Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (04-14)

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

First Named Inventor:	Herriot Tabuteau et al.	Nonprovisional Application Number (if known):	
Title of Invention:	Osteoclast Inhibitors of Knee Conditions		

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)(1) and the prioritized examination fee set forth in 37 CFR 1.17(c) have been filed with the request. The publication fee requirement is met because that fee, set forth in 37 CFR 1.18(d), is currently $0. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims, and that any request for an extension of time will cause an outstanding Track I request to be dismissed.

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 inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) 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 2015-12-11
Name (Print/Typed) Brent A. Johnson	Practitioner 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.**

☑ *Total of 1 forms are submitted.

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.

PTO/AIA/14 (07-14)
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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	1958603.00116
	Application Number	
Title of Invention	Osteoclast Inhibitors for Knee Conditions	

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	State/Province	Country of Residence
New York	NY	US

Mailing Address of Inventor:

Address 1	25 Broadway, 9th Floor
Address 2	

City	State/Province	Postal Code	Country
New York	NY	10004	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Graeme		Jones	

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

City	Country of Residence
Hobart TAS	AU

Mailing Address of Inventor:

Address 1	Medical Science 2
Address 2	17 Liverpool St.

City	State/Province	Postal Code	Country
Hobart TAS		7000	AU

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

Correspondence Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00116
	Application Number	
Title of Invention	Osteoclast Inhibitors for Knee Conditions	

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	OCpatents@klgates.com	Add Email	Remove Email

Application Information:

Title of the Invention	Osteoclast Inhibitors for Knee Conditions		
Attorney Docket Number	1958603.00116	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	14	**Suggested Figure for Publication (if any)**	

Filing By Reference :

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

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		

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00116
	Application Number	
Title of Invention	Osteoclast Inhibitors for Knee Conditions	

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(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.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending	Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	
	Continuation of	14/604524	2015-01-23	
Prior Application Status	Abandoned	Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	
14/604524	Continuation in part of	14/536526	2014-11-07	
Prior Application Status	Patented	Remove		

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/536526	Continuation in part of	14/446184	2014-07-29	9006279	2015-04-14
Prior Application Status	Patented	Remove			

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/446184	Division of	14/288716	2014-05-28	8835650	2014-09-16
Prior Application Status	Expired	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)		
14/288716	Claims benefit of provisional	61/933608	2014-01-30		
Prior Application Status	Patented	Remove			

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/536526	Continuation in part of	14/279229	2014-05-15	9034889	2015-05-19
Prior Application Status	Patented	Remove			

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/279229	Continuation of	14/063979	2013-10-25	8802658	2014-08-12
Prior Application Status	Pending	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)		
14/063979	Continuation in part of	13/894274	2013-05-14		
Prior Application Status	Expired	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)		
13/894274	Claims benefit of provisional	61/803721	2013-03-20		
Prior Application Status	Expired	Remove			

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00116
	Application Number	
Title of Invention	Osteoclast Inhibitors for Knee Conditions	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/767647	2013-02-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/767676	2013-02-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/764563	2013-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/762225	2013-02-07
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/655541	2012-06-05
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/655527	2012-06-05
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/654383	2012-06-01
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/654292	2012-06-01
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/647478	2012-05-15
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/894274	Claims benefit of provisional	61/646538	2012-05-14
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00116
	Application Number	
Title of Invention	Osteoclast Inhibitors for Knee Conditions	

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. 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(i)(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

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.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

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

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00116
	Application Number	
Title of Invention	Osteoclast Inhibitors for Knee Conditions	

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 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	

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 Avenue, Suite 2000		
Address 2			
City	New York	**State/Province**	NY
Country	US	Postal Code	10111
Phone Number		Fax Number	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00116
	Application Number	
Title of Invention	Osteoclast Inhibitors for Knee Conditions	

Email Address	

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

Assignee Information including 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 if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

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

Mailing Address Information For Assignee including Non-Applicant Assignee:

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

Additional Assignee or Non-Applicant 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 A. Johnson/			Date (YYYY-MM-DD)	2015-12-11
First Name	Brent A.	Last Name	Johnson	Registration Number	51851

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

PTO/AIA/14 (07-14)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1958603.00116
	Application Number	
Title of Invention	Osteoclast Inhibitors for Knee Conditions	

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 C o o p eration 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.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	OSTEOCLAST INHIBITORS FOR KNEE CONDITIONS

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [■] The attached application, or
- [ ] United States application or PCT international application number _____

filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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) years, or both.

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.

LEGAL NAME OF INVENTOR

Inventor: Herriot Tabuteau Date (Optional) : _____

Signature: /Herriot Tabuteau/

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/AIA/01 (06-12)
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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	OSTEOCLAST INHIBITORS FOR KNEE CONDITIONS

As the below named inventor, I hereby declare that:

This declaration is directed to:

- [■] The attached application, or
- [ ] United States application or PCT international application number _____ filed on _____.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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LEGAL NAME OF INVENTOR

Inventor: Graeme Jones Date (Optional): 15 JAN 2015

Signature: _____

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

OSTEOCLAST INHIBITORS FOR KNEE CONDITIONS

Inventors: Herriot Tabuteau and Graeme Jones

SUMMARY

[0001] 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.

[0002] Patchy osteoporosis and bone marrow edema may result from osteoclast hyperactivity. Zoledronic acid is a potent inhibitor of bone resorption and osteoclast activity. Nitrogen containing bisphosphonates, such as zoledronic acid, also inhibit the mevalonate pathway in the osteoclast thereby interrupting normal osteoclast function.

[0003] 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.

[0004] Some embodiments include a method of enhancing the oral bioavailability of zoledronic acid comprising orally administering a dosage form containing zoledronic acid in the disodium salt form.

[0005] Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the bioavailability, in a mammal, of zoledronic acid in the disodium salt form is greater than the bioavailability of zoledronic acid in the diacid form would be in the same dosage form.

[0006] Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng•h/mL to about 2000 ng•h/mL to a human being to which the dosage form is administered.

[0007] Some embodiments include a dosage form comprising zoledronic acid in the disodium salt form, wherein the disodium salt form is present in a lower molar amount than

would be present if the zoledronic acid were in the diacid form; and wherein the zoledronic acid in the disodium salt form has an improved bioavailability as compared to the zoledronic acid in the diacid form to the extent that the lower molar amount of the disodium salt in the dosage form does not reduce the amount of zoledronic acid delivered to the plasma of a mammal.

[0008] 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.

[0009] 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.

[0010] 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.

[0011] 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.

[0012] 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%.

[0013] 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.

[0014] Some embodiments include a method of relieving inflammatory pain comprising administering an oral dosage form containing zoledronic acid to a mammal in need thereof.

[0015] In some embodiments, the mammal receives a total monthly dose of zoledronic acid that is about 800 mg/m^2 or less.

[0016] 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.

[0017] Some embodiments include a method of relieving inflammatory pain comprising orally administering zoledronic acid to a mammal in need thereof.

[0018] 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.

[0019] 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

[0020] 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.

[0021] FIG. 2A is a graph depicting reversal of arthritis pain for two different doses of zoledronic acid in a rat model of arthritis pain.

[0022] FIG. 2B is a graph depicting pain thresholds for two different doses of zoledronic acid in a rat model of arthritis pain.

[0023] FIG. 3 is a graph summarizing the results for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[0024] FIG. 4 depicts hindpaw pain thresholds for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[0025] FIG. 5 depicts weight bearing for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[0026] FIG. 6 depicts paw thickness change for vehicle and zoledronic acid treated rats in a rat model of complex regional pain syndrome.

[0027] FIG. 7 depicts the aqueous solubility of disodium zoledronate tetrahydrate as compared to the diacid form of zoledronic acid.

[0028] FIG. 8 depicts the plasma concentration of zoledronic acid in dogs over time after administration of 150 mg of the disodium salt form of zoledronic acid and the diacid form of zoledronic acid.

[0029] FIG. 9 depicts the compressibility of dosage forms containing zoledronic acid in the disodium salt form as compared to the diacid form.

[0030] FIG. 10 depicts the change in VAS pain score compared to placebo at three months with zoledronic acid treatment in patients with osteoarthritis of the knee, bone marrow lesions, and different degrees of joint space narrowing.

[0031] FIG. 11 depicts the change in VAS pain score compared to baseline at three months with zoledronic acid treatment in patients with osteoarthritis of the knee, bone marrow lesions, and different degrees of joint space narrowing.

[0032] FIG. 12 depicts the change in VAS pain score compared to placebo at three months with zoledronic acid treatment in different subgroups of patients with osteoarthritis of the knee and bone marrow lesions.

[0033] FIG. 13 depicts the change in BML lesion size compared to placebo at six months with zoledronic acid treatment in patients with osteoarthritis of the knee, bone marrow lesions, and different degrees of joint space narrowing.

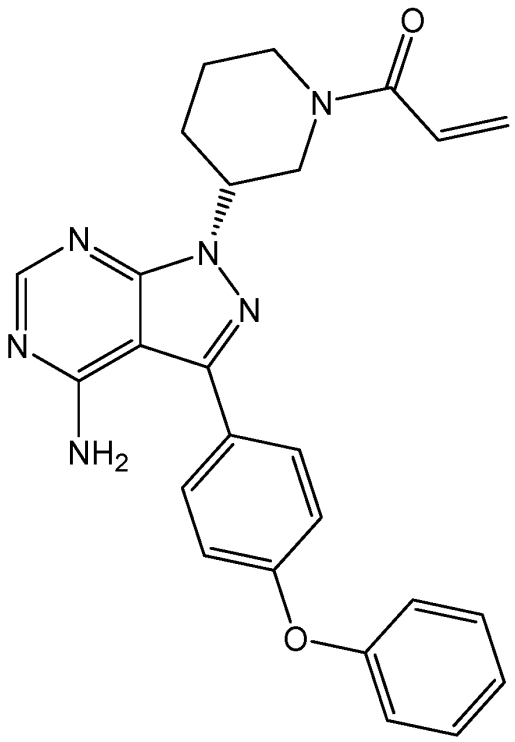
DETAILED DESCRIPTION

[0034] Inhibitors of osteoclast activity include 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, cimadronate or cimadronic acid, zoledronate or zoledronic acid, etidronate or etidronic acid, clodronate or clodronic acid, tiludronate or tiludronic acid, etc.

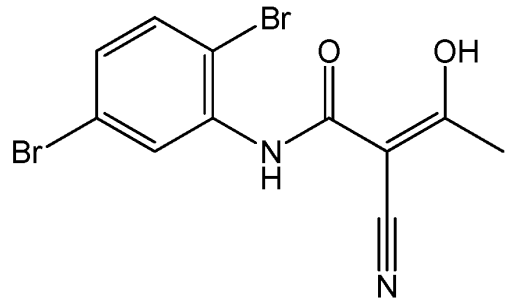
[0035] RANK/RANKL antagonists may be inhibitors of osteoclast activity. RANK/RANKL antagonists include but are not limited to OPG (osteoprotegerin) or a variant thereof, an anti-RANKL antibody such as denosumab, a monoclonal anti-RANKL antibody, a small interfering RNA, a microRNA, a precursor molecule, a ribozyme, an antisense nucleic acid, or an aptamer targeting RANKL. Antibodies such as AB-25E9, small molecules, small

interfering RNAs, microRNAs, precursor molecules, ribozymes, antisense nucleic acids, or aptamers that target the cell-surface protein Siglec-15 may be osteoclast inhibitors.

[0036] Some Bruton's tyrosine kinase (BTK) inhibitors may be inhibitors of osteoclast activity. BTK inhibitors can include ONO-4059; ibrutinib; Benzo[*b*]thiophene-2-carboxamide, *N*-[3-[6-[[4-[(2*R*)-1,4-dimethyl-3-oxo-2-piperazinyl]phenyl]amino]-4,5-dihydro-4-methyl-5-oxo-2-pyrazinyl]-2-methylphenyl]-4,5,6,7-tetrahydro- (GDC-0834); RN-486; Benzamide, 4-(1,1-dimethylethyl)-*N*-[3-[8-(phenylamino)imidazo[1,2-*a*]pyrazin-6-yl]phenyl]- (CGI-560); Benzamide, *N*-[3-[4,5-dihydro-4-methyl-6-[[4-(4-morpholinylcarbonyl)phenyl]amino]-5-oxo-2-pyrazinyl]-2-methylphenyl]-4-(1,1-dimethylethyl)- (CGI-1746CAS Registry No. 910232-84-7); HM-71224; 2-Propenamide, *N*-[3-[[5-fluoro-2-[[4-(2-methoxyethoxy)phenyl]amino]-4-pyrimidinyl]amino]phenyl]- (CC-292, CAS Registry No. 1202757-89-8); 2-Pyridinecarboxamide, 4-[4-[[5-fluoro-4-[[3-[(1-oxo-2-propen-1-yl)amino]phenyl]amino]-2-pyrimidinyl]amino]phenoxy]-*N*-methyl- (CNX-774, CAS Registry No. 1202759-32-7), AVL-101 (CAS Registry No. 1552307-34-2), AVL-291 (CAS Registry No. 1552307-35-3), and AVL-292 (CAS Registry No. 1552307-36-4), [*N*-(2-chloro-6-methylphenyl)-2-(6-(4-(2-hydroxyethyl) piperazin-1-yl)-2-methylpyrimidin-4-ylamino)thiazole-5-carboxamide] (dasatinib), alpha-cyano-beta-hydroxy-beta-methyl-*N*-(2,5-bromophenyl) propenamide (LFM-A13), and ONO-WG-307.



Ibrutinib



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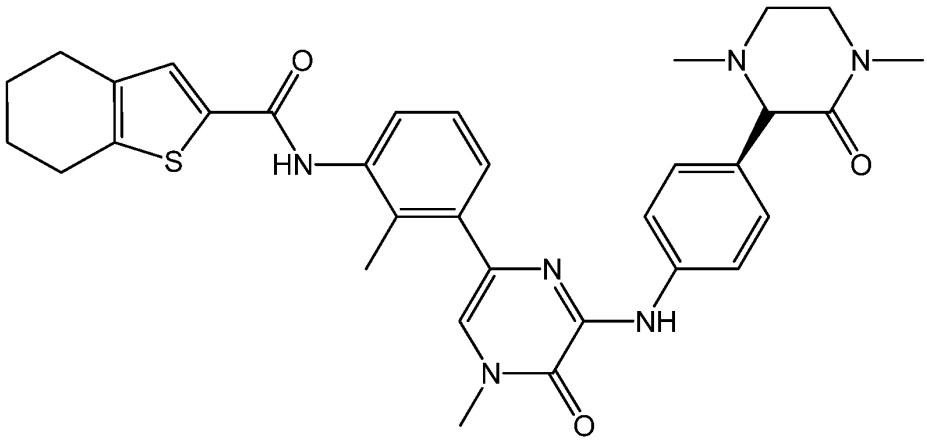

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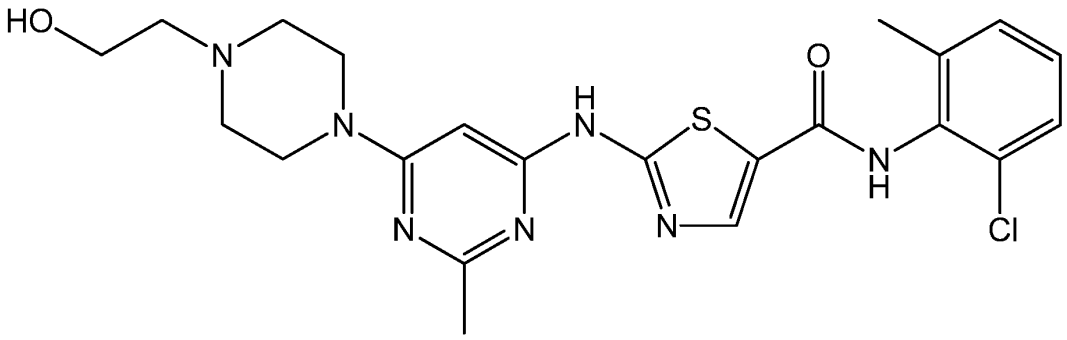

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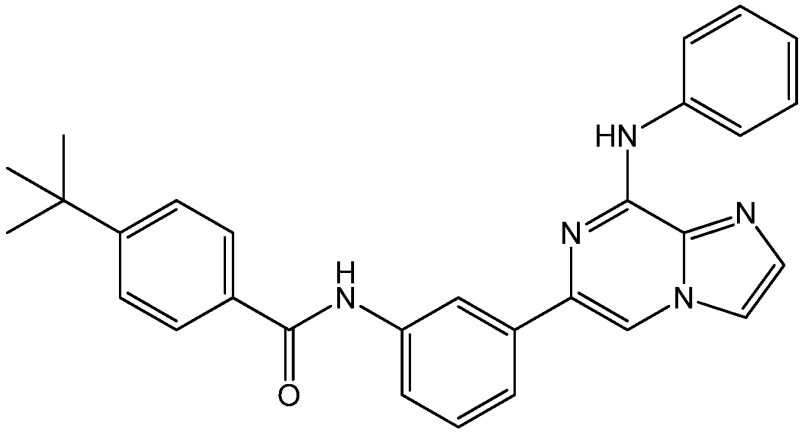

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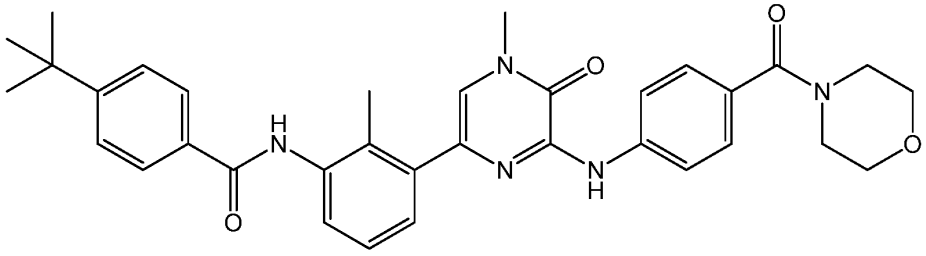

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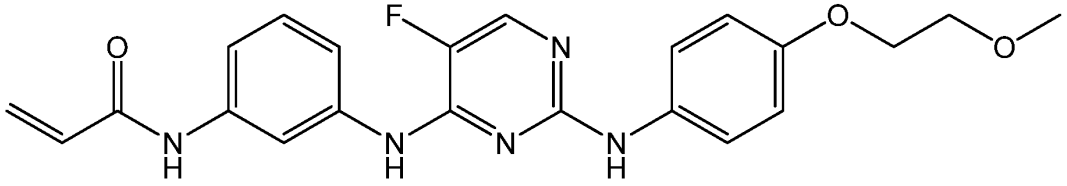

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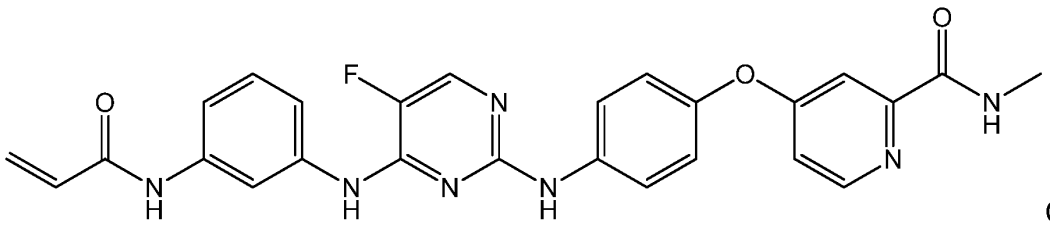
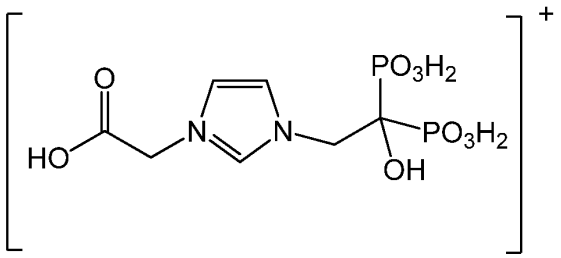


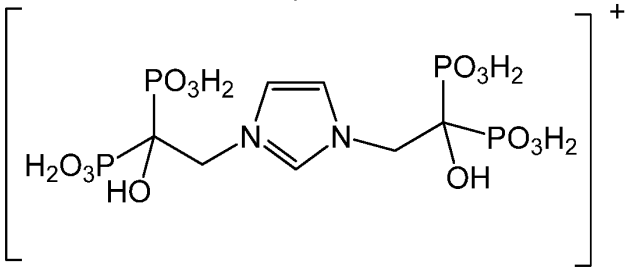
CNX-774

[0037] Inhibitors of osteoclast activity 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.

