I am a principal in SDG, LLC, and provide consulting services to Horizon Pharma, USA, Inc. I understand that Horizon Pharma, USA, Inc., is a wholly owned subsidiary of Horizon Pharma, Inc., which owns the U.S. rights to VIMOVO®, a fixed dose combination product comprising naproxen and esomeprazole. I am being compensated for my time in this proceeding at my standard consulting rate. My compensation in no way depends on the outcome of this proceeding or the content of my opinions. I am not employed by, nor receiving grant support from, Horizon Pharma, or any of its related companies.

4. I was a National Institutes of Health (NIH) funded investigator for 12 years working at the "wet bench" developing methodologies for in vitro measures approximating collagen turnover including the development of a commercial assay for measuring the carboxy-terminal portion of type I procollagen as a marker of new bone synthesis (1981–1993).

5. I served for two terms on the Board of Directors of the American College of Rheumatology (ACR) (1991–1993, 1994–1997), served as the Chair of Education for the ACR and on the Education Committee of the National Arthritis Foundation. I served as the Scientific Abstract Selection Chair of the Annual Meeting of the ACR (2002).

6. I was awarded the 2003 Distinguished Service Award of the ACR and have been awarded the 2003 Scientific Leadership Award of the Lupus Research Institute. I served on the Steering Committee of IMPAACT, a group developing recommendations for the design and implementation of clinical trials investigating pain. I am on the Steering Committee and was Co-chair of the 2004, 2012 OMERACT (Outcome Measures in Rheumatology) Biannual Meeting. OMERACT is a constituent group of the World Health Organization (WHO) through the International League of Associations of Rheumatology (ILAR). I served on the Steering Committee of the NIH Osteoarthritis Initiative (2001–2003).

7. I have been on the editorial board of multiple journals and have authored more than 110 original publications, review articles and chapters, and have served as a co-editor of 4 books. I

was Co-chair of the American Pain Society Guideline on the Treatment of Chronic Pain in Chronic Arthritis (1999–2001).

8. I served on the Scientific Advisory Committee of the National Osteoporosis Foundation, have been the Vice Chair of Medical Affairs of the Arthritis Foundation, Massachusetts Chapter as well as serving on its Board of Trustees (1992–2001). I was an Associate Professor of Medicine at Harvard Medical School (1995–2003) where I had been full time faculty since 1981, an Associate Chief of Medicine, Beth Israel Deaconess Medical Center (BIDMC) (1999–2001), Director of the Core Medicine Clerkship (1986-2000), Director of Clinical Rheumatology Research (1995–2001), Director of Graduate Medical Education at the BIDMC and the Deaconess Hospital (1989–2001), and Chair of Rehabilitation Services at the Deaconess Hospital (1986–1995), Harvard Medical School before joining the FDA.

9. As a clinical investigator, I have conducted numerous clinical trials assessing the gastrointestinal morbidity associated with chronic NSAID use. In my clinical investigator role, I have participated in many clinical trials. I am the first author of the first endoscopy trial regarding the first in human use of celecoxib compared with naproxen and placebo (1998), I am the first author of a 3 month experience in patients treated with naproxen versus celecoxib and placebo including placebo and collaborated on clinical protocol design, interpretation of evidence on multiple reports regarding important NSAID induced outcomes regarding adverse events in patients treated for either one year or six months. I have written multiple review articles and book chapters regarding safety of the NSAIDs and Coxibs. Representative publications in this area of which I am an author include:

- **Simon LS**, Hatoum HT, Bittman RM, Archambault WT, Polisson RP. Risk factors for serious nonsteroidal-induced gastrointestinal complications: Regression analysis of the MUCOSA trial. Fam Med 1996; 28: 202-208;
- **Simon LS**, Lanza FL, Lipsky PE, Hubbard RC, Talwalker S, Schwartz BD, Isakson PC, Geis GS Preliminary study of the safety and efficacy of SC- 58635, A novel cyclooxygenase 2 inhibitor Arthritis Rheum 1998; 41: 1591- 1602;

