



(43) International Publication Date
11 February 2016 (11.02.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/022753 A1

(51) International Patent Classification:
C12N 15/113 (2010.01) *C07H 21/00* (2006.01)
A61K 31/712 (2006.01)

(21) International Application Number:
PCT/US2015/043926

(22) International Filing Date:
6 August 2015 (06.08.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/034,739 7 August 2014 (07.08.2014) US
62/062,749 10 October 2014 (10.10.2014) US
62/143,434 6 April 2015 (06.04.2015) US

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(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).

Published:

- with international search report (Art. 21(3))
- with sequence listing part of description (Rule 5.2(a))

(54) Title: TARGETING MICRORNAS FOR METABOLIC DISORDERS

(57) Abstract: Described herein are compounds comprising modified oligonucleotides that are complementary to miR-103 and/or miR-107 and methods of treating diseases and disorders using the compounds.



WO 2016/022753 A1

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

SCARR, Rebecca B.
500 W. Silver Spring Drive
Suite K-200
Glendale, Wisconsin 53217
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 09 January 2017 (09.01.2017)	
Applicant's or agent's file reference 1138-19-PCT	IMPORTANT NOTIFICATION
International application No. PCT/US2015/043926	International filing date (day/month/year) 06 August 2015 (06.08.2015)

1. The following indications appeared on record concerning: ☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative		
Name and Address REGULUS THERAPEUTICS INC. 3545 John Hopkins Ct., Suite 210 San Diego, California 92121-1121 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: ☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence		
Name and Address REGULUS THERAPEUTICS INC. 10614 Science Center Drive San Diego, California 92121 United States of America	State of Nationality US	State of Residence US
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to: ☒ the receiving Office ☐ the International Preliminary Examining Authority ☒ the International Searching Authority ☒ the designated Offices concerned ☐ the Authority(ies) specified for supplementary search ☐ the elected Offices concerned ☐ other:		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Beard Nathalie e-mail pt06.pct@wipo.int Telephone No. +41 22 338 74 06
Facsimile No. +41 22 338 89 70	

ADVANCE E-MAIL

From the INTERNATIONAL BUREAU

PCTNOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
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To:

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500 W. Silver Spring Drive
Suite K-200
Glendale, Wisconsin 53217
ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year) 09 January 2017 (09.01.2017)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 1138-19-PCT	
International application No. PCT/US2015/043926	International filing date (day/month/year) 06 August 2015 (06.08.2015)

1. The following indications appeared on record concerning: ☐ the applicant ☒ the inventor ☐ the agent ☐ the common representative		
Name and Address MACKENNA, Diedre 3545 John Hopkins Ct., Suite 210 San Diego, California 92121 United States of America	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	
2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning: ☐ the person ☒ the name ☐ the address ☐ the nationality ☐ the residence		
Name and Address MACKENNA, Deidre 3545 John Hopkins Ct., Suite 210 San Diego, California 92121 United States of America	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	
3. Further observations, if necessary:		
4. A copy of this notification has been sent to: ☒ the receiving Office ☐ the International Preliminary Examining Authority ☒ the International Searching Authority ☒ the designated Offices concerned ☐ the Authority(ies) specified for supplementary search ☐ the elected Offices concerned ☐ other:		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 89 70	Authorized officer Beard Nathalie e-mail pt06.pct@wipo.int Telephone No. +41 22 338 74 06
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PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

Scarr, Rebecca B.
MCNEILL BAUR PLLC
500 W. Silver Spring Drive, Suite K-200
Glendale, Wisconsin 53217
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing (day/month/year) 9 November 2015 (09-11-2015)	
Applicant's or agent's file reference 1138-19-PCT	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2015/043926	International filing date (day/month/year) 6 August 2015 (06-08-2015)
Applicant REGULUS THERAPEUTICS INC.	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

How? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see PCT Applicant's Guide, International Phase, paragraphs 9.004 - 9.011.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to any protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with any applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

The applicant may **submit comments on an informal basis on the written opinion of the International Searching Authority** to the International Bureau. These comments will be made available to the public after international publication. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established.

Shortly after the expiration of **18 months from the priority date, the international application will be published** by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau before the completion of the technical preparations for international publication (Rules 90*bis*.1 and 90*bis*.3).