[0038] The following compounds may also be osteoclast inhibitors:



Compound 1



Compound 2

[0039] 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.

[0040] 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. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0041] 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.

[0042] 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. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0043] 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. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0044] 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. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0045] 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.

[0046] 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 arthropathies including Charcot's foot, axial spondyloarthritis including ankylosing spondylitis, and SAPHO syndrome.

[0047] In some embodiments, a human being that is treated for arthritis by an oral dosage form of zoledronic acid has an age of about 10 years to about 90 years, about 20 years to about 80 years, about 30 years to about 75 years old, about 40 years to about 70 years, about 1 year to about 16 years, or about 80 years to about 95 years.

[0048] In some embodiments, a human being that is treated for arthritis by an oral dosage form of zoledronic acid has suffered from the arthritis for at least 1 month, at least 2 months, at least 6 months, or at least 1 year.

[0049] In some embodiments, the arthritis affects a knee, an elbow, a wrist, a shoulder, an ankle, the spine, or a hip.

[0050] For treatment of arthritis or joint pain, such as knee pain, in some embodiments the person being treated has OARSI Grade 0, or Kellgren and Lawrence Grades 0 or 1, joint space narrowing.

[0051] In some embodiments, the person has lesions, such as bone marrow lesions. In some embodiments the person being treated for bone marrow lesions has normal joint space knee pain, OARSI Grade 0, or Kellgren and Lawrence Grades 0 or 1, joint space narrowing.

[0052] In some embodiments, the person has baseline pain intensity of 5 or greater measured using the 0-10 numerical rating scale (NRS), or 50 mm or greater using the 100 mm visual analog scale (VAS). In some embodiments the person being treated for pain has normal joint space knee pain, OARSI Grade 0, or Kellgren and Lawrence Grades 0 or 1, joint space narrowing.

[0053] Bone marrow lesions (BMLs) include regional bone marrow signal intensity alterations on magnetic resonance imaging (MRI). BMLs can be present in the knee and can be an important feature of osteoarthritis of the knee. BMLs have also been described in other rheumatic conditions such as rheumatoid arthritis, osteonecrosis, ankylosing spondylitis, and transient osteoporosis of the hip and are often referred to as bone marrow edema (BME).

[0054] In some embodiments, a person being treated for arthritis, such as with zoledronic acid, has osteoarthritis of the knee associated with bone marrow lesions.

[0055] In some embodiments, an inhibitor of osteoclast activity can be used to treat bone marrow lesions.

[0056] In some embodiments, an inhibitor of osteoclast activity can be used to treat bone marrow lesions of the knee, shoulder, ankle, wrist, hand, fingers, spine, or hip.

[0057] Commonly used measures of pain intensity include the visual analog scale (VAS) and the numerical rating scale (NRS). With the VAS approach, patients rate the severity of their pain by marking a point on a 10-cm (or 100 mm) VAS (0=no pain and 10=worst possible pain). With the NRS approach, patients rate the severity of their pain by verbally

responding to a 10-point NRS (0=no pain and 10=worst possible pain). VAS and NRS scores have been shown to be strongly correlated (slope of regression line, 1.01), indicating that a score on the 10-cm VAS is equivalent to the same score on 10-point NRS (Bijur PE et al. *Acad Emerg Med* 2003; 10:390-392). For example, a VAS score of 5 cm (or 50 mm) is equivalent to an NRS score of 5. Knee pain in a person with a VAS score of 5 cm or 50 mm or higher, or an NRS score of 5 or higher, may be referred to herein as moderate to severe knee pain.

[0058] In some embodiments, the patient suffering from pain, inflammation, a similar condition, or any of the conditions described herein, has an NRS of 5 or greater, or a VAS of 5 cm or greater. In some embodiments, the patient has an NRS of 4 or greater, or a VAS of 4 cm or greater. In some embodiments, the patient has an NRS of 6 or greater, or a VAS of 6 cm or greater. In some embodiments, the patient has an NRS of 7 or greater, or a VAS of 7 cm or greater. In some embodiments, the patient has an NRS of about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, or about 10. In some embodiments, the patient has a VAS of about 1 cm, about 2 cm, about 3 cm, about 4 cm, about 5 cm, about 6 cm, about 7 cm, about 8 cm, about 9 cm, or about 10 cm.

[0059] For knee pain or pain associated with bone marrow lesions, in some embodiments, treatment with a nitrogen-containing bisphosphonate such as zoledronic acid may decrease the visual analog (VAS) pain score measured using a 100 mm scale, by at least about 5 mm, at least about 8 mm, at least about 10 mm, at least about 15 mm, up to about 50 mm, or up to about 100 mm. In some embodiments, the VAS score, may be decreased by at least about 5 mm, at least about 8 mm, at least about 10 mm, at least about 15 mm, up to about 50 mm, or up to about 100 mm, as compared to a placebo.

[0060] Treatment with a nitrogen-containing bisphosphonate such as zoledronic acid may decrease the numerical rating scale (NRS) pain score measured using a 0-10 scale, by at least about 0.1, at least about 0.5, at least about 0.8, at least about 1, at least about 1.5, up to about 5, or up to about 10. In some embodiments, the NRS score may be decreased by at least about 0.1, at least about 0.5, at least about 0.8, at least about 1, at least about 1.5, up to about 5, or up to about 10, as compared to a placebo.

[0061] In some embodiments, an inhibitor of osteoclast activity can be used to reduce the size of bone marrow lesions. The area of the lesions may be measured as the total

area of all lesions or as the area of any one lesion. In some embodiments, the total area includes the medial tibial area, the medial femoral area, the lateral tibial area, and the lateral femoral area. In some embodiments the bone marrow lesion in located in the patella.

[0062] In some embodiments, the use of an inhibitor of osteoclast activity achieves a reduction in the total area of the bone marrow lesions of at least about 240 mm^2. In some embodiments, the reduction in total area is at least about 220 mm^2, at least about 200 mm^2, at least about 150 mm^2, at least about 100 mm^2, or at least about 50 mm^2. In some embodiments, the reduction in size of bone marrow lesions represents a reduction relative to baseline of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70% at least about 80%, at least about 90%, or about 100%. In some embodiments, the reduction in area of bone marrow lesions represents an improvement relative to placebo of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 120%, at least about 150%, at least about 170%, at least about 200%, at least about 250%, at least about 300%, at least about 350%, at least about 400%, or at least about 450%. In some embodiments, the use of an inhibitor of osteoclast activity inhibits an increase in the size of the bone marrow lesions over time.

[0063] Joint space narrowing (JSN) is typically graded using the Osteoarthritis Research Society International (OARSI) atlas criteria, or the Kellgren and Lawrence (K/L) system. The OARSI atlas criteria grades JSN using a 0-3 scale with Grade 0 indicating an absence of JSN, and Grades 1, 2 and 3 indicating mild, moderate, and severe JSN, respectively (Altman and Gold, *Osteoarthritis Cartilage* 2007;15(Suppl A):A1-A56). The K/L system grades JSN using a 0-4 scale with Grade 0 indicating an absence of JSN, Grade 1 indicating doubtful JSN, and grades 2, 3 and 4 indicating minimal, moderate, and severe JSN, respectively (Kellgren and Lawrence , *Ann Rheum Dis* 1957;16:494–502). Based on these criteria, OARSI Grade 0 (absence of JSN), approximates K/L Grades 0-1 (absence of, or doubtful presence of JSN). Knee pain in a person having OARSI Grade 0 or K/L Grade or 1 JSN in the knee where the pain occurs may be referred to herein as a "normal joint space knee pain."

[0064] In some embodiments for patients having OARSI Grade 0 or K/L Grades 0-1 JSN, the use of an inhibitor of osteoclast activity achieves a reduction in the total area of the bone marrow lesions of at least about 240 mm^2. In some embodiments, the reduction in total area is at least about 220 mm^2, at least about 200 mm^2, at least about 150 mm^2, at least about 100 mm^2, or at least about 50 mm^2. In some embodiments, the reduction in size of bone marrow lesions represents a reduction relative to baseline of at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70% at least about 80%, at least about 90%, or about 100%. In some embodiments, the reduction in area of bone marrow lesions represents an improvement relative to placebo of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 120%, at least about 150%, at least about 170%, at least about 200%, at least about 250%, at least about 300%, at least about 350%, at least about 400%, or at least about 450%. In some embodiments, the use of an inhibitor of osteoclast activity inhibits an increase in the size of bone marrow lesions over time.

[0065] In some embodiments for patients having OARSI Grades 1-2 or K/L Grades 2-4 JSN, the use of an inhibitor of osteoclast activity achieves a reduction in the total area of the bone marrow lesions of at least about 100 mm^2. In some embodiments, the reduction in total area is at least about 50 mm^2, at least about 60 mm^2, at least about 80 mm^2, at least about 85 mm^2, at least about 90 mm^2, at least about 100 mm^2, at least about 105 mm^2, at least about 110 mm^2, or at least about 115 mm^2. In some embodiments, the reduction in size of bone marrow lesions represents a reduction relative to baseline of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70% at least about 80%, at least about 90%, or about 100%. In some embodiments, the reduction in area of bone marrow lesions represents an improvement relative to placebo of at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 115%, at least about 125%, at least about 135%, at least about 150%, at least about 170%, at least about 200%, at least about 250%, at least about 300%, at least about 350%, at least about 400%, or at least about 450%. In some

embodiments, the use of an inhibitor of osteoclast activity inhibits an increase in the size of bone marrow lesions over time.

[0066] In some embodiments, an inhibitor of osteoclast activity, such as a nitrogen-containing bisphosphonate, including e.g. zoledronic acid, minodronic acid, etc., is used to treat fibromyalgia.

[0067] According to some embodiments, administration of an inhibitor of osteoclast activity achieves a reduction in pain that lasts at least about one month, two months, three months, four months, six months, or even at least about 12 months. According some embodiments, administration of an inhibitor of osteoclast activity achieves a reduction in pain that is observed at greater than three hours, at about one day, at about two to about five days, at about one week, at about two weeks, at about three weeks, at about one month, at about five weeks, at about six weeks, at about seven weeks, at about two months, at about nine weeks, at about ten weeks, at about eleven weeks, at about three months, at about four months, at about six months, or at about 12 months after administration of the inhibitor of osteoclast activity.

[0068] According some embodiments, administration of an inhibitor of osteoclast activity achieves a reduction in pain that is observed at greater than three hours, but at or before one week, two weeks, three weeks, four weeks, five weeks, six weeks, seven weeks, eight weeks, nine weeks, 10 weeks, 11 weeks, 12 weeks, four months, five months, or six months.

[0069] According some embodiments, administration of an inhibitor of osteoclast activity achieves a reduction in pain that is observed at greater than three hours with a duration of no more than about three months, no more than about four months, no more than about five months, or no more than about six months.

[0070] According to some embodiments, after the administration of an inhibitor of osteoclast activity, the area of bone marrow lesions relative to the size prior to administration remains reduced for up to three months, four months, five months, six months, or even up to 12 months or more. According to some embodiments, after the administration of an inhibitor of osteoclast activity, the area of bone marrow lesions relative to the size prior to administration is

reduced at about three months, at about four months, at about five months, at about six months, or at about 12 months.

[0071] According to some embodiments, after administration of an inhibitor of osteoclast activity, the size of Modic changes or VESCs relative to the size prior to administration remains reduced for up to three months, four months, five months, six months, or even up to 12 months or more. According to some embodiments, after the administration of an inhibitor of osteoclast activity, the size of Modic changes or VESCs relative to the size prior to administration is reduced at about three months, at about four months, at about five months, at about six months, or at about 12 months.

[0072] In some embodiments, an osteoclast inhibitor, such as a nitrogen-containing bisphosphonate, e.g. zoledronic acid, ibandronic acid or minodronic acid, may be administered 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.

[0073] 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.

[0074] Complex regional pain syndrome is a debilitating pain syndrome. It is characterized by severe pain in a limb that can be accompanied by edema, and autonomic, motor and sensory changes.

[0075] In some embodiments, an osteoclast inhibitor, such as a nitrogen-containing bisphosphonate, e.g. zoledronic acid or minodronic acid, may be used to reduce the use of non-steroidal anti-inflammatory drug (NSAIDs), opioids, or other pain medications, for a patient suffering from pain, inflammation, a similar condition, or any condition described herein. For example, use of NSAIDs, opioids, or other pain medications may be reduced by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%, up to about

100%, as compared to the use of NSAIDs, opioids or other pain medications without administration of the osteoclast inhibitor. Use of the opioids, NSAIDs, or other pain medications may be reduced by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, or at least about 90%, up to about 100%, as compared to the use of NSAIDS, opioids, or other pain medications at baseline.

[0076] The reduction in the use of NSAIDs, opioids, or other pain medications may be observed at about one week, about two weeks, about three weeks, about one month, about two months, about three months, about four months, about five months, about six months, about seven months, about eight months, about nine months, about 10 months, about 11 months, or about one year or more, after the administration of osteoclast inhibitor.

[0077] 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. In some embodiments, a human being treated has significant pain relief at three months, six months, nine months, or one year after administration of the most recent dose of an osteoclast inhibitor such as zoledronic acid.

[0078] With respect to the treatment of any condition recited herein, in some embodiments a first oral dosage form comprising zoledronic acid is administered and a second oral dosage form comprising oral zoledronic acid is administered. The timing of the

administration of the two dosage forms may be such that, with respect to the first oral dosage form, the second oral dosage with respect to the first oral dosage form, the second oral dosage form is administered at 5 x T_{max} or greater (e.g., if T_{max} is 1 hour, at 5 hours or later), at least 10 x T_{max} or greater, at least about 15 x T_{max} or greater, at least about 20 x T_{max} or greater, at least about 50 x T_{max} or greater, or at least about 200 x T_{max} or greater, wherein T_{max} is the time of maximum plasma concentration for the first oral dosage

[0079] Some embodiments include treatment of a condition recited herein, such as inflammatory pain, arthritis, or complex regional pain syndrome, wherein the treatment comprises either: administering only one dosage form to a mammal to treat the condition, or administering a first dosage form to the mammal, followed by administering a second dosage form to the mammal. If two or more dosage forms are administered, the second oral dosage form is administered before the maximum pain relieving effect of the first oral dosage form is achieved, or before a peak in the pain relieving effect of the first oral dosage form is experienced by a mammal, receiving the dosage form. In some embodiments, the second oral dosage form is administered before an observable pain relieving effect is achieved. In some embodiments, the second dosage form is administered about 12 hours to about 60 days, about 24 hours to about 28 days, about 24 hours to about 7 days, about 24 hours to about 14 days, or about 24 hours to about 21 days, after the first dosage form is administered.

[0080] Some embodiments include treatment of a condition recited herein, such as inflammatory pain, arthritis, or complex regional pain syndrome, wherein the treatment comprises administering a first dosage form to the mammal, followed by administering a second dosage form to the mammal, wherein the second dosage form is administered after the maximum pain relieving effect of the first oral dosage form is achieved, and the second oral dosage form is administered while the mammal is still experiencing pain relief from the first oral dosage form, or while the pain relieving effect from the first oral dosage form is observable. In some embodiments, the second dosage form is administered about 12 hours to about 60 days, about 24 hours to about 28 days, about 24 hours to about 7 days, about 24 hours to about 14 days, or about 24 hours to about 21 days, after the first dosage form is administered.

