

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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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/US2019/034701

International filing date (day/month/year)
30.05.2019

Priority date (day/month/year)
30.05.2018

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K47/68

Applicant
ABBVIE STEMCENTRX LLC

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:



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this opinion

see form
PCT/ISA/210

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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>1-20</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	<u>4, 8-20</u>
	No: Claims	<u>1-3, 5-7</u>
Industrial applicability (IA)	Yes: Claims	<u>1-8, 10-14, 16, 17, 20</u>
	No: Claims	<u>9, 15, 18, 19</u>

2. Citations and explanations

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 WO 2015/031698 A1 (STEM CENTRX inc. [US] 05.03.2015)
- D2 WO 2013/126810 A1 (STEM CENTRX inc. [US]) 29.08.2013)
- D3 WO 2016/172273 A1 (STEM CENTRX inc. [US]) 27.10.2016)
- D4 WO 2017/112803 A1 (ABBVIE STEM CENTRX LLC [US] 29.06.2017)
- D5 WO 03/092623 A2 (WYETH corp. [US]; Kunz, A. [US] et al. 13.11.2003)
- D6 WO 2005/089808 A2 (WYETH corp. [US]; Kunz, A. [US] et al. 29.08.2005)
- D7 Jain, N. et al. (2015) Current ADC linker chemistry. Pharm Res, vol. 32, no. 11, 11 March 2015 (2015-03-11), 3526 - 3540.

D1 - D3 all disclosed isolated antibodies that specifically bind to human SEZ6 as well as anti-SEZ6 drug conjugates (ADCs) (cf. D1: Example 7, Fig. 1, 3, 9, SEQ ID NOs: 513, 514; D2: Examples 12 - 19, claims 1 - 17; D3: Examples 3, 4, 9 - 12, Fig. 1, 7, Table 8).

D4 and D5 disclosed ADCs for the treatment of cancer, in case of D4 'lung cancer' (both small cell and non-small cell) (cf. D4: p. 63, l. 23 - p. 64, l. 7, claims 8 - 15, 17 - 24, 28, 29, 35, 36; D5: examples 3 - 6, tables 2 - 6, Fig. 17, claim 71, 72, 107, 108, 161, 162, 175, 180, 193, 194).

D6 disclosed monomeric calicheamicin derivative/anti-Lewis Y antibody conjugates, compositions comprising the conjugates and medical uses thereof (D6: abstract, Examples 2 - 7, Fig. 2 - 6, 9, 13, 15, 17, 22, 23, Tables 2 - 7, 9 - 16).

D7 disclosed the then state of the art with regard to ADC linker chemistry, amongst other based on linker-calicheamicin motives (cf. D7: abstract, p. 3528 - Fig. 1 - 10, 14 Table I-IV)

Novelty (Art. 33(1)(2) PCT)

A sequence search revealed that the amino acid sequences of SEQ ID NO: 3 had not been known prior to the application's disclosure. The combination of SEQ ID NO: 3 and SEQ ID NO: 4 had not been known either.

Therefore, the subject-matter of claim 1 is novel in the sense of Art. 33(1)(2) PCT as well as the one of any claim(s) referring back to it and/or being dependent thereof. The same applies to the subject-matter of any claims defined by said combination.

Taken together the subject-matter of claim 1 - 19 is novel in the sense of Art. 33(1)(2) PCT.

Calicheamicin is frequently used as anti-cancer drug, employed in from as a antibody-drug-conjugate (cf. D1 - D7). However, the calicheamicin drug linker as defined by formula II of claim 20, i.e. comprising a long PEG linker had not been known prior to the application's disclosure. Therefore, the subject-matter of claim 20 appears as novel in the sense of Art. 33(1)(2) PCT.

Inventive step (Art. 33(2)(3) PCT)

The antibody ss1 disclosed in D1 is considered as closest prior art to the subject-matter of claim 1 and comprises a heavy chain sequence of SEQ ID NO: 515 that is 99.8% identical to the heavy chain of SEQ ID NO: 3 and a light chain of SEQ ID NO: 513 that is 100% identical to the light chain of SEQ ID NO: 4.

