IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WARNER CHILCOTT COMPANY, LLC and HOFFMANN-LA ROCHE INC.,	)	
Plaintiffs,	)	C.A. No. 08-627-LPS
v.	)	
TEVA PHARMACEUTICALS USA, INC., et al.,	)	
Defendants.	)	

DECLARATION OF JOHN P. BILEZIKIAN, M.D.
IN SUPPORT OF PLAINTIFFS' OPENING CLAIM CONSTRUCTION BRIEF
REGARDING U.S. PATENT NO. 7,192,938 AND U.S. PATENT NO. 7,718,634

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Dated: April 18, 2011

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I. INTRODUCTION

I have been retained by the firm of WilmerHale LLP on behalf of Warner Chilcott Company, LLC ("Warner Chilcott") and Hoffmann-La Roche Inc. ("Roche") (collectively, "Plaintiffs") to provide expert testimony in the above-captioned matter concerning the claim construction of U.S. Patent No. 7,192,938 (the "'938 patent") and U.S. Patent No. 7,718,634 ("'634 patent"). The '938 patent pertains to new therapeutic methods for treating or inhibiting osteoporosis by a "once-monthly" dosing regimen of bisphosphonates. The '634 patent pertains to new therapeutic methods for treating or inhibiting postmenopausal osteoporosis by a "once-monthly" dosing regimen of bisphosphonates.

A. QUALIFICATIONS

1. I am a Professor of Medicine and Pharmacology at the College of Physicians & Surgeons, Columbia University and Chief of the Division of Endocrinology and Director of the Metabolic Bone Diseases Program at Columbia University Medical Center. I completed my undergraduate training at Harvard College in 1965 and medical training at the College of Physicians & Surgeons at Columbia University in 1969. I completed four years of house staff training (internship and residency), including the Chief Medical Residency of the Medical Service at Columbia Presbyterian Medical Center in 1975. I received training in Metabolic Bone Diseases and in Endocrinology at the National Institutes of Health (NIH), where I served as a Clinical Associate in the Mineral Metabolism Branch under the tutelage of Dr. Gerald Aurbach. I belong to a number of professional societies related to the study of bone diseases, including the American Society for Bone and Mineral Research, of which I served as President in 1995-1996, and the International Society of Clinical Densitometry, of which I served as President in 1999-2001.

2. I am a member of the Endocrine Society, the American Federation for Clinical Research, the American Society for Clinical Investigation, the Association of American Physicians, the American Association of Clinical Endocrinologists, and the American Society for Pharmacology and Experimental Therapeutics. I am also a member of the American College of Endocrinology, which has designated me as Master, a title reserved for fewer than 5% of the members of the American Association of Clinical Endocrinologists. I was Editor-in-Chief of the *Journal of Clinical Endocrinology and Metabolism* (2000-2004). I was Associate Editor of the journal *Osteoporosis International* (2006-2008). I am currently Senior Associate Editor of the Journal of Bone and Mineral Research (2008-present). My books include Editor-in-Chief of The Parathyroids (1994, 2001), and co-editor of Principles of Bone Biology (1996, 2002, 2008), The Aging Skeleton (1999), Dynamics of Bone and Cartilage Metabolism (1999, 2006), and Osteoporosis in Men (2010). I have served on numerous panels, including serving as Chair of the NIH Consensus Development Panel on Optimal Calcium Intake (1994) and Co-chair of the NIH Workshops on Primary Hyperparathyroidism (2002, 2008). I served as Co-Moderator of the Consensus Development Conference on Fracture Risk Assessment, a joint meeting of the International Society of Clinical Densitometry and the International Osteoporosis Foundation that was held in Bucharest, Romania, November, 2010. I am an active member of the Board of both organizations. I am considered a major national and international spokesperson in the field of metabolic bone diseases.