[0081] Zoledronic acid or another bisphosphonate may also be administered orally to relieve cancer-related pain, including pain associated with multiple myeloma and bone

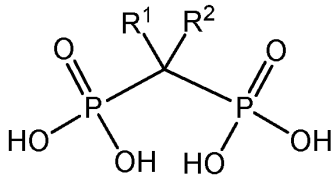
metastases from solid tumors. In some embodiments, zoledronic acid is used to treat pain that is not cancer-related pain. For example, zoledronic acid may be used to treat pain that is not associated with multiple myeloma, bone metastasis from solid tumors, hypercalcemia of malignancy, giant cell tumor of bone, blood cancers or leukemias, or solid tumors or cancers. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0082] 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 occurring. In addition to any pain relief zoledronic acid or another bisphosphonate may or may not provide, zoledronic acid or another bisphosphonate 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. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0083] 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. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0084] 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. In some embodiments, enhanced bioavailability of the zoledronic acid may be achieved in treating one of these conditions by administering a dosage form comprising zoledronic acid in the form of a disodium salt. This may allow a reduced molar amount of the disodium salt to be used as compared to what would be used with the diacid form.

[0085] Some nitrogen-containing bisphosphonates may be represented by Formula A:



Formula A

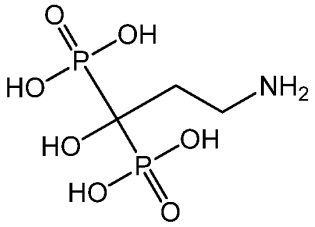
[0086] With respect to Formula A, R^1 is F, Cl, Br, H, or OH. In some embodiments, R^1 is OH.

[0087] With respect to Formula A, R^2 is aminoalkyl, such as aminoethyl, aminopropyl, aminopentyl, dimethylaminoethyl, methylpentylaminoethyl, etc; or optionally substituted heterocyclyl alkyl, such as optionally substituted imidazolylmethyl, optionally substituted pyridinymethyl, etc. In some embodiments R^2 is optionally substituted imidazolylalkyl.

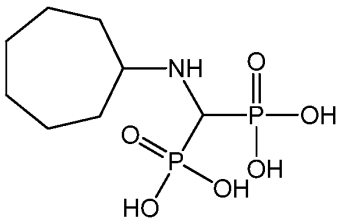
[0088] Unless otherwise indicated, when a compound or chemical structural feature such as heterocyclyl alkyl is referred to as being "optionally substituted," it includes a feature that has no substituents (i.e. unsubstituted), or a feature that is substituted, meaning that the feature has one or more substituents. The term "substituent" has the broadest meaning known to one of ordinary skill in the art, and includes a moiety that replaces one or more hydrogen atoms in a parent compound or structural feature. The term "replaces" is merely used herein for convenience, and does not require that the compound be formed by replacing one atom with another. In some embodiments, a substituent may be any ordinary organic moiety known

in the art, which may have a molecular weight (e.g. the sum of the atomic masses of the atoms of the substituent) of 15 g/mol to 50 g/mol, 15 g/mol to 100 g/mol, 15 g/mol to 150 g/mol,15 g/mol to 200 g/mol, 15 g/mol to 300 g/mol, or 15 g/mol to 500 g/mol. In some embodiments, a substituent comprises, or consists of: 0-30, 0-20, 0-10, or 0-5 carbon atoms; and 0-30, 0-20, 0-10, or 0-5 heteroatoms, wherein each heteroatom may independently be: N, O, P, S, Si, F, Cl, Br, or I; provided that the substituent includes one C, N, O, P, S, Si, F, Cl, Br, or I atom. In some embodiments, substituents can independently have a molecular weight of about 15 Da to about 600 Da and can consist of 2 to 5 chemical elements, wherein the chemical elements are independently C, H, O, N, P, S, Si, F, Cl, or Br. In some embodiments, a substituent is optionally substituted alkyl, –O-alkyl (e.g. $–OCH_3$, $-OC_2H5$, $-OC_3H_7$, $-OC_4H_9$, etc.), -S-alkyl (e.g. $–SCH_3$, $-SC_2H_5$, $-SC_3H_7$, $-SC_4H_9$, etc.), -NR'R", –OH, -SH, -CN, $-CF_3$, $-NO_2$, perfluoroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted amine or a halogen, wherein R' and R" are independently H or optionally substituted alkyl. Wherever a substituent is described as "optionally substituted," that substituent can be substituted with the above substituents.

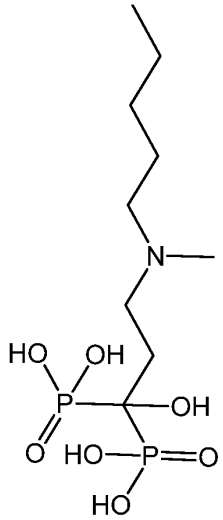
[0089] Examples of nitrogen-containing bisphosphonates include but are not limited to pamidronic acid, incadronic acid, ibandronic acid, risedronic acid, minodronic acid, cimadronic acid, neridronic acid, alendronic acid, olpadronic acid, zoledronic acid, etc.



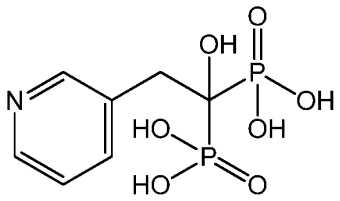
pamidronic acid



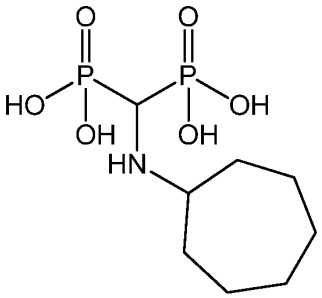
incadronic acid



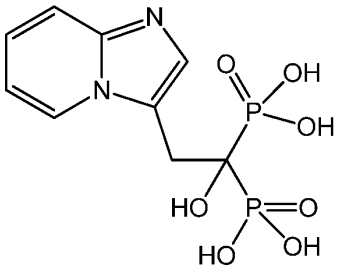
ibandronic acid



risedronic acid

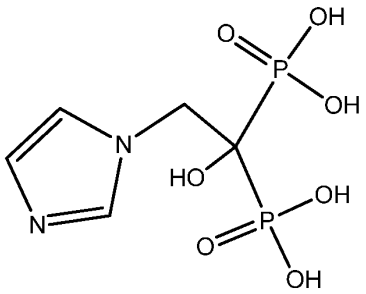


cimadronic acid



minodronic acid

[0090] Zoledronic acid has the structure shown below, and is also referred to as zoledronate.



Zoledronic acid

[0091] 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.

[0092] 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.

[0093] In some embodiments, the administration of an osteoclast inhibitor, such as a nitrogen-containing bisphosphonate, including, e.g. zoledronic acid, minodronic acid, etc., to a patient or mammal in need thereof affects Modic changes (MCs). For example, any of the above compounds could be used to treat Modic changes, or vertebral endplate signal changes (VESC) and bone marrow changes visible using magnetic resonance imaging (MRI), or neck pain or back pain associated with Modic changes.

[0094] Modic changes, as used herein, includes its ordinary meaning in the art and refers to pathological vertebral endplate and bone marrow changes visible using magnetic resonance imaging (MRI). Modic changes may also be referred to as vertebral endplate signal changes (VESC). Modic changes, can be classified into various types including type 1 (M1), type 2 (M2), and type 3 (M3) lesions or changes, any of which may be treated using an osteoclast inhibitor, such as a nitrogen-bisphosphonate, including, e.g. zoledronic acid, minodronic acid, etc. Different types of Modic changes may occur in the same patient, for example type 1 and type 2 Modic changes (M1/2). In some cases, M1 changes are related to lower back pain than other types of Modic change.

[0095] VESCs may be found in patients with different types of low back pain including but not limited to spondylitis, trauma, spondyloarthropathies including ankylosing spondylitis, Schmorl's nodes, fracture, tumor, and spinal cord infarction. Lesions in ankylosing spondylitis include osteitis and spondylodiscitis, which can be detected using MRI or another medical imaging instrument.

[0096] Modic changes may be found in the cervical, thoracic, lumbar, and sacral spine. Modic changes may be found at various spinal levels such as at C1/2, C2/3, C3/4, C4/5, C5/6, C6/7, C7/T1, T1/2, T2/3, T3/4, T4/5, T5/6, T6/7, T7/8, T8/9, T9/10, T10/11, T11/12, T12/L1, L1/2, L2/3, L3/4, L4/5, L5/S1, etc., any of which may be treated using an osteoclast inhibitor, such as a nitrogen-bisphosphonate, including, e.g. zoledronic acid, minodronic acid, etc.

[0097] In some embodiments, the Modic change being treated is located at L2/3. In some embodiments, the Modic change being treated is located at L3/4. In some

embodiments, the Modic change being treated is located at L4/5. In some embodiments, the Modic change being treated is located at L5/S1.

[0098] In some embodiments, the Modic change being treated is located at C3/4. In some embodiments, the Modic change being treated is located in at C4/5. In some embodiments, the Modic change being treated is located in at C5/6. In some embodiments, the Modic change being treated is located in at C6/7.

[0099] In some embodiments, the Modic change being treated is located at T5/6. In some embodiments, the Modic change being treated is located in at T6/7. In some embodiments, the Modic change being treated is located in at T7/8. In some embodiments, the Modic change being treated is located in at T8/9. In some embodiments, the Modic change being treated is located at T9/10.

[0100] In some embodiments, the patient being treated has predominantly M1. In some embodiments, the patient being treated has predominantly M1/M2. In some embodiments, the patient being treated has predominantly M2. In some embodiments, the patient being treated has predominantly M3.

[0101] In some embodiments, the worst type of lesion that the patient being treated has is M1. In some embodiments, the worst type of lesion that the patient being treated has is M1/2. In some embodiments, the worst type of lesion that the patient being treated has is M2.

[0102] In some embodiments, the use of an inhibitor of osteoclast activity, such as a nitrogen-containing bisphosphonate, including e.g. zoledronic acid, minodronic acid, etc., to a patient or mammal in need thereof, achieves a reduction relative to baseline in the size of Modic changes or VESCs of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70% at least about 80%, at least about 90%, or about 100%. In some embodiments, the reduction the size of Modic changes or VESCs represents an improvement relative to placebo of at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, at least about 120%, at least about 150%, at least about 170%, at least about 200%, at least about 250%, at least about 300%, at least about 350%, at least about 400%, or at least about 450%.

In some embodiments, the use of an inhibitor of osteoclast activity inhibits an increase in the size of Modic changes or VESCs over time.

[0103] The oral bioavailability of zoledronic acid may be enhanced by orally administering the zoledronic acid in the disodium salt form. For example, the bioavailability of zoledronic acid may be improved by at least about 10%, at least about 20**%**, at least about 30%, at least about 50%, and/or up to about 100%, or up to about 200%, as compared to administration of zoledronic acid in the diacid form.

[0104] Because of the improved bioavailability of the disodium salt a dosage form may contain, or a mammal, such as a human being, may receive, on a molar basis, less of the disodium salt form of zoledronic acid than would otherwise be administered of the diacid form of zoledronic acid. For example, a dosage form may contain, or a mammal may receive, at least about 10 mole% less, at least about 20 mole% less, at least about 40 mole% less, at least about 50 mole% less, and/or up to about 90 mole% less or 95 mole% less, of the disodium salt form as compared the amount of the diacid form of zoledronic acid that would otherwise be administered, such as a molar amount that would be administered of zoledronic acid in the diacid form in order to achieve the same plasma levels of zoledronic acid.

[0105] In some embodiments, a dosage form contains, or a mammal (such as a human being) is administered, an amount of the disodium salt form, on a molar basis, that has a value of about $0.8n_d$ to about $1.2n_d$ or about $0.9n_d$ to about $1.1n_d$, wherein:

$$n_d = (b_a/b_d)(n_a)$$

wherein b_a is the bioavailability of the diacid form, b_d is the bioavailability of the disodium salt form, and n_a is the number of moles of the diacid that would be administered in a dosage form containing the diacid form of zoledronic acid. For example, if the diacid form has a bioavailability (b_a) of 0.01 and the disodium salt form has a bioavailabity (b_d) of 0.015, and a dosage form would normally contain 0.001 moles of the diacid, n_d would be (0.01/0.015)(0.001 moles), or about 0.00067 moles. In some embodiments, the disodium salt is administered in an amount that has a value of about n_d.

[0106] With respect to oral dosage forms comprising a reduced molar amount of the disodium salt of zoledronic acid as compared to the diacid form of zoledronic acid, in some

embodiments, the bioavailability of the zoledronic acid in the disodium salt form is sufficiently high that, if the drug is administered to a mammal, at least as much zoledronic acid is present in the blood of the mammal as would be present if zoledronic acid were administered in the diacid form.

[0107] With respect to oral dosage forms comprising the disodium salt form of zoledronic acid, in some embodiments, the disodium salt form is present in a lower molar amount than would be present if the zoledronic acid were in the diacid form; and the zoledronic acid in the disodium salt form has an improved bioavailability as compared to the zoledronic acid in the diacid form to the extent that the lower molar amount of the disodium salt in the dosage form does not reduce the amount of zoledronic acid delivered to the plasma of a mammal.

[0108] In some embodiments, the zoledronic acid in the disodium salt form is present in an amount such that the oral dosage form provides an area under the plasma concentration curve of zoledronic acid of about 4 ng•h/mL to about 2000 ng•h/mL to the mammal each time the zoledronic acid in the disodium salt is administered.

[0109] In some embodiments, the zoledronic acid in the disodium salt form is present in an amount such that the oral dosage form provides an area under the plasma concentration curve of zoledronic acid of about 100 ng•h/mL to about 2000 ng•h/mL, about 100 ng•h/mL to about 1000 ng•h/mL, about 500 ng•h/mL to about 1000 ng•h/mL, or about 500 ng•h/mL to about 700 ng•h/mL in the mammal to which the dosage form is administered. This amount may be suitable for administration of the oral dosage form about every 3 to 4 weeks.

[0110] In some embodiments, the zoledronic acid in the disodium salt form is present in an amount such that the oral dosage form provides an area under the plasma concentration curve of zoledronic acid of about 20 ng•h/mL to about 700 ng•h/mL, about 50 ng•h/mL to about 500 ng•h/mL, or about 100 ng•h/mL to about 200 ng•h/mL, in the mammal to which the dosage form is administered. This amount may be suitable for weekly administration of the oral dosage, or for administration of 3 to 5 individual dosages during a month. The individual dosages could be given at regular intervals, given during the first week, or at any other schedule that provides 3 to 5 dosages during the month.

[0111] In some embodiments, the zoledronic acid in the disodium salt form is present in an amount such that the oral dosage form provides an area under the plasma concentration curve of zoledronic acid of about 4 ng•h/mL to about 100 ng•h/mL, about 10 ng•h/mL to about 50 ng•h/mL, or about 10 ng•h/mL to about 30 ng•h/mL, in the mammal to which the dosage form is administered. This amount may be suitable for daily administration of the oral dosage form.

[0112] Oral administration of zoledronic acid, particularly oral administration of the disodium salt form of zoledronic acid, can result in more sustained plasma levels of the drug as compared to parenteral modes of administration, such intravenous or subcutaneous. For example, the amount of zoledronic acid in the plasma can be significantly higher for oral administration of the disodium salt about 24 hours or 48 hours, or longer, after administration. In some embodiments, oral zoledronic acid has a 24 hour sustained plasma level factor of about 1 or higher, such as about 1 to about 10, about 1 to about 5, about 3 to about 5, or about 3 to about 4. In some embodiments, an orally administered dosage form of zoledronic acid has a 24 hour sustained plasma level factor or a 48 hour sustained plasma level factor that is higher, such as at least 1.2 times, at least about 2 times, at least about 5 times, about 1.2 times to about 20 times, about 2 times to about 15 times, about 5 times to about 10 times, or about 8 to about 15 times that of intravenously administered zoledronic acid. A "sustained plasma level factor," p_f, is determined by the equation:

$$p_f = 1000 (C_t/C_{max})$$

wherein C_{max} is the maximum plasma concentration of zoledronic acid after it is administered and C_t is the plasma concentration of zoledronic acid at the time of interest, such as 24 hours. For parenteral administration, the C_{max} can be about the C_0, or the concentration right after injection of the entire amount of the drug into the body. Sustained plasma level factors can also be obtained for other times, such as 48 hours, by using the plasma concentration of zoledronic acid for C_t in the equation above. For example, if the maximum plasma level of zoledronic acid after administration is 1000 ng/mL and the plasma level of zoledronic acid at 24 hours is 1 ng/mL, the 24 hour sustained plasma level factor is 1.

[0113] In some embodiments, the disodium salt form of zoledronic acid provides an enhancement to bioavailability, as compared to the diacid form of zoledronic acid, which adds

to any enhancement to bioavailability provided by any bioavailability-enhancing agents in the dosage form. In some embodiments, the disodium salt form of zoledronic acid provides an enhancement to bioavailability, as compared to the diacid form of zoledronic acid, which is greater than any enhancement to bioavailability provided by any bioavailability-enhancing agents in the dosage form. In some embodiments, the disodium salt form of zoledronic acid may be administered in a dosage form that is substantially free of bioavailability-enhancing agents.

[0114] In some embodiments, a dosage form comprising a disodium salt of zoledronic acid is a solid.

[0115] In some embodiments, a dosage form comprising a disodium salt of zoledronic acid is used to treat an inflammatory condition.

[0116] In some embodiments, a dosage form comprising a disodium salt of zoledronic acid is used to treat arthritis.

[0117] In some embodiments, a dosage form comprising a disodium salt of zoledronic acid is used to treat complex regional pain syndrome.

[0118] 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).

[0119] The disodium salt form of zoledronic acid can be more compressible than the diacid form of zoledronic acid. This can make it easier for a dosage form to have a desired hardness. It can also make it easier to increase the drug load, so that a smaller tablet can be given for a given dosage strength. In some embodiments, a solid dosage form of zoledronic acid, such as the diacid form of zoledronic acid or the disodium salt form of zoledronic acid, can have a hardness of about 5 kPa to about 20 kPa or about 5 kPa to about 14 kPa.

[0120] 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.

[0121] 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.

