IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	**:**	**Not yet assigned**
Appln. No.	**:**	**Not yet assigned**
Applicant	**:**	**Herriot Tabuteau**
Filed	**:**	**Herewith**
TC/A.U.	**:**	**Not yet assigned**
Examiner	**:**	**Not yet assigned**
Docket No.	**:**	**1958603.00021**
Customer No.	**:**	**45200**
Title	**:**	**COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE**

PRELIMINARY AMENDMENT

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

Dear Sir:

Applicant submits the following Preliminary Amendment for the above-referenced patent application.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks appear on p. 4 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1-39. (Canceled)

40. (Original) An oral dosage form comprising zoledronic acid, wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.01% to about 4%.

41. (Original) The oral dosage form of claim 40, wherein the oral dosage form contains about 10 mg to about 300 mg of zoledronic acid.

42. (Original) The oral dosage form of claim 40, wherein the oral dosage form contains about 10 mg to about 50 mg of zoledronic acid.

43. (Currently Amended) The oral dosage form of ~~any of~~ claim[[s]] 40[[-42]], wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2%.

44. (Original) A pharmaceutical product comprising more than one unit of an oral dosage form of claim 40.

45. (Original) The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 1 mg to about 50 mg of zoledronic acid.

46. (Original) The pharmaceutical product of claim 45, comprising 28, 29, 30, or 31 units of the oral dosage form, for a total of about 28 mg to about 1600 mg of zoledronic acid to be administered in about 1 month.

47. (Original) The pharmaceutical product of claim 45, comprising 85 to 95 units of the oral dosage form, for a total of about 85 mg to about 4800 mg of zoledronic acid to be administered in about 3 months.

48. (Original) The pharmaceutical product of claim 45, comprising 170 to 200 units of the oral dosage form, for a total of about 170 mg to about 10,000 mg of zoledronic acid to be administered in about 6 months.

49. (Original) The pharmaceutical product of claim 45, comprising 350 to 380 units of the oral dosage form, for a total of about 350 mg to about 19,000 mg of zoledronic acid to be administered in about 1 year.

50. (Original) The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 10 mg to about 300 mg.

51. (Original) The pharmaceutical product of claim 50, comprising 4 or 5 units of the oral dosage form, for a total of about 40 mg to about 1500 mg of zoledronic acid to be administered within a period of about 1 month.

52. (Original) The pharmaceutical product of claim 50, comprising 8 or 9 units of the oral dosage form, for a total of about 80 mg to about 2700 mg of zoledronic acid to be administered in about 2 months.

53. (Original) The pharmaceutical product of claim 50, comprising 12, 13 or 14 units of the oral dosage form, for a total of about 120 mg to about 4200 mg of zoledronic acid to be administered in about 3 months.

54. (Original) The pharmaceutical product of claim 50, comprising 22 to 30 units of the oral dosage form, for a total of about 220 mg to about 9000 mg of zoledronic acid to be administered in about 6 months.

55. (Original) The pharmaceutical product of claim 50, comprising 45 to 60 units of the oral dosage form, for a total of about 450 mg to about 18000 mg of zoledronic acid to be administered in about 1 year.

56. (Original) The pharmaceutical product of claim 44, comprising 1 to 10 units of the oral dosage form, wherein the product contains about 200 mg to about 2000 mg of zoledronic acid.

57. (Currently Amended) The oral dosage form of ~~any preceding~~ claim 40, wherein the zoledronic acid is in the form of a sodium salt.

58-59. (Canceled)

60. (Original) An oral dosage form comprising zoledronic acid and an excipient, wherein the zoledronic acid is in a form that has an aqueous solubility greater than 1% (w/v).

61. (Original) The oral dosage form of claim 60, wherein the zoledronic acid is in a form that has an aqueus solubility of about 5% (w/v) to about 50% (w/v).

62-119. (Canceled)

REMARKS/ARGUMENTS

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: May 14, 2013

/Brent A. Johnson/
Brent A. Johnson, Ph.D.
Registration No. 51,851
CUSTOMER NUMBER: 45200

K&L GATES LLP
1 Park Plaza, Twelfth Floor
Irvine, California 92614
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Facsimile: (949) 253-0902

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Filer:	Louis C. Cullman/Courtney Lines
Attorney Docket Number:	1958603.00021

Filed as Small Entity

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300
OTHER PUBLICATION PROCESSING FEE	1808	1	130	130
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**3160**

Electronic Acknowledgement Receipt

EFS ID:	15776947
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Courtney Lines
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	14-MAY-2013
Filing Date:	
Time Stamp:	19:08:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$3160
RAM confirmation Number	6136
Deposit Account	503207
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Application Data Sheet	21aia0014.pdf	1503026 9d16fccb0ab144cab9ac2b841daff2f6ff9e7c20	no	7
Warnings:					
Information:					
2	First Action Interview - Enrollment Request	21sb0413c.pdf	46444 024b27652cb706369f13150c6eed39ca8d4167cb	no	3
Warnings:					
Information:					
3	Oath or Declaration filed	Declaration21.pdf	1142738 44afcac86071b52b2591924febc416e41e28d6b5	no	2
Warnings:					
Information:					
4	Drawings-only black and white line drawings	FIGS_Antecip21.pdf	303024 0144faaada2b4eb015f1b96fe3d2686e9b210517	no	8
Warnings:					
Information:					
5	TrackOne Request	Track_1_Request.pdf	43740 4301236711735c394ba91899b9f353ea8b8b9e7f	no	2
Warnings:					
Information:					
6		Application_Antecip21.pdf	168804 2516dc319fef2881bd135c5f8e646dbc875bd810	yes	37

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Specification	1	26
	Claims	27	36
	Abstract	37	37

Warnings:					
Information:					
7		Preliminary_Amendment_21.pdf	79331 9d0afa1457912f2cf29b3f9c48bf359156b92813	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**

	Preliminary Amendment		1	1	
	Claims		2	3	
	Applicant Arguments/Remarks Made in an Amendment		4	4	
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	40191 e9f158b254b935d55fa9a33e3c02a850022fc17f	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	3327298		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Herriot		Tabuteau	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	New York	State/Province	NY	Country of Residence i	US

Mailing Address of Inventor:

Address 1	260 Park Avenue South, Apt. B		
Address 2			
City	New York	**State/Province**	NY
Postal Code	10010	**Country** i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	45200		
Email Address	chicago.patents@klgates.com	Add Email	Remove Email

Application Information:

Title of the Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease		
Attorney Docket Number	1958603.00021	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	8	**Suggested Figure for Publication (if any)**	

PTO/AIA/14 (03-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	45200		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61646538	2012-05-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61647478	2012-05-15
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61654292	2012-06-01
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61654383	2012-06-01
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61655527	2012-06-05
Prior Application Status	Pending		Remove

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61655541	2012-06-05
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61762225	2013-02-07
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61764563	2013-02-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61767647	2013-02-21
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61767676	2013-02-21
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61803721	2013-03-20
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code [i] (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			Add

PTO/AIA/14 (03-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◯ Assignee	◯ Legal Representative under 35 U.S.C. 117	◯ Joint Inventor
◯ Person to whom the inventor is obligated to assign.	◯ Person who shows sufficient proprietary interest	

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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information:

Address 1			
Address 2			
City		**State/Province**	
Country [i]		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

Remove

If the Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Mailing Address Information:			
Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications					
Signature	/Brent Johnson/			Date (YYYY-MM-DD)	2013-05-14
First Name	Brent	Last Name	Johnson	Registration Number	51851

Additional Signature may be generated within this form by selecting the Add button. Add

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: FAI.REQ
Document Description: Request First Action Interview

PTO/SB/413C (05-11)
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U.S. Patent and Trademark Office; U. S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REQUEST FOR FIRST ACTION INTERVIEW (FULL PILOT PROGRAM)

Attorney Docket Number: 1958603.00021	Application Number (if known):	Filing date: May 14, 2013
First Named Inventor: Herriot Tabuteau	Title: COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE	

APPLICANT HEREBY REQUESTS A FIRST ACTION INTERVIEW IN THE ABOVE-IDENTIFIED APPLICATION. See Instruction Sheet on page 2.

1. The application must contain three (3) or fewer independent claims and twenty (20) or fewer total claims.

2. The application must not contain any multiple dependent claims.

3. By filing this request:

   Applicant is agreeing to make an election without traverse if the Office determines that the claims are not obviously directed to a single invention; and

   Applicant is agreeing not to request for a refund of the search fee and any excess claims fee paid in the application after the mailing or notification of the pre-interview communication prepared by the examiner.

4. Other attachments: .....

Signature /Brent A. Johnson/	Date May 14, 2013
Name (Print/Typed) Brent A. Johnson	Registration Number 51851

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☒ *Total of 1 forms are submitted

The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/413C (05-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U. S. DEPARTMENT OF COMMERCE

Instruction Sheet for Request for First Action Interview (Full Pilot Program)

(Not to be Submitted to the USPTO)

A grantable request must meet the following conditions:

1. The application must be a new non-reissue utility application filed under 35 U.S.C. 111(a) or an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).

2. The application must contain three (3) or fewer independent claims and twenty (20) or fewer total claims. The application may not contain any multiple dependent claims.

3. The request must be filed electronically using the Office's electronic filing system, EFS-Web.

4. The claims must be directed to a single invention. If the Office determines that the claims are directed to multiple inventions (*e.g.*, in a restriction requirement), the applicant must make an election without traverse.

5. The request must be filed at least one day before a first Office action on the merits of the application appears in the Patent Application Information Retrieval (PAIR) system (*i.e.*, at least one day prior to the date when a first Office action on the merits, notice of allowability or allowance, or action under Ex parte Quayle, 1935 Dec. Comm'r Pat. 11 (1935) appears in the PAIR system). Applicant may check the status of the application using the PAIR system.

6. The request for a first action interview must include a statement that applicant agrees not to file a request for a refund of the search fee and any excess claims fees paid in the application after the mailing or notification of the Pre-Interview Communication. Any petition for express abandonment under 37 CFR 1.138(d), and request for a refund of the search fee and any excess claims fees, filed after the mailing or notification of the Pre-Interview Communication will not be granted.

For more information, see notice "Full First Action Interview Pilot Program" available on the USPTO web site at http://www.uspto.gov/patents/init_events/faipp_full.jsp

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Doc Code: FAI.REQ
Document Description: Request First Action Interview

PTO/SB/413C (05-11)
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REQUEST FOR FIRST ACTION INTERVIEW (FULL PILOT PROGRAM)

Attorney Docket Number: 1958603.00021	Application Number (if known):	Filing date: May 14, 2013
First Named Inventor: Herriot Tabuteau	Title: COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE	

APPLICANT HEREBY REQUESTS A FIRST ACTION INTERVIEW IN THE ABOVE-IDENTIFIED APPLICATION. **See Instruction Sheet on page 2.**

1. The application must contain three (3) or fewer independent claims and twenty (20) or fewer total claims.

2. The application must not contain any multiple dependent claims.

3. By filing this request:

   Applicant is agreeing to make an election without traverse if the Office determines that the claims are not obviously directed to a single invention; and

   Applicant is agreeing not to request for a refund of the search fee and any excess claims fee paid in the application after the mailing or notification of the pre-interview communication prepared by the examiner.

4. Other attachments: .....

Signature /Brent A. Johnson/	Date May 14, 2013
Name (Print/Typed) Brent A. Johnson	Registration Number 51851

***Note**: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below*.*

☒ *Total of 1 forms are submitted

The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 hours to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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PTO/SB/413C (05-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U. S. DEPARTMENT OF COMMERCE

Instruction Sheet for Request for First Action Interview (Full Pilot Program)

(Not to be Submitted to the USPTO)

A grantable request must meet the following conditions:

1. The application must be a new non-reissue utility application filed under 35 U.S.C. 111(a) or an international application that has entered the national stage in compliance with 35 U.S.C. 371(c).

2. The application must contain three (3) or fewer independent claims and twenty (20) or fewer total claims. The application may not contain any multiple dependent claims.

3. The request must be filed electronically using the Office's electronic filing system, EFS-Web.

4. The claims must be directed to a single invention. If the Office determines that the claims are directed to multiple inventions (*e.g.*, in a restriction requirement), the applicant must make an election without traverse.

5. The request must be filed at least one day before a first Office action on the merits of the application appears in the Patent Application Information Retrieval (PAIR) system (*i.e.*, at least one day prior to the date when a first Office action on the merits, notice of allowability or allowance, or action under Ex parte Quayle, 1935 Dec. Comm'r Pat. 11 (1935) appears in the PAIR system). Applicant may check the status of the application using the PAIR system.

6. The request for a first action interview must include a statement that applicant agrees not to file a request for a refund of the search fee and any excess claims fees paid in the application after the mailing or notification of the Pre-Interview Communication. Any petition for express abandonment under 37 CFR 1.138(d), and request for a refund of the search fee and any excess claims fees, filed after the mailing or notification of the Pre-Interview Communication will not be granted.

For more information, see notice "Full First Action Interview Pilot Program" available on the USPTO web site at http://www.uspto.gov/patents/init_events/faipp_full.jsp

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/SB/01A (09-12)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

As the below named inventor(s), I/we declare that:

This declaration is directed to:

- [■] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____
  - [ ] As amended on _____ (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application. The above-identified application was made or authorized to be made by me/us.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

All statements made herein of my/our own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon. I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5), or both.

FULL NAME OF INVENTOR(S)

Inventor one: Herniot Tabuteau Date: 5-13-2013

Signature: _____ Citizen of: US

Inventor two: _____ Date: _____

Signature: _____ Citizen of: _____

[ ] Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

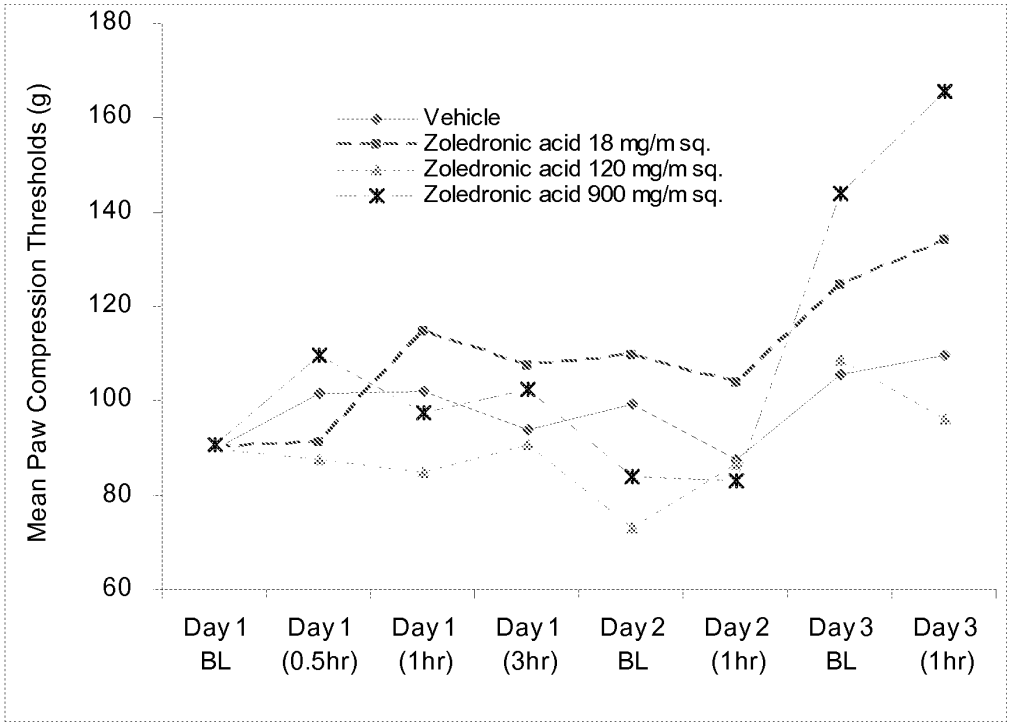
Mean Paw Compression Thresholds (g)
180
160
140
120
100
80
60
Vehicle
Zoledronic acid 18 mg/m sq.
Zoledronic acid 120 mg/m sq.
Zoledronic acid 900 mg/m sq.
Day 1 BL
Day 1 (0.5hr)
Day 1 (1hr)
Day 1 (3hr)
Day 2 BL
Day 2 (1hr)
Day 3 BL
Day 3 (1hr)

FIG. 1

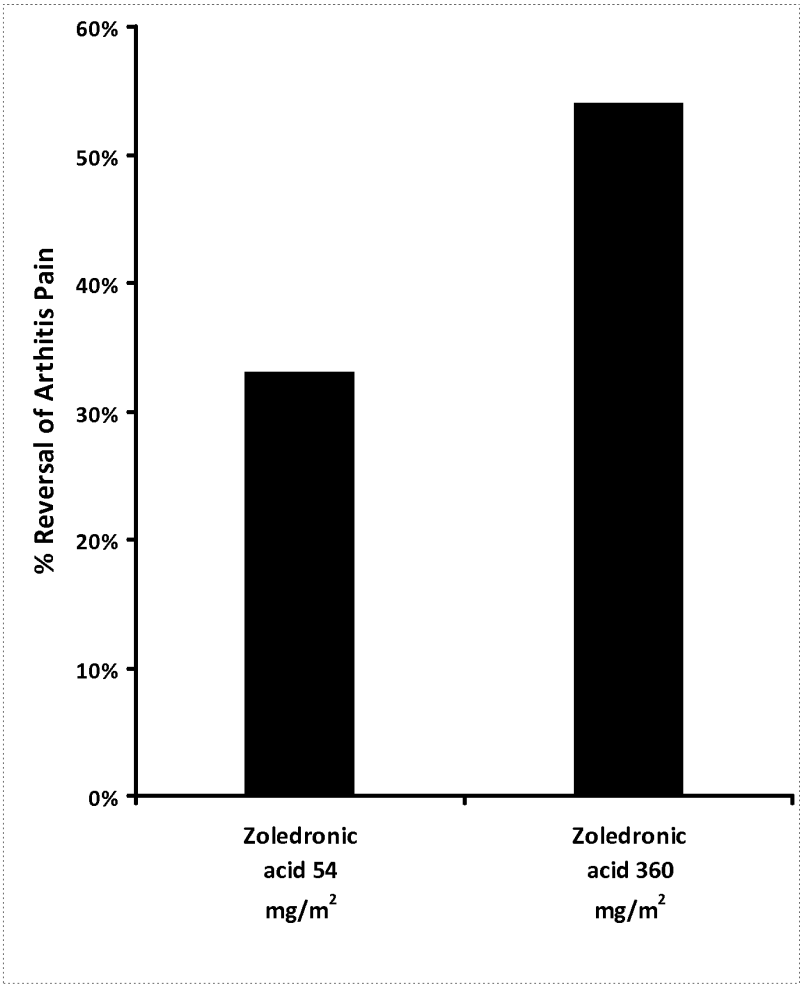
60%
50%
40%
30%
20%
10%
0%
% Reversal of Arthitis Pain
Zoledronic acid 54 mg/m2
Zoledronic acid 360 mg/m2

FIG. 2A

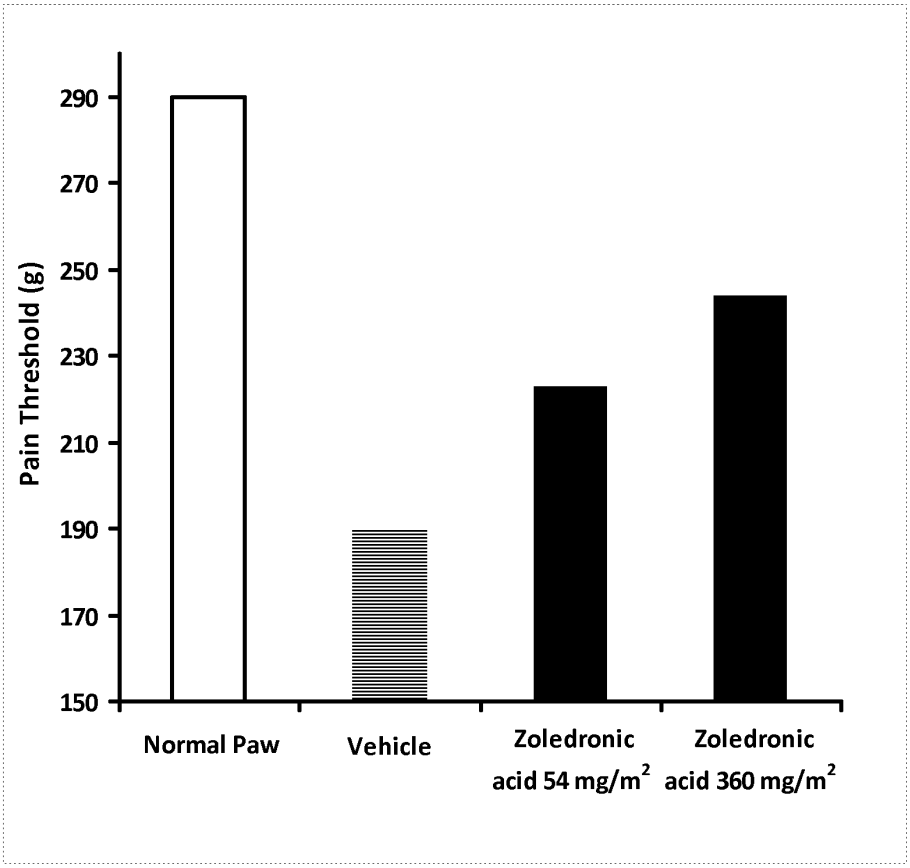
Pain Threshold (g)
290
270
250
230
210
190
170
150
Normal Paw
Vehicle
Zoledronic acid 54 mg/m2
Zoledronic acid 360 mg/m2

FIG. 2B

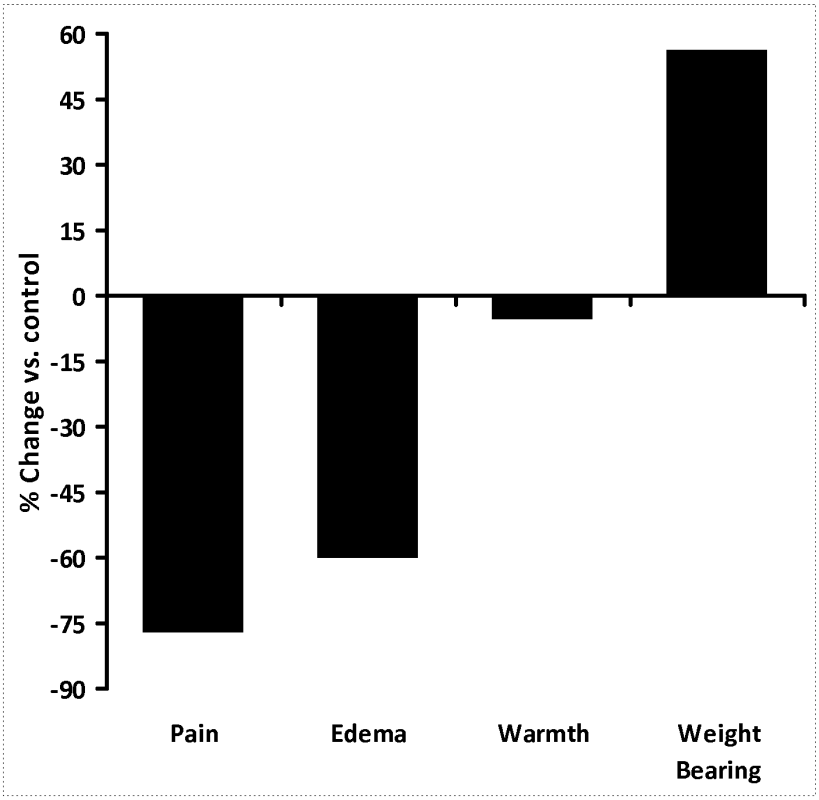
60
45
30
15
0
-15
-30
-45
-60
-75
-90
% Change vs. control
Pain
Edema
Warmth
Weight Bearing

FIG. 3

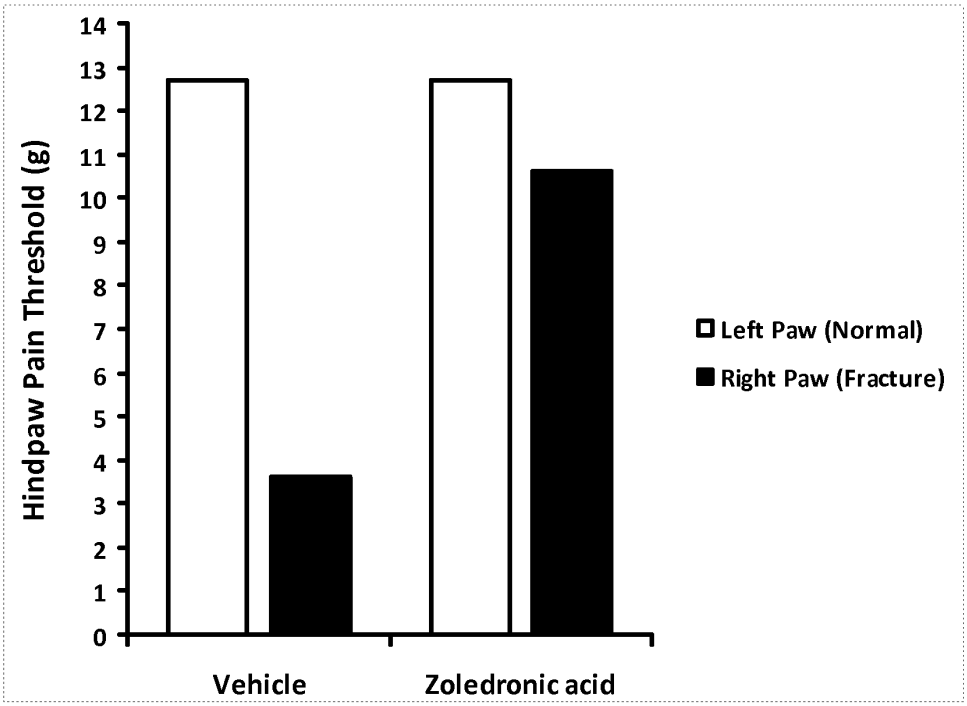
Hindpaw Pain Threshold (g)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Vehicle
Zoledronic acid
Left Paw (Normal)
Right Paw (Fracture)

FIG. 4

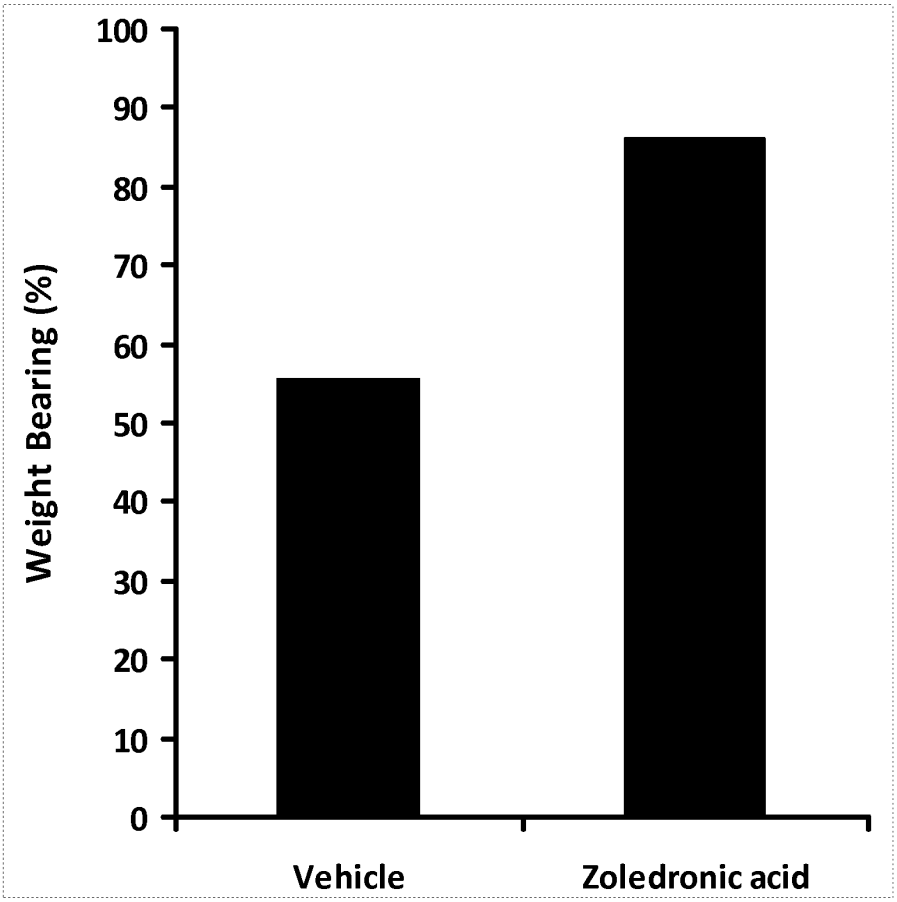
100
90
80
70
60
50
40
30
20
10
0
Weight Bearing (%)
Vehicle
Zoledronic acid

FIG. 5

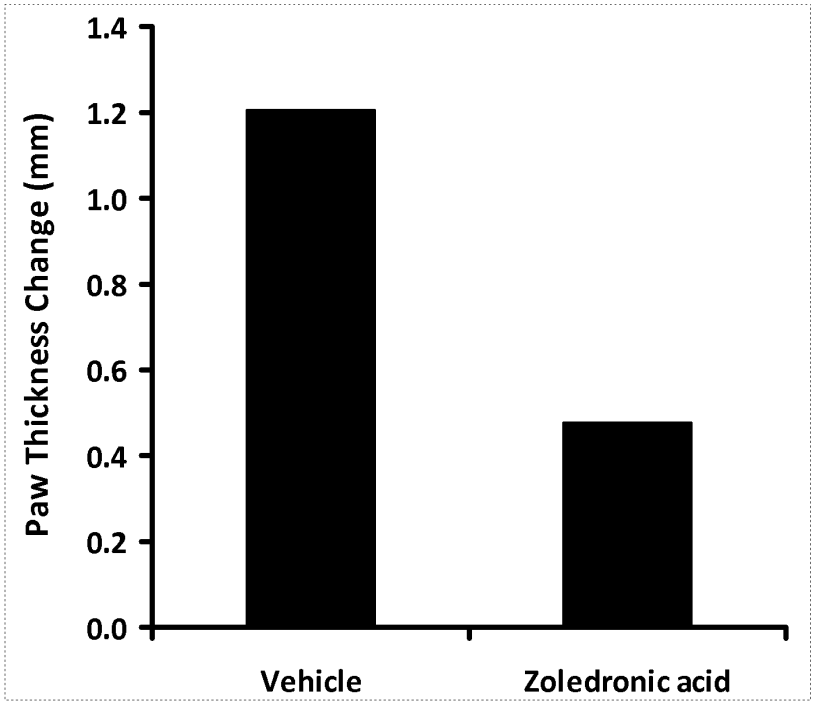
Paw Thickness Change (mm)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Vehicle
Zoledronic acid

FIG. 6

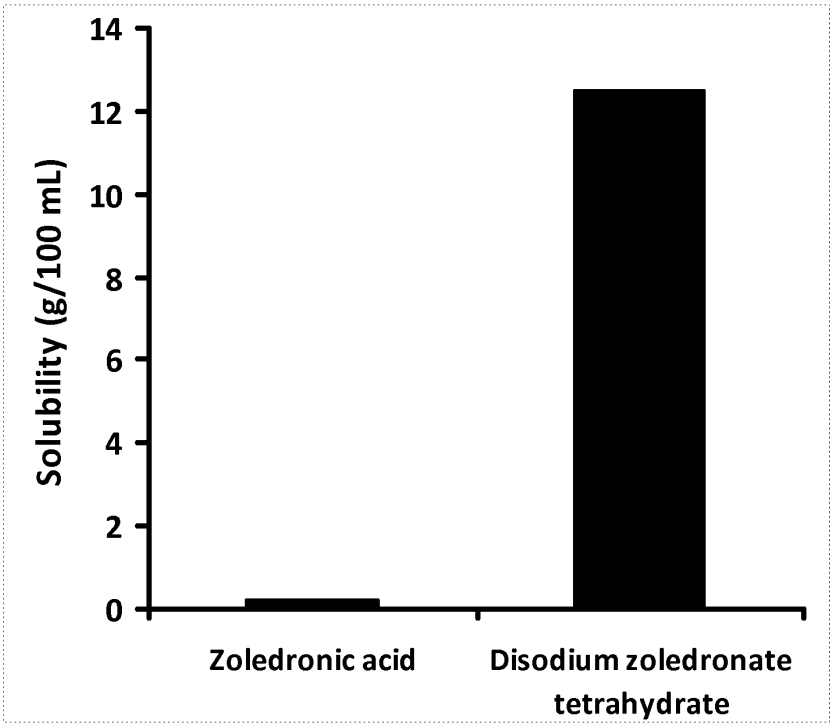
14
12
10
8
6
4
2
0
Solubility (g/100 mL)
Zoledronic acid
Disodium zoledronate tetrahydrate

FIG. 7

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/SB/424 (12-11)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	Herriot Tabuteau	Nonprovisional Application Number (if known):	
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, examination fee, and any required excess claims and application size fees are filed with the request or have been already been paid.

2. The application contains or is amended to contain no more than four independent claims and no more than thirty total claims, and no multiple dependent claims.

3. The applicable box is checked below:

I. ☑ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original nonprovisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed oath or declaration under 37 CFR 1.63 is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original nonprovisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Brent A. Johnson/	Date May 14, 2013
Name (Print/Typed) Brent A. Johnson	Practitioner Registration Number 51,851

***Note**: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the form of the signature. If necessary, submit multiple forms for more than one signature, see below*.*

☐ *Total of _____ forms are submitted.

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COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of United States Provisional Applications 61/646,538, filed May 14, 2012; 61/647,478, filed May 15, 2012; 61/654,292, filed June 1, 2012; 61/654,383, filed June 1, 2012; 61/655,527, filed June 5, 2012; 61/655,541, filed June 5, 2012; 61/762,225, filed February 7, 2013; 61/764,563, filed February 14, 2013; 61/767,647, filed February 21, 2013; 61/767,676, filed February 21, 2013; and 61/803,721, filed March 20, 2013, all of which are incorporated by reference in their entirety herein.

BACKGROUND

[002] Bisphosphonate compounds are potent inhibitors of osteoclast activity, and are used clinically to treat bone-related conditions such as osteoporosis and Paget's disease of bone; and cancer-related conditions including multiple myeloma, and bone metastases from solid tumors. They generally have low oral bioavailability.

SUMMARY

[003] It has been discovered that oral dosage forms of bisphosphonate compounds, such as zoledronic acid, can be used to treat or alleviate pain or related conditions. Although an oral dosage form with enhanced bioavailability with respect to the bisphosphonate compound can be used, the treatment can also be effective using an oral dosage form that includes a bisphosphonate compound, such as zoledronic acid, wherein the bioavailability of the bisphosphonate is unenhanced, or is substantially unenhanced.

[004] Some embodiments include a method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof, wherein the mammal experiences significant pain relief more than 3 hours after administration of the dosage form.

[005] Some embodiments include a method of relieving pain associated with an arthritis comprising administering an oral dosage form containing zoledronic acid to a human being in need thereof.

[006] Some embodiments include a method of treating complex regional pain syndrome comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof.

[007] Some embodiments include an oral dosage form comprising zoledronic acid, wherein the oral bioavailability of zoledronic acid is substantially unenhanced. For example, in some embodiments, the oral bioavailability in the dosage form is about 0.01% to about 4%.

[008] Some embodiments include a pharmaceutical product comprising more than one unit of an oral dosage form described herein. In some embodiments, each unit of the oral dosage form contains about 1 mg to about 50 mg of zoledronic acid.

