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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/US2019/014113	International filing date (day/month/year) 18.01.2019	Priority date (day/month/year) 12.03.2018
International Patent Classification (IPC) or both national classification and IPC INV. C07K16/22 A61K39/395 A61P19/02 A61P29/00		
Applicant ZOETIS SERVICES LLC		

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 Irion, Andrea 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	<u>1-42</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-42</u>
Industrial applicability (IA)	Yes: Claims	<u>1-42</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Item V

V.1 Reference is made to the following documents:

- D1 WO 2012/153121 A1 (NVIP PTY LTD [AU]; GEARING DAVID [AU]) 15 November 2012 (2012-11-15)
- D2 WO 2012/153122 A1 (NVIP PTY LTD [AU]; GEARING DAVID [AU]) 15 November 2012 (2012-11-15)
- D3 WO 2012/024650 A2 (ABBOTT LAB [US]; LACEY SUSAN E [US]; BARBON JEFFREY A [US]; CHHAYA MEH) 23 February 2012 (2012-02-23)
- D4 WO 2013/034900 A1 (GEARING DAVID [AU]; NVIP PTY LTD [AU]) 14 March 2013 (2013-03-14)
- D5 WO 2013/184871 A1 (ZOETIS LLC [US]) 12 December 2013 (2013-12-12)
- D6 D P GEARING ET AL: "A fully caninised anti-NGF monoclonal antibody for pain relief in dogs", BMC VETERINARY RESEARCH, vol. 9, no. 1, 1 January 2013 (2013-01-01), page 226, XP55248168
- D7 D X LASCELLES B ET AL: "A canine-specific anti-nerve growth factor antibody alleviates pain and improves mobility and function in dogs with degenerative joint disease-associated pain", BMC VETERINARY RESEARCH, vol. 11, no. 1, 30 April 2015 (2015-04-30), page 101, XP021221315
- D8 M E GRUEN ET AL: "A Feline-Specific Anti-Nerve Growth Factor Antibody Improves Mobility in Cats with Degenerative Joint Disease-Associated Pain: A Pilot Proof of Concept Study", JOURNAL OF VETERINARY INTERNAL MEDICINE, vol. 30, no. 4, 1 July 2016 (2016-07-01), pages 1138-1148, XP055570894
- D9 D P GEARING ET AL: "In Vitro and In Vivo Characterization of a Fully Felinized Therapeutic Anti-Nerve Growth Factor Monoclonal Antibody for the Treatment of Pain in Cats", JOURNAL OF VETERINARY INTERNAL MEDICINE, vol. 30, no. 4, 15 June 2016 (2016-06-15), pages 1129-1137, XP055370276
- D10 PANKA D J ET AL: "Defining the structural correlates responsible for loss of arsonate affinity in an Id CRantibody isolated from an autoimmune mouse", MOLECULAR IMMUNOLOGY, vol. 30, no. 11, 1 August 1993 (1993-08-01), pages 1013-1020, XP023969623

- D11 B J KOBRIN ET AL: "A V region mutation in a phosphocholine-binding monoclonal antibody results in loss of antigen binding", THE JOURNAL OF IMMUNOLOGY, 15 March 1991 (1991-03-15), page 2017, XP055277424,
- D12 CHIEN N C ET AL: "Significant structural and functional change of an antigen-binding site by a distant amino acid substitution: Proposal of a structural mechanism", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 86, no. 14, 1 January 1989 (1989-01-01), pages 5532-5536, XP009187738
- D13 RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity", PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 79, 1 March 1982 (1982-03-01), pages 1979-1983, XP007901436
- D14 WINKLER K ET AL: "Changing the antigen binding specificity by single point mutations of an anti-p24 (HIV-1) antibody", THE JOURNAL OF IMMUNOLOGY, vol. 165, no. 8, 15 October 2000 (2000-10-15), pages 4505-4514, XP002579393
- D15 H KOBAYASHI ET AL: "Tryptophan H33 plays an important role in pyrimidine (6-4) pyrimidone photoproduct binding by a high-affinity antibody", PROTEIN ENGINEERING, 1 January 1999 (1999-01-01), pages 879-884, XP055364172
- D16 CASIPIT C L ET AL: "Improving the binding affinity of an antibody using molecular modeling and site-directed mutagenesis", PROTEIN SCIENCE, vol. 7, 1 August 1998 (1998-08-01), pages 1671-1680, XP001007633
- D17 JOEL F SCHILDBACH ET AL: "Modulation of antibody affinity by a non-contact residue", PROTEIN SCIENCE, vol. 2, no. 2, 1 February 1993 (1993-02-01), pages 206-214, XP55103868
- D18 M J BETTS and R B RUSSELL, Chapter 14: "Amino acid properties and consequences of substitutions"; In: Edited by M R Barnes and I C Gray: "Bioinformatics for Geneticists", 1 January 2003 (2003-01-01), John Wiley & Sons, Ltd, ISBN: 0-470-84393-4, pages 289-316