- **Simon LS**, SZ. Zhao, LM. Arguelles, JB. Lefkowith, SD. Dedhiya, JG. Fort, and KE. Johnson. Economic and Gastrointestinal Safety Comparisons of Etodolac, Nabumetone, and Oxaprozin from Insurance Claims Data from Patients with Arthritis. Clinical Therap 1999; 20: 1218-1235;
- **Simon LS**, Weaver AL, Graham DY, Kivitz AJ, Lipsky PE, Hubbard RC, Isakson PC, Verburg KM, Shawn SY, Zhao WW, Geis GS The antiinflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: A randomized, controlled trial *JAMA* 1999; 282: 1921-1928;
- Silverstein FE, Faich G, Goldstein JL, **Simon LS**, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS Gastrointestinal toxicity with celecoxb vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: The CLASS study, a randomized controlled trial *JAMA* 2000;284(10):1247-5;
- Chan FKL, Cryer B, Goldstein JL, Lanas A, Peura DA, Scheiman JM, **Simon LS**, Singh G, Stillman MA, Wilcox CM, Berger MF, Breazna A, Dodge W A novel composite endpoint to evaluate the gastrointestinal (GI) effects of non-steroidal anti-inflammatory drugs through the entire GI tract. J Rheumatol. 2009;36:12;
- Cryer B, Li C, **Simon, LS**, Singh G*, Stillman, MJ, Berger, MF GI-REASONS: A Novel 6-Month, Prospective, Randomized, Open-Label, Blinded Endpoint (PROBE) Trial Am J Gastroenterol. 2013 Feb 12. doi: 10.1038/ajg.2012.467. [Epub ahead of print]; and
- Moore RA, Derry S, **Simon LS**, Emery P Nonsteroidal Anti-Inflammatory Drugs, Gastroprotection, and Benefit-Risk 2013 Pain Pract. 2013 Aug 14. doi: 10.1111/papr.12100. [Epub ahead of print].

10. A copy of my *curriculum vitae* is attached as **Exhibit A.**

11. I understand that claim 62 of the subject application relates to a method of treating a disease or disorder comprising administering to the patient naproxen, or pharmaceutically acceptable salt thereof, and esomeprazole, or pharmaceutically acceptable salt thereof.

concomitant with administration of low dose aspirin. The method is important in that the patient is also taking low dose aspirin (LDA) and so is already at elevated risk for developing ulcers, and the use of NSAIDs, such as naproxen, is typically, and by FDA label, contraindicated in such patients. The method involves the concomitant administration of low dose aspirin with 20 mg esomeprazole, or pharmaceutically acceptable salt thereof, in combination with 500 mg naproxen, or a pharmaceutically acceptable salt thereof, which is one of the approved dosages of VIMOVO®. As discussed below, it has now been demonstrated that, instead of increasing the already elevated risk of developing ulcers, patients treated in accordance with the method have a reduced risk of developing ulcers. Claim 76 is similar to claim 62.

12. I am familiar with the data presented in the subject application as well as Angiolillo *et al.*, *J Thromb Thrombolysis* (published online: December 25, 2013 ("Angiolillo"). For clarity, some of the data in Angiolillo is also disclosed in the specification of the present application, but Angiolillo provides helpful analysis of the pooled data with respect to LDA use versus LDA non-use.

13. Angiolillo pooled data from 5 Phase III clinical studies of a fixed-dose combination of enteric-coated naproxen (500 mg) and immediate-release esomeprazole magnesium (20 mg) ("NAP/ESO") in patients (as compared to enteric-coated ("EC") naproxen (500 mg) alone), and stratified the data based on LDA use (≤325 mg daily, administered at any time during the study) and LDA non-use. *Id.* Angiolillo analyzed data from 2317 patients receiving treatment, of which 1157 received NAP/ESO. Of the patients that received NAP/ESO, 298 also received concomitant LDA.

14. The studies analyzed in Angiolillo found "that NAP/ESO-treated patients were substantially less likely than those taking EC naproxen to develop [a gastric ulcer], *irrespective* of whether they were taking LDA or not." *See* Angiolillo, Discussion (emphasis in original). In addition, there was also "a trend in the NAP/ESO group for those taking LDA to be less likely to have a [gastric ulcer] at each of months 1, 3, and 6 than those not taking [LDA]." *Id.* (emphasis added). This finding is illustrated in Figure 2 of Angiolillo (shown below), which summarizes

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