[009] Some embodiments include a method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof.

[010] In some embodiments, the mammal receives a total monthly dose of zoledronic acid that is about 800 mg/m^2 or less.

[011] In some embodiments, the dosage form contains about 10 mg/m^2 to about 20 mg/m^2 based upon the body surface area of the mammal.

[012] Some embodiments include a method of relieving inflammatory pain comprising orally administering zoledronic acid to a mammal in need thereof.

[013] In some embodiments, about 300 mg/m^2 to about 600 mg/m^2 of zoledronic acid is administered per month, based upon the body surface area of the mammal.

[014] In some embodiments, about 50 mg/m^2 to about 600 mg/m^2 of zoledronic acid is administered per month, based upon the body surface area of the mammal.

BRIEF DESCRIPTION OF DRAWINGS

[015] FIG. 1 is a plot of pain compression thresholds in a rat model of inflammatory pain using three different doses of zoledronic acid. Measurements were taken at baseline (BL) and at various time points after dosing on the days indicated.

[016] FIG. 2A is a graph depicting reversal of arthritis pain for two different doses of zoledronic acid in a rat model of arthritis pain.

[017] FIG. 2B is a graph depicting pain thresholds for two different doses of zoledronic acid in a rat model of arthritis pain.

[018] FIG. 3 is a graph summarizing the results for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[019] FIG. 4 depicts hindpaw pain thresholds for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[020] FIG. 5 depicts weight bearing for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[021] FIG. 6 depicts paw thickness change for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[022] FIG. 7 depicts the aqueous solubility of disodium zoledronate tetrahydrate as compared to the diacid form of zoledronic acid.

DETAILED DESCRIPTION

[023] Bisphosphonate compounds such as pamidronate or pamidronic acid, neridronate or neridronic acid, olpadronate or olpadronic acid, alendronate or alendronic acid, incadronate or incadronic acid, ibandronate or ibandronic acid, risedronate or risedronic acid, zoledronate or zoledronic acid, etidronate or etidronic acid, clodronate or clodronic acid, tiludronate or tiludronic

acid, etc., may be used for a number of medical purposes, such as treatment of undesirable conditions or diseases, including pain relief. This may be accomplished in many instances by administration of oral dosage forms. Generally, an oral dosage form comprising a bisphosphonate such as zoledronic acid is administered orally to a mammal, such as a human being, at least once, to treat a disease or condition, or to relieve pain.

[024] The term "treating" or "treatment" broadly includes any kind of treatment activity, including the diagnosis, cure, mitigation, or prevention of disease in man or other animals, or any activity that otherwise affects the structure or any function of the body of man or other animals.

[025] An oral dosage form of a bisphosphonate such as zoledronic acid may be used to treat, or provide relief of, any type of pain including, but not limited to, inflammatory pain, arthritis pain, complex regional pain syndrome, lumbosacral pain, musculoskeletal pain, neuropathic pain, chronic pain, cancer-related pain, acute pain, postoperative pain, etc. In some instances, pain relief may be palliative, or pain relief may be provided independent of improvement of the disease or condition or the underlying cause of the disease or condition. For example, although the underlying disease may not improve, or may continue to progress, an individual suffering from the disease may experience pain relief.

[026] In some embodiments, the mammal being treated is not suffering from bone metastasis. In some embodiments, the mammal being treated is not suffering from cancer. In some embodiments, the mammal being treated is not suffering from osteoporosis.

[027] For example, zoledronic acid or another bisphosphonate may be administered orally to relieve musculoskeletal pain including low back pain, and pain associated with rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, axial spondyloarthritis including ankylosing spondylitis, Paget's disease, fibrous

dysplasia, SAPHO syndrome, transient osteoarthritis of the hip, vertebral crush fractures, osteoporosis, etc.

[028] In some embodiments, zoledronic acid or another bisphosphonate may also be administered orally to relieve neuropathic pain, including diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, monoradiculopathies, phantom limb pain, and central pain. Other causes of neuropathic pain include cancer-related pain, lumbar nerve root compression, spinal cord injury, post-stroke pain, central multiple sclerosis pain, HIV-associated neuropathy, and radio-therapy or chemo-therapy associated neuropathy.

[029] In some embodiments, zoledronic acid or another bisphosphonate may be administered orally to relieve inflammatory pain including musculoskeletal pain, arthritis pain, and complex regional pain syndrome.

[030] Examples of musculoskeletal pain include low back pain; and pain associated with vertebral crush fractures, fibrous dysplasia, osteogenesis imperfecta, Paget's disease of bone, transient osteoporosis, and transient osteoporosis of the hip.

[031] Arthritis refers to inflammatory joint diseases that can be associated with pain. Examples of arthritis pain include pain associated with osteoarthritis, erosive osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, sero-negative (non-rheumatoid) arthropathies, non-articular rheumatism, peri-articular disorders, neuropathic arthropaties including Charcot's foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome.

[032] In some embodiments, zoledronic acid or another bisphosphonate may be administered orally to relieve complex regional pain syndrome, such as complex regional pain syndrome type I (CRPS-I), complex regional pain syndrome type II (CRPS-II), CRPS-NOS, or another type of CRPS. CRPS is a type of inflammatory pain. CRPS can also have a neuropathic component.

[033] Complex regional pain syndrome is a debilitating pain syndrome. It is characterized by severe pain in a limb accompanied by edema, and autonomic, motor and sensory changes.

[034] With respect to use of oral zoledronic acid for relieving pain associated with an inflammatory condition, relief of pain can be short-term, e.g. for a period of hours after administration of the dosage form, and/or relief of pain can be long-term, e.g. lasting for days, weeks, or even months after oral administration of zoledronic acid. In some embodiments, a mammal, such as a human being, experiences significant pain relief at least about 3 hours, at least about 6 hours, at least about 12 hours, at least about 24 hours, at least about 48 hours, at least about one week, at least about 2 weeks, or at least about 3 weeks after administration of an oral dosage form comprising zoledronic acid. In some embodiments, a mammal, such as a human being, experiences significant pain relief during at least part of the time from about 3 hours to about 2 weeks, about 3 hours to about 3 weeks, about 3 hours to about 24 hours, about 6 hours to about 2 weeks, or about 6 hours to about 24 hours, about 3 days to about 2 weeks, about 6 days to about 2 weeks, after administration of an oral dosage form comprising zoledronic acid.

[035] Zoledronic acid or another bisphosphonate may also be administered orally to relieve cancer-related pain, including pain associated with multiple myeloma and bone metastases from solid tumors. In some embodiments, zoledronic acid is used to treat pain that is not cancer-related pain. For example, zoledronic acid may be used to treat pain that is not associated with multiple myeloma, bone metastasis from solid tumors, hypercalcemia of malignancy, giant cell tumor of bone, blood cancers or leukemias, or solid tumors or cancers.

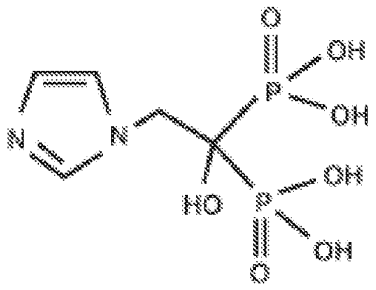
[036] In addition to relieving pain, oral administration of zoledronic acid or another bisphosphonate may also be useful to treat diseases or conditions that may or may not include a pain component. For example, zoledronic acid or another bisphosphonate may be useful to treat any of the pain

conditions or types of conditions listed above, including treatment that does not simply relieve the pain of those conditions, and treatment that is carried out in such a way that the condition is treated without pain relief occuring. In addition to any pain relief zoledronic acid or another bisphosphonate may or may not provide, zoledronic acid or another bisphosphonates may be used to treat a disease or condition such as a metabolic disease or condition; an inflammatory disease or condition, including an inflammatory disease or condition that is not associated with pain; a cancer disease or condition; a neurological disease or condition; etc.

[037] In some embodiments, oral administration of zoledronic acid or another bisphosphonate may also be useful to treat complex regional pain syndrome, rheumatoid arthritis, osteoarthritis, erosive osteoarthritis, axial spondyloarthritis including ankylosing spondylitis, acute vertebral crush fracture, fibrous dysplasia, SAPHO syndrome, osteoporosis, transient osteoporosis, or transient osteoporosis of the hip.

[038] In some embodiments, oral administration of zoledronic acid or another bisphosphonate may also be useful to treat hypercalcemia of malignancy, multiple myeloma, bone metastases from solid tumors, Paget's disease of bone, giant cell tumor of bone, blood cancers or leukemias, or solid tumors or cancers.

[039] Zoledronic acid has the structure shown below, and is also referred to as zoledronate.



Zoledronic acid

[040] Unless otherwise indicated, any reference to a compound herein, such as zoledronic acid, by structure, name, or any other means, includes pharmaceutically acceptable salts, such as the disodium salt; alternate solid forms, such as polymorphs, solvates, hydrates, etc.; tautomers; or any other chemical species that may rapidly convert to a compound described herein under conditions in which the compounds are used as described herein.

[041] In some embodiments, zoledronic acid is administered in a dosage form comprising a salt form, such as a salt of a dianion of zoledronic acid. In some embodiments, zoledronic acid is administered in a dosage form comprising a disodium salt form of zoledronic acid. In some embodiments, zoledronic acid is administered in a sodium salt form, such as a monosodium salt, a disodium salt, a trisodium salt, etc. In some circumstances, use of the disodium salt may be desirable. For example, the disodium salt is much more soluble in water than the diacid form. As a result, in some processes, the disodium salt can be easier to work with than the diacid form. Additionally, the sodium salt may be more bioavailable and/or more rapidly absorbed when taken orally as compared to the diacid form.

[042] In some embodiments, zoledronic acid is in a form that has an aqueous solubility, meaning the solubility in water, greater than 1% (w/v), about 5% (w/v) to about 50% (w/v), about 5% (w/v) to about 20% (w/v), about 10% (w/v) to about 15% (w/v), or about 12% (w/v) to about 13% (w/v).

[043] Zoledronic acid or another bisphosphonate may be combined with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice as described, for example, in Remington's Pharmaceutical Sciences, 2005, the disclosure of which is hereby incorporated herein by reference, in its entirety. The relative proportions of active ingredient and carrier may be determined, for example, by the solubility and chemical nature of the compounds, chosen route of administration and standard pharmaceutical practice.

[044] Zoledronic acid or another bisphosphonate may be administered by any means that may result in the contact of the active agent(s) with the desired site or site(s) of action in the body of a patient. The compounds may be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. For example, they may be administered as the sole active agents in a pharmaceutical composition, or they can be used in combination with other therapeutically active ingredients.

[045] Zoledronic acid or another bisphosphonate may be administered to a human patient in a variety of forms adapted to the chosen route of administration, e.g., orally, rectally, or parenterally. Parenteral administration in this respect includes, but is not limited to, administration by the following routes: pulmonary, intrathecal, intravenous, intramuscular, subcutaneous, intraocular, intrasynovial, transepithelial including transdermal, sublingual and buccal; topically; nasal inhalation via insufflation; and rectal systemic.

[046] The effective amount of zoledronic acid or another bisphosphonate will vary depending on various factors known to the treating physicians, such as the severity of the condition to be treated, route of administration, formulation and dosage forms, physical characteristics of the bisphosphonate compound used, and age, weight and response of the individual patients.

[047] The amount of zoledronic acid or another bisphosphonate in a therapeutic composition may vary. For example, some liquid compositions may comprise about 0.0001% (w/v) to about 50% (w/v), about 0.01% (w/v) to about 20% (w/v), about 0.01% to about 10% (w/v), about 0.001% (w/v) to about 1% (w/v), about 0.1% (w/v) to about 0.5% (w/v), about 1% (w/v) to about 3% (w/v), about 3% (w/v) to about 5% (w/v), about 5% (w/v) to about 7% (w/v), about 7% (w/v) to about 10% (w/v), about 10% (w/v) to about 15% (w/v), about 15% (w/v) to about 20% (w/v), about 20% (w/v) to about 30% (w/v), about 30% (w/v) to about 40% (w/v), or about 40% (w/v) to about 50% (w/v) of zoledronic acid.

[048] Some solid compositions may comprise at least about 5% (w/w), at least about 10% (w/w), at least about 20% (w/w), at least about 50% (w/w), at least about 70% (w/w), at least about 80%, about 10% (w/w) to about 30% (w/w), about 10% (w/w) to about 20% (w/w), about 20% (w/w) to about 30% (w/w), about 30% (w/w) to about 50% (w/w), about 30% (w/w) to about 40% (w/w), about 40% (w/w) to about 50% (w/w), about 50% (w/w) to about 80% (w/w), about 50% (w/w) to about 60% (w/w), about 70% (w/w) to about 75% (w/w), about 70% (w/w) to about 80% (w/w), or about 80% (w/w) to about 90% (w/w) of zoledronic acid.

[049] Any suitable amount of zoledronic acid may be used. Some solid or liquid oral dosage forms, or units of oral dosage forms (referred to collectively herein as “oral dosage form(s)”) may contain about 0.005 mg to about 20 mg, about 0.1 mg to about 10 mg, about 0.5 mg to about 10 mg, about 0.2 mg to about 5 mg, about 1 mg to about 500 mg, about 1 mg to about 50 mg, about 10 mg to about 250 mg, about 100 mg to about 300 mg, about 20 mg to about 200 mg, about 20 mg to about 150 mg, about 30 mg to about 100 mg, about 1 mg to about 1,000 mg, about 10 mg to about 50 mg, about 10 mg to about 300 mg, about 10 mg to about 150 mg, about 10 mg to about 100 mg, about 40 mg to about 150 mg, about 10 mg to about 600 mg, about 40 mg to about 600 mg, about 40 mg to about 2000 mg, about 40 mg to about 800 mg, about 25 mg to about 800 mg, about 30 mg to about 800 mg, about 10 mg to about 500 mg, about 50 mg to about 150 mg, about 50 mg, about 100 mg, about 50 mg to about

500 mg, about 100 mg to about 2000 mg, about 300 mg to about 1500 mg, about 200 mg to about 1000 mg, about 100 mg to about 500 mg, or about 150 mg of zoledronic acid, or any amount of zoledronic in a range bounded by, or between, any of these values. In some embodiments, the oral zoledronic acid is administered daily, weekly, monthly, every two or three months, once a year, or twice a year.

[050] In some embodiments, an oral dosage form may contain about 10 mg/m^2 to about 20 mg/m^2, about 15 mg/m^2 to about 20 mg/m^2, about 18 mg/m^2, about 80 mg/m^2 to about 150 mg/m^2, about 90 mg/m^2 to about 150 mg/m^2, about 100 mg/m^2 to about 150 mg/m^2 of zoledronic acid, or any amount of zoledronic in a range bounded by, or between, any of these values. All dosage ranges or amounts expressed in mg/m^2 are based upon the body surface area of the mammal.

[051] In some embodiments the daily oral dose of zoledronic acid is about 0.005 mg to about 20 mg, about 0.1 mg to about 10 mg, about 0.5 mg to about 10 mg, about 0.2 mg to about 5 mg, or any amount of zoledronic acid in a range bounded by, or between, any of these values. In some embodiments, the daily oral dose of zoledronic acid is less than about 35 mg/m^2, less than about 30 mg/m^2, less than about 25 mg/m^2, about 1 mg/m^2 to about 35 mg/m^2, about 1 mg/m^2 to about 30 mg/m^2, about 1.5 mg/m^2 to about 25 mg/m^2, about 1.8 mg/m^2 to about 20 mg/m^2, about 10 mg/m^2 to about 20 mg/m^2, about 10 mg/m^2 to about 30 mg/m^2, about 15 mg/m^2 to about 20 mg/m^2, about 18 mg/m^2, or any amount of zoledronic acid in a range bounded by, or between, any of these values.

[052] In some embodiments the weekly oral dose of zoledronic acid is about 1 mg to about 1000 mg, about 1 mg to about 500 mg, about 10 mg to about 250 mg, about 100 mg to about 300 mg, about 10 mg to about 100 mg, about 10 mg to about 150 mg, about 10 mg to about 100 mg, about 10 mg to about 300 mg, about 20 mg to about 150 mg, or about 30 mg to about 100 mg. In some embodiments, the weeky oral dose of zoledronic acid is less than about 250 mg/m^2, less than about 200 mg/m^2, less than about 175 mg/m^2, about 6

mg/m^2 to about 250 mg/m^2, about 10 mg/m^2 to about 210 mg/m^2, about 10 mg/m^2 to about 170 mg/m^2, about 4 mg/m^2 to about 140 mg/m^2, about 100 mg/m^2 to about 140 mg/m^2, about 126 mg/m^2, or any amount of zoledronic acid in a range bounded by, or between, any of these values. The weekly oral dose may be given as a single dose, given once during the week, or may be given in 2, 3, 4, 5, 6, or 7 individual doses during the week.

[053] In some embodiments, the monthly dose of zoledronic acid, or the amount of zoledronic acid that is administered over a period of a month, is about 5000 mg or less, about 4000 mg or less, about 3000 mg or less, about 2000 mg or less, about 1000 mg or less, about 700 mg or less, about 600 mg or less, about 1 mg to about 4,000 mg, about 1 mg to about 1,000 mg, about 10 mg to about 1000 mg, about 50 mg to about 1000 mg, about 10 mg to about 600 mg, about 40 mg to about 600 mg, about 50 mg to about 600 mg, or about 100 mg to about 600 mg, about 40 mg to about 2000 mg, about 40 mg to about 800 mg, about 50 mg to about 800 mg, or about 100 mg to about 800 mg, about 40 mg to about 1000 mg, about 50 mg to about 1000 mg, or about 100 mg to about 1000 mg, or any monthly dose in a range bounded by, or between, any of these values. In some embodiments, the monthly oral dose of zoledronic acid is less than about 1000 mg/m^2, less than about 800 mg/m^2, less than about 600 mg/m^2, about 10 mg/m^2 to about 1000 mg/m^2, about 50 mg/m^2 to about 800 mg/m^2, about 70 mg/m^2 to about 700 mg/m^2, about 100 mg/m^2 to about 700 mg/m^2, about 100 mg/m^2 to about 600 mg/m^2, about 50 mg/m^2 to about 200 mg/m^2, about 300 mg/m^2 to about 600 mg/m^2, about 450 mg/m^2 to about 600 mg/m^2, about 300 mg/m^2 to about 1000 mg/m^2, about 400 mg/m^2 to about 1000 mg/m^2, about 500 mg/m^2 to about 1000 mg/m^2, about 400 mg/m^2 to about 700 mg/m^2, about 500 mg/m^2 to about 600 mg/m^2, about 540 mg/m^2, or any amount of zoledronic acid in a range bounded by, or between, any of these values. A monthly dose may be given as a single dose, or as two or more individual doses administered during the month. In some embodiments, the monthly dose is administered in 2 or 3 weekly doses. In some embodiments, the monthly dose is administered in 4 or 5 weekly doses. In some embodiments, the monthly dose is

administered in 28 to 31 daily doses. In some embodiments, the monthly dose is administered in 5 to 10 individual doses during the month. The monthly dose may be administered for only 1 month, or may be repeatedly administered for 2 or more months.

[054] The oral zoledronic acid, or disodium salt thereof, may be administered in combination with about 0.1 mg to about 10 mg of zoledronic acid, or a salt thereof, administered parenterally, such as intravenously. In some embodiments, about 50 mg, about 100 mg, or about 150 mg of the disodium salt of zoledronic acid is administered orally in combination with 1 mg parenteral, such as intravenous, zoledronic acid. In some embodiments the parenteral dose of zoledronic acid is about 0.25 mg to about 25 mg, about 0.25 mg to about 10 mg, or about 0.5 mg to about 7.5 mg.

[055] The oral bioavailability of zoledronic acid in a dosage form can vary. Some dosage forms may have ingredients added to enhance the bioavailability. However, bioavailability enhancement is not necessary for an oral dosage form to be effective. In some embodiments, the dosage form is substantially free of bioavailability-enhancing agents. In some embodiments, an oral dosage form may have an oral bioavailability of zoledronic acid of about 0.01% to about 10%, about 0.1% to about 7%, about 0.1% to about 5%, etc. Without ingredients or other methods to enhance bioavailability, zoledronic acid typically has a low bioavailability in an oral dosage form. In some embodiments, the oral bioavailability of zoledronic acid is unenhanced or substantially unenhanced. For example, the oral bioavailability of zoledronic acid can be about 0.01% to about 5%, about 0.01% to about 4%, about 0.1% to about 3%, about 0.1% to about 2%, about 0.2% to about 2%, about 0.2% to about 1.5%, about 0.3% to about 1.5%, about 0.3% to about 1%, about 0.1% to about 0.5%, about 0.3% to about 0.5%, about 0.5% to about 1%, about 0.6% to about 0.7%, about 0.7% to about 0.8%, about 0.8% to about 0.9%, about 0.9%, about 1% to about 1.1%, about 1.1% to about 1.2%, about 1.2% to about 1.3%, about 1.3% to about 1.4%, about 1.4% to about 1.5%, about 1.5% to about 1.6%, about 1.6% to about 1.8%, or about 1.8% to about 2%.

[056] One embodiment is a pharmaceutical composition comprising zoledronic acid wherein the oral bioavailability of zoledronic acid in the dosage form is from about 0.01% to about 10%.

[057] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.01% to about 5%.

[058] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 7%.

[059] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 5%.

[060] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 3%.

[061] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2%.

[062] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.2% to about 2%.

[063] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.2% to about 1.5%.

[064] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.3% to about 1.5%.

[065] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.3% to about 1.0%.

[066] In some embodiments, an oral dosage form comprises about 10 mg to about 300 mg of zoledronic acid, and is administered daily for about 2 to about 15 consecutive days. This regimen may be repeated once monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once yearly, or once every two years.

[067] In some embodiments, an oral dosage form comprises about 10 mg to about 150 mg or about 10 mg to about 100 mg of zoledronic acid, and is

administered daily for about 2 to about 15 consecutive days. This regimen may be repeated once monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once yearly, or once every two years.

[068] In some embodiments, an oral dosage form comprises about 10 mg to about 150 mg or about 10 mg to about 100 mg of zoledronic acid, and is administered daily for about 5 to about 10 consecutive days. This regimen may be repeated once monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once yearly, or once every two years.

[069] In some embodiments, an oral dosage form comprises about 40 mg to about 150 mg of zoledronic acid, and is administered daily for about 5 to about 10 consecutive days. This regimen may be repeated once monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once yearly, or once every two years.

[070] In some embodiments, the oral zoledronic acid may be administered as one dose of about 100 mg to about 2000 mg. In some embodiments, the oral zoledronic acid may be administered as one dose of about 300 mg to about 1500 mg. In some embodiments, the oral zoledronic acid may be administered as one dose of about 200 mg to about 1000 mg. The dose of zoledronic acid may be administered in a single or divided dose.

[071] Zoledronic acid may be formulated for oral administration, for example, with an inert diluent or with an edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, compressed into tablets, or incorporated directly with the food of the diet. For oral therapeutic administration, the active compound may be incorporated with an excipient and used in the form of ingestible tablets, buccal tablets, coated tablets, troches, capsules, elixirs, dispersions, suspensions, solutions, syrups, wafers, patches, and the like.

[072] Tablets, troches, pills, capsules and the like may also contain one or more of the following: a binder such as gum tragacanth, acacia, corn

starch or gelatin; an excipient, such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; or a flavoring agent such as peppermint, oil of wintergreen or cherry flavoring. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coating, for instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring, such as cherry or orange flavor. It may be desirable for material in a dosage form or pharmaceutical composition to be pharmaceutically pure and substantially non toxic in the amounts employed.

[073] Some compositions or dosage forms may be a liquid, or may comprise a solid phase dispersed in a liquid.

[074] Zoledronic acid may be formulated for parental or intraperitoneal administration. Solutions of the active compounds as free acids or pharmacologically acceptable salts can be prepared in water suitably mixed with a surfactant, such as hydroxypropylcellulose. A dispersion can also have an oil dispersed within, or dispersed in, glycerol, liquid polyethylene glycols, and mixtures thereof. Under ordinary conditions of storage and use, these preparations may contain a preservative to prevent the growth of microorganisms.

[075] In some embodiments, an oral dosage form may comprise a silicified microcrystalline cellulose such as Prosolv. For example, about 20% (wt/wt) to about 70% (wt/wt), about 10% (wt/wt) to about 20% (wt/wt), about 20% (wt/wt) to about 40% (wt/wt), about 25% (wt/wt) to about 30% (wt/wt), about 40% (wt/wt) to about 50% (wt/wt), or about 45% (wt/wt) to about 50% (wt/wt) silicified microcrystalline cellulose may be present in an oral dosage form or a unit of an oral dosage form.

[076] In some embodiments, an oral dosage form may comprise a crosslinked polyvinylpyrrolidone such as crospovidone. For example, about 1% (wt/wt) to about 10% (wt/wt), about 1% (wt/wt) to about 5% (wt/wt), or about 1% (wt/wt) to about 3% (wt/wt) crosslinked polyvinylpyrrolidone may be present in an oral dosage form or a unit of an oral dosage form.

[077] In some embodiments, an oral dosage form may comprise a fumed silica such as Aerosil. For example, about 0.1% (wt/wt) to about 10% (wt/wt), about 0.1% (wt/wt) to about 1% (wt/wt), or about 0.4% (wt/wt) to about 0.6% (wt/wt) fumed silica may be present in an oral dosage form or a unit of an oral dosage form.

[078] In some embodiments, an oral dosage form may comprise magnesium stearate. For example, about 0.1% (wt/wt) to about 10% (wt/wt), about 0.1% (wt/wt) to about 1% (wt/wt), or about 0.4% (wt/wt) to about 0.6% (wt/wt) magnesium stearate may be present in an oral dosage form or a unit of an oral dosage form.

[079] An oral dosage form comprising zoledronic acid or another bisphosphonate may be included in a pharmaceutical product comprising more than one unit of the oral dosage form.

[080] A pharmaceutical product containing oral dosage forms for daily use can contain 28, 29, 30, or 31 units of the oral dosage form for a monthly supply. An approximately 6 week daily supply can contain 40 to 45 units of the oral dosage form. An approximately 3 month daily supply can contain 85 to 95 units of the oral dosage form. An approximately six-month daily supply can contain 170 to 200 units of the oral dosage form. An approximately one year daily supply can contain 350 to 380 units of the oral dosage form.

[081] A pharmaceutical product containing oral dosage forms for weekly use can contain 4 or 5 units of the oral dosage form for a monthly supply. An approximately 2 month weekly supply can contain 8 or 9 units of the oral dosage form. An approximately 6 week weekly supply can contain about 6 units of the oral dosage form. An approximately 3 month weekly supply can contain

12, 13 or 14 units of the oral dosage form. An approximately six-month weekly supply can contain 22 to 30 units of the oral dosage form. An approximately one year weekly supply can contain 45 to 60 units of the oral dosage form.

[082] A pharmaceutical product may accommodate other dosing regimes. For example, a pharmaceutical product may comprise 5 to 10 units of the oral dosage form, wherein each unit of the oral dosage form contains about 40 mg to about 150 mg of zoledronic acid. Some pharmaceutical products may comprise 1 to 10 units of the oral dosage form, wherein the product contains about 200 mg to about 2000 mg of zoledronic acid. For such a product, each unit of the oral dosage form may be taken daily for 1 to 10 days or 5 to 10 days during a month, such as at the beginning of a month.

[083] Some oral dosage forms comprising zoledronic acid or a salt thereof may have enteric coatings.

[084] In the examples below, zoledronic acid was administered in the disodium salt form as disodium zoledronate tetrahydrate. No bioavailability enhancing agents were used in the test compositions.

Example 1

Effect of Orally Administered Zoledronic Acid in Rat Model of Inflammatory Pain

Method:

[085] The effect of orally administered zoledronic acid on inflammatory pain was examined using the rat complete Freund's adjuvant (CFA) model. Inflammatory pain was induced by injection of 100% CFA in a 75 µL volume into the left hind paws of Sprague-Dawley rats on day 0, followed by assessments on days 1-3. Animals were orally administered vehicle (control), zoledronic acid 18 mg/m^2 (or 3 mg/kg), zoledronic acid 120 mg/m^2 (or 20 mg/kg), or zoledronic acid 900 mg/m^2 (or 150 mg/kg) daily on days 1-3. Drug was dissolved in distilled water and prepared fresh daily. Animals were fasted prior to dosing. Under current FDA guidelines for extrapolating starting dosages from

animals to humans, dosages expressed in mg/m^2 are considered equivalent between mammalian species. Thus, for example, 18 mg/m^2 in a rat is considered equivalent to 18 mg/m^2 in a human being, while 3 mg/kg in a rat may not be equivalent to 3 mg/kg in a human being.

[086] Values for inflammatory pain (mechanical hyperalgesia) in the vehicle and drug-treated animals were obtained on day 0 prior to CFA injection, and at baseline and post-treatment on days 1-3. Pain was assessed using a digital Randall-Selitto device (dRS; IITC Life Sciences, Woodland Hills, CA). Animals were placed in a restraint sling that suspended the animal, leaving the hind limbs available for testing. Paw compression threshold was measured by applying increasing pressure to the plantar surface of the hind paw with a dome-shaped tip placed between the 3rd and 4th metatarsus. Pressure was applied gradually over approximately 10 seconds. Measurements were taken from the first observed nocifensive behavior of vocalization, struggle or withdrawal. A cut-off value of 300 g was used to prevent injury to the animal.

[087] Reversal of inflammatory pain was calculated according to the formula:

% reversal = (Post-treatment – Post-CFA baseline)/(Pre-CFA baseline – Post-CFA baseline) x 100.

[088] The experiment was carried out using 9-10 animals per group.

Results:

[089] Oral administration of zoledronic acid significantly improved inflammatory pain thresholds compared to vehicle. Pain threshold measurements taken at various times are shown in FIG. 1. Paw compression thresholds in the 18 mg/m^2 group were higher than for vehicle during the entire measurement period after 30 minutes from the start of treatment. On day three, paw compression thresholds for both the 18 mg/m^2 and 900 mg/m^2 groups were greater than for vehicle. An improvement in pain threshold of 49% and 83% from baseline was observed for the 18 mg/m^2 and the 900 mg/m^2 groups respectively.

[090] Orally administered zoledronic acid produced a 29% reversal of inflammatory pain at the 18 mg/m^2, and a 48% reversal at the 900 mg/m^2 dose. This magnitude of effect is comparable to that obtained with clinical doses of commercially available NSAIDs when tested in a similar model of inflammatory pain. Under current FDA guidelines, the reference body surface area of a human adult is 1.62 m^2. Thus, a daily dose of 18 mg/m^2 corresponds to a monthly dose of about 500-560 mg/m^2 or a human dose of about 800-900 mg.

[091] Surprisingly, the two higher doses resulted in thresholds that were lower than vehicle on the first two days of dosing. The 120 mg/m^2 group was approximately equal or inferior to vehicle at all time points during the assessment period. While the 900 mg/m^2 group showed effectiveness on day 3, this result was accompanied by significant toxicity necessitating euthanization of all the animals in this group two days after cessation of dosing.

Example 2

Effect of Orally Administered Zoledronic Acid in Rat Model of Arthritis Pain

Method:

[092] The effect of orally administered zoledronic acid on arthritis pain was examined in the rat complete Freund's adjuvant (CFA) model of arthritis pain. In this model, injection of 100% complete Freund's adjuvant (CFA) in a 75 µL volume into the left hind paws is followed by a 10-14 day period to allow for the development of arthritis pain. Animals were orally administered vehicle (control), zoledronic acid 54 mg/m^2 (or 9 mg/kg), or zoledronic acid 360 mg/m^2 (or 60 mg/kg), divided in three equal daily doses on the first three days post CFA injection. Drug was dissolved in distilled water and prepared fresh daily. Animals were fasted prior to dosing.

[093] Arthritis pain (mechanical hyperalgesia) in the vehicle and drug-treated animals was evaluated on day 14 post CFA injection using a digital Randall-Selitto device (dRS; IITC Life Sciences, Woodland Hills, CA). Animals were placed in a restraint sling that suspended the animal, leaving the hind limbs

available for testing. Paw compression threshold was measured by applying increasing pressure to the plantar surface of the hind paw with a dome-shaped tip placed between the 3rd and 4th metatarsus. Pressure was applied gradually over approximately 10 seconds. Measurements were taken from the first observed nocifensive behavior of vocalization, struggle or withdrawal. A cut-off value of 300 g was used to prevent injury to the animal.

[094] Reversal of arthritis pain in the ipsilateral (CFA-injected) paw was calculated according to the formula:

% reversal = (ipsilateral drug threshold – ipsilateral vehicle threshold)/(contralateral vehicle threshold – ipsilateral vehicle threshold) x 100.

[095] The experiment was carried out using 7-10 animals per group.

Results:

[096] Oral administration of zoledronic acid significantly improved arthritis pain thresholds compared to vehicle. As shown in FIGS. 2A and 2B, orally administered zoledronic acid produced a dose-dependent reversal of arthritis pain. A reversal of 33% was observed in the 54 mg/m^2 group, and reversal of 54% was observed in the 360 mg/m^2 group. Under current FDA guidelines, the reference body surface area of a human adult is 1.62 m^2. Thus, 54 mg/m^2 in a rat is equivalent to an implied human dose of about 87 mg, and 360 mg/m^2 in a rat is equivalent to an implied human dose of about 583 mg.

Example 3. Treatment of Complex Regional Pain Syndrome with Orally Administered Zoledronic Acid.

[097] The effect of orally administered zoledronic acid was examined in the rat tibia fracture model of complex regional pain syndrome (CRPS). CRPS was induced in the rats by fracturing the right distal tibias of the animals and casting the fractured hindpaws for 4 weeks, as described in Guo TZ et al. (*Pain*. 2004;108:95–107). This animal model has been shown to replicate the inciting trauma, natural history, signs, symptoms, and pathologic changes observed in human CRPS patients (Kingery WS et al., *Pain*. 2003;104:75–84).

[098] Animals were orally administered either vehicle (control) or zoledronic acid, in a dosage of 18 mg/m^2/day (3 mg/kg/day) for 28 days, starting on the day of fracture and casting. Drug was dissolved in distilled water and administered by gavage. Animals were fasted for 4 hours before and 2 hours after dosing. At the end of the 28-day period, casts were removed, and on the following day, the rats were tested for hindpaw pain, edema, and warmth.

Pain assessments

[099] Pain was assessed by measuring hyperalgesia, and weight bearing.

[0100] To measure hyperalgesia, an up-down von Frey testing paradigm was used. Rats were placed in a clear plastic cylinder (20 cm in diameter) with a wire mesh bottom and allowed to acclimate for 15 minutes. The paw was tested with one of a series of eight von Frey hairs ranging in stiffness from 0.41 g to 15.14 g. The von Frey hair was applied against the hindpaw plantar skin at approximately midsole, taking care to avoid the tori pads. The fiber was pushed until it slightly bowed and then it was jiggled in that position for 6 seconds. Stimuli were presented at an interval of several seconds. Hindpaw withdrawal from the fiber was considered a positive response. The initial fiber presentation was 2.1 g and the fibers were presented according to the up-down method of Dixon to generate six responses in the immediate vicinity of the 50% threshold. Stimuli were presented at an interval of several seconds.

[0101] An incapacitance device (IITC Inc. Life Science, Woodland, CA, USA) was used to measure hindpaw weight bearing, a postural effect of pain. The rats were manually held in a vertical position over the apparatus with the hindpaws resting on separate metal scale plates and the entire weight of the rat was supported on the hindpaws. The duration of each measurement was 6 seconds and 10 consecutive measurements were taken at 60-second intervals. Eight readings (excluding the highest and lowest ones) were averaged to calculate the bilateral hindpaw weight-bearing values. Weight bearing data were

analyzed as the ratio between right (fracture) and left hindpaw weight bearing values ((2R/(R+L)) ×100%).