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for **entry into the national phase** before those designated Offices. In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months. For details about the applicable time limits, Office by Office, see www.wipo.int/pct/en/texts/time_limits.html and the *PCT Applicant's Guide*, National Chapters.

Within **19 months from the priority date, the applicant may request that a supplementary international search be carried out** by a different International Searching Authority that offers this service (Rule 45*bis*.1). The procedure for requesting supplementary international search is described in the *PCT Applicant's Guide*, International Phase, paragraphs 8.006-8.032.

Name and mailing address of the International Searching Authority



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

Authorized officer

VAN ROOIJEN, Babara
Tel: +31 (0)70 340-4567

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1138-19-PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/US2015/043926	International filing date (<i>day/month/year</i>) 6 August 2015 (06-08-2015)	(Earliest) Priority Date (<i>day/month/year</i>) 7 August 2014 (07-08-2014)
Applicant REGULUS THERAPEUTICS INC.		

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 5 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. _____
- ☐ 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/US2015/043926

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. ☒ 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 13ter.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 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.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/US2015/043926

A. CLASSIFICATION OF SUBJECT MATTER

INV. C12N15/113 A61K31/712 C07H21/00
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)

C12N A61K C07H

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, EMBASE, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2010/133970 A1 (ETH ZUERICH [CH]; STOFFELL MARKUS [CH]; TRAJKOVSKI MIRKO [CH]) 25 November 2010 (2010-11-25) cited in the application the whole document	1-49
Y	WO 2013/040429 A1 (RANA THERAPEUTICS INC [US]; UHLMANN EUGEN [DE]; WEBER MARKUS [DE]; SUB) 21 March 2013 (2013-03-21) paragraph [0009] - paragraph [0012] paragraph [0020] - paragraph [0022] paragraph [00299] - paragraph [00306]	1-49
A	WO 2014/076195 A1 (SANTARIS PHARMA AS [DK]) 22 May 2014 (2014-05-22) page 22, line 29 - page 24 page 69, line 15 - page 71 page 77, line 10 - page 98 ----- -/-	1-49

☒ 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

26 October 2015

Date of mailing of the international search report

09/11/2015

Name and mailing address of the ISA/

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

Authorized officer

Andres, Serge

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2015/043926

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MIRKO TRAJKOVSKI ET AL: "MicroRNAs 103 and 107 regulate insulin sensitivity", NATURE, vol. 474, no. 7353, 30 June 2011 (2011-06-30), pages 649-653, XP055222703, United Kingdom ISSN: 0028-0836, DOI: 10.1038/nature10112 cited in the application the whole document -----	1-49
A	WO 2011/117353 A1 (MIRRX THERAPEUTICS AS [DK]; MOELLER THORLEIF [SE]; UDESEN CHRISTINA [S]) 29 September 2011 (2011-09-29) the whole document -----	1-49
A	WO 2013/033230 A1 (ISIS PHARMACEUTICALS INC [US]; PRAKASH THAZHA P [US]; SWAYZE ERIC E [U]) 7 March 2013 (2013-03-07) cited in the application the whole document -----	1-49
A	ZHONGHAN LI ET AL: "Therapeutic targeting of microRNAs: current status and future challenges", NATURE REVIEWS. DRUG DISCOVERY, vol. 13, no. 8, 11 July 2014 (2014-07-11), pages 622-638, XP055222651, GB ISSN: 1474-1776, DOI: 10.1038/nrd4359 the whole document -----	1-49
A	YIPING MAO ET AL: "MicroRNAs as pharmacological targets in diabetes", PHARMACOLOGICAL RESEARCH, vol. 75, 1 September 2013 (2013-09-01), pages 37-47, XP055091416, ISSN: 1043-6618, DOI: 10.1016/j.phrs.2013.06.005 the whole document -----	1-49

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2015/043926

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2010133970	A1	25-11-2010	AU 2010250838 A1	08-12-2011
			CA 2763016 A1	25-11-2010
			CN 102459598 A	16-05-2012
			EP 2432880 A1	28-03-2012
			JP 2012527444 A	08-11-2012
			US 2012122959 A1	17-05-2012
			US 2014113953 A1	24-04-2014
			US 2015038550 A1	05-02-2015
			WO 2010133970 A1	25-11-2010

