(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
10 July 2008 (10.07.2008)

(10) International Publication Number
WO 2008/082563 A3

(51) **International Patent Classification:**
A61K9/00 **(2006.01)** ***A61K38/00*** **(2006.01)**
A61K9/14 **(2006.01)** ***A61K38/18*** **(2006.01)**

(21) **International Application Number:**
PCT/US2007/025956

(22) **International Filing Date:**
19 December 2007 (19.12.2007)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
60/876,292 21 December 2006 (21.12.2006) US

(71) **Applicant** *(for all designated States except US):* **STRYKER CORPORATION** [US/US]; 2725 Fairfield Road, Kalamazoo, **MI** 49005 (US).

(72) **Inventor; and**
(75) **Inventor/Applicant** *(for US only):* **JAWOROWICZ, Warren** [US/US]; 383 South Bolton Road, Bolton, MA 01740 (US).

(74) **Agents: KOMM, Crystal, A.** et al; KirkPatrick & Lockhart Preston Gates Ellis LIp, State Street Financial Center, One Lincoln Street, Boston, MA 021 11-2950 (US).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, **BR,** BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, **HR,** HU, **ID,** IL, IN, IS, **JP,** KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, LV, MC, MT, 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*
— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

(88) **Date of publication of the international search report:**
27 November 2008

WO 2008/082563 A3

(54) Title: SUSTAINED-RELEASE FORMULATIONS COMPRISING CRYSTALS, MACROMOLECULAR GELS, AND PARTICULATE SUSPENSIONS OF BIOLOGIC AGENTS

(57) Abstract: The present invention is directed to sustained release formulations of biologic agents which permit persistent bioavailability. Preferred biologic agents include bone morphogenetic proteins. Diseases susceptible to amelioration and/or treatment with the formulations of the present invention include skeletal tissue diseases such as, but not limited to, osteoarthritis and other osteochondral diseases. The sustained release formulations of the present invention are especially suitable for treatment of minimally-vascularized or non- vascularized tissue sites such as, but not limited to, intrajoint, interarticular, or intraminiscal sites.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/025956

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/14 A61K38/00 A61K38/18

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 , EMBASE, BIOSIS, **WPI Data**

C. DOCUMENTS CONSIDERED TO **BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	JEN A ET AL: "Transforming growth factor beta-3 crystals as reservoirs for slow release of active TGF-beta3" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 78, no. 1-3, 17 January 2002 (2002-01-17), pages 25-34, XP004329803 ISSN: 0168-3659 the whole document	1-7,9-38

-/--

[X] Further documents are listed in the continuation of Box C

[X] 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	Date of mailing of the international search report
30 June 2008	29/08/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040, Tx 31 651 epo nl, Fax (+3.1-70) 340-3016	Hagenmaier , **Susanne**

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/025956

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	LUGINBUEHL V ET AL: "Localized delivery of growth factors for bone repair" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 58, no. 2, 1 September 2004 (2004-09-01), pages 197-208, XP004526306 ISSN: 0939-6411 page 200, right-hand column, last paragraph - page 201, left-hand column, paragraph FIRST the whole document	1-7,9-38
X	BEALS ET AL: "Enhancing exposure of protein therapeutics" DRUG DISCOVERY TODAY: TECHNOLOGIES, ELSEVIER, vol. 3, no. 1, 1 April 2006 (2006-04-01), pages 87-94, XP005409090 ISSN: 1740-6749 page 91 - page 92 the whole document	1-7,9-38
X	JELIC M ET AL: "Regeneration of articular cartilage chondral defects by osteogenic protein-1 (bone morphogenetic protein-7) in sheep" GROWTH FACTORS, HARWOOD ACADEMIC PUBLISHERS GMBH, XX, vol. 19, no. 2, 1 January 2001 (2001-01-01), pages 101-113, XP008093561 ISSN: 0897-7194 the whole document	1-7, 9-11, 15, 16, 18, 19, 22-25, 27,28, 30-37
X	BASU S K ET AL: "PROTEIN CRYSTALS FOR THE DELIVERY OF BIOPHARMACEUTICALS" EXPERT OPINION ON BIOLOGICAL THERAPY, ASHLEY, LONDON, GB, vol. 4, no. 3, 1 March 2004 (2004-03-01), pages 301-317, XP009040451 ISSN: 1471-2598 the whole document	1-7,9-38
X	PECHENOV S ET AL: "Injectable controlled release formulations incorporating protein crystals" JOURNAL OF CONTROLLED RELEASE, ELSEVIER, AMSTERDAM, NL, vol. 96, no. 1, 16 April 2004 (2004-04-16), pages 149-158, XP004500740 ISSN: 0168-3659 the whole document	1-7,9-38

