PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
56955-WO-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/IB2016/053790	24 June 2016 (24-06-2016)	26 June 2015 (26-06-2015)
Applicant		
NOVARTIS AG		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 8 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☒ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title,**
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. 1
      ☒ as suggested by the applicant
      ☐ as selected by this Authority, because the applicant failed to suggest a figure
      ☐ as selected by this Authority, because this figure better characterizes the invention
   b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053790

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2016/053790

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.:

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.:

1-9, 12, 13, 27, 30, 32, 35, 36, 46-52(completely); 15-26, 28, 29, 34 37-45(partially)

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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2016/053790

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/36
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

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)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, SCISEARCH, 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 2013/167669 A1 (BAYER PHARMA AG [DE]) 14 November 2013 (2013-11-14) figures 7,8,11-16, 20, 23; examples 1-9 page 30, line 21 - page 31, line 2 -----	1-9,12, 13, 34-36, 42-52
X	A. MATAFONOV ET AL: "Evidence for factor IX-independent roles for factor XIa in blood coagulation", JOURNAL OF THROMBOSIS AND HAEMOSTASIS, vol. 11, no. 12, 1 December 2013 (2013-12-01), pages 2118-2127, XP055293618, GB ISSN: 1538-7933, DOI: 10.1111/jth.12435 page 2119, left-hand column, paragraph -----	2-9,12, 13,35,36
	-/--	

[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 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	Date of mailing of the international search report
9 August 2016	14/10/2016

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, Fax: (+31-70) 340-3016	Domingues, Helena

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/080623 A2 (UNIV OREGON HEALTH & SCIENCE [US]; UNIV VANDERBILT [US]; GRUBER ANDRAS) 15 July 2010 (2010-07-15) examples 1-7	1-9,12, 13, 15-30, 32,34-52
A	WO 2009/067660 A2 (UNIV OREGON HEALTH & SCIENCE [US]; UNIV VANDERBILT [US]; GRUBER ANDRAS) 28 May 2009 (2009-05-28) examples 1-3	1-9,12, 13, 15-30, 32,34-52
X	Cristina Puy ET AL: "Activated factor XI increases the procoagulant activity of the extrinsic pathway by inactivating tissue factor pathway inhibitor", , 13 January 2015 (2015-01-13), XP055293619, DOI: 10.1182/blood- Retrieved from the Internet: URL:http://www.bloodjournal.org/content/bloodjournal/125/9/1488.full.pdf [retrieved on 2016-08-04] the whole document -& Reagents: "SUPLEMMENTAL METHODS AND DATA", , 13 January 2015 (2015-01-13), XP055293645, Retrieved from the Internet: URL:http://www.bloodjournal.org/content/bloodjournal/suppl/2015/01/13/blood-2014-10-604587.DC1/blood-2014-10-604587-1.pdf [retrieved on 2016-08-04] the whole document	2-9,12, 13,35,36
A	M. L. VAN MONTFOORT ET AL: "Two novel inhibitory anti-human factor XI antibodies prevent cessation of blood flow in a murine venous thrombosis model", THROMBOSIS AND HAEMOSTASIS, vol. 110, no. 5, 8 August 2013 (2013-08-08), pages 1065-1073, XP055293624, DE ISSN: 0340-6245, DOI: 10.1160/TH13-05-0429 the whole document	1-9,12, 13, 15-30, 32,34-52

-/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	A. YAMASHITA ET AL: "Factor XI contributes to thrombus propagation on injured neointima of the rabbit iliac artery", JOURNAL OF THROMBOSIS AND HAEMOSTASIS, vol. 4, no. 7, 1 July 2006 (2006-07-01), pages 1496-1501, XP055025684, ISSN: 1538-7933, DOI: 10.1111/j.1538-7836.2006.01973.x the whole document -----	1-9,12, 13, 15-30, 32,34-52
A	TAKAHASHI M ET AL: "Inhibition of factor XI reduces thrombus formation in rabbit jugular vein under endothelial denudation and/or blood stasis", THROMBOSIS RESEARCH, TARRYTOWN, NY, US, vol. 125, no. 5, 1 May 2010 (2010-05-01), pages 464-470, XP027027163, ISSN: 0049-3848 [retrieved on 2010-04-23] the whole document -----	1-9,12, 13, 15-30, 32,34-52

