

(43) International Publication Date
5 November 2009 (05.11.2009)

PCT

(10) International Publication Number
WO 2009/134487 A3(51) International Patent Classification:
C07H 21/04 (2006.01)(21) International Application Number:
PCT/US2009/032743(22) International Filing Date:
30 January 2009 (30.01.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/024,968	31 January 2008 (31.01.2008)	US
61/039,083	24 March 2008 (24.03.2008)	US
61/076,548	27 June 2008 (27.06.2008)	US
61/188,765	11 August 2008 (11.08.2008)	US

(71) Applicant (for all designated States except US): **ALNYLAM PHARMACEUTICALS, INC.** [US/US]; 300 Third Street, Third Floor, Cambridge, MA 02142 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **FITZGERALD, Kevin** [US/US]; C/o Alnylam Pharmaceuticals, Inc., 300 Third Street, Third Floor, Cambridge, MA 02142 (US). **DE FOUGEROLLES, Antonin** [CA/US]; C/o Alnylam Pharmaceuticals, Inc., 300 Third Street, Third Floor, Cambridge, MA 02142 (US). **AKINC, Akin** [US/US]; C/o Alnylam Pharmaceuticals, Inc., 300 Third Street, Third

Floor, Cambridge, MA 02142 (US). **KOTELIANSKI, Victor, E.** [US/US]; C/o Alnylam Pharmaceuticals, Inc., 300 Third Street, Third Floor, Cambridge, MA 02142 (US).

(74) Agents: **SHUSTER, Michael, J.** et al.; Fenwick & West LLP, Silicon Valley Center, 801 California Street, Mountain View, CA 94041 (US).

(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, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR),

[Continued on next page]

(54) Title: OPTIMIZED METHODS FOR DELIVERY OF DSRNA TARGETING THE PCSK9 GENE

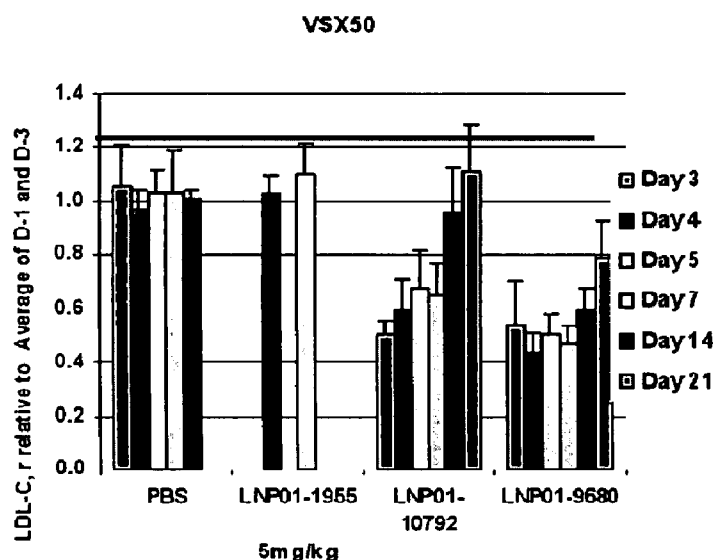


FIG. 12A

(57) Abstract: This invention relates to optimized methods for treating diseases caused by PCSK9 gene expression.



OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
MR, NE, SN, TD, TG).

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

Published:

(88) Date of publication of the international search report:

4 February 2010

- 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))

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/32743

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07H 21/04 (2009.01)

USPC - 536/24.5

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)

USPC - 536/24.5

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

USPC - 435/455; 514/44 (text search, see terms below)

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

PubWEST(PGPB,USPT,EPAB,JPAB); Google/Scholar; PubMed (text search, see terms below)

Search Terms: PCSK9, FH3, HCHOLA3, NARC-1, NARC1, RNA interference, LDL, cholesterol, modified nucleotide, dsRNA, double stranded RNA, inhibiting, expression.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/134161 A2 (TAN et al.) 22 November 2007 (22.11. 2007); Table 1, SEQ ID NOS:1229 and 1230 (page 80), (page 4, ln 15-22), (page 6, ln 22), (page 27, ln 2-10).	1-3, 43-45
A	FITZGERALD et al., Abstract 583: RNAi therapeutics for the lowering of cholesterol. Circulation, 2007, vol 116, pp II_105.	1-3, 43-45

☐ Further documents are listed in the continuation of Box C.


* 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 November 2009 (26.11.2009)

Date of mailing of the international search report

10 DEC 2009

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 09/32743

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.: 4-42 and 46-50
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:

Group I: Claims 1-3 and 43-45, drawn to compositions and methods comprising a dsRNA targeted to a PCSK9 gene, wherein the dsRNA is AD-9680 represented by sense strand SEQ ID NO: 1531 and antisense strand SEQ ID NO: 1532.

Group II: Claims 1-3 and 43-45, drawn to compositions and methods comprising a dsRNA targeted to a PCSK9 gene, wherein the dsRNA is selected from the group consisting of AD-3267, AD-3268, AD-3269, AD-3270, AD-3271, AD-3272, AD-3273, AD-3274, or AD-3275, with sense and antisense strands described in Table 6.

Group III: Claims 1-3 and 43-45, drawn to compositions and methods comprising a dsRNA targeted to a PCSK9 gene, wherein the dsRNA is selected from the group consisting of AD-14676, AD-3276, AD-3277, AD-3278, AD-3279, AD-3280, AD-3281, AD-3282, AD-3283, AD-3284, with sense and antisense strands described in Table 6.

---Please see continuation on extra 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 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.:
1-3 and 43-45, limited to AD-9680 and SEQ ID NOs: 1531 and 1532

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/US 09/32743

Continuation of Box No. III Observations where unity of invention is lacking

Group IV: Claims 1-3 and 43-45, drawn to compositions and methods comprising a dsRNA targeted to a PCSK9 gene, wherein the dsRNA is AD-3511 represented by sense strand SEQ ID NO: 1521 and antisense strand SEQ ID NO: 1522.

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The only technical feature shared by the inventions listed as Groups I-IV are double stranded RNA (dsRNA) inhibitors of PCSK9 gene expression. This shared technical feature does not provide a contribution over the prior art, as evidenced by McSwiggen et al. (US 2007/0173473 A1, published 26 July 2007), which teaches use of double stranded nucleic acid molecules, including dsRNA, to modulate PCSK9 gene expression. In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature. Otherwise, the inventions listed as Groups I - IV do not share any significant structural similarities that would represent a shared special technical feature. Without a shared special technical feature, the inventions lack unity with one another.