3. My major research interests are related to the clinical investigation of metabolic bone diseases, particularly osteoporosis and primary hyperparathyroidism. I am the recipient of the Distinguished Physician Award of the Endocrine Society and of the Frederic C. Bartter Award of the American Society for Bone and Mineral Research for Excellence in Clinical

Research. I also have an active laboratory program in the biochemical mechanisms of the hormones that regulate calcium metabolism. I have had extensive involvement in clinical research at all levels. I have led investigator-initiated original research on new aspects of pharmacological actions of drugs that influence mineral metabolism. I have participated in Phase II, III and IV studies with many pharmacological agents. I currently serve as consultant to many pharmaceutical and diagnostic companies such as Amgen, Merck & Co., Inc., Warner-Chilcott, Eli Lilly & Co., Inc., NPS Pharmaceuticals, Inc., GlaxoSmithKline, Novartis, and Johnson and Johnson. For these companies, I have served on and chaired consultant boards, and have spoken at continued medical education (CME) certified and non-CME certified educational programs sponsored by various companies. I have helped to design clinical trials. I have helped to develop CME-based instructional materials for wide distribution.

4. I also have an extensive background in clinical research, independent of pharmaceutical company involvement, having received continuous peer-reviewed funding from the NIH since 1974. I have been recognized by the extramural program of the NIH by being in the top 5% of all NIH grantees over an uninterrupted 25-year period.

5. In addition to my academic activities, for most of my career I have also maintained a private practice in which I see patients with osteoporosis and other metabolic bone diseases on a regular basis. I also am in charge of the clinical training of endocrinology fellows at the College of Physicians and Surgeons, Columbia University. My clinical responsibilities further include serving as attending physician on the clinical endocrinology and general medical services of the Department of Medicine at Columbia University and the Medical Service of New York Presbyterian Hospital (Columbia Campus).

6. My publications, which number over 600, are generally directed to endocrinology and metabolic bone diseases such as osteoporosis and primary hyperparathyroidism.

7. My complete curriculum vitae, which includes a publication list, is attached as **Exhibit A**.

B. STATEMENT OF COMPENSATION

8. I am being compensated at my usual consulting rate of $600/hour plus expenses for my time in this case. This compensation does not depend upon the outcome of this case.

C. LIST OF OTHER CASES

9. In the previous 4 years, I testified as an expert in the following cases (each of which involved bisphosphonate compounds, including alendronate, risedronate, ibandronate, and zoledronate):

a) *Procter & Gamble Co. v. TevaPharms. USA, Inc.*, 536 F. Supp. 2d 476 (D. Del. 2008); I was deposed on May 25, 2006 and appeared at trial before the District of Delaware on November 6, 2006 on behalf of P&G.

b) *Procter & Gamble Pharms., Inc. v. Hoffmann-La Roche, Inc.*, 2006 U.S. Dist. LEXIS 64363 (S.D.N.Y. 2006); I was deposed on April 6, 2006 and appeared at trial before the Southern District Court of New York during the summer of 2006 on behalf of P&G.

c) *In re FOSAMAX Prods. Liab. Litig.*, Master File MDL No. 1789, 1:06-MD-1789-JFK, 248 F.R.D. 389 (S.D.N.Y. 2008); I was deposed twice in this litigation on July 7, 2007 and April 17, 2009 on behalf of Merck. I appeared at trial before the Southern District of New York City on August 28, 2009 and June 23, 2010.

d) *Novartis Corp. v. Teva Pharms. USA, Inc.* (D. Del. 08-CV-459-SLR); I was deposed on April 20, 2010 on behalf of Novartis.

e) *Hoffman-La Roche Inc. v. Apotex Inc. et al.*, D.N.J. Case No. 07-4417-SRC-MAS (consolidated); I was deposed in multiple sessions from January through March 2010 on behalf of Roche.

II. SUMMARY OF OPINIONS

10. The asserted claims of the '938 patent claim methods for treating or inhibiting osteoporosis, starting with a human patient orally taking or being given a pharmaceutical composition that contains about 100 mg to 150 mg of risedronic acid, or an amount of a pharmaceutically acceptable salt of risedronic acid that is equivalent to about 100 mg to 150 mg of a risedronic acid, and the human patient continuing the treatment by taking the same pharmaceutical composition of risedronic acid/risedronate in the same amount on a monthly basis thereafter.

