

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

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UNITED STATES OF AMERICA**

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing

(day/month/year)

04 September 2024 (04.09.2024)

Applicant's or agent's file reference

208103011001PRO2

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US2024/036942

International filing date (day/month/year)

05 July 2024 (05.07.2024)

Priority date (day/month/year)

07 July 2023 (07.07.2023)

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

IPC: See continuation sheet

CPC: **A61K 31/535; A61K 31/519; A61K 31/437; A61K 31/573; A61P 35/00; C07D 475/08**

Applicant

ACROTECH BIOPHARMA 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/US

**Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, VA
22313-1450**

Date of completion of this opinion

26 August 2024 (26.08.2024)

Authorized officer

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/036942

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:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/036942

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. See claims listed below

because:

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

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 5-8, 18-27 are so unclear that no meaningful opinion could be formed (*specify*):

Claims 5-8 and 18-27 are multiple dependent claims not drafted in accordance with the second and third sentences of Rule 6.4(a).

- ☐ 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. 5-8, 18-27

- ☐ 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.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/036942

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	2, 4, 10-12, 15-17	YES
	Claims	1, 3, 9, 13, 14	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-4, 9-17	NO
Industrial applicability (IA)	Claims	1-4, 9-17	YES
	Claims	None	NO

2. Citations and explanations:

----- EXPLANATION -----

Claims 1, 3, and 9 lack novelty under PCT Article 33(2) as being anticipated by Advani et al. "A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial" (hereinafter, "Advani").

Regarding claim 1, Advani discloses a method for treating peripheral T-cell lymphoma (PTCL) (Pg. 2, Summary, Peripheral T-cell lymphomas [PTCL] ... This phase 2 study evaluated a novel front-line combination whereby cyclophosphamide, etoposide, vincristine and prednisone (CEOP) alternated with pralatrexate (CEOP-P) in PTCL) comprising administering to a subject in need thereof a combination comprising Cyclophosphamide, Vincristine, Prednisone and Pralatrexate, wherein the combination does not comprise doxorubicin (Pg. 4, first paragraph, Patients $\geq$ 18 years with PTCL stages II-IV with no prior therapy ... Each cycle consisted of CEOP (A) administered as: cyclophosphamide 750 mg/m² IV day 1, etoposide 100 mg/m² IV days 1-3 {or 100 mg/m² IV day 1 and 200 mg/m² PO days 2-3}, vincristine 2 mg IV day 1 and prednisone 100 mg/day x 5 alternating with P (B) 30 mg/m² IV days 15, 22 and 29).

Regarding claim 3, Advani discloses the method according to claim 1, wherein the administering occurs in a three-week cycle (Pg. 12, Figure 1. CEOP-P Treatment Schema, wherein Figure 1 shows each course includes 3 weeks of cycle A and 3 weeks of cycle B), optionally comprising a drug holiday.

Regarding claim 9, Advani discloses the method according to claim 1, wherein the Cyclophosphamide and/or Vincristine, and/or Prednisone is administered daily for days 1-15, or for days 1-10, or for days 1-8, or for days 1-6, or for days 1-5, or for days 1-4, or for days 1-3 of the treatment cycle (Pg. 4, first paragraph, prednisone 100 mg/day x 5; Pg. 12, Figure 1. CEOP-P Treatment Schema, wherein Figure 1 includes Cycle A ... prednisone 100 mg PO days 1-5).

Claims 13 and 14 lack novelty under PCT Article 33(2) as being anticipated by US 2022/0331252 to Pharmacyclics LLC (hereinafter, "Pharmacyclics").

Regarding claim 13, Pharmacyclics discloses a kit comprising Pralatrexate (Para. [0682] Such kits include a carrier, package, or container; Para. [0685] the container(s) include Compound 1, optionally in a composition or in combination with another agent; Para. [0655] Additional cancer treatment regimens include ... pralatrexate), Cyclophosphamide, Vincristine, and Prednisone (Para. [0643] the second cancer treatment regimen comprises a chemotherapeutic agent; Paras. [0645] and [0648] the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone ... the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone), wherein said kit does not comprise doxorubicin (Para. [0648] the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone).

Regarding claim 14, Pharmacyclics discloses the kit of claim 13, wherein the Pralatrexate, is formulated separately from the Cyclophosphamide, the Vincristine, and the Prednisone (Para. [0685] the container(s)

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

include Compound 1, optionally in a composition or in combination with another agent; Para. [0236] The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures; Para. [0639] The individual compounds of such combinations ... in separate or combined pharmaceutical formulations; Para. [0655] Additional cancer treatment regimens include ... pralatrexate; Paras. [0643] and [0648] the second cancer treatment regimen comprises a chemotherapeutic agent ... the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone).

