

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference 20896D009W01		Date of mailing (day/month/year) 19 March 2024
FOR FURTHER ACTION See paragraph 2 below		
International application No. PCT/CN2024/071901	International filing date (day/month/year) 11 January 2024	Priority date (day/month/year) 11 January 2023
International Patent Classification (IPC) or both national classification and IPC A61K47/65(2017.01)i; A61K47/60(2017.01)i; A61K47/54(2017.01)i; A61K47/56(2017.01)i; A61K47/61(2017.01)i; C07H5/06(2006.01)i; A61P35/00(2006.01)i		
Applicant PROFOUNDBIO US CO. et al.		

1. This opinion contains indications relating to the following items:

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|-------------------------------------|--------------|---|
| ☒ | 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 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/ CHINA NATIONAL INTELLECTUAL PROPERTY ADMINISTRATION 6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China	Date of completion of this opinion 28 February 2024	Authorized officer WAN,Guang Telephone No. (+86) 010-53961859
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**WRITTEN OPINION OF THE
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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 43*bis*.1(b)).
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.
 - b. ☐ furnished subsequent to the international filing date for the purposes of international search (Rule 13*ter*.1(a)),
☐ accompanied by a statement to the effect that the sequence listing does not go beyond the disclosure in the international application as filed.
4. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, this opinion has been established to the extent that a meaningful opinion could be formed without a WIPO Standard ST.26 compliant sequence listing.
5. Additional comments:

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Box No. II

Priority

1. ☐ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

The application claims the right of priority of earlier application PCT/CN2023/071778.

PCT/CN2023/071778 does not disclose the Linker unit having structure (iii-a) or structure (iii-b), or the Drug-Linker compound of Formula (A). PCT/CN2023/071778 does not disclose some of the specific compounds in claims 70-71, 77, 101, 110 either. Therefore, the priority claim is considered to be valid for claims 1, 3 and claims (all partially) 2, 4-116, and invalid for claims 117-136 and claims (all partially) 2, 4-116.

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 116

because:

☒ the said international application, or the said claims Nos. 116 relate to the following subject matter which does not require an international search (*specify*):

Claim 116 relates to a method of treating cancer or an autoimmune disease, and thus does not warrant an international search according to the criteria set out in PCT Rule 39.1(iv). The opinion is based on the use of the conjugate of any one of claims 102 to 114 or the pharmaceutical composition of claim 115 for the manufacturing of a medicament for the treatment of cancer or an autoimmune disease.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing complying with WIPO Standard ST.26, and such listing was not available to the International Searching Authority in the form, language and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a).

☐ See Supplemental Box for further details.

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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		
1. Statement	Novelty (N)	Claims	5-29, 31-57, 61, 63, 65, 70-71, 76-77, 81-84, 87-101, 105, 107-108, 110, 117-136 YES 1-4, 30, 58-60, 62, 64, 66-69, 72-75, 78-80, 85-86, 102-104, 106, 109, 111-116 NO
	Inventive step (IS)	Claims	None YES 1-136 NO
	Industrial applicability (IA)	Claims	1-136 YES None NO
2. Citations and explanations: Claim 116 does not warrant an international search according to the criteria set out in PCT Rule 39.1(iv). The citations and explanations of claim 116 are carried out below and based on the expected subject-matter in Box III. Claim 55 is dependent on claims 57-49 and does not meet the requirements of PCT Article 6. The citations and explanations are based on claim 55 depended on claims 47-49. I. Reference is made to the following documents: D1: WO2020236841A2. D2: WO2022207699A1. D3: WO2019104289A1. II. Novelty D1 discloses a Linker-Drug group of Formula (II), an Antibody Drug Conjugate of Formula (IV) and a linker having the structure of Formula (VI), wherein R² is a hydrophilic moiety selected from polyethylene glycol, polyalkylene glycol, a sugar, an oligosaccharide, a polypeptide, and a polysarcosine. The example compounds comprise L7-P1, L10-P1, L11-P1, L12-P1, L14-P1, L15-P1, L16-P1, L17-P1, L18-P1, L19-P1, L22-P1, L23-P1, L24-P1, L30-P1, L32-P1, L33-P1, L43-P1, L48-P1, L50-P1, L51-P1, L57-P1, L58-P1, L71-P1, L72-P1, L74-P1, L75-P1, L89-P1, L97-P1, L102-P1, L134-P1, L140-P2, L142-P2, L144-P2, L146-P2, L147-P2, L169-P2, etc. The linkers described herein, which comprise a hydrophilic moiety, contribute to the overall hydrophilicity of ADCs and improve aqueous solubility of the ADC. The linkers described herein also unexpectedly reduce ADC aggregation and improve pharmacokinetic and pharmacodynamic properties of ADCs (see claims 1-48, description, line 27 on page 1 to line 11 on page 2, line 32 on page 2 to line 16 on page 3, line 11 on page 4 to line 4 on page 5, line 22 on page 5 to line 14 on page 6, Embodiments 1-85 on pages 32-89, Embodiments 126-139 on pages 99-103, Embodiments 167-188 on pages 106-110, Tables 4A-4C on pages 205-254). The subject-matter of claims (all partially) 1-4, 30, 58-60, 62, 64, 66-69, 72-75, 78-80, 102 is not novel in the sense of PCT Article 33(2) over D1. D2 discloses that WO2017089895 describes the use of a glycosidase-sensitive cleavable drug- linker based on the 2-hydroxy-5-(hydroxymethyl)benzoic acid self-immolative chemical spacer. D2 provides a Ligand-Drug-Conjugate compound (LDC) having formula (I), wherein K is an optional hydrophobicity masking entity, preferably selected from polysarcosine and polyethylene glycol. The example compounds comprise DL12-DL13, etc. The example conjugates comprise ADC201-ADC202, etc. (see claims 1-17, description, lines 4-7 on page 2, line 19 on page 2 to line 18 on page 4, lines 6-9 on page 22, compounds DL12-DL13 on pages 70-71, the table on pages 78-81, Figures 8-9). The subject-matter of claims (all partially) 1-3, 30, 59-60, 64, 78-80, 85-86, 102-104, 106, 109, 111-116 is not novel in the sense of PCT Article 33(2) over D2. Neither D1 nor D2 discloses the other linker compounds. Therefore, the subject-matter of claims 5-29, 31-57, 61, 63, 65, 70-71, 76-77, 81-84, 87-101, 105, 107-108, 110, 117-136 and claims (all partially) 1-4, 30, 58-60, 62, 64, 66-69, 72-75, 78-80, 85-86, 102-104, 106, 109, 111-116 is novel in the sense of PCT Article 33(2). III. Inventive step			