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2016/053790

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2013167669 A1	14-11-2013	AR 091024 A1	30-12-2014
		AU 2013258043 A1	13-11-2014
		CA 2872926 A1	14-11-2013
		CN 104684932 A	03-06-2015
		EP 2847228 A1	18-03-2015
		HK 1207091 A1	22-01-2016
		JP 2015517305 A	22-06-2015
		KR 20150008166 A	21-01-2015
		SG 11201406719U A	27-11-2014
		TW 201400504 A	01-01-2014
		US 2015099298 A1	09-04-2015
		WO 2013167669 A1	14-11-2013
WO 2010080623 A2	15-07-2010	AU 2009335643 A1	07-07-2011
		CA 2747519 A1	15-07-2010
		EP 2373691 A2	12-10-2011
		US 2011250207 A1	13-10-2011
		US 2013129745 A1	23-05-2013
		US 2015093395 A1	02-04-2015
		WO 2010080623 A2	15-07-2010
WO 2009067660 A2	28-05-2009	AU 2008326348 A1	28-05-2009
		CA 2705851 A1	28-05-2009
		DK 2222707 T3	11-04-2016
		EP 2222707 A2	01-09-2010
		EP 3002298 A1	06-04-2016
		ES 2566963 T3	18-04-2016
		JP 2011504371 A	10-02-2011
		US 2011020349 A1	27-01-2011
		US 2012276112 A1	01-11-2012
		US 2013171144 A1	04-07-2013
		US 2014322219 A1	30-10-2014
		US 2015322163 A1	12-11-2015
		WO 2009067660 A2	28-05-2009

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-9, 12, 13, 27, 30, 32, 35, 36, 46-52(completely); 15-26, 28, 29, 34, 37-45(partially)

   Concerns aspects related to an isolated anti-FXI and/or anti-FXIa antibody or fragment thereof that binds within the catalytic domain of FXI and/or FXIa, particularly to an antibody comprising a variable heavy chain of SEQ ID NO: 9 and a variable light chain of SEQ ID NO: 19 (mAb NOV1090).

   ---

2. claims: 31, 33(completely); 15-26, 28, 29, 34, 37-45(partially)

   Concerns aspects related to an isolated anti-FXI and/or anti-FXIa antibody or fragment thereof that binds within the catalytic domain of FXI and/or FXIa, particularly to an antibody comprising a variable heavy chain of SEQ ID NO: 29 and a variable light chain of SEQ ID NO: 39 (mAb NOV1401).

   ---

3. claims: 10, 11(completely); 34, 38-45(partially)

   Concerns aspects related to an isolated anti-FXI and/or anti-FXIa antibody or fragment thereof that binds within the catalytic domain of FXI and/or FXIa, wherein said antibody or fragment blocks FXI and/or FXIa binding to one or more of Factor IX, Factor Xlla, and thrombin.

   ---

4. claim: 14

   An isolated antibody or fragment thereof that binds to a human FXI and/or FXIa protein with a KD of less than or equal to 34 nM, as measured by BIACORETM assay, or less than or equal to 4 pM, as measured by solution equilibrium titration assay (SET).

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 December 2016 (29.12.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/207858 A1

(51) International Patent Classification:
C07K 16/36 (2006.01)

(21) International Application Number:
PCT/IB2016/053790

(22) International Filing Date:
24 June 2016 (24.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

62/184,955	26 June 2015 (26.06.2015)	US
62/341,568	25 May 2016 (25.05.2016)	US

(71) Applicant *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, 4056 Basel (CH).

(72) Inventors; and

(71) Applicants *(for US only)*: **EDER, Jorg** [CH/CH]; Novartis Pharma AG, Postfach, 4022 Basel (CH). **EWERT, Stefan** [CH/CH]; Novartis Pharma AG, Postfach, 4022 Basel (CH). **HASSIEPEN, Ulrich** [CH/CH]; Novartis Pharma AG, Postfach, 4022 Basel (CH). **KHDER, Yasser** [CH/CH]; Novartis Pharma AG, Postfach, 4022 Basel (CH). **MAYR, Lorenz M.** [DE/DE]; Fritz-Schülin-Weg 16, 79589 Binzen (DE). **MELKKO, Samu** [CH/CH]; c/o Molecular Partners AG, Wagistrasse 14, 8952 Schlieren (CH). **SCHIERING, Nikolaus** [CH/CH]; Novartis Pharma AG, Postfach, 4022 Basel (CH).

[Continued on next page]

(54) **Title**: FACTOR XI ANTIBODIES AND METHODS OF USE

(57) **Abstract**: The present invention relates to monoclonal antibodies and antigen binding fragments thereof that bind to human Factor XI and activated Factor XI ("Factor XIa"), and pharmaceutical compositions and methods of treatment comprising the same.