Claim 2 lacks an inventive step under PCT Article 33(3) as being obvious over Advani et al. "A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial" (hereinafter, "Advani") in view of US 2022/0331252 to Pharmacyclics LLC (hereinafter, "Pharmacyclics").

Regarding claim 2, Advani discloses the method according to claim 1, but Advani fails to explicitly disclose wherein the combination consists of Cyclophosphamide, Vincristine, Prednisone and Pralatrexate.

Pharmacyclics is in the art of lymphoma (Abstract) and teaches wherein the combination consists of Cyclophosphamide, Vincristine, Prednisone (Para. [0643] the second cancer treatment regimen comprises a chemotherapeutic agent; Para. [0648] the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone).

It would have been obvious to one of ordinary skill in the art before the priority date to modify Advani to include wherein the combination consists of Cyclophosphamide, Vincristine, and Prednisone taught by Pharmacyclics.

The motivation for doing so would be to provide an effective personalized combinations of chemotherapeutic agents for individual patients (see Pharmacyclics, Paras. [0643] the second cancer treatment regimen comprises a chemotherapeutic agent; Para. [0645] In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone; Para. [0648] In some embodiments, the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone; Para. [0649] the second cancer treatment regimen comprises etoposide, doxorubicin, vincristine, cyclophosphamide, prednisolone).

Further, it would have been obvious to one of ordinary skill in the art before the priority date to modify Advani to include wherein the combination consists of Cyclophosphamide, Vincristine, Prednisone and Pralatrexate, since where the general conditions of the claim are disclosed in the prior art (Advani, Pg. 2, Summary, Peripheral T-cell lymphomas (PTCL) ... This phase 2 study evaluated a novel front-line combination whereby cyclophosphamide, etoposide, vincristine and prednisone (CEOP) alternated with pralatrexate (CEOP-P) in PTCL; Pharmacyclics, Para. [0101] a method of treating cancer in a patient in need of such treatment, comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition or formulation described herein; Para. [0109] peripheral T-cell lymphoma not otherwise specified (PTCL-NOS); Pharmacyclics, Para. [0643] the second cancer treatment regimen comprises a chemotherapeutic agent; Para. [0648] the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone), replacing CEOP with CVP involves only routine skill in the art. The motivation for doing so would be to provide select an effective personalized combinations of chemotherapeutic agents for individual patients (see Pharmacyclics, Paras. [0643]-[0648]).

Claims 4 and 10-12 lack an inventive step under PCT Article 33(3) as being obvious over Advani et al. "A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial" (hereinafter, "Advani") in view of Shustov et al. "Pralatrexate in Combination with Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (CHOP) in Previously Untreated Patients with Peripheral T-Cell Lymphoma(PTCL): A Phase 1 Dose-Escalation Study" (hereinafter, "Shustov").

Regarding claim 4, Advani discloses the method according to claim 3, but Advani fails to explicitly disclose wherein the Cyclophosphamide, Vincristine, Prednisone and Pralatrexate are independently

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

administered daily, weekly, or once every two weeks for at most two weeks of the three-week cycle, such that the three-week cycle contains a weeklong drug holiday.

Shustov is in the art of PTCL (Pg. 1, Title) and teaches administering a combination comprising Cyclophosphamide, Vincristine, Prednisone and Pralatrexate, wherein the Cyclophosphamide, Vincristine, Prednisone and Pralatrexate are independently administered daily, weekly, or once every two weeks for at most two weeks of the three-week cycle, such that the three-week cycle contains at least a weeklong drug holiday (Pg. 1, first paragraph, Phase 1 multi-center dose-escalation study of pralatrexate in combination with standard CHOP ... in treatment-naïve PTCL patients; Pg. 1, third paragraph, Part 1 of this 3+3 dose-escalation study, pralatrexate was administered at 10, 15, 20, 25, or 30 mg/m² as an IV push on days 1 and 8 of a standard 21-day CHOP regimen {cyclophosphamide 750 mg/m² ... vincristine 1.4 mg/m² [maximum 2 mg] on day 1 and oral prednisone 100 mg on days 1-5} ... patients were treated with up to 6 cycles of therapy).

It would have been obvious to one of ordinary skill in the art before the priority date to modify Advani with the teaching of Shustov.

The motivation for doing so would be to combine an antifolate agent proven as an effective agent in PTCL with chemotherapeutic agents, thereby providing an effective first line PTCL treatment (see Shustov, Pg. 1, first paragraph, Pralatrexate, a second-generation antifolate, demonstrated a single agent activity in patients with relapsed and refractory PTCL ... We conducted a Phase 1 multi-center dose-escalation study of pralatrexate in combination with standard CHOP ... in treatment-naïve PTCL patients).

