

PATENT COOPERATION TREATY

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To:

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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/GB2024/050364

International filing date (day/month/year)
09.02.2024

Priority date (day/month/year)
09.02.2023

International Patent Classification (IPC) or both national classification and IPC
INV. C07K14/705 A61K38/00 A61P19/02 A61P25/04 A61P29/00 C07K16/28

Applicant
PETMEDIX LTD

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.

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Date of completion of
this opinion

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PCT/ISA/210

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2024/050364

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.
 - 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:

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has, within the applicable time limit:
- ☐ paid additional fees
 - ☐ paid additional fees under protest and, where applicable, the protest fee
 - ☐ paid additional fees under protest but the applicable protest fee was not paid
 - ☐ not paid additional fees
2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
 - ☐ the parts relating to claims Nos.

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>2, 3, 7-12, 14-34</u>
	No: Claims	<u>1, 4-6, 13</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-34</u>
Industrial applicability (IA)	Yes: Claims	<u>1-34</u>
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2024/050364

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 IV

1 **LACK OF UNITY OF INVENTION** (Art. 17(3)(a) PCT, Rule 13.1 PCT)

1.1 This Authority considers that the application does not meet the requirements of unity of invention and that there are **4 sub-inventions** which are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT. The reasons are as follows:

1.2 **Different claimed inventions and respective claims**

1.2.1 The claims and the sub-inventions to which the separate inventions relate may be grouped as follows.

1.2.2 **Invention 1: Claims 1-34:** An isolated polypeptide comprising a companion animal p75neurotrophin receptor (p75NTR) extracellular domain, wherein said p75NTR comprises a variant amino acid at one or more of position 75, 109, 133 and/or 134; A fusion protein comprising such companion animal p75NTR extracellular domain with a variant amino acid and a half-life extending moiety; An isolated nucleic acid encoding said isolated polypeptide or fusion protein; A vector comprising said nucleic acid; A host cell comprising such nucleic acid or vector; A pharmaceutical composition comprising such isolated polypeptide or fusion protein; Medical use and method for treating an NGF-related disorder in a companion animal comprising administering an effective amount of said products, especially for treating osteoarthritis; A method of inhibiting NGF activity and/or pro-NGF activity in a companion animal comprising administering said polypeptide or fusion protein.

1.2.3 **Sub-invention 1.1:** As invention 1, wherein said p75NTR comprises at least a variant amino acid at position 75.

1.2.4 **Sub-invention 1.2:** As invention 1, wherein said p75NTR comprises at least a variant amino acid at position 109.

1.2.5 **Sub-invention 1.3:** As invention 1, wherein said p75NTR comprises at least a variant amino acid at position 133.

1.2.6 **Sub-invention 1.4:** As invention 1, wherein said p75NTR comprises at least a variant amino acid at position 134.

1.3 **Common matter**

1.3.1 The **common matter** linking together the alternatives within independent claim 1 is that they relate to a companion animal p75neurotrophin receptor (p75NTR) extracellular domain comprising a variant amino acid at one or more of position 75, 109, 133 and/or 134. Such common matter suffers from some objections of

lack of clarity concerning the species included by the term "**companion animal**", such that basically any non-human animal could be considered to fall under it, or at least, it is broad and includes, not only mammals, but also birds, fish, small reptiles, insects and others; human p75NTR would not be included. In addition, there is no specific sequence and no specific companion animal thus, the term "**variant**" includes also possible natural variations of p75NTR; another possible interpretation is that the term also includes a variant compared to the consensus sequence, e.g. as shown in Fig. 1 of the application. Also the numbering of the positions is in reference to specific SEQ ID NOs as in Fig. 1, but these correspond to positions E103, S137, V161, D162 in full length human p75NTR or, positions E103, S139, V163, D164 of dog p75NTR.

1.4 **Reasons why the common matter does not provide a single general inventive concept**

1.4.1 This common matter **does not comprise a single general inventive concept, based on same or corresponding special technical features** within the meaning of Rule 13.2 PCT, because in the prior art, variants of human p75NTR were well known, some even at the same positions and leading to changes in the affinity of the variant/mutant p75NTR to some of its ligands.

1.4.2 The prior art is listed below under Box V.

1.4.3 **D1** (WO2022226170) discloses mutations in the ECD of human p75NTR which result in changes in the affinity to the p75NTR ligands. Fig. 3A shows that eight point mutations in the p75NTR protein with SEQ ID NO: 8 at positions F136, S137, S137, E147, P150, P150, L165, and R182 exhibited significant reduction in binding of the p75NTR protein to B7-1. For example, the F136D, S137A, S137D, E147D, P150A, P150D, L165A, and R182A mutant p75NTR proteins exhibited greater than 50% reduction in binding to B7-1 (Examples, Fig. 3 A and 3D). Of these mutations, only one (R182A) affected binding of the p75NTRprotein to PTPRF. However, mutations at positions L36, Y37, T38, and L49 of the p75NTR proteins also reduce or eliminate binding of the p75NTRprotein to PTPRF, while still maintaining binding to B7-1. Mutations at positions M95, D162, E171, or D104 of the P75NTR protein can reduce or eliminate hydrogen or electrostatic bonds with NGF, proNGF, or NT3, while binding to B7-1 is maintained, for example, L36D, M95A, D104R, D162A, D162R, and/or E171A (see pages 17-19). Mutations in human p75 neurotrophin receptor **S137A, S137D** (see e.g. Ex. 4, GSP:BLZ26470) corresponds to position **109** in present SEQ ID NO: 73 or 7, the ECD of p75NTR from human. Mutation **D162A, D162R** in D1 (page 18, lines 19-35) corresponds to position

D134 in claim 1 and the present application. D1 discloses that these molecules can be used as B7-1 inhibitors e.g. in model animals, like mice, which can be also considered as "companion animals" or pets (e.g. claims 13, 14). Also as animal models for diseases including sclerosis, pain and others (e.g. claims 14-15).