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/025956

C(Contlnuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	CENDROS ET AL: "Pharmacoki netics and popul ati on pharmacodynamic analysi s of l anreotide Autogel " METABOLISM, CLINICAL AND EXPERIMENTAL, W. B. SAUNDERS CO. , PHILADELPHIA, PA, US, vol . 54, no. 10, 1 October 2005 (2005-10-01) , pages 1276-1281 , XP005067925 ISSN: 0026-0495 the whole document	1-7 ,9-38
X	WO 03/006049 A (FERRING BV [NL] ; LUECK MARTIN [DK] ; BROQUA PIERRE [GB]) 23 January 2003 (2003-01-23) page 2 , paragraph 2 page 3 , l ast paragraph page 4 , l ast paragraph - page 5 , paragraph FIRST the whole document	1-7,9-38
X	WO 2004/060920 A (ALTUS BIOLOG INC [US] ; KHALAF NAZER [US] ; GOVARDHAN CHANDRIKA [US]) 22 July 2004 (2004-07-22) c l aims 3,55 the whole document	1-7 ,9-38
X	WO 2004/030650 A (BAXTER HEALTHCARE SA [CH] ; BAUER HORST [DE] ; REISSMANN THOMAS [DE] ; RO) 15 Apri l 2004 (2004-04-15) the whole document	1-7,9-38
X	US 5 595 760 A (CHERIF-CHEIKH ROLAND [FR]) 21 January 1997 (1997-01-21) the whole document	1-7 ,9-38
X	US 6 503 534 Bl (PELLET MARC [FR] ET AL) 7 January 2003 (2003-01-07) the whole document	1-7,9-38
A	US 2006/257492 Al (WEN HAI B [US] ET AL) 16 November 2006 (2006-11-16) page 7 ; example 4 the whole document	
A	PHILLIPS ET AL: "In vivo BMP-7 (OP-I) enhancement of osteoporotic vertebral bodies i n an ovi ne model " THE SPINE JOURNAL, ELSEVIER , vol . 6 , no. 5 , 1 September 2006 (2006-09-01) , pages 500-506, XP005612783 ISSN: 1529-9430 the whole document	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/025956

Box No. 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 No. 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 additi onal sheet

1. D As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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.:

1-7 , 35 , 36 (al l parti al ly) and 9-34 , 37, 38 (al l compl etely)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCTΛSA/ 210

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

1. claims: 1-7,35,36 (all partially) and 9-34,37,38 (all completely)

A composition suitable for implantation at a tissue site comprising a biologic agent wherein said agent is selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, wherein said biologic agent is released in a sustained-release manner at a tissue site in an amount effective to ameliorate an injury or disease at a tissue site, wherein in particular the biologic agent is a member of the TGFbeta superfamily of proteins and wherein in particular said protein is BMP-7 as well as a pharmaceutical composition for treatment of an injured or diseased tissue and a kit comprising the said composition; a method of treatment of an injured or diseased tissue, the method comprising the step of: providing to a tissue site a composition suitable for implantation at, adjacent or in the vicinity of an injured or diseased tissue wherein the composition comprises a biologic agent selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, and further wherein said biologic agent is released in a sustained-release manner at the tissue site in an amount effective to treat the injured or diseased tissue, wherein in particular said agent is the BMP-7 protein; a composition suitable for systemic administration, the composition comprising a biologic agent wherein said biologic agent is selected from the group consisting of a crystal, a macromolecular gel, or a particulate suspension and further wherein said biologic agent is released in a timed-release manner in an amount effective to ameliorate an injury or disease.

---

2. claims: 1-7,35,36 (all partially)

A composition suitable for implantation at a tissue site comprising a biologic agent wherein said agent is selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, wherein said biologic agent is released in a sustained-release manner at a tissue site in an amount effective to ameliorate an injury or disease at a tissue site, wherein said biologic agent is the BMP-2 protein, as well as a pharmaceutical composition for treatment of an injured or diseased tissue and a kit comprising the said composition.

---

3. claims: 1-6,35,36 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A composition suitable for implantation at a tissue site comprising a biologic agent wherein said agent is selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, wherein said biologic agent is released in a sustained-release manner at a tissue site in an amount effective to ameliorate an injury or disease at a tissue site, wherein said biologic agent is the BMP-4 protein, as well as a pharmaceutical composition for treatment of an injured or diseased tissue and a kit comprising the said composition.