[0122] In some embodiments, an osteoclast inhibitor is co-administered with a steroid. Suitable steroids include, for example, hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, prednisone, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, halcinonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-valerate, acleometasone dipropionate, betamethasone valerate, betamethasone dippropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortilone caproate, fluocortolone pivalate, and fluprednidene acetate, hydrocortisone-17-butyrate, 17-aceponate, 17-buteprate, and prednicarbate.

[0123] Any effective dose of steroid can be administered to a person. In some embodiment, the dose of steroids may be about 1 to about 500 mg of the steroid. In some embodiments, the dose of steroids does not exceed the 25 mg of the steroid, and is not less than 5 mg of the steroid.

[0124] The steroid can be given orally (for example, 7.5 mg of prednisone), by a separate infusion (for example, 7.5 mg of methyl prednisolone), mixed in with zoledronic acid in the same infusion, or be administered intramuscularly, subcutaneously, by rectal suppository, by inhalation, or injected directly into a joint.

[0125] 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.

[0126] 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.

[0127] 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.

[0128] 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.

[0129] Any suitable amount of an osteoclast inhibitor, including a bisphosphonate, such as a nitrogen-containing bisphosphonate, e.g. zoledronic acid, minodronic acid, ibandronic 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 40 mg to about 60 mg, about 50 mg to about 60 mg, about 55 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 osteoclast inhibitor in a range bounded by, or between, any of these values. In some embodiments, the oral osteoclast inhibitor is administered daily, weekly, monthly, every two or three months, once a year, or twice a year.

[0130] Some oral dosage forms 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 40 mg to about 60 mg, about 50 mg to about 60 mg, about 55 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 osteoclast inhibitor, or any amount of osteoclast inhibitor in a range bounded by, or between, any of these values. In some embodiments, the oral osteoclast inhibitor is administered daily, weekly, monthly, every two or three months, once a year, or twice a year.

[0131] 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.

[0132] In some embodiments, the daily oral dose of an osteoclast inhibitor, including a bisphosphonate, such as a nitrogen-containing bisphosphonate, e.g. zoledronic acid, minodronic acid, ibandronic 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 in a range bounded by, or between, any of these values. In some embodiments, the daily oral dose of osteoclast inhibitor 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.

[0133] In some embodiments, the daily oral dose of an osteoclast inhibitor, including a bisphosphonate, such as a nitrogen-containing bisphosphonate, e.g. zoledronic acid, minodronic acid, ibandronic 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 osteoclast inhibitor in a range bounded by, or between, any of these values. In some embodiments, the daily oral dose of osteoclast inhibitor 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 osteoclast inhibitor in a range bounded by, or between, any of these values.

[0134] 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.

[0135] In some embodiments, the weekly oral dose of the osteoclast inhibitor, including a bisphosphonate, such as a nitrogen-containing bisphosphonate, e.g. zoledronic acid, minodronic acid, ibandronic 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, about 20 mg to about 60 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 50 mg to about 70 mg, about 50 mg, about 55 mg, about 100 mg to about 150 mg, or about 30 mg to about 100 mg. In some embodiments, the weeky oral dose of the osteoclast inhibitor 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 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.

[0136] 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, about 20 mg to about 60 mg, about 30 mg to about 70 mg, about 40 mg to about 60 mg, about 50 mg to about 70 mg, about 50 mg, about 55 mg, about 100 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.

[0137] In some embodiments, the monthly dose of the osteoclast inhibitor, including a bisphosphonate, such as a nitrogen-containing bisphosphonate, e.g. zoledronic acid, minodronic acid, ibandronic acid, or the amount of the osteoclast inhibitor 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, about 40 mg to about 400 mg, about 50 mg to about 200 mg, about 200 mg to about 300 mg, about 250 mg to about 350 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 the osteoclast inhibitor 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 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.

[0138] 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, about 40 mg to about 400 mg, about 50 mg to about 200 mg, about 200 mg to about 300 mg, about 250 mg to about 350 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.

[0139] In some embodiments, the osteoclast inhibitor comprises zoledronic acid, and 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.

[0140] With respect to oral administration of an osteoclast inhibitor, such as zoledronic acid, minodronic acid, ibandronic acid, or another bisphosphonate, for the treatment of pain associated with inflammation, arthritis, CRPS, or any other condition recited herein, it may helpful if the mammal or human being to which the osteoclast inhibitor is administered does not eat food or drink beverage, (other than any water required to swallow the oral dosage form) for at least about 1 hour, at least about 2 hours, at least about 4 hours, at least about 6 hours, at least about 8 hours, at least about 10 hours, or at least about 12 hours before the osteoclast inhibitor is administered. It may also be helpful if the mammal or human being to which the osteoclast inhibitor is administered does not eat food or drink beverage for at least about 30 minutes, at least about 1 hour, at least about 2 hours, at least about 3 hours, or at least about 4 hours after the osteoclast inhibitor is administered. In some embodiments, a human being to which the zoledronic acid is administered avoids lying down, or remains upright or sits upright, for at least about 30 minutes or about 1 hour after receiving a dosage form containing the osteoclast inhibitor. Avoiding food or beverage before or after oral administration of the osteoclast inhibitor can improve the bioavailability of the osteoclast inhibitor.

[0141] The oral bioavailability of osteoclast inhibitor 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 the osteoclast inhibitor—such as zoledronic acid, minodronic acid, ibandronic 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, bisphosphonates such as zoledronic acid typically have 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 1% to about 3%, about 1.2% to about 3.5%, about 1.2% to about 3%, about 1% to about 4%, about 1.5% to about 4.5%, 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%.

[0142] One embodiment is a pharmaceutical composition comprising an osteoclast inhibitor such as zoledronic acid, minodronic acid, or ibandronic acid wherein the oral bioavailability of zoledronic acid in the dosage form is from about 0.01% to about 10%.

[0143] In some embodiments, the oral bioavailability of the osteoclast inhibitor in the dosage form is about 0.01% to about 5%, about 0.1% to about 7%, about 0.1% to about 5%, 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%, or about 0.3% to about 1.0%.

[0144] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.01% to about 5%.

[0145] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 7%.

[0146] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 5%.

[0147] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 3%.

[0148] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.1% to about 2%.

[0149] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.2% to about 2%.

[0150] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.2% to about 1.5%.

[0151] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.3% to about 1.5%.

[0152] In some embodiments, the oral bioavailability of zoledronic acid in the dosage form is about 0.3% to about 1.0%.

[0153] In some embodiments, an oral dosage form comprises about 10 mg to about 300 mg of zoledronic acid, minodronic acid, or ibandronic 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.

[0154] 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, minodronic acid, or ibandronic 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.

[0155] 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, minodronic acid, or ibandronic 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.

[0156] In some embodiments, an oral dosage form comprises about 40 mg to about 150 mg of zoledronic acid, minodronic acid, or ibandronic 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.

[0157] In some embodiments, the oral zoledronic acid, minodronic acid, or ibandronic acid may be administered as one dose of about 100 mg to about 2000 mg. In some embodiments, the oral zoledronic acid, minodronic acid, or ibandronic acid may be administered as one dose of about 300 mg to about 1500 mg. In some embodiments, the oral zoledronic acid, minodronic acid, or ibandronic acid may be administered as one dose of about 200 mg to about 1000 mg. The dose of zoledronic acid, minodronic acid, or ibandronic acid may be administered in a single or divided dose.

[0158] An osteoclast inhibitor, such as zoledronic acid, minodronic acid, or ibandronic 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.

[0159] 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.

[0160] Some compositions or dosage forms may be a liquid, or may comprise a solid phase dispersed in a liquid.

[0161] An osteoclast inhibitor, such as zoledronic acid, minodronic acid, or ibandronic 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.

[0162] 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.

[0163] 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.

[0164] 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.

[0165] 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.

[0166] An oral dosage form comprising zoledronic acid or another bisphosphonate or osteoclast inhibitor may be included in a pharmaceutical product comprising more than one unit of the oral dosage form.

[0167] 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.

[0168] 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.

[0169] 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, minodronic acid, or ibandronic 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, minodronic acid, or ibandronic 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.

[0170] Some oral dosage forms comprising an osteoclast inhibitor—such as suitable bisphosphonates like zoledronic acid, minodronic acid, or ibandronic acid or salts thereof—may have enteric coatings or film coatings. In some embodiments, an oral dosage form of an osteoclast inhibitor comprises a tablet having an enteric coating. In some embodiments, an oral dosage form of an osteoclast inhibitor comprises a capsule having an enteric coating. In some embodiments, an oral dosage form of an osteoclast inhibitor comprises a tablet having a film coating. In some embodiments, an oral dosage form of an osteoclast inhibitor comprises a capsule having a film coating.

[0171] Useful doses for an antibody against RANK or RANKL, such as denosumab, may range from about 0.1 mg/kg to about 20 mg/kg, about 0.75 mg/kg to about 7.5 mg/kg, about 0.1 mg/kg to about 5 mg/kg, about 1 mg/kg to about 2 mg/kg, about 10 mg/kg to about 20 mg/kg, about 12 to about 17 mg/kg, about 15 mg/kg to about 20 mg/kg, about 1 mg/kg, about 1 mg/kg to about 10 mg/kg, or any value bounded by or in between these ranges based on the body weight of the mammal. The chosen dose may be administered repeatedly, particularly for chronic conditions, or the amount per dose may be increased or decreased as treatment progresses. The chosen dose may be administered one or more times per week, monthly, every two months, every three months, every six months, or every year.

[0172] In some embodiments, 60 mg of denosumab is administered subcutaneously to patient in need of treatment. In some embodiments, the administration is repeated every six months.

[0173] 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:

[0174] 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.

[0175] 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.

[0176] Reversal of inflammatory pain was calculated according to the formula:

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

[0177] The experiment was carried out using 9-10 animals per group.

Results:

[0178] 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.

[0179] 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.

[0180] 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:

[0181] 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.

[0182] 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.

[0183] 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.

[0184] The experiment was carried out using 7-10 animals per group.

Results:

[0185] 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.

[0186] 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).

[0187] 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

[0188] Pain was assessed by measuring hyperalgesia, and weight bearing.

[0189] 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.

[0190] 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

[0191] 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

[0192] 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

[0193] 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.

[0194] 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.

[0195] 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).

[0196] 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.

[0197] Zoledronic acid reduced hindpaw warmth by 5% versus vehicle treatment.

[0198] 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

[0199] 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

[0200] 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.

Example 7. Bioavailability of Orally Administered Zoledronic Acid and Disodium Zoledronate

[0201] Tablets were manufactured containing either pure zoledronic acid or the disodium salt of zoledronic acid (disodium zoledronate tetrahydrate). Both types of tablets

contained 50 mg of zoledronic acid equivalent per tablet. Identical excipients were used in both types of tablets, with amounts adjusted to account for the difference in molecular weights between the acid and the disodium salt.

[0202] Beagle dogs were orally administered tablets containing 150 mg zoledronic acid equivalent either in the form of disodium zoledronate (Group 1) or pure zoledronic acid (Group 2). Each animal was given three 50 mg equivalent tablets (150 mg total), which were administered together. The animal's oral cavity was wetted with water before placing the tablets on the back of the animal's tongue. Animals were fasted before and after dosing. Animals were 6 to 9 months of age and weighed 6 to 10 kg on the day of dosing. There were three dogs per group.

[0203] Serial blood samples were collected from each animal by venipuncture of the jugular vein at various points after dosing for measurement of plasma concentrations of zoledronic acid. Blood samples were collected into chilled tubes containing K_2EDTA as the anticoagulant. Samples were then centrifuged at approximately 3000 rpm at +4°C for 10 minutes for plasma derivation. Plasma concentrations of zoledronic acid were measured using an LC/MS/MS method.

Results

[0204] The average plasma concentrations of zoledronic acid for each group of dogs is summarized in Table 1 and illustrated in FIG. 8. Detectable plasma levels of zoledronic acid were observed for the entire 48 hours that they were measured.

Table 1
Zoledronic Acid plasma concentrations in beagle dogs

		Time (hour)	Plasma concentration (ng/mL)
Group 1 (N=3)	Disodium Zoledronate Tablets (150 mg acid equivalent)	0	0.00
		0.25	1193.97
		0.5	1852.12
		0.75	1776.51
		1	1626.56
		2	640.57
		4	136.93

		6	53.11
		8	26.97
		12	13.74
		24	6.78
		48	5.39
Group 2 (N=3)	Zoledronic Acid Tablets (150 mg acid equivalent)	0	0.00
		0.25	390.92
		0.5	846.19
		0.75	819.15
		1	831.77
		2	477.76
		4	90.11
		6	28.22
		8	15.10
		12	6.13
		24	3.18
		48	1.84

[0205] Disodium zoledronate produced significantly higher plasma levels of zoledronic acid than pure zoledronic acid, indicating improved oral absorption with the salt form. Measured using peak plasma concentrations (C_{max}), the disodium salt resulted in a 119% actual and 74% weight-adjusted increase in bioavailability as compared to pure zoledronic acid. Measured using area under the plasma concentration curve ($AUC_{0-\infty}$), bioavailability was 84% and 46% greater with the disodium salt than with pure zoledronic acid, on an actual and weight-adjusted basis respectively. The average $AUC_{0-\infty}$ for the disodium salt was 4073 ng•hr/mL and the average $AUC_{0-\infty}$ for the diacid was 2217 ng•hr/mL. The $AUC_{0-\infty}$ was found to be dose proportional. Thus, for beagle dogs similar to those tested, about 3 mg to about 4 mg of the disodium salt would be expected to result in an $AUC_{0-\infty}$ of about 100 ng•hr/mL, and about 7 mg to about 8 mg of the disodium salt would be expected to result in an $AUC_{0-\infty}$ of about 200 ng•hr/mL.

Example 8

[0206] Tablets were prepared by blending zoledronic acid, either in the form of the free acid or the disodium salt, with identical excipients. For dosage forms with a greater

amount of active, the amount of the excipients was reduced proportionally to keep the weight of the tablet at about 100 mg. After blending, the ingredients were compressed at varying pressures, followed by a film coating. The resulting tablets were then tested for hardness using a Dr. Schleuniger Pharmatron 8M Tablet Hardness Tester. The results are shown in Table 2 and FIG. 9.

Table 2

Compression Force	Hardness (kPa)		
(psi)	Diacid 50 mg	Disodium Salt 50 mg	Disodium Salt 71 mg
800	4.0	8.7	4.8
1100	6.1	11.2	6.8
1500	7.7	13.7	7.4
2000	8.7	16.3	10.7
2400	8.7		11.3
3000	11.4		14.1
4400	12.5		14.9
5500	12.8		18.2
6100	13.0		

Example 9

[0207] Some embodiments related to joint pain, bone marrow lesions, and osteoarthritis were conceived as a result of analyzing data from a clinical study. Some of the results of this study were reported by Laslett et. al. in *Ann Rheum Dis* 2012;71:1322-1328. Some of the description and data reported below was not published prior to filing the present application. Fifty-two (52) patients with clinical knee osteoarthritis and knee bone marrow lesions (BML) were randomized to receive either intravenous zoledronic acid (5 mg) or placebo in a double blind fashion. All patients had to have at least one bone marrow lesion (BML) in the affected knee on magnetic resonance imaging (MRI). All patients had x-ray of the knee for determination of joint space narrowing (JSN), which was graded according to the Osteoarthritis Research Society International (OARSI) atlas. Patients had either no joint space narrowing (OARSI Grade 0), or greater degrees of joint space narrowing (OARSI Grade 1 and Grade 2). Twenty six patients were treated with zoledronic acid (8, 6, and 12 with OARSI Grades 0, 1,

and 2, respectively). Twenty six patients received placebo (8, 8, and 10 with OARSI Grades 0, 1 and 2, respectively).

[0208] Pain intensity was assessed, at baseline and at three months, using a 100 mm visual analog scale (VAS), with zero representing no pain and 100 representing extreme pain. The change in pain intensity from baseline to 3 months was calculated.

[0209] With zoledronic acid treatment, pain was reduced significantly as compared to placebo in patients with no joint space narrowing (OARSI Grade 0), but not in patients with joint space narrowing (OARSI Grades 1-2). As shown in Table 3 and FIG. 10, average VAS scores were reduced by 15 mm as compared to placebo in the OARSI Grade 0 group, but only by 0.28 as compared to placebo in patients with OARSI Grades 1-2.

[0210] In the zoledronic acid group, average VAS scores at 3 months decreased from baseline by approximately 25 mm and 21 mm in patients with OARSI Grades 0 and 1, respectively, but only by 9 mm in the OARSI Grade 2 patients (FIG. 11).

Table 3. Change in VAS Pain Scores at Three Months by OARSI Grade (mm)

	OARSI Grade 0	OARSI Grades 1-2
Zoledronic Acid	-24.6	-13.2
Placebo	-9.6	-12.9
Difference from Placebo	-15.0	-0.28

[0211] With zoledronic acid treatment, pain was reduced significantly as compared to placebo in patients with baseline VAS pain intensity scores of 50 mm or greater, but not in patients with baseline VAS scores less than 50 mm. As shown in Table 4, average VAS scores were reduced by 9 mm as compared to placebo in the patients with baseline VAS ≥ 50 mm, but only by 0.6 as compared to placebo in patients with baseline VAS < 50 mm.

Table 4. Change in VAS Pain Scores at Three Months by Baseline VAS (mm)

	Baseline VAS ≥ 50 mm	Baseline VAS < 50 mm
Zoledronic Acid	-26.2	-7.3
Placebo	-17.2	-6.7
Difference from Placebo	-9.0	-0.6

[0212] As summarized in Table 5 and illustrated in FIG. 12, pain reduction was greater in patients with baseline VAS ≥ 50 mm, greater still in patients with OARSI Grade 0 joint space narrowing, and greatest in patients with both baseline VAS ≥ 50 mm and OARSI Grade 0 joint space narrowing.

Table 5. Pain Reduction Compared to Placebo at Three Months (mm)

	VAS Change
All patients	-4.8
Baseline VAS ≥ 50 mm	-9.0
OARSI Grade 0	-15.0
Baseline VAS ≥ 50 mm + OARSI Grade 0	-19.4

[0213] BMLs were evaluated using proton density-weighted fat saturation MR images. BMLs were scored using Osiris software (University of Geneva, Geneva, Switzerland). The maximum size was measured in mm^2 using software cursors applied to the greatest area of each lesion. The lesion with the highest score was used if more than one was present at the same site. Each patient was given a BML score (mm^2) at each of the four sites (medial tibial, medial femoral, lateral tibial, and lateral femoral sites) and these were summed to create a total BML score (mm^2). The change in the total area of BMLs from baseline to 6 months was calculated.

