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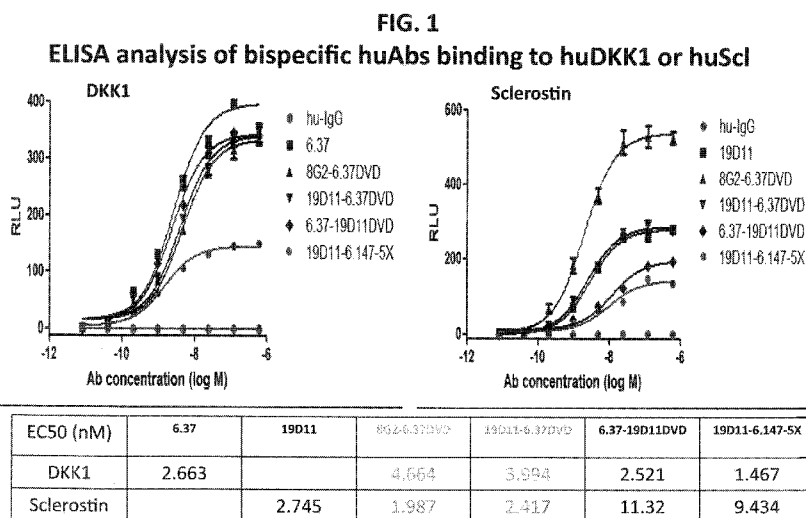
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Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

[Continued on next page]

(54) Title: SCLEROSTIN AND DKK-1 BISPECIFIC BINDING AGENTS



(57) Abstract: The invention relates to bispecific anti-sclerostin/anti-DKK1 binding agents and combinations of anti-sclerostin and anti-DKK1 binding agents, and related methods of treatment.



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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/027154

A. CLASSIFICATION OF SUBJECT MATTER

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ADD.

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)

C07K A61K A61P

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

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

EP0-Internal, BIOSIS, Sequence Search, EMBASE, 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	WO 2009/047356 A1 (NOVARTIS AG) 16 April 2009 (2009-04-16) cited in the application the whole document in particular abstract page 2, line 18 - page 3, line 29 page 5, line 22 - page 7, line 14 page 41, line 21 - page 43, line 23 page 51, line 9 - page 52, line 30 claims 1-48; figures 1-23; examples 1-13 ----- -/--	1-44, 47-63, 65-98



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 application or patent 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

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25/01/2013

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/149189 A2 (ABBOTT LAB [US]; GHAYUR TARIQ [US]; ISAKSON PETER C [US]; OLSON LISA M) 10 December 2009 (2009-12-10) cited in the application the whole document in particular abstract page 1, line 12 - page 31, line 31 claims 1-76; figure 1; examples	1-44, 47-63, 65-98
A	WO 2006/015373 A2 (AMGEN INC [US]; LI JI [US]; SHEN WENYAN [US]; LU HSIENG SEN [US]; RICH) 9 February 2006 (2006-02-09) the whole document in particular abstract page 2, line 5 - page 5, line 15 claims 1-46; figures 1-4; examples 1-9; sequences 84,91	1-44, 47-63, 65-98
A	WO 2006/119062 A2 (UCB SA [GB]; AMGEN INC [US]; LU HSIENG SEN [US]; PASZTY CHRISTOPHER [U]) 9 November 2006 (2006-11-09) the whole document in particular abstract page 2, line 27 - page 8, line 31 claims 1-66; figures 1-25; examples 1-11; sequences 185, 205, 209, 329, 332, 364, 376, 378, 380, 383	1-44, 47-63, 65-98
A	HOLT L J ET AL: "Domain antibodies: proteins for therapy", TRENDS IN BIOTECHNOLOGY, ELSEVIER PUBLICATIONS, CAMBRIDGE, GB, vol. 21, no. 11, 1 November 2003 (2003-11-01), pages 484-490, XP004467495, ISSN: 0167-7799, DOI: 10.1016/J.TIBTECH.2003.08.007 the whole document	1-44, 47-63, 65-98
A	DAVIES J ET AL: "Affinity improvement of single antibody VH domains: residues in all three hypervariable regions affect antigen binding", IMMUNOTECHNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, NL, vol. 2, no. 3, 1 September 1996 (1996-09-01), pages 169-179, XP004070292, ISSN: 1380-2933, DOI: 10.1016/S1380-2933(96)00045-0 the whole document	1-44, 47-63, 65-98
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INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/027154