V.2 Novelty (Article 33(2) PCT)

V.2.1 Prior art documents

Document D1 describes caninized anti-NGF antibodies based on the rat anti-hNGF antibody designated α D11 (Examples 1-11, p. 63-69). After intravenously administered said antibody demonstrates long serum half-life and lack of immunogenicity (Examples 12-13, p. 69-70) and reduces inflammatory pain in vivo (Example 14, p. 71-72).

Document D2 describes felinized anti-NGF antibodies based on the rat anti-hNGF antibody designated α D11 (Examples 1-7, p. 67-77). Said antibody may be safely used in vivo and reduces inflammatory pain in vivo (Examples 8-11, p. 77-80).

Document D3 describes several anti-hNGF antibodies raised in mice. Said antibodies are humanized and caninized (p. 61/62 Table 1A, Examples 13-15). Said antibodies are used for treating NGF-associated diseases (p. 68 l. 8 - p. 69 l. 3).

Document D4 describes caninized, humanized, felinized and equinized anti-NGF antibodies (Example 4 p. 73-74). The CDRs of α D11 are grafted into ubiquitous species-specific framework regions (p. 33 l. 20 - p. 35 l. 5).

Document D5 describes caninized anti-NGF antibodies based on the mouse anti-NGF antibody designated RN911 (Examples 1-5 p. 53-68). Said antibodies showed therapeutic efficacy in a dog synovitis model (Example 7 p. 69) and in a rat MIA model (Osteoarthritis) (Example 9 p. 69-74).

Document D6 and D7 describe the fully caninised anti-NGF antibody, i.e. NV-01 based on α D11, that showed to be effective in pain treatment in dogs (abstract).

Documents D8 and D9 describe a fully felinized anti-NGF antibody (NV-02) showing efficacy in the treatment of degenerative joint disease-associated pain or inflammatory pain in cats (abstract).

Documents D10-D14 show that single amino acid replacements (within the CDRs as well as in the framework region) may have large impact on the binding properties of an antibody.

Documents D15-D17 describe that even conservative amino acid substitutions influence the binding affinity of an antibody. Conservative substitution of Trp H33 by Tyr or Phe resulted in moderate losses of binding affinity (**D15**: abstract). The TA1 antibody Tyr37Phe mutation results in a 50% reduction in affinity and Arg55Lys mutation results in a 70% reduction in affinity (**D16**: p. 1675 right-hand col. 4th paragraph). Both substitutions are considered as being conservative. Even conservative replacements of non-contact residues can alter affinity indirectly through their impact on contact residue placements (**D17**: abstract, p. 209 left-hand col. 2nd paragraph - right-hand col. 1st paragraph).

Document D18 describes structural consequences resulting from amino acid substitutions in polypeptides.

V.2.2 With respect to claims 1-42

None of the documents cited describes an anti-NGF antibody defined in claims 1-42. Therefore, claims 1-42 are considered novel in the sense of Article 33(2) PCT.

V.3 Inventive step (Article 33(3) PCT)

V.3.1 With respect to claims 1-42

The subject-matter of claims 1-42 differs from the prior art anti-NGF antibodies of D1-D9 in the sequence of the CDRs, VH, VL.

The technical effect based on said difference is not apparent from the application as originally filed since comparative data are missing.

The technical problem to be solved may be regarded as providing an alternative anti-NGF antibody suitable for therapy in human beings, canines or felines.

The solution proposed in claims 1-42 of the present application cannot be considered involving an inventive step in the sense of Article 33(3) PCT for the following reasons:

Given the fact that methods to obtain monoclonal antibodies directed against any antigen (such as NGF) and to screen such antibodies in order to select antibodies showing a desired property are routine in the art, and the skilled person would recognize the need of such alternative/further antibodies, the skilled person would consider obvious producing further anti-NGF antibodies to solve the technical problem posed. In order to do so, the skilled person would only apply standard techniques. An inventive step could only be acknowledged if the antibodies (or combination thereof) would show unexpected properties.