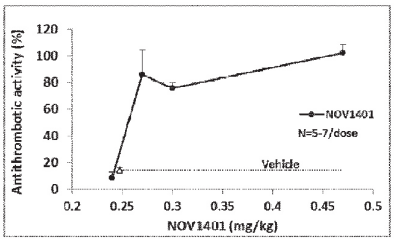

FIG 1A

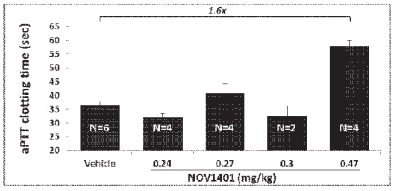

FIG 1B

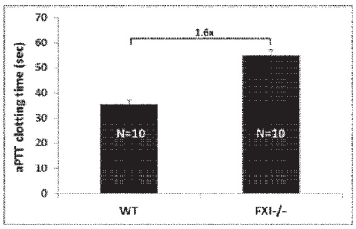

FIG 1C

WO 2016/207858 A1

(74) **Common Representative**: **NOVARTIS AG**; Lichtstrasse 35, 4056 Basel (CH).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, 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, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, 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, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2016/053790	24.06.2016	26.06.2015

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/36

Applicant
NOVARTIS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of this opinion
see form PCT/ISA/210

Authorized Officer
Domingues, Helena
Telephone No. +49 89 2399-0

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☒ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☒ forming part of the international application as filed:

      ☒ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 10, 11, 14, 31, 33(completely); 15-26, 28, 29, 34, 37-45(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 10, 11, 14, 31, 33(completely); 15-26, 28, 29, 34, 37-45(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:

   ☐ paid additional fees

   ☐ paid additional fees under protest and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☒ not paid additional fees

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-9, 12, 13, 27, 30, 32, 35, 36, 46-52(completely); 15-26, 28, 29, 34, 37-45(partially)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	27, 30, 32(completely); 15-26, 28, 29, 37-41(partially)
	No:	Claims	1-9, 12, 13, 35, 36, 46-52(completely); 34, 42-45(partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9, 12, 13, 15-30, 32, 34-52(all partially)
Industrial applicability (IA)	Yes:	Claims	1-9, 12, 13, 27, 30, 32, 35, 36, 46-52(completely); 15-26, 28, 29, 34, 37-45(partially)
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item IV

This opinion is based on the following documents cited in the international search report (ISR):

D1 WO 2013/167669 A1 (BAYER PHARMA AG [DE]) 14 November 2013 (2013-11-14)

D2 A. MATAFONOV ET AL: "Evidence for factor IX-independent roles for factor XIa in blood coagulation", JOURNAL OF THROMBOSIS AND HAEMOSTASIS, vol. 11, no. 12, 1 December 2013 (2013-12-01), pages 2118-2127, XP055293618, GB ISSN: 1538-7933, DOI: 10.1111/jth.12435

D3 WO 2010/080623 A2 (UNIV OREGON HEALTH & SCIENCE [US]; UNIV VANDERBILT [US]; GRUBER ANDRAS) 15 July 2010 (2010-07-15)

D4 WO 2009/067660 A2 (UNIV OREGON HEALTH & SCIENCE [US]; UNIV VANDERBILT [US]; GRUBER ANDRAS) 28 May 2009 (2009-05-28)

D5 Cristina Puy ET AL: "Activated factor XI increases the procoagulant activity of the extrinsic pathway by inactivating tissue factor pathway inhibitor", 13 January 2015 (2015-01-13), XP055293619, DOI: 10.1182/blood-Retrieved from the Internet: URL:http://www.bloodjournal.org/content/bloodjournal/125/9/1488.full.pdf [retrieved on 2016-08-04] ; -& Reagents: "SUPLEMMENTAL METHODS AND DATA", 13 January 2015 (2015-01-13), XP055293645, Retrieved from the Internet: URL:http://www.bloodjournal.org/content/bloodjournal/suppl/2015/01/13/blood-2014-10-604587.DC1/blood-2014-10-604587-1.pdf [retrieved on 2016-08-04]

D6 M. L. VAN MONTFOORT ET AL: "Two novel inhibitory anti-human factor XI antibodies prevent cessation of blood flow in a murine venous thrombosis model", THROMBOSIS AND HAEMOSTASIS, vol. 110, no. 5, 8 August 2013 (2013-08-08), pages 1065-1073, XP055293624,DE ISSN: 0340-6245, DOI: 10.1160/TH13-05-0429

D7 A. YAMASHITA ET AL: "Factor XI contributes to thrombus propagation on injured neointima of the rabbit iliac artery", JOURNAL OF THROMBOSIS AND HAEMOSTASIS, vol. 4, no. 7, 1 July 2006 (2006-07-01), pages 1496-1501, XP055025684, ISSN: 1538-7933, DOI: 10.1111/j.1538-7836.2006.01973.x

D8 TAKAHASHI M ET AL: "Inhibition of factor XI reduces thrombus formation in rabbit jugular vein under endothelial denudation and/or blood stasis", THROMBOSIS RESEARCH, TARRYTOWN, NY, US, vol. 125, no. 5, 1 May 2010 (2010-05-01), pages 464-470, XP027027163, ISSN: 0049-3848 [retrieved on 2010-04-23]

1. Lack of unity of invention, Rule 13 PCT

The application deals with the provision of anti-FXI/FXIa antibodies or fragments thereof that bind to the catalytic domain of these coagulation factors. The examples describe two antibodies which are covered by the present claims (e.g. claim 26), notably mAb NOV1090 and NOV1401. These antibodies have been isolated by screening a human antibody phage library (example 1).