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	TILMAN D RACHNER ET AL: "Osteoporosis: now and the future", THE LANCET, vol. 377, no. 9773, 1 April 2011 (2011-04-01), pages 1276-1287, XP55031012, ISSN: 0140-6736, DOI: 10.1016/S0140-6736(10)62349-5 the whole document	1-44, 47-63, 65-98
E	WO 2012/058393 A2 (AMGEN INC [US]; RICHARDS WILLIAM GLEASON [US]; LU HSIENG SEN [US]; KE) 3 May 2012 (2012-05-03) the whole document	1-44, 47-63, 65-98

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/027154

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 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 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 report covers only those claims for which fees were paid, specifically claims Nos.:
33, 34, 36, 37, 39, 41, 42, 57, 59(completely); 1-32, 35, 38, 40, 43, 44
47-56, 58, 60-63, 65-98(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 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 PCT/ISA/ 210

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

1. claims: 1-26, 33, 34, 36, 37, 39, 41, 42, 47-50, 57, 59, 65-98(all partially)

Subject-matter of claims 1-26, 33, 34, 36, 37, 39, 41, 42, 47-50, 57, 59 and 65-98 insofar as it relates to a binding molecule (e.g. dual variable domain-immunoglobulin or DVD-Ig) comprising a polypeptide chain, wherein said polypeptide chain comprises VH1-(X1)_n-VH2-C-(X2)_n and/or VL1-(X1)_n-VL2-C-(X2)_n, wherein VH1/VL1 is a first heavy/light chain variable domain obtained from a first parent antibody, VH2/VL2 is a second heavy/light chain variable domain obtained from a second parent antibody, C is a heavy/light chain constant domain, (X1)_n is a linker, wherein said (X1)_n is either present or absent and (X2)_n is an Fc region, wherein said (X2)_n is either present or absent, wherein the binding molecule specifically binds both sclerostin (also known as SOST) and DKK-1 (also known as dickkopf-1) and wherein said binding molecule contains the sclerostin binder Ab5/Ab5K/13C7Mu/13C7Rat/13C7Hu that comprises the sequences as set forth in SEQ ID Nos. 94/94/199/207/215 and 95/96/200/208/216 (these sclerostin binders share their 6 CDRs).

2. claims: 1-26, 35, 38, 40, 43-50, 58, 60-98(all partially)

Subject-matter of claims 1-26, 35, 38, 40, 43-50, 58 and 60-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the sclerostin binder Ab23 that comprises the sequences as set forth in SEQ ID Nos. 103 and 104.

3. claims: 1-25, 47-50, 65-98(all partially)

Subject-matter of claims 1-25, 47-50 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the sclerostin binder 13F3 that comprises the sequences as set forth in SEQ ID Nos. 111 and 112.

4. claims: 1-26, 31, 47-50, 55, 65-98(all partially)

Subject-matter of claims 1-26, 31, 47-50, 55 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the sclerostin binder 20C3.1 that comprises the sequences as set forth in SEQ ID Nos. 119 and 120.

- 5-7. claims: 1-25, 47-50, 65-98(all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Subject-matter of claims 1-25, 47-50 and 65-98 insofar as said binding molecules which specifically bind both sclerostin and DKK-1 contain, respectively, the sclerostin binder 38B12.1 that comprises the sequences as set forth in SEQ ID Nos. 127 and 128 (Invention 5), the sclerostin binder 46H1 that comprises the sequences as set forth in SEQ ID Nos. 135 and 136 (Invention 6) and the sclerostin binder 2B8.1 that comprises the sequences as set forth in SEQ ID Nos. 144 and 145 (Invention 7).

8. claims: 1-26, 29, 30, 47-50, 53, 54, 65-98(all partially)

Subject-matter of claims 1-26, 29, 30, 47-50, 53, 54 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the sclerostin binder 8G2.1 that comprises the sequences as set forth in SEQ ID Nos. 151 and 152.

9. claims: 1-28, 47-52, 65-98(all partially)

Subject-matter of claims 1-28, 47-52 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the sclerostin binder 19D11.1 that comprises the sequences as set forth in SEQ ID Nos. 159 and 160.

10. claims: 1-25, 47-50, 65-98(all partially)

Subject-matter of claims 1-25, 47-50 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the sclerostin binder 34H3.1 that comprises the sequences as set forth in SEQ ID Nos. 167 and 168.

11. claims: 1-26, 32, 47-50, 56, 65-98(all partially)

Subject-matter of claims 1-26, 32, 47-50, 56 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the sclerostin binder 27H6.1 that comprises the sequences as set forth in SEQ ID Nos. 175 and 176.