11. Claims 9 and 10 of the '634 patent claim methods for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman, starting with a human patient orally taking or being given a tablet that contains a pharmaceutically acceptable salt of risedronic acid that is equivalent to about 150 mg of risedronic acid, and the human patient continuing the administration by taking the same pharmaceutical composition of risedronic acid/risedronate in the same amount on a monthly basis thereafter.

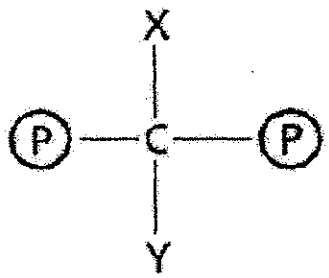
III. INFORMATION REVIEWED OR CONSIDERED IN PREPARING OPINION

12. In arriving at my opinions in this matter, I have relied upon my personal knowledge of osteoporosis, bisphosphonates, and methods of treatment of osteoporosis, as well as my years of experience as a doctor and professor, and my work on this litigation. I have also reviewed the '938 and '634 patents and portions of their prosecution histories.

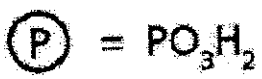
IV. BACKGROUND

A. The '938 and '634 Patents

13. "Bisphosphonic acids" are compounds that have the following general structural formula:



where X is the 'head' of the molecule, where Y is the 'tail' of the molecule, and where



14. Generally speaking, the term "bisphosphonate" is used to refer to the salt forms of bisphosphonic acids. For example, the term "risedronate" is the salt form of risedronic acid. More specifically, the term "sodium risedronate" or "risedronate sodium" is the sodium salt form of risedronic acid.

15. When given orally, bisphosphonates may result in upper gastrointestinal tract side effects because they can irritate mucous membranes, *e.g.*, through direct esophageal or gastric contact. *See* '938 Patent col. 1 ll. 57-67; '634 Patent col. 1 ll. 62-66. Bisphosphonates also have low oral bioavailability. *See* '938 Patent col. 2 ll. 31-32; '634 Patent col. 1 ll. 66-67.

16. The '938 and '634 patents have descriptive sections that explain that bisphosphonates are potent inhibitors of bone resorption and are therefore useful for treating or preventing diseases involving abnormal bone resorption, especially osteoporosis. *See* '938 Patent col. 1 ll. 41-51; col. 2 ll. 9-28; '634 Patent col. 1 ll. 44-53; col. 2 ll. 11-30.

17. The '938 and '634 patents claim an oral dosing regimen that was not known in 2000-2002. The method relates to administering a bisphosphonate, such as risedronate, "once-monthly." *See* '938 Patent col. 2 ll. 41-58; col. 2 l. 66 to col. 3 l. 2; col. 3 ll. 51-67; and col. 4 ll. 10-14; '634 Patent col. 2 ll. 43-59; col. 2 l. 67 to col. 3 l. 3; col. 3 ll. 53 to col. 4, ll. 3; and col. 4 ll. 14-22.

18. The once-monthly method is stated to include an amount of the bisphosphonic acid that is about 150 mg or an amount of a salt form of the bisphosphonic acid that would be equivalent to 150 mg of the free acid form, which is taken orally one day per month. *See* '938 Patent col. 3 ll. 13-21; col. 6 l. 55 to col. 7 l. 20; and claims 1 and 16; '634 Patent col. 3 ll. 14-22; col. 6 l. 55 to col. 7 l. 20; and claims 9 and 10.

19. Before Roche's once-monthly dosing methods, the only oral administration methods approved in the United States for treating or inhibiting osteoporosis that employed a bisphosphonate compound involved daily or weekly administrations.