However, anti-FXI/FXIa antibodies that bind to the catalytic domain are known from the prior art. For example, D1 describes antibody 076D-M007-H04 which has been isolated by screening a human phage library (example 1). The crystal structure of the Fab fragment in complex with the catalytic domain has been determined (example 7) and the epitope which is disclosed in example 8 comprises several of the amino acids that are part of the epitope defined in the present claims, including Pro410, Arg413 and Lys527. The antibody (i) inhibits the conversion of FXI to FXIa by FXIIa (Figs. 7 and 8), (ii) reduces platelet CD62P expression and platelet micro-aggregate formation (Figs. 11-13) (iii) inhibits $FeCl_3$-induced arterial occlusion, resulting in reduced thrombus weight, without increasing the ear bleeding time in rabbits (Figs. 14-16), (iv) increases the *in vitro* aPTT clotting time in plasma samples collected from baboons (Figs. 20 and 23) and (v) shows antithrombotic effect in these primates (Fig. 29).

D2 discloses a murine anti-FXI/FXIa antibody that was obtained by immunizing mice with the catalytic domain of FXIa (see pg. 2119, lhc, penultimate §).

Therefore, given the fact that antibodies that bind to the catalytic domain of FXI/FXIa are known from the prior art, the antibodies covered by independent claims 1, 2 and 10 and claims dependent thereupon are not linked by a common inventive concept. Moreover, independent claim 14 does not contain the requirement that the antibodies bind to the catalytic domain; they just need to have a Kd as defined in the claim. Therefore, no common inventive concept links the antibodies defined in this claim with the other claimed anti-FXI/FXIa antibodies. In view of this and in the absence of a special technical feature within the meaning of Rule 13.2 PCT, the application lacks unity.

The following inventions can be identified:

Invention 1: claims 1 -9, 12, 13, 15-26 (all partially), 27, 28 (partially), 29 (partially), 30, 32, 34 (partially), 35, 36, 37-45 (all partially), 46-52.

Concerns aspects related to an isolated anti-FXI and/or anti-FXIa antibody or fragment thereof that binds within the catalytic domain of FXI and/or FXIa, particularly to an antibody comprising a variable heavy chain of SEQ ID NO: 9 and a variable light chain of SEQ ID NO: 19 (mAb NOV1090).

Invention 2: claims 15-26 (all partially), 28, 29 (both partially), 31, 33, 34 (partially), 37-45 (all partially)

Concerns aspects related to an isolated anti-FXI and/or anti-FXIa antibody or fragment thereof that binds within the catalytic domain of FXI and/or FXIa, particularly to an antibody comprising a variable heavy chain of SEQ ID NO: 29 and a variable light chain of SEQ ID NO: 39 (mAb NOV1401).

Invention 3: claim 10, 11, 34 (partially) and 38-45 (all partially)

Concerns aspects related to an isolated anti-FXI and/or anti-FXIa antibody or fragment thereof that binds within the catalytic domain of FXI and/or FXIa, wherein said antibody or fragment blocks FXI and/or FXIa binding to one or more of Factor IX, Factor XIIa, and thrombin.

Invention 4: claim 14

An isolated antibody or fragment thereof that binds to a human FXI and/or FXIa protein with a KD of less than or equal to 34 nM, as measured by BIACORE™ assay, or less than or equal to 4 pM, as measured by solution equilibrium titration assay (SET).

The search report and this opinion cover the invention first mentioned in the claims i.e. invention 1.

Re Item V

2. Novelty (Art. 33(2) PCT) and inventive step (Art. 33(3) PCT) of invention 1

2.1 D1 and D2 have been described above. D1 takes away the novelty of claims 1-9 and 13. In addition, since it cannot be excluded beyond doubt that the antibody described in D1 (mAb 076D-M007-H04) blocks binding to platelet receptors, claim 12 also lacks novelty. The same applies to claims 34-36 and 42-45.

Concerning claims 46-52, it is noted that these claims refer to conformational changes that are induced in FXI and/or FXIa upon binding of the antibody. Since, as explained above, mAb 076D-M007-H04 binds to an epitope on the catalytic site of these coagulation factors that largely overlaps with the epitope bound by the antibodies described in the application, it will necessarily bring about conformational changes according to claims 46-52. Hence, these claims lack novelty.