Regarding claim 10, Advani discloses the method of claim 1, wherein the method comprises a 21 day treatment cycle (Pg. 12, Figure 1. CEOP-P Treatment Schema, wherein Figure 1 shows each course includes 3 weeks of cycle A and 3 weeks of cycle B), the treatment cycle comprising: b) administering Cyclophosphamide in a dosage of at least about 700 mg/m² intravenously (Pg. 4, first paragraph, Each cycle consisted of CEOP (A) administered as: cyclophosphamide 750 mg/m² IV day 1; Pg. 12, Figure 1, Cycle A: cyclophosphamide 750 mg/m² day 1 IV) and Vincristine in a dosage of at least about 1 mg/m² intravenously, on day 1 (Pg. 4, first paragraph, Each cycle consisted of CEOP (A) administered as ... vincristine 2 mg IV day 1; Figure 1, Cycle A: vincristine 1.4 mg/m² {capped at 2 mg} day 1 IV), wherein the Cyclophosphamide and/or Vincristine are independently optionally administered following or concomitantly with the administration of Pralatrexate on day 1; and c) administering Prednisone in a dosage of at least about 50 mg orally on each of day 1 to day 5 (Pg. 4, first paragraph, Each cycle consisted of CEOP (A) administered as ... prednisone 100 mg/day x 5; (Pg. 12, Figure 1, Cycle A ... prednisone 100 mg PO days 1-5; see Pg. 15, Ln. 11 of the instant application, orally (PO)), wherein the prednisone is optionally administered on day 1 following the administration of Pralatrexate.

Advani fails to explicitly disclose a) administering Pralatrexate in a dosage of at least about 10 mg/m² intravenously on day 1 and day 8.

Shustov further teaches administering Pralatrexate in a dosage of at least about 10 mg/m² intravenously on day 1 and day 8 (Pg. 1, third paragraph, Part 1 of this 3+3 dose-escalation study, pralatrexate was administered at 10 ... mg/m² as an IV push on days 1 and 8 of a standard 21-day CHOP regimen (cyclophosphamide 750 mg/m² ... vincristine 1.4 mg/m² [maximum 2 mg] on day 1 and oral prednisone 100 mg on days 1-5).

It would have been obvious to one of ordinary skill in the art before the priority date to modify Advani with the teaching of Shustov.

The motivation for doing so would be to combine an antifolate agent proven as an effective agent in PTCL with chemotherapeutic agents, thereby providing an effective first line PTCL treatment (see Shustov, Pg. 1, first paragraph).

Regarding claim 11, modified Advani discloses the method of claim 10, but Advani fails to explicitly disclose wherein the 21 day cycle is repeated between 1 to 6 times.

Shustov further teaches wherein the 21 day cycle is repeated between 1 to 6 times (Pg. 1, third paragraph, Part 1 of this 3+3 dose-escalation study, pralatrexate was administered ... as an IV push on days 1 and 8 of a standard 21-day CHOP regimen ... patients were treated with up to 6 cycles of therapy).

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

It would have been obvious to one of ordinary skill in the art before the priority date to modify Advani with the teaching of Shustov.

The motivation for doing so would be to combine an antifolate agent proven as an effective agent in PTCL with chemotherapeutic agents, thereby providing an effective first line PTCL treatment (see Shustov, Pg. 1, first paragraph).

Regarding claim 12, modified Advani discloses the method of claim 10, and Advani further disclose wherein the treatment cycle comprises at least one of: a) administering Pralatrexate in a dosage of about 20 to about 30 mg/m² intravenously on day 1 and day 8; b1) administering Cyclophosphamide in a dosage of from about 700 mg/m² to about 800 mg/m² on day 1 (Pg. 4, first paragraph, Each cycle consisted of CEOP (A) administered as: cyclophosphamide 750 mg/m² IV day 1; Pg. 12, Figure 1, Cycle A: cyclophosphamide 750 mg/m² day 1 IV); b2) administering Cyclophosphamide in a dosage of about 750 mg/m² intravenously on day 1; b3) administering Vincristine in a dosage of from about 1 mg/m² to about 2 mg/m² intravenously on day 1; b4) administering Vinicristine in a dosage of about 1.2 mg/m² to about 1.6 mg/m² intravenously on day 1; b5) administering Vinicristine in a dosage of about 1.4 mg/m², intravenously, on day 1; C1) administering Prednisone in a dosage of from about 50 mg to 150 mg on day 1 following administration of Pralatrexate; c2) administering Prednisone in a dosage of from about 80 mg to about 120 mg on day 1 following administration of Pralatrexate; and c3) administering Prednisone in a dosage of about 100 mg orally on day 1 following administration of Pralatrexate.

Claims 15-17 lack an inventive step under PCT Article 33(3) as being obvious over US 2022/0331252 to Pharmacyclics LLC (hereinafter, "Pharmacyclics") in view of Advani et al. "A phase II study of cyclophosphamide, etoposide, vincristine and prednisone (CEOP) Alternating with Pralatrexate (P) as front line therapy for patients with peripheral T-cell lymphoma (PTCL): final results from the T- cell consortium trial" (hereinafter, "Advani").