B. Osteoporosis

20. Osteoporosis is a common, chronic disorder of human bone metabolism characterized by reduced bone density and reduced bone quality (based on factors such as bone size, bone shape, microarchitecture, mineralization, and matrix quality) leading to a reduction in bone strength and increased susceptibility to fractures. (NIH Consensus Development Panel, 2000, *see, e.g.*, NIH Consensus Development Panel on Osteoporosis Prevention Diagnosis, and Therapy, Journal of the American Medical Association, 285 (2001): 785-795). This definition of osteoporosis has replaced earlier definitions that were focused primarily on reduced bone density. Although I am aware that certain other animals may experience periods of altered bone metabolism associated temporarily with redirection of calcium stores from bone, these are not,

under normal conditions, osteoporotic in terms of the widely accepted definition. Osteoporosis, a chronic condition, does not afflict other animals besides human beings. Animal models of osteoporosis are due to genetic or physiological manipulations and are not thought to occur in nature.

21. Osteoporosis results from an imbalance in the bone remodeling process that develops, in part, as a component of the aging process. Throughout a person's life, his or her bones undergo a continuous process of resorption and formation brought about by the complex interaction of different types of cells, called osteoclasts and osteoblasts. This process, called bone remodeling, is the means by which older bone is replaced by younger, more resilient bone. It is important that bone remodeling be balanced, that is, the amount of bone removed (or "resorbed") is balanced by the amount of bone gained ("formed").

22. The process of bone remodeling is initiated by activation of the osteoclast, a multinucleated giant cell that is part of the macrophage lineage. The precise signaling mechanisms that lead to osteoclast activation are not well understood. The osteoclast resorbs a small amount of bone over a period of about 2-5 weeks. The resorption pit formed is the remodeling unit of bone. Eventually, over the next 3-5 months, the bone remodeling unit is filled in by new bone. New bone is formed by the actions of the osteoblast, a mononuclear cell that migrates into the resorption pit and deposits the organic matrix of bone, Type I collagen. Type I collagen is a fibrillar molecule that is arranged in orderly and regular microfibrils.

23. By mechanisms that are not well understood, the next step in the process of bone remodeling is for the Type I collagen fibrils to be mineralized. The chemical composition of this mineral phase of bone is a crystal, called hydroxyapatite. The hydroxyapatite crystal is formed by a number of inorganic ions, the most important ones of which are calcium, phosphorus,

magnesium, carbonate, and other inorganic ions. At the end of this 3-5 month bone remodeling cycle, the bone remodeling unit now consists of newly mineralized bone. It is stronger and more resilient. It is both stiff and tough. When the human skeleton is in calcium balance, the renewed bone remodeling unit contains the same amount of calcium and crystal structure as it did before it was remodeled. Bone is neither gained nor lost.

24. With aging, however, the bone remodeling unit becomes unbalanced. At the end of the bone remodeling cycle, there is less bone than there was at the beginning of the bone remodeling cycle. This is due to the osteoclast being overly active or the osteoblast not being active enough or a combination of both abnormalities. Hormonal and other regulators of normal calcium homeostasis are thought to be responsible for the negative calcium balance that characterizes the adult human skeleton.

25. Osteoporosis primarily occurs in postmenopausal women of all races and ethnic backgrounds, although Caucasian and Asian women are believed to be at greatest risk. In postmenopausal women, the rapid reduction in estrogen levels, because of menopause, stimulates the loss of bone specifically by activating the resorption side of the bone remodeling cycle. The activated osteoclast removes more bone than it does when estrogen levels are normal. The osteoblast is not activated to the same extent, thus leading to a negative balance in the bone remodeling process. In addition to activation of the individual osteoclast, estrogen deficiency is associated with more remodeling units being created over a given period of time. Since each of these bone remodeling units is a negative experience, the larger number of bone remodeling units activated in a given period of time will lead to a more rapid rate of bone loss.

