

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
17 November 2005 (17.11.2005)

PCT

(10) International Publication Number  
WO 2005/107714 A3

- (51) International Patent Classification:  
A61K 9/16 (2006.01)
- (21) International Application Number:  
PCT/US2005/015757
- (22) International Filing Date: 5 May 2005 (05.05.2005)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
60/568,467 5 May 2004 (05.05.2004) US
- (71) Applicant (for all designated States except US): **ALK-ERMES CONTROLLED THERAPEUTICS, INC.** [US/US]; 88 Sidney Street, 2nd Floor, Cambridge, MA 02139 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **FIGUEIREDO, Maria, C.** [US/US]; 1 Olive Square, Somerville, MA 02143 (US). **KUMAR, Rajesh** [IN/US]; 142 Riverside Street, #6, Lowell, MA 01854 (US). **MALONEY, Maura, J.** [US/US]; P.O. Box 536, Hingham, MA 02043 (US). **SCHER, David, S.** [US/US]; 54 Laurel Drive, Hudson, MA 01749 (US). **YEOH, Thean, Y.** [MY/US]; 22 Spruce Street, Foxboro, MA 02035 (US). **ZALE, Stephen, E.** [US/US]; 1 Norcross Street, Hopkinton, MA 01748 (US). **PRINN, Kristin** [US/US]; 60 Elm Street, #2, Somerville, MA 02144 (US). **TROIANO, Gregory** [US/US]; 17 Elinor Road, Weymouth, MA 02190 (US).
- (74) Agent: **PIERCE, Scott, N.**; Hamilton, Brook, Smith & Reynolds, P.C., 530 Virginia Road, P.O. Box 9133, Concord, MA 01742-9133 (US).
- (81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:  
— with international search report  
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report:  
28 September 2006
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: METHOD OF FORMING MICROPARTICLES THAT INCLUDE A BISPHOSPHONATE AND A POLYMER

(57) Abstract: Microparticles that includes a bisphosphonate and a polymer are produced by a method that includes forming a water-in-oil emulsion by mixing an aqueous solution of the bisphosphonate with a combination of a biocompatible polymer and a polymer solvent. At least one aqueous liquid can be mixed with the water-in-oil emulsion to form a water-in-oil-in-water emulsion and to extract the polymer solvent from the polymer, thereby forming the microparticles. Methods of treating a patient in need of therapy include administering the microparticles described to the patient. In one embodiment, the microparticles are formulated for the sustained release of the bisphosphonate.

WO 2005/107714 A3

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/015757

A. CLASSIFICATION OF SUBJECT MATTER  
 INV. A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

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

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PAOLA PERUGINI; ET AL.: "Long-term Release of Clodronate from Biodegradable Microspheres" AAPS PHARMSCITECH, vol. 2, no. 3, 2001, pages 1-9, XP002377414	1-8, 13-24
Y	page 2, right-hand column - page 3, left-hand column ----- -/--	9-12

Further documents are listed in the continuation of Box C.

See patent family annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

26 April 2006

Date of mailing of the international search report

07.08.2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Ventura Amat, A

## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2005/015757

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>U. WEIDENAUER; ET AL.:  "Microencapsulation of hydrophylic drug substances using biodegradable polyesters. Part I: Evaluation of different techniques for the encapsulation of Pamidronate di-sodium salt."  J. MICROENCAPSULATION, vol. 20, no. 4, August 2003 (2003-08), pages 509-524, XP001162189  gb  page 511, paragraph 2 - page 513, paragraph 1</p> <p>-----</p>	9,10
Y	<p>DATABASE WPI  Section Ch, Week 200371  Derwent Publications Ltd., London, GB;  Class A96, AN 2003-753276  XP002378274  &amp; KR 2002 080 018 A (KOREA RES INST CHEM TECHNOLOGY) 23 October 2002 (2002-10-23)  the whole document</p> <p>-----</p>	11,12
P,X	<p>WO 2004/043441 A (AMOREPACIFIC)  27 May 2004 (2004-05-27)  page 12; example 1</p> <p>-----</p>	1,9,10, 18,19,22
A	<p>EP 0 709 085 A (TAKEDA CHEMICAL INDUSTRIES) 1 May 1996 (1996-05-01)  page 13; example 1</p> <p>-----</p>	1-24
A	<p>US 6 572 874 B1 (DONALD C. HARRISON; ET AL.) 3 June 2003 (2003-06-03)  claims 14,21  column 14, paragraph 2 - paragraph 3  page 18, paragraph 3  page 18, paragraph 7</p> <p>-----</p>	1-24

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2005/015757

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

## 1. claims: 1-24

A method of forming micro particles that include a bisphosphonate and a polymer, comprising the steps of:  
a) forming a water-in-oil emulsion by mixing an aqueous solution of the bisphosphonate with a combination of a poly(lactide) or a poly(lactide-co-glycolide) polymer and a polymer solvent wherein the molar ratio of the lactide component to the glycolide component in the polymer is at least about 65:35; and  
b) Mixing at least one aqueous liquid with the water-in-oil emulsion to form a water-in-oil-in-water emulsion and to extract the polymer solvent from the polymer, thereby forming the micro particles.

---

## 2. claims: 25-37

A method of forming microparticles that include a bisphosphonate and a polymer, comprising the steps of  
a) forming a water-in-oil emulsion by mixing an aqueous solution of the bisphosphonate with a combination of a biocompatible polymer and a polymer solvent, wherein the concentration of the bisphosphonate in the aqueous solution is greater than the room temperature solubility limit of the bisphosphonate;  
b) forming a water-in-oil-in-water emulsion by mixing a first aqueous liquid with the water-in-oil emulsion; and  
c) extracting the polymer solvent from the polymer into a second aqueous liquid, thereby forming the microparticles.