D2 is considered novelty destroying for claim 1. In addition, given the fact that the murine antibody described therein binds to the catalytic site of FXI and/or FXIa it cannot be excluded beyond doubt that it binds to one or more of the amino acids defined in claims 2-9 and/or that it blocks the binding to platelet receptors. Hence, D2 also destroys the novelty of claims 2-9, 12, 13, 35 and 36.

D5 (pg. 1489, lhc, under methods; pg. 1491, rhc) refers to two anti-FXI and/or FXIa antibodies that bind to the catalytic domain (see Fig. S2 of the supplemental data). The antibodies, termed 10C9 and 12F5, are a mentioned with reference to D2. Hence, D5 is also considered novelty destroying for claims 2-9, 12, 13, 35 and 36.

2.2 Turning now to claims 15-26, 27, 28, 29, 30, 32 and 37-41 these claims appears to be novel but they lack inventive step for the reasons discussed below.

D1 is considered to represent the closest prior art on file. The antibodies defined in claims 15-26, 27, 28, 29, 30, 32 and 37, notably mAb NOV1090, differ from the mAb 076D-M007-H04 described in D1 by their structure (sequence). However, no surprising technical effects with regard to the technical effects shown in D1 for antibody mAb 076D-M007-H04 can be identified. Of note D1 (pg. 30, lines 21 to pg. 31 line 2) explicitly states that the antibodies described therein are suitable for the treatment of thromboembolic diseases, for example deep vein thrombosis (DVT) and thrombotic/thromboembolic stroke.

Therefore, the technical problem is the provision of alternative human antibodies that can bind to the catalytic domain of FXI and/or FXIa, useful in the treatment of thromboembolic disorders such as DVT or ischemic stroke.

The application provides no evidence that an antibody comprising only a particular CDR defined in table 1 and/or only a VH or VL can bind to the catalytic domain of FXI and/or FXIa. It also does not show that and antibody comprising and VH and/or VL sequence less than 100% identical to the sequences of mAb NOV1090 (SEQ ID NO: 9 and 19) can display this property. Hence, the technical problem is not solved over the entire scope of the claims 15-25.

Regarding claims 26, 27-30, 32 and 37-41, it is noted that, at the priority date of the application, the skilled person would have been able to provide alternative human antibodies able to bind to the catalytic domain of FXI and/or FXIa using routine methods, for example by screening one of the various human antibody libraries available in the art. They would also be able to assess the antithrombotic potential of the antibodies using standard *in vitro* assays and animal models well known in the art, for example those described in D1.

In view of the above, the antibodies covered by the claims under discussion, notably mAb NOV1090, are regarded as an arbitrary choice among all the possible antibodies directed to the catalytic domain of FXI and/or FXIa at which the skilled person would arrive without the need of inventive skill. Consequently claims 26, 27-30, 32 and 37-41 cannot be deemed inventive.

3. Attention is drawn to the fact that claims 38-41 are directed to a method of treatment of the human body and may not be accepted in the regional phase in Europe.

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<223> /note="Descripción de la Secuencia Artificial:
polinucleotio sintético"

<400> 12
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agctgcgcgg cgtccggatt caccttttct actgctgcta tgtcttgggt gcgccaggcc 120

ccgggcaaag gtctcgagtg ggtttccggt atctctggtt ctggttcttc tacctactat 180

gcggatagcg tgaaaggccg ctttaccatc agccgcgata attcgaaaaa caccctgtat 240

ctgcaaatga acagcctgcg tgcggaagat acggccgtgt attattgcgc gcgtgaactg 300

tcttacctgt actctggtta ctacttcgat tactggggcc aaggcaccct ggtgactgtt 360

agctcagcct ccaccaaggg tccatcggtc ttcccctgg caccctcctc caagagcacc 420

tctgggggca cagcggccct gggctgcctg gtcaaggact acttccccga accggtgacg 480

gtgtcgtgga actcaggcgc cctgaccagc ggcgtgcaca ccttcccggc tgtcctacag 540

tcctcaggac tctactccct cagcagcgtg gtgaccgtgc cctccagcag cttgggcacc 600

cagacctaca tctgcaacgt gaatcacaag cccagcaaca ccaaggtgga caagagagtt 660

gagcccaaat cttgtgacaa aactcacaca tgcccaccgt gcccagcacc tgaagcagcg 720

gggggaccgt cagtcttcct cttcccccca aaacccaagg acaccctcat gatctcccgg 780

accctgagg tcacatgcgt ggtggtggac gtgagccacg aagaccctga ggtcaagttc 840

aactggtacg tggacggcgt ggaggtgcat aatgccaaga caaagccgcg ggaggagcag 900

tacaacagca cgtaccgggt ggtcagcgtc ctcaccgtcc tgcaccagga ctggctgaat 960

ggcaaggagt acaagtgcaa ggtctccaac aaagccctcc cagccccat cgagaaaacc 1020

atctccaaag ccaaagggca gccccgagaa ccacaggtgt acaccctgcc cccatcccgg 1080

gaggagatga ccaagaacca ggtcagcctg acctgcctgg tcaaaggctt ctatcccagc 1140

gacatcgccg tggagtggga gagcaatggg cagccggaga acaactacaa gaccacgcct 1200

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tacacgcaga agagcctctc cctgtctccg ggtaaa 1356