[0214] The size of BMLs was reduced with zoledronic acid treatment. As shown in FIG. 13 and Table 6, average BML area decreased by approximately 190 mm^2 as compared to placebo in the OARSI Grade 0 group, but only by approximately 33 mm^2 as compared to placebo in patients with OARSI Grades 1-2.

Table 6. Change in BML Size (mm^2)

	OARSI Grade 0	OARSI Grades 1-2
Zoledronic Acid	-244	-117
Placebo	-55	-84
Difference from Placebo	-190	-33

[0215] The following embodiments are specifically contemplated:

Embodiment 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.

Embodiment 2. The method of embodiment 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.

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

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

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

Embodiment 6. The method of embodiment 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.

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

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

Embodiment 9. The method of embodiment 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.

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

Embodiment 11. The method of embodiment 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.

Embodiment 12. The method of embodiment 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.

Embodiment 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.

Embodiment 14. The method of embodiment 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.

Embodiment 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.

Embodiment 16. The method of embodiment 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.

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

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

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

Embodiment 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.

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

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

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

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

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

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

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

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

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

Embodiment 30. The method of embodiment 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.

Embodiment 31. The method of embodiment 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.

Embodiment 32. The method of any of embodiments 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.

Embodiment 33. The method of embodiment 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.

Embodiment 34. The method of any of embodiments 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.

Embodiment 35. The method of any of embodiments 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.

Embodiment 36. The method of embodiment 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.

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

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

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

Embodiment 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%.

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

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

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

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

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

Embodiment 46. The pharmaceutical product of embodiment 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.

Embodiment 47. The pharmaceutical product of embodiment 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.

Embodiment 48. The pharmaceutical product of embodiment 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.

Embodiment 49. The pharmaceutical product of embodiment 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.

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

Embodiment 51. The pharmaceutical product of embodiment 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.

Embodiment 52. The pharmaceutical product of embodiment 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.

Embodiment 53. The pharmaceutical product of embodiment 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.

Embodiment 54. The pharmaceutical product of embodiment 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.

Embodiment 55. The pharmaceutical product of embodiment 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.

Embodiment 56. The pharmaceutical product of embodiment 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.

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

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

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

Embodiment 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).

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

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

Embodiment 63. The method of embodiment 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.

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

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

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

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

Embodiment 68. The method of embodiment 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.

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

Embodiment 70. The method of embodiment 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.

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

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

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

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

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

Embodiment 76. The method of any of embodiments 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.

Embodiment 77. The method of embodiment 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Embodiment 120. A method of enhancing the oral bioavailability of zoledronic acid comprising orally administering a dosage form containing zoledronic acid in the disodium salt form.

Embodiment 121. The method of embodiment 120, wherein the zoledronic acid in the disodium salt form provides an enhancement to bioavailability, as compared to zoledronic acid in the diacid form, which adds to any enhancement to bioavailability provided by any bioavailability-enhancing agents in the dosage form.

Embodiment 122. The method of embodiment 120, wherein the dosage form is substantially free of bioavailability-enhancing agents.

Embodiment 123. The method of embodiment 120, wherein the zoledronic acid in the disodium salt form is administered to a mammal in an amount that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng•h/mL to about 2000 ng•h/mL to the mammal each time the zoledronic acid in the disodium salt is administered.

Embodiment 124. The method of embodiment 123, wherein the zoledronic acid in the disodium salt form is administered at an interval of about 3 to about 4 weeks in an amount that provides an area under the plasma concentration curve of zoledronic acid of about 100 ng•h/mL to about 2000 ng•h/mL to the mammal each time the zoledronic acid in the disodium salt form is administered.

Embodiment 125. The method of embodiment 123, wherein the zoledronic acid in the disodium salt form is administered weekly, or 3 to 5 times in a month, in an amount that provides an area under the plasma concentration curve of zoledronic acid of about 20 ng•h/mL to about 700 ng•h/mL to the mammal each time the zoledronic acid in the disodium salt form is administered.

Embodiment 126. The method of embodiment 123, wherein the zoledronic acid in the disodium salt form is administered daily in an amount that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng•h/mL to about 100 ng•h/mL to the mammal each time the zoledronic acid in the disodium salt form is administered.

Embodiment 127. The method of embodiment 120, wherein the dosage form is a solid.

Embodiment 128. The method of embodiment 120, 121, 122, 123, 124, 125, 126, or 127, wherein the bioavailability of zoledronic acid is improved by at least about 20**%** as compared to administration of zoledronic acid in the diacid form.

Embodiment 129. The method of embodiment 120, 121, 122, 123, 124, 125, 126, 127, or 128, further comprising administering, on a molar basis, less of the zoledronic acid in the disodium salt form than would be administered of zoledronic acid in the diacid form in order to achieve the same plasma levels of zoledronic acid.

Embodiment 130. The method of embodiment 129, wherein at least about 10 mole% less of the disodium salt form is administered as compared the amount of zoledronic acid in the diacid form that would be administered in order to achieve the same plasma levels of zoledronic acid.

Embodiment 131. The method of embodiment 129, wherein the disodium salt form is administered in an amount, on a molar basis, that has a value of about $0.8n_d$ to about $1.2n_d$, wherein:

$$n_d = (b_a/b_d)(n_a)$$

wherein b_a is the bioavailability of the diacid form, b_d is the bioavailability of the disodium salt form, and n_a is the number of moles of zoledronic acid in the diacid form that would be administered in order to achieve the same plasma levels of zoledronic acid.

Embodiment 132. The method of embodiment 131, wherein the disodium salt is administered in an amount that has a value of about n_d.

Embodiment 133. The method of any of embodiments 120-132, wherein the zoledronic acid is used to treat an inflammatory condition.

Embodiment 134. The method of embodiment 133, wherein the zoledronic acid is used to treat arthritis.

Embodiment 135. The method of embodiment 133, wherein the zoledronic acid is used to treat complex regional pain syndrome.

Embodiment 136. The method of any of embodiments 1-39, 62-77, and 120-135, wherein:

a first oral dosage form is administered; and

a second oral dosage form is administered;

wherein, with respect to the first oral dosage form, the second oral dosage form is administered at 10 x T_{max} or greater, wherein T_{max} is the time of maximum plasma concentration for the first oral dosage form.

Embodiment 137. A dosage form comprising zoledronic acid in the disodium salt form, wherein the bioavailability, in a mammal, of zoledronic acid in the disodium salt form is greater than the bioavailability of zoledronic acid in the diacid form would be in the same dosage form.

Embodiment 138. A dosage form comprising zoledronic acid in the disodium salt form, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that

provides an area under the plasma concentration curve of zoledronic acid of about 4 ng•h/mL to about 2000 ng•h/mL to a human being to which the dosage form is administered.

Embodiment 139. The dosage form of embodiment 138, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 100 ng•h/mL to about 2000 ng•h/mL to a human being to which the dosage form is administered.

Embodiment 140. The dosage form of embodiment 138, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 20 ng•h/mL to about 700 ng•h/mL to a human being to which the dosage form is administered.

Embodiment 141. The dosage form of embodiment 138, wherein the dosage form contains an amount of zoledronic acid in the disodium salt form that provides an area under the plasma concentration curve of zoledronic acid of about 4 ng•h/mL to about 100 ng•h/mL to a human being to which the dosage form is administered.

Embodiment 142. A dosage form comprising zoledronic acid in the disodium salt form,

wherein the disodium salt form is present in a lower molar amount than would be present if the zoledronic acid were in the diacid form; and

wherein the zoledronic acid in the disodium salt form has an improved bioavailability as compared to the zoledronic acid in the diacid form to the extent that the lower molar amount of the disodium salt in the dosage form does not reduce the amount of zoledronic acid delivered to the plasma of a mammal.

Embodiment 143. The dosage form of embodiment 137, 138, 139, 140, 141, or 142, wherein the dosage form is a solid.

Embodiment 144. The dosage form of embodiment 142 or 143, wherein the bioavailability of zoledronic acid in the disodium salt form is improved by at least about 10% as compared to an otherwise identical dosage form containing zoledronic acid in the diacid form.

Embodiment 145. The dosage form of embodiment 142, 143, or 144, containing at least about 20 mole% less of the disodium salt form as compared to the amount of the

zoledronic acid in the diacid form that would be present if the zoledronic acid were in the diacid form.

Embodiment 146. The dosage form of embodiment 142, wherein the disodium salt form is present in an amount, on a molar basis, that has a value of about 0.9nd to about 1.1nd, wherein:

$$n_d = (b_a/b_d)(n_a)$$

wherein b_a is the bioavailability of the diacid form, b_d is the bioavailability of the disodium salt form, and n_a is the number of moles of the diacid form that would be present if the zoledronic acid were in the diacid form.

Embodiment 147. The dosage form of embodiment 146, wherein the disodium salt is administered in an amount that has a value of about n_d.

Embodiment 148. The method of any of embodiments 1-39, 62-77, and 120-136, wherein:

only a single oral dosage form is administered; or

a first oral dosage form is administered, and a second oral dosage form is administered after the first oral dosage form, wherein the second oral dosage form is administered before the maximum pain relieving effect of the first oral dosage form is achieved, or the second oral dosage form is administered before an observable pain relieving effect is achieved.

Embodiment 149. The method of embodiment 148, wherein the second oral dosage form is administered before an observable pain relieving effect is achieved.

Embodiment 150. The method of any of embodiments 1-39, 62-77, and 120-132, wherein a first dosage form is administered, followed by administration of a second dosage form, wherein the second dosage form is administered after the maximum pain relieving effect of the first oral dosage form is achieved, and the second oral dosage form is administered while a pain relieving effect from the first oral dosage form is observable.

Embodiment 151. The method of embodiment 148, 149, or 150, wherein the second oral dosage form is administered about 24 hours to about 28 days after the first oral dosage form is administered.

Embodiment 152. The method of any of embodiments 20-39, wherein the human being is about 30 years old to about 75 years old.

Embodiment 153. The method of any of embodiments 20-39, wherein the human being is about 1 year old to about 16 years old.

Embodiment 154. The method of any of embodiments 20-39, wherein the human being is about 80 years old to about 95 years old.

Embodiment 155. The method of any of embodiments 20-39, wherein the human being has suffered from the arthritis for at least 2 months.

Embodiment 156. The method of any of embodiments 20-39, wherein the arthritis affects, a knee, an elbow, a wrist, a shoulder, or a hip.

Embodiment 157. The method of any of embodiments 1-44, 62-133, and 144-156, wherein the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage for at least 1 hour before the zoledronic acid is administered.

Embodiment 158. The method of embodiment 157, wherein the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage for at least 2 hours before the zoledronic acid is administered.

Embodiment 159. The method of embodiment 158, wherein the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage for at least 4 hours before the zoledronic acid is administered.

Embodiment 160. The method of embodiment 159, wherein the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage for at least 6 hours before the zoledronic acid is administered.

Embodiment 161. The method of any of embodiments 157-160, wherein the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage for at least 30 minutes after the zoledronic acid is administered.

Embodiment 162. The method of embodiment 161, wherein the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage for at least 1 hour after the zoledronic acid is administered.

Embodiment 163. The method of embodiment 161, where in the mammal or human being to which the zoledronic acid is administered does not eat food or drink beverage for at least 2 hours after the zoledronic acid is administered.

Embodiment 164. The method, dosage form, or product, of any preceding embodiment, wherein the zoledronic acid in the oral dosage form has a 24 hour sustained plasma level factor of about 1 or higher.

Embodiment 165. The method, dosage form, or product, of any preceding embodiment, wherein the zoledronic acid in the oral dosage form has a 24 hour sustained plasma level factor that is higher than that of intravenously administered zoledronic acid.

Embodiment 166. The method, dosage form, or product, of any preceding embodiment, wherein the oral dosage form is a solid that has a hardness of about 5 kPa to about 20 kPa.

Embodiment 167. A method of treating bone marrow lesions comprising: selecting a patient having a bone marrow lesion and OARSI grade 0 of joint space narrowing, and administering an inhibitor of osteoclast activity to the patient for the treatment of the bone marrow lesion.

Embodiment 168. The method of embodiment 167, wherein the inhibitor of osteoclast activity is administered at least twice.

Embodiment 169. The method of embodiment 167, wherein the inhibitor of osteoclast activity is administered about every three months, or more frequently.

Embodiment 170. The method of embodiment 167, wherein the inhibitor of osteoclast activity comprises a nitrogen-containing bisphosphonate.

Embodiment 171. The method of any one of embodiments 167-170, wherein the inhibitor of osteoclast activity is or comprises zoledronic acid.

Embodiment 172. The method of any one of embodiments 167-170, wherein the inhibitor of osteoclast activity is or comprises pamidronic acid.

Embodiment 173. The method of any one of embodiments 167-170, wherein the inhibitor of osteoclast activity is or comprises neridronic acid.

Embodiment 174. The method of any one of embodiments 167-170, wherein the inhibitor of osteoclast activity is or comprises olpadronic acid.

Embodiment 175. The method of any one of embodiments 167-170, wherein the inhibitor of osteoclast activity is or comprises alendronic acid.

Embodiment 176. The method of any one of embodiments 167-170, wherein the inhibitor of osteoclast activity is or comprises incadronic acid.

Embodiment 177. The method of any one of embodiments 167-170, wherein the inhibitor of osteoclast activity is or comprises ibandronic acid.

Embodiment 178. The method of any one of embodiments 167-170, wherein the inhibitor of osteoclast activity is or comprises risedronic acid.

Embodiment 179. The method of any one of embodiments 167-178, wherein the inhibitor of osteoclast activity is administered orally.

Embodiment 180. The method of any one of embodiments 167-178, wherein the inhibitor of osteoclast activity is administered intravenously.

Embodiment 181. The method of any one of embodiments 167-180, wherein the patient experiences a reduction in bone marrow lesion size that is at least about 100% greater than a reduction in bone marrow lesion size achieved with a placebo.

Embodiment 182. The method of any one of embodiments 167-180, wherein the patient experiences a reduction in bone marrow lesion size that is at least about 150% greater than a reduction in bone marrow lesion size achieved with a placebo.

Embodiment 183. The method of any one of embodiments 167-182, wherein the inhibitor of osteoclast activity is administered at least twice over a period of at least four weeks.

Embodiment 184. The method of any one of embodiments 167-183, wherein the inhibitor of osteoclast activity is administered once weekly for a period of six weeks.

Embodiment 185. The method of any one of embodiments 167-184, wherein the inhibitor of osteoclast activity comprises zoledronic acid, and the weekly dose is between about 25 mg and about 75 mg.

Embodiment 186. A method of treating knee pain comprising: selecting a patient having knee pain and OARSI grade 0 of joint space narrowing, and administering an inhibitor of osteoclast activity to the patient for the treatment of the knee pain.

Embodiment 187. The method of embodiment 186, wherein the inhibitor of osteoclast activity is administered at least twice.

Embodiment 188. The method of any one of embodiments 186-187, wherein the inhibitor of osteoclast activity is administered about every three months, or more frequently.

Embodiment 189. The method of any one of embodiments 186-188, wherein the inhibitor of osteoclast activity comprises a nitrogen-containing bisphosphonate.

Embodiment 190. The method of any one of embodiments 186-189, wherein the patient experiences pain relief three months after administration of the inhibitor of osteoclast activity.

Embodiment 191. The method of any one of embodiments 186-190, wherein the inhibitor of osteoclast activity is or comprises zoledronic acid.

Embodiment 192. The method of any one of embodiments 186-190, wherein the inhibitor of osteoclast activity is or comprises pamidronic acid.

Embodiment 193. The method of any one of embodiments 186-190, wherein the inhibitor of osteoclast activity is or comprises neridronic acid.

Embodiment 194. The method of any one of embodiments 186-190, wherein the inhibitor of osteoclast activity is or comprises olpadronic acid.

Embodiment 195. The method of any one of embodiments 186-190, wherein the inhibitor of osteoclast activity is or comprises alendronic acid.

Embodiment 196. The method of any one of embodiments 186-190, wherein the inhibitor of osteoclast activity is or comprises incadronic acid.

Embodiment 197. The method of any one of embodiments 186-190, wherein the inhibitor of osteoclast activity is or comprises ibandronic acid.

Embodiment 198. The method of any one of embodiments 186-190, wherein the inhibitor of osteoclast activity is or comprises risedronic acid.

Embodiment 199. The method of any one of embodiments 186-198, wherein the patient experiences a reduction in pain intensity—when using a 100 mm visual analog scale—of at least about 20.

[0216] 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.

[0217] 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.

[0218] 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.

[0219] 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.

[0220] 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

What is claimed is:

1. A method of treating a bone marrow lesion of the knee comprising: selecting a patient having a bone marrow lesion of the knee and OARSI Grade 0 or Kellgren and Lawrence Grade 0 or Grade 1 of joint space narrowing, and administering an inhibitor of osteoclast activity to the patient for the treatment of the bone marrow lesion, wherein the inhibitor of osteoclast activity is ibandronic acid, risedronic acid, or alendronic acid.

2. The method of claim 1, wherein the inhibitor of osteoclast activity is administered at least twice.

3. The method of claim 2, wherein the inhibitor of osteoclast activity is administered about every three months, or more frequently.

4. The method of claim 1, wherein the inhibitor of osteoclast activity is ibandronic acid.

5. The method of claim 1, wherein the inhibitor of osteoclast activity is risedronic acid.

6. The method of claim 1, wherein the inhibitor of osteoclast activity is alendronic acid.

7. The method of claim 1, wherein the inhibitor of osteoclast activity is administered orally.

8. The method of claim 1, wherein the inhibitor of osteoclast activity is administered intravenously.

9. The method of claim 1, wherein the patient experiences a reduction in bone marrow lesion size that is at least about 15% within about six months after the inhibitor of osteoclast activity is administered to the patient.