Edema assessment

[0102] A laser sensor technique was used to determine the dorsal-ventral thickness of the hindpaw. Before baseline testing the bilateral hindpaws were tattooed with a 2 to 3 mm spot on the dorsal skin over the midpoint of the third metatarsal. For laser measurements each rat was briefly anesthetized with isoflurane and then held vertically so the hindpaw rested on a table top below the laser. The paw was gently held flat on the table with a small metal rod applied to the top of the ankle joint. Using optical triangulation, a laser with a distance measuring sensor was used to determine the distance to the table top and to the top of the hindpaw at the tattoo site and the difference was used to calculate the dorsal-ventral paw thickness. The measurement sensor device used in these experiments (4381 Precicura, Limab, Goteborg, Sweden) has a measurement range of 200 mm with a 0.01 mm resolution.

Hindpaw temperature measurement

[0103] The temperature of the hindpaw was measured using a fine wire thermocouple (Omega, Stanford, CT, USA) applied to the paw skin. Six sites were tested per hindpaw. The six measurements for each hindpaw were averaged for the mean temperature.

Results

[0104] As illustrated in FIG. 3, treatment with orally administered zoledronic acid reversed pain, restored weight bearing, and prevented edema as compared to vehicle treated animals.

[0105] As illustrated in FIG. 4, von Frey pain thresholds for the right (fracture) hindpaw were reduced by 72% versus the contralateral (normal) hindpaw in vehicle treated animals. Zoledronate treatment reversed fracture induced pain by 77% as compared to vehicle treatment.

[0106] As illustrated in FIG. 5, reduction in weight bearing, a postural effect of pain, was significantly higher in the vehicle treated group as compared to the zoledronic acid treated group. Weight bearing on the fracture hindlimb was reduced to 55% of normal in the vehicle treated group. Zoledronate treatment significantly restored hindlimb weight bearing as compared to vehicle treatment (86% of normal).

[0107] As illustrated in FIG. 6, the expected increase in hindpaw thickness was greater in the vehicle treated group as compared to the zoledronic acid treated group, reflecting the development of edema. Zoledronate treatment reduced hindpaw edema by 60% versus vehicle treatment.

[0108] Zoledronic acid reduced hindpaw warmth by 5% versus vehicle treatment.

[0109] The daily dose in the above experiment was 18 mg/m^2/day. Under current FDA guidelines, the reference body surface area of a human adult is 1.62 m^2. Thus, a daily dose of 18 mg/m^2 corresponds to a monthly dose of about 500-560 mg/m^2 or a human dose of about 800-900 mg.

Example 6. Solubility of Disodium Salt of Zoledronic Acid

[0110] The aqueous solubility of zoledronic acid and disodium zoledronate tetrahydrate was determined. One gram of the test compound was measured in to a beaker. Demineralized water (pH 5.5) was then added in small increments to the test compound, and sonification was applied to the mixture. The procedure was continued until complete dissolution was achieved. Full dissolution was determined to have been reached when a clear solution was present with no visible material. The volume of water required to reach full dissolution was used to calculate a solubility value expressed in grams per 100 mL. The procedure was performed for each compound.

Results

[0111] As shown in FIG. 7, the aqueous solubility of disodium zoledronate tetrahydrate is approximately 50 times that of zoledronic acid.

Disodium zoledronate tetrahydrate has a solubility of 12.5 g/100 mL compared to only 0.25 g/100 mL for zoledronic acid.

[0112] Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood in all instances as indicating both the exact values as shown and as being modified by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0113] The terms "a," "an," "the" and similar referents used in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of any claim. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the invention.

[0114] Groupings of alternative elements or embodiments disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs,

the specification is deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

[0115] Certain embodiments are described herein, including the best mode known to the inventors for carrying out the invention. Of course, variations on these described embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than specifically described herein. Accordingly, the claims include all modifications and equivalents of the subject matter recited in the claims as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is contemplated unless otherwise indicated herein or otherwise clearly contradicted by context.

[0116] In closing, it is to be understood that the embodiments disclosed herein are illustrative of the principles of the claims. Other modifications that may be employed are within the scope of the claims. Thus, by way of example, but not of limitation, alternative embodiments may be utilized in accordance with the teachings herein. Accordingly, the claims are not limited to embodiments precisely as shown and described.

CLAIMS

1. A method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof, wherein the mammal receives a total monthly dose of zoledronic acid that is about 800 mg/m^2 or less based upon the body surface area of the mammal.

2. The method of claim 1, wherein the mammal is a human being that receives a total monthly dose of zoledronic acid that is about 30 mg/m^2 to about 700 mg/m^2.

3. The method of claim 2, wherein the total monthly dose is administered in 4 or 5 weekly doses.

4. The method of claim 2, wherein the total monthly dose is administered in 28 to 31 daily doses.

5. The method of claim 2, wherein the total monthly dose is administered in 5 to 10 individual doses during the month.

6. The method of claim 1, wherein the mammal is a human being that receives a total weekly dose of zoledronic acid that is about 10 mg to about 300 mg.

7. The method of claim 6, wherein the total weekly dose is a single dose, administered once a week.

8. The method of claim 6, wherein the total weekly dose is administered in 2 to 7 individual doses during the week.

9. The method of claim 1, wherein the mammal is a human being that receives a total weekly dose of zoledronic acid that is about 10 mg to about 150 mg.

10. The method of any preceding claim, wherein the mammal experiences significant pain relief more than 3 hours after administration of the dosage form.

11. The method of claim 10, wherein the mammal experiences significant pain relief during at least a part of a time from about 3 hours to about 24 hours after administration of the dosage form.

12. The method of claim 10, wherein the mammal experiences significant pain relief during at least a part of a time from about 3 hours to about 3 weeks after administration of the dosage form.

13. A method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof, wherein the oral dosage form contains about 10 mg/m^2 to about 20 mg/m^2 of zoledronic acid based upon the body surface area of the mammal.

14. The method of claim 13, wherein the oral dosage form contains about 15 mg/m^2 to about 20 mg/m^2 of zoledronic acid based upon the body surface area of the mammal.

15. A method of relieving inflammatory pain comprising orally administering to a mammal in need thereof, about 300 mg/m^2 to about 600 mg/m^2 of zoledronic acid per month to the mammal, based upon the body surface area of the mammal.

16. The method of claim 15, comprising orally administering about 450 mg/m^2 to about 600 mg/m^2 of zoledronic acid per month to the mammal, based upon the body surface area of the mammal.

17. The method of any preceding claim, wherein the mammal is not suffering from bone metastasis.

18. The method of any preceding claim, wherein the mammal is not suffering from cancer.

19. The method of any preceding claim, wherein the zoledronic acid is administered as a salt of a dianion of zoledronic acid.

20. A method of relieving pain associated with an arthritis comprising administering an oral dosage form containing zoledronic acid to a human being in need thereof.

21. The method of claim 20, wherein the human being receives a total monthly dose of zoledronic acid that is about 40 mg to about 2000 mg.

22. The method of claim 21, wherein the total monthly dose is administered in 4 or 5 weekly doses.

23. The method of claim 21, wherein the total monthly dose is administered in 28 to 31 daily doses.

24. The method of claim 21, wherein the total monthly dose is administered in 5 to 10 individual doses during the month.

25. The method of claim 20, wherein the human being receives a total weekly dose of zoledronic acid that is about 100 mg to about 300 mg.

26. The method of claim 25, wherein the total weekly dose is a single dose, administered once a week.

27. The method of claim 25, wherein the total weekly dose is administered in 2 to 7 individual doses during the week.

28. The method of claim 20, wherein the human being receives a total weekly dose of zoledronic acid that is about 10 mg to about 100 mg.

29. The method of any of claims 20-28, wherein the human being experiences significant pain relief more than 3 hours after administration of the dosage form.

30. The method of claim 29, wherein the human being experiences significant pain relief during at least a part of a time from about 3 hours to about 24 hours after administration of the dosage form.

31. The method of claim 29, wherein the human being experiences significant pain relief during at least a part of a time from about 3 hours to about 3 weeks after administration of the dosage form.

32. The method of any of claims 20-31, wherein the dosage form contains about 10 mg/m^2 to about 20 mg/m^2 of zoledronic acid based upon the body surface area of the human being.

33. The method of claim 32, wherein the dosage form contains about 15 mg/m^2 to about 20 mg/m^2 of zoledronic acid based upon the body surface area of the human being.

34. The method of any of claims 20-33, wherein about 50 mg/m^2 to about 200 mg/m^2 of zoledronic acid is orally administered per month, based upon the body surface area of the human being.

35. The method of any of claims 20-31, wherein the dosage form contains about 80 mg/m^2 to about 150 mg/m^2 of zoledronic acid based upon the body surface area of the human being.

36. The method of claim 35, wherein about 300 mg/m^2 to about 1000 mg/m^2 of zoledronic acid is orally administered per month, based upon the body surface area of the human being.

37. The method of any of claims 20-36, wherein the human being is not suffering from bone metastasis.

38. The method of any of claims 20-37, wherein the human being is not suffering from cancer.

39. The method of any preceding claim, wherein the zoledronic acid is in the disodium salt form.

40. An oral dosage form comprising zoledronic acid, wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.01% to about 4%.

41. The oral dosage form of claim 40, wherein the oral dosage form contains about 10 mg to about 300 mg of zoledronic acid.

42. The oral dosage form of claim 40, wherein the oral dosage form contains about 10 mg to about 50 mg of zoledronic acid.

43. The oral dosage form of any of claims 40-42, wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2%.

44. A pharmaceutical product comprising more than one unit of an oral dosage form of claim 40.

45. The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 1 mg to about 50 mg of zoledronic acid.

46. The pharmaceutical product of claim 45, comprising 28, 29, 30, or 31 units of the oral dosage form, for a total of about 28 mg to about 1600 mg of zoledronic acid to be administered in about 1 month.

47. The pharmaceutical product of claim 45, comprising 85 to 95 units of the oral dosage form, for a total of about 85 mg to about 4800 mg of zoledronic acid to be administered in about 3 months.

48. The pharmaceutical product of claim 45, comprising 170 to 200 units of the oral dosage form, for a total of about 170 mg to about 10,000 mg of zoledronic acid to be administered in about 6 months.

49. The pharmaceutical product of claim 45, comprising 350 to 380 units of the oral dosage form, for a total of about 350 mg to about 19,000 mg of zoledronic acid to be administered in about 1 year.

50. The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 10 mg to about 300 mg.

51. The pharmaceutical product of claim 50, comprising 4 or 5 units of the oral dosage form, for a total of about 40 mg to about 1500 mg of zoledronic acid to be administered within a period of about 1 month.

52. The pharmaceutical product of claim 50, comprising 8 or 9 units of the oral dosage form, for a total of about 80 mg to about 2700 mg of zoledronic acid to be administered in about 2 months.

53. The pharmaceutical product of claim 50, comprising 12, 13 or 14 units of the oral dosage form, for a total of about 120 mg to about 4200 mg of zoledronic acid to be administered in about 3 months.

54. The pharmaceutical product of claim 50, comprising 22 to 30 units of the oral dosage form, for a total of about 220 mg to about 9000 mg of zoledronic acid to be administered in about 6 months.

55. The pharmaceutical product of claim 50, comprising 45 to 60 units of the oral dosage form, for a total of about 450 mg to about 18000 mg of zoledronic acid to be administered in about 1 year.

56. The pharmaceutical product of claim 44, comprising 1 to 10 units of the oral dosage form, wherein the product contains about 200 mg to about 2000 mg of zoledronic acid.

57. The oral dosage form of any preceding claim, wherein the zoledronic acid is in the form of a sodium salt.

58. The oral dosage form of any preceding claim, wherein the zoledronic acid is in a form that has an aqueous solubility greater than 1% (w/v).

59. The oral dosage form of any preceding claim, wherein the zoledronic acid is in a form that has an aqueous solubility of about 5% (w/v) to about 50% (w/v).

60. An oral dosage form comprising zoledronic acid and an excipient, wherein the zoledronic acid is in a form that has an aqueous solubility greater than 1% (w/v).

61. The oral dosage form of claim 60, wherein the zoledronic acid is in a form that has an aqueus solubility of about 5% (w/v) to about 50% (w/v).

62. A method of treating complex regional pain syndrome comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof.

63. The method of claim 62, wherein the mammal is a human being that receives an amount of zoledronic acid that is about 30 mg/m^2 to about 700 mg/m^2 in a period of one month or less.

64. The method of claim 63, wherein 4 or 5 weekly doses are administered in a period of one month or less.

65. The method of claim 63, wherein 28 to 31 daily doses are administered in a period of one month or less.

66. The method of claim 63, wherein 5 to 10 individual doses are administered during a period of one month or less.

67. The method of claim 63, wherein about 30 mg/m^2 to about 700 mg/m^2 of zoledronic acid is administered during only one month.

68. The method of claim 63, wherein about 30 mg/m^2 to about 700 mg/m^2 of zoledronic acid is administered in a period of one month or less for 2 or more consecutive months.

69. The method of claim 62, wherein the mammal receives about 10 mg/m^2 to about 30 mg/m^2 of zoledronic acid daily.

70. The method of claim 62, wherein the mammal is a human being that receives a total weekly dose of zoledronic acid that is about 10 mg to about 300 mg.

71. The method of claim 70, wherein the total weekly dose is a single dose, administered once a week.

72. The method of claim 70, wherein the total weekly dose is administered in 2 to 7 individual doses during the week.

73. The method of any of claims 62-72, wherein the complex regional pain syndrome is complex regional pain syndrome type I.

74. The method of any of claims 62-72, wherein the complex regional pain syndrome is complex regional pain syndrome type II.

75. The method of any preceding claim, wherein the zoledronic acid is in a salt form.

76. The method of any of claims 62-75, wherein the dosage form contains about 10 mg/m^2 to about 20 mg/m^2 of zoledronic acid based upon the body surface area of the mammal.

77. The method of claim 76, wherein the dosage form contains about 15 mg/m^2 to about 20 mg/m^2 of zoledronic acid based upon the body surface area of the mammal.

78. A method of treating complex regional pain syndrome, comprising administering pamidronic acid to a human being in need thereof.

79. A method of treating complex regional pain syndrome, comprising administering neridronic acid to a human being in need thereof.

80. A method of treating complex regional pain syndrome, comprising administering olpadronic acid to a human being in need thereof.

81. A method of treating complex regional pain syndrome, comprising administering alendronic acid to a human being in need thereof.

82. A method of treating complex regional pain syndrome, comprising administering incadronic acid to a human being in need thereof.

83. A method of treating complex regional pain syndrome, comprising administering ibandronic acid to a human being in need thereof.

84. A method of treating complex regional pain syndrome, comprising administering risedronic acid to a human being in need thereof.

85. A method of treating pain, comprising administering pamidronic acid to a human being in need thereof.

86. A method of treating pain, comprising administering neridronic acid to a human being in need thereof.

87. A method of treating pain, comprising administering olpadronic acid to a human being in need thereof.

88. A method of treating pain, comprising administering alendronic acid to a human being in need thereof.

89. A method of treating pain, comprising administering incadronic acid to a human being in need thereof.

90. A method of treating pain, comprising administering ibandronic acid to a human being in need thereof.

91. A method of treating pain, comprising administering risedronic acid to a human being in need thereof.

92. A method of treating arthritis pain, comprising administering pamidronic acid to a human being in need thereof.

93. A method of treating arthritis pain, comprising administering neridronic acid to a human being in need thereof.

94. A method of treating arthritis pain, comprising administering olpadronic acid to a human being in need thereof.

95. A method of treating arthritis pain, comprising administering alendronic acid to a human being in need thereof.

96. A method of treating arthritis pain, comprising administering incadronic acid to a human being in need thereof.

97. A method of treating arthritis pain, comprising administering ibandronic acid to a human being in need thereof.

98. A method of treating arthritis pain, comprising administering risedronic acid to a human being in need thereof.

99. A method of treating inflammatory pain, comprising administering pamidronic acid to a human being in need thereof.

100. A method of treating inflammatory pain, comprising administering neridronic acid to a human being in need thereof.

101. A method of treating inflammatory pain, comprising administering olpadronic acid to a human being in need thereof.

102. A method of treating inflammatory pain, comprising administering alendronic acid to a human being in need thereof.

103. A method of treating inflammatory pain, comprising administering incadronic acid to a human being in need thereof.

104. A method of treating inflammatory pain, comprising administering ibandronic acid to a human being in need thereof.

105. A method of treating inflammatory pain, comprising administering risedronic acid to a human being in need thereof.

106. A method of treating complex regional pain syndrome, comprising administering etidronic acid to a human being in need thereof.

107. A method of treating pain, comprising administering etidronic acid to a human being in need thereof.

108. A method of treating arthritis pain, comprising administering etidronic acid to a human being in need thereof.

109. A method of treating inflammatory pain, comprising administering etidronic acid to a human being in need thereof.

110. A method of treating complex regional pain syndrome, comprising administering clodronic acid to a human being in need thereof.

111. A method of treating pain, comprising administering clodronic acid to a human being in need thereof.

112. A method of treating arthritis pain, comprising administering clodronic acid to a human being in need thereof.

113. A method of treating inflammatory pain, comprising administering clodronic acid to a human being in need thereof.

114. A method of treating complex regional pain syndrome, comprising administering tiludronic acid to a human being in need thereof.

115. A method of treating pain, comprising administering tiludronic acid to a human being in need thereof.

116. A method of treating arthritis pain, comprising administering tiludronic acid to a human being in need thereof.

117. A method of treating inflammatory pain, comprising administering tiludronic acid to a human being in need thereof.

118. The method of any of claims 78-117, wherein the active compound is orally administered.

119. The method of any of claims 78-117, wherein the active compound is parenterally administered.

ABSTRACT

Oral dosage forms of bisphosphonate compounds, such as zoledronic acid, can be used to treat or alleviate pain or related conditions. Although an oral dosage form with enhanced bioavailability with respect to the bisphosphonate compound can be used, the treatment can also be effective using an oral dosage form that includes a bisphosphonate compound, such as zoledronic acid, wherein the bioavailability of the bisphosphonate is unenhanced, or is substantially unenhanced.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	13894244
Filing Date	2013-05-14
First Named Inventor	Tabuteau
Art Unit	N/A
Examiner Name	N/A
Attorney Docket Number	1958603.00021

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	Examiner Name	N/A
	Attorney Docket Number	1958603.00021

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Signature	/Brent A. Johnson/	Date (YYYY-MM-DD)	2013-05-15
Name/Print	Brent A. Johnson	Registration Number	51851

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(54) **Title:** METHODS FOR TREATING ARTHRITIC CONDITIONS IN DOGS

(57) **Abstract:** The present invention relates to a method for eliciting a disease modifying effect on an arthritic condition in a hip or stifle of a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate. The present invention also relates to method for eliciting a disease modifying effect on hip dysplasia or stifle instability, the pain associated with hip dysplasia or stifle instability, joint swelling, shallowing of the acetabulum, narrowing of the joint space, subchondral bone sclerosis, preventing osteophyte formation and preventing joint destruction in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

WO 2005/107751 A1

TITLE OF THE INVENTION

METHODS FOR TREATING ARTHRITIC CONDITIONS IN DOGS

BACKGROUND OF THE INVENTION

Osteoarthritis (OA) is a degenerative joint disease characterized by pain, cartilage loss and joint stiffness. It is a common disease that affects dogs of all ages, but is most prevalent in older animals. It may be a primary disease, the result of general wear and tear, or a secondary disease, the result of injury, infection, non healing fracture or developmental abnormalities.

Hip Dysplasia is a developmental disease of dogs in which a deformity between the head of the femur and the acetabulum creates joint instability allowing excessive movement of the femoral head. This is a common condition in dogs, particularly in large breeds. The exact cause is not known, although there is a genetic component. While the disease may be inherited, the expression of the defect is very largely influenced by factors such as nutrition, growth rates, obesity and exercise.

Initially, hip dysplasia is seen as a loss of joint tightness, allowing the head of the femur excessive movement around the ball of the acetabulum. In the extreme, the joint subluxates. Over time, these abnormal joint interactions create injury and erosion of the articular cartilage covering the ends of the opposing bones. There is pain, joint swelling, a narrowing of the joint space, eburnation (articulation of bone on bone), and structural changes to the joint, including shallowing of the acetabulum, femoral head remodeling and osteophyte development.

The pain associated with this disease can be controlled with varying efficacy by the use of non-steroidal anti-inflammatory drugs. More potent pain relief may be achieved using narcotics. However, these therapies are purely palliative and do not prevent the progression of the osteoarthritis. Eventually, surgery to remove the femoral head, or complete hip replacement, must be considered as the only treatment which is effective in providing pain relief.

Rupture of, or damage to the cruciate ligaments usually occurs due to sudden rotation or hyperextension of the stifle joint during exercise. It commonly involves the cranial cruciate and may be quite painful and involve other injury to the joint. If the ligament is ruptured the resultant joint instability usually leads to degenerative joint changes including joint thickening, meniscal cartilage degeneration, narrowing of the joint space and periarticular osteophyte formation.

If cruciate rupture is diagnosed, surgery to stabilize the joint is indicated. In dogs where surgery is not performed or is not successful, chronic joint instability is likely, leading to development of osteoarthritis. The selection of analgesics that are used to treat hip dysplasia are indicated in dogs with osteoarthritis involving the stifle joint. The analgesics relieve discomfort but do not treat the primary disorder.

SUMMARY OF THE INVENTION

The present invention relates to a method for eliciting a disease modifying effect on an arthritic condition in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate. The present invention also relates to method for eliciting a disease modifying effect on hip dysplasia, the pain associated with hip dysplasia, joint swelling, shallowing of the acetabulum, subchondral bone sclerosis, preventing osteophyte formation and preventing joint destruction in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for eliciting a disease modifying effect on an arthritic condition in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

The present invention relates to a method for treating osteoarthritis resulting from hip dysplasia or stifle instability associated with cruciate ligament damage in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

The present invention relates to a method for treating pain associated with hip dysplasia or stifle instability in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

The present invention relates to a method for reducing joint swelling in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

The present invention relates to a method for preventing shallowing of the acetabulum hip in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

The present invention relates to a method for preventing osteophyte formation in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

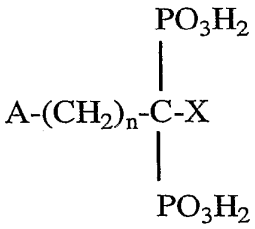
The present invention relates to a method for treating subchondral bone sclerosis in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

The present invention relates to a method for preventing joint deterioration in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate.

The present invention relates to a method for eliciting a disease modifying effect on an arthritic condition in a canine which comprises administering to the canine a therapeutically effective amount of a bisphosphonate and a therapeutically effective amount of a nonsteroidal anti-inflammatory

drug. The present invention further relates to a pharmaceutical composition comprising a bisphosphonate and a nonsteroidal anti-inflammatory drug.

"Bisphosphonate" includes, but is not limited to, compounds of the chemical formula



wherein n is an integer from 0 to 7 and wherein A and X are independently selected from the group consisting of H, OH, halogen, NH_2, SH, phenyl, C1-C30 alkyl, C3-C30 branched or cycloalkyl, bicyclic ring structure containing two or three N, C1-C30 substituted alkyl, C1-C10 alkyl substituted NH_2, C3-C10 branched or cycloalkyl substituted NH_2, C1-C10 dialkyl substituted NH_2, C1-C10 alkoxy, C1-C10 alkyl substituted thio, thiophenyl, halophenylthio, C1-C10 alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazolyl, imidazopyridinyl, and benzyl, such that both A and X are not selected from H or OH when n is 0; or A and X are taken together with the carbon atom or atoms to which they are attached to form a C3-C10 ring.

In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic, provided sufficient atoms are selected for the chemical formula. The C1-C30 substituted alkyl can include a wide variety of substituents, nonlimiting examples which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH_2, C1-C10 alkyl or dialkyl substituted NH_2, OH, SH, and C1-C10 alkoxy.

The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, non-limiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantyl, and chlorophenylthio.

Pharmaceutically acceptable salts and derivatives of the bisphosphonates are also useful herein. Non-limiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di-, tri-, or tetra-C1-C30-alkyl-substituted ammonium. Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. More preferred are sodium salts. Non-limiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

It should be noted that the terms "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, bisphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these

materials. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a bisphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein. For example, the phrase "about 5 mg of a bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof, on an alendronic acid active weight basis" means that the amount of the bisphosphonate compound selected is calculated based on 5 mg of alendronic acid.

Non-limiting examples of bisphosphonates useful herein include the following:

Alendronate, which is also known as alendronic acid, alendronate sodium or alendronate monosodium trihydrate, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid and 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate, are described in U.S. Patents 4,922,007, to Kieczykowski *et al.*, issued May 1, 1990; 5,019,651, to Kieczykowski *et al.*, issued May 28, 1991; 5,510,517, to Dauer *et al.*, issued April 23, 1996; 5,648,491, to Dauer *et al.*, issued July 15, 1997, all of which are incorporated by reference herein in their entirety.

Cycloheptylaminomethylene-1,1-bisphosphonic acid, YM 175, Yamanouchi (incadronate, formerly known as cimadronate), as described in U.S. Patent 4,970,335, to Isomura *et al.*, issued November 13, 1990, which is incorporated by reference herein in its entirety.

1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and *J. Org. Chem 32*, 4111 (1967), both of which are incorporated by reference herein in their entirety.

1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053).

1-hydroxyethane-1,1-diphosphonic acid (etidronic acid).

1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Patent No. 4,927,814, issued May 22, 1990, which is incorporated by reference herein in its entirety.

1-hydroxy-2-imidazo-(1,2-a)pyridin-3-yethylidene (minodronate).

6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate).

3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate).

3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate).

[2-(2-pyridinyl)ethylidene]-1,1-bisphosphonic acid (piridronate) is described in U.S. Patent No. 4,761,406, which is incorporated by reference in its entirety.

1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate).

(4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Patent 4,876,248, to Breliere *et al.*, October 24, 1989, which is incorporated by reference herein in its entirety.

1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zoledronate).

Non-limiting examples of bisphosphonates include alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, and zolendronate, and pharmaceutically acceptable salts and esters thereof. A particularly preferred bisphosphonate is alendronate, especially a sodium, potassium, calcium, magnesium or ammonium salt of alendronic acid. Exemplifying the preferred bisphosphonate is a sodium salt of alendronic acid, especially a hydrated sodium salt of alendronic acid. The salt can be hydrated with a whole number of moles of water or non whole numbers of moles of water. Further exemplifying the preferred bisphosphonate is a hydrated sodium salt of alendronic acid, especially when the hydrated salt is alendronate monosodium trihydrate.

It is recognized that mixtures of two or more of the bisphosphonate actives can be utilized.

Definitions

"Arthritic condition" or "arthritic conditions" refers to a disease wherein inflammatory lesions are confined to the joints or any inflammatory conditions of the joints.

"Joint Swelling" refers to an expansion of the external circumference of the joint due to effusion into the joint space or to external thickening of the joint capsule and surrounding structures.

"Shallowing of the acetabulum" refers to a remodeling of the shape of the acetabulum so that the depth of the cup into which the head of the femur normally opposes is reduced and the cup shape is flattened.

"Narrowing of the joint space" refers to apparent reduction in the distance between the opposing bones which articulate within a joint. It is the result of the reduction in thickness of cartilage covering the articular surface of the bones, this reduction permitting the bones to be in closer proximity to each other than in a normal joint.

"Subchondral bone sclerosis" as used herein means the increase in bone density and volume in the subchondral region.

"Osteophyte" as used herein refer to newly formed bony structures located at the joint margins, and their occurrence is strongly associated with the late stage of OA progression. The current hypothesis is that osteophytes originate from activated periosteum leading to new cartilaginous outgrowths that eventually turns into bone by the process of endochondral bone formation.

"Joint destruction" as used herein refers to the destruction of articular cartilage.

The term "disease modifying effect" refers to an agent that can slow, retard or prevent the progression of a disease. For example, in the case of osteoarthritis, a disease modifying effect could include slowing the loss of cartilage and preventing osteophyte formation.

A "Nonsteroidal anti-inflammatory drug (NSAID)" refers to non steroidal therapeutics that limit the formation of inflammation. Nonlimiting examples of NSAIDS include, but are not limited to, carprofen, etodolac, ibuprofen, ketoprofen, meloxicam, naproxen and selective cyclooxygenase-2 inhibitors (COX-2 inhibitors). Nonlimiting examples of COX-2 inhibitors include: celecoxib, deracoxib, etoricoxib, firocoxib, lumaricoxib, parecoxib, rofecoxib, and valdecoxib.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The term "therapeutically effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician.

The terms "treating" or "treatment" of a disease as used herein includes: preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a canine that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

As used herein, the term "pharmaceutically acceptable salts" includes the conventional non-toxic salts of the compounds of this invention as formed inorganic or organic acids. For example, conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like, as well as salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like. The preparation of the pharmaceutically acceptable salts described above and other typical pharmaceutically acceptable salts is more fully described by Berg *et al.*, "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977:66:1-19, hereby incorporated by reference. The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic or acidic moiety by conventional chemical methods. Generally, the salts of the basic compounds are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents. Similarly, the salts of the acidic compounds are formed by reactions with the appropriate inorganic or organic base.

Utilities

The compositions and methods of the present invention are useful for eliciting a disease modifying effect on arthritic conditions, especially for eliciting a disease modifying effect on osteoarthritis and hip dysplasia in canines, including the treatment of pain associated with hip dysplasia, reduction of joint swelling, and prevention of the shallowing of the acetabulum, subchondral bone resorption, osteophyte formation and ultimately joint deterioration/destruction.

The methods of the present invention have an unexpected disease modifying effect in the treatment of arthritic conditions in canines.

The compositions of the present invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, pastes, tinctures, sterile solutions or suspensions, syrups, flavored treats and emulsions. Likewise, it may also be administered in intravenous (bolus or infusion), intraperitoneal, topical (e.g., ocular eyedrop), intranasal, inhaled, subcutaneous, intramuscular or transdermal (e.g., patch) form, metered aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but non-toxic amount of the compositions desired can be employed. The compositions are intended for oral, parenteral, intranasal, sublingual, or rectal administration, or for administration by inhalation or insufflation. Formulation of the compositions according to the invention can conveniently be effected by methods known from the art, for example, as described in Remington's Pharmaceutical Sciences, 17th ed., 1995.

The dosage regimen utilizing the compositions of the present invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the subject; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the subject; and the particular compound or salt thereof employed. An ordinarily skilled veterinarian or clinician can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Advantageously, the compounds of the present invention may be administered in a single quarterly, monthly, weekly or daily dose, or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, the compound of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The dose may be administered in a single daily dose or the total daily dosage may be administered in divided doses of two, three or four times daily. Furthermore, based on the properties of the individual compound selected for administration, the dose may be administered less frequently, e.g.,

weekly, twice weekly, monthly, etc. The unit dosage will, of course, be correspondingly larger for the less frequent administration.

The precise dosage of the bisphosphonate will vary with the dosing schedule, the oral potency of the particular bisphosphonate chosen, the age, size, sex and condition of the canine, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. For canines, an effective oral dose of bisphosphonate is typically from about 1.5 to about 20,000 μg/kg body weight and preferably about 10 to about 10,000 μg/kg of body weight.

In alternative dosing regimens, the bisphosphonate can be administered at intervals other than daily, for example once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing. In a once weekly dosing regimen, alendronate monosodium trihydrate would be administered at dosages of about 2.5 mg/week to about 280 mg/week. Nonlimiting examples of doses include 140 mg/week and 280 mg/week. The bisphosphonates may also be administered monthly, ever six months, yearly or even less frequently, see WO 01/97788 (published December 27, 2001) and WO 01/89494 (published November 29, 2001).

According to a further aspect of the present invention, it may be desirable to treat any of the aforementioned conditions with a combination of a bisphosphonate and one or more other pharmacologically active agents suitable for the treatment of the specific condition. The bisphosphonate and the other pharmacologically active agent(s) may be administered to a subject simultaneously, sequentially or in combination. For example, the present compound may be employed directly in combination with the other active agent(s), or it may be administered prior, concurrent or subsequent to the administration of the other active agent(s). In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

The compositions and methods of the present invention are administered and carried out until the desired therapeutic effect is achieved.

The identification of a bisphosphonate which is able to have utility in the present invention may be readily determined without undue experimentation by methodology well known in the art, such as the assay described herein.

ASSAY

Materials and Methods

Osteoarthritis model and treatment -- All procedures were carried out according to the Institutional Animal Care and Use Committee Guide in Merck Research Labs. Ninety-five 20-week old male Sprague-Dawley rats (Taconic, NJ) were used following experiments. Osteoarthritis (OA) model was surgically induced in 20-wk-old male rat knee joints or in 7-10 month old male NZ White rabbits. Briefly, the animals were anesthetized by isoflurane. The right knee joint was shaved, disinfected with

iodine, and exposed though the medial parapatellar approach. The patella was dislocated laterally and the knee placed in full flexion. All operation procedures were performed using a surgical loupe. Anterior cruciate ligament (ACL) was transected with micro-scissors. To confirm complete transection of ACL, Lachman test was performed. After surgery, the joint surface was washed with sterile saline solution, and both capsule and skin were sutured using Vicryl 4-0 (Ethicon, Edinburgh, UK), absorbable suture and monofilament 4-0 Nylon threads (Ethicon, Edinburgh, UK). In Sham operation, the wound was closed by layers after subluxation of patella and saline washing. Buprenorphine hydrochloride (0.1 mg/kg) (Reckitt & Colman Products Ltd., Hull, England) was given as an analgesic. Animals were allowed to move freely in the soft bedding plastic cages.

A test compound was administered by either subcutaneous injection or orally dosing. Drug was dosed prior to the surgery in the prevention mode. In treatment mode, drug was dosed 1 or 2 weeks post-surgery. Endpoints were histological analysis, histomorphometry and evaluation of serum markers. In all studies, the animals were always included the following groups: ACL transection with vehicle, ACLT with a low and a higher doses of the drug, sham operation with vehicle, and sham operation with the high dose of the drug. Animals were sacrificed on 2- and 10-wk post-surgery with CO_2. In both time points, rats were injected 10-mg/kg calcein 3 days before the necropsy. In a separate study, the same groups of animals received either sham- or ACLT-operation and with or without drug treatment were used for TGF-β assay. These animals were sacrificed on 2-wk post-surgery.

Gross morphology, Tissue preparation and histology -- After the disarticulation of the right joint, both femur and tibia were carefully cleaned free of muscles, and fixed in 4% paraformaldehyde (Fisher Scientific, NJ) in phosphate buffer saline (PBS) for 24 hrs. Gross appearance of the distal femur was taken by digital camera (DIX, Nikon, Japan) with 1:4 Nikkor lens (Nikon, Japan) to evaluate osteophyte formation. Tibia was then cut in a half at the center of articular surface along with medial collateral ligament in frontal section with band saw (EXAKT Technologies, Inc, Norderstedt, Germany). Anterior parts were re-immersed in 4% paraformaldehyde for another 24 hrs for paraffin embedding. Posterior parts were changed into 70% ethanol, and then embedded in methylmethacrylate. Sections at 5 μm thick were stained Masson's trichrome staining as described previously, see Gruber, H.E., G.J. Marshall, L.M. Nolasco, M.E. Kirchen, and D.L. Rimoin, 1988, "Alkaline and acid phosphatase demonstration in human bone and cartilage: effects of fixation interval and methacrylate embedments," *Stain Technol.* 63:299-306 and Yamamoto, M., J.E. Fisher, M. Gentile, J.G. Seedor, C.T. Leu, S.B. Rodan, and G.A. Rodan, 1998, "The integrin ligand echistatin prevents bone loss in ovariectomized mice and rats" *Endocrinology.* 139:1411-9. Specimens were labeled with randomly assigned identification numbers to blind the investigator to the group designation during subsequent measurements.

