

From the INTERNATIONAL SEARCHING AUTHORITY

To:

PCTWRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)**02 December 2024**

Applicant's or agent's file reference

MTP230389**FOR FURTHER ACTION**

See paragraph 2 below

International application No.

PCT/CN2024/116083

International filing date (day/month/year)

30 August 2024

Priority date (day/month/year)

01 September 2023

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

C07D498/18(2006.01)i; C07D519/00(2006.01)i; A61K31/504(2006.01)i; A61P35/00(2006.01)i

Applicant

GENFLEET THERAPEUTICS (SHANGHAI) 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/CN2024/116083

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. 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	1-16	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-16	NO
Industrial applicability (IA)	Claims	1-16	YES
	Claims	None	NO

2. Citations and explanations:

2.1 Cited documents

D1: CN 116209438 A

D2: CN 114786777 A

D3: CN 114867735 A

D4: WO 2022235870 A1

D5: CN 114621186 A

2.2 Novelty

Both D1 and D2 disclose compounds A239 and A500, a structure of general formula I, a pharmaceutical composition comprising the compound, and a use thereof in the preparation of a drug for preventing and/or treating RAS protein-related cancers such as pancreatic cancer and colorectal cancer (see D1, claims 44 and 52, and description, paragraphs [0838]-[0876], [1288], [1314]-[1315], [2533], and [2583]; D2, claims 31 and 34-37, and description, paragraphs [0596] and [0647]).

D3 discloses a plurality of specific compounds A1-B263, a structure of general formula I, a pharmaceutical composition comprising same, and a use in the preparation of a drug for preventing and/or treating RAS protein-related cancers such as pancreatic cancer and colorectal cancer (see claims 1, 34 and 36-37, and description, paragraphs [0431]-[0610]).

D4 discloses a compound of general formula I, a pharmaceutical composition comprising same, and a use in the preparation of a drug for preventing and/or treating RAS protein-related cancers such as pancreatic cancer and colorectal cancer (see claims 1, 16 and 19, and description, page 82, line 32 to page 83, line 4).

D5 discloses a compound of general formula I, a pharmaceutical composition comprising same, and a use thereof as an RAS signaling pathway regulator (see abstract, claims 1-9, and description, paragraph [0045]).

None of D1-D5 discloses the subject matter of claims 1-16. Therefore, claims 1-16 are novel in the sense of PCT Article 33(2).

2.3 Inventive Step

D1 is the prior art document closest to claim 1. The compound of general formula (I) set forth in claim 1 differs from compound A239 or A500 disclosed in D1: in respect of the definition of Y₃, and in that claim 1 further comprises other definitions for each substituent. The technical problem to be essentially solved by claim 1 is to provide an alternative RAS inhibitor compound. With regard to the described differences, D1 further discloses general formula I, wherein A is -N(H or CH₃)C(O)-(CH₂)-, wherein amino nitrogen is bound to the carbon atom of -CH(R¹⁰)-, optionally substituted 3 to 6-membered cycloalkylene, optionally substituted 3 to 6-membered heterocycloalkylene, optionally substituted 6-membered arylene, or optionally substituted 5 to 10-membered heteroarylene; B is absent, etc.; G is optionally substituted C₁-C₄ alkylene, etc.; L is absent or a linker; W is hydrogen, optionally substituted C₁-C₄ hydroxyalkyl, optionally substituted C₁-C₄ aminoalkyl, optionally substituted C₁-C₄ haloalkyl, optionally substituted C₁-C₄ alkyl, optionally substituted 3 to 11-membered heterocycloalkyl, optionally substituted 3 to 8-membered cycloalkyl, or optionally substituted 3 to 8-membered heteroaryl; X¹ can be optionally substituted C₁-C₂ alkylene; X² can be NH; X³ can be CH; Y¹ can

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Box No. V

**Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement**

be C, CH, or N; Y², Y³, Y⁴, and Y⁷ are independently C or N; Y⁵ is CH, CH₂, or N; Y⁶ is C(O), CH, CH₂, or N; R¹ can be optionally substituted 5 to 10-membered heteroaryl; R² is absent, hydrogen, optionally substituted C₁-C₆ alkyl, optionally substituted C₂-C₆ alkenyl, optionally substituted C₂-C₆ alkynyl, optionally substituted 3 to 6-membered cycloalkyl, optionally substituted 3 to 7-membered heterocycloalkyl, optionally substituted 6-membered aryl, optionally substituted 5 or 6-membered heteroaryl; R³ is absent; R⁴ is absent, hydrogen, halogen, or methyl optionally substituted with 1 to 3 halogens; R⁵ is hydrogen; R^{7a} and R^{8a} are independently hydrogen, halo, optionally substituted C₁-C₃ alkyl, or combine with the carbon to which they are attached to form carbonyl; R¹⁰ is hydrogen, halo, hydroxy, C₁-C₃ alkoxy, or C₁-C₃ alkyl; R^{10a} is hydrogen or halo; and R¹¹ and R¹⁶ are hydrogen or C₁-C₃ alkyl. Hence, some of the substituents of claim 1 are disclosed in D1. On this basis, a person skilled in the art would be able to further appropriately adjust and replace each substituent, which is a conventional technical means in the art for exploring similar compounds. Therefore, claim 1 lacks an inventive step in the sense of PCT Article 33(3).

Claims 2-12 refer to claim 1, and further define each substituent. On the basis of the same reasoning, claims 2-12 also lack an inventive step in the sense of PCT Article 33(3).

Claim 13 sets forth a pharmaceutical composition, and claims 14-16 set forth a use of a compound. D1 discloses a pharmaceutical composition comprising the compound and a use thereof in the preparation of a drug for preventing and/or treating a disease or disorder related to RAS protein activity, wherein the disease is cancer, and the cancer is pancreatic cancer, colorectal cancer, etc. (see claims 44 and 52, and description, paragraphs [1314]-[1315]). Therefore, claims 13-16 lack an inventive step in the sense of PCT Article 33(3).

2.5 Industrial Applicability

Claims 1-16 can be made and used in the field of drugs, and are therefore industrially applicable in the sense of PCT Article 33(4).

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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:

The expression "for example" appearing in claims 1 and 4 and the expression "such as" appearing in claims 1 and 3-5 define different scopes of protection of one claim. Therefore, the scopes of protection of claims 1 and 3-5 are unclear, and thus, said claims do not comply with PCT Article 6. The present written opinion is formed on the basis of all the scopes.