<210> 13
<211> 13
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 13
Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Asp Val Ser
1 5 10

<210> 14
<211> 7
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 14
Lys Asn Tyr Asn Arg Pro Ser
1 5

<210> 15
<211> 11
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 15

Ser Ala Trp Asp Gln Arg Gln Phe Asp Val Val
1 5 10

<210> 16
<211> 9
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 16
Ser Ser Ser Asn Ile Gly Ser Asn Asp
1 5

<210> 17
<211> 3
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 17
Lys Asn Tyr
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<210> 18
<211> 8
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 18
Trp Asp Gln Arg Gln Phe Asp Val
1 5

<210> 19
<211> 110
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polipéptido sintético"

<400> 19
Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

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Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Asp Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Lys Asn Tyr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ala Trp Asp Gln Arg Gln
                85                  90                  95

Phe Asp Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
            100                 105                 110
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<210> 20
<211> 330
<212> ADN
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polinucleotido sintético"

<400> 20
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agctgtagcg gcagcagcag caacattggt tctaacgacg tgtcttggta ccagcagctg 120

ccgggcacgg cgccgaaact gctgatctac aaaaactaca accgcccgag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagacg aagcggatta ttactgctct gcttgggacc agcgtcagtt cgacgttgtg 300

tttggcggcg gcacgaagtt aaccgtccta 330

<210> 21
<211> 216
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polipéptido sintético"

<400> 21
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Asp Ile Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15
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Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
            20                  25                  30

Asp Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
        35                  40                  45

Ile Tyr Lys Asn Tyr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ala Trp Asp Gln Arg Gln
                85                  90                  95

Phe Asp Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
            100                 105                 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
        115                 120                 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
    130                 135                 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145                 150                 155                 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
                165                 170                 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
            180                 185                 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
        195                 200                 205

Thr Val Ala Pro Thr Glu Cys Ser
    210                 215
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<210> 22
<211> 648
<212> ADN
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polinucleotido sintético"

<400> 22
gatatcgtgc tgacccagcc gccgagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagcagcag caacattggt tctaacgacg tgtcttggta ccagcagctg 120

ccgggcacgg cgccgaaact gctgatctac aaaaactaca accgcccgag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagacg aagcggatta ttactgctct gcttgggacc agcgtcagtt cgacgttgtg 300

tttggcggcg gcacgaagtt aaccgtccta ggtcagccca aggctgcccc ctcggtcact 360

ctgttcccgc cctcctctga ggagcttcaa gccaacaagg ccacactggt gtgtctcata 420

agtgacttct acccgggagc cgtgacagtg gcctggaagg cagatagcag ccccgtcaag 480

gcgggagtgg agaccaccac accctccaaa caaagcaaca acaagtacgc ggccagcagc 540

tatctgagcc tgacgcctga gcagtggaag tcccacagaa gctacagctg ccaggtcacg 600

catgaaggga gcaccgtgga gaagacagtg gcccctacag aatgttca 648

<210> 23
<211> 5
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 23
Thr Ala Ala Met Ser
1 5

<210> 24
<211> 17
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 24
Gly Ile Ser Gly Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> 25
<211> 13
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 25
Glu Leu Ser Tyr Leu Tyr Ser Gly Tyr Tyr Phe Asp Tyr
1 5 10

<210> 26
<211> 7
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 26
Gly Phe Thr Phe Ser Thr Ala
1 5

<210> 27
<211> 6
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 27
Ser Gly Ser Gly Ser Ser
1 5

<210> 28
<211> 13
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 28
Glu Leu Ser Tyr Leu Tyr Ser Gly Tyr Tyr Phe Asp Tyr
1 5 10

<210> 29
<211> 122
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:

polipéptido sintético"

<400> 29
Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Ala
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Ser Gly Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Leu Ser Tyr Leu Tyr Ser Gly Tyr Tyr Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> 30
<211> 366
<212> ADN
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polinucleotido sintetico"

<400> 30
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agctgcgctg ctagtggctt cacctttagc accgccgcta tgagctgggt tcgacaggcc 120

ccagggaaag gcctcgagtg ggtctcaggg attagcggta gcggctctag cacctactac 180

gccgatagcg tgaagggccg gttcactatc tctagggata actctaagaa caccctgtac 240

ctgcagatga atagcctgag agccgaggac accgccgtct actactgcgc tagagagctg 300

agctacctgt atagcggcta ctacttcgac tactggggtc aaggcaccct ggtcaccgtg 360

tctagc 366

<210> 31
<211> 452

<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polipéptido sintético"

