

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:

see form PCT/ISA/220

## 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/US2018/041400

International filing date (day/month/year)  
10.07.2018

Priority date (day/month/year)  
10.07.2017

International Patent Classification (IPC) or both national classification and IPC  
INV. A61P7/04 A61K31/713

Applicant  
GENZYME CORPORATION

### 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  
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

Habedanck, Robert

Telephone No. +49 89 2399-0



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**Box No. I Basis of the opinion**

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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 43bis.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 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).
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:

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

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1. Statement

|                               |             |                                |
|-------------------------------|-------------|--------------------------------|
| Novelty (N)                   | Yes: Claims | <u>35-39, 41-43, 45-47, 56</u> |
|                               | No: Claims  | <u>1-34, 40, 44, 48-55</u>     |
| Inventive step (IS)           | Yes: Claims |                                |
|                               | No: Claims  | <u>1-56</u>                    |
| Industrial applicability (IA) | Yes: Claims | <u>1-56</u>                    |
|                               | No: Claims  |                                |

2. Citations and explanations

see separate sheet

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**Box No. VIII Certain observations on the international application**

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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

**Re Item V**

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

Reference is made to the following documents:

- D1        US 2017/159053 A1 (AKINC AKIN [US] ET AL) 8 June 2017  
(2017-06-08)
- D2        Pasi ET AL: "Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: Updated Results from a Phase 1 and Phase 1/2 Extension Study in Patients with Inhibitors | Blood Journal",  
Blood, 1 January 2016 (2016-01-01), page 1397, XP055508028,  
Retrieved from the Internet:  
URL:<http://www.bloodjournal.org/content/128/22/1397?sso-checked=true>  
[retrieved on 2018-09-19]
- D3        Ragni ET AL: "Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: Updated Results from a Phase 1 and Phase 1/2 Extension Study in Patients without Inhibitors | Blood Journal",  
Blood, 1 January 2016 (2016-01-01), page 2572, XP055508061,  
Retrieved from the Internet:  
URL:<http://www.bloodjournal.org/content/128/22/2572?sso-checked=true>  
[retrieved on 2018-09-19]
- D4        Ragni ET AL: "Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: Results from Phase 1 and Phase 2 Extension Studies in Patients without Inhibitors",  
, 4 December 2016 (2016-12-04), XP055508067,  
Retrieved from the Internet:  
URL:[http://www.alnylam.com/web/assets/ASH-2016\\_Fitusiran\\_NONINHIBITORS\\_04Dec2016\\_CAPELLA2.pdf](http://www.alnylam.com/web/assets/ASH-2016_Fitusiran_NONINHIBITORS_04Dec2016_CAPELLA2.pdf)  
[retrieved on 2018-09-19]

- D5        Anonymous: "Drugs & Biologics Search Results: Fitusiran",  
Integrity, 22 July 2012 (2012-07-22), XP055508082,  
Retrieved from the Internet:  
URL: [https://integrity.thomson-pharma.com/integrity/xmlxsl/  
pk\\_qcksrch.show\\_records?  
sessionID=1&history=&query=fitusiran&abbreviation=PRO&language=en](https://integrity.thomson-pharma.com/integrity/xmlxsl/pk_qcksrch.show_records?sessionID=1&history=&query=fitusiran&abbreviation=PRO&language=en)  
[retrieved on 2018-09-19]

**Novelty - Article 33(3) PCT**

- 1        The siRNA compound used in the examples of the present application is known as AT3SC-001 or AD-57213 (see page 42, lines 8-11 of the description), or fitusiran (see the abstract of D5).
- 2        D1 discloses the same compound AD-57213 (claims 1-42, paragraph 54) for use in the treatment of bleeding disorders including hemophilia A or B (claims 13, 17-18) at a fixed dose of 50mg or 80mg (claims 5, 6, 8) administered subcutaneously (claim 19). In particular, example 2 (paragraphs 766-785) relates to the results of part D of a phase I clinical trial in hemophilia patients were administered 50mg or 80mg of AD-57213 monthly three times (paragraph 768), wherein the patients had Hemophilia A or B with antibody inhibitors and were also administered their standard bypassing agent such as FVII or APCC (paragraph 781). Antithrombin levels were lowered and thrombin generation was increased similarly to patients without inhibitors (paragraph 781-782, fig. 14-16). Bleed events were also reduced (paragraphs 783-784). Results from a Phase II open label extension study are also disclosed (paragraphs 786-792), whereby patients without inhibitors were administered subcutaneously 50mg or 80mg AD-57213 (paragraph 786-787) resulting in a reduction in bleeding rates (paragraph 790). A patient undergoing a surgical procedure received 50mg AD-57213 and FVIII during the operation, wherein the FVIII was used at a 5-fold less amount (paragraph 791).
- 3        D1 discloses the subject-matter of claims 1-34, 40, 44, 48-55.
- 4        Claims 1-34, 40, 44, 48-55 are therefore not novel.

**Inventive step - Article 33(3) PCT**

- 5 The application does not fulfil the requirements of Article 33(3) PCT because claims 1-56 lack an inventive step.
- 6 D1 is the closest prior art to the subject-matter of claims 1-56.
- 7 Claims that are not novel are also not inventive as no technical difference can be identified. Claims 1-34, 40, 44 and 48-55 therefore also lack an inventive step.
- 8 Dependent claims 35-39, 41-43 and 45-47 not further discussed do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT with respect to inventive step because the features claimed therein are not associated with any technical effect or represent one of several straightforward possibilities which the skilled person would select, depending on the circumstances, without exercising inventive skill.

#### **Re Item VIII**

##### **Certain observations on the international application**

- 9 Although claims 1-4 and 50, 51 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.
- 10 The terms 'about' and substantially used throughout the claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.