For paraffin embedding, tissues were decalcified in 0.5 M ethylenedinitrilo-tetra acetic acid solution (pH 7.6, Fisher Scientific, NJ) for 7 to 10 days, then treated with a graded ethanol series, followed by xylene, prior to embedding into paraffin wax (Fisher Scientific, NJ) as previously described, see Nakase, T., K. Takaoka, K. Hirakawa, S. Hirota, T. Takemura, H. Onoue, K. Takebayashi, Y. Kitamura, and S. Nomura, 1994, "Alterations in the expression of osteonectin, osteopontin and osteocalcin mRNAs during the development of skeletal tissues in vivo," *Bone Miner.* 26:109-22 and Hayami, T., N. Endo, K. Tokunaga, H. Yamagiwa, H. Hatano, M. Uchida, and H.E. Takahashi, 2000, "Spatiotemporal change of rat collagenase (MMP-13) mRNA expression in the development of the rat femoral neck," *J Bone Miner Metab.* 18:185-93.

Paraffin embedded specimen was sectioned and examined by histological analysis and immunohistochemistry. Paraffin sections were stained with toluidine blue-O (0.2% toluidine blue-O/ 0.1M sodium acetate buffer, pH 4.0) for proteoglycan content. Occasionally, sections were also stained with tartrate resistant acid phosphatase (TRAP) stain for osteoclast localization, as previously described, see Nakamura, Y., A. Yamaguchi, T. Ikeda, and S. Yoshiki, 1991, "Acid phosphatase activity is detected preferentially in the osteoclastic lineage by pre-treatment with cyanuric chloride," *J Histochem Cytochem.* 39:1415-20.

Histopathological scores (modified Mankin score) -- Semi-quantitative histopathological grading was performed according to a modified Mankin scoring system, which is a well established grading system in OA research, with some modifications, see Cake, M.A., R.A. Read, B. Guillou, and P. Ghosh, 2000, "Modification of articular cartilage and subchondral bone pathology in an ovine meniscectomy model of osteoarthritis by avocado and soya unsaponifiables (ASU)," *Osteoarthritis Cartilage.* 8:404-11; Little, C., S. Smith, P. Ghosh, and C. Bellenger, 1997, "Histomorphological and immunohistochemical evaluation of joint changes in a model of osteoarthritis induced by lateral meniscectomy in sheep," *J Rheumatol.* 24:2199-209; Wenz, W., S.J. Breusch, J. Graf, and U. Stratmann, 2000, "Ultrastructural findings after intraarticular application of hyaluronan in a canine model of arthropathy," *J Orthop Res.* 18:604-12.

Mankin score normally consists of five subcategories, including structure, chondrocyte number, chondrocyte clustering, proteoglycan content (stainability for toluidine blue-O), and subchondral plate and/or tidemark change including vascular invasion in cartilage. Since vascular invasion into cartilage was independently evaluated using Masson's trichrome staining, we omitted this category in the Mankin score. Three sections 100 μm apart were measured in each sample. Total possible score is 26 and scoring was done by a single observer with blinded according to a five-point scale (Cake *et al.* 2000). Low total score are consistent with minor degenerative cartilaginous lesions, whereas high total score indicative of

more pronounced cartilaginous regions. In toluidine blue-O staining stainability, we use the terminology as previously described (Little, *et al.* 1997), "mild" was used when there was decreased toluidine blue-O staining with intact articular surface, "moderate" when there was decreased toluidine blue-O staining in association with surface fibrillation and clefts extending to but not below the middle zone, and "severe" when cartilage was lost down to the level of the calcified cartilage.

Bone histomorphometry -- For quantification of the histological parameters, we used Image Pro plus (version 4, Media Cybernetics, MD) image analysis program. Images of articular cartilage and subchondral bone were examined using a Olympus fluorescence microscope (BX51, Japan) with ×4 objective lens and were recorded using a CCD/RGB color video camera (RT Slider SPOT, Diagnostic instrument. Inc., MI).

Histomorphometric measurements of both medial and lateral tibial plateaux were determined in two separate sections per knee joint, spaced 100 μm apart. Since subchondral region has been reported that affected in OA development, we developed a macro to measure subchondral bone volume per tissue area. Two areas from either medial or lateral tibial plateau, 600 μm depth × 800 μm width, were measured with the center of the tibial plateau being semi-automatically determined according to the width of the tibial surface. To consistently place the area to be measured, the top of the rectangle always horizontally aligned along the surface of articular cartilage and its sides vertically aligned along the center line of the tibia. The data from two areas were combined for the medial or lateral tibial plateau, and measurements of 6 knees per group were averaged in each group.

Trabecular bone volume (BV/TV: percentage of endosteal bone and marrow compartment occupied by osteoid and mineralized bone) in subchondral region was measured by histomorphometric methods that complied with the nomenclature and were calculated according to the ASBMR guidelines, see Parfitt, A.M., M.K. Drezner, F.H. Glorieux, J.A. Kanis, H. Malluche, P.J. Meunier, S.M. Ott, and R.R. Recker, 1987, "Bone histomorphometry: standardization of nomenclature, symbols, and units," Report of the ASBMR Histomorphometry Nomenclature Committee. *J Bone Miner Res.* 2:595-610. To detect active bone remodeling surfaces in the subchondral region, we also injected the rats with calcein (10 mg/kg) 3 days before necropsy. Labeled mineralized surfaces in the plastic sections can be viewed using the same Olympus fluorescence microscope as described above.

Vascular invasion into calcified cartilage -- Vascular invasion into the calcified cartilage was quantified by counting the number of times the calcified cartilage contacted by subchondral marrow space as previously described, see O'Connor, K.M., 1997, "Unweighting accelerates tidemark advancement in

articular cartilage at the knee joint of rats," *J Bone Miner Res.* 12:580-9. The results from two sections, spaced 100 μm apart were measured.

Osteoclast score -- TRAP positive cells were counted in calcified cartilage and osteophyte regions. The number of TRAP positive cells from two sections in each sample spaced 100 μm apart were measured and then averaged from 6 knees per group.

Osteophytes score and area -- Osteophytes were defined as outgrowth of the bone and cartilage occurring at the joint margins in the tibial plateau. To evaluate incident of osteophyte formation (osteophyte score), total osteophyte number from 5 sections including 3 paraffin (anterior part of tibia) and 2 plastic sections (posterior part of tibia) at 100 μm apart, were evaluated from each knee joint. Surface area of each osteophyte was manually determined in Masson' s trichrome stained sections using image pro analysis. Two sections, each section is 100 μm apart, were evaluated.

Serum and Urinary levels of COMP, CTX-I and CTX-II -- Blood was obtained from cardiac puncture at each necropsy, 2- and 10-wk post-surgery. Serum samples were collected, and frozen in aliquots -70°C. Serum cartilage oligomeric matrix protein (COMP) were determined by AnaMar Medical AB (Uppsala, Sweden) using a modified enzyme-liked immunosorbent assay as previously described, see Larsson, E., A. Mussener, D. Heinegard, L. Klareskog, and T. Saxne, 1997, "Increased serum levels of cartilage oligomeric matrix protein and bone sialoprotein in rats with collagen arthritis," *Br J Rheumatol.* 36:1258-61 and Saxne, T., and D. Heinegard, 1992, "Cartilage oligomeric matrix protein: a novel marker of cartilage turnover detectable in synovial fluid and blood," *Br J Rheumatol.* 31:583-91.All determinations were done in duplicate.

Twenty-four-hour urine samples were collected from the individual animal's metabolic cages at 2 wk-post surgery. Samples were centrifuged and frozen in aliquots at -70°C. Assays for bone related degradation product from C-terminal telopeptide of type I collagen (CTX-I/ Ratlaps, Nordic Bioscience Diagnostics, Denmark) were performed in our laboratory according to the manufacturer's instruction. Assays for cartilage related C-terminal telopeptide of type II collagen (CTX-II/ CartiLaps) were performed by Nordic Bioscience Diagnostics, Denmark. Urinary creatinine determination was measured in each sample as a test for normal urinary output. CTX-I and CTX-II values were reported after normalized to the creatine concentration in the same sample.

Immunohistochemistry -- Tissue sections were deparaffinized in xylene, hydrated in graded ethanol, then treated with 500 U/ml testicular hyaluronidase (Sigma, MO) at 37°C for 20 min. Tissue sections were then incubated with using either anti-rat CD31 mAb (Endogen, MA), or anti-activated TGF-β, which

recognizes only active form of TGF-β1, 2, and 3 (R&D) as described previously, see Fernandez, T., S. Amoroso, S. Sharpe, G.M. Jones, V. Bliskovski, A. Kovalchuk, L.M. Wakefield, S.J. Kim, M. Potter, and J.J. Letterio, 2002, "Disruption of transforming growth factor beta signaling by a novel ligand-dependent mechanism," *J Exp Med.* 195:1247-55, anti-MMP-13 Ab, anti-MMP-9 Ab for over night at 4°C as described previously, see Hayami, T., H. Funaki, K. Yaoeda, K. Mitui, H. Yamagiwa, K. Tokunaga, H. Hatano, J. Kondo, Y. Hiraki, T. Yamamoto, L.T. Duong, and N. Endo, 2003, "Expression of the cartilage-derived anti-angiogenic factor Chondromodulin-I decreases in the early stage of experimental osteoarthritis," *J. Rheumatol.* (in press). In CD31 immunostaining, after rinsing in PBS with 0.3 % Tween 20, they were incubated with biotin-conjugated anti-mouse Ab (LSAB2 kit, Dako, CA) for 10 min and followed with alkaline phosphatase-conjugated streptavidin for 10 min (Dako, CA). These sections were rinsed with PBS, and developed using fast red substrate system (Dako, CA) for 5 min and counterstained with hematoxyline. Double-labeled immuno-histochemical stainings with MMP-9/ MMP-13 and TGF-β Abs were performed as previously described, see Hayami, T., H. Funaki, K. Yaoeda, K. Mitui, H. Yamagiwa, K. Tokunaga, H. Hatano, J. Kondo, Y. Hiraki, T. Yamamoto, L.T. Duong, and N. Endo, 2003, "Expression of the cartilage-derived anti-angiogenic factor Chondromodulin-I decreases in the early stage of experimental osteoarthritis," *J. Rheumatol.* (in press). Briefly, tissue sections were incubated with TGF-β mAb, followed by AP-conjugated anti-mouse Ab, and developed to blue color with AP blue (Vector Laboratories, CA USA). They were washed twice with PBS with 0.3% Tween 20 for 1 hr, incubated with anti-MMP-9 or MMP-13 polyclonal Ab, followed by HRP-anti-rabbit Ab (DAKO, CA), and developed to brown color by 0.5 mg/ml 3,3'-diaminobenzidine tetrahydrochloride. As negative controls, the same procedures were carried out either without primary Ab or with mouse mAb IgG instead of primary antibody.

Mink Lung epithelial growth inhibition assay for TGF-β in supernatant from tibial plateaux/patellae organ culture -- Patellae and tibial plateau were isolated from either ACLT- or sham operated joints with or without drug treatment. After disarticulation and dissection of the patellae, tibiae were carefully removed of soft tissue. Articular cartilage and subchondral bone tissue were cut by a bone saw (Buehler Isomet, IL) at 480 μm thickness from the articular surface. Dissected patellae and tibial plateaux were transferred to 24 well culture dishes, washed with 0.1% BSA α-MEM for 3 times, then incubated in same media at 37°C under 5% CO_2. Supernatant after 12 hrs incubation was collected and frozen at -70°C. Active TGF-β was measured as described previously by using the mink lung epithelial cell bioassay, see Docagne, F., N. Colloc'h, V. Bougueret, M. Page, J. Paput, M. Tripier, P. Dutartre, E.T. MacKenzie, A. Buisson, S. Komesli, and D. Vivien, 2001, "A soluble transforming growth factor-beta (TGF-beta) type I receptor mimics TGF-beta responses," *J Biol Chem.* 276:46243-50. Briefly, mink lung cells (Mv1Lu, ATCC, MD) were plated at 10,000 cells/well in 96-well CytoStar scintillating microplates (Amersham,

NJ) in E-MEM, 10% FBS containing sodium pyruvate and non-essential amino acids. After 24 hrs, TGF-β1 was diluted in α-MEM (1:4) as final concentration and 50 μl was added to duplicate wells as a control, followed by adding condition media (50 μl/well). After 20 hrs, [^{14}C-methyl]-thymidine was added to each well to a final dilution of 0.5 μCi/ml. Plates were counted after 4 hr and 24 hr. Data reported was from the 24 hr-time point.

Statistical analysis -- Statistical comparisons were generated using Statview (SAS Institute Inc., NC). All data in tables 1-3 were shown as means ± SD. Results are expressed as mean ± SEM. Significance of difference between groups was evaluated with a one-way analysis of variance (ANOVA) to analyze variance across treatment groups, and Fisher's analysis of least significant difference (Fisher's PLSD) to compare treatment group means except where indicated. Difference in values was considered significant when p value was < 0.05.

EXAMPLES

The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention as many variations thereof are possible without departing from the spirit and scope of the invention.

Pharmaceutical Tablet Compositions

Tablets are prepared using standard mixing and formation techniques as described in U.S. Patent No. 5,358,941, to Bechard et al., issued October 25, 1994, which is incorporated by reference herein in its entirety.

Tablets containing about 6.5 mg of alendronate monosodium trihydrate, on an alendronic acid active basis are prepared using the following relative weights of ingredients.

Ingredient	Per 84 mg Tablet	Per 4000 Tablets
Alendronate Monosodium Trihydrate	6.5255mg	26.10 g
Anhydrous Lactose, NF	35.66mg	142.64 g
Microcrystalline Cellulose,NF	40.0 mg	160.0 g
Magnesium Stearate, NF	0.5 mg	20 g
Croscarmellose Sodium, NF	1.0 mg	4.0 g

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of osteoarthritis associated with hip dysplasia or cruciate ligament damage in a canine in need thereof.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, tablets containing combinations of bisphosphonates are similarly prepared.

Non Beef Based Chewable Treats

The resulting chewable treats are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a dog in need thereof.

Similarly, chewable treats comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, chewable treats containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, chewable treats containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/W
Alendronate Monosodium Trihydrate	2
Soy Protein fines	42
Propylene glycol	6
Water	22
Artificial beef flavor	2
Corn starch	25
Citric Acid	1

Suspensions

The resulting suspensions are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, suspensions comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, suspensions containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate,

olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, suspensions containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/W
Alendronate Monosodium Trihydrate	1.3%w/w
Colloidal Silicon dioxide	3.0
Alpha-tocopherol	0.2
Fish Oil	95.5

Solutions

The resulting solutions are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, solutions comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared.

Also, solutions containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, solutions containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/V
Alendronate Monosodium Trihydrate	1.3%w/v
Citric Acid	1.0
Sodium Citrate	0.5
Butterscotch Flavor	0.2
Purified Water	97.0

Ointments

The resulting ointments are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, ointments comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, ointments containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, ointments containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/W
Alendronate Monosodium Trihydrate	1.3%w/w
Lecithin	3.0
Malt Syrup	45.0
White Petrolatum	50.7

Gels

The resulting gels are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, gels comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, gels containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, gels containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/W
Alendronate Monosodium Trihydrate	1.3%w/w
Citric Acid	1.0
Sodium Citrate	0.5
Poloxamer	20.0
Propylene Glycol	20.0
Benzyl Alcohol	2.0
Purified Water	57.0

Pastes

The resulting pastes are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, pastes comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, pastes containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, pastes containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/W
Alendronate Monosodium Trihydrate	1.3%w/w
Sodium Carboxymethylcellulose	2.0
Magnesium aluminum Silicate	2.0
Methyl paraben	0.18
Propyl Paraben	0.02
Sorbitol Solution	20.0
Propylene Glycol	20.0
Purified Water	54.5

Composition For Transdermal Delivery

The resulting composition is useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, a composition comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, compositions containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, compositions containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/V
Alendronate Monosodium Trihydrate	1.3%w/v
Butylated Hydroxyanisole	0.02
Polysorbate 80	3.0
Diethyleneglycol monobutyl ether	5.0
n-Methylpyrrolidone	90.7

Composition For Transdermal Delivery (Skin Patch)

The resulting composition is useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, compositions comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, compositions containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, compositions containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/W
Alendronate Base	5.0%w/w
Alcohol	15.0
Hydoxypropylcellulose	1.0
Mineral oil	0.2
Polyisobutylene	QSAD
Ethylenevinyl acetate	QSAD

Injectables (IV/IM,SC/IP)

The resulting injectables are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of osteoarthritis lesions in a mammal in need thereof.

Similarly, injectables comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared.

Also, injectables containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, injectables containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/V
Alendronate Monosodium Trihydrate	2.0%w/v
Sodium Citrate	0.5
Benzyl Alcohol	2.0
Edetate Sodium	0.01
Sodium Metabisulfite	0.02
Water for Injection	95.5

Compositions for Intra-Nasal Delivery

The resulting composition is useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, compositions comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, compositions containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, compositions containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/W
Alendronate Monosodium Trihydrate	2.0%w/w
Carboxymethylcellulose sodium	0.2
Dextrose	0.9
Benzylalkonium chloride	0.01
Polysorbate 80	3.0
Hydrochloric acid	0.01
Purified Water	93.9

Sustained-Release Tablets

The resulting tablets are useful for administration in accordance with the methods of the present invention for inhibiting, i.e. treating or reducing the risk of, osteoarthritis lesions in a mammal in need thereof.

Similarly, tablets comprising other relative weights of alendronate, on an alendronic acid active weight basis are prepared. Also, tablets containing other bisphosphonates at appropriate active levels are similarly prepared: e.g., cimadronate, ibandronate, neridronate, olpandronate, risedronate, piridronate, pamidronate, zolendronate, and pharmaceutically acceptable salts thereof. In addition, tablets containing combinations of bisphosphonates are similarly prepared.

Ingredient	Percent W/W
Alendronate Monosodium Trihydrate	1.3%w/w
Citric Acid	1.0
Sodium Citrate	0.5
Cellulosic Polymer	1.0
Corn Starch	5.0
Sodium Starch Glycolate	5.0
Titanium Dioxide	0.5
Vanillin	0.5
Hydrogenated Castor Oil	6.0
Povidone	5.0
Acetylated Monoglycerides	1.0
Microcrystalline Cellulose	18.0
Lactose	55.2

In addition to the ingredients exemplified above, formulations can also contain additional suitable buffers, colors, dispersants, flavors, stabilizers and preservatives as necessary.

WHAT IS CLAIMED IS:

1. A method for treating osteoarthritis in dogs resulting from joint instability associated with hip dysplasia or cruciate ligament damage in canines which comprises administering to the mammal a therapeutically effective amount of a bisphosphonate.

2. The method of Claim 1 wherein the bisphosphonate is alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, zolendronate, or a combination thereof.

3. The method of Claim 2 wherein the bisphosphonate is alendronate or a pharmaceutically acceptable salt thereof.

4. A method for treating pain associated with osteoarthritis associated with hip dysplasia or cruciate ligament damage in canines which comprises administering to the mammal a therapeutically effective amount of a bisphosphonate.

5. The method of Claim 4 wherein the bisphosphonate is alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, zolendronate, or a combination thereof.

6. The method of Claim 5 wherein the bisphosphonate is alendronate or a pharmaceutically acceptable salt thereof.

7. A method for reducing joint swelling in canines which comprises administering to the mammal a therapeutically effective amount of a bisphosphonate.

8. The method of Claim 7 wherein the bisphosphonate is alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, zolendronate, or a combination thereof.

9. The method of Claim 8 wherein the bisphosphonate is alendronate or a pharmaceutically acceptable salt thereof.

10. A method for preventing the shallowing of the acetabulum in the hip of a canine which comprises administering to the mammal a therapeutically effective amount of a bisphosphonate.

11. The method of Claim 10 wherein the bisphosphonate is alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, zolendronate, or a combination thereof.

12. The method of Claim 11 wherein the bisphosphonate is alendronate or a pharmaceutically acceptable salt thereof.

13. A method for preventing osteophyte formation in the hip or stifle of a canine which comprises administering to the mammal a therapeutically effective amount of a bisphosphonate.

14. The method of Claim 13 wherein the bisphosphonate is alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, zolendronate, or a combination thereof.

15. The method of Claim 14 wherein the bisphosphonate is alendronate or a pharmaceutically acceptable salt thereof.

16. A method for treating osteoarthritis associated with hip dysplasia or cruciate ligament damage in canines which comprises administering to the mammal a therapeutically effective amount of a bisphosphonate and a nonsteroidal anti-inflammatory agent.

17. The method of Claim 16 wherein the bisphosphonate is alendronate, cimadronate, clodronate, etidronate, ibandronate, incadronate, minodronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate, zolendronate, or a combination thereof; and the nonsteroidal anti-inflammatory agent is carprofen, etodolac, ibuprofen, ketoprofen, meloxicam, naproxen, celecoxib, deracoxib, etoricoxib, firocoxib, lumaricoxib, parecoxib, rofecoxib, or valdecoxib.

18. The method of Claim 17 wherein the bisphosphonate is alendronate or a pharmaceutically acceptable salt thereof and the non-steroidal anti-inflammatory agent is rofecoxib.

19. The method of Claim 17 wherein the bisphosphonate is alendronate or a pharmaceutically acceptable salt thereof and the non-steroidal anti-inflammatory agent is firocoxib.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/15187

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/445, 31/19
US CL : 514/320, 166
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/320, 166

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,869,471 (HOVANCIK et al) 9 February 1999 (9.2.1999), column 7, lines 15-65; column 8, lines 55-65; column 40, lines 40-65.	1-2, 4-5, 7-8, 10, 13-14, 16-18 --- 1-19
Y	US 5,412,141 (NUGENT) 2 May 1995 (2.5.1995), column 8, lines 45-65.	1-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

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Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	1958603-00021-IDS-05-14-13.pdf	614527 1b5e00fc48e1badab3f14bb16b0929ead63f1fc9	no	7

Warnings:	
Information:	

2	Foreign Reference	WO2005107751-1.pdf	343475 67a29be0e6ff038e920cbb763368cdc43e1cd307	no	24
Warnings:					
Information:					
3	Non Patent Literature	Bertorelli1999.pdf	177142 f835ca8e6da421df7d59af9bb95426aa60e9e974	no	7
Warnings:					
Information:					
4	Non Patent Literature	Bingham2006.pdf	239223 053498bdaf438b2831d9f6242a6980989f0f733e	no	14
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Information:					
5	Non Patent Literature	MER-101Nov2007AAPSPoster.pdf	131307 67354d91b75ff097477cb1c3de0aca1c4740da32	no	1
Warnings:					
Information:					
6	Non Patent Literature	deCastro2011.pdf	149933 e4402a6e58e164fe7e76c17d34ff8980a85ed2a9	no	3
Warnings:					
Information:					
7	Non Patent Literature	EUProductlabels-1.pdf	345358 b15dd8a961a04d04bfabf46ef42e905db5da6a59	no	68
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8	Non Patent Literature	Gile2006.pdf	156134 eb5330d3483db89b4d55afeace521b666362c95a	no	3
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Information:					
9	Non Patent Literature	Guo2004.pdf	534947 ddbfd7a5cf0a18e023a71345e41d4f8f6c5f3417	no	13
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10	Non Patent Literature	Kingery2003.pdf	372298 de24de63d6d490ad3dde8738886f4fd73eb33024	no	10
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11	Non Patent Literature	Laslett2012-4.pdf	1300824 2d402223f8f6733125bb6c86eebb41953cf8fa1b	no	7
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12	Non Patent Literature	MER101-Posterpresnt-Leonard.pdf	97721 08f4808d19a6314f8487df99e12a7d909a8dfbfa	no	1
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13	Non Patent Literature	MER-101Nov2009EORTCPoster.pdf	174743 fa613dfc171b1a6815d021a1aa39420a2f46cfd5	no	1
Warnings:					
Information:					
14	Non Patent Literature	MER-1012009ASCOBCPoster.pdf	145313 df4d7e438db093de23f075d6101d53c6edb28900	no	1
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15	Non Patent Literature	MER-101May2009ASCOPoster.pdf	112932 c9b64fb73e80fd5e109635a3f60471f08d76112a	no	1
Warnings:					
Information:					
16	Non Patent Literature	Nagae2006.pdf	977837 d723bc99a5bb12c65eefac56648babb582ffcd85	no	9
Warnings:					
Information:					
17	Non Patent Literature	Nagae2007.pdf	225003 09a869374488b2aafa9d32549ed253e576410875	no	6
Warnings:					
Information:					
18	Non Patent Literature	Nagakura2003.pdf	301483 922dab2ee289748c3f55c1285e3d88e10e459c1b	no	8
Warnings:					
Information:					
19	Non Patent Literature	ORAZOLpptpresentation2011.pdf	548080 beaf9e8c135c86426ecd7961e9b86c39619bc091	no	15
Warnings:					
Information:					

20	Non Patent Literature	Reid2002.pdf	131697 85b172b676ecc2df19d10bb84ec00fa923c5da5d	no	9
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Information:					
21	Non Patent Literature	Ringe2007.pdf	424443 bc1b26aa8da6ba6baeae40262735b9fb106c5537	no	9
Warnings:					
Information:					
22	Non Patent Literature	ClinicalStudy2013.pdf	63669 d099778f5f73c3bd98989c13d92ec3851c8a822e	no	3
Warnings:					
Information:					
23	Non Patent Literature	USproductlablelZometa-1.pdf	319000 7c4902b29e39cdd6fff21879ed494a2cafa7dfe8	no	46
Warnings:					
Information:					
24	Non Patent Literature	Walker2002.pdf	896898 81ad31afcf007e8add8d4d859096051637e91c1e	no	11
Warnings:					
Information:					
25	Non Patent Literature	Zaspel2007.pdf	121576 7c0a55f9ead6455f9b39a646824ac85afc216cb8	no	5
Warnings:					
Information:					
26	Non Patent Literature	Future2000.pdf	772744 4b9b93cbbeb8e6ae48fc2a8e4240ff47939bcdd0	no	10
Warnings:					
Information:					
27	Non Patent Literature	ZometaFDAPharmacologyReviewP1.pdf	1165059 9a6b063aab40306e48795c1de84e23d277699dac	no	53
Warnings:					
Information:					
28	Non Patent Literature	ZometaFDAPharmacologyReviewP2.pdf	1161181 5085da111d5c34793cf8b19c68fe88715b4c4d3a	no	53
Warnings:					
Information:					

29	Non Patent Literature	ZometaFDAPharmacologyReviewP3.pdf	965261 259e0a198ae7eb8ac09b6201beb51afb4e9bed16	no	52
Warnings:					
Information:					
30	Non Patent Literature	ZometaFDAPharmacologyReviewP4.pdf	651616 0fda2da1803ed9032c5f2297db735dbfbd36d4f9	no	52
Warnings:					
Information:					
31	Non Patent Literature	ZometaFDAPharmacologyReviewP5.pdf	650964 a3c04e190d6b95fdb69037c8483f1b3151335db6	no	52
Warnings:					
Information:					
			Total Files Size (in bytes):	14272388	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/894,244

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	730		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/894,244	05/14/2013	1629	1030	1958603.00021	20	2

CONFIRMATION NO. 1033

45200
K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

FILING RECEIPT

OC000000061834511

Date Mailed: 06/17/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Herriot Tabuteau, New York, NY;

Applicant(s)

Herriot Tabuteau, New York, NY;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/646,538 05/14/2012
and claims benefit of 61/647,478 05/15/2012
and claims benefit of 61/654,292 06/01/2012
and claims benefit of 61/654,383 06/01/2012
and claims benefit of 61/655,527 06/05/2012
and claims benefit of 61/655,541 06/05/2012
and claims benefit of 61/762,225 02/07/2013
and claims benefit of 61/764,563 02/14/2013
and claims benefit of 61/767,647 02/21/2013
and claims benefit of 61/767,676 02/21/2013
and claims benefit of 61/803,721 03/20/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 06/10/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/894,244**

Projected Publication Date: Perfected

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific

countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/894,244

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	20 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	730		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

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*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/894,244	05/14/2013	1629	1030	1958603.00021	20	2

CONFIRMATION NO. 1033

45200
K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

FILING RECEIPT

OC000000061834511

Date Mailed: 06/19/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Herriot Tabuteau, New York, NY;

Applicant(s)

Herriot Tabuteau, New York, NY;

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 61/646,538 05/14/2012
and claims benefit of 61/647,478 05/15/2012
and claims benefit of 61/654,292 06/01/2012
and claims benefit of 61/654,383 06/01/2012
and claims benefit of 61/655,527 06/05/2012
and claims benefit of 61/655,541 06/05/2012
and claims benefit of 61/762,225 02/07/2013
and claims benefit of 61/764,563 02/14/2013
and claims benefit of 61/767,647 02/21/2013
and claims benefit of 61/767,676 02/21/2013
and claims benefit of 61/803,721 03/20/2013

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

If Required, Foreign Filing License Granted: 06/10/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/894,244**

Projected Publication Date: 11/14/2013

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

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technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021	1033

45200 7590 06/19/2013

K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

EXAMINER	
ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
06/19/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chicago.patents@klgates.com
maria.nadal@klgates.com

Doc Code: TRACK1.GRANT

Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 13894244

1. THE REQUEST FILED 5/14/2013 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).

B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;

B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;

C. filing a **request for continued examination**;

D. filing a notice of appeal;

E. filing a request for suspension of action;

F. mailing of a notice of allowance;

G. mailing of a final Office action;

H. completion of examination as defined in 37 CFR 41.102; or

I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Mano Padmanabhan at 571-272-4210. In his/her absence, calls may be directed to Kakali Chaki, 571-272-3719.

/Mano Padmanabhan/ Supervisory Patent Examiner, AU2188

First Action Interview Office Action Summary	Application No.	Applicant(s)	
	13/894,244	TABUTEAU, HERRIOT	
	Examiner	Art Unit	Page 1 of 4
	SVETLANA M. IVANOVA	1627	

The MAILING OR NOTIFICATION DATE of this communication appears on the cover sheet with the correspondence address.

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **ONE MONTH OR THIRTY (30) DAYS,** WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.

☒ Applicant's request to not have a first-action interview is acknowledged (or the time period for reply set forth in the Pre-Interview Communication has expired and the Office did not receive any reply).

Status

1) ☒ Responsive to communication(s) filed on *14 May, 2013* and interview conducted on _____.

2) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

3) ☒ Claim(s) *40-61* is/are pending in the application.

3a) Of the above claim(s) _____ is/are withdrawn from consideration.

4) ☐ Claim(s) _____ is/are allowed.

5) ☒ Claim(s) *40-61* is/are rejected.

6) ☐ Claim(s) _____ is/are objected to.

7) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

8) ☐ The specification is objected to by the Examiner.

9) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

10) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

Contact Information

Examiner's Telephone Number: (571)270-3277
Examiner's Typical Work Schedule: Mon.-Fri. 8:30-5:00
Supervisor's Name: Sreenivasan Padmanabhan
Supervisor's Telephone Number: (571)272-0629

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/2013*.	4) ☐ Other: _____.

First Action Interview Office Action Summary	Application No. 13/894,244	Applicant(s) TABUTEAU, HERRIOT	
	Examiner SVETLANA M. IVANOVA	Art Unit 1627	Page 2 of 4

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	40-43,57,60,61	EP1127573 to Day et al.	102(b)	Day teaches a composition of a polyphosphonate (zoledronate) and a statin, which is formulated for oral administration, and does not require bioavailability-enhancing agents, which is 10-1000 microg/kg (i.e. 0.7-70 mg
				for a 70 kg man), and can be formulated with water. (para [0035],[0037],[0038],[0060],[0061]). Such a formulation will inherently possess the bioavailability, aqueous solubility of Applicant's claims.
2	40-45,57,60,61	US 2004/0063670	102(b)	Fox teaches an composition of an oral dosage form of zoledronic acid and its sodium salt, and does not require bioavailability-enhancing agents, which is 0.75-700mg for a 75 kg man, and can be with more than one unit
				(para [0063-65],[0070-71],[0079-81]). Such a formulation will inherently possess the bioavailability, aqueous solubility of Applicant's claims
3	44-56	EP1127573, Chandler	103(a)	Day is discussed above. It does not explicly disclose the specific number of units, mg, duration of administration. Chandler discloses guidelines for labeling of unit dosage forms, which guidelines disclose that such

Expanded Discussion/Commentary

1		The following guidance from the specification pertains to the claim 1 limitation "wherein the oral availability of zoledronic acid in the dosage form is about 0.01% to about 4%"- [055]. In accordance with it, the Examiner interprets this limitation as an oral dosage form with very low bioavailability, namely one which is substantially free of bioavailability-enhancing agents.
2		The following guidance from the specification pertains to the claim 1 limitation "wherein the oral availability of zoledronic acid in the dosage form is about 0.01% to about 4%"- [055]. In accordance with it, the Examiner interprets this limitation as an oral dosage form with very low bioavailability, namely one which is substantially free of bioavailability-enhancing agents.
3		Labeling of unit dose packages of drugs, Department of Pharmacy Policy, University of Kentucky Hospital Chandler Medical Center, policy number: PH-04-06, 11/09 ("Chandler").
4		Labeling of unit dose packages of drugs, Department of Pharmacy Policy, University of Kentucky Hospital Chandler Medical Center, policy number: PH-04-06, 11/09 ("Chandler").
		(5, 6, 7) ODP= obviousness-type double patenting

DATE:		

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
				units, strength in mg and duration of administration should be used for labeling drug unit dose packages. Accordingly, it would be obvious to optimize the exact amounts and timing of administration, and prepare unit dosage forms labelling with such information.
4	46-56	US20040063670 ,Chandler	103(a)	Fox is discussed above. It does not explicly disclose the specific number of units, mg, duration of administration. Chandler discloses guidelines for labeling of unit dosage forms, which guidelines disclose that such units, strength in mg and duration of
				administration should be used for labeling drug unit dose packages. Accordingly, it would be obvious to optimize the exact amounts and timing of administration, and prepare unit dosage forms labelling with such information.
5	40-61	13/894,262	ODP	of claims 1-19. In order to practice the method, it is necessary to have possession of the oral dosage form.
6	40-61	13/894,252	ODP	of claims 20-39. In order to practice the method, it is necessary to have possession of the oral dosage form.

Expanded Discussion/Commentary

DATE:		

First Action Interview Office Action Summary	Application No. 13/894,244	Applicant(s) TABUTEAU, HERRIOT	
	Examiner SVETLANA M. IVANOVA	Art Unit 1627	Page 4 of 4

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
7	40-61	13/894,274	ODP	of claims 62-77. In order to practice the method, it is necessary to have possession of the oral dosage form.