WO 2013040429	A1	21-03-2013	AU 2012308320 A1	01-05-2014
			CA 2848753 A1	21-03-2013
			EP 2756080 A1	23-07-2014
			HK 1200484 A1	07-08-2015
			JP 2014527819 A	23-10-2014
			US 2015299695 A1	22-10-2015
			WO 2013040429 A1	21-03-2013

WO 2014076195	A1	22-05-2014	AU 2013346767 A1	28-05-2015
			CA 2889044 A1	22-05-2014
			CA 2889596 A1	22-05-2014
			CN 104837996 A	12-08-2015
			CN 104884618 A	02-09-2015
			EP 2920304 A1	23-09-2015
			EP 2920307 A1	23-09-2015
			IL 238448 A	30-06-2015
			KR 20150082643 A	15-07-2015
			KR 20150083920 A	20-07-2015
			US 2015275212 A1	01-10-2015
			US 2015291958 A1	15-10-2015
			WO 2014076195 A1	22-05-2014
			WO 2014076196 A1	22-05-2014

WO 2011117353	A1	29-09-2011	EP 2550360 A1	30-01-2013
			US 2013079505 A1	28-03-2013
			WO 2011117353 A1	29-09-2011

WO 2013033230	A1	07-03-2013	EP 2751270 A1	09-07-2014
			US 2015018540 A1	15-01-2015
			WO 2013033230 A1	07-03-2013

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.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.
PCT/US2015/043926

International filing date (day/month/year)
06.08.2015

Priority date (day/month/year)
07.08.2014

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/113 A61K31/712 C07H21/00

Applicant
REGULUS THERAPEUTICS INC.

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 43bis.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 notified the International Bureau under Rule 66.1bis(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
P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Andres, Serge

Telephone No. +31 70 340-0



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2015/043926

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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2015/043926

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	<u>1-49</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-49</u>
Industrial applicability (IA)	Yes: Claims	<u>1-49</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Prior art

Reference is made to the following documents:

- D1 WO 2010/133970 A1 (25 November 2010)
cited in the application
 - D2 WO 2013/040429 A1 (21 March 2013)
 - D3 WO 2014/076195 A1 (22 May 2014)
 - D4 NATURE, vol. 474, (30 June 2011), pages 649-653 [XP055222703]
cited in the application
 - D5 WO 2011/117353 A1 (29 September 2011)
 - D6 WO 2013/033230 A1 (7 March 2013)
cited in the application
 - D7 NATURE REVIEWS. DRUG DISCOVERY, vol. 13, (11 July 2014), pages
622-638 [XP055222651]
 - D8 PHARMACOLOGICAL RESEARCH, vol. 75, (September 2013), pages
37-47 [XP055091416]
-

Item V.

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- 1 Concerning claims 33-42, it is noted that the patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

2 NOVELTY (Art. 33(2) PCT), INVENTIVE STEP (Art. 33(3) PCT)

2.1 None of the available prior art documents discloses a bivalent construct comprising two antagomir sequences targeted to miR-103/107. Hence, the claimed subject-matter is considered as novel in the sense of Art. 33(2) PCT

2.2 The document D1 discloses the inhibition of miR-103 and/or miR-107 with antagomirs in the treatment of metabolic disorders. The antagomirs are preferably chemically modified and conjugated to compounds enhancing their delivery (see the examples and claims).

2.3 The subject-matter of the independent claims therefore differs from this known teaching in that the miR-103/107 antagomirs are in the form of divalent molecules, as defined in claim 1. The problem to be solved by the present invention may therefore be regarded as the provision of alternative structures of miR-103/107 antagomirs for use in the treatment of metabolic disorders.

2.4 The solution proposed in the independent claims of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons. Indeed, these forms of divalent antagomirs have already been employed for the same purpose in document D2 (see also document D5). It would be obvious to the person skilled in the art, namely when the same result is to be achieved, to apply these features with corresponding effect to the antagomirs disclosed in D1, thereby arriving at the claimed subject-matter.

2.5 The dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (see the documents D3-D8).

3 INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

The subject-matter of claims 1-49 is considered as being industrially applicable in the sense of Art. 33(4) PCT.

Item VIII.

Certain observations on the international application

- 4 Present claim 11 recites a technical feature already present in claim 1, and seems therefore redundant.

- 5 Present claim 31 refers to a non-existing claim 163.

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