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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

Claims (all partially) 1-4, 30, 58-60, 62, 64, 66-69, 72-75, 78-80, 85-86, 102-104, 106, 109, 111-116 are not novel, thus do not meet the requirements of PCT Article 33(3).

D1 is considered to be the closest prior art to the subject-matter of claim 1 (partially). The difference between claim 1 (partially) and D1 is that D1 does not disclose the other linker compounds. The problem to be solved may therefore be regarded as the provision of similar linker compounds with hydrophilic moiety.

D1 discloses the hydrophilic moiety R² is selected from polyethylene glycol, polyalkylene glycol, a sugar, an oligosaccharide, a polypeptide, a polysarcosine, etc. (see the relevant passages mentioned above). D3 discloses an ADC of Formula (I), wherein T' is a hydrophilic group. The hydrophilic group comprises a polyalcohol or a derivative thereof, a polyether or a derivative thereof, an amino polyalcohol, glucamine, etc. The example conjugates have Formulas (XIVj), (XIVk), (XIVl), etc. (see claims 1-39, description, Table 2 on page 202, Formulas (XIVj), (XIVk), (XIVl) on page 208). It would be obvious for a person skilled in the art to obtain the other linker compounds in view of D1 and D3. The present application just involved the pharmacodynamic studies of the conjugates of Drug-Linker 4. There is, however, no data on file which demonstrates the beneficial technical effect arising from the entire scope covered by the present claims. The subject-matter of claim 1 (partially) does not involve an inventive step in the sense of PCT Article 33(3).

The other linker compounds, the Drug-Linker compounds, the conjugates, the pharmaceutical composition, as well as the method mentioned by the present claims are either disclosed by D1/D3 or common practice for a person skilled in the art. Therefore, the subject-matter of claims 5-29, 31-57, 61, 63, 65, 70-71, 76-77, 81-84, 87-101, 105, 107-108, 110, 117-136 and claims (all partially) 2-4, 30, 58-60, 62, 64, 66-69, 72-75, 78-80, 85-86, 102-104, 106, 109, 111-116 does not involve an inventive step in the sense of PCT Article 33(3).

IV. Industrial applicability

The subject-matter of claims 1-136 can find industrial applicability in medication, and meets the requirements of PCT Article 33(4).

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

1. Claims 7, 9-12, 29-45, 47-49, 54-67, 70-72, 74, 107, 109-113, 122-134 are multiple dependent claims, however they respectively refer to the preceding multiple dependent claims. Therefore, claims 7, 9-12, 29-45, 47-49, 54-67, 70-72, 74, 107, 109-113, 122-134 do not meet the criteria of PCT Rule 6.4(a).
2. Claim 59 contains spelling error 'any o one f'.

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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:

Claim 55 is dependent on claims 57-49 and does not meet the requirements of PCT Article 6. The citations and explanations are based on claim 55 depended on claims 47-49.