<400> 31

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Gln Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Ala
            20                  25                  30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Ile Ser Gly Ser Gly Ser Ser Thr Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Glu Leu Ser Tyr Leu Tyr Ser Gly Tyr Tyr Phe Asp Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser
    210                 215                 220
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Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu
225                 230                 235                 240

Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu
                245                 250                 255

Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Ala Val Ser
            260                 265                 270

His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu
        275                 280                 285

Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr
    290                 295                 300

Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn
305                 310                 315                 320

Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Ala Ala Pro
                325                 330                 335

Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln
            340                 345                 350

Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val
        355                 360                 365

Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val
    370                 375                 380

Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro
385                 390                 395                 400

Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr
                405                 410                 415

Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val
            420                 425                 430

Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu
        435                 440                 445

Ser Pro Gly Lys
    450
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<210> 32

<211> 1356
<212> ADN
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polinucleotido sintético"

<400> 32
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agctgcgctg ctagtggctt cacctttagc accgccgcta tgagctgggt tcgacaggcc 120

ccagggaaag gcctcgagtg ggtctcaggg attagcggta gcggctctag cacctactac 180

gccgatagcg tgaagggccg gttcactatc tctagggata actctaagaa caccctgtac 240

ctgcagatga atagcctgag agccgaggac accgccgtct actactgcgc tagagagctg 300

agctacctgt atagcggcta ctacttcgac tactggggtc aaggcaccct ggtcaccgtg 360

tctagcgcta gcactaaggg cccctccgtg ttccctctgg ccccttccag caagtctacc 420

tccggcggca cagctgctct gggctgcctg gtcaaggact acttccctga gcctgtgaca 480

gtgtcctgga actctggcgc cctgacctct ggcgtgcaca ccttccctgc cgtgctgcag 540

tcctccggcc tgtactccct gtcctccgtg gtcacagtgc cttcaagcag cctgggcacc 600

cagacctata tctgcaacgt gaaccacaag ccttccaaca ccaaggtgga caagcgggtg 660

gagcctaagt cctgcgacaa gacccacacc tgtcctccct gccctgctcc tgaactgctg 720

ggcggccctt ctgtgttcct gttccctcca aagcccaagg acaccctgat gatctcccgg 780

acccctgaag tgacctgcgt ggtggtggcc gtgtcccacg aggatcctga agtgaagttc 840

aattggtacg tggacggcgt ggaggtgcac aacgccaaga ccaagcctcg ggaggaacag 900

tacaactcca cctaccgggt ggtgtccgtg ctgaccgtgc tgcaccagga ctggctgaac 960

ggcaaagagt acaagtgcaa agtctccaac aaggccctgg ccgcccctat cgaaaagaca 1020

atctccaagg ccaagggcca gcctagggaa ccccaggtgt acaccctgcc acccagccgg 1080

gaggaaatga ccaagaacca ggtgtccctg acctgtctgg tcaagggctt ctacccttcc 1140

gatatcgccg tggagtggga gtctaacggc cagcctgaga acaactacaa gaccacccct 1200

cctgtgctgg actccgacgg ctccttcttc ctgtactcca aactgaccgt ggacaagtcc 1260

cggtggcagc agggcaacgt gttctcctgc tccgtgatgc acgaggccct gcacaaccac 1320

tacacccaga agtccctgtc cctgtctccc ggcaag 1356

<210> 33
<211> 13
<212> PRT
<213> Secuencia Artificial

<220>

<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 33
Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn Asp Val Ser
1 5 10

<210> 34
<211> 7
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 34
Lys Asn Tyr Asn Arg Pro Ser
1 5

<210> 35
<211> 11
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 35
Ser Ala Trp Asp Gln Arg Gln Phe Asp Val Val
1 5 10

<210> 36
<211> 9
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 36
Ser Ser Ser Asn Ile Gly Ser Asn Asp
1 5

<210> 37
<211> 3
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 37
Lys Asn Tyr
1

<210> 38
<211> 8
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 38
Trp Asp Gln Arg Gln Phe Asp Val
1 5

<210> 39
<211> 110
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polipéptido sintético"

<400> 39
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Asp Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Lys Asn Tyr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ala Trp Asp Gln Arg Gln
85 90 95

Phe Asp Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu
100 105 110

<210> 40
<211> 330
<212> ADN

<213> Secuencia Artificial

<220>
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<223> /note="Descripción de la Secuencia Artificial:
polinucleotido sintetico"