---

4. claims: 1-6,35,36 (all partially)

A composition suitable for implantation at a tissue site comprising a biologic agent wherein said agent is selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, wherein said biologic agent is released in a sustained-release manner at a tissue site in an amount effective to ameliorate an injury or disease at a tissue site, wherein said biologic agent is the BMP-5 protein, as well as a pharmaceutical composition for treatment of an injured or diseased tissue and a kit comprising the said composition.

---

5. claims: 1-6,35,36 (all partially)

A composition suitable for implantation at a tissue site comprising a biologic agent wherein said agent is selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, wherein said biologic agent is released in a sustained-release manner at a tissue site in an amount effective to ameliorate an injury or disease at a tissue site, wherein said biologic agent is the BMP-6 protein, as well as a pharmaceutical composition for treatment of an injured or diseased tissue and a kit comprising the said composition.

---

6. claims: 1-8,35,36 (all partially)

A composition suitable for implantation at a tissue site comprising a biologic agent wherein said agent is selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, wherein said biologic agent is released in a sustained-release manner at a tissue site in an amount effective to ameliorate an injury or disease at a tissue site, wherein said biologic agent is the GDF-5 protein, as well as a pharmaceutical composition for treatment of an injured or diseased tissue and a kit comprising the said composition.

---

7. claims: 1-8,35,36 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A composition suitable for implantation at a tissue site comprising a biologic agent wherein said agent is selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, wherein said biologic agent is released in a sustained-release manner at a tissue site in an amount effective to ameliorate an injury or disease at a tissue site, wherein said biologic agent is the GDF-6 protein, as well as a pharmaceutical composition for treatment of an injured or diseased tissue and a kit comprising the said composition.

---

8. claims: 1-8,35,36 (all partially)

A composition suitable for implantation at a tissue site comprising a biologic agent wherein said agent is selected from the group consisting of a crystal, a macromolecular gel or a particulate suspension, wherein said biologic agent is released in a sustained-release manner at a tissue site in an amount effective to ameliorate an injury or disease at a tissue site, wherein said biologic agent is the GDF-7 protein, as well as a pharmaceutical composition for treatment of an injured or diseased tissue and a kit comprising the said composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/025956

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03006049 A	23-01-2003	EP 1404357 A1	07-04-2004
		JP 2005511491 T	28-04-2005
		US 2004038903 A1	26-02-2004
		US 2005245455 A1	03-11-2005
		UY 27378 A1	28-02-2003
WO 20040609L0 A	22-07-2004	AU 2003300126 A1	29-07-2004
		BR 0317896 A	06-12-2005
		CA 2512001 A1	22-07-2004
		EP 1585771 A1	19-10-2005
		JP 2006523609 T	19-10-2006
		KR 20050094832 A	28-09-2005
		MX PA05007182 A	07-04-2006
		ZA 200505306 A	27-09-2006
WO 2004030650 A	15-04-2004	AU 2003287950 A1	23-04-2004
		BR 0314546 A	09-08-2005
		CA 2507524 A1	15-04-2004
		CN 1684703 A	19-10-2005
		EP 1565160 A2	24-08-2005
		IS 7750 A	17-03-2005
		JP 2006505538 T	16-02-2006
		KR 20050084829 A	29-08-2005
		MX PA05003318 A	12-09-2005
US 5595760 A	21-01-1997	ZA 9601904 A	07-02-1997
US 6503534 B1	07-01-2003	AT 241377 T	15-06-2003
		AU 756148 B2	02-01-2003
		AU 2938499 A	18-10-1999
		CA 2324901 A1	30-09-1999
		CZ 20003432 A3	14-02-2001
		DE 69908326 D1	03-07-2003
		DE 69908326 T2	25-03-2004
		DK 1066049 T3	29-09-2003
		EP 1066049 A1	10-01-2001
		ES 2200507 T3	01-03-2004
		FR 2776520 A1	01-10-1999
		WO 9948517 A1	30-09-1999
		HU 0101545 A2	28-11-2001
		JP 2002507578 T	12-03-2002
		NO 20004741 A	22-11-2000
		PL 343005 A1	30-07-2001
		PT 1066049 T	31-10-2003
		RU 2224538 C2	27-02-2004
US 2006257492 A1	16-11-2006	NONE	