12. claims: 1-25, 47-50, 65-98(all partially)

Subject-matter of claims 1-25, 47-50 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the sclerostin binder 42F4HZ/42F4MU that comprises the sequences as set forth in SEQ ID Nos. 183/191 and 184/192 (these sclerostin binders

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

share their 6 CDRs).

13-30. claims: 1-25, 47-50, 65-98(all partially)

Subject-matter of claims 1-25, 47-50 and 65-98 insofar as said binding molecules which specifically bind both sclerostin and DKK-1 contain, respectively, the DKK-1 binder 11H10Hu that comprises the sequences as set forth in SEQ ID Nos. 223 and 224 (Invention 13), the DKK-1 binder 11H10Rat that comprises the sequences as set forth in SEQ ID Nos. 231 and 232 (Invention 14), the DKK-1 binder 2.4.1 that comprises the sequences as set forth in SEQ ID Nos. 239 and 240 (Invention 15), the DKK-1 binder 2.20.1 that comprises the sequences as set forth in SEQ ID Nos. 247 and 248 (Invention 16), the DKK-1 binder 2.37.1 that comprises the sequences as set forth in SEQ ID Nos. 255 and 256 (Invention 17), the DKK-1 binder 2.40.1 that comprises the sequences as set forth in SEQ ID Nos. 263 and 264 (Invention 18), the DKK-1 binder 2.41.1 that comprises the sequences as set forth in SEQ ID Nos. 271 and 272 (Invention 19), the DKK-1 binder 2.47.1 that comprises the sequences as set forth in SEQ ID Nos. 279 and 280 (Invention 20), the DKK-1 binder 5.17.1 that comprises the sequences as set forth in SEQ ID Nos. 287 and 288 (Invention 21), the DKK-1 binder 5.23.1 that comprises the sequences as set forth in SEQ ID Nos. 295 and 296 (Invention 22), the DKK-1 binder 5.25.1 that comprises the sequences as set forth in SEQ ID Nos. 303 and 304 (Invention 23), the DKK-1 binder 5.31.1 that comprises the sequences as set forth in SEQ ID Nos. 311 and 312 (Invention 24), the DKK-1 binder 5.35.1 that comprises the sequences as set forth in SEQ ID Nos. 319 and 320 (Invention 25), the DKK-1 binder 5.40.1 that comprises the sequences as set forth in SEQ ID Nos. 327 and 328 (Invention 26), the DKK-1 binder 5.65.1 that comprises the sequences as set forth in SEQ ID Nos. 335 and 336 (Invention 27), the DKK-1 binder 5.76.1 that comprises the sequences as set forth in SEQ ID Nos. 343 and 344 (Invention 28), the DKK-1 binder 5.77.1 that comprises the sequences as set forth in SEQ ID Nos. 351 and 352 (Invention 29) and the DKK-1 binder 5.78.1 that comprises the sequences as set forth in SEQ ID Nos. 359 and 360 (Invention 30).

31. claims: 1-26, 45-50, 64-98(all partially)

Subject-matter of claims 1-26, 45-50 and 64-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the DKK-1 binder 5.80.1 that comprises the sequences as set forth in SEQ ID Nos. 367 and 368.

32. claims: 1-25, 47-50, 65-98(all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Subject-matter of claims 1-25, 47-50 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the DKK-1 binder 5.85.1 that comprises the sequences as set forth in SEQ ID Nos. 375 and 376.

33. claims: 1-30, 35, 38, 43, 47-54, 58, 60, 62, 65-98(all partially)

Subject-matter of claims 1-30, 35, 38, 43, 47-54, 58, 60, 62 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the DKK-1 binder 6.37.5 that comprises the sequences as set forth in SEQ ID Nos. 383 and 384.

34-35. claims: 1-25, 47-50, 65-98(all partially)

Subject-matter of claims 1-25, 47-50 and 65-98 insofar as said binding molecules which specifically bind both sclerostin and DKK-1 contain, respectively, the DKK-1 binder 6.116.6 that comprises the sequences as set forth in SEQ ID Nos. 391 and 392 (Invention 34) and the DKK-1 binder 6.139.5 that comprises the sequences as set forth in SEQ ID Nos. 399 and 400 (Invention 35).

36. claims: 1-26, 31-34, 36, 37, 39-42, 44, 47-50, 55-57, 59, 61, 63, 65-98(all partially)

Subject-matter of claims 1-26, 31-34, 36, 37, 39-42, 44, 47-50, 55-57, 59, 61, 63 and 65-98 insofar as said binding molecule which specifically binds both sclerostin and DKK-1 contains the DKK-1 binder 6.147.4 that comprises the sequences as set forth in SEQ ID Nos. 407 and 408.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/027154

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