<400> 40
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agctgtagcg gctctagctc taatatcggc tctaacgacg tcagctggta tcagcagctg 120

cccggcaccg cccctaagct gctgatctat aagaactata ataggcctag cggcgtgccc 180

gataggttta gcggatctaa atcagggact tctgctagtc tggctattag cggcctgcag 240

tcagaggacg aggccgacta ctactgtagc gcctgggatc agcgtcagtt cgacgtggtg 300

ttcggcggag gcactaagct gaccgtgctg 330

<210> 41
<211> 216
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polipéptido sintético"

<400> 41
Gln Ser Val Leu Thr Gln Pro Pro Ser Ala Ser Gly Thr Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Asn
20 25 30

Asp Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Leu Leu
35 40 45

Ile Tyr Lys Asn Tyr Asn Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Ser Gly Leu Gln
65 70 75 80

Ser Glu Asp Glu Ala Asp Tyr Tyr Cys Ser Ala Trp Asp Gln Arg Gln
85 90 95

Phe Asp Val Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
115 120 125

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
130 135 140

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
145 150 155 160

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
165 170 175

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
180 185 190

Arg Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
195 200 205

Thr Val Ala Pro Thr Glu Cys Ser
210 215

<210> 42
<211> 648
<212> ADN
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
polinucleotide sintético"

<400> 42
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agctgtagcg gctctagctc taatatcggc tctaacgacg tcagctggta tcagcagctg 120

cccggcaccg cccctaagct gctgatctat aagaactata ataggcctag cggcgtgccc 180

gataggttta gcggatctaa atcagggact tctgctagtc tggctattag cggcctgcag 240

tcagaggacg aggccgacta ctactgtagc gcctgggatc agcgtcagtt cgacgtggtg 300

ttcggcggag gcactaagct gaccgtgctg ggtcaaccta aggctgcccc cagcgtgacc 360

ctgttccccc ccagcagcga ggagctgcag gccaacaagg ccaccctggt gtgcctgatc 420

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gccggcgtgg agaccaccac ccccagcaag cagagcaaca acaagtacgc cgccagcagc 540

tacctgagcc tgacccccga gcagtggaag agccacaggt cctacagctg ccaggtgacc 600

cacgagggca gcaccgtgga aaagaccgtg gccccaaccg agtgcagc 648

<210> 43
<211> 8
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 43
Gly Phe Thr Phe Ser Thr Ala Ala
1 5

<210> 44
<211> 8
<212> PRT
<213> Secuencia Artificial

<220>
<221> source
<223> /note="Descripción de la Secuencia Artificial:
péptido sintético"

<400> 44
Ile Ser Gly Ser Gly Ser Ser Thr
1 5

<210> 45
<211> 15
<212> PRT
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péptido sintético"

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1 5 10

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<220>
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1 5

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1 5

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1 5

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1               5                  10                  15

Thr Leu His Thr Thr Ser Pro Thr Gln Arg His Leu Cys Gly Gly Ser
            20                  25                  30

Ile Ile Gly Asn Gln Trp Ile Leu Thr Ala Ala His Cys Phe Tyr Gly
        35                  40                  45

Val Glu Ser Pro Lys Ile Leu Arg Val Tyr Ser Gly Ile Leu Asn Gln
    50                  55                  60

Ser Glu Ile Lys Glu Asp Thr Ser Phe Phe Gly Val Gln Glu Ile Ile
65                  70                  75                  80

Ile His Asp Gln Tyr Lys Met Ala Glu Ser Gly Tyr Asp Ile Ala Leu
                85                  90                  95

Leu Lys Leu Glu Thr Thr Val Asn Tyr Thr Asp Ser Gln Arg Pro Ile
            100                 105                 110

Cys Leu Pro Ser Lys Gly Asp Arg Asn Val Ile Tyr Thr Asp Cys Trp
        115                 120                 125

Val Thr Gly Trp Gly Tyr Arg Lys Leu Arg Asp Lys Ile Gln Asn Thr
    130                 135                 140

Leu Gln Lys Ala Lys Ile Pro Leu Val Thr Asn Glu Glu Cys Gln Lys
145                 150                 155                 160

Arg Tyr Arg Gly His Lys Ile Thr His Lys Met Ile Cys Ala Gly Tyr
                165                 170                 175

Arg Glu Gly Gly Lys Asp Ala Cys Lys Gly Asp Ser Gly Gly Pro Leu
            180                 185                 190

Ser Cys Lys His Asn Glu Val Trp His Leu Val Gly Ile Thr Ser Trp
        195                 200                 205

Gly Glu Gly Cys Ala Gln Arg Glu Arg Pro Gly Val Tyr Thr Asn Val
    210                 215                 220

Val Glu Tyr Val Asp Trp Ile Leu Glu Lys Thr Gln Ala Val
225                 230                 235
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