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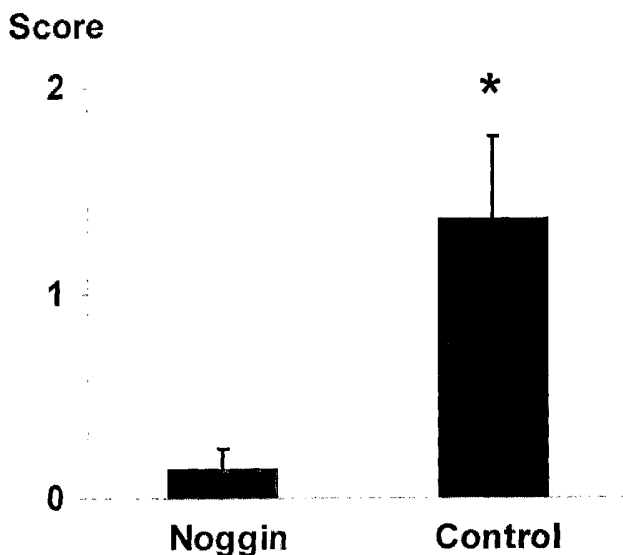
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GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv)) for US only

[Continued on next page]

(54) Title: BMP INHIBITORS FOR THE TREATMENT OF SPONDYLOARTHROPATHIES



Microscopic disease severity score in arthritis in aging male DBA/1 mice with or without Noggin treatment

(57) Abstract: The present invention is concerned with a method and composition for use in the medical art. It relates to the prevention and/or minimization of Spondyloarthropathies (SpA) and/or SpA enthesitis. SpA are an important group of chronic inflammatory disorders, affecting both the axial and peripheral skeleton. A particular method and composition optionally including a suitable dispensing device for such compositions can be used for ameliorating or preventing SpA. The invention applies to human and veterinary applications. To date, no single therapeutic approach has proven universally effective in preventing SpA or ameliorating SpA. Therefore, there is a need for compositions and methods which may be used safely and effectively to prevent SpA in a variety of different contexts.

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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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/BE 03/00018

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 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)
IPC 7 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)

WPI Data, PAJ, EPO-Internal, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 56879 A (WEBER FRANZ E ;UNIV ZUERICH (CH); SAILER HERMANN F (CH)) 28 September 2000 (2000-09-28) page 4, line 26-29 page 5, line 7-9 page 15, line 10-15; claims 15-17 page 13, line 16-21 page 14, line 8-13	1-5, 37, 38, 40-46, 48-53
Y	abstract	1-6, 8-15, 37, 38, 40-46, 48-53
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Further documents are listed in the continuation of box C.

Patent family members are listed in 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

6 November 2003

Date of mailing of the international search report

- 9. 12. 2003

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/BE 03/00018

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>WO 02 080952 A (CHAMPION BRIAN ROBERT ;DALLMAN MARGARET JANE (GB); LORANTIS LTD (G) 17 October 2002 (2002-10-17)</p> <p>page 5, line 20-30 page 87, line 10-12 -page 91, line 5-13; claim 17; table 3</p> <p>---</p>	<p>1-6, 8-10,37, 38, 40-46, 48-53</p>
Y	<p>NATSUME T. ET AL: "Interaction between soluble type I receptor for bone morphogenetic protein and bone morphogenetic protein-4" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 17, 25 April 1997 (1997-04-25), pages 11535-11540, XP002246635 abstract; figure 4 page 11539, column 2 -page 11540, column 1</p> <p>---</p>	<p>1-6, 8-11,37, 38, 40-46, 48-53</p>
Y	<p>WO 98 49296 A (ECONOMIDES ARIS N ;ROJAS EDUARDO A (US); STAHL NEIL E (US); REGENE) 5 November 1998 (1998-11-05)</p> <p>page 16; claims 11-13,15,16 page 14 -page 15</p> <p>---</p>	<p>1-6, 8-10, 12-15, 37,38, 40-46, 48-53</p>
Y	<p>WO 99 61044 A (UNIV ARKANSAS) 2 December 1999 (1999-12-02)</p> <p>claims 5,7,9,12</p> <p>---</p>	<p>1-6, 8-10, 12-15, 37,38, 40-46, 48-53</p>
Y	<p>US 5 932 216 A (CELESTE ANTHONY J ET AL) 3 August 1999 (1999-08-03)</p> <p>column 7, line 9-15; claims 1,2</p> <p>---</p>	<p>1-6, 8-10, 12-15, 37,38, 40-46, 48-53</p>
A	<p>WO 96 01845 A (MCPHERRON ALEXANDRA C ;LEE SE JIN (US); UNIV JOHNS HOPKINS MED (US) 25 January 1996 (1996-01-25)</p> <p>claims 12-15</p> <p>-----</p>	<p>1-6, 8-10, 12-15, 37,38, 40-46, 48-53</p>

INTERNATIONAL SEARCH REPORT

national application No.
PCT/BE 03/00018

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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:

Although claims 40-53 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: partially 1-6, 8-11, 37, 38, 40-46, 48-53
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:
see FURTHER INFORMATION sheet PCT/ISA/210
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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

see additional sheet

As a result of the prior review under R. 40.2(e) PCT,
no additional fees are to be refunded.