The subject-matter of claim 1 differs from said known anti-SEZ6 antibody with regard to its primary sequence, i.e. comprising 'a conservative mutation. . . in the heavy chain variable region to improve molecular stability and facilitate antibody production. . . , a substitution of serine to asparagine at Kabat position 60 (S60N) was incorporated into the heavy chain to eliminate the glycosylation site. . .' (cf. application: Example 2, p. 35, [0114], Table 3B).

The application disclosed that 'the S60N mutation and removal of the glycosylation site in the heavy chain variable region does not materially alter the binding properties of hSEZ6-1.ss1 antibodies when compared with the parent antibody lacking the mutation' (cf. application: Example 5, p. 47, [0128], Fig. 2).

Therefore, the application cannot be considered as disclosing any technical effect associated with the above differences over the state of the art.

The technical problem is thus considered as the provision of a further anti-SEZ6 antibody displaying the same or similar binding properties as the one known from D1.

In view of the lack of any technical effect, the claimed solution is considered as arbitrary and no inventive step in the sense of Art. 33(1)(3) PCT can be acknowledged to such an arbitrary solution.

The same reasoning applies to the subject-matter of claims 5 - 7 referring back to claim 1.

Dependent claim 2 and 3 do not appear to contain any additional features which, in combination with the features of any claim to which it refers, meet the requirements of the PCT in respect of inventive step as D1 already suggested N-Ac calicheamicin as 'exemplary payload compatible with the teachings herein. . .' (cf. D1: p. 51, l. 24). Therefore, the skilled person would have considered the claimed modification as straightforward alternative of the anti-SEZ6 antibody known from D1.

By means of an alternative line of argumentation, in light of the the technical evidence disclosed in the application, the technical problem as identified above cannot be be considered as having been credibly solved over the whole breadth of claim 1, i.e. for any calicheamicin payload known in the art or still to be discovered. Therefore, no inventive step can be acknowledged to the subject-matter of dependent claim 2 and 3.

ADC2 or ADC4 of D4 appear as closest prior art to the subject-matter of claims 4 and 8.

The subject-matter of claims 4 abd 8 differs from these known ADCs with regard to antibody's primary sequence and specificity, and moreover with regard to linker used to join the drug and the antibody.

The technical effects associated with said difference are '... ADC1... [being] particularly active in SCLC', the linker being flexible (like all long PEG linkers), and being a redox-sensitive linker (cf. S-S) (cf. application: Example 10, p. 51, [0145] - p. 52, [0149], Fig. 5).

The technical problem to be solved therefore can be considered as the provision of a better ADC suitable for the treatment of 'lung cancer (both small cell and non-small cell)' (cf. D4: claim 24).

The solution provided by the application appears as non-obvious as it appears unlikely that the skilled person starting from D4 would have arrived at the solution proposed by claim 8 in a straightforward manner, i.e. without having to use any inventive activity. None of D1 - D3 provided an incentive to modify the primary sequence of the heavy chain and neither to link the so obtained antibody to a conjugate of formula II. Therefore, an inventive step in the sense of Art. 33(1)(3) PCT can be acknowledged to the subject-matter of claim 8 and the same applies to the subject-matter of any claim(s) referring back to it and/or dependent thereof.

D6 or D7 can be considered as closest prior art to the subject-matter of claim 20 and disclosed calicheamicin linked to a labile or to a protease-cleavable linker (cf. D6: D7: passages referred above).

The subject-matter of claim 20 differs from these known calicheamicin variants with regard to the type of linker.

The technical effect associated with said difference over the state of the art is considered as the provision of a structural modifications resulting in a structure that is at the same time redox-sensitive and flexible.

The technical problem to be solved therefore is considered as the provision of a further calicheamicin-linker molecule.

The solution proposed by the application is PEG8-SS.

While PEG8 linkers may have been suggested in D4 (cf. D4: ADC2 or ADC4), neither D4 nor any other documents of the prior art suggested to combine calicheamicin to a PEG8 linker with a disulphide to render it redox-sensitive. An inventive step in the sense of Art. 33(1)(3) PCT therefore can be acknowledged to the subject-matter of claim 20.

Industrial applicability (Art. 33(1)(4) PCT)

Claim 9, 15, 18 and 19 relates to subject-matter and features which is/are considered by this authority to be covered by the provisions of Rule 39.1(iii) and/or (vi) / 67.1(iii) and/or (vi) PCT.

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.