26. Osteoporosis also occurs in men. While much less is known about osteoporosis in men than in postmenopausal women, the basic pathophysiology appears to be similar. The bone

remodeling unit is not in balance. There is more resorption than formation occurring and, thus, bone mass is diminished, leading to increased risk of fractures.

27. For both women and men, the major consequence of osteoporosis is increased risk of fracture. Over two million osteoporotic fractures occur in the United States yearly with economic consequences that extend into the tens of billions of dollars. For some osteoporotic fractures, such as hip fractures, patients suffer morbidity and increased mortality. Over half of women who sustain an osteoporotic hip fracture are no longer able to return to their former life style. Some become partially or totally dependent for activities of daily living.

28. Osteoporosis can be defined in operational terms by a bone density test, a very accurate and precise technology by which bone calcium concentration (grams/cm^2) can be determined. Bone mineral density is directly related to fracture risk. It is one of the most powerful surrogate markers in the field of medicine. It is as powerful an indicator of osteoporosis as blood pressure is a predictor of stroke. For every standard deviation reduction in bone mineral density, fracture risk is doubled. The widespread availability of bone mineral density testing by the dual energy X-ray absorptiometer (DXA), along with enactment of the Bone Mass Measurement Act of 1998, which entitles all women over the age of 65 to a bone mineral density test, has helped to increase recognition of osteoporosis as a disease.

C. Osteoporosis Treatment Using Bisphosphonates

29. In osteoporosis, there is an imbalance between bone resorption and bone formation in favor of bone resorption, resulting in bone loss and deterioration of bone architecture. The net outcome of these changes is increased bone fragility and increased risk of

fractures. The aim, therefore, of any treatment of osteoporosis is to reduce the incidence of fractures.

30. The primary pharmacological action of bisphosphonates is the reduction of bone resorption, which makes them candidate drugs for the treatment of osteoporosis.

31. Bisphosphonates have, in addition, other pharmacological properties which differentiate them from other drugs that decrease bone resorption (e.g. calcitonin). They are taken up preferentially by the skeleton, where they bind strongly to hydroxyapatite crystals of the bone mineral. During resorption, they are liberated from the mineral, they are taken up by the osteoclasts and reduce their activity and/or their life span by well characterized intracellular mechanisms. They are later embedded in bone, where they can remain, apart from active remodeling units, for a long time.

V. LEVEL OF ORDINARY SKILL IN THE ART

32. I have been advised and understand that the claims of a patent are to be interpreted as they would be by one of ordinary skill in the art to which the claims pertain. I further have been advised and understand that the date for determining how one would have interpreted the claims of the '938 and '634 patents is "at the time the invention was made." In this case, I have been instructed to conduct this analysis as of 2000-2002.

33. It is my opinion that a person of ordinary skill in the art to which the claimed methods of the '938 and '634 patents pertain would have possessed an M.D. or Ph.D. in anatomy, physiology, or pharmacology. A person of ordinary skill in the art would have additional training in the form of residency or fellowship in internal medicine or obstetrics or gynecology, with a focus on endocrinology or other area related to metabolic bone diseases; or

post-doctoral work or training in anatomy, physiology or pharmacology, with emphasis on skeletal anatomy, pathology, physiology and pharmacology as it relates to metabolic bone disease. A person of ordinary skill in the art would also have at least 1-3 years of practical experience in preclinical studies that included efficacy and toxicology studies using various models and techniques available at that time, or in clinical research relating to the treatment of metabolic bone diseases.

34. As reflected in Section I.A discussing my qualifications, as of 2000-2002, and also today, I satisfy these criteria for a person of ordinary skill in the art.