10. The method of claim 1, wherein the patient experiences a reduction in bone marrow lesion size that is at least about 25% within about six months after the inhibitor of osteoclast activity is administered to the patient.

11. The method of claim 2, wherein the inhibitor of osteoclast activity is administered at least twice over a period of at least four weeks.

12. The method of claim 9, wherein the inhibitor of osteoclast activity is administered once weekly for a period of six weeks.

13. The method of claim 9, wherein the weekly dose of the inhibitor of osteoclast activity is between about 25 mg and about 75 mg.

14. The method of claim 10, wherein the inhibitor of osteoclast activity is administered once weekly for a period of six weeks.

15. The method of claim 10, wherein the weekly dose of the inhibitor of osteoclast activity is between about 25 mg and about 75 mg.

16. The method of claim 1, wherein the patient is about 10 years to about 90 years old.

17. The method of claim 1, wherein the patient has had knee pain associated with a bone marrow lesion of the knee for at least two months.

18. The method of claim 4, wherein the patient has had knee pain associated with a bone marrow lesion of the knee for at least two months.

19. The method of claim 5, wherein the patient has had knee pain associated with a bone marrow lesion of the knee for at least two months.

20. The method of claim 6, wherein the patient has had knee pain associated with a bone marrow lesion of the knee for at least two months.

ABSTRACT

Oral dosage forms of osteoclast inhibitors, such as nitrogen-containing bisphosphonates, can be used to treat or alleviate pain or related conditions.

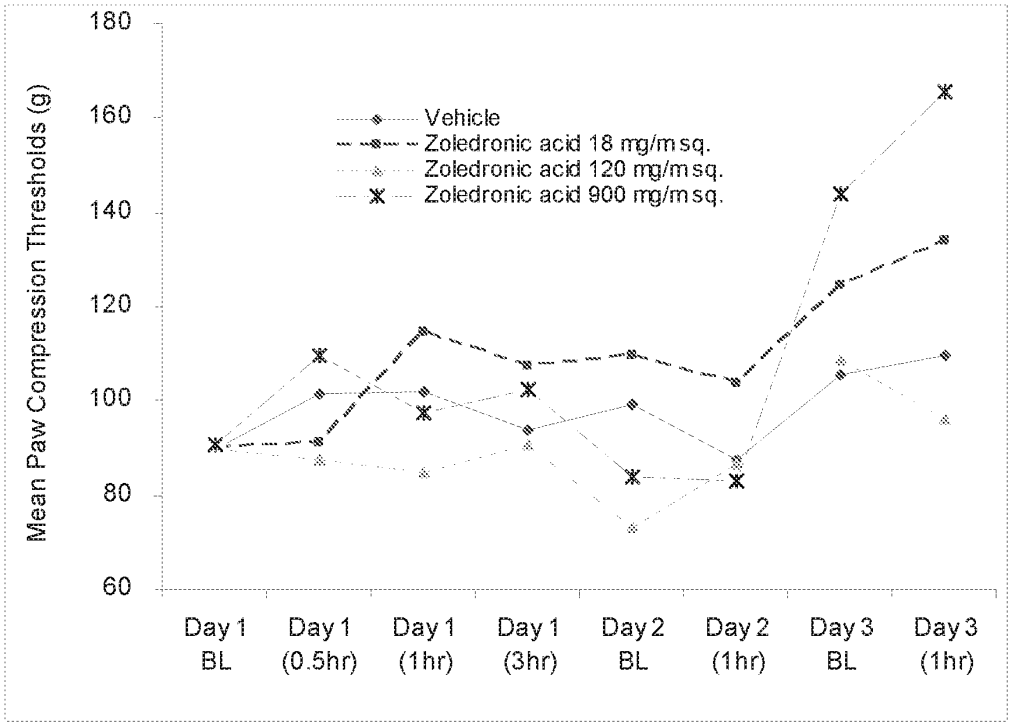

Mean Paw Compression Thresholds (g)
180
160
140
120
100
80
60
Vehicle
Zoledronic acid 18 mg/m sq.
Zoledronic acid 120 mg/m sq.
Zoledronic acid 900 mg/m sq.
Day 1 BL
Day 1 (0.5hr)
Day 1 (1hr)
Day 1 (3hr)
Day 2 BL
Day 2 (1hr)
Day 3 BL
Day 3 (1hr)

FIG. 1

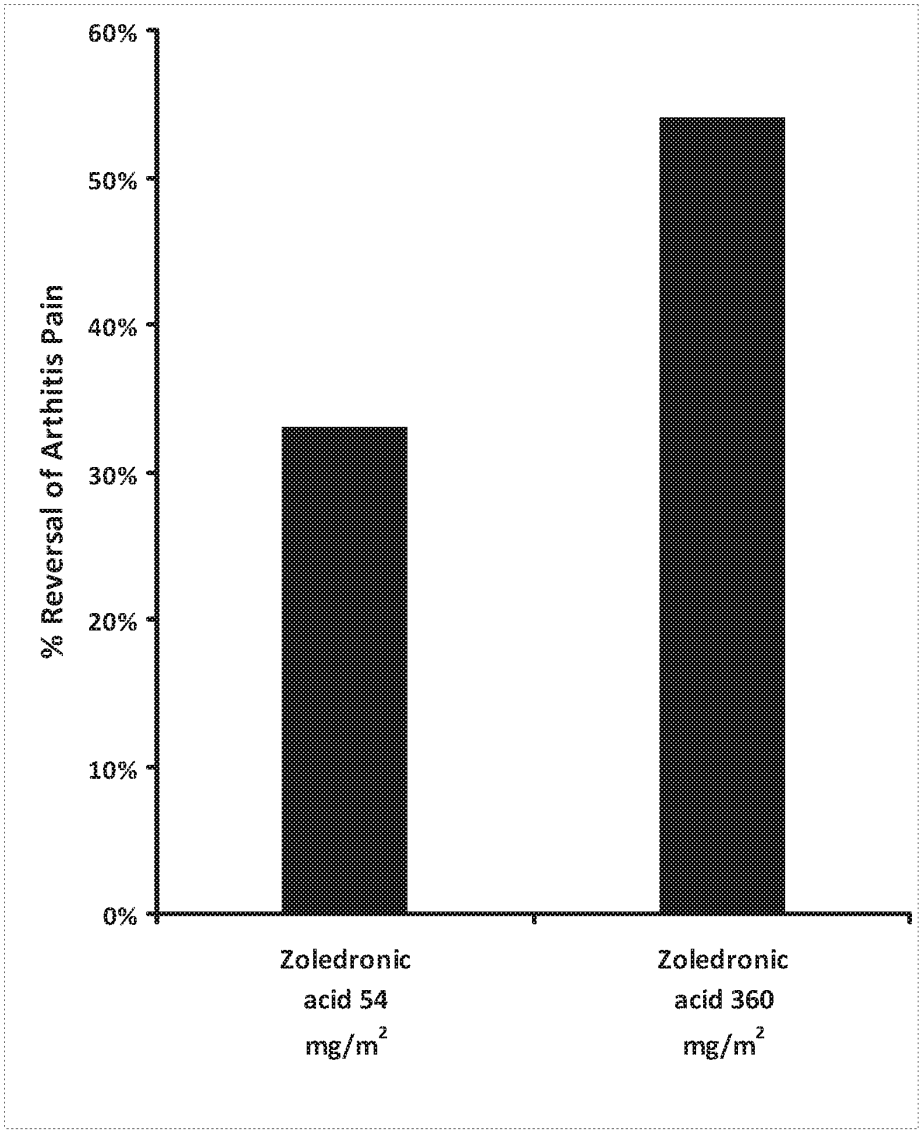

60%
50%
40%
30%
20%
10%
0%
% Reversal of Arthritis Pain
Zoledronic acid 54 mg/m2
Zoledronic acid 360 mg/m2

FIG. 2A

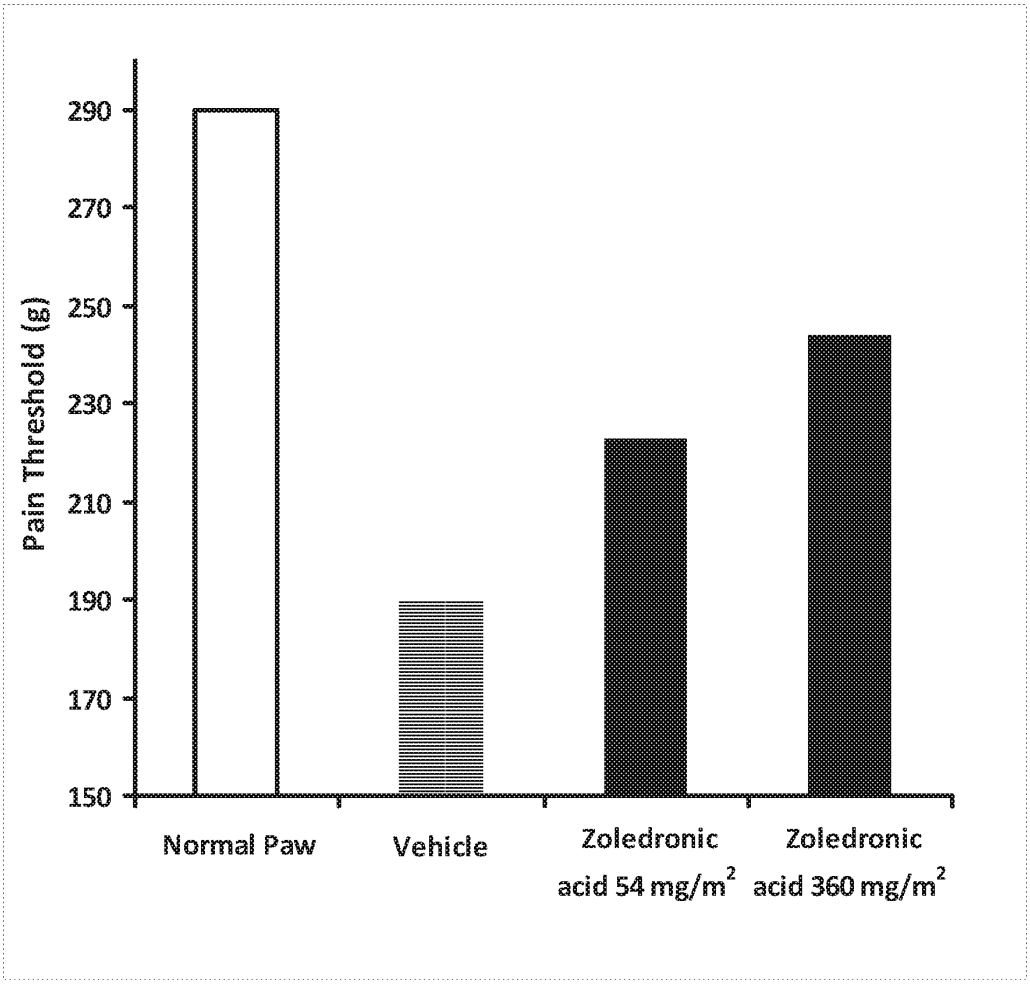

Pain Threshold (g)
290
270
250
230
210
190
170
150
Normal Paw
Vehicle
Zoledronic acid 54 mg/m2
Zoledronic acid 360 mg/m2

FIG. 2B

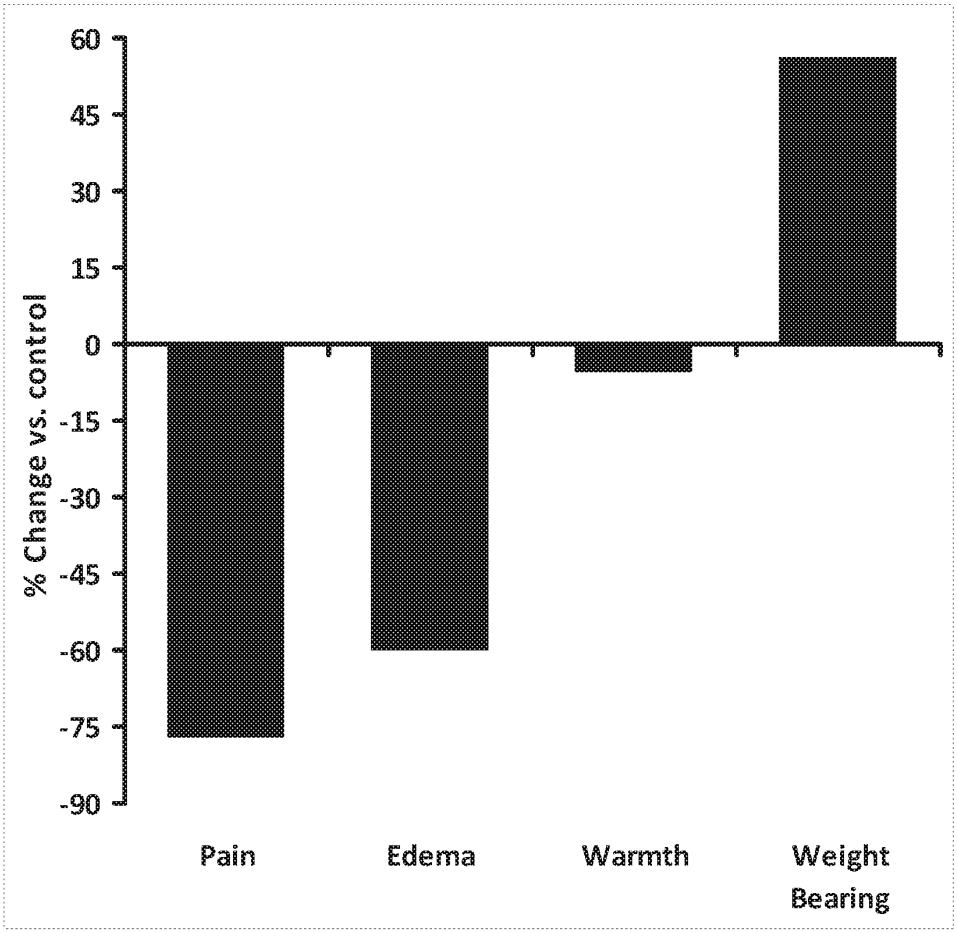

60
45
30
15
0
-15
-30
-45
-60
-75
-90
% Change vs. control
Pain
Edema
Warmth
Weight Bearing

FIG. 3

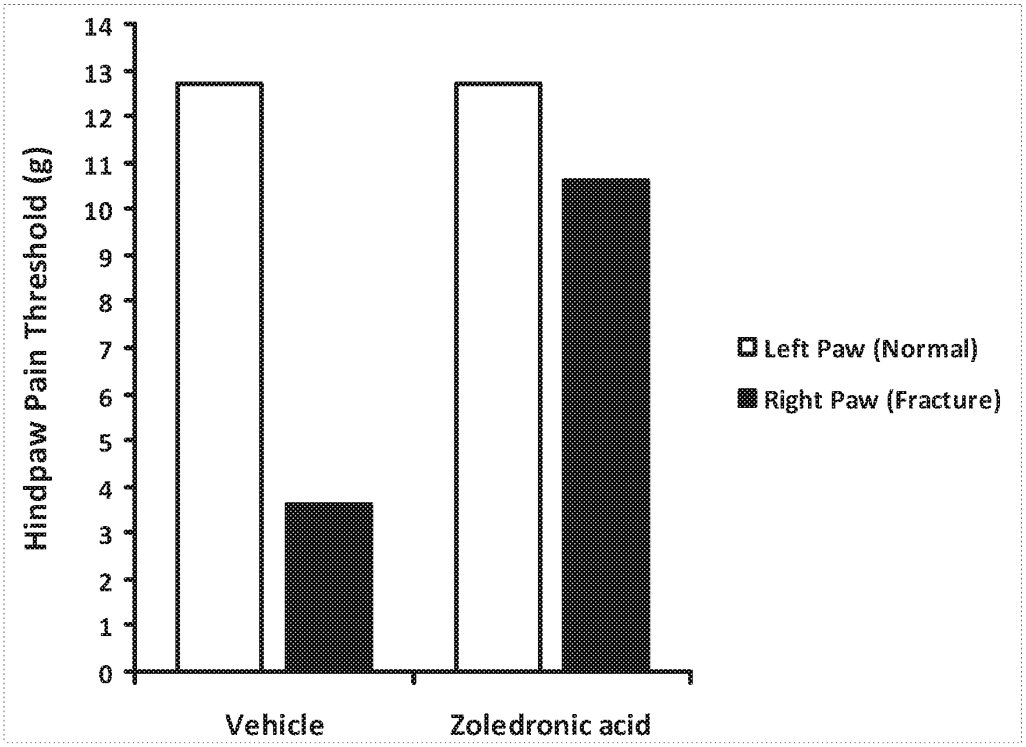

Hindpaw Pain Threshold (g)
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
Vehicle
Zoledronic acid
Left Paw (Normal)
Right Paw (Fracture)