Expanded Discussion/Commentary

DATE:	/SVETLANA M. IVANOVA/ Examiner, Art Unit 1627	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13894244	TABUTEAU, HERRIOT
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/15/2013								
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13894244	TABUTEAU, HERRIOT
	Examiner	Art Unit
	SVETLANA M IVANOVA	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	SVETLANA M IVANOVA	1627

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	07/15/2013								
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CONFIRMATION NO. 1033

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/894,244	05/14/2013 RULE	514	1627	1958603.00021

APPLICANTS

Herriot Tabuteau, New York, NY;

**** CONTINUING DATA **************************

This appln claims benefit of 61/646,538 05/14/2012
and claims benefit of 61/647,478 05/15/2012
and claims benefit of 61/654,292 06/01/2012
and claims benefit of 61/654,383 06/01/2012
and claims benefit of 61/655,527 06/05/2012
and claims benefit of 61/655,541 06/05/2012
and claims benefit of 61/762,225 02/07/2013
and claims benefit of 61/764,563 02/14/2013
and claims benefit of 61/767,647 02/21/2013
and claims benefit of 61/767,676 02/21/2013
and claims benefit of 61/803,721 03/20/2013

**** FOREIGN APPLICATIONS **************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
06/10/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /SVETLANA M IVANOVA/ Examiner's Signature	☐ Met after Allowance si Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	8	20	2

ADDRESS

K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614
UNITED STATES

TITLE

Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

FILING FEE RECEIVED		
1030	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	4	("20040063670" | "20100215743" | "20110028435" | "20120190647").PN.	US-PGPUB	OR	ON	2013/07/12 17:16
S2	2	"1127573"	US-PGPUB; EPO	OR	ON	2013/07/12 17:29

EAST Search History (Interference)

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	Examiner	Art Unit

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	13894244
Filing Date	2013-05-14
First Named Inventor	Tabuteau
Art Unit	N/A
Examiner Name	N/A
Attorney Docket Number	1958603.00021

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20040063670		2004-04-01	Fox et al.	
	2	20100215743		2010-08-26	Leonard	
	3	20110028435		2011-02-03	Hanna et al.	
	4	20120190647		2012-07-26	Hanna et al.	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Tabuteau
	Art Unit	N/A
	Examiner Name	N/A
	Attorney Docket Number	1958603.00021

	1	2005/107751	WO	A1	2005-11-17	Merck & Co., Inc.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	BERTORELLI et al., Nociceptin and the ORL-1 ligand [Phe1(CH2-NH)Gly2]nociceptin(1-13)NH2 exert anti-opioid effects in the Freund's adjuvant-induced arthritic rat model of chronic pain. British Journal of Pharmacology (1999) 128, 1252-1258.	☐
	2	BINGHAM III et al., Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medical compartment osteoarthritis of the knee. Arthritis & Rheumatism, Vol. 54, No. 11, 2006, 3494-3507.	☐
	3	CULLEN et al., MER-101: A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae. Poster Presentation, November 2007. not reviewed due to very small illegible font /S.I./	☐
	4	DE CASTRO et al., Zoledronic acid to treat complex regional pain syndrome type I in adult (case report). Rev. Dor. Sao Paulo, 2011, 12(1): 71-73.	☐
	5	EU Product Label for Zometa, accessed 2013.	☐
	6	GILES, Risedronate not an Effective Disease Modifier in Knee Osteoarthritis. Arthritis News (website) 2006. Accessed at http://www.hopkinsarthritis.org/arthritis-news/risedronate-not-an-effective-disease-modifier-in-knee-osteoarthritis.	☐
	7	GUO et al., Substance P signaling contributes to the vascular and nociceptive abnormalities observed in a tibial fracture rat model of complex regional pain syndrome type I. Pain 108 (2004) 95-107.	☐
	8	KINGERY et al., A substance P receptor (NK1) antagonist can reverse vascular and nociceptive abnormalities in a rat model of complex regional pain syndrome type II. Pain 104 (2003) 75-84.	☐

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	Examiner Name	N/A
	Attorney Docket Number	1958603.00021

	9	LASLETT, Extended report: Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomized controlled trial. Ann. Rheum. Dis. 2012, 71: 1322-1328.	☐
	10	~~LEONARD et al., MER-101 Tablets: A pilot bioavailability study of a novel oral formulation of zoledronic acid. Poster Presentation, October 2007.~~ not reviewed due to very small illegible font /S.I./	☐
	11	~~LEONARD et al., Safety Profile of Zoledronic acid in a novel oral formulation. Poster Presentation, November 2009.~~ not reviewed due to very small illegible font /S.I./	☐
	12	~~LEONARD et al., Studies of bioavailability and food effects of MER-101 Zoledronic Acid Tablets in Postmenopausal Women. Poster Presentation, October 2009.~~ not reviewed due to very small illegible font /S.I./	☐
	13	~~MCHUGH et al., MER-101-03, A multi center, phase II study to compare MER-101 20mg tablets to intravenous Zometa 4mg in prostate cancer patients. Poster Presentation, May 2009.~~ not reviewed due to very small illegible font /S.I./	☐
	14	NAGAE et al., Acidic microenvironment created by osteoclasts causes bone pain associated with tumor colonization. J. Bone Miner. Metab. (2007) 25: 99-104.	☐
	15	NAGAE et al., Osteoclasts play a part in pain due to the inflammation adjacent to bone. Bone 39 (2006) 1107-1115.	☐
	16	NAGAKURA et al., Allodynia and hyperalgesia in adjuvant-induced arthritic rats: time course of progression and efficacy of analgesics. The Journal of Pharmacology and Experimental Therapeutics 306: 490-497, 2003.	☐
	17	ORAZOL(R): Novel approach to adjuvant therapy for improving outcomes in breast cancer. Merrion Pharmaceuticals, accessed 2013.	☐
	18	REID et al., Intravenous Zoledronic Acid in Postmenopausal Women with Low Bone Mineral Density. N. Engl. J. Med., Vol. 346, No. 9, 2002.	☐
	19	RINGE et al., A review of bone pain relief with ibandronate and other bisphosphonates in disorders of increased bone turnover. Clin. Exp. Rheumatol. 2007; 25: 766-774.	☐

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	Examiner Name	N/A
	Attorney Docket Number	1958603.00021

	20	Study: The Use of Zoledronic Acid to Complex Regional Pain Syndrome (Aclasta) sponsored by University of Sao Paulo General Hospital. 2012. Clinical Trials.gov. Accessed on April 5, 2013 at http://clinicaltrials.gov/ct2/show/ NCT01788176.	☐
	21	US Product Label for Zometa, accessed 2013.	☐
	22	WALKER et al., Disease modifying and anti-nociceptive effects of the bisphosphonate, zoledronic acid in a model of bone cancer pain. Pain 100 (2002) 219-229.	☐
	23	ZASPEL et al., Treatment of early stage CRPS I - cortisone (methylprednisolone) versus bisphosphonate (zoledronic acid). German Congress of Orthopedics and Traumatology. 71st Annual Meeting of the German Society of Trauma Surgery, 93rd Meeting of the German Society for Orthopedics and Orthopedic Surgery, 48th Meeting of the Professional Association of Specialists in Orthopedics. Berlin, October 24-27, 2007. German Medical Science GMS Publishing House; 2007.	☐
	24	Zoledronate Disodium: Treatment of Tumor-Induced Hypercalcemia Angiogenesis Inhibitor, Drugs of the Future 2000, 25(3) 259-268.	☐
	25	Zometa FDA Pharmacology Review, part 1, accessed 2013.	☐
	26	Zometa FDA Pharmacology Review, part 2, accessed 2013.	☐
	27	Zometa FDA Pharmacology Review, part 3, accessed 2013.	☐
	28	Zometa FDA Pharmacology Review, part 4, accessed 2013.	☐
	29	Zometa FDA Pharmacology Review, part 5, accessed 2013.	☐
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	Filing Date	2013-05-14
	First Named Inventor	Tabuteau
	Art Unit	N/A
	Examiner Name	N/A
	Attorney Docket Number	1958603.00021

EXAMINER SIGNATURE			
Examiner Signature	/Svetlana Ivanova/	Date Considered	07/12/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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	Filing Date	2013-05-14
	First Named Inventor	Tabuteau
	Art Unit	N/A
	Examiner Name	N/A
	Attorney Docket Number	1958603.00021

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Brent A. Johnson/	Date (YYYY-MM-DD)	2013-05-15
Name/Print	Brent A. Johnson	Registration Number	51851

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Patent US5264222 - Oral pharmaceutical compositions in unit ...
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In vivo evaluation of a theophylline oral controlled-release unit ...
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IVANOVA, SVETLANA M	
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	Examiner SVETLANA M. IVANOVA	Art Unit 1627	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-2004/0063670	04-2004	Fox et al.	514/102
*	B	US-13/894,274	05-2013	Tabuteau	514/249
*	C	US-13/894,262	05-2013	Tabuteau	514/249
*	D	US-13/894,252	05-2013	Tabuteau	514/108
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FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	EP 1127573 A1	08-2001	European Patent	DAY et al.	
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	P					
	Q					
	R					
	S					
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NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Labeling of unit dose packages of drugs, Department of Pharmacy Policy, University of Kentucky Hospital Chandler Medical Center, policy number: PH-04-06, 11/09
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	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
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(54) Compostitions and methods for treating osteoporosis

(57) This invention relates to methods, pharmaceutical compositions and kits useful in promoting bone formation and/or preventing bone loss and/or treating atherosclerosis. The compositions are comprised of a polyphosphonate as a first active component and a statin as a second active component and a pharmaceutically acceptable vehicle, carrier or diluent.

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Description

FIELD OF THE INVENTION

[0001] This invention relates to pharmaceutical compositions comprising combinations of polyphosphonates and statins, and pharmaceutically acceptable salts thereof, kits comprising such combinations and methods of using such combinations to prevent bone loss and/or promote bone formation and/or treat atherosclerosis. The compositions and methods are useful for treating subjects suffering from osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease, metastatic bone disease, osteolytic bone disease, or undergoing orthopedic or oral surgery.

BACKGROUND OF THE INVENTION

[0002] A variety of disorders in humans and other mammals involve or are associated with abnormal bone resorption. Such disorders include, but are not limited to, osteoporosis, Paget's disease, periprosthetic bone loss or osteolysis, metastatic bone disease, hypercalcemia of malignancy, multiple myeloma, periodontal disease, and tooth loss. The most common of these disorders is osteoporosis, which in its most frequent manifestation occurs in postmenopausal women. Osteoporosis is a systemic skeletal disease characterized by a low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Because osteoporosis, as well as other disorders associated with bone loss, are chronic conditions, it is believed that appropriate therapy will generally require chronic treatment.

[0003] Multinucleated cells called osteoclasts are responsible for causing bone loss through a process known as bone resorption. Polyphosphonates are selective inhibitors of osteoclastic bone resorption, making these compounds important therapeutic agents in the treatment or prevention of a variety of generalized or localized bone disorders caused by or associated with abnormal bone resorption. See H. Fleisch, Bisphosphonates In Bone Disease, From The Laboratory To The Patient, 2nd Edition, Parthenon Publishing (1995).

[0004] At present, a great amount of preclinical and clinical data exists for the polyphosphonate compound alendronate. Evidence suggests that other polyphosphonates such as risedronate, tiludronate, ibandronate and zolendronate, have many properties in common with alendronate, including high potency as inhibitors of osteoclastic bone resorption. An older polyphosphonate compound, etidronate, also inhibits bone resorption. However, unlike the more potent polyphosphonates, etidronate impairs mineralization at doses used clinically, and may give rise to osteomalacia, a condition resulting in an undesirable decrease in bone mineralization (Boyce, B. F., Fogelman, I., Ralston, S. et al. Lancet 1984;8381:821-824, and Gibbs, C. J., Aaron, J. E.; Peacock, M., Br. Med. J., 1986;292:1227-1229.

[0005] Statins exhibit a bone-forming effect in addition to a cholesterol-lowering effect. Statins inhibit the enzyme HMG-CoA reductase that catalyzes the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate in an early and rate-limiting step in the cholesterol biosynthetic pathway. It is believed that this effect is responsible for statins being considered as potent lipid lowering agents. The bone-forming effect of statins may be due to their ability to increase bone formation rate possibly through the stimulation of growth factors such as bone morphogenic protein-2 (BMP-2) (Mundy, G., et al., Science, 1999;286:1946-1949).

[0006] Statins include such compounds as simvastatin, disclosed in U.S. 4,444,784; pravastatin, disclosed in U.S. 4,346,227; cerivastatin, disclosed in U.S. 5,502,199; mevastatin, disclosed in U.S. 3,983,140; velostatin, disclosed in U.S. 4,448,784 and U.S. 4,450,171; fluvastatin, disclosed in U.S. 4,739,073; compactin, disclosed in U.S. 4,804,770; lovastatin, disclosed in U.S. 4,231,938; dalvastatin, disclosed in European Patent Application Publication No. 738510 A2; fluindostatin, disclosed in European Patent Application Publication No. 363934 A1; atorvastatin, disclosed in U.S. Patent No. 4,681,893; atorvastatin hemicalcium salt, disclosed in U.S. Patent No. 5,273,995; dihydrocompactin, disclosed in U.S. 4,450,171; ZD-4522, disclosed in U.S. Patent No. 5,260,440; bervastatin, disclosed in U.S. Patent No. 5,082,859; and NK-104, disclosed in U.S. Patent No. 5,102,888.

[0007] Bone is a tissue that is subject to turnover. Bone homeostasis is balanced by the osteoblasts that produce new bone and the osteoclasts that destroy bone. The activities of these cells are regulated by a large number of cytokines and growth factors, many of-which have now been identified and cloned. Mundy has described the current knowledge related to these factors (Mundy, G. R. Clin Orthop 1996;324:24-28; Mundy, G. R. J Bone Miner Res 1993; 8:S505-10).

[0008] Growth factors that stimulate bone formation have been identified. Among these factors are transforming growth factor, the heparin-binding growth factors (acidic and basic fibroblast growth factor), the insulin-like growth factors (insulin-like growth factor I and insulin-like growth factor II), and a recently described family of proteins called bone morphogenetic proteins (BMPs). All of these growth factors have effects on other types of cells, as well as on bone cells. The BMPs are novel factors in the extended transforming growth factor β superfamily. The BMPs were identified by Wozney J. et al. Science 1988;242: 1528-34, following earlier descriptions characterizing the biological

activity in extracts of demineralized bone (Urist M. Science 1965;150: 893-99). Recombinant BMP2 and BMP4 can induce new bone formation when they are injected locally into the subcutaneous tissues of rats (Wozney J. Molec Reprod Dev 1992;32:160-67). These factors are expressed by normal osteoblasts as they differentiate, and have been shown to stimulate osteoblast differentiation and bone nodule formation in vitro as well as bone formation in vivo (Harris S. et al. J. Bone Miner Res 1994;9:855-63).

[0009] As osteoblasts differentiate from precursors to mature bone-forming cells, they express and secrete a number of enzymes and structural proteins of the bone matrix, including Type-1 collagen, osteocalcin, osteopontin and alkaline phosphatase (Stein G. et al. Curr Opin Cell Biol 1990;2:1018-27; Harris S. et al. (1994), supra). They also synthesize a number of growth regulatory peptides which are stored in the bone matrix, and are presumably responsible for normal bone formation. These growth regulatory peptides include the BMPs (Harris S. et al. (1994), supra). In studies of primary cultures of fetal rat calvarial osteoblasts, BMPs 1, 2, 3, 4,and 6 are expressed by cultured cells prior to the formation of mineralized bone nodules (Harris S. et al. (1994), supra). Like alkaline phosphatase, osteocalcin and osteopontin, the BMPs are expressed by cultured osteoblasts as they proliferate and differentiate.

SUMMARY OF THE INVENTION

[0010] This invention relates to pharmaceutical compositions useful for promoting bone formation and/or preventing bone loss and/or treating atherosclerosis. The compositions are comprised of a bone resorption inhibiting polyphosphonate and a statin and, optionally, a pharmaceutically acceptable carrier, vehicle or diluent. The compositions exert an effect which is additive or greater than the sum of the individual effects of the bone resorption inhibiting polyphosphonates and statins when administered separately.

[0011] A second aspect of the invention relates to methods of promoting bone formation and/or preventing bone loss and/or treating atherosclerosis. The methods comprise the administration of an effective amount of the pharmaceutical compositions comprising a bone resorption inhibiting polyphosphonate and a statin as described herein or co-administration of a polyphosphonate and a statin.

[0012] As a third aspect, the present invention provides for kits for use by a consumer to promote bone formation and/or prevent bone loss and/or treat atherosclerosis. The kits comprise: a) a pharmaceutical composition comprising a bone resorption inhibiting polyphosphonate and a pharmaceutically acceptable carrier, vehicle or diluent; b) a pharmaceutical composition comprising a statin and a pharmaceutically acceptable carrier, vehicle or diluent; and, optionally, c) instructions describing a method of using the pharmaceutical compositions for promoting bone formation and/or preventing bone loss and/or treating atherosclerosis. The instructions may also indicate that the kit is for promoting bone formation and/or preventing bone loss and/or treating atherosclerosis or another specific condition related to these effects. The bone resorption inhibiting polyphosphonate and the statin contained in the kit may be optionally combined in the same pharmaceutical composition.

[0013] As a fourth aspect, the present invention provides for the use of bone resorption inhibiting polyphosphonate and statins for the manufacture of a medicament to promote bone formation and/or prevent bone loss and/or treat atherosclerosis.

[0014] A fifth aspect of the invention is that the compositions and methods of the invention can further comprise a histamine H2 receptor blocker (i.e. antagonist) and/or a proton pump blocker.

DETAILED DESCRIPTION OF THE INVENTION

[0015] The present invention relates to compositions and methods for promoting bone formation and/or preventing bone loss and/or treating atherosclerosis. Unless otherwise specified, the following terms have the meanings as defined below:

[0016] As used herein, "limit", "treat" and "treatment" are interchangeable terms as are "limiting" and "treating" and, as used herein, include preventative (e.g., prophylactic) and palliative treatment or the act of providing preventative or palliative treatment. The terms include a postponement of development of bone deficit symptoms and/or a reduction in the severity of such symptoms that will or are expected to develop. The terms further include ameliorating existing bone or cartilage deficit symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, preventing or reversing bone resorption and/or encouraging bone growth. By "bone deficit" is meant an imbalance in the ratio of bone formation to bone resorption, such that, if unmodified, the subject will exhibit less bone than desirable, or the subject's bones will be less intact than desired. Bone deficit may also result from fracture, from surgical intervention or from dental or periodontal disease. By "cartilage defect" is meant damaged cartilage, less cartilage than desired, or cartilage that is less intact than desired. The terms, "limit", "treat" and "treatment and "limiting" and "treating" further include the lowering of existing blood cholesterol levels and the prevention of the elevation of blood cholesterol levels and the symptoms and conditions caused or related to the blood cholesterol levels such as atherosclerosis and hyperlipidemia, or increased cardiac risk and the inhibition of calcification of atherosclerotic

plaques or the stabilization of atherosclerotic plaques.

[0017] Representative uses of the compositions and methods of the present invention include: repair of bone defects and deficiencies, such as those occurring in closed, open and nonunion fractures; prophylactic use in closed and open fracture reduction; promotion of bone healing in plastic surgery; stimulation of bone ingrowth into non-cemented prosthetic joints and dental implants; elevation of peak bone mass in perimenopausal women, treatment of growth deficiencies; treatment of periodontal disease and defects, and other tooth repair processes; increase in bone formation during distraction osteogenesis; and treatment of other skeletal disorders, such as age-related osteoporosis, postmenopausal osteoporosis, glucocorticoid-induced osteoporosis or disuse osteoporosis and arthritis, or any condition that benefits from stimulation of bone formation. The compositions and methods of the present invention can also be useful in repair of congenital, trauma-induced or surgical resection of bone (for instance, for cancer treatment), and in cosmetic surgery. Further, the compositions and methods of the present invention can be used for treating cartilage defects or disorders, and are useful in wound healing or tissue repair. Additionally, the compositions and methods of the present invention can be used to treat atherosclerosis.

[0018] Bone or cartilage deficit or defect and atherosclerosis can be treated in vertebrate subjects by administering the compositions of the invention. The compositions of the invention may be administered systemically or locally. For systemic use, the compounds herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration can be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration can be performed at intervals ranging from weekly to once to three times daily or more. Alternatively, the compositions disclosed herein may be administered in a cyclical manner (administration of disclosed composition, followed by no administration, followed by administration of disclosed compositions, and the like). Treatment will continue until the desired outcome is achieved.

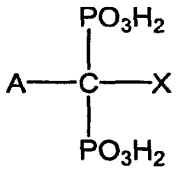
[0019] A "subject" is an animal including a human that is in need of treatment with the compositions, methods and kits of the present invention. The term "subject" or "subjects" is intended to refer to both the male and female gender unless one gender is specifically indicated.

[0020] The term "post-menopausal women" is defined to include not only women of advanced age who have passed through menopause, but also women who have been hysterectomized or for some other reason have suppressed estrogen production, such as those who have undergone long-term administration of corticosteroids, suffer from Cushions' syndrome or have gonadal dysgenesis.

[0021] "Co-administration" of a combination of a statin and a polyphosphonate means that these components can be administered together as a composition or as part of the same, unitary dosage form. "Co-administration" also includes administering a statin and a polyphosphonate separately but as part of the same therapeutic treatment program or regimen. The components need not necessarily be administered at essentially the same time, although they can if so desired. Thus "co-administration" includes, for example, administering a statin and a polyphosphonate as separate dosages or dosage forms, but at the same time. "Co-administration" also includes separate administration at different times and in any order. For example, where appropriate a patient may take one or more component(s) of the treatment in the morning and the one or more of the other component(s) at night.

[0022] A statin and a bone resorption inhibiting polyphosphonate when co-administered either as part of the same pharmaceutical composition or as separate pharmaceutical compositions is/are effective in promoting bone formation and/or preventing bone loss and/or treating atherosclerosis. By producing these effects, the compositions and methods of the invention are suitable for treating a variety of conditions. These conditions include osteoporosis, including age-related osteoporosis and osteoporosis associated with post-menopausal hormone status. Other conditions characterized by the need for bone growth include primary and secondary hyperparathyroidism, disuse osteoporosis, diabetes-related osteoporosis, and glucocorticoid-related osteoporosis. The results of the methods in enhancing bone formation make the compositions and methods useful for bone repair and bone deficit conditions. Such conditions include bone fracture and facial reconstruction surgery and bone segmental defects, periodontal disease, metastatic bone disease, osteolytic bone disease and conditions where connective tissue repair is beneficial, such as healing or regeneration of cartilage defects or injury. Additionally the compositions and methods are useful for treating atherosclerosis and hyperlipidemia and for preventing calcification of atherosclerotic plaques or stabilizing such plaques.

[0023] By "bone resorption inhibiting polyphosphonate" as used herein is meant a polyphosphonate such as the type disclosed in U.S. Patent No. 3,683,080 or formula I below. Preferred polyphosphonates are geminal diphosphonates (also referred to as bisphosphonates). The polyphosphonates may be administered in the form of the acid, or of a soluble alkali metal salt or alkaline earth metal salt. Polyphosphonates of the present invention include those of chemical formula I:



(I)

wherein

[0024] A and X are independently selected from the group consisting of H, OH, halogen, NH_2, SH, phenyl, C_1-C_{30} alkyl, C_1-C_{30} substituted alkyl, C_1-C_{10} alkyl or dialkyl substituted NH_2, C_1-C_{10} alkoxy, C_1-C_{10} alkyl or phenyl substituted thio, C_1 - C_{10} alkyl substituted phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, and benzyl.

[0025] In the foregoing chemical formula, the alkyl groups can be straight, branched, or cyclic. The C_1-C_{30} substituted alkyl can include a wide variety of substituents, nonlimiting examples of which include those selected from the group consisting of phenyl, pyridyl, furanyl, pyrrolidinyl, imidazonyl, NH_2, and C_1-C_{10} alkyl or dialkyl substituted NH_2, OH, SH, and C_1-C_{10} alkoxy.

[0026] In the foregoing chemical formula, A can include X and X can include A such that the two moieties can form part of the same cyclic structure.

[0027] The foregoing chemical formula is also intended to encompass complex carbocyclic, aromatic and hetero atom structures for the A and/or X substituents, nonlimiting examples of which include naphthyl, quinolyl, isoquinolyl, adamantly, and chlorophenylthio.

[0028] Preferred structures are those in which A is selected from the group consisting of H, OH, and halogen, and X is selected from the group consisting of C_1-C_{30} alkyl, C_1-C_{30} substituted alkyl, halogen, and C_1-C_{10} alkyl or phenyl substituted thio.

[0029] More preferred structures are those in which A is selected from the group consisting of H, OH, and Cl, and X is selected from the group consisting of C_1-C_{30} alkyl, C_1-C_{30} substituted alkyl, Cl, and chlorophenylthio.

[0030] Most preferred is when A is OH and X is a 3-aminopropyl moiety, so that the resulting compound is a 4-amino-1-hydroxybutylidene-1,1-bisphosphonate, i.e. alendronate.

[0031] Pharmaceutically acceptable salts and derivatives of the polyphosphonates are also useful herein. Nonlimiting examples of salts include those selected from the group consisting alkali metal, alkaline metal, ammonium, and mono-, di, tri-, or tetra-C_1-C_{30}-alkyl-substituted ammonium.

[0032] Preferred salts are those selected from the group consisting of sodium, potassium, calcium, magnesium, and ammonium salts. Nonlimiting examples of derivatives include those selected from the group consisting of esters, hydrates, and amides.

[0033] The terms "polyphosphonate", "bisphosphonate" and "bisphosphonates", as used herein in referring to the therapeutic agents of the present invention are meant to also encompass diphosphonates, biphosphonic acids, and diphosphonic acids, as well as salts and derivatives of these materials and are examples of bone resorption inhibiting polyphosphonates. The use of a specific nomenclature in referring to the bisphosphonate or bisphosphonates is not meant to limit the scope of the present invention, unless specifically indicated. Because of the mixed nomenclature currently in use by those of ordinary skill in the art, reference to a specific weight or percentage of a polyphosphonate compound in the present invention is on an acid active weight basis, unless indicated otherwise herein.

[0034] Nonlimiting examples of polyphosphonates useful herein include the following:

a) alendronic acid, 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid;

b) alendronate (also known as alendronate sodium or monosodium trihydrate), 4-amino-1-hydroxybutylidene-1,1-bisphosphonic acid monosodium trihydrate;

c) alendronic acid and alendronate are described in U.S. Pat. No. 4,922,007, to Kieczykowski et al., issued May 1, 1990, and U.S. Pat. No. 5,019,651, to Kieczykowski, issued May 28, 1991;

d) cycloheptylaminomethylene-1,1-bisphosphonic add, YM 175, Yamanouchi (cimadronate), as described in U.S. Pat. No. 4,970,335, to Isomura et al., issued Nov. 13, 1990;

e) 1,1-dichloromethylene-1,1-diphosphonic acid (clodronic acid), and the disodium salt (clodronate, Procter and Gamble), are described in Belgium Patent 672,205 (1966) and J. Org. Chem., 1967;32:4111;

f) 1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid (EB-1053);

g) 1-hydroxyethane-1,1-diphosphonic acid (etidronic acid);

h) 1-hydroxy-3-(N-methyl-N-pentylamino)propylidene-1,1-bisphosphonic acid, also known as BM-210955, Boehringer-Mannheim (ibandronate), is described in U.S. Pat. No. 4,927,814, issued May 22, 1990;

i) 6-amino-1-hydroxyhexylidene-1,1-bisphosphonic acid (neridronate);

j) 3-(dimethylamino)-1-hydroxypropylidene-1,1-bisphosphonic acid (olpadronate);
k) 3-amino-1-hydroxypropylidene-1,1-bisphosphonic acid (pamidronate);
l) [2-(2-pyridinyl)ethylidene]- 1,1 -bisphosphonic acid (piridronate) as described in U.S. Pat. No. 4,761,406;
m) 1-hydroxy-2-(3-pyridinyl)-ethylidene-1,1-bisphosphonic acid (risedronate);
n) (4-chlorophenyl)thiomethane-1,1-disphosphonic acid (tiludronate) as described in U.S. Pat. No. 4,876,248, to Breliere et al., Oct. 24, 1989; and
o) 1-hydroxy-2-(1H-imidazol-1-yl)ethylidene-1,1-bisphosphonic acid (zolendronate).

[0035] Preferred are polyphosphonates selected from the group consisting of alendronate, cimadronate, clodronate, tiludronate, etidronate, ibandronate, risedronate, piridronate, pamidronate, zolendronate, pharmaceutically acceptable salts thereof, and mixtures thereof.

[0036] More preferred is alendronate, pharmaceutically acceptable salts thereof, and mixtures thereof with alendronate monosodium trihydrate being the most preferred.

[0037] The precise dosage of the polyphosphonate will vary with the dosing schedule, the oral potency of the particular polyphosphonate chosen, the age, size, sex and condition of the mammal, the nature and severity of the disorder to be treated, and other relevant medical and physical factors. Thus, a precise pharmaceutically effective amount cannot be specified in advance and can be readily determined by the caregiver or clinician.

[0038] Generally, an appropriate amount of polyphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of the polyphosphonate is administered. For humans, an effective oral dose of polyphosphonate is typically from about 1.5 to about 6000 μg/kg body weight and preferably about 10 to about 2000 μg/kg of body weight.

[0039] For human oral compositions comprising alendronate, a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable derivative thereof, a unit dosage typically comprises from about 8.75 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis.

[0040] For once-weekly dosing, an oral unit dosage comprises from about 17.5 mg to about 70 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 35 mg of the alendronate compound, and a unit dosage which is useful for treating osteoporosis comprising about 70 mg of the alendronate compound.

[0041] For twice-weekly dosing, an oral unit dosage comprises from about 8.75 mg to about 35 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of twice-weekly oral dosages include a unit dosage which is useful for osteoporosis prevention comprising about 17.5 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising about 35 mg of the alendronate compound.

[0042] For biweekly or twice-monthly dosing, an oral unit dosage comprises from about 35 mg to about 140 mg of the alendronate compound, on an alendronic acid active weight basis. Examples of biweekly or twice-monthly oral dosages include a unit dosage which is useful for useful for osteoporosis prevention comprising about 70 mg of the alendronate compound, and a unit dosage which is useful for osteoporosis treatment, comprising. about 140 mg of the alendronate compound.

[0043] In further embodiments, the methods and compositions of the present invention can also comprise a histamine H_2 receptor blocker (i.e. antagonist) and/or a proton pump inhibitor. Histamine H_2 receptor blockers and proton pump inhibitors are well known therapeutic agents for increasing gastric pH. See L. J. Hixson, et al., Current Trends in the Pharmacotherapy for Peptic Ulcer Disease, Arch. Intern. Med., 1992;152:726-732. It is found in the present invention that the sequential oral administration of a histamine H_2 receptor blocker and/or a proton pump inhibitor, followed by a polyphosphonate can help to further minimize adverse gastrointestinal effects. In these embodiments, the histamine H_2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 24 hours prior to the administration of the polyphosphonate. In more preferred embodiments, the histamine H_2 receptor blocker and/or proton pump inhibitor is administered from about 30 minutes to about 12 hours prior to the administration of the polyphosphonate.

[0044] The dosage of the histamine H_2 receptor blocker and/or proton pump inhibitor will depend upon the particular compound selected and factors associated with the mammal to be treated, i.e. size, health, etc.

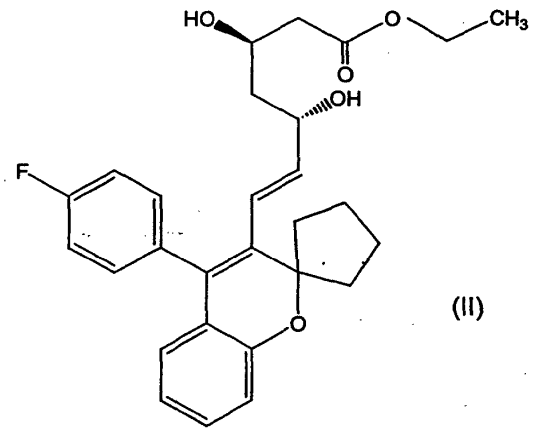
[0045] Nonlimiting examples of histamine H_2 receptor blockers and/or proton pump inhibitors include those selected from the group consisting of cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansoprazole.

[0046] The other active component of the combinations of this invention is a statin. The term "statin", where used in the description and the appendant claims, is synonymous with the terms "3-hydroxy-3-methylglutaryl-Coenzyme A reductase inhibitor" and "HMG-CoA reductase inhibitor." These three terms are used interchangeably throughout the description and appendant claims. As the synonyms suggest, statins are inhibitors of 3-hydroxy-3-methylglutaryl-Coenzyme A reductase and as such are effective in lowering the level of blood plasma cholesterol and promoting bone formation. Statins and pharmaceutically acceptable salts thereof are particularly useful in preventing bone loss and/or promoting bone formation and in lowering low density lipoprotein cholesterol (LDL-C) levels in mammals and particularly

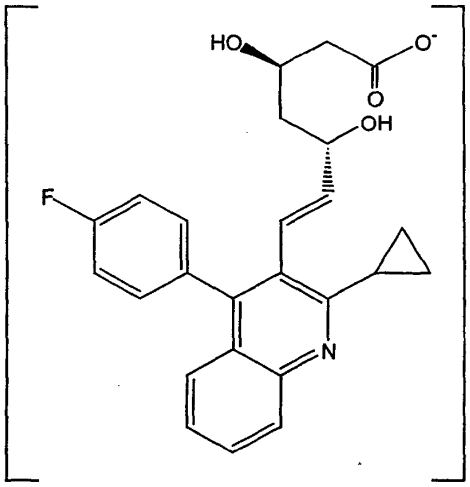
in humans.

[0047] The statins suitable for use herein include, but are not limited to, simvastatin, pravastatin, cerivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, lovastatin, atorvastatin, bervastatin, NK-104 and ZD-4522 and pharmaceutically acceptable salts thereof.

[0048] The statins disclosed herein are prepared by methods well known to those skilled in the art. Specifically, simvastatin may be prepared according to the method disclosed in U.S. 4,444,784. Pravastatin may be prepared according to the method disclosed in U.S. 4,346,227. Cerivastatin may be prepared according to the method disclosed in U.S. 5,502,199. Cerivastatin may alternatively be prepared according to the method disclosed in European Patent Application Publication No. EP617019. Mevastatin may be prepared according to the method disclosed in U.S. 3,983,140. Velostatin may be prepared according to the methods disclosed in U.S. 4,448,784 and U.S. 4,450,171. Fluvastatin may be prepared according to the method disclosed in U.S. 4,739,073. Compactin may be prepared according to the method disclosed in U.S. 4,804,770. Lovastatin may be prepared according to the method disclosed in U.S. 4,231,938. Dalvastatin may be prepared according to the method disclosed in European Patent Application Publication No. EP738510. Fluvastatin may be prepared according to the method disclosed in European Patent Application Publication No. EP363934. Dihydrocompactin may be prepared according to the method disclosed in U.S. 4,450,171. Atorvastatin may be prepared according to the methods disclosed in U.S. 4,681,893 and U.S. 5,273,995. Bervastatin, as shown in formula II below, may be prepared according to the methods disclosed in U.S. Patent No. 5,082,859. NK-104, as shown in formula III below, may be prepared by the methods disclosed in U.S. Patent No. 5,102,888. ZD-4522, shown in formula IV below, may be prepared by the methods disclosed in U.S. Patent No. 5,260,440.

