

From the INTERNATIONAL SEARCHING AUTHORITY

To:

PCTWRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing

(day/month/year)

16 August 2024

Applicant's or agent's file reference

SH1903-24P451368**FOR FURTHER ACTION**

See paragraph 2 below

International application No.

PCT/CN2024/091814

International filing date (day/month/year)

09 May 2024

Priority date (day/month/year)

09 May 2023

International Patent Classification (IPC) or both national classification and IPC

A61K47/68(2017.01)i; C07D491/22(2006.01)i; C07K16/28(2006.01)i; A61P35/00(2006.01)i

Applicant

SHANGHAI HENLIUS BIOTECH, 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 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/

Date of completion of this opinion

Authorized officer

WRITTEN OPINION OF THE
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International application No.

PCT/CN2024/091814

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(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 13ter.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. 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. 36-42

because:

☒ the said international application, or the said claims Nos. 36-42 relate to the following subject matter which does not require an international search (*specify*):

Claims 36-42 relate to a method for treating a disease as defined in PCT Rule 39.1(iv). However, the opinion is still formed on the basis of the pharmaceutical use thereof.

☐ 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 13ter.1(a).

☐ See Supplemental Box for further details.

**WRITTEN OPINION OF THE
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International application No.

PCT/CN2024/091814**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	5-6, 9-12, 18-23, 25-26	YES
	Claims	1-4, 7-8, 13-17, 24, 27-49	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-49	NO
Industrial applicability (IA)	Claims	1-49	YES
	Claims	None	NO

2. Citations and explanations:

Claims 36-42 relate to a method for treating a disease as defined in PCT Rule 39.1(iv). However, the citations and explanations are still formed on the basis of the pharmaceutical use thereof.

Reference is made to the following documents:

D1: WO 2021067776 A2

D2: WO 2018080812 A1

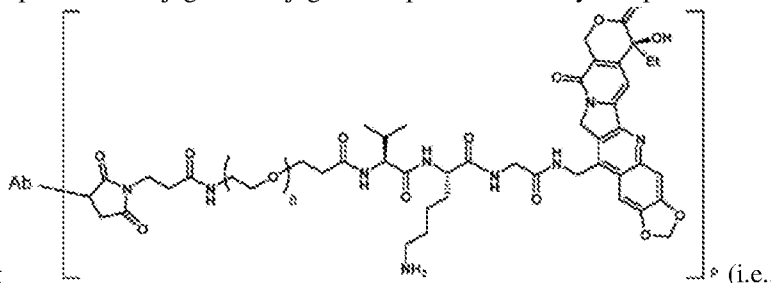
D3: WO 2023046202 A1

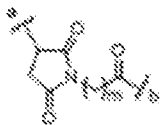
D4: WO 2020236817 A2

I. Novelty

D1 discloses a PD-L1 antibody-camptothecin conjugated conjugate or a pharmaceutically acceptable salt

thereof, the structure thereof being



L1 is selected from , m is 2, and D is a cytotoxic agent), wherein P is 8; Ab is an antibody or an antigen-binding fragment thereof specifically binding to human PD-L1, wherein the antibody or the antigen-binding fragment thereof may be a humanized antibody, an immunoglobulin, Fv, Fab, Fab', Fab'-SH, F(ab')₂, a bispecific antibody, ScFv, or a multispecific antibody; the antibody comprises a heavy chain region of an IgG Fc region, wherein the IgG may be selected from IgG1, IgG2, IgG3, or IgG4; the antibody may lack a lysine at the C-terminus of the heavy chain; or the antibody may conjugate a lysine residue to a linker; the conjugate may be prepared with a pharmaceutically acceptable carrier, a diluent, or an excipient into a pharmaceutical composition or a kit, and may be used for treating PD-L1-related cancer, wherein the cancer may be selected from melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), triple-negative breast cancer (TNBC), ovarian cancer, urothelial carcinoma, hepatocellular carcinoma (HCC), gastric cancer, or cervical cancer, and the kit may further comprise instructions for using the conjugate; further, the conjugate may be administered in combination with other agents, such as an anti-tubulin agent, a DNA minor groove binder, a DNA replication inhibitor, an alkylating agent, or an anthracycline, or may be used in combination with radiotherapy (see claims 1, 20, and 27-36, and description, paragraphs 68, 93-100, 175-176, 182, 210, 236, and 242-246).