---

## 3. claims: 38-43

A method of forming micro particles that include a bisphosphonate and a polymer, comprising the steps of:  
a) Preparing an aqueous mixture of the bisphosphonate and a surfactant;  
b) Forming a water-in-oil emulsion by mixing the aqueous mixture with a combination of a biocompatible polymer and a polymer solvent;  
c) Forming a water-in-oil-in-water emulsion by mixing the water-in-oil emulsion with an aqueous liquid; and  
d) Removing the polymer solvent from the polymer, thereby forming the micro particles.

---

## 4. claim: 44

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of forming micro particles that include a bisphosphonate and a polymer, comprising the steps of:  
a) Forming a water-in-oil emulsion by mixing an aqueous solution consisting essentially of water and the bisphosphonate with a combination of a biocompatible polymer and a polymer solvent; and  
b) Mixing at least one aqueous liquid with the water-in-oil emulsion to form a water-in-oil-in-water emulsion and to extract the polymer solvent from the polymer, thereby forming the micro particles.

---

## 5. claim: 45

A method of forming micro particles that include a bisphosphonate and a polymer, comprising the steps of:  
a) Forming a bisphosphonate suspension in a combination consisting essentially of a biocompatible polymer and a polymer solvent; and  
b) Mixing at least one aqueous liquid with the bisphosphonate suspension to form a solid-in-oil-in-water emulsion and to extract the polymer solvent from the polymer, thereby forming the micro particles.

---

## 6. claims: 46-56

A method of forming micro particles that include a bisphosphonate and a polymer, comprising the steps of:  
a) Forming a water-in-oil emulsion by mixing an aqueous solution of the bisphosphonate with a combination of a biocompatible polymer and a polymer solvent; and  
b) Mixing at least one aqueous liquid with the water-in-oil emulsion to form a water-in-oil-in-water emulsion and to extract the polymer solvent from the polymer, thereby forming the micro particles.

---

## 7. claims: 57-77

A method of forming micro particles that include a bisphosphonate and a polymer, comprising the steps of:  
a) forming a water-in-oil emulsion by mixing an aqueous solution of the bisphosphonate with a combination of a biocompatible polymer and a polymer solvent, wherein the concentration of the bisphosphonate in the aqueous solution is greater than the room temperature solubility limit of the bisphosphonate;  
b) Forming a water-in-oil-in-water emulsion by mixing a first aqueous liquid with the water-in-oil emulsion; and  
c) Extracting the polymer solvent from the polymer into a second aqueous liquid, thereby forming the micro particles.

---

## 8. claims: 78-87

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Micro particles consisting essentially of a biocompatible polymer and at least about 3 weight percent of risedronate or a salt thereof.

---

9. claims: 88-97,116-119

Micro particles consisting essentially of a bisphosphonate and a biocompatible polymer wherein the microparticles have an in vitro 24-hour cumulative bisphosphonate release of less than about 15 weight percent.

---

10. claims: 98-101

Micro particles consisting essentially of a bisphosphonate and a biocompatible polymer wherein the microparticles cause a local site reaction in vivo upon parenteral administration to a patient that is substantially similar to a local site reaction caused by placebo micro particles that include a biocompatible polymer.

---

11. claims: 102-107

Micro particles comprising:

- a) a poly(d,l-lactide-co-glycolide) polymer having about 75 mol% d,l-lactide, about 25 mol% glycolide, and a lauryl ester end group; and
  - b) Risedronate or a salt thereof;
- Wherein the volume median diameter of the micro particles is about 20 to about 60 microns.

---

12. claims: 108-111

Micro particles comprising:

- a) a poly(d,l-lactide-co-glycolide) polymer having about 65 mol% d,l-lactide, about 35 mol% glycolide, and a lauryl ester end group; and
  - b) Risedronate or a salt thereof;
- Wherein the volume median diameter of the micro particles is about 40 to about 60 microns.

---

13. claims: 112-115

Micro particles comprising:

- a) A poly (d, l-lactide-co-glycolide) polymer having a methyl ester end group; and
  - b) Risedronate or a salt thereof;
- Wherein the volume median diameter of the micro particles is about 40 to about 60 microns.

---

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2005/015757

Patent document cited in search report	A	Publication date	Patent family member(s)	Publication date
KR 2002080018	A	23-10-2002	NONE	
<hr style="border-top: 1px dashed black;"/>				
WO 2004043441	A	27-05-2004	AU 2003282403 A1	03-06-2004
			EP 1578405 A1	28-09-2005
			US 2006057221 A1	16-03-2006
<hr style="border-top: 1px dashed black;"/>				
EP 0709085	A	01-05-1996	AT 231390 T	15-02-2003
			AT 198981 T	15-02-2001
			CA 2159552 A1	31-03-1996
			DE 69520021 D1	08-03-2001
			DE 69520021 T2	13-09-2001
			DE 69529486 D1	27-02-2003
			DE 69529486 T2	04-12-2003
			DK 1022020 T3	03-03-2003
			DK 709085 T3	19-02-2001
			US 6117455 A	12-09-2000
<hr style="border-top: 1px dashed black;"/>				
US 6572874	B1	03-06-2003	NONE	
<hr style="border-top: 1px dashed black;"/>				