FIG. 4

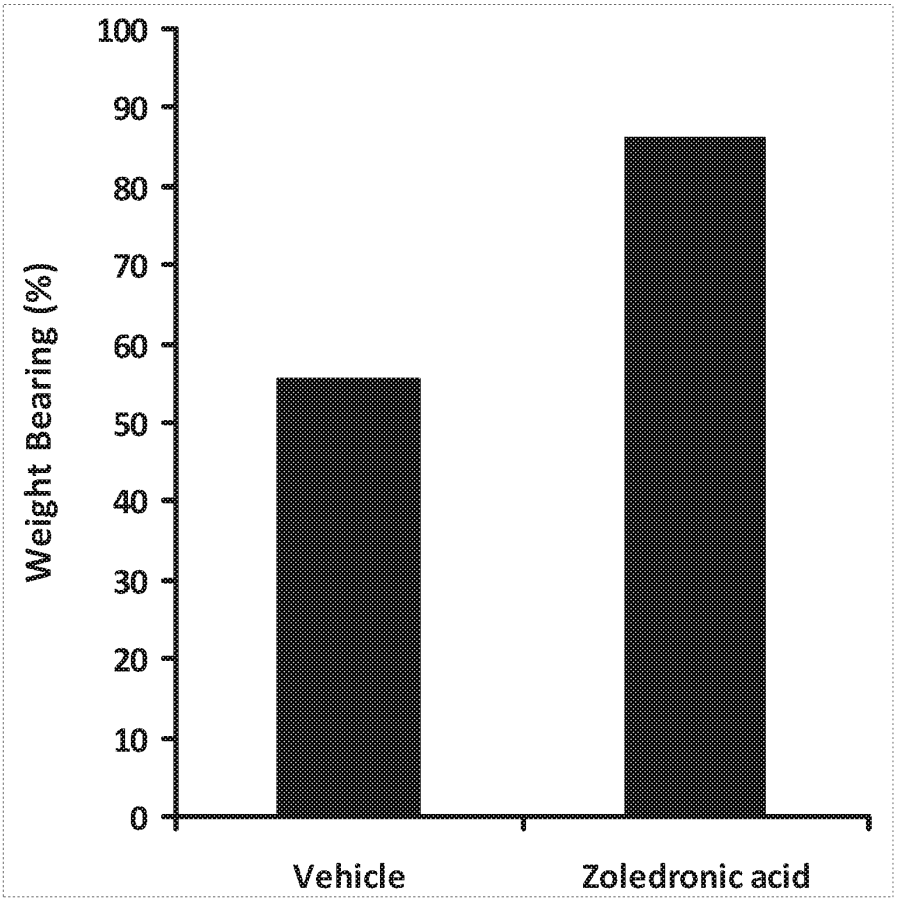

100
90
80
70
60
50
40
30
20
10
0
Weight Bearing (%)
Vehicle
Zoledronic acid

FIG. 5

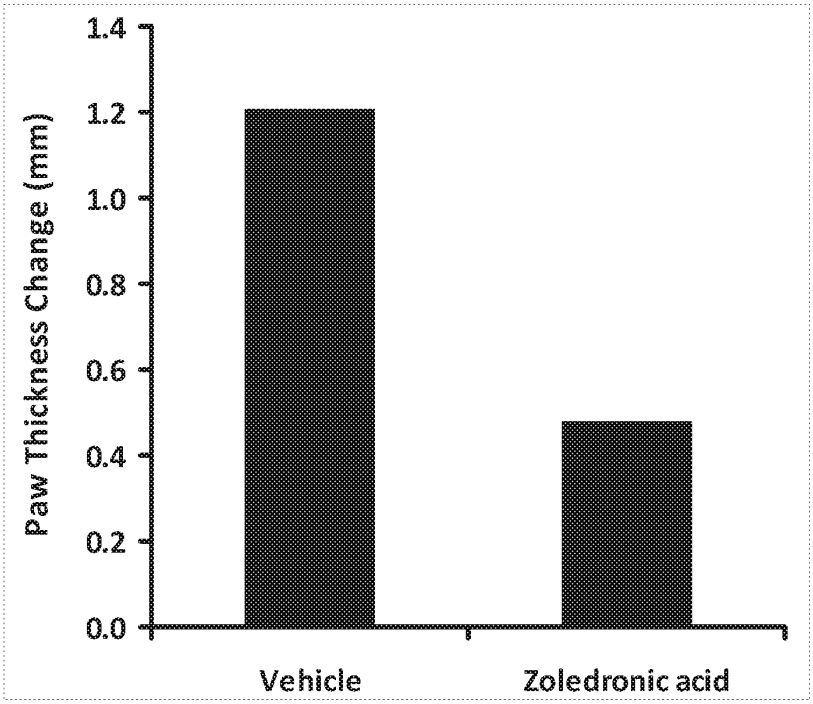

Paw Thickness Change (mm)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Vehicle
Zoledronic acid

FIG. 6

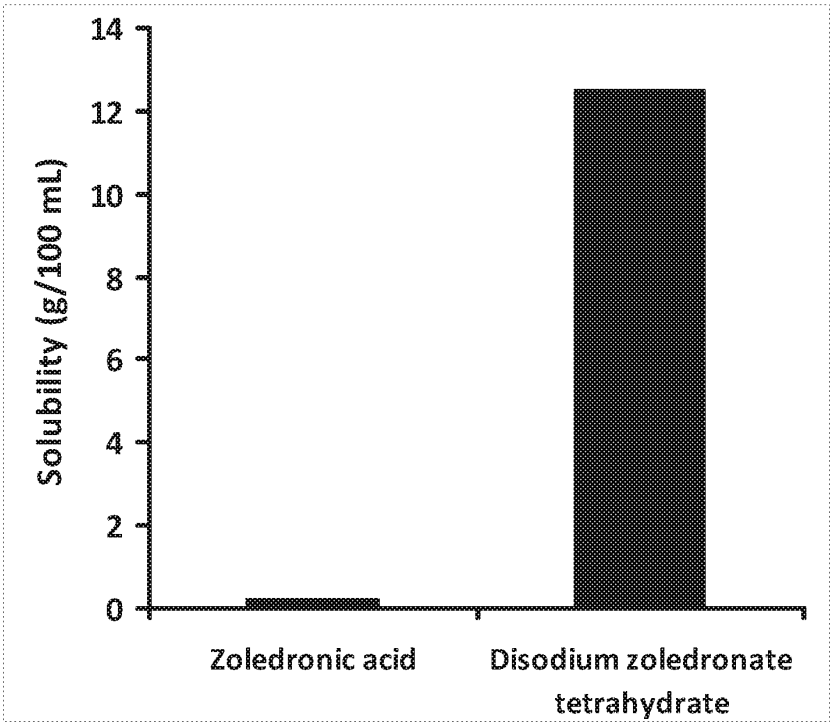

14
12
10
8
6
4
2
0
Solubility (g/100 mL)
Zoledronic acid
Disodium zoledronate tetrahydrate

FIG. 7

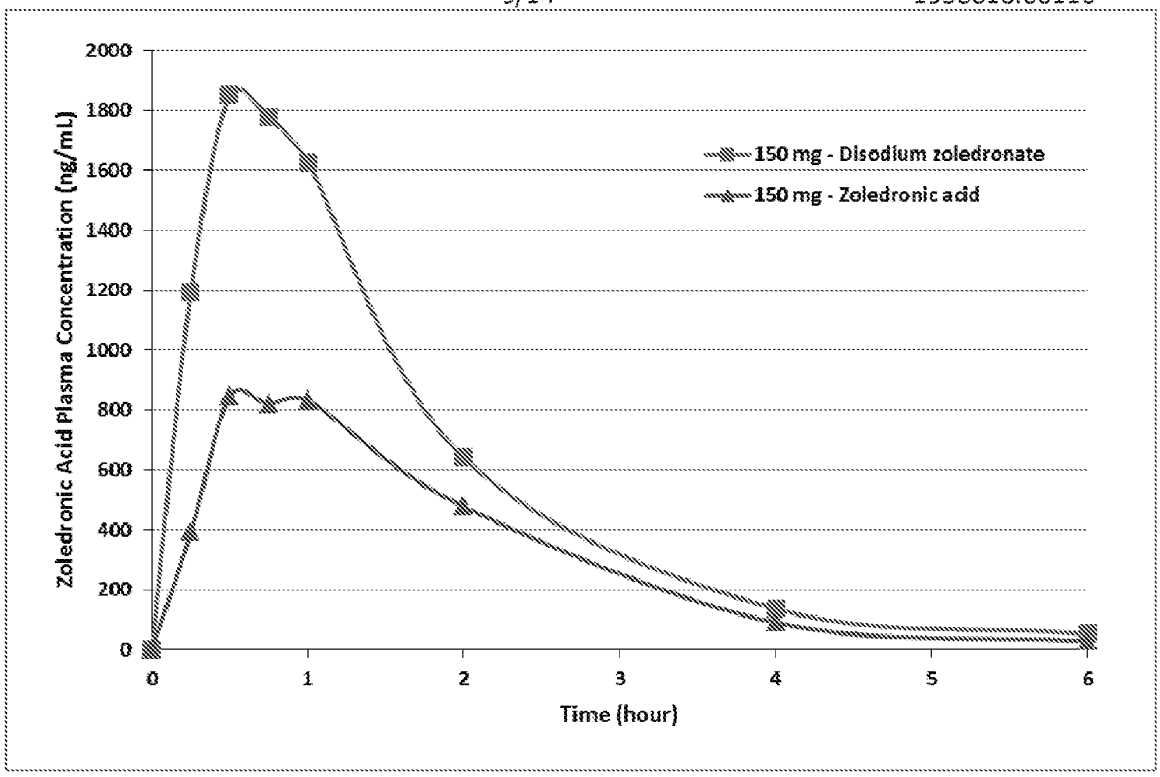

2000
1800
1600
1400
1200
1000
800
600
400
200
0
Zoledronic Acid Plasma Concentration (ng/mL)
0
1
2
3
4
5
6
Time (hour)
150 mg - Disodium zoledronate
150 mg - Zoledronic acid

FIG. 8

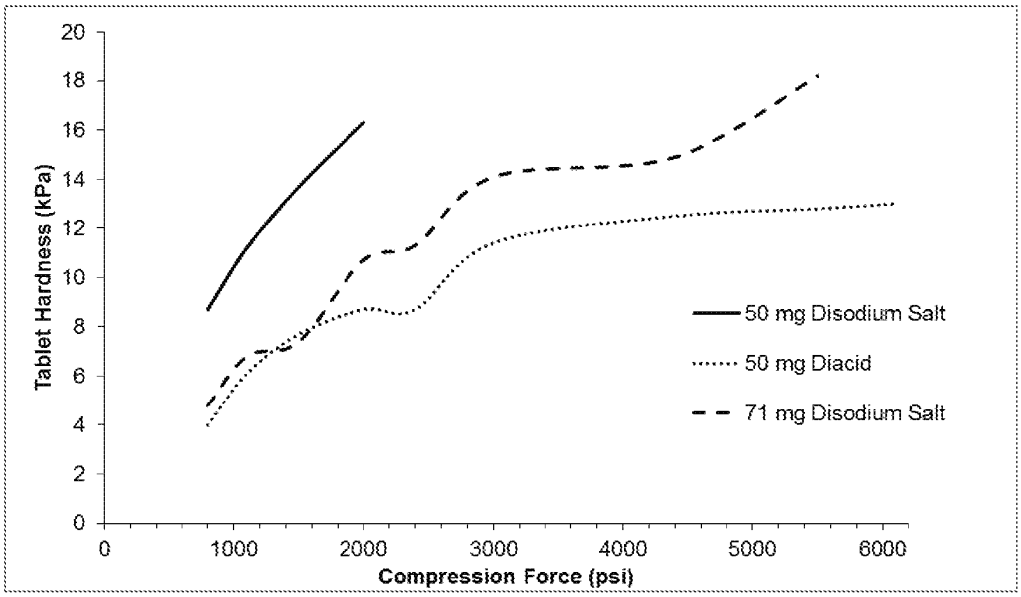

20
18
16
14
12
10
8
6
4
2
0
Tablet Hardness (kPa)
0
1000
2000
3000
4000
5000
6000
Compression Force (psi)
50 mg Disodium Salt
50 mg Diacid
71 mg Disodium Salt

FIG. 9

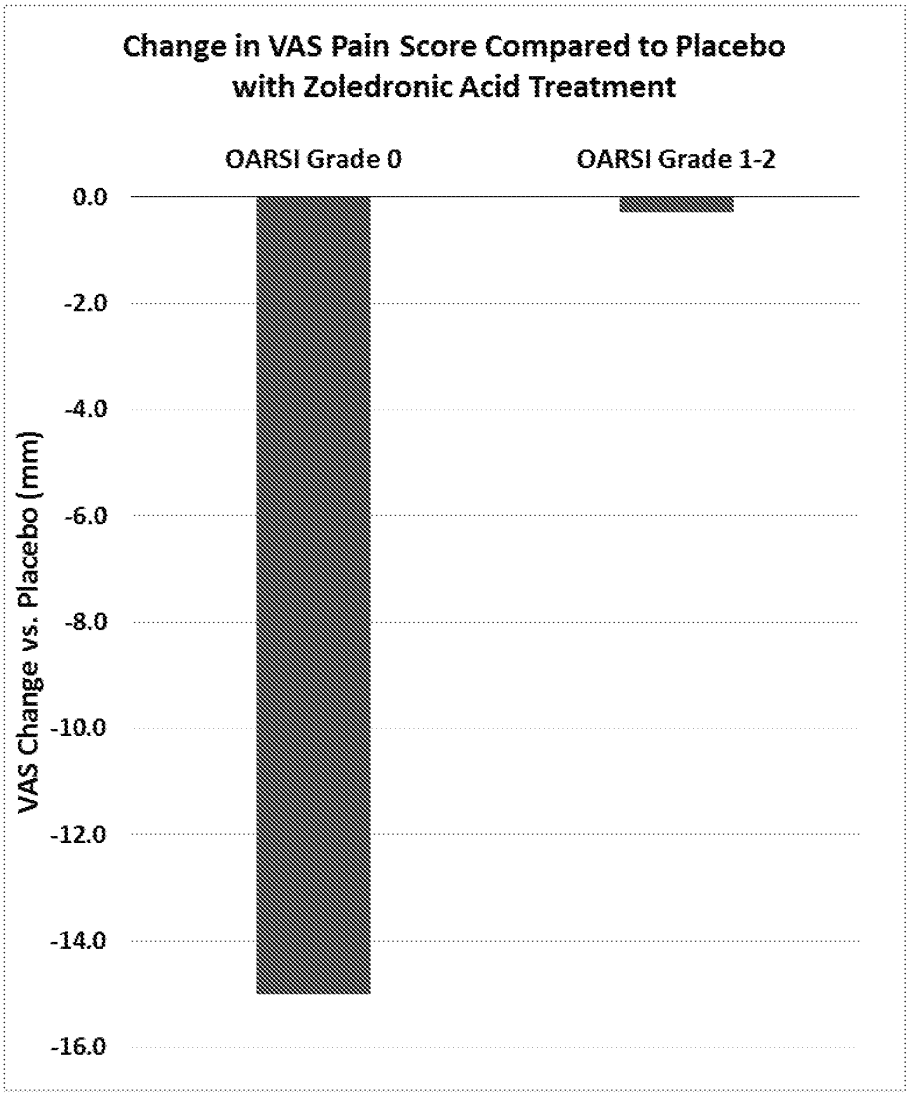

Change in VAS Pain Score Compared to Placebo with Zoledronic Acid Treatment
OARSI Grade 0
OARSI Grade 1-2
VAS Change vs. Placebo (mm)
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-14.0
-16.0

FIG. 10

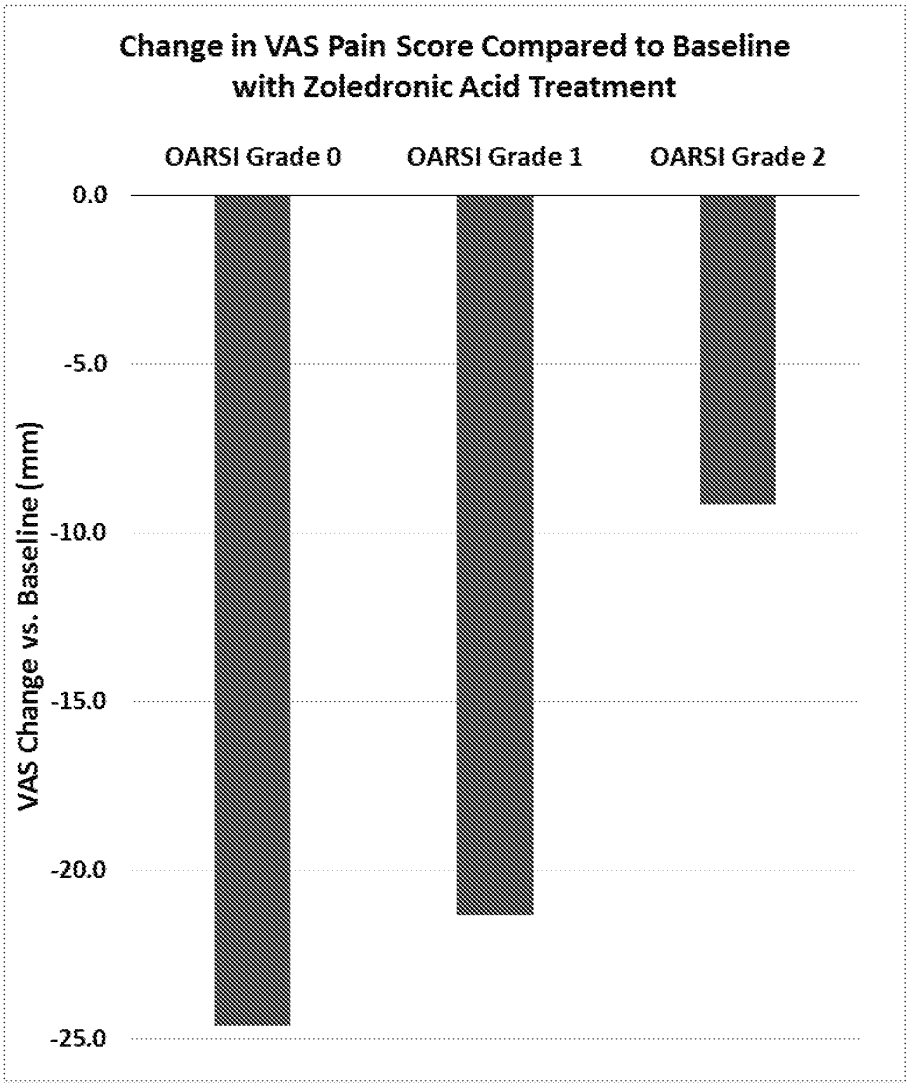

Change in VAS Pain Score Compared to Baseline with Zoledronic Acid Treatment
OARSI Grade 0
OARSI Grade 1
OARSI Grade 2
0.0
-5.0
-10.0
-15.0
-20.0
-25.0
VAS Change vs. Baseline (mm)