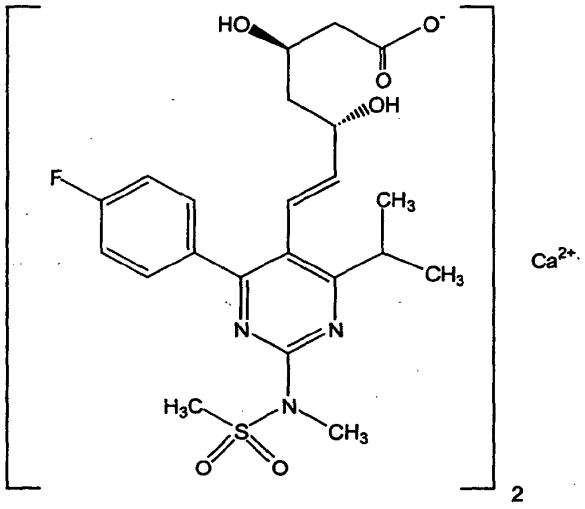


(II)



Ca^{2+}

(III)



(IV)

[0049] It will be recognized that certain of the above bone resorption inhibiting polyphosphonates and statins contain either a free carboxylic acid or a free amine group as part of the chemical structure. Further, certain polyphosphonates and statins within the scope of this invention contain lactone moieties, which exist in equilibrium with the free carboxylic acid form. These lactones can be maintained as carboxylates by preparing pharmaceutically acceptable salts of the lactone. Thus, this invention includes pharmaceutically acceptable salts of those carboxylic acids or amine groups. The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. "Pharmaceutically acceptable salts" further include mutual salts formed between statins and polyphosphonates. The expression "pharmaceutically-acceptable cationic salts" is intended to define but is not limited to such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g. calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically-acceptable acid addition salts" is intended to define but is not limited to such salts as the hydrochloride, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

[0050] The pharmaceutically-acceptable cationic salts of statins and polyphosphonates containing free carboxylic acids may be readily prepared by reacting the free acid form of the statin and/or polyphosphonate with an appropriate base, usually one equivalent, in a co-solvent. Typical bases are sodium hydroxide, sodium methoxide, sodium ethoxide, sodium hydride, potassium methoxide, magnesium hydroxide, calcium hydroxide, benzathine, choline, diethanolamine, piperazine and tromethamine. The salt is isolated by concentration to dryness or by addition of a non-solvent. In many cases, salts are preferably prepared by mixing a solution of the acid with a solution of a different salt of the cation (sodium or potassium ethylhexanoate, magnesium oleate), employing a solvent (e.g., ethyl acetate) from which the desired cationic salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent. In this manner, mutual salts of the statins may also be prepared with polyphosphonates.

[0051] The pharmaceutically acceptable acid addition salts of statins and polyphosphonates containing free amine groups may be readily prepared by reacting the free base form of the statin and/or polyphosphonate with the appropriate acid. When the salt is of a monobasic acid (e.g., the hydrochloride, the hydrobromide, the p-toluenesulfonate, the acetate), the hydrogen form of a dibasic acid (e.g., the hydrogen sulfate, the succinate) or the dihydrogen form of a tribasic acid (e.g., the dihydrogen phosphate, the citrate), at least one molar equivalent and usually a molar excess of the acid is employed. However when such salts as the sulfate, the hemisuccinate, the hydrogen phosphate or the phosphate are desired, the appropriate and exact chemical equivalents of acid will generally be used. The free base and the acid are usually combined in a co-solvent from which the desired salt precipitates, or can be otherwise isolated by concentration and/or addition of a non-solvent. Mutual salts of statins and polyphosphonates can be similarly prepared in this manner: For example, the mutual salt of atorvastatin and alendronic acid.

[0052] One of ordinary skill in the art will recognize that certain bone resorption inhibiting polyphosphonates and

statins of this invention will contain one or more atoms which may be in a particular stereochemical, tautomeric, or geometric configuration, giving rise to stereoisomers, tautomers and configurational isomers. All such isomers and mixtures thereof are included in this invention. Hydrates and solvates of the compounds of this invention are also included.

[0053] The subject invention also includes isotopically-labeled bone resorption inhibiting polyphosphonates and statins, which are structurally identical to those disclosed above, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl, respectively. Compounds of the present invention, derivatives thereof, and pharmaceutically acceptable salts of said compounds and of said derivatives which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention and derivatives thereof can generally be prepared by carrying out known or referenced procedures and by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

[0054] Those of ordinary skill in the art will recognize that physiologically active compounds which have accessible hydroxy groups are frequently administered in the form of pharmaceutically acceptable esters. The compounds of this invention can be effectively administered as an ester, formed on the hydroxy groups, just as one skilled in pharmaceutical chemistry would expect. It is possible, as has long been known in pharmaceutical chemistry, to adjust the rate or duration of action of the compound by appropriate choices of ester groups.

[0055] Certain ester groups are preferred as constituents of the compounds of this invention. The statins and/or compounds of formula I, II, III or IV may contain ester groups at various positions as defined herein above, where these groups are represented as $-COOR^{9}$, R^{9} is C_1 -C_{14} alkyl, C_1 -C_3 chloroalkyl, C_1 -C_3 fluoroalkyl, C_5 -C_7 cycloalkyl, phenyl, or phenyl mono- or disubstituted with C_1 -C_4 alkyl, C_1 -C_4 alkoxy, hydroxy, nitro, chloro, fluoro or tri(chloro or fluoro) methyl.

[0056] As used herein, the term "effective amount" means an amount of compound of the compositions, kits and methods of the present invention that is capable of treating the symptoms of the described conditions. The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the state of being of the patient, and the severity of the condition being treated.

[0057] The dose of a compound of this invention to be administered to a subject is rather widely variable and subject to the judgement of the attending physician. It should be noted that it may be necessary to adjust the dose of a compound when it is administered in the form of a salt, such as a laureate, the salt forming moiety of which has an appreciable molecular weight.

[0058] The following dosage amounts and other dosage amounts set forth elsewhere in this description and in the appendant claims are for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a subject whose weight falls outside the 65 kg to 70 kg range, based upon the medical history of the subject and the presence of diseases, e.g., diabetes, in the subject. Calculation of the dosage amount for other forms of the free base form such as salts or hydrates is easily accomplished by performing a simple ratio relative to the molecular weights of the species involved.

[0059] In general, in accordance with this invention, representative statins are administered in the following daily dosage amounts:

simvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg;
pravastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 40 mg;
cerivastatin, generally about 25μg to about 5 mg and preferably about 1 mg to about 3.2 mg;
fluvastatin, generally about 2.5 mg to about 160 mg and preferably about 20 mg to about 80 mg;
lovastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 80 mg; and
atorvastatin, generally about 2.5 mg to about 160 mg and preferably about 10 mg to about 80 mg.

[0060] In general, the pharmaceutical compositions will include a bone resorption inhibiting polyphosphonate as a first active ingredient and a statin as a second active ingredient in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water, borate-buffered saline containing trace metals or the like. Formulations may further include one or more excipients, preservatives, solubilizers, buffering agents, lubricants,

fillers, stabilizers, etc. Methods of formulation are well known in the art and are disclosed, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Pharmaceutical compositions for use within the present invention can be in the form of sterile, non-pyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art. The oral compositions may also include an H_2 histamine receptor blocker and/or a proton pump inhibitor. Local administration may be by injection at the site of injury or defect, or by insertion or attachment of a solid carrier at the site, or by direct, topical application of a viscous liquid, or the like. For local administration, the delivery vehicle preferably provides a matrix for the growing bone or cartilage, and more preferably is a vehicle that can be absorbed by the subject without adverse effects.

[0061] The active ingredient compounds are known to be absorbed from the alimentary tract, and so it is usually preferred to administer a compound orally for reasons of convenience. However, the compounds may equally effectively be administered percutaneously, locally at the site of injury or as suppositories for absorption by the rectum or vagina, if desired in a given instance. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, troches, suppositories and suspensions. Compositions are formulated to contain a daily dose, or a convenient fraction of daily dose, in a dosage unit, which may be a single tablet or capsule or convenient volume of a liquid.

[0062] Capsules are prepared by mixing the compound or compounds with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

[0063] Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound or compounds. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidine and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

[0064] A lubricant may be necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

[0065] Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound or compounds. They include starches, clays, celluloses, algins and gums, more particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used as well as sodium lauryl sulfate.

[0066] Tablets are often coated with sugar as a flavor and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets, by using relatively large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established in the art.

[0067] When it is desired to administer a compound as a suppository, the typical bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

[0068] The effect of the compounds may be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the compound may be prepared and incorporated in a tablet or capsule. The technique may be improved by making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules may be coated with a film which resists dissolution for a predictable period of time. Even the parenteral preparations may be made long-acting by dissolving or suspending the compound or compounds in oily or emulsified vehicles which allow dispersion slowly in the serum.

[0069] The combinations of this invention may be administered in a controlled release formulation such as a slow release or a fast release formulation. Such controlled release formulations of the combination of this invention may be prepared using methods well known to those skilled in the art. The method of administration will be determined by the attendant physician or other person skilled in the art after an evaluation of the subject's condition and requirements.

[0070] The term "prodrug" means compounds that are transformed in vivo to yield a compound of the present invention. The transformation may occur by various mechanisms, such as through hydrolysis in blood. A good discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the *A.C.S. Symposium Series,* and in *Bioreversible Carriers in Drug Design,* ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987. The term, "prodrug" also encompasses mutual prodrugs in which one or more statins are combined with one or more polyphosphonates in a single molecule that may then undergo transformation to yield the statins and polyphosphonates of the present invention.

[0071] For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug

can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_1-C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di(C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl.

[0072] Similarly, if a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6) alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[0073] If a compound of the present invention comprises an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R^X-carbonyl, R^XO-carbonyl, $NR^XR^{X'}$-carbonyl where R^X and $R^{X'}$ are each independently ((C_1-C_{10})alkyl, (C_3-C_7)cycloalkyl, benzyl, or R^X-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl, -C(OH)C(O)OY^X wherein (Y^X is H, (C_1-C_6)alkyl or benzyl), -C(OY^{X0}) Y^{X1} wherein Y^{X0} is (C_1-C_4) alkyl and Y^{X1} is ((C_1-C_6)alkyl, carboxy(C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N- or di-N,N-(C_1-C_6)alkylaminoalkyl, -C(Y^{X2}) Y^{X3} wherein Y^{X2} is H or methyl and Y^{X3} is mono-N- or di-N,N-(C_1-C_6) alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

[0074] Advantageously, the present invention also provides kits for use by a consumer for promoting bone formation and/or preventing bone loss and/or treating atherosclerosis. The kits comprise a) a pharmaceutical composition comprising a bone resorption inhibiting polyphosphonate and a pharmaceutically acceptable carrier, vehicle or diluent; b) a pharmaceutical composition comprising a statin and a pharmaceutically acceptable carrier, vehicle or diluent; and, optionally, c) instructions describing a method of using the pharmaceutical compositions for promoting bone formation and/or preventing bone loss and/or treating atherosclerosis. The polyphosphonate and the statin contained in the kit may be optionally combined in the same pharmaceutical composition.

[0075] A "kit" as used in the instant application includes a container for containing the pharmaceutical compositions such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

[0076] An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0077] It maybe desirable to provide a written memory aid, where the written memory aid is of the type containing information and/or instructions for the physician, pharmacist or subject, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested or a card which contains the same type of information. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday,"... etc.... "Second Week, Monday, Tuesday,..." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. Also a daily dose of one or more component(s) of the kit can consist of one tablet or capsule while a daily dose of another one or more component(s) of the kit can consist of several tablets or capsules.

[0078] Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time in the order of their intended use. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

[0079] Based on a reading of the present description and claims, certain modifications to the compositions and methods described herein will be apparent to one of ordinary skill in the art. The claims appended hereto are intended to encompass these modifications.

[0080] All references and patents cited herein are incorporated by reference.

EXAMPLES

Example 1: Effect of Bone Resorption Inhibiting Polyphosphonates and Statins in the Ovariectomized Rat Model: A Model of Post-Menopausal Osteoporosis.

[0081] In women, estrogen deficiency during the menopause results in increased bone turnover leading to bone loss. Ovariectomy in rats produces estrogen deficiency and increased bone turnover leading to trabecular bone loss similar to that observed in post-menopausal women (Kalu, D.N., Bone and Mineral 1991;15:175; Frost, H.M., Jee W.S.S., Bone and Mineral 1992;18:227; Wronski, T.J., Yen, C-F, Cells Materials 1991;(suppl. 1):69). The OVX rat is thus an appropriate model to evaluate compounds for the prevention and treatment of post-menopausal osteoporosis. The ability of bone resorption inhibiting polyphosphonates and statins alone and in combination to inhibit estrogen deficiency bone loss is assessed in OVX rats, since ovariectomy causes significant bone loss in the lumbar vertebrae, proximal tibia, and distal femoral metaphyses (Ke, H.Z., et al., Endocrin 1995;136:2435; Chen, H.K., et al., J Bone Miner Res 1995:10:1256).

[0082] Seventy-five day old female Sprague Dawley rats (weight range of 225 to 275 g) are obtained from Charles River Laboratories (Portage, Mich.). They are housed in groups of 3 and have ad libitum access to food (calcium content approximately 1%) and water. Room temperature is maintained at 22.2° ± 1.7°C. with a minimum relative humidity of 40%. The photoperiod in the room is 12 hours light and 12 hours dark. One week after arrival, the rats undergo bilateral ovariectomy under anesthesia (44 mg/kg Ketamine™ and 5 mg/kg Xylazine™ (Butler, Indianapolis, Ind.) administered intramuscularly). Treatment with vehicle or the test compositions is initiated either on the day of surgery following recovery from anesthesia or 35 days following the surgery. The rats are treated either with vehicle containing bone resorption inhibiting polyphosphonate or statin or bone resorption inhibiting polyphosphonate and statin or with vehicle only. Oral dosage is by gavage in 0.5 mL of pH-adjusted 1% carboxymethylcellulose (CMC). Body weight is determined at the time of surgery and weekly during the study, and the dosage is adjusted with changes in body weight. Vehicle-treated ovariectomized (OVX) rats and non-ovariectomized (intact) rats are evaluated in parallel with each experimental group to serve as negative and positive controls. The rats are treated daily for 35 days (6 rats per treatment group) and sacrificed by decapitation on the 36th day. The 35-day time period is sufficient to allow maximal reduction in bone density, measured as described below. At the time of sacrifice, the uteri are removed, dissected free of extraneous tissue, and the fluid contents are expelled before determination of wet weight in order to confirm estrogen deficiency associated with complete ovariectomy. Uterine weight is routinely reduced about 75% in response to ovariectomy. The uteri are then placed in 10% neutral buffered formalin to allow for subsequent histological analysis.

[0083] Calcein at 10 mg/kg is injected s.c. to all rats 12 and 2 days before necropsy as a fluorochrome bone marker to measure bone dynamic histomorphometric parameters. The effects of polyphosphonate, statin and combination polyphosphonate and statin on the following end points are determined: (a) serum osteocalcin, a biochemical marker of bone turnover, (b) bone mineral density of lumbar vertebrae and distal femoral metaphyses, (c) bone histomorphometry of fifth lumbar vertebral body and proximal tibial metaphyses.

[0084] For the measurement of the endpoints, serum osteocalcin concentration is determined by radioimmunoassay assays known in the art, and bone mineral content (BMC) and bone mineral density (BMD) are measured by standard procedures as described below:

[0085] The first to the sixth lumbar vertebrae from each rat are removed during necropsy. These were then scanned *ex vivo* using dual-energy X-ray absorptiometry. The scan images are analyzed, and bone area, BMC, and BMD of whole lumbar vertebrae (WLV), and LV1 through LV6 is determined.

[0086] Using dual-energy X-ray absorptiometry, the right femur of each rat is scanned *ex vivo.* Bone mineral density (BMD) of the distal femoral metaphyses (second 0.5 cm from the distal end of femur) and the proximal femur (the first 0.5 cm from the proximal end of femur, which contains the femoral head, neck, and greater trochanter) is determined. In order to determine the effects of polyphosphonates and statins on long bone metaphyses, histomorphometric analyses are performed on the proximal tibiae.

Example 2: Reduction of Cholesterol levels of 0.2% Cholesterol-Fed New-Zealand White Rabbits

[0087] New Zealand White rabbits (female, aged 3-4 months, weighing less than 3 Kg), six in each group, are fed a control diet of 0.2% cholesterol (100 g rabbit chow daily containing 0.2 g cholesterol) or a diet of 0.2% cholesterol and a pharmaceutical composition containing a bone resorption inhibiting polyphosphonate or a diet of 0.2% cholesterol and a pharmaceutical composition containing a statin or a diet of 0.2% cholesterol and a pharmaceutical composition containing a bone resorption inhibiting polyphosphonate and a statin at a dose equivalent to the doses of the polyphosphonate and statin administered to the groups receiving diet containing only polyphosphonate and only statin. After 56 days, blood is collected from the rabbits and plasma and/or serum cholesterol levels are determined using the enzymatic method of Mao, et al., Clin.Chem. (1983) 29: 1890-1897.

Claims

1. A pharmaceutical composition comprising:

   (a) a polyphosphonate or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug of either; and
   (b) a statin or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug of either.

2. A pharmaceutical composition as claimed in claim 1 wherein the ploy phosphonate is alendronic acid, alendronate, cimadronate, clodronic acid, clodronate, 1-hydroxy-3-(1-pyrrolidinyl)-propylidene-1,1-bisphosphonic acid, etidronic acid, ibandronate, neridronate, olpadronate, pamidronate, piridronate, risedronate, tiludronate or zolendronate.

3. A pharmaceutical composition as claimed in either of claims 1 and 2 wherein the statin is simvastatin, pravastatin, cerivastatin, mevastatin, fluindostatin, velostatin, fluvastatin, dalvastatin, dihydrocompactin, compactin, lovastatin, atorvastatin, bervastatin, NK-104 or ZD-4522.

4. A pharmaceutical composition as claimed in any preceding claim wherein the polyphosphonate is alendronate.

5. A pharmaceutical composition as claimed in any preceding claim wherein the statin is atorvastatin.

6. A pharmaceutical composition as claimed in claim 1 wherein the polyphosphonate is alendronate sodium or a hydrate thereof and said statin is atorvastatin hemicalcium salt or a hydrate thereof.

7. A pharmaceutical composition as claimed in any preceding claim further comprising an H_2 histamine receptor antagonist or a proton pump inhibitor or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug thereof.

8. A pharmaceutical composition as claimed in any one of claims 1 to 7 for use as a medicament.

9. The use of a pharmaceutical composition, as claimed in any one of claims 1 to 7 in the manufacture of a medicament for promoting bone formation, preventing bone loss or treating atherosclerosis or any combination thereof.

10. A kit for use by a consumer to promote bone formation, prevent bone loss or treat atherosclerosis, or any combination thereof, said kit comprising

    (a) a polyphosphonate or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug of either; and
    (b) a statin or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug of either; and, optionally,
    (c) instructions describing a method of using the polyphosphonate and statin to promote bone formation, prevent bone loss or treat atherosclerosis, or any combination thereof.

11. A kit as claimed in claim 10 which further comprises an H_2 histamine receptor antagonist or a proton pump inhibitor or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug thereof.

12. A kit as claimed in claim 10 wherein said polyphosphonate and/or statin is as defined in any one of claims 2 to 6.

13. A product containing

(a) a polyphosphonate or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug of either; and
(b) a statin or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug of either; as a combined preparation for simultaneous, separate or sequential use to promote bone formation, prevent bone loss or treat atherosclerosis, or any combination thereof.

14. The use of

(a) a polyphosphonate or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or prodrug of either; and
(b) a statin or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug of either;

for the manufacture of a medicament for simultaneous, separate or sequential use to promote bone formation, prevent bone loss or treat atherosclerosis, or any combination thereof.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 30 1276

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X Y	WO 99 45923 A (FISHER JOHN E ;MERCK & CO INC (US); RODAN GIDEON A (US)) 16 September 1999 (1999-09-16) * page 5, line 24 - line 29 * * claims 6-13 * * page 8, line 23 - line 30 * * page 15, line 10 - line 19 * * page 18 * ---	1-3, 8-10, 12-14 4-7,11	A61K31/66 A61P9/00 A61P19/10
X Y	WO 93 13801 A (PROCTER & GAMBLE) 22 July 1993 (1993-07-22) * page 1, paragraph 1 * * claims 1,6,8,9 * * page 18 - page 19 * ---	1-3, 8-10, 12-14 4-7,11	
Y	ZHU B Q (REPRINT) ET AL: "EFFECTS OF ETIDRONATE AND LOVASTATIN ON REGRESSION OF ATHEROSCLEROSIS IN CHOLESTEROL-FED RABBITS" CIRCULATION, (OCT 1994) VOL. 90, NO. 4, PART 2, PP. 461. ISSN: 0009-7322., XP000999915 PROCTER & GAMBLE PHARMACEUT, CINCINNATI, OH, 00000;UNIV CALIF SAN FRANCISCO, SAN FRANCISCO, CA, 94143 * abstract * ---	1-14	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61K
Y	ZHU B Q ET AL: "Effects of etidronate and lovastatin on the regression of atherosclerosis in cholesterol-fed rabbits." CARDIOLOGY, (1994) 85 (6) 370-7. , XP000999688 * abstract * * page 377 * --- -/--	1-14	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	22 May 2001	Brunnauer, H

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 01 30 1276

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	ROGERS M J: "Statins: lower lipids and better bones?." NATURE MEDICINE, (2000 JAN) 6 (1) 21-3. , XP000999880 * page 21 * * page 23 *	1-14	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
MUNICH	22 May 2001	Brunnauer, H

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P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 30 1276

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

22-05-2001

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9945923 A	16-09-1999	AU 2901199 A	27-09-1999
		EP 1061917 A	27-12-2000
WO 9313801 A	22-07-1993	AU 3473193 A	03-08-1993
		MX 9300240 A	29-07-1994

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021	1033

45200 7590 07/31/2013

K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

EXAMINER	
IVANOVA, SVETLANA M	
ART UNIT	**PAPER NUMBER**
1627	

NOTIFICATION DATE	DELIVERY MODE
07/31/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chicago.patents@klgates.com
maria.nadal@klgates.com

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	13/894,244	TABUTEAU, HERRIOT	
	Examiner	Art Unit	
	SVETLANA M. IVANOVA	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *SVETLANA M. IVANOVA*. (3)_____.

(2) *BRENT JOHNSON*. (4)_____.

Date of Interview: *23 July 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: _____.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant called and inquired about form PTO-326, on which a box was checked that Applicant's request to not have a first-action interview is acknowledged. Applicant did wish to have an interview, and was further calling to schedule one. The Examiner indicated that she inadvertently checked that box, not seeing the word "not", and that she is treating the application as filed under the first action interview program, which will be clarified for the record with the instant interview summary. An interview date of August 12, 2013 at 4PM EST was scheduled. .

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/S. M. I./ Examiner, Art Unit 1627	

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

———

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021	1033

45200 7590 08/19/2013

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1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

EXAMINER	
IVANOVA, SVETLANA M	
ART UNIT	**PAPER NUMBER**
1627	

NOTIFICATION DATE	DELIVERY MODE
08/19/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

chicago.patents@klgates.com
maria.nadal@klgates.com

Applicant-Initiated Interview Summary	**Application No.**	**Applicant(s)**	
	13/894,244	TABUTEAU, HERRIOT	
	Examiner	**Art Unit**	
	SVETLANA M. IVANOVA	1627	

All participants (applicant, applicant's representative, PTO personnel):

(1) *SVETLANA M. IVANOVA*. (3)_____.

(2) *BRENT JOHNSON*. (4)_____.

Date of Interview: *12 August 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☒ Yes ☐ No.
If Yes, brief description: *see attached fax*.

Issues Discussed ☐101 ☐112 ☒102 ☒103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *all pending claims in general*.

Identification of prior art discussed: _____.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicant sent a fax shortly before the interview on which Applicant had largely premised its arguments.

Re: Fox, Applicant pointed to a plot on page 3/ 23 of the fax. Applicant claimed to have plotted data on reversal of hyperalgesia with a subcutaneous zoledronic acid formulation of Fax versus oral formulation made by the Applicant. Applicant believed this plot to show unexpected results.

The Examiner questioned why: 1) Applicant is presenting an argument on unexpected results, when Applicant has 102(b) rejections; 2) Applicant is comparing a subcutaneous to an oral formulation, when Fox specifically teaches also an oral formulation, e.g. [071]); 3) Applicant is presenting an argument on method of treatment, when Applicant's claims are directed to a composition.

Applicant indicated that it will consider amending claim 40 with a limitation, such as in claim 46, so as to overcome the anticipation rejection. The Examiner responded that per Chandler, guidelines for labeling of unit dosage forms are very well known in the pharmaceutical arts based on which this will create at least a very strong obviousness rejection.

Applicant next pointed to Applicant's submissions to the Committee for Orphan Medicinal Products, wherein Applicant applied for an oral formulation, but only relied on data from the prior art on i.v. administration, to which the Committee responded that it would not be plausible to demonstrate based on this data that zolendronate could be used for the treatment of CRPS, where no oral data has been provided. The Examiner indicated that, not being an expert on FDA submissions, it did not seem suprising that the committee would like to see data with the specific product in the application, and not with some other product. For instance, considerations would include issues of pharmacokinetics, etc. between the different routes of administration. Rather, Applicant would need to address that oral formulations of zoledronic acid were already taught in the art. Applicant's next step will be to respond formally to the office action in writing. .

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It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

K&L|GATES

FAX

Date	2013-08-12 11:25:26 PDT
To	'Examiner Svetlana Ivanova
Company/Firm	USPTO
Fax	15712704277
From	Brent Johnson
Subject	Today's Interview

Comments:

Dear Examiner Ivanova,

Please see the attached materials that I would like to discuss during today's interview. There is no need to review it ahead of time.

Best regards,

Brent Johnson

[http://www.klgates.com/FCWSite/email_images/KLG_Logo_Boxed_Gray_RGB_128x31.jpg]<http://www.klgates.com/>

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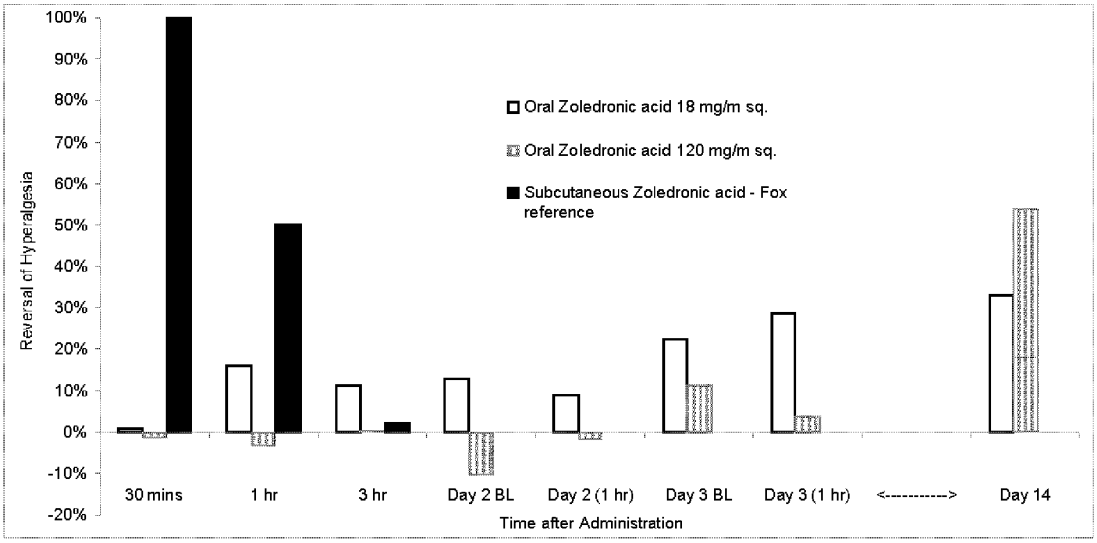
If you have received this e-mail in error, please contact me at brent.johnson@klgates.com.

PAGE 2/23 * RCVD AT 8/12/2013 2:25:27 PM [Eastern Daylight Time] * SVR:W-PTOFAX-003/3 * DNIS:2704277 * CSID:19496234452 * DURATION (mm-ss):09-12


100%
90%
80%
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60%
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10%
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-20%
Reversal of Hyperalgesia
Oral Zoledronic acid 18 mg/m sq.
Oral Zoledronic acid 120 mg/m sq.
Subcutaneous Zoledronic acid - Fox reference
30 mins
1 hr
3 hr
Day 2 BL
Day 2 (1 hr)
Day 3 BL
Day 3 (1 hr)
<---------->
Day 14
Time after Administration

Subject: Review of DRAFT PSO EMA/OD/125/12

From: Diana.Lupescu@ema.europa.eu

To: htabuteau@axsome.com, Cinzia.NDiamoi@ema.europa.eu, federica.castellani@ema.europa.eu, Frederique.Dubois@ema.europa.eu, Diana.Lupescu@ema.europa.eu

Sent: Thu, 7 Mar 2013 12:15:53 +0000

Expiration: Fri, 22 Mar 2013 12:15:53 +0000

Reply Reply To All

Dear Dr Tabuteau,

Further to your application for orphan designation, the Committee for Orphan Medicinal Products adopted a negative opinion for orphan designation of Zoledronic acid for the treatment of complex regional pain syndrome on 06 February 2013.

Please find attached the DRAFT Public Summary of Opinion (PSO) related to your application (EMA/COMP/125/12/draft). This is a summary in understandable language, which has been written to inform the general public about the reasons that lead to the negative opinion on this orphan designation. The PSO will be published on the website of the European Medicines Agency.

Please let us know by no later than Wednesday, 13 March 2013, 17:00 hrs, UK time if you consider any of the information contained in the PSO to be confidential in nature and unsuitable for disclosure to the public. Also, should you have any additional comments, please make sure that they reach us by the same date. All comments will be taken into account, but only comments considered relevant by the Agency will be implemented. If no comments are received by the deadline, the text of the PSO will be considered to be suitable for publication.

Finally, could you please confirm that the sponsor's contact details as included in the PSO under 'For more information'are correct and provide us with a corporate email address. In the absence of this information, the email address <htabuteau@axsome.com> will be used as contact point.

Please do not hesitate to contact me should you require any further clarification.

Yours sincerely,
Diana

Diana Lupescu
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Filename	Type	Size
PSO 125-12 Zoledronic acid.doc	MS Word Document	134kb

To save the file, click on the file name.

Please click on the button below to confirm that you have successfully downloaded the files in this package.

Confirm

This will be noted in the package sender's tracking log.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<date of sign off>
EMA/COMP/102965/2013
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Zoledronic acid for the treatment of complex regional pain syndrome

On 6 February 2013, the Committee for Orphan Medicinal Products (COMP) adopted a negative opinion on the orphan designation application for zoledronic acid for the treatment of complex regional pain syndrome (CRPS). A negative decision was issued by the European Commission on <date of decision>.

The sponsor applied for orphan designation on the basis of the seriousness and the rarity of the condition.

The negative opinion was based on the following reasons:

- The data submitted by the sponsor were not considered sufficient to demonstrate that the medicine could plausibly be used in the treatment of CRPS. The main data provided in support of the application consisted of a conference abstract describing a study in 24 patients with CRPS treated with zoledronic acid by injection, but lacking relevant details that would be necessary for an in-depth assessment of the results.
- No data had been provided on zoledronic acid given by mouth, which was the proposed route of administration for the product in this application.

Requests for designation as an orphan medicinal product are made for investigational products. Absence of orphan designation does not preclude the development of this product, including its use in clinical trials. A marketing authorisation can still be obtained if quality, safety and efficacy are demonstrated.

For more information:

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For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases which includes a directory of patients' organisations registered in Europe.
- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Field Code Changed

Field Code Changed

Pre-submission Meeting Minutes

Sponsor's template

Sponsor:	Axsome Therapeutics Limited
Orphan indication:	Complex regional pain syndrome
Active substance:	Zoledronic acid
Date of meeting:	June 17, 2013
Sponsor participants:	Herriot Tabuteau, M.D.
	Robert Niecestro, Ph.D.
EMA participants:	Dr Segundo Mariz
	Dr Stylianos Tsigkos
	Dr Laura Fregonese

The opinions expressed during the meeting by EMA staff are personal opinions and these are not intended to pre-empt any decisions by the COMP, which is the Committee adopting opinions.

After introduction of the participants from the EMA and the Sponsor, Dr. Tabuteau gave a presentation which provided a background on the condition, the scientific rationale for the use of zoledronic acid in complex regional pain syndrome (CRPS), calculation of the prevalence of the condition in the E.U., and an update on the development status of the medicinal product. The scientific rationale focused on results of studies conducted using orally delivered zoledronic acid in the rat tibia fracture model of CRPS.

After the presentation, Drs Mariz, Tsigkos and Fregonese provided feedback and guidance on the application form and on sections A-E of the Sponsor's application, and entertained questions from the Sponsor.

Overall comments

Overall, Drs Mariz, Tsigkos and Fregonese felt that the current application for designation was significantly improved over the prior application as a result of the inclusion of new animal data.

Dr. Tsigkos started the discussion by reviewing the grounds of the final negative opinion that was previously received. Dr. Tsigkos stated that the conclusion of the COMP was that 1) the entity was considered to be distinct, so therefore appropriate for designation, 2) there exists no satisfactory method to treat the condition that has been authorised, and 3) the prevalence was below the threshold for orphan designation in Europe. The only thing that was considered missing was data with the specific formulation in the specific condition. With the current application, he and his colleagues see that Axsome now has this data, which significantly improves the application. Consequently, they have good reason to believe that the application can go through easily this time around. This does not pre-empt the final opinion of the COPMP, which is the result of the view of all Committee members.

Drs Mariz, Tsigkos and Fregonese had suggestions for improving the application and to assure a smooth review. These suggestions are outlined below.

Application form guidance:

Date of protocol assistance should be clarified.

Sections A to E (scientific supporting document):

Section A1

No suggestions. Classification is clear. It was accepted before. No reason to believe that it will not be accepted now.

Section A3

Dr. Tsigkos stated that, going forward, the EMA is trying to make it more explicit that for orphan applications they would like to see data with the specific product in the application and not with other formulations.

Results of the two animal studies presented in the application now provide the missing data that would allow the committee, based on their personal experience, to go ahead and possibly designate the medicinal product for the condition.

The clinical studies with IV zoledronic acid should be mentioned in the current application as they are supportive and in line with the results from the animal studies. These studies were included in the prior application.

Dr. Mariz stated that it makes it easier to assess medical plausibility now that Axsome has animal data with the active substance delivered orally, as opposed to what was presented in the previous application which was an abstract using an IV formulation.

Dr. Fregonese stated that the committee previously discussed the relevance of pain as an endpoint in CRPS and concluded that it was quite relevant. The reduction of edema in the animal model also indicates an anti-inflammatory effect.

Section A4

This section is well prepared and it was previously acknowledged by the committee that the condition is debilitating. So this section is fine.

Section B1

The section on prevalence should include a discussion of cases with disease duration greater than one year. Such cases should be accounted for in the application even if they represent a small percentage of the overall patient population.

Section D

No comments

Section E2

Paediatric requirements: Sponsor should indicate its plans to consult with the paediatric section office. Paediatric consultation process is free. Compliance with the Paediatric Investigation Plan (PIP) can confer a two-year extension to marketing exclusivity.

Scientific advice: Parallel scientific advice with EMA/FDA should be considered after Phase I or Phase II.

Japan orphan designation: Sponsor may want to consider applying to Japan for orphan designation. One benefit would be scientific advice from the Japanese regulatory body.

Small to medium enterprise status: Sponsor should apply for small to medium enterprise status. This will be needed for fee reductions and free scientific advice assuming orphan designation is granted.

Questions from the Sponsor for EMA staff

Question: Just to be clear, the two animal studies that we submitted and the supportive clinical reports should be adequate for designation?

Answer: Yes. We cannot talk on behalf of the committee, but we think it is fine, and this is based on our experience with the committee.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Medicines Agency - Science, medicines, health

COMP members

This page lists the current members and alternates of the Committee for Orphan Medicinal Products (COMP). It lists each person's:

- contact details;
- *curriculum vitae*;
- public declaration of interests and confidentiality undertaking.

For more information, see handling conflicts of interests.

