

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/US2017/020529	International filing date (day/month/year) 02.03.2017	Priority date (day/month/year) 02.03.2016
International Patent Classification (IPC) or both national classification and IPC INV. A61K47/68		
Applicant EISAI 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 Schleifenbaum, A Telephone No. +31 70 340-0
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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 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:

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

1. Statement

Novelty (N)	Yes: Claims	<u>2-123, 125-141, 143-150, 152-156, 158-162, 164-168, 170-174, 177-183</u>
	No: Claims	<u>1, 124, 142, 151, 157, 163, 169, 175, 176</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-183</u>
Industrial applicability (IA)	Yes: Claims	<u>1-183</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

1 Reference is made to the following documents:

- D1 WO 2014/089335 A2 (AMGEN INC [US]) 12 June 2014 (2014-06-12)
- D2 ZHENG W ET AL: "Macrocyclic ketone analogues of halichondrin B" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL vol. 14, no. 22, 15 November 2004 (2004-11-15), pages 5551-5554, XP004598592 ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2004.08.069
- D3 SRIDHAR NARAYAN ET AL: "Novel second generation analogs of eribulin. Part II: Orally available and active against resistant tumors in vivo" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL vol. 21, no. 6, 20 January 2011 (2011-01-20), pages 1634-1638, XP028169543 ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.01.097
- D4 NIKOLAOS DIAMANTIS ET AL: "Antibody-drug conjugates-an emerging class of cancer treatment" BRITISH JOURNAL OF CANCER vol. 114, no. 4, 16 February 2016 (2016-02-16), pages 362-367, XP55371017GB ISSN: 0007-0920, DOI: 10.1038/bjc.2015.435

2 Claims 124-150 and 157-162 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.

2.1 However, an opinion is given based on the effect of the compounds/compositions.

2.2 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.

Article 33(2) PCT - Novelty

3 The subject-matter of claims 1, 124, 142, 151, 157, 163, and 169 is not novel in the sense of Article 33(2) PCT:

- 3.1 D1 discloses internalizing (D1, Fig 9) BCMA antigen binding antibodies and conjugates thereof; D1 suggests eribulin as suitable drug (D1, claim 53: E7389). D1 discloses pharmaceutical compositions and the use in the treatment of in particular cancers (D1, claims 197-204).
- 3.2 The subject-matter of claims 2-123, 125-141, 143-150, 152-156, 158-162, 164-168, 170-175 and 177-183 is novel since the prior art does not disclose the antibody-drug ratio, linkers or the claimed antibodies.
- 4 The subject-matter of claims 175 and 176 is not novel in the sense of Article 33(2) PCT:
- 4.1 D2 (compounds 38 - 40) and D3 (compounds 17, 29) disclose eribulin compounds with a cleavable linker (amide or ester) and a further moiety (substituted phenyl, benzoyl, ethyl or propyl) at the C-35 amine.

Article 33(3) PCT - Inventive Step

- 5 The subject-matter of claims 1-183 in so far as novel is not regarded to comply with Article 33(3) PCT:
- 5.1 The claims define different parts of the conjugate (like the linker, the antibody or the disease to be treated) which provide for a distinguishing feature.
- 5.2 For none of these features taken alone an unexpected effect was demonstrated. The problem to be solved is therefore the provision of different embodiments of the conjugates suggested in D1. The solutions provided cannot be regarded to be inventive since the different technical features are well known designs of antibody drug conjugates, eg like those well known ADC summarized in D4, and would be chosen by the skilled person according to circumstances (eg according to the target cell or cleavage conditions the appropriate antibody or peptide cleavage sequence would be selected).

Article 33(4) PCT - Industrial Applicability

- 6 The application meets the requirements of Article 33(4) PCT since its subject-matter can be used in industry.