FIG. 11

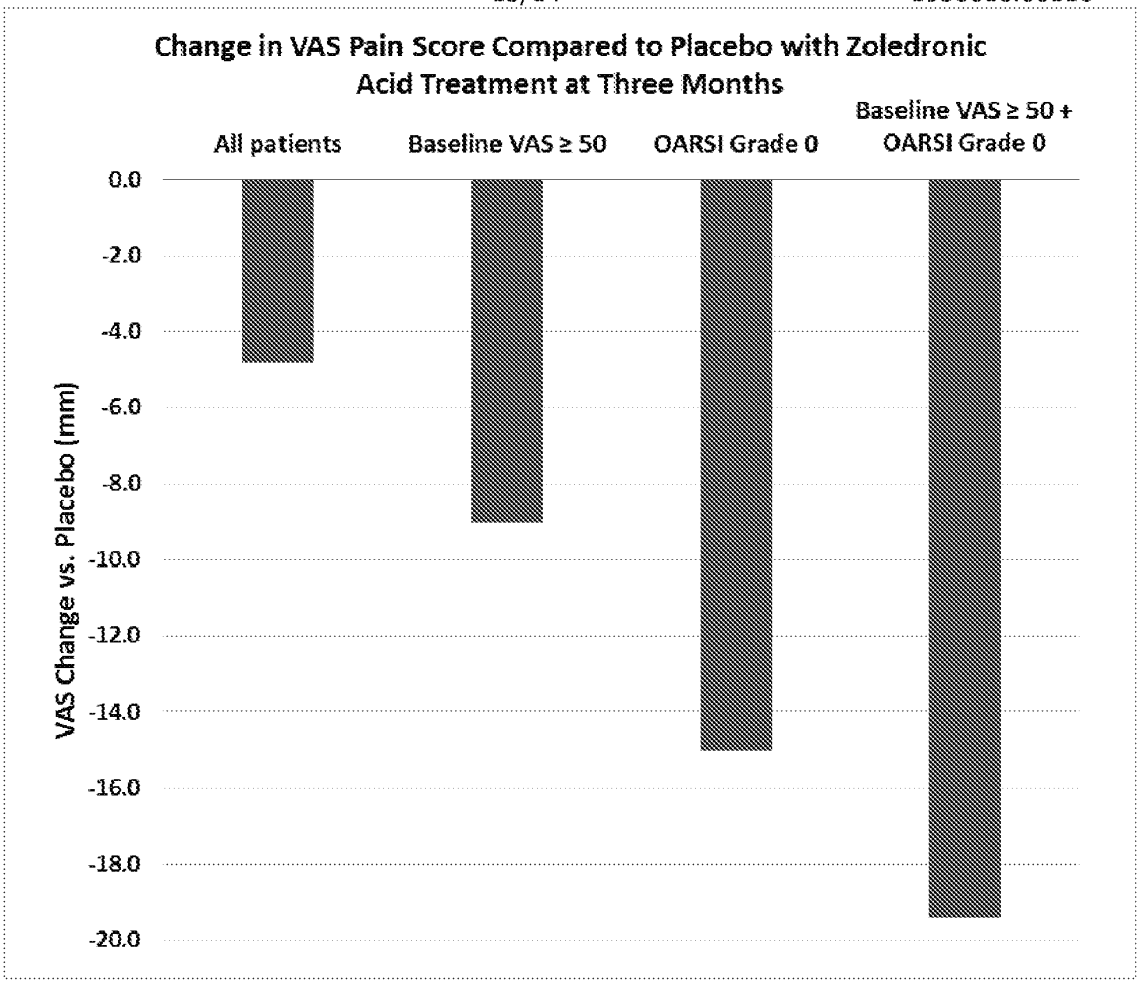

Change in VAS Pain Score Compared to Placebo with Zoledronic Acid Treatment at Three Months
All patients
Baseline VAS ≥ 50
OARSI Grade 0
Baseline VAS ≥ 50 + OARSI Grade 0
VAS Change vs. Placebo (mm)
0.0
-2.0
-4.0
-6.0
-8.0
-10.0
-12.0
-14.0
-16.0
-18.0
-20.0

FIG. 12

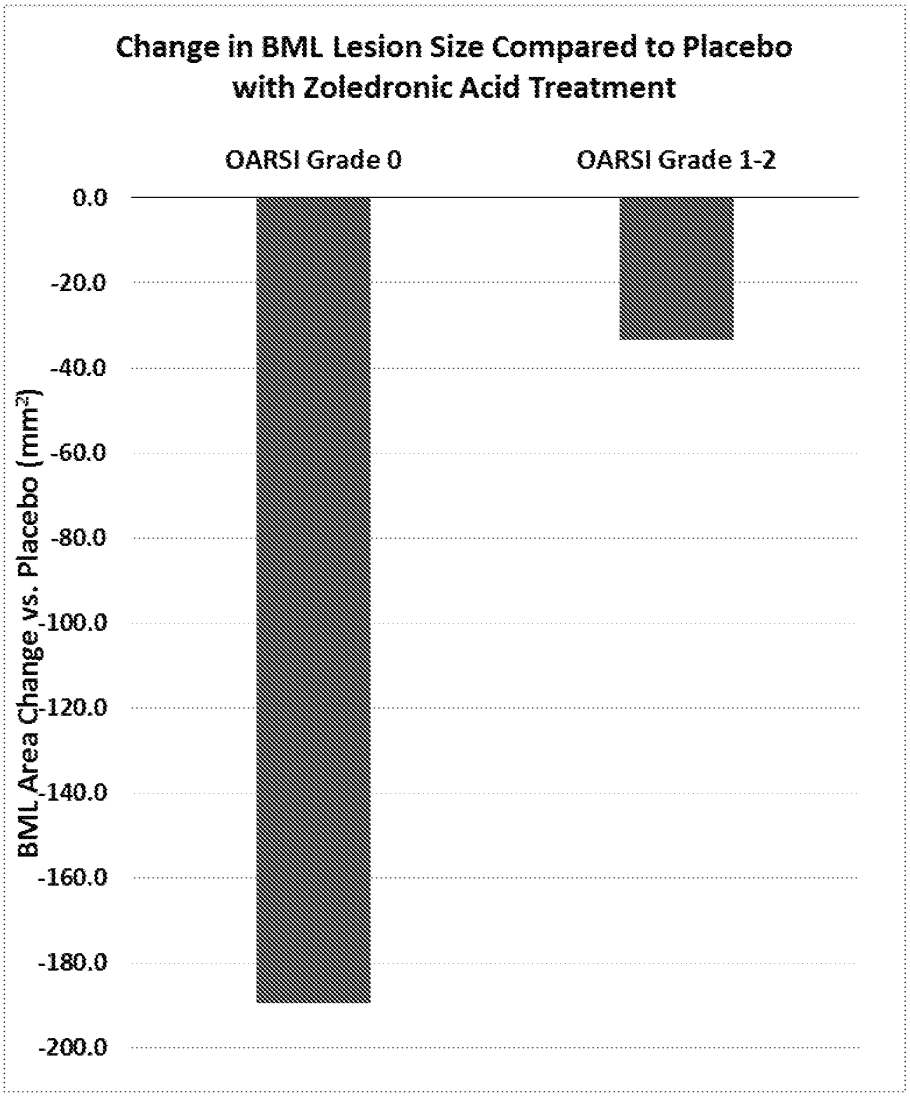

Change in BML Lesion Size Compared to Placebo with Zoledronic Acid Treatment
OARSI Grade 0
OARSI Grade 1-2
0.0
-20.0
-40.0
-60.0
-80.0
-100.0
-120.0
-140.0
-160.0
-180.0
-200.0
BML Area Change vs. Placebo (mm²)

FIG. 13

Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	Osteoclast Inhibitors for Knee Conditions
First Named Inventor/Applicant Name:	Herriot Tabuteau
Filer:	Louis C. Cullman/Maria Nadal
Attorney Docket Number:	1958603.00116
Filed as Small Entity	

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

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($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2800**

Electronic Acknowledgement Receipt	
EFS ID:	24343208
Application Number:	14967224
International Application Number:	
Confirmation Number:	1942
Title of Invention:	Osteoclast Inhibitors for Knee Conditions
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:	1958603.00116
Receipt Date:	11-DEC-2015
Filing Date:	
Time Stamp:	20:51:32
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2800
RAM confirmation Number	5995
Deposit Account	021818
Authorized User	ACHARYA, RANJINI
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	1958603_00116_AUTHORIZATION_TO_CHARGE_FEES_TRACK_ONE.pdf	63285 f37a457f6152326b516b3f992da51551c338e0c1	no	1
Warnings:					
Information:					
2	TrackOne Request	1958603_00116_TRACK_ONE_REQUEST.pdf	114185 b8631645dfb8908434297ec920a40dcb6c2d87a8	no	2
Warnings:					
Information:					
3	Application Data Sheet	1958603_00116_ADS.pdf	1820268 57c0040b3a4c545906937ac25c4f4cbffcb1b201	no	9
Warnings:					
Information:					
4	Oath or Declaration filed	1958616_00116_EXECUTED_DECLARATIONS.pdf	310252 2bb29587c17a40b1a7e87c2cc75a963eda50f274	no	2
Warnings:					
Information:					
5		1958603_00116_CON_PATENT_APPLICATION.pdf	339594 01999712f36433685104007f4afa07c43e9cb970	yes	75

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	72
Claims	73	74
Abstract	75	75

Warnings:					
Information:					
6	Drawings-only black and white line drawings	1958603_00116_DRAWINGS.pdf	206079 ac3bc580e79c524626c80b1a69f6d69a2e1a75fd	no	14

Warnings:					
Information:					
7	Fee Worksheet (SB06)	fee-info.pdf	40362 11be8195f74128e41222d877ddbe564c23d2a760	no	2
Warnings:					
Information:					
			Total Files Size (in bytes):	2894025	

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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.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Confirmation No.	**:**	
Appln. No.	**:**	
Applicant	**:**	**Antecip Bioventures II LLC**
First Inventor	**:**	**Herriot Tabuteau**
Filed	**:**	
TC/A.U.	**:**	
Examiner	**:**	
Docket No.	**:**	**1958603.00116**
Customer No.	**:**	**45200**
Title	**:**	**Osteoclast Inhibitors for Knee Conditions**

AUTHORIZATION TO CHARGE FEES

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

Dear Commissioner,

In the event that any of the following are not paid by EFS-Web, please charge the fee to deposit account No. 021818.

1. The processing fee set forth in 37 CFR 1.17(i)(1);
2. The prioritized examination fee set forth in 37 CFR 1.17(c);
3. The publication fee, which is currently $0;
4. The basic filing fee;
5. The search fee;
6. The examination fee; and
7. Any excess claims fees or application size fee.

The Commissioner is authorized to charge or credit any fee which may be required in connection with the Track One application filing to deposit account No. 021818.

Respectfully submitted,

Dated: 11 December 2015

/Brent A. Johnson/
Brent A. Johnson, PhD
Registration No. 51851
CUSTOMER NUMBER: 45200

K&L GATES LLP
1 Park Plaza, 12th Floor
Irvine, California 92614-7319
Telephone: (949) 253-0900
Facsimile: (949) 253-0902

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 14967224 Document Date: 12/11/2015

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

- Drawings – Other than Black and White Line Drawings

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded in PALM, and no paper documents or physical media exist. The TIFF images in the IFW record were created from the original documents that are stored in SCORE.

To access the documents in the SCORE database, refer to instructions below.

At the time of document entry (noted above):

- Examiners may access SCORE content via the eDAN interface.
- Other USPTO employees can bookmark the current SCORE URL (http://Score.uspto.gov/ScoreAccessWeb/).
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Form Revision Date: September 30, 2013

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/967,224	12/11/2015	Herriot Tabuteau	1958603.00116	1942

45200 7590 02/16/2016

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

EXAMINER	
SHIAO, REI TSANG	

ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
02/16/2016	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):

uspatentmail@klgates.com

Office Action Summary	Application No. 14/967,224	Applicant(s) TABUTEAU ET AL.	
	Examiner REI-TSANG SHIAO	Art Unit 1628	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/11/2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ 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*

5)☒ Claim(s) *1-20* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* is/are rejected.

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

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

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

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

11)☒ The drawing(s) filed on *12/11/2015* 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

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

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

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.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

1. This application claims priority of the provisional applications: 61/646,538 with a filing date 05/14/2012; 61/647,478 with a filing date 05/15/2012; 61/654,292 with a filing date 06/01/2012; 61/654,383 with a filing date 06/01/2012; 61/655,527 with a filing date 06/05/2012; 61/655,541 with a filing date 06/05/2012; 61/764,563 with a filing date 02/14/2013; 61/762,225 with a filing date 02/07/2013; 61/767,647 with a filing date 02/21/2013; 61/767,676 with a filing date 02/21/2013; and 61/803,721 with a filing date 03/20/2013.

2. Claims 1-20 are pending in the application.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20 are rejected under the judicially created doctrine of the obviousness-type double patenting as being unpatentable over claim 1 of Tabuteau et al. US 9,216,153. Although the conflicting claims are not identical, they are not patentably distinct from each other and reasons are as follows.

Applicants claim methods of use for treating bone marrow lesion of the knee in a patient using an inhibitor of osteoclast activity selected from ibandronic acid, risedronic acid, or alendronic acid, see claim 1. Dependent claims 2-20 further limit the scope of methods of use, i.e., the patient has knee pain in claim 17, and treating dose or period in claims 2-16 and 18-20.

Tabuteau et al. ‘153 claims methods of use for treating knee pain (i.e., bone marrow lesion of the knee) using zoledronic acid, minodronic acid, risedronic acid or neridronic acid, see column 56

The difference between instant claims and Tabuteau et al. ‘153 is that the instant inhibitors of osteoclast activity are embraced within the scope of Tabuteau et al. ‘153. Tabuteau's ‘153 methods of use overlap with the instant invention.

One having ordinary skill in the art would find the claims 1-20 prima facie obvious because one would be motivated to employ the methods of use of Tabuteau et al. ‘153

to obtain instant invention. Dependent claims 2-20 are also rejected along with claim 1 under the obviousness-type double patenting.

The motivation to make the claimed methods of use derived from the known methods of use of Tabuteau et al. '153 would possess similar activity to that which is claimed in the reference.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen, can be reached on (571)272-3157. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the

automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO/

Rei-tsang Shiao, Ph.D.
Primary Examiner
Art Unit 1628

February 08, 2016

Notice of References Cited	Application/Control No. 14/967,224	Applicant(s)/Patent Under Reexamination TABUTEAU ET AL.	
	Examiner REI-TSANG SHIAO	Art Unit 1628	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	CPC Classification	US Classification
*	A	US-9,216,153 B2	12-2015	Tabuteau; Herriot	A61K9/0053	1/1
	B	US-				
	C	US-				
	D	US-				
	E	US-				
	F	US-				
	G	US-				
	H	US-				
	I	US-				
	J	US-				
	K	US-				
	L	US-				
	M	US-				

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	CPC Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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

NOTICE OF ALLOWANCE AND FEE(S) DUE

45200 7590 05/23/2016

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

EXAMINER
SHIAO, REI TSANG

ART UNIT	PAPER NUMBER
1628	

DATE MAILED: 05/23/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/967,224	12/11/2015	Herriot Tabuteau	1958603.00116	1942

TITLE OF INVENTION: Osteoclast Inhibitors for Knee Conditions

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	08/23/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

45200 7590 05/23/2016
K&L Gates LLP-Orange County
1 Park Plaza
Twelfth Floor
IRVINE, CA 92614

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/967,224	12/11/2015	Herriot Tabuteau	1958603.00116	1942

TITLE OF INVENTION: Osteoclast Inhibitors for Knee Conditions

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0	$0	$480	08/23/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
SHIAO, REI TSANG	1628	514-108000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
❑ Issue Fee
❑ Publication Fee (No small entity discount permitted)
❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
❑ A check is enclosed.
❑ Payment by credit card. Form PTO-2038 is attached.
❑ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
❑ Applicant certifying micro entity status. See 37 CFR 1.29
NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27
NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.
NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

PTOL-85 Part B (10-13) Approved for use through 10/31/2013. OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/967,224	12/11/2015	Herriot Tabuteau	1958603.00116	1942

45200 7590 05/23/2016

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

EXAMINER	
SHIAO, REI TSANG	

ART UNIT	PAPER NUMBER
1628	

DATE MAILED: 05/23/2016

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. 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 12 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, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. 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.

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.

Notice of Allowability	Application No. 14/967,224	Applicant(s) TABUTEAU ET AL.	
	Examiner REI-TSANG SHIAO	Art Unit 1628	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *amendment filed on 3/21/2016*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-30*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   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)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date 2/18/16,5/17/16,5/18/16
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/REI-TSANG SHIAO/
Primary Examiner, Art Unit 1628

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

1. This application claims priority of the provisional applications: 61/646,538 with a filing date 05/14/2012; 61/647,478 with a filing date 05/15/2012; 61/654,292 with a filing date 06/01/2012; 61/654,383 with a filing date 06/01/2012; 61/655,527 with a filing date 06/05/2012; 61/655,541 with a filing date 06/05/2012; 61/764,563 with a filing date 02/14/2013; 61/762,225 with a filing date 02/07/2013; 61/767,647 with a filing date 02/21/2013; 61/767,676 with a filing date 02/21/2013; and 61/803,721 with a filing date 03/20/2013.

2. Amendment including addition of claims 21-30 and a terminal disclaimer in the amendment filed on 3/21/2016 is acknowledged. Claims 1-30 are pending in the application. No new matter has been found. Since the newly added claims 21-30 are commensurate within the scope of invention, claims 1-30 are prosecuted in the case.

Reasons for Allowance

3. Since the terminal disclaimer against Tabuteau et al. '153 has been filed and approved in the Office, the rejection of claims 1-20 under the obviousness-type double patenting has been overcome in the amendment filed on 3/21/2016

4. Claims 1-30 are neither anticipated nor rendered obvious over the art of record, and therefore are allowable. A suggestion for modification of a reference to obtain the instant methods of use has not been found. Claims 1-30 are allowed.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably

accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance".

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rei-tsang Shiao whose telephone number is (571) 272-0707. The examiner can normally be reached on 8:30 AM - 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Winston Shen, can be reached on (571)272-3157. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO/

Rei-tsang Shiao, Ph.D.
Primary Examiner
Art Unit 1628

April 29, 2016