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Eurordis

Name

Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13894244
	Filing Date	2013-05-14
	First Named Inventor	Herriot Tabuteau
	Art Unit	1627
	Examiner Name	Svetlana M. Ivanova
	Attorney Docket Number	1958603.00021

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	1	CULLEN et al., MER-101: A bioavailability study of various GIPET formulations in beagle dogs with intraduodenal cannulae. Poster Presentation, November 2007.	☐
	2	LEONARD et al., MER-101 Tablets: A pilot bioavailability study of a novel oral formulation of zoledronic acid. Poster Presentation, October 2007.	☐
	3	LEONARD et al., Safety Profile of Zoledronic acid in a novel oral formulation. Poster Presentation, November 2009.	☐
	4	LEONARD et al., Studies of bioavailability and food effects of MER-101 Zoledronic Acid Tablets in Postmenopausal Women. Poster Presentation, October 2009.	☐
	5	MCHUGH et al., MER-101-03, A multi center, phase II study to compare MER-101 20mg tablets to intravenous Zometa 4mg in prostate cancer patients. Poster Presentation, May 2009.	☐

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[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Brent A. Johnson/	Date (YYYY-MM-DD)	2013-08-20
Name/Print	Brent A. Johnson	Registration Number	51851

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Patent Application Fee Transmittal

Application Number:	13894244
Filing Date:	14-May-2013
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Filer:	Louis C. Cullman/Maria Nadal
Attorney Docket Number:	1958603.00021

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	2806	1	90	90
		Total in USD ($)		**90**

Electronic Acknowledgement Receipt

EFS ID:	16638159
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Maria Nadal
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	20-AUG-2013
Filing Date:	14-MAY-2013
Time Stamp:	16:57:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$90
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	1958603-00021-IDS-08-20-13.pdf	612123 fa4c62bbb6e8c16020eea4219389a45e9f196417	no	4
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3	Non Patent Literature	Leonard2007.pdf	545490 0031410b8df75ac032fe2a5a66c6e74d295cb2cc	no	6
Warnings:					
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4	Non Patent Literature	LeonardNov2009.pdf	1026870 6cd938d96db927573ecf713f7b8224a03ab3f727	no	9
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5	Non Patent Literature	LeonardOct2009.pdf	570340 18d5e059e7e0afbc968ad5f178dc026f0d828c40	no	8
Warnings:					
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6	Non Patent Literature	McHugh2009.pdf	619113 fa5cd166ab635f8d35de0413273d19f0726f78dc	no	6
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National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	**:**	**1033**
Appln. No.	**:**	**13/894,244**
Applicant	**:**	**Herriot Tabuteau**
Filed	**:**	**05/14/2013**
TC/A.U.	**:**	**1627**
Examiner	**:**	**Svetlana M. Ivanova**
Docket No.	**:**	**1958603.00021**
Customer No.	**:**	**45200**
Title	**:**	**COMPOSITIONS FOR ORAL ADMINISTRATION OF ZOLEDRONIC ACID OR RELATED COMPOUNDS FOR TREATING DISEASE**

AMENDMENT AND REMARKS

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

Dear Sir:

Applicant submits the following Amendment and Remarks in Response to the Office Action dated July 23, 2013 in the above referenced patent application.

Interview Summary begins on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 6 of this paper.

Interview Summary

Applicant thanks Examiner for the interview that was conducted on August 12, 2013 between Examiner Svetlana M. Ivanova and Applicant's representative Brent A. Johnson. In the interview, Applicant presented evidence of disbelief of experts and unexpected results, as presented below. No agreement was reached.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-39. (Canceled)

40. (Currently Amended) An oral dosage form comprising at least about 10 mg of zoledronic acid, wherein the oral bioavailability of zoledronic acid in the dosage form is about ~~0.01% to about 4%~~ about 0.1% to about 2% in a human being, and wherein zoledronic acid is the sole therapeutically active agent in the dosage form.

41. (Original) The oral dosage form of claim 40, wherein the oral dosage form contains about 10 mg to about 300 mg of zoledronic acid.

42. (Original) The oral dosage form of claim 40, wherein the oral dosage form contains about 10 mg to about 50 mg of zoledronic acid.

43. (Currently Amended) The oral dosage form of claim 40, wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 1 [[2]]%.

44. (Original) A pharmaceutical product comprising more than one unit of an oral dosage form of claim 40.

45. (Currently Amended) The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 10 mg to about 50 mg of zoledronic acid.

46. (Currently Amended) The pharmaceutical product of claim 45, comprising 28, 29, 30, or 31 units of the oral dosage form, for a total of about 280 mg to about 1600 mg of zoledronic acid to be administered in about 1 month.

47. (Currently Amended) The pharmaceutical product of claim 45, comprising 85 to 95 units of the oral dosage form, for a total of about 850 mg to about 4800 mg of zoledronic acid to be administered in about 3 months.

48. (Currently Amended) The pharmaceutical product of claim 45, comprising 170 to 200 units of the oral dosage form, for a total of about 1700 mg to about 10,000 mg of zoledronic acid to be administered in about 6 months.

49. (Currently Amended) The pharmaceutical product of claim 45, comprising 350 to 380 units of the oral dosage form, for a total of about 3500 mg to about 19,000 mg of zoledronic acid to be administered in about 1 year.

50. (Original) The pharmaceutical product of claim 44, wherein each unit of the oral dosage form contains about 10 mg to about 300 mg.

51. (Original) The pharmaceutical product of claim 50, comprising 4 or 5 units of the oral dosage form, for a total of about 40 mg to about 1500 mg of zoledronic acid to be administered within a period of about 1 month.

52. (Original) The pharmaceutical product of claim 50, comprising 8 or 9 units of the oral dosage form, for a total of about 80 mg to about 2700 mg of zoledronic acid to be administered in about 2 months.

53. (Original) The pharmaceutical product of claim 50, comprising 12, 13 or 14 units of the oral dosage form, for a total of about 120 mg to about 4200 mg of zoledronic acid to be administered in about 3 months.

54. (Original) The pharmaceutical product of claim 50, comprising 22 to 30 units of the oral dosage form, for a total of about 220 mg to about 9000 mg of zoledronic acid to be administered in about 6 months.

55. (Original) The pharmaceutical product of claim 50, comprising 45 to 60 units of the oral dosage form, for a total of about 450 mg to about 18000 mg of zoledronic acid to be administered in about 1 year.

56. (Original) The pharmaceutical product of claim 44, comprising 1 to 10 units of the oral dosage form, wherein the product contains about 200 mg to about 2000 mg of zoledronic acid.

57. (Previously presented) The oral dosage form of claim 40, wherein the zoledronic acid is in the form of a sodium salt.

58-59. (Canceled)

60. (Currently Amended) An oral dosage form comprising zoledronic acid and an excipient, wherein the zoledronic acid is in a form that has an aqueous solubility greater than 1% (w/v), and wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2% in a human being.

61. (Currently amended) The oral dosage form of claim 60, wherein the zoledronic acid is in a form that has an aqueous solubility of about 5% (w/v) to about 50% (w/v).

62-119. (Canceled)

REMARKS/ARGUMENTS

Claims 40-42, 43, 45-49, and 60-61 are amended herein. The amendments are supported by at least ¶¶ 23, 44, 49, and 55 of the specification.

35 U.S.C. §102 Rejections

Fox

Claims 40-45, 57, 60, and 61 are rejected as allegedly being anticipated by Fox (US 2004/0063670). While Applicant does not admit the rejection is correct, the claims are amended herein solely to expedite prosecution. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference."[1] The rejected claims are not anticipated at least because Fox does not teach the claim element "wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2% in a human being."

Fox does not teach the claim element "wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2%."

Fox does not expressly teach this claim element, so Fox does not anticipate this claim unless this element is inherent in a composition taught by Fox. "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'"[2] The Office Action has not provided any information that even suggests that the claimed oral bioavailability range is necessarily

[1] MPEP 2131, quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

[2] MPEP 2112(IV), quoting, *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)

present in any composition of Fox. Therefore this element is not inherently taught in Fox.

Furthermore, it is known in the art that many excipients and structural features of a dosage form can affect the bioavailability of a drug in a dosage form. For example, Day (EP 112757 below) states that "[t]he effect of the compounds may be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the compound may be prepared and incorporated in a tablet or capsule. The technique may be improved by making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules may be coated with a film which resists dissolution for a predictable period of time. Even the parenteral preparations may be made long-acting by dissolving or suspending the compound or compounds in oily or emulsified vehicles which allow dispersion slowly in the serum."[3] Thus, for any particular oral dosage form that might be present in Fox (if there are any at all), a person of ordinary skill in the art would have no way of knowing what the bioavailability of zoledronic acid in that dosage form might be.

By contrast, it is known that dosage forms having bioavailability outside of the claimed range exist. In fact, one reference states "the 20 mg tablet delivers approximately 1 mg of zoledronic acid to the systemic circulation."[4] Thus, this particular oral dosage form does not have an oral bioavailability within the claimed range. Therefore, it cannot be said that the bioavailability range of the claims is necessarily present in any composition of Fox. For at least these reasons, Fox does not anticipate the rejected claims, and the rejection should be withdrawn.

Day

Claims 40-43, 57, 60, and 61 are rejected as allegedly being anticipated by Day (EP 112757). While Applicant does not admit the rejection is correct, the claims are

[3] Day, p. 10, lines 41-46.
[4] US 2010/0215743, ¶ 0085, cited in the May 14, 2013 IDS

amended herein solely to expedite prosecution. The claims are not anticipated at least because Day does not teach the claim element "wherein zoledronic acid is the sole therapeutically active agent in the dosage form" or the claim element "wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2%."

Day does not teach the claim element "wherein zoledronic acid is the sole therapeutically active agent in the dosage form."

Day states that its "compositions are comprised of a polyphosphonate as a first active component and a statin as a second active component."[5] Since this claim element excludes a statin, the claim is not anticipated.

Day does not teach the claim element "wherein the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2%."

Day does not expressly teach this claim element, so Day does not anticipate this claim unless this element is inherent in a composition taught by Day. The Office Action has not provided any information that even suggests that the claimed oral bioavailability range is necessarily present in any composition of Day. Therefore, this element is not inherently taught in Day.

Furthermore, it is known in the art that many factors can affect the bioavailability of a drug in a dosage form. For example, Day states that "[t]he effect of the compounds may be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the compound may be prepared and incorporated in a tablet or capsule. The technique may be improved by making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules may be coated with a film which resists dissolution for a predictable period of time. Even the parenteral preparations may be made long-acting by dissolving or suspending the compound or compounds in oily or emulsified vehicles which allow dispersion slowly in the serum."[6] In fact, one reference states "the 20 mg tablet delivers approximately 1 mg of zoledronic

[5] Day, Abstract.

acid to the systemic circulation."[7] Thus, this particular oral dosage form does not have an oral bioavailability within the claimed range. Therefore, it cannot be said that the bioavailability range of the claims is necessarily present in any composition of Day. For at least these reasons, Day does not anticipate the rejected claims, and the rejection should be withdrawn.

35 U.S.C. §103 Rejections

Claims 44-56 are rejected as allegedly being obvious over the combination of Day, Fox, and Chandler (Labeling Of Unit Dose Packages Of Drugs, Department Of Pharmacy Policy, University Of Kentucky Hospital Chandler Medical Center, Policy Number: PH-04-06, 11/09). While Applicant does not admit the rejection is correct, the claims are amended herein solely to expedite prosecution. In order to make a proper *prima facie* case of obviousness, the Office must show: 1) that all elements of the claims are taught or suggested in the prior art;[8] 2) that there is an apparent reason to combine the prior art elements in the manner claimed;[9] and 3) that the result is predictable.[10] In making this determination, the Patent Office must examine the prior art, design demands, marketplace demands, and the background knowledge of a person of ordinary skill in the art.[11] These factors must be considered as a whole, including anything that teaches away from the claimed invention.[12] The rejected claims are not obvious at least because the cited references do not teach or suggest the claimed bioavailability range, the result of using an oral dosage form is not predictable, the claimed oral dosage form can produce unexpected results, and skepticism of experts with respect to the efficacy of the claimed oral dosage form.

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[6] Day, p. 10, lines 41-46.
[7] US 2010/0215743, ¶ 0085, cited in the May 14, 2013 IDS
[8] *KSR v. Teleflex*, 127 S. Ct. 1727, 1740-1741 (2007); *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003); *In re Royka*, 490 F.2d 981, 985 (CCPA 1974).
[9] *KSR*, 127 S. Ct. at 1740-1741.
[10] *Id.*
[11] *Id.*
[12] *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983).

The cited references do not teach or suggest the claimed bioavailability range.

All of the cited references are silent with respect to the bioavailability of an oral dosage form of zoledronic acid. The Office Action alleges that this element is met by inherency. However, as explained above, this element is not inherent in any composition described in the cited references. Furthermore, inherency cannot be the basis of showing that prior art references[13] teach or suggest a claim element in an obviousness rejection.[14] Therefore, the cited references do not teach or suggest all elements of the rejected claims, and the rejected claims are not *prima facie* obvious.

The cited references do not teach or suggest the claimed amount of zoledronic acid in the pharmaceutical product.

The cited references do not teach or suggest the claim element "for a total of about 280 mg to about 1600 mg of zoledronic acid to be administered in about 1 month" that is recited in claim 46. None of the references, alone or in combination, provide any indication of the amount of zoledronic acid to be administered in about one month via one or more units of an oral dosage form. Therefore, the references do not teach or suggest this element.

The Office Action identified the following passage from Fox as being potentially relevant to the rejected claims: "[n]ormally the dosage is such that a single dose of the bisphosphonate active ingredient from 0.002-20.0 mg/kg, especially 0.01-10.0 mg/kg, is administered to a warm-blooded animal weighing approximately 75 kg. If desired, this dose may also be taken in several, optionally equal, partial doses."[15] Similarly, the Office Action identified the following passage from Day as being potentially relevant to the rejected claims. "Generally, an appropriate amount of polyphosphonate is chosen to obtain a bone resorption inhibiting effect, i.e. a bone resorption inhibiting amount of

[13] Applicant does not admit that any cited reference is prior art.
[14] *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993)("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.") The BPAI has recently taken a similar position, see *Ex Parte Vigano*, BPAI Appeal 2010-007666, Jan. 3, 2012 ("Second, the examiner's determination shrinkage limitation would have been met inherently is legal error obviousness rejection.")

the polyphosphonate is administered. For humans, an effective oral dose of polyphosphonate is typically from about 1.5 to about 6000 µg/kg body weight and preferably about 10 to about 2000 µg/kg of body weight."[16] The Office Action did not identify any passage from Chandler that included an amount of zoledronic acid to be administered in about one month or a dosage range of zoledronic acid. The combination of these concepts does not provide any suggestion as to how much zoledronic acid should be administered orally in about 1 month. Therefore, the combination of references does not teach or suggest the element "for a total of about 280 mg to about 1600 mg of zoledronic acid to be administered in about 1 month" from claim 46. Thus, claim 46 is not obvious.

The cited references do not teach or suggest the claim element "for a total of about 850 mg to about 4800 mg of zoledronic acid to be administered in about 3 months" that is recited in claim 47. Therefore, the claim is not obvious.

The cited references do not teach or suggest the claim element "for a total of about 1700 mg to about 10,000 mg of zoledronic acid to be administered in about 6 months" that is recited in claim 48. Therefore, the claim is not obvious.

The cited references do not teach or suggest the claim element "for a total of about 3500 mg to about 19,000 mg of zoledronic acid to be administered in about 1 year" that is recited in claim 49. Therefore, the claim is not obvious.

The cited references do not teach or suggest the claim element "for a total of about 40 mg to about 1500 mg of zoledronic acid to be administered within a period of about 1 month" that is recited in claim 51. Therefore, the claim is not obvious.

---

[15] Fox, p. 4, ¶ [0075].
[16] Day, p. 6, lines 18-21.

The cited references do not teach or suggest the claim element "for a total of about 80 mg to about 2700 mg of zoledronic acid to be administered in about 2 months" that is recited in claim 52. Therefore, the claim is not obvious.

The cited references do not teach or suggest the claim element "for a total of about 120 mg to about 4200 mg of zoledronic acid to be administered in about 3 months" that is recited in claim 53. Therefore, the claim is not obvious.

The cited references do not teach or suggest the claim element "for a total of about 220 mg to about 9000 mg of zoledronic acid to be administered in about 6 months" that is recited in claim 54. Therefore, the claim is not obvious.

The cited references do not teach or suggest the claim element "for a total of about 450 mg to about 18000 mg of zoledronic acid to be administered in about 1 year" that is recited in claim 55. Therefore, the claim is not obvious.

The cited references do not teach or suggest the claim element "the product contains about 200 mg to about 2000 mg of zoledronic acid" that is recited in claim 56. Therefore, the claim is not obvious.

The result is not predictable.

The rejected claims are not obvious because the efficacy of the claimed oral dosage form is not predictable. "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness."[17] As explained below, a panel of experts in the field asserted that it was not plausible to expect that the claimed dosage form would be effective in treating complex regional pain syndrome. The reasoning for this position can also be applied to the uses for zoledronic acid included in the cited references. Therefore, the rejected claims are not

[17] MPEP 2143.02 (II), citing *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976)

prima facie obvious because there was no reasonable expectation of success before the disclosure of the present application.

A panel of experts was skeptical with respect to the efficacy of the claimed dosage form.

The claimed composition is also not obvious because a panel of experts expressed disbelief that a claimed composition would be effective. "Expressions of disbelief by experts constitute strong evidence of nonobviousness."[18] Recently, Applicant applied for orphan drug status for a claimed composition with the European Medicines Agency. The application was considered by the Committee for Orphan Medicinal Products ("the Committee"), which includes over thirty experts that are independent of the EMA. Information on this committee, including CVs of the members, is attached herewith as Exhibit A, and can be obtained on the internet at the address below.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/2010/02/people_listing_000005.jsp&mid=WC0b01ac0580028e76

One of the requirements for obtaining orphan drug status is to demonstrate that use of the formulation in the treatment of the disease indicated, in this case complex regional pain syndrome (CRPS), is medically plausible. The application was denied, and Applicant appealed the decision. In the process, Applicant, and two paid consultants with knowledge in the field, made the most persuasive arguments that they could to the committee that the use of the claimed composition in the treatment of CRPS was medically plausible. These arguments were based upon the prior art of which Applicant was aware, and the references used to make these arguments have been submitted to the Office.

[18] MPEP 716.05, quoting *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698, 218 USPQ 865, 869 (Fed. Cir. 1983) (citing *United States v. Adams*, 383 U.S. 39, 52, 148 USPQ 479, 483-484 (1966), emphasis added.

However, the Committee denied the application, stating that "[t]he data submitted by the sponsor were not considered sufficient to demonstrate that the medicine could plausibly be used in the treatment of CRPS."[19] According to a standard dictionary, the term "plausible" has the meaning "superficially fair, reasonable, or valuable but often specious."[20] Thus, it is fair to say that the Committee, having over 30 experts, expressed disbelief that a claimed composition would be effective in treating CRPS. Furthermore, this demonstrates that the experts on the Committee did not believe there was a reasonable expectation of success in the treatment.

The Committee observed that "[t]he main data provided in support of the application consisted of a conference abstract describing a study in 24 patients with CRPS treated with zoledronic acid by injection, but lacking relevant details that would be necessary for an in-depth assessment of the results."[21] The Committee further stated that "[n]o data had been provided on zoledronic acid given by mouth, which was the proposed route of administration for the product in this application." [22] The rationale described above is readily applied to Day and Fox. The only data provided in these references are from subcutaneous injection into rats. The references lack the relevant details that would be necessary for an in-depth assessment of the results. Furthermore, there is no data in these references for zoledronic acid given by mouth. Thus, the Committee would likely have said the same thing with respect to Day and Fox: that it was not plausible that an oral zoledronic acid would work for the indications recited in those references. Therefore, the use of the claimed oral dosage forms in treating the conditions included in the cited references does not have a reasonable expectation of success.

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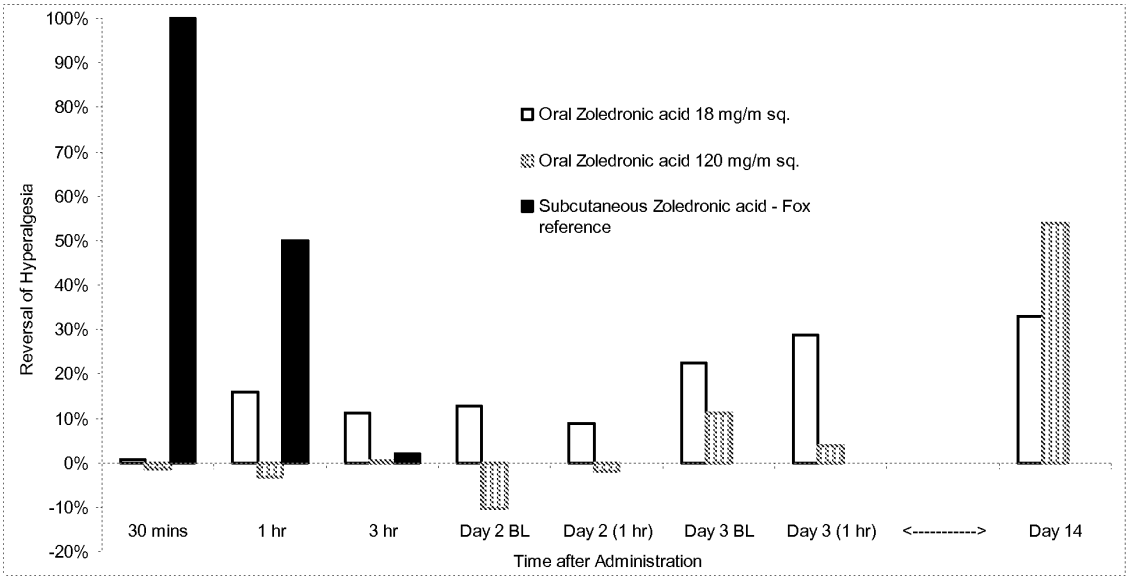
[19] Draft Public Summary of Opinion prepared by the Committee For Orphan Medicinal Products Of The European Medicines Agency (Draft Public Summary), emphasis added.
[20] Merriam Webster's Collegiate Dictionary, Tenth Edition, Merriam-Webster, Incorporated, Springfield, Mass., 1997, p. 892.
[21] Draft Public Summary
[22] Id. Please note that this statement was not included in the published Summary of Opinion because Applicant felt the information was confidential, and did not want it publicly disclosed at that time.

It should be noted that since the rejection of the orphan drug application, Applicant has submitted the data from the experiment described in Example 3 to the Committee, and has resubmitted the orphan drug application. As shown in the attached minutes from an initial meeting with the EMA, experts from the EMA now believe that the Committee is likely to agree that treatment of CRPS with an embodiment of the claimed dosage form is plausible. For example, the minutes state that it is "easier to assess medical plausibility now that [Applicant] has animal data with the active substance delivered orally, as opposed to what was presented in the previous application which was an abstract using an IV formulation."[23]

An Embodiment of a Claimed Dosage Form Produces Unexpected Results

In addition to the reasons described above, the claimed composition is not obvious because of the unexpected results presented in the specification as compared to the Fox reference. "Usually, a showing of unexpected results is sufficient to overcome a *prima facie* case of obviousness."[24] Fox states that "in a model of inflammatory hyperalgesia induced by unilateral hind paw injection of complete Freund's adjuvant [CFA] zoledronate (0.003-0.1 $mgkg^{-1}$ s.c.) produced a dose-dependent reversal of mechanical hyperalgesia. The effect was rapid in onset, with a maximal reversal of 100% within 30 minutes, and a short duration with no significant activity 3 hours following administration."[25] Based upon these results, one of ordinary skill in the art would have expected a claimed composition to have a rapid, short-term effect in a model of inflammatory hyperalgesia. Unexpectedly, the embodiment of a claimed composition was tested that had little or no short-term effect in a model of inflammatory hyperalgesia, but had a significant effect many days after the composition was administered, as illustrated in the figure below.

[23] Pre-submission Meeting Minutes, p. 2.
[24] MPEP 2145, citing *In re Albrecht*, 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975)
[25] Fox, p. 6, ¶ 0102.



The figure is a compilation of the data from Examples 1 and 2 of the specification and the Fox reference. The experiment of Examples 1 and 2 were actually carried out on the same animals, with the effect of the oral administration being a model for either inflammatory pain or arthritis pain, depending upon the time between injection of the CFA and the measurement of paw compression threshold. The values at one hour and 3 hours for the Fox reference are not actual values reported in Fox, but are added to provide a visual approximation based upon the statement "maximal reversal of 100% within 30 minutes, and a short duration with no significant activity 3 hours following administration."[26]

This figure clearly demonstrates that the activity of the subcutaneous injection reported in Fox is nearly the opposite of the activity observed for the orally administered zoledronic acid. For the oral administration, either no significant effect (18 mg/m^2) or a slight increase in pain (120 mg/m^2) was observed at 30 minutes, in contrast with the maximum effect for the subcutaneous administration reported in Fox at the same time point. On the other hand, Fox stated that there was "no significant activity 3 hours

[26] Fox, p. 6, ¶ 0102.

following administration." Thus, it is surprising that at both dosage levels, the oral zoledronic acid had a significant reversal of hyperalgesia 14 days after the first administration and 11 days after administration of the final oral dose (which occurred on day 3).[27] Therefore, the rejected claims are also not obvious because of these unexpected results, and the rejection should be withdrawn.

DOUBLE PATENTING

The Office has indicated that provisional obviousness type double patenting might exist with respect to Application No. 13/894,262, claims 1-19 and Application No. 13/894,252. Without addressing the propriety of any of the Office's rejections above, and specifically the Office's interpretation of what the cited references teach or suggest, Applicant respectfully and properly defers addressing the present rejections until there is otherwise allowable subject matter in each application. Only then is it proper to assess the propriety of the Office's rejection in view of the potentially allowable claims. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejections, or that the rejections be held in abeyance until claims are allowable in the present application and in at least one of the applications cited above.

CONCLUSION

For at least the reasons given above, Applicant submits that the claims are patentable. Therefore, Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

[27] A higher oral dose was also administered, but the animals were euthanized after 3 days due to the high toxicity level of this dose, so these results are not included in the figure.

The Commissioner is authorized to charge any fee which may be required in connection with this Amendment to deposit account No. 50-3207.

Respectfully submitted,

Dated: August 20, 2013

/Brent Johnson/

Registration No. 51857
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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<date of sign off>
EMA/COMP/102965/2013
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Zoledronic acid for the treatment of complex regional pain syndrome

On 6 February 2013, the Committee for Orphan Medicinal Products (COMP) adopted a negative opinion on the orphan designation application for zoledronic acid for the treatment of complex regional pain syndrome (CRPS). A negative decision was issued by the European Commission on <date of decision>.

The sponsor applied for orphan designation on the basis of the seriousness and the rarity of the condition.

The negative opinion was based on the following reasons:

- The data submitted by the sponsor were not considered sufficient to demonstrate that the medicine could plausibly be used in the treatment of CRPS. The main data provided in support of the application consisted of a conference abstract describing a study in 24 patients with CRPS treated with zoledronic acid by injection, but lacking relevant details that would be necessary for an in-depth assessment of the results.
- No data had been provided on zoledronic acid given by mouth, which was the proposed route of administration for the product in this application.

Requests for designation as an orphan medicinal product are made for investigational products. Absence of orphan designation does not preclude the development of this product, including its use in clinical trials. A marketing authorisation can still be obtained if quality, safety and efficacy are demonstrated.

For more information:

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Telefax: +44 208 0432 268
E-mail: htabuteau@axsome.com

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases which includes a directory of patients' organisations registered in Europe.
- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Field Code Changed

Field Code Changed

Subject: Review of DRAFT PSO EMA/OD/125/12

From: Diana.Lupescu@ema.europa.eu

To: htabuteau@axsome.com, Cinzia.NDiamoi@ema.europa.eu, federica.castellani@ema.europa.eu, Frederique.Dubois@ema.europa.eu, Diana.Lupescu@ema.europa.eu

Sent: Thu, 7 Mar 2013 12:15:53 +0000

Expiration: Fri, 22 Mar 2013 12:15:53 +0000

Reply Reply To All

Dear Dr Tabuteau,

Further to your application for orphan designation, the Committee for Orphan Medicinal Products adopted a negative opinion for orphan designation of Zoledronic acid for the treatment of complex regional pain syndrome on 06 February 2013.

Please find attached the DRAFT Public Summary of Opinion (PSO) related to your application (EMA/COMP/125/12/draft). This is a summary in understandable language, which has been written to inform the general public about the reasons that lead to the negative opinion on this orphan designation. The PSO will be published on the website of the European Medicines Agency.

Please let us know by no later than Wednesday, 13 March 2013, 17:00 hrs, UK time if you consider any of the information contained in the PSO to be confidential in nature and unsuitable for disclosure to the public. Also, should you have any additional comments, please make sure that they reach us by the same date. All comments will be taken into account, but only comments considered relevant by the Agency will be implemented. If no comments are received by the deadline, the text of the PSO will be considered to be suitable for publication.

Finally, could you please confirm that the sponsor's contact details as included in the PSO under 'For more information' are correct and provide us with a corporate email address. In the absence of this information, the email address <htabuteau@axsome.com> will be used as contact point.

Please do not hesitate to contact me should you require any further clarification.

Yours sincerely,
Diana

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Filename	Type	Size
PSO 125-12 Zoledronic acid.doc	MS Word Document	134kb

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Pre-submission Meeting Minutes

Sponsor's template

Sponsor:	Axsome Therapeutics Limited
Orphan indication:	Complex regional pain syndrome
Active substance:	Zoledronic acid
Date of meeting:	June 17, 2013
Sponsor participants:	Herriot Tabuteau, M.D.
	Robert Niecestro, Ph.D.
EMA participants:	Dr Segundo Mariz
	Dr Stylianos Tsigkos
	Dr Laura Fregonese

The opinions expressed during the meeting by EMA staff are personal opinions and these are not intended to pre-empt any decisions by the COMP, which is the Committee adopting opinions.

After introduction of the participants from the EMA and the Sponsor, Dr. Tabuteau gave a presentation which provided a background on the condition, the scientific rationale for the use of zoledronic acid in complex regional pain syndrome (CRPS), calculation of the prevalence of the condition in the E.U., and an update on the development status of the medicinal product. The scientific rationale focused on results of studies conducted using orally delivered zoledronic acid in the rat tibia fracture model of CRPS.

After the presentation, Drs Mariz, Tsigkos and Fregonese provided feedback and guidance on the application form and on sections A-E of the Sponsor's application, and entertained questions from the Sponsor.

Overall comments

Overall, Drs Mariz, Tsigkos and Fregonese felt that the current application for designation was significantly improved over the prior application as a result of the inclusion of new animal data.

Dr. Tsigkos started the discussion by reviewing the grounds of the final negative opinion that was previously received. Dr. Tsigkos stated that the conclusion of the COMP was that 1) the entity was considered to be distinct, so therefore appropriate for designation, 2) there exists no satisfactory method to treat the condition that has been authorised, and 3) the prevalence was below the threshold for orphan designation in Europe. The only thing that was considered missing was data with the specific formulation in the specific condition. With the current application, he and his colleagues see that Axsome now has this data, which significantly improves the application. Consequently, they have good reason to believe that the application can go through easily this time around. This does not pre-empt the final opinion of the COPMP, which is the result of the view of all Committee members.

Drs Mariz, Tsigkos and Fregonese had suggestions for improving the application and to assure a smooth review. These suggestions are outlined below.

Application form guidance:

Date of protocol assistance should be clarified.

Sections A to E (scientific supporting document):

Section A1

No suggestions. Classification is clear. It was accepted before. No reason to believe that it will not be accepted now.

Section A3

Dr. Tsigkos stated that, going forward, the EMA is trying to make it more explicit that for orphan applications they would like to see data with the specific product in the application and not with other formulations.

Results of the two animal studies presented in the application now provide the missing data that would allow the committee, based on their personal experience, to go ahead and possibly designate the medicinal product for the condition.

The clinical studies with IV zoledronic acid should be mentioned in the current application as they are supportive and in line with the results from the animal studies. These studies were included in the prior application.

Dr. Mariz stated that it makes it easier to assess medical plausibility now that Axsome has animal data with the active substance delivered orally, as opposed to what was presented in the previous application which was an abstract using an IV formulation.

Dr. Fregonese stated that the committee previously discussed the relevance of pain as an endpoint in CRPS and concluded that it was quite relevant. The reduction of edema in the animal model also indicates an anti-inflammatory effect.

Section A4

This section is well prepared and it was previously acknowledged by the committee that the condition is debilitating. So this section is fine.

Section B1

The section on prevalence should include a discussion of cases with disease duration greater than one year. Such cases should be accounted for in the application even if they represent a small percentage of the overall patient population.

Section D

No comments

Section E2

Paediatric requirements: Sponsor should indicate its plans to consult with the paediatric section office. Paediatric consultation process is free. Compliance with the Paediatric Investigation Plan (PIP) can confer a two-year extension to marketing exclusivity.

Scientific advice: Parallel scientific advice with EMA/FDA should be considered after Phase I or Phase II.

Japan orphan designation: Sponsor may want to consider applying to Japan for orphan designation. One benefit would be scientific advice from the Japanese regulatory body.

Small to medium enterprise status: Sponsor should apply for small to medium enterprise status. This will be needed for fee reductions and free scientific advice assuming orphan designation is granted.

Questions from the Sponsor for EMA staff

Question: Just to be clear, the two animal studies that we submitted and the supportive clinical reports should be adequate for designation?

Answer: Yes. We cannot talk on behalf of the committee, but we think it is fine, and this is based on our experience with the committee.

Exhibit A

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Medicines Agency - Science, medicines, health

COMP members

This page lists the current members and alternates of the Committee for Orphan Medicinal Products (COMP). It lists each person's:

- contact details;
- *curriculum vitae*;
- public declaration of interests and confidentiality undertaking.

For more information, see handling conflicts of interests.

Jump to section:

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Patients' organisations

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European Commission representative

European Commission

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General Observers

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Eurordis

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr André Lhoir

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP), since 2000

Membership in EMA working parties / groups

- Expert of the CHMP working party

Professional background

Current positions:

- General Public Health Protection, Head of Registration unit (since 01.08.2004)

Education

- Doctor in human medicine, Free University of Brussels (1982)

Areas of expertise

- General practitioner

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Annie Lorence

Scientific profile

Membership in the European Medicines Agency scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP) since 2012

Professional background

Current positions:

- RTU (Temporary Recommandations for Use) correspondent (since October 12)
- Orphan medicinal products correspondent

Other relevant positions:

- Pre-authorisations (Clinical trials, temporary authorisations for use (ATU), hospital preparations) (until September 12)

Education

- Pharmacist Doctor

Areas of expertise

- Regulatory affairs

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Aušra Matulevičienė

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP) since 2006

Professional background

Current positions:

- Clinical Geneticist, Medical Genetics Centre of Vilnius University Hospital, Santariškių Clinics (Lithuania)
- Junior research associate, Department of Human and Medical Genetics, Faculty of Medicine, Vilnius University (Lithuania)

Other relevant positions:

- Chief of the Primary Evaluation Department, Marketing Authorisation Division, States Medicines Control Agency, Lithuania (2005-2006)
- Member of the Board of Lithuanian Society of Human Genetics from 2001
- Member of the Lithuanian Society of Doctors from 2006
- Member of the European Society of Human Genetics from 2007

Education

- Speciality of Paediatrics, Faculty of Medicine, Vilnius University
- MD, Paediatrics (postgraduate studies), Faculty of Medicine, Vilnius University
- Doctor Resident of Clinical Geneticist, Department of Human and Medical Genetics, Vilnius University (postgraduate studies)

Areas of expertise

- Genetic counselling
- Clinical genetics
- Clinical dysmorphology

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Ana Corrêa Nunes

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP) since 2005

Membership in the EMA working parties / groups

- Member of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Steering Group (ENCePP SG), representing COMP (since 2012)

Professional background

Current positions:

- Coordinator of the clinical assessment Department – Infarmed (since April 2002)

Other relevant positions:

- Member of the National Committee for New Drug Licensing of INFARMED (since 1993)
- Member of Signal reviewers expert team of the WHO Drug International Monitoring Centre - the Uppsala Monitoring Centre (since 1999)
- Member of the Committee for the Portuguese National Programme for Rare Diseases (since 2007)
- Has developed a National Drug Safety Monitoring System at INFARMED being head of this Department (the National Pharmacovigilance Centre) and member of the EU pharmacovigilance working group (1992-1999)
- Adviser for drug policy at the Ministry of Health – Portugal (2000-2002)
- Working at Ciba-Geigy – Medical Dep./ I&D - before joining INFARMED (1981 – 1989)
- Teaching at Medical and Pharmaceutical Universities (in Portugal) – Clinical trials methodology, pre-marketing assessment of Efficacy and Safety, post-marketing safety follow-up and assessment

Education

- Medicine - Classical University of Lisbon
- Qualified in Internal Medicine and Pharmaceutical Medicine

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Areas of expertise

- As above

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Ms Birthe Byskov Holm

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP), since 2003. Vice-Chair 2006-2012.