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.:

11-15 complete, 1-6, 8-10, 37, 38, 40-46, 48-53 partially
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.:

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: 11 complete; 1-6, 8-10, 37, 38, 40-46, 48-53 partially

Use of a soluble receptor of bone morphogenetic protein for the manufacture of a medicament for preventing, minimising and treating spondyloarthropathies or spondyloarthropathy enthesitis in a mammal.

2. Claims: 12-15 complete; 1-6, 8-10, 37, 38, 40-46, 48-53 partially

Use of an antibody of bone morphogenetic protein for the manufacture of a medicament for preventing, minimising and treating spondyloarthropathies or spondyloarthropathy enthesitis in a mammal.

3. Claims: 16-22 complete; 1-6, 8-10, 37, 38, 40-46, 48-53 partially

Use of a protein ligand of bone morphogenetic protein for the manufacture of a medicament for preventing, minimising and treating spondyloarthropathies or spondyloarthropathy enthesitis in a mammal.

4. Claims: 7 complete; 1-5, 37, 38, 40-46, 48-53 partially

Use of a ligand of the receptor of bone morphogenetic protein for the manufacture of a medicament for preventing, minimising and treating spondyloarthropathies or spondyloarthropathy enthesitis in a mammal.

5. Claims: 23-28 complete; 1-4, 37, 38, 40-46, 48-53 partially

Use of an antisense nucleic acid against mRNA of bone morphogenetic protein for the manufacture of a medicament for preventing, minimising and treating spondyloarthropathies or spondyloarthropathy enthesitis in a mammal.

6. Claims: 29-31 complete; 1-4, 37, 38, 40-46, 48-53 partially

Use of a ribozyme that cleaves mRNA of a protein member of

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

bone morphogenetic protein for the manufacture of a medicament for preventing, minimising and treating spondyloarthropathies or spondyloarthropathy enthesitis in a mammal.

7. Claims: 32-35 complete; 1-4, 37, 38, 40-46, 48-53 partially

Use of small interfering RNA (siRNA) or short hairpin RNA (shRNA) that correspond to the mRNA of a protein member of bone morphogenetic protein for the manufacture of a medicament for preventing, minimising and treating spondyloarthropathies or spondyloarthropathy enthesitis in a mammal.

8. Claims: 36 complete; 1-4, 37, 38, 40-46, 48-53 partially

Use of a small molecule as inhibitor of bone morphogenetic protein for the manufacture of a medicament for preventing, minimising and treating spondyloarthropathies or spondyloarthropathy enthesitis in a mammal.

9. Claim : 39

Use of agents selected from the group of bone morphogenetic protein (BMP), cartilage derived morphogenetic protein (CDMP), growth/differentiation factor or member of the transforming growth factor beta (TGF β) superfamily for the manufacture of a medicament for preventing or treating spondyloarthropathies or spondyloarthropathy enthesitis.

10. Claim : 47

Treatment or prevention of spondyloarthropathies or spondyloarthropathy enthesitis by modulating the Alk-2, Alk-3 and Alk-6 signalling pathway.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: partially 1-6, 8-11, 37, 38, 40-46, 48-53

Present claims 1-6, 8-11, 37, 38, 40-46, 48-53 relate to compounds defined by reference to desirable characteristics or properties, namely "inhibitor of bone morphogenetic protein" (claim 1), "antagonist of bone morphogenetic protein" (claim 5), "ligand of bone morphogenetic protein" (claim 6), "soluble receptor" (claim 11).

The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved "inhibitor of bone morphogenetic protein" (claim 1), "antagonist of bone morphogenetic protein" (claim 5), "ligand of bone morphogenetic protein" (claim 6). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search for the first invention has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the BMP receptors as mentioned in the description page 3 lines 18-27 in relation to their use for the treatment or prevention of spondyloarthropathies or spondyloarthropathy enthesitis, with due regard to the general idea underlying the present application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/BE 03/00018

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0056879	A	28-09-2000	WO 0056879 A1 28-09-2000 AU 3269399 A 09-10-2000
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