VI. THE CLAIMS OF THE '938 AND '634 PATENTS

A. Claims 6, 8, 9, 13-15, 21, 23, 24, 28-30 of the '938 Patent

35. I have been advised and understand that Plaintiffs assert infringement of at least claims 6, 8, 9, 13-14, 21, 23, 24, 28-30 of the '938 patent. Independent claim 1 of the '938 patent recites:

> 1. A method for treating or inhibiting osteoporosis comprising commencing treatment by orally administering to a subject in need of such treatment a first dose, on a single day, of a pharmaceutical composition comprising from about 100 mg to about 150 mg of bisphosphonic acid or an amount of a pharmaceutically acceptable salt thereof that is equivalent to about 100 mg to about 150 mg of said bisphosphonic acid and continuing said treatment by orally administering, once monthly on a single day, a pharmaceutical composition comprising from about 100 mg to about 150 mg of bisphosphonic acid or an amount of a pharmaceutically acceptable salt thereof that is equivalent to from about 100 mg to about 150 mg of bisphosphonic acid.
>
> '938 Patent col. 7 ll. 23-35 (emphasis added).

36. Claim 6 recites the method of claim 1 "wherein said bisphosphonic acid is risedronate or a pharmaceutically acceptable salt thereof." '938 Patent col. 7 ll. 54-56.

37. Claim 8, depending from claims 1 and 3, when rewritten as an independent claim, recites risedronic acid as the bisphosphonic acid:

> 8. A method for treating or inhibiting osteoporosis comprising commencing treatment by orally administering to a subject in need of such treatment a first dose, on a single day, of a pharmaceutical composition comprising about 150 mg of risedronic acid or an amount of a pharmaceutically acceptable salt thereof that is equivalent to about 100 mg to about 150 mg of said risedronic acid and continuing said treatment by orally administering, once monthly on a single day, a pharmaceutical composition comprising from about 100 mg to about 150 mg of risedronic acid or an amount of a pharmaceutically acceptable salt thereof that is equivalent to from about 100 mg to about 150 mg of risedronic acid.

'938 Patent col. 7 ll. 23-35 (emphasis added).

38. Claim 9, depending from claims 1 and 5, when rewritten as an independent claim, recites 150 mg of risedronic acid:

> 9. A method for treating or inhibiting osteoporosis comprising commencing treatment by orally administering to a subject in need of such treatment a first dose, on a single day, of a pharmaceutical composition comprising 150 mg of risedronic acid or an amount of a pharmaceutically acceptable salt thereof that is equivalent to about 100 mg to about 150 mg of said risedronic acid and continuing said treatment by orally administering, once monthly on a single day, a pharmaceutical composition comprising from about 100 mg to about 150 mg of risedronic acid or an amount of a pharmaceutically acceptable salt thereof that is equivalent to from about 100 mg to about 150 mg of risedronic acid.

39. Claims 13-15, which depend directly or indirectly from claim 1, recite "said pharmaceutical composition is a solid pharmaceutical composition."

40. Independent claim 16 of the '938 patent recites:

> 16. A method for treating or inhibiting osteoporosis consisting of orally administering to a subject in need of such treatment once monthly, a pharmaceutical composition comprising from about 100 mg to about 150 mg of bisphosphonic acid or an amount of a

> pharmaceutically acceptable salt thereof that is equivalent to about 100 mg to about 150 mg of said bisphosphonic acid.

41. Claims 21, 23, and 24, which depend directly or indirectly from claim 16, recite "wherein said bisphosphonic acid is risedronic acid or a pharmaceutically acceptable salt thereof."

42. Claims 28-30, which depend directly or indirectly from claim 16, recite "wherein said pharmaceutical composition is a solid pharmaceutical composition."

B. Claims 9 and 10 of the '634 Patent

43. I have been advised and understand that Plaintiffs assert infringement of claims 9 and 10 of the '634 patent. Claims 9 and 10 of the '634 patent recite:

> 9. A method for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman in need of treatment or inhibition of postmenopausal osteoporosis by administration of a pharmaceutically acceptable salt of risedronic acid, comprising:
>
> (a) commencing the administration of the pharmaceutically acceptable salt of risedronic acid by orally administering to the postmenopausal woman, on a single day, a first dose in the form of a tablet, wherein the tablet comprises an amount of the pharmaceutically acceptable salt of risedronic acid that is equivalent to about 150 mg of risedronic acid; and
>
> (b) continuing the administration by orally administering, once monthly on a single day, a tablet comprising an amount of the pharmaceutically acceptable salt of risedronic acid that is equivalent to about 150 mg of risedronic acid
>
> 10. A method for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman in need of treatment or inhibition of postmenopausal osteoporosis by administration of a pharmaceutically acceptable salt of risedronic acid, consisting essentially of orally administering to the postmenopausal woman, once monthly on a single day, a tablet comprising an amount of the pharmaceutically acceptable salt of risedronic acid that is equivalent to about 150 mg of risedronic acid.
>
> '634 Patent col. 7 ll. 23-45 (emphasis added).

C. "commencing treatment...and continuing said treatment" (claims 6, 8, 9,13-15 of the '938 Patent)

44. A person of ordinary skill in the art would understand that the term "commencing treatment" plainly refers to beginning treatment with monthly risedronate as specified in the claims. The term "continuing said treatment" means proceeding with the same treatment specified for the commencing of treatment with monthly risedronate as specified in the claims. A person of ordinary skill in the art would understand that previous treatments for osteoporosis other than taking risedronate at a dose appropriate for monthly intervals as specified in the claims would not constitute "commencing treatment." Rather, the claims discuss a method of monthly administration of risedronate, and other previous treatments (such as daily or weekly dosing) that would not relate to the monthly regimen being commenced and would therefore not constitute commencement of the monthly method described.

D. "treating or inhibiting" (all asserted claims of the '938 and '634 Patents)

45. The claim language in the '938 patent states "a method of treating or inhibiting osteoporosis." The claim language in the '634 patent states "a method of treating or inhibiting postmenopausal osteoporosis." The '938 and '634 patents state that pharmacologically active bisphosphonates are potent inhibitors of bone resorption and are therefore useful for treating or preventing diseases involving abnormal bone resorption, especially osteoporosis. *See* '938 Patent col. 1 ll. 41-51; col. 2 ll. 9-28; '634 Patent col. 1 ll. 44-53; col. 2 ll. 20-39.

46. From my review of portions of the '938 patent's prosecution history, the term "inhibiting" replaced the term "preventing," and "inhibiting" was considered to include "preventing." *See* Prosecution History of U.S. Application No. 10/998,849, Amendment (Feb. 2, 2006) at 7.

47. From my review of portions of the '634 patent's prosecution history, the term "inhibiting" encompasses the term "preventing." *See* Prosecution History of U.S. Application No. 12/139,587, Amendment (October 14, 2009) at 6 (Applicants stated that the "inhibiting" claim term "is considered to be appropriate as it encompasses prevention of osteoporosis in women who do not yet suffer from the disorder but are likely candidates to develop it, as well as inhibition of further osteoporosis in women who already suffer from the disorder.").

48. Moreover, osteoporosis is a progressive, chronic condition in which osteoclasts become overactive relative to osteoblasts, resulting in a net loss of bone over time. Once the progression of bone loss has reached a certain degree (as determined by bone density or the occurrence of a fragility fracture), a patient is said to have osteoporosis. A patient may have lost bone, however, and not yet have reached a level that would meet the definition of osteoporosis. By inhibiting or reducing the actual or relative overactivity of osteoclasts, progression of the disorder may be counteracted or inhibited and further loss of bone – and thus osteoporosis – may be prevented. Because bisphosphonates inhibit osteoclast activity, and therefore prevent osteoporosis, the term "treating or inhibiting osteoporosis" includes "preventing" osteoporosis.

49. Subjects who have lost bone mass, but not to the degree that meets the definition of osteoporosis, are said to have osteopenia. Osteopenia may progress to osteoporosis. Since "treating or inhibiting osteoporosis" includes "preventing" osteoporosis, the claimed method can be practiced by "preventing" or "inhibiting" the advancement of osteopenia to osteoporosis. Thus, practicing the claimed method of "treating or inhibiting osteoporosis" would encompass treating osteopenia.