The mere provision of an alternative can only be regarded as demonstrating inventive step when the alternative provides some sort of technical advantage, otherwise the specific choice is merely an arbitrary selection of one among a number of equally viable known alternatives .

Dependent claims do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

Hence the subject-matter of claims 1-42 is not considered inventive in the sense of Article 33(3) PCT.

V.4 Industrial applicability

V.4.1 With respect to claims 1-42

The subject-matter of claims 1-42 appears to be susceptible of industrial application.

V.5 Further remarks

V.5.1 With respect to claims 1-6

Claims 1- 6 refer to

variants [...] having one or more conservative amino acid substitutions

The application as originally filed defines said conservative amino acid substitutions on p. 37 I. 5-23. It appears that there is an inconsistency between the statement in lines 16/17 and line 22.

Lines 16/17 read

Polar, positively charged residues: Arg and Lys; His and

Large aromatic residues: Trp and Tyr; Phe

whereas lines 21-22 reads

Lys (Arg; Gln; Glu); Met (Ile; Leu); Phe (Met; Leu; Tyr) [...]

Therefore, according to line 16 Lys could be replaced by Arg or His, whereas lines 21-22 defines that Lys could be replaced by Arg, Gln or Glu.

According to line 17 Phe could be replaced by Trp or Tyr, whereas line 22 defines that Phe could be replaced by Met, Leu or Tyr.

Therefore, the meaning of a "conservative amino acid substitution" is unclear (Article 6 PCT).

Furthermore, **Document D18** indicates that Asn can be substituted by other polar amino acids, especially Asp (p. 306, 14.5.14.1). However, Asp is neither suggested in p. 37 I. 11-17 nor in p. 37 I. 19-23 of the application as originally filed being a suitable amino acid for replacing Asn. Finally, D18 indicates that Gln can be substituted by other polar amino acids, especially Glu (p. 306, 14.5.15.1), which is not suggested in the application.

Consequently, the meaning of "conservative substitution" is unclear in the sense of Article 6 PCT.

V.5.2 With respect to claims 1-6

Claims 1-6 refer to an antigen binding protein defined by comprising a partially defined CDR sequence (claim 1), six partially defined CDR sequences (claims 2 and 3), or a combination of partially defined VH and VL sequences. In this context "partially defined sequence" means a sequence being defined as having at least about 90% sequence identity to a CDR sequences, six CDR sequences, VH/VL sequences. (NOTE: The CDR sequences of SEQ ID NO. 1, 21, 4, 24, 5, and 25 consist of eight amino acids, the CDR sequences of SEQ ID NO. 2 and 22 consist of three amino acids. The sequence of a CDR is unclear which should have at least 90% sequence identity to a sequence having less than ten amino acids, since 90% of eight amino acid residues is 7.2 residues, 90% of three is 2.7.)

The term "about" used in claims 2 and 3 is vague and unclear and leaves the reader in doubt as to the meaning of the technical feature to which it refers, thereby rendering the definition of the subject-matter of said claim unclear, Article 6 PCT.

Furthermore, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain regions in order to form functional antigen binding sites.

A claim to an antibody which is structurally characterised by less than the full sequence of all the CDRs, and their specific order, cannot be seen to sufficiently disclose an antibody with any particular properties.

Furthermore, even single changes in the amino acid sequences of the heavy and light chain variable regions, particularly in the CDRs may dramatically affect antigen-binding function (see **D10-D14**).

Even conservative substitutions may have a negative impact on binding characteristics of an antibody (see **D15-D17**).

V.5.3 With respect to claims 4-6

The antigen binding protein of claim 4 is not defined by comprising the CDRs of the antibodies designated 9L12 or 48L2, since a sequence having at least 90% sequence identity to one of the cited amino acid sequences does not necessarily contain said CDR sequences. However, anti-NGF antibodies not comprising said CDR sequences are not supported by the application (Article 6 PCT).

V.5.4 With respect to claim 4

Claim 4 refers to VH and VL sequences derived from the anti-NGF antibodies designated 9L12 and 48L2. An antibody comprising VH of 9L12 and VL of 48L2 (and vice versa) is not supported by the application (Article 6 PCT). The VH and VL sequences of both antibodies show significant differences so that it is doubted that VH(9L12)xVL(48L2) would bind NGF (and vice versa).

V.5.5 With respect to claims 31-42

The subject-matter of claims 31-42 is considered to be a method of treatment by therapy of the human or animal body.

For the assessment of the present claims 31-42 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

Patentability, in particular novelty and inventive step, of claims 31-42 has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.