Professional background

Current positions:

- Patient organisations: Board member in the Danish Umbrella Association of Rare Disorders
- Board member in the Danish Osteogensins Imperfecta Society
- Chairperson on the board of the Danish Information Centre of Rare Disorders
- Solicitor (practicing in Copenhagen), since 2003

Other relevant positions:

- Regional Director of a Regional Customs and Tax administration in the area of Copenhagen (before 2003)

Education

- Master in Law, University of Copenhagen

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Prof. Brigitte Blöchl-Daum

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP), since 2005.

Membership in EMA working parties / groups

- COMP representative in the Scientific Advise Working Party (SAWP)

Professional background

Current positions:

- Vice Chair of the Department of Clinical Pharmacology, Medical University Vienna

Other relevant positions:

- Consultant for Internal Medicine
- Consultant for Clinical Pharmacology

Education

- Medicine, Professor for Clinical Pharmacology

Areas of expertise

- Clinical Pharmacology
- Internal medicine
- Oncology

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Bożenna Dembowska-Bagińska

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP) since 2006

Professional background

Current positions:

- Position - Professor, Vice-Head, Department of Paediatric Oncology, the Children's Memorial Health Institute, Al Dzieci Polskich 20, 04-730 Warsaw, Poland (since 1996)

Other relevant positions:

- Lecturer for Medical Centre for Continuous Postgraduate Training, Warsaw, Poland on paediatric oncology for fellows specialising in paediatrics, paediatric surgery, paediatric oncology, family doctors, dentists, nurses (since 1990)

Education

- Habilitation (May 2009)
- 2nd degree in Paediatric Oncology and Haematology (February 2003)
- Postgraduate degree in " Planning and Management of Health Care Systems" at the International School of Managers and International School of Commerce and Finances, Warsaw (March 2000)
- 2nd degree specialisation in Clinical Oncology (April 1993)
- Doctorate Thesis (MD, PhD) (May 1990)
- 1st degree in General Paediatrics (October 1984)
- Medical doctor 1980
- Medical Academy, Warsaw, Poland (1975 – 1980)

Other relevant courses, education and training:

- Maria Curie-Skłodowska Institute of Oncology, Warsaw
- Institute of Haematology, Warsaw

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- Division of Paediatric Oncology of the Children's Hospital of Philadelphia (CHOP)
- Department of Oncology of the University of Pennsylvania
- Working visits at many international centres treating children with cancer (United States, Germany, France, Belgium, Netherlands, Japan, China, Russia)
- Member of the Scientific Committee of European Trial for High Risk Neuroblastoma (subcommittee-immunology)
- Member of the Proposed Cochrane Childhood Cancer Review Group
- Member of a team which created UE project "Centre of Excellence-PERFECT" at the Children's Memorial Health Institute
- Evaluation of the Medicinal Products in Children, organised by ESDP-EUDIPHARM, Belgium (2006)
- Numerous courses in paediatric oncology, clinical oncology, genetics, statistics
- Active participant at annual National and International Conferences on Paediatric Oncology (Chairman of many sessions on national level and on international symposium)
- Active participant at conferences organised by the Polish Society of Clinical Oncology
- Member of organising and scientific committees of numerous national and international symposiums organised in Poland, e.g.

  – International Conference for Young Paediatric Oncologists Warsaw (1994)

  – I, II, III Polish Symposium on Paediatric Neurooncology – 1998, 2000, 2002, 2004,2007,2009,2011 with international guests

  – Third Symposium of the Society of Paediatric Oncology and Haematology (2005)

Areas of expertise

- Clinical, Oncology, Paediatric Oncology, Paediatrics

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Antonio Blázquez

Scientific profile

Membership in the European Medicines Agency scientific committees

- Observer in the Committee for Orphan Medicinal Products (COMP), since 2011.

Membership in European Medicines Agency working parties / groups

- Member of the Blood Products Working Party (BPWP), 2009-2010.

Professional background

Current positions:

Head of Service, Pharmacology and Clinical Assessment Division, Medicines for Human Use Department, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain.

Education

- PharmD. Universidad de Salamanca, Spain.
- PhD. Pharmacy (Pharmacoepidemiology). Universidad de Salamanca, Spain.

Areas of expertise

- Blood Products, Pharmacokinetics.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Irena Mesholam Bradinova

Membership in the European Medicines Agency scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP), since 2012.

Professional background

Current positions:

- Genetic counsellor, National Genetic Laboratory, UHOG "Maichin dom", Sofia.

Education

1991-1997 Medical University, Sofia, Faculty of medicine: Medical Doctor.

1998-2006 Department of paediatrics, Medical University, Sofia: PhD and Specialization in Paediatrics.

Areas of expertise

- Paediatrics, Medical Genetics, Clinical Genetics.

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Professional background

Current positions:

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Education

1991-1997 Medical University, Sofia, Faculty of medicine: Medical Doctor.

1998-2006 Department of paediatrics, Medical University, Sofia: PhD and Specialization in Paediatrics.

Areas of expertise

- Paediatrics, Medical Genetics, Clinical Genetics.

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EUROPEAN MEDICINES AGENCY
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Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Medicinal Products for Human Use (CHMP), since April 2012. Alternate member (2008-2011)
- Member of the Committee for Orphan Medicinal Products (COMP), since 2011

Membership in the EMA working parties / groups

- Member of the Mutual Recognition & Decentralised Procedures - Human (CMDh) (2005-2008)
- Alternate member of the Management Board (2003-2005) and (2007-2008)

Professional background

Current positions:

- Scientific Expert , National Organisation for Medicines, Greece

Other relevant positions:

- Head of Evaluation Division (2004-2011), Head of Public Relations Division (2000-2004), National Organisation for Medicines, Greece

Education

- Pharmacist, PhD (University of Athens)
- Fellow in the Univ. of London Ontario, Canada (Post Doc Research in Biotechnology)

Areas of expertise

- Clinical and quality assessment of medicines
- Regulatory affairs, Pharmaceutical legislation

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Daniel O'Connor

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP), since 2010

Membership in the EMA working parties / groups

- COMP representative in the EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP), since 2012

Professional background

Current position:

- Medical Assessor at the Medicines and Healthcare products Regulatory Agency (MHRA), UK

Education

- BSc. Physiology with Biochemistry, Queen Mary's, London
- PhD. Tumour Suppressor Genes, Imperial College and the Ludwig Institute for Cancer Research
- MB ChB. Medicine, Leicester University Medical School, University of Leicester, UK

Areas of expertise

- Oncology
- Histopathology

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Prof. Henri Metz

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP) since 2000

Professional background

Current positions:

- President of the Luxembourg Society of Medical Sciences
- Administrator of the National Research Fund
- Member of the National Ethic Commission

Other relevant positions:

- Honorary State Councelor
- Vice-President of the Cerebral Palsy Foundation
- Lecturer in Paediatric Neurology at the High School for medical professions
- Professor emeritus at the Catholic University of Louvain

Education

- Medical qualifications at the universities of Strasburg and Paris
- Specialisation in Neurology at the Hospital "La Salpétriére" in Paris and the National Hospital Queen Square
- Specialisation in Paediatric Neurology at the Great Ormond Hospital
- FRCP (Edin)
- Master of Hospital Sciences at the Catholic University of Louvain
- Superior clinical course for CEO in Harvard)

Areas of expertise

- Epilepsy

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- Degenerative Diseases of the Nervous System
- Cerebrovascular diseases, cerebral palsy

European Medicines Agency

Mr. Ioannis Kkolos

Membership in the EMEA scientific committees

- Member of the Committee on Orphan Medicinal Products (COMP) (since 2004)

Membership in working parties

- Member of Good Clinical Practice ad hoc working group

Professional background

Current positions:

- Pharmacist, Drug Regulatory Sector, Pharmaceutical Services, Ministry of Health, Cyprus (since 2000)

Other relevant positions:

- Pharmacist, Drug Information and Poison Control Centre, Division of Clinical Pharmacy, Lefkosia General Hospital, Cyprus (1996)

Education

- Bachelor of Science in Pharmacy, Massachusetts College of Pharmacy and Allied Health Sciences Boston, Massachusetts, USA (1992)
- Master of Science in Clinical Pharmacy, International Policy and Practice, University of London, School of Pharmacy, London, U.K. (1999)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Judit Eggenhofer

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP) since 2004

Professional background

Current positions:

- Scientific Adviser, National Institute for Quality- and Organisational Development in Healthcare and Medicines, Budapest, Hungary (since 2011)

Other relevant positions:

- Invited lecturer in pharmacology, clinical pharmacology, GCP
  - Semmelweis Medical University, Budapest, Hungary
  - University of Debrecen Medical and Health Science Centre, Debrecen, Hungary
- Member of Hungarian Society for Experimental and Clinical Pharmacology
- Member of Editorial Board of Journal of the Hungarian Society of Internal Medicine

Education

- Pharmacist, Semmelweis Medical University, Budapest, Hungary
- PhD in pharmacology and toxicology

Areas of expertise

- Clinical pharmacology, pharmacology, SmPC/PL of drugs

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Prof. Josep Torrent-Farnell

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP) since 2000. Chair 2000-2006

Membership in EMA working parties / groups

- COMP representative in the Scientific Advise Working Party (SAWP) 2012-2013

Professional background

Current positions:

- General Director, Dr Robert Foundation, Autonomous University organisation devoted to continuing medical education and postgraduate training

Education

- M.D.m PhD, Pharm.D specialised in Internal Medicine and in Clinical Pharmacology
- Postgraduate diploma in: Public Health, European Law and EU Institutions, Health Education,
- Postgraduate courses change management

Areas of expertise

- Methodology of clinical trials
- Clinical Pharmacokinetic
- Pharmacodynamics amendment in non-therapeutic trials
- Drug utilization
- Outcome research
- Neurology

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Kateřina Kubáčková

Scientific profile

Membership in the European Medicines Agency scientific committees

Member of the Committee for Orphan Medicinal Products (COMP) since 2012

Professional background

Current positions:

- Senior physician at Comprehensive Cancer Centre

Other relevant positions:

- EUCERD member, Ministry of Health - Task Group for Rare Diseases

Education

Charles University in Prague - Medical Faculty

Areas of expertise

Medical Oncology- lymphoma, myeloma, solid tumours

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Prof. Dainis Krievins

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP) since 2009

Professional background

Current positions:

- Professor of Surgery, University of Latvia
- Vascular surgeon, Stradins Universtity Hospital, Riga, Latvia
- Director of Science and Education, Stradins University Hospital, Riga, Latvia

Other relevant positions:

- Chairman, Clinical Research Scientific Advisory Committee, Clinical Research Foundation EEU

Education

- Medical Academy of Latvia, (MD degree)
- Riga Stradins University, Latvia (PhD degree)
- Stranford University, USA (Fellowship in Surgery, Research in Vascular Surgery)

Areas of expertise

- Clinical and research expertise in angiology and surgery

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Prof. Kerstin Westermark

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP) since 2000. Chair 2006-2012.

Membership in the EMA working parties / groups

- COMP representative in the Scientific Advise Working Party (SAWP) 2004-2008 and since 2013.

Professional background

Current positions:

- Senior Expert, Medical Products Agency, Uppsala, Sweden (since 2005)
- Adjunct Professor of Medicine, Dept. of Medical Sciences, Uppsala University (since 2008)

Other relevant positions:

- Senior Consultant, Dept. of Internal Medicine, Uppsala University Hospital (1993-1995)
- Head of Section for Endocrinology and Diabetes, Uppsala University Hospital (1995 – 1996)
- Head of National Centre for Wilson's Disease, Dept. of Internal Medicine, Uppsala University Hospital (1996-2000)
- Director of Studies, Dept. of Internal Medicine, Uppsala University (1986 – 1992)
- Associate Professor, Dept. of Internal Medicine, Uppsala University (1989 – 2008)
- Member of the Board of the Faculty of Medicine, Uppsala University (1990 – 1993)
- Member of the Board of the Swedish Endocrine Society (1991 – 1999)
- Head of Department of Clinical Trials, Medical Products Agency (1997-2005)
- Senior Lecturer, Dept. of Medical Science, Uppsala University (1999-2008)

Education

- MD, Faculty of Medicine, Uppsala University, Uppsala, Sweden
- Specialist in Internal Medicine, Uppsala University Hospital

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- Specialist in Endocrinology, Uppsala University Hospital
- PhD, Dept. of Internal Medicine, Uppsala University

Areas of expertise

- Internal Medicine, Endocrinology
- Research in Experimental Thyroidology
- Research in Wilson's Disease

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Lars Gramstad

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP), since 2004

Professional background

Current positions:

- Chief Consultant, Dept. for Medicinal Product Assessment, Norwegian Medicines Agency (NoMA), since 2001

Other relevant positions:

- Member of the CPMP (2000 – 2004)
- Senior Consultant, Medical Dept., NoMA (1993 – 2001)
- Senior Consultant, Dept. of Anaesthesia, Norwegian Radium Hospital, Oslo (1992 – 1993)
- Senior Lecturer in anaesthesiology, Rikshospitalet, University of Oslo (1987 – 1992)

Education

- MD, University of Oslo (1974)
- DMSc, University of Oslo (1989)
- Certified specialist in anaesthesiology (1991)
- Judged competent for full professorship in anaesthesiology, University of Oslo (1993)

Areas of expertise

- Pharmacology in anaesthesiology

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mrs Lesley Claire Greene

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP), since 2009. Vive-Chair since September 2012

Membership in EMA working parties / groups

- Member of the Working Group with Patient Organisations: Product Information, 2003-2006

Professional background

Current positions:

- Volunteer EURORDIS Patient Advocate

Other relevant positions:

- Development Manager and Founder CLIMB (Children Living with Inherited Metabolic Diseases in Children) 1981-2009
- Advisory Group for Genetic Research (UK Department of Health) 2004-2007
- EURORDIS Director 1997-2003
- EURORDIS President 2001-2003

Education

- Bachelor of Arts (Hons) Postgraduate Certificate of Education

Areas of expertise

- Development of lay-friendly information for metabolic diseases
- Patient Advocate, metabolic diseases
- Management of helpline and advocacy services

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Armando Magrelli

Scientific profile

Membership in the European Medicines Agency scientific committees

Member of the Committee for Orphan Medicinal Products (COMP), since 2012.

Professional background

Current positions:

- Senior Researcher

Education

PhD Molecular Biology

Areas of expertise

Molecular Biology; Rna Biology; Rare Diseases; Bioinformatics and Sistems theory; Gene Therapy; Molecular biology of Hepatoblastomas, Hailey-Hailey disease, Epidermolysis Bullosa, Juvenile Parkinsons, chronic lymphocytic leukemia, Multiple Exostosis, Left Clip Palate.

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Maria Mavris

Scientific profile

Membership in the European Medicines Agency scientific committees

Permanent observer and patient representatives' scientific support at the Committee for Orphan Medicinal Products (COMP)

Professional background

Current positions:

- Drug Development Programme Manager at EURORDIS, the European Organisation for Rare Diseases

Other relevant positions:

- Medical Writer at Contract Research Organisation specialised in oncology, Paris, France
- Post-doctoral Scientist at Ecole Veterinaire Alfort, Maison-Alfort, France
- Post-doctoral Scientist at Institut Pasteur, Paris, France

Education

- PhD in Molecular Microbiology from University of Adelaide, Australia

Areas of expertise

- Molecular microbiology
- Training for Patients' representatives
- Health and research policies

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mr Martin Možina

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP) since 2004

Membership in EMA working parties / groups

- Co-Chairman of Pharmacovigilance Working Group of CEE Accession Countries (1999 – 2004)

Professional background

Current positions:

- Poison Control Centre, Head (since 1990)
- National Pharmacovigilance Centre (since 1983)

Education

- Medical Faculty, Ljubljana. Specialist of internal medicine
- Postgraduate courses in intensive care medicine, clinical toxicology, pharmacovigilance, GCP
- Postgraduate study in clinical pharmacology

Areas of expertise

- Internal medicine
- Intensive care
- Clinical pharmacology and toxicology
- Pharmacovigilance
- GCP
- Antidotes

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Frauke Naumann-Winter

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP), since 2013.

Professional background

Current positions:

- Responsible for orphan medicinal products at "Unit EU/International Affairs" at the Federal Institute for Drugs and Medical Devices (BfArM), DE
- Clinical assessor at the BfArM

Education

- PhD Molecular Biology, University of Cologne
- European MSc. Epidemiology, University of Mainz

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Pauline Evers

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP), since 2006

Professional background

Current positions:

- Employed by Dutch Federation of Cancer Patient Organisations (since 2008)
- Representative for EGAN, European Genetic Alliances Network (since 2005)

Other relevant positions:

- VSOP, Dutch Genetic Alliance, Soestdijk, The Netherlands (2003-2008)
- Genzyme, Manager Regulatory Affairs Europe, Naarden, The Netherlands (1997 – 2003)
- Chiron, Manager Regulatory Affairs Europe, Amsterdam, The Netherlands (1988 – 1997)

Education

- Masters Degree in Medical Biology, State University Groningen, The Netherlands (1983)
- PhD in Medicines, Department of Human Genetics, Free University Amsterdam, The Netherlands (1988)
- Teaching degree in Biology for secondary schools, State University Groningen, The Netherlands (1983)

Areas of expertise

- Patient advocacy
- Genetics, rare diseases, biotechnology
- Reimbursement issues

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Flavia Saleh

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP) since 2007

Membership in EMA working parties / groups

- Member of the Product Information Management Working Party (PIM WP)

Professional background

Current positions:

- Head of European Procedures Evaluation Unit (since 2010), European Procedures Department, National Agency for Medicines and Medical Devices, Bucharest, Romania

Education

- Medicine Faculty "Carol Davila" University in Bucharest, Romania (1990)
- Training in anaesthesiology "Fundeni" Universitary Clinical Hospital in Bucharest, Romania (1992 – 1995)
- Training in clinical pharmacology "Sf Pantelimon" Emergency University Clinical Hospital in Bucharest, Romania (2004 – 2007)

Areas of expertise

- Clinical pharmacology

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Prof. Bruno Sepodes, PharmD MSc PhD

Scientific profile

Membership in the European Medicines Agency scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP), since 2008.
- Member of the Committee for Medicinal Products for Human Use (CHMP), since 2012
- Member of the Committee for Advanced Therapies (CAT), since May 2013

Membership in European Medicines Agency working parties / groups

- Member of the Patients' and Consumers' Working Party, since 2012.

Professional background

Current positions:

- Professor of Pharmacology, Immunopharmacology and Pharmacotherapy at the University of Lisbon (Faculty of Pharmacy), Portugal
- Member of the Evaluation Board of Medicines of the Portuguese National Authority of Medicines and Health Products - INFARMED, I.P.
- Preclinical Expert for the Portuguese National Authority of Medicines and Health Products - INFARMED, I.P.
- Member of the Portuguese National Formulary of Medicines Working Group
- Preclinical and Pharmaceutical Expert for the Portuguese National Authority for Animal Health (Direção Geral de Veterinária, DGV)

Other relevant positions:

- Research scientist at the Research Institute for Medicines and Pharmaceutical Sciences (iMED.FFUL) – University of Lisbon, Portugal (since 2007)

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Education

- **PharmD**, Pharmaceutical Sciences degree by the Faculty of Pharmacy at the University of Lisbon, Portugal (2001)
- **MSc**, Master degree in Regulation and Evaluation of Medicines and Health Products, Faculty of Pharmacy, University of Lisbon, Portugal (2006)
- **PhD** in Pharmacology by the University of Lisbon, Portugal (2008)
- Author and co-author of more than 70 scientific publications in international journals, and 90 scientific communications (on pharmacology, immunopharmacology, pharmacotoxicology and therapeutics), presented to national and international scientific meetings.

Areas of expertise

- Orphan medicinal products development and evaluation
- Pharmacology of inflammation
- Ischemia-reperfusion injury
- Human medicines evaluation
- Pharmacodinamics and non-clinical pharmacokinetics
- Pharmacology in laboratory and target animals
- General and special toxicology
- Non-clinical drug development

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NIKOLAOS SYPSAS

Scientific profile

Membership in the European Medicines Agency scientific committees

- Member of the Committee for Orphan Medicinal Products - COMP, since August 2012.

Professional background

Current positions:

- Assistant Professor, Medical School, National and Kapodistrian University of Athens, Athens, Greece
- Attending Physician, Internal Medicine/Infectious Diseases Laikon General Hospital, Athens, Greece

Other relevant positions:

- External Advisor, National Organization for Medicines, Athens, Greece

Education

M.D. Degree:	Athens University Medical School, Greece; 1985
Thesis:	Zurich University Medical School, Switzerland; 1990 Athens University Medical School, Greece; 1997
Internship:	Department of Medicine, Athens Naval Hospital, 2/1987-2/1988
Residency:	Department of Internal Medicine, Laikon General Hospital and Athens University Medical School, 7/1990-7/1994
Fellowship:	Infectious Disease Unit, Massachusetts General Hospital and Harvard Medical School, Boston, USA, 10/1994-4/1997
Sabbatical:	M.D. Anderson Cancer Center, University of Texas, Houston, Texas, USA, 3/2007-6/2007

Areas of expertise

- Internal Medicine
- Infectious Diseases (HIV infection, Zoonoses, Medical Mycology)

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Sigurður Thorsteinsson

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee for Orphan Medicinal Products (COMP), since 2003

Professional background

Current positions:

- Chairman Icelandic Pharmaceutical Committee, since 1984

Other relevant positions:

- Chief, Div. of Pharmaceutical Affairs, Landspitali-University Hospital, Reykjavík, Iceland (until 2012)
- Associate professor, Internal Medicine/Infectious Diseases, University of Iceland (1990 – 2003)

Education

- M.D., American boards of Internal Medicine
- Post graduate training in Internal Medicine and Infectious Diseases, Baylor College of Medicine, Houston, Texas, USA

Areas of expertise

- Infectious Diseases and anti-infectives and HIV/AIDS

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Violeta Stoyanova-Beninska

Scientific profile

Membership in the European Medicines Agency scientific committees

- Member of the Committee on Orphan Medicinal Products (COMP) since 2012

Membership in European Medicines Agency working parties / groups

- Alternate member of the Scientific Advise Working Party (SAWP) (2010 – 2012)
- Additional expert of Central Nervous System Drafting Group (CNS DG) since 2009

Professional background

Current positions:

- Clinical Assessor at Medicines Evaluation Board (MEB), Utrecht, The Netherlands

Other relevant positions:

- Guest physician at Division of Mood disorders, Department of Psychiatry, Amsterdam Medical Centre (AMC), Amsterdam, The Netherlands

Education

- Medicine, PhD in molecular genetics, Master of public health

Areas of expertise

- Psychiatry
- Genetics
- CNS

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Prof. Albert Vincenti

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP) since 2008

Professional background

Current positions:

- Director, Pathology Services, St Thomas's Hospital, Malta (private hospital)
- Chairman, Academy of Nutritional Medicine (UK)

Other relevant positions:

Former

- Pathology Department Head & Deputy Dean, Malta University Medical School
- Consultant Surgical Pathologist and Chairman, Pathology Services, Maltese National Health Service
- Consultant Surgical Pathologist & Pathology Services Director to Winchester & Eastleigh Health Care Trust, Hampshire, England
- Consultant Pathologist to HM Coroner in Central Hampshire, England
- London University Lecturer & Pathologist to HM Coroner in Central London

Education

- Undergraduate training in Malta
- Postgraduate training at Royal Marsden, St George's, Royal Free, Charing Cross & The Middlesex hospitals in London

Areas of expertise

- Surgical pathology (histopathology & cytopathology)
- Nutritional medicine

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Veijo Saano

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP) since 2004

Membership in EMA working parties / groups

- Member of Mutual Recognition Facilitation Group (MFRG) (1996 – 2003), Chairman from July to December 1999

Professional background

Current positions:

- Senior Medical Officer, Finish Medicines Agency (since 1993)

Other relevant positions:

- Docent in clinical pharmacology, Medical Faculty, University of Tampere, Finland (since 1995)
- Docent in pharmacology, Medical Faculty, University of Eastern Finland, Finland (since 1992)
- 1 year visiting fellow; Humanpharmakologisches Institut Ciba-Geigy, Tübingen, Germany (1990 – 1991)
- Acting senior medical officer; National Agency for Health, Finland (3 months in 1998)
- Assistant physician; Dept. of Oncology, University Hospital, Kuopio, Finland (3 months in 1987 – 1988)
- 1 year acting house officer; City Hospital, Kuopio, Finland (1987 – 1988)
- 1 year acting associate professor in pharmacology; University of Kuopio, Finland (1985 – 1986)
- Assistant professor in pharmacology; University of Kuopio, Finland (1980 – 1993)
- Assistant, senior lecturer in pharmacology; University of Kuopio, Finland (1974 – 1880)

Education

- M.D., fully authorised physician; University of Kuopio, Finland (1977)

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- Ph.D. in pharmacology; University of Kuopio, Finland (1982)
- Authorised specialist in clinical pharmacology; University of Kuopio, Finland (1989)

Areas of expertise

- Respiratory pharmacology

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Dr Vallo Tillmann

Scientific profile

Membership in the European Medicines Agency (EMA) scientific committees

- Member of the Committee of Orphan Medicinal Product (COMP), since 2003

Professional background

Current positions:

- Professor in Paediatrics, Tartu University Children's Clinic, Estonia

Other relevant positions:

- Consultant in Paediatric Endocrinology, Tartu University Children's Clinic, Estonia

Education

- Medical Doctor (cum laude), University of Tartu, Estonia
- M.D. (Doctor of Medicine), University of Manchester
- Qualified Doctor in Paediatrics, University of Tartu, Estonia
- Certificate in Paediatric Endocrinology, European Society of Paediatric Endocrinology
- Registered Doctor in Paediatrics and Endocrinology, Estonian Health Care Board

Areas of expertise

- Paediatrics
- Endocrinology
- Normal growth
- Growth hormone deficiency in children
- Disorders of puberty
- Late effects of childhood cancer treatment

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Electronic Acknowledgement Receipt

EFS ID:	16638350
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Dawn Avila
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	20-AUG-2013
Filing Date:	14-MAY-2013
Time Stamp:	17:25:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1958603-21-Response_to_OA.pdf	130882 dfdb8add39ad024e2d1e2ac84e36c17bb0762a3a	yes	18

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Applicant summary of interview with examiner	2	2
	Claims	3	5
	Applicant Arguments/Remarks Made in an Amendment	6	18

Warnings:					
Information:					
2	Miscellaneous Incoming Letter	1958603-21_Draft_Public_Statement.pdf	76318 06e26bc473c09e3de23de76e5b22db75d8477fc3	no	2
Warnings:					
Information:					
3	Miscellaneous Incoming Letter	1958603-21_EMA_Letter.pdf	37159 2415c16529b8a1c7f2902807a7a8464e584bcee2	no	2
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	1958603-21_Minutes_Presubmission_meeting_Axsome_17_June_2013_v2.pdf	37565 bfb8b5eca041c741aba513c3dc5a5b8268016767	no	3
Warnings:					
Information:					
5	Miscellaneous Incoming Letter	1958603-21-Exhibit_A.pdf	471726 d9729037fbcddd0bd1b1e76b36816c078eb19c27	no	55
Warnings:					
Information:					
		Total Files Size (in bytes):	753650		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 45200

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 45200

OR

☐ Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address:

Antecip Bioventures II LLC
2711 Centerville Road, Suite 400
Wilmington, DE 19808

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	[signature]	Date	6-20-12
Name	HERRIOT TABUTEAU	Telephone	646-688-2824
Title	MANAGING MEMBER		

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	17140963
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Dawn Avila
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	16-OCT-2013
Filing Date:	14-MAY-2013
Time Stamp:	13:37:08
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73.	1958603-21_STATEMENT_UNDER_373.pdf	325717 951e3a22d59ee21630710df730764c67146c6f68	no	2

Warnings:	
Information:	

2	Power of Attorney	ANTECIP.pdf	758369 f31e979557426 1f4166dea8c6a83fcca34b6c52d	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	1084086	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/96 (01-09)
Approved for use through 02/28/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Herriot Tabuteau

Application No./Patent No.: 13/894,244 Filed/Issue Date: 05/14/2013

Titled:
Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

Antecip Bioventures II LLC , a corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in
(The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 030421, Frame 0213, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Brent A. Johnson/ 10/16/2013
Signature Date

Brent A. Johnson Attorney
Printed or Typed Name Title

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021

CONFIRMATION NO. 1033

IMPROPER CPOA LETTER

45200
K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

OC000000064448105

Date Mailed: 10/22/2013

NOTICE REGARDING POWER OF ATTORNEY

This is in response to the power of attorney filed 10/16/2013. The power of attorney in this application is not accepted for the reason(s) listed below:

- The power of attorney has not been accepted because the party who is giving power of attorney has not been identified. Power of attorney may only be signed by the applicant for patent (37 CFR 1.42) or the patent owner. A patent owner who was not the applicant must appoint any power of attorney in compliance with 37 CFR 3.71 and 3.73. See 37 CFR 1.32(b)(4).

/snguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021

CONFIRMATION NO. 1033

45200
K&L Gates LLP
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

IMPROPER CFR REQUEST

OC000000064448130

Date Mailed: 10/22/2013

RESPONSE TO REQUEST FOR CORRECTED FILING RECEIPT

Power of Attorney, Claims, Fees, System Limitations, and Miscellaneous

In response to your request for a corrected Filing Receipt, the Office is unable to comply with your request because:

- Any request to correct or update the name of the applicant must include an application data sheet (ADS) in compliance with 37 CFR 1.76 specifying the correct or updated name of the applicant in the applicant information section. Any request to change the applicant after an original applicant has been specified under 37 CFR 1.46(b) must include a new ADS in compliance with 37 CFR 1.76 specifying the applicant in the applicant information section and comply with 37 CFR 3.71 and 3.73. See 37 CFR 1.46(c).

/snguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	:	**1033**
Appln. No.	:	13/894,244
Applicant	:	Herriot Tabuteau
Filed	:	05/14/2013
Docket No.	:	1958603.00021
Customer No.	:	45200
Title	:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

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UPDATED APPLICATION DATA SHEET IN RESPONSE TO NOTICE REGARDING POWER OF ATTORNEY

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

Dear Sirs:

In response to the Notice Regarding Power of Attorney mailed October 22, 2013, Applicants submit the attached Updated Application Data Sheet with updates underlined. Also attached is the Power of Attorney and 3.73 Statement.

The Commissioner is authorized to charge any fee which may be required in connection with this Notice or credit any overpayment to deposit account No. 50-3207.

Respectfully submitted,

Dated: November 5, 2013

/Brent A. Johnson/
Brent A. Johnson Ph.D.
Registration No. 51851
Customer No. 45,200

K&L GATES, LLP
1 Park Plaza, 12th Floor
Irvine, California 92614-7319
Telephone: 949.253.0900
Facsimile: 949.253.0902

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Herriot		Tabuteau	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	New York	State/Province	NY	Country of Residence	US

Mailing Address of Inventor:

Address 1	260 Park Avenue South, Apt. B		
Address 2			
City	New York	State/Province	NY
Postal Code	10010	Country	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	45200		
Email Address	chicago.patents@klgates.com	Add Email	Remove Email

Application Information:

Title of the Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease		
Attorney Docket Number	1958603.00021	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	8	Suggested Figure for Publication (if any)	

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)
☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	45200		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61646538	2012-05-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61647478	2012-05-15
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61654292	2012-06-01
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61654383	2012-06-01
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61655527	2012-06-05
Prior Application Status	Pending		Remove

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61655541	2012-06-05
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61762225	2013-02-07
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61764563	2013-02-14
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61767647	2013-02-21
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61767676	2013-02-21
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	non provisional of	61803721	2013-03-20

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date o f filing this Authorization.

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :	

If the Applicant is an Organization check here. ☒

Organization Name	Antecip Bioventures II LLC		
Mailing Address Information For Applicant:			
Address 1	630 Fifth Ave.		
Address 2			
City	New York	**State/Province**	NY
Country	US	Postal Code	10111
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Non-Applicant Assignee Information:

Providing assignment information in this section does not subsitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1

Complete this section only if non-applicant assignee information is desired to be included on the patent application publication in accordance with 37 CFR 1.215(b). Do not include in this section an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest), as the patent application publication will include the name of the applicant(s).

If the Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

PTO/AIA/14 (03-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00021
	Application Number	
Title of Invention	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease	

Mailing Address Information For Non-Applicant Assignee:			
Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Signature	/Brent Johnson/			Date (YYYY-MM-DD)	2013-11-05
First Name	Brent	Last Name	Johnson	Registration Number	51851

Additional Signature may be generated within this form by selecting the Add button.

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

PTO/SB/96 (01-09)
Approved for use through 02/28/2009. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Herriot Tabuteau

Application No./Patent No.: 13/894,244 Filed/Issue Date: 05/14/2013

Titled: Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease

Antecip Bioventures II LLC , a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 030421, Frame 0213, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Brent A. Johnson/ 10/16/2013

Signature Date

Brent A. Johnson Attorney

Printed or Typed Name Title

PTO/SB/80 (11-08)
Approved for use through 11/30/2011. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(b).

I hereby appoint:

☑ Practitioners associated with the Customer Number: 45200

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

as attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(b).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(b) to:

☑ The address associated with Customer Number: 45200

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Assignee Name and Address:

Antecip Bioventures II LLC
2711 Centerville Road, Suite 400
Wilmington, DE 19808

A copy of this form, together with a statement under 37 CFR 3.73(b) (Form PTO/SB/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(b) may be completed by one of the practitioners appointed in this form if the appointed practitioner is authorized to act on behalf of the assignee, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	[signature]	Date	6-20-12
Name	HERRIOT TABUTEAU	Telephone	646-688-2824
Title	MANAGING MEMBER		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Acknowledgement Receipt

EFS ID:	17323278
Application Number:	13894244
International Application Number:	
Confirmation Number:	1033
Title of Invention:	Compositions for Oral Administration of Zoledronic Acid or Related Compounds for Treating Disease
First Named Inventor/Applicant Name:	Herriot Tabuteau
Customer Number:	45200
Filer:	Louis C. Cullman/Dawn Avila
Filer Authorized By:	Louis C. Cullman
Attorney Docket Number:	1958603.00021
Receipt Date:	05-NOV-2013
Filing Date:	14-MAY-2013
Time Stamp:	18:39:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1958603-21_UPDATED_ADS_ETC.pdf	265026 a46f71bb42c97fc721a0506ad7c9e65feaa9db4d	yes	9

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Response to Pre-Exam Formalities Notice	1	1
	Application Data Sheet	2	7
	Assignee showing of ownership per 37 CFR 3.73.	8	8
	Power of Attorney	9	9
Warnings:			
Information:			
	Total Files Size (in bytes):	265026	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/894,244	05/14/2013	Herriot Tabuteau	1958603.00021	1033

45200 7590 11/06/2013

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.