Therefore, D1 discloses the technical features of claims 1-4 (in part), 7-8 (in part), 13-17 (in part), 24 (in part), and 27-49 (in part). However, D1 does not disclose the prodrug, solvate, specific antibody structure and L1-L2-L3-D structure involved in the present application. Therefore, claims 1-4 (in part), 7-8 (in part), 13-17 (in part),

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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**

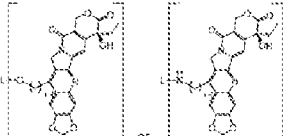
24 (in part), and 27-49 (in part) lack novelty in the sense of PCT Article 33(2), and claims 1-4 (in part), 5-6, 7-8 (in part), 9-12, 13-17 (in part), 18-23, 24 (in part), 25-26, and 27-49 (in part) are novel in the sense of PCT Article 33(2).

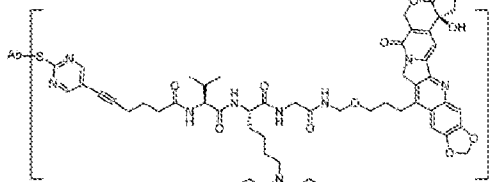
II. Inventive Step

Because claims 1-4 (in part), 7-8 (in part), 13-17 (in part), 24 (in part), and 27-49 (in part) lack novelty, said claims also lack an inventive step in the sense of PCT Article 33(3).

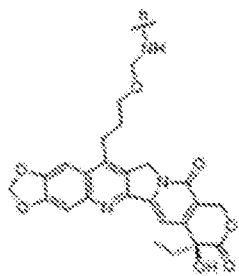
By using D1 as the closest prior art document, claims 5-6 and 9-12 further define the antibody structure thereof. D2 discloses an anti-PD-L1 antibody, comprising: L-CDR1-3 as shown in SEQ ID NOs: 65, 42, and 71 (which are completely identical to SEQ ID NOs: 4-6 involved in the present application); H-CDR1-3 as shown in SEQ ID NOs: 52, 56, and 77 (which are completely identical to SEQ ID NOs: 1-3 involved in the present application); or VH and VL as shown in SEQ ID NOs: 18 and 16 (which are completely identical to SEQ ID NOs: 7-8 involved in the present application) (see description, page 6, table 1, page 89, second-to-last paragraph, and page 90, paragraph 2). Therefore, D2 provides optional anti-PD-L1 antibody structures. In order to further expand the variety of anti-PD-L1 antibody-drug conjugates, a person skilled in the art would be able to select a suitable anti-PD-L1 antibody structure from D2. Therefore, claims 5-6 and 9-12 lack an inventive step in the sense of PCT Article 33(3).

With regard to the conjugate structure involved in claims 17-26, D3 discloses an antibody-drug conjugate, the structure thereof being Ab-[L-D]_q, wherein L is a linker, D is a cytotoxic

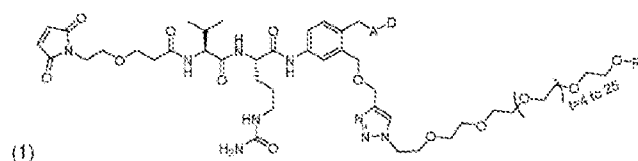
drug, the L-D unit comprises a  structure, and the ADC structure

may specifically be  (i.e., L1 is selected from

, L2 is selected from , L3 is a single bond, and D is selected from



) (see claims 1-14). D4 discloses an antibody conjugate having a structure of



R is H, -CH₃, or -CH₂CH₂C(=O)OH;

(see claims 1-22). Hence, D3 provides an

optional L1-L2-L3-D structure, and D4 further provides an optional L3 structure. In order to further expand the variety of the anti-PD-L1 antibody-drug conjugates, a person skilled in the art would be able to select a suitable L1-L2-L3-D structure from D3 to obtain the antibody-drug conjugate involved in claims 17-21, 22 (in part),

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and 24-26 (in part), and would further combine D4 to obtain the antibody-drug conjugate involved in claims 22 (in part), 23, and 24-26 (in part). Therefore, claims 17-26 lack an inventive step in the sense of PCT Article 33(3).

The prodrug, solvate, antibody structure, pharmaceutical composition, and kit, and treatment method thereof and pharmaceutical use thereof involved in the present application are merely conventional techniques in the art. Therefore, claims 1-4, 7-8, 13-16, and 27-49 also lack an inventive step in the sense of PCT Article 33(3).

III. Industrial Applicability

Claims 1-49 can be used in the pharmaceutical field. Therefore, claims 1-49 are industrially applicable in the sense of PCT Article 33(4).