E. "administration" or "administering" (all asserted claims of the '938 and '634 Patents)

50. The term "administration" or "administering" refers to both a patient self-administering the medication (*i.e.*, taking the medication) and another person who administers the medication to the patient (*i.e.*, giving the medication). A person of ordinary skill in the art would therefore understand that "administration" or "administering" includes the patient taking the medication by self-administering or being given the medication by someone else.

F. "subject" (all asserted claims of the '938 Patent)

51. The term "subject" means "a human subject" or "a human patient." As discussed above, osteoporosis occurs most commonly in postmenopausal women of all races and ethnic backgrounds. It also occurs in men. Osteoporosis is not known to occur naturally in non-human animals. A person of ordinary skill in the art would therefore understand that the term "subject" refers to human beings, not non-human animals.

G. "in need of such treatment" (all asserted claims in the '938 Patent) and "in need of treatment or inhibition (claims 9 and 10 of the '634 Patent)

52. The term "in need of such treatment" in the '938 patent refers to treating patients who have osteoporosis as well as treating patients at risk of developing osteoporosis to prevent a progression to osteoporosis.

53. Similarly, the term "in need of treatment or inhibition" in the '634 patent refers to treating patients who have postmenopausal osteoporosis as well as treating patients at risk of postmenopausal osteoporosis to prevent a progression to postmenopausal osteoporosis.

H. "a pharmaceutical composition comprising from about 100 mg to about 150 mg of bisphosphonic acid" (claims 6, 8, 9, 13-15 of the '938 Patent)

54. A person of ordinary skill in the art would understand the two references to "a pharmaceutical composition comprising from about 100 mg to about 150 mg of bisphosphonic acid" in claim 1 of the '938 patent to refer to the *same* pharmaceutical composition, not to two distinct compositions. A physician would not typically begin a course of monthly bisphosphonate treatment with one bisphosphonate and then switch to another. In the case of the asserted claims at issue here, that bisphosphonate is risedronate.

55. Moreover, a person of ordinary skill in the art would understand the term "a pharmaceutical composition comprising from about 100 mg to about 150 mg of bisphosphonic acid" to refer to a single pharmaceutical composition that contains between about 100 mg and 150 mg of a bisphosphonic acid, not multiple different pharmaceutical compositions or "subdoses" that added together total about 100 mg to about 150 mg of bisphosphonic acid.

I. "a bisphosphonic acid" (claims 6, 8, 9, 13-15 of the '938 Patent)

56. Just as with "a pharmaceutical composition," the two references to "a bisphosphonic acid" in claim 1 of the '938 patent refer to the *same* bisphosphonic acid, not to two distinct bisphosphonic acids. A physician would not begin a course of monthly bisphosphonate treatment with one bisphosphonate and then switch to another. In the case of the asserted claims at issue here, that bisphosphonic acid is risedronic acid.

VII. RESERVATION OF RIGHTS TO SUPPLEMENT OR AMEND

57. I reserve the right to amend or supplement my declaration in the event that additional documents, evidence, or information is brought to my attention.

VIII. DEMONSTRATIVE EXHIBITS TO SUMMARIZE AND/OR EXPLAIN OPINIONS

58. I intend to use exhibits (including demonstrative exhibits I have not yet created) if called for a tutorial or at a hearing in connection with the issue of claim construction to summarize and illustrate my assertions. In the event that additional information becomes available, I may supplement this declaration to take into account such additional information.

59. If it is helpful to the Court, I am ready to provide additional background regarding, for example, the treatment and inhibition of osteoporosis.

I declare under penalty of perjury that the foregoing is true and correct to the best of my own personal knowledge.

Dated: April 18, 2011

John P. Bilezikian, M.D.

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I hereby certify that on April 18, 2011, I electronically filed the foregoing document with the Clerk of Court using CM/ECF which will send notification of such filing(s) and have sent by Electronic Mail to the following:

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