Regarding claim 15, Pharmacyclics discloses the kit of claim 13, wherein the kit comprises a first pharmaceutical composition comprising Pralatrexate and a first pharmaceutically acceptable excipient and/or a second pharmaceutical composition comprising Cyclophosphamide and a second pharmaceutically acceptable excipient, and/or a third pharmaceutical composition comprising Vinicristine and a third pharmaceutically acceptable excipient, and/or a fourth pharmaceutical composition comprising Prednisone and a fourth pharmaceutically acceptable excipient (Para. [0685] the container(s) include Compound 1, optionally in a composition or in combination with another agent; Para. [0639] The individual compounds of such combinations ... in separate or combined pharmaceutical formulations; Para. [0640] The combinations ... are conveniently presented for use in the form of a pharmaceutical compositions together with a pharmaceutically acceptable diluent(s) or carrier(s); Para. [0655] Additional cancer treatment regimens include ... pralatrexate; Paras. [0643] and [0648] the second cancer treatment regimen comprises a chemotherapeutic agent ... the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone).

Pharmacyclics fails to explicitly disclose about 20 to 30 mg/m² Pralatrexate; about 500-1000 mg/m² Cyclophosphamide; about 1-3 mg/m² Vinicristine; and about 50-150 mg Prednisone.

Advani is in the art of cancer (Pg. 1, Title) and teaches about 20 to 30 mg/m² Pralatrexate (Pg. 12, Figure 1, pralatrexate 30 mg/m²); about 500-1000 mg/m² Cyclophosphamide (Pg. 12, Figure 1, cyclophosphamide 750 mg/m²) about 1-3 mg/m² Vinicristine (Pg. 12, Figure 1, vincristine 1.4 mg/m² (capped at 2 mg)); and about 50-150 mg Prednisone (prednisone 100 mg).

It would have been obvious to one of ordinary skill in the art before the priority date to modify Pharmacyclics with the teaching of Advani.

The motivation for doing so would be to provide unit dosage forms of chemotherapeutic agents, thereby providing effective combination of chemotherapy.

Regarding claim 16, modified Pharmacyclics discloses the kit according to claim 15, and Pharmacyclics further discloses wherein at least two of the first pharmaceutical composition, second pharmaceutical composition, third pharmaceutical composition and fourth pharmaceutical composition are the same pharmaceutical composition (Para. [0639] The individual compounds of such combinations ... in

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/036942

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**

separate or combined pharmaceutical formulations ... the individual compounds will be administered simultaneously in a combined pharmaceutical formulation; Para. [0236] The compounds can be used singly or in combination with one or more therapeutic agents as components of mixtures; Para. [0640] The combinations ... are conveniently presented for use in the form of a pharmaceutical compositions together with a pharmaceutically acceptable diluent(s) or carrier(s); Paras. [0643] and [0648] the second cancer treatment regimen comprises a chemotherapeutic agent ... the second cancer treatment regimen comprises cyclophosphamide, vincristine, and prednisone).

Regarding claim 17, modified Pharmacyclics discloses the kit of claim 15, but Pharmacyclics fails to explicitly disclose wherein the first pharmaceutical composition is an intravenous composition.

Advan further teaches an intravenous composition of Pralatrexate (Pg. 12, Figure 1, pralatrexate 30 mg/m² day 1 IV).

It would have been obvious to one of ordinary skill in the art before the priority date to modify Pharmacyclics with the teaching of Advani.

The motivation for doing so would be to provide unit dosage forms of Pralatrexate, thereby providing easy-to-use anticancer agents for combination therapy.

Claims 1-4 and 9-17 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US2024/036942

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:

Claims 4 and 9 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because Claims 4 and 9 are indefinite for the following reason(s):

With regards to 4, the claim recites the phrase “for at most two weeks of the three-week cycle, such that the three-week cycle contains a weeklong drug holiday.” For purposes of this written Opinion, claim 24 is best interpreted as “for at most two weeks of the three-week cycle, such that the three-week cycle contains at least a weeklong drug holiday.”

With regards to claim 9, the claim recites the phrase "The method according to claim In another aspect..." which appears to be a typographical error. For the purposes of this written opinion, claim 9 is best interpreted to read as:

9. The method according to claim 1, wherein the Cyclophosphamide and/or Vinicristine, and/or Prednisone is administered daily for days 1-15, or for days 1-10, or for days 1-8, or for days 1-6, or for days 1-5, or for days 1-4, or for days 1-3 of the treatment cycle.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of IPC: *A61K 31/535* (2024.01); *A61K 31/573* (2024.01); *A61P 35/00* (2024.01); *A61K 31/437* (2024.01);
A61K 31/519 (2024.01); *C07D 475/08* (2024.01)