

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)

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/US2015/059571	International filing date (day/month/year) 06.11.2015	Priority date (day/month/year) 07.11.2014
International Patent Classification (IPC) or both national classification and IPC INV. A61K9/00 A61K39/395 A61P27/02		
Applicant NOVARTIS AG		

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:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Schifferer, Hermann Telephone No. +49 89 2399-0	
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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	
	No: Claims	<u>1-26</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-26</u>
Industrial applicability (IA)	Yes: Claims	<u>1-26</u>
	No: Claims	

2. Citations and explanations

see separate sheet

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:

see separate sheet

Item V

Reasoned statement pursuant to Rule 43.bis.(1)(a)(i) with regard to novelty, inventive step and industrial applicability

1. Documents

Reference is made to the following documents:

- D1 WO 2009/155724 A2 (ESBATECH AN ALCON BIOMEDICAL R [CH]; BORRAS LEONARDO [CH]; URECH DAVID) 30 December 2009 (2009-12-30)
- D2 US 2006/088523 A1 (ANDYA JAMES [US] ET AL) 27 April 2006 (2006-04-27)
- D3 US 2013/004484 A1 (DEMEULE BARTHELEMY [US] ET AL) 3 January 2013 (2013-01-03)

Unless otherwise specified, reference is drawn onto the quotations given in the search report.

2. Novelty - Article 33(1) and (2) PCT

2.1) D1-D3 comprise compositions with Anti VEGF antibodies in higher concentrations, namely 50 mg/ml and 100 mg/ml and further sucrose or trehalose, citrate or histidine buffer and polysorbate.

All three documents refer to a sequence which is identical to SEQ ID No. 1, as disclosed in claim 1 of present application.

2.2) Following this analysis, the subject-matter of claims 1-26 is not considered as novel according to Article 33(1) and (2) PCT.

3. Inventive Step - Article 33(1) and (3) PCT

The problem to be solved was the search for an improved formulation with high concentration of anti-VEGF antibodies and low levels of antibody aggregation and sub-visible particles, that are suitable for the administration to a human in particular to a human eye.

According to the Applicant the problem has been solved by a composition comprising 50 mg/ml of an anti-VEGF antibody (comprises SEQ ID No. 1 and 2), sucrose or trehalose, citrate or histidine, polysorbate 80.

D1-D3 have already solved the problem.

The technical objective problem would be merely the search for an alternative.

The examples refer to SEQ ID No. 4 - not to No. 1 and 2 as disclosed in claim 1.

As a consequence it seems that the examples cannot provide a suitable support for the claims submitted.

A surprising or an unexpected effect has not been shown in comparison to the prior art.

Therefore, the subject-matter of claims 1-26 is considered as not inventive according to Article 33(1) and (3) PCT.

Item VIII

Certain observations on the international application (clarity)

1. Whilst claim 1 refers to SEQ ID NO. 1 and 2, the examples deal with SEQ ID No. 4. This leads to a discrepancy between the claims and the description and thus to doubts on the scope of the invention and to a lack of clarity according to Article 6 PCT.

2. As a precaution it is mentioned that claims 15-17, 19-21, 23-25 currently disclose methods for delivering anti-VEGF antibodies being not suitable and clear as such in a European procedure.

This would have to be altered to compositions for use for administering such anti VEGF antibodies.