- 1.4.4 In addition, sequences of animal p75NTR were known which have amino acids at the positions indicated in claim 1, differing from those of the consensus. For instance, **D7** (XP093149849; see also **D7a**, 093149848) discloses *Xenopus laevis* p75NTR (UNIPROT:Q9PRG7), which has 57.8% identity to the extracellular domain (ECD) of human p75NTR of SEQ ID NO: 73 of the application and, comprises a "variant" V133R as compared to the sequence of human and other mammalian p75NTR; the numbering corresponds to that used in claim 1 and SEQ ID NO: 73, 5, 36, 110, 101, 7 or 38 (see Fig. 1).
- 1.5 **Lack of technical relationship between the remaining technical features in the different groups**
- 1.5.1 (a) The technical features representing the **difference** over the non-inventive common matter of each sub-invention are the positions where the variant amino acid occurs, namely, 75, 109, 133 and/or 134 (apparently in respect to specific sequences of the p75NTR-ECD (Fig. 1 and SEQ ID NO: referred therein).
- 1.5.2 (b) These features (variant amino acids) provide the alleged technical effect that the variant p75NTR has an altered affinity to the p75NTR ligands as compared to the "companion animal" sequence. This was shown in the application only for very few substitutions at these positions, specifically in canine p75NTR-ECD. Thus, there is no technical effect over the whole scope claimed, which covers any possible variants at these positions and covering any undefined "companion animals". The **technical problem** is thus, seen as providing polypeptides comprising variants of "companion animal" p75NTR extracellular domain. The **solution** of the sub-inventions is to alter positions selected from 75, 109, 133 and/or 134.
- 1.5.3 (c) This technical problem is known from the prior art and is not inventive because, as discussed above, in **D1**, there is a clear disclosure of variants/ mutants of human p75NTR even at one of the positions indicated in claim 1, namely, **S137A** (D1, Ex. 4) corresponds to position 109 in p75NTR from human, dog, cat, horse and others (see Fig. 1 of the application and SEQ ID NO:s referred therein).

- 1.5.4 Starting from the common concept, each sub-invention comprises the additional feature that a different position is varied/mutated/substituted. As discussed above, there is no effect of said additional feature, because the original sequence and the specific replacement is not specified. Hence, invention 1 solves the problem discussed above of providing further companion animal p75NTR-ECD variants.
- 1.5.5 Consequently, the features of each of sub-inventions 1.1, 1.2, 1.3 and 1.4 which make a technical contribution over the common matter are different.
- 1.5.6 Even if the claims would be more limited to specific sequences of companion animal p75NTR ECD, and the specific mutations specified, the application even shows evidence that they have different technical effects:
- 1.5.7 In the application fusion proteins of the ECD of canine p75NTR to canine Fc (named PetML119) were produced in CHO cells, as well as variants thereof with 5 single mutations. Variants with **S109Y**, **S109H** and **V133R** lead to a high affinity molecules while variants with **E75T** and **D134L** show lower affinity than the original PetML119 (dog-p75TNR:dog-Fc).
- 1.5.8 Thus, as the problems they solve are either obvious or different, these are not corresponding features. Moreover, even for those mutations with a common effect (e.g. increased affinity to ligands) is not sufficient to achieve unity but a significant structural element is also required, e.g. that the substituted amino acid is always the same or that at least, the position mutated is the same.
- 1.5.9 Thus, the requisite unity of invention (Rule 13.1 PCT) therefore no longer exists inasmuch as a technical relationship involving one or more of the same or corresponding special technical features in the sense of Rule 13.2 PCT does not exist between the subject-matter of the different sub-inventions. Consequently there is lack of unity (Rule 13.1 PCT, Art. 17(3)(a) PCT).
- 1.5.10 The attention of the Applicant is brought to the fact that the grouping of the sub-inventions was made considering the best possibilities for the Applicant, but other groupings are possible, like including variants with at least two, three or four of these substitutions, or dividing the inventions according to the specific "companion animal" (dog, cat, horse,...). However, in view of the high degree of identity of at least some mammalian companion animals (about 90%), the grouping chosen seems to be the most meaningful one.
- 1.5.11 It is also noted that, although a search was carried out for all sub-inventions, the objections of lack of unity are very severe. In view of the objections of lack of inventive step (see below), a common preliminary opinion will be provided for

all sub-inventions. However, later if the application enters into the (international/regional) examination phase, the Applicant would be requested to choose one of the sub-inventions for further prosecution.

Item V

2 CITATIONS

2.1 The following **documents** are relevant for the present application:

- D1 WO 2022/226170 A1 (UNIV CORNELL [US]; ALBERT EINSTEIN COLLEGE OF MEDICINE [US] ET AL.) 27 October 2022 (2022-10-27)
- D2 WO 2020/191289 A1 (KINDRED BIOSCIENCES INC [US]) 24 September 2020 (2020-09-24)
- D3 WO 2016/146841 A1 (LEVICEPT LTD [GB]) 22 September 2016 (2016-09-22)
- D4 WO 2015/040398 A1 (LEVICEPT LTD [GB]) 26 March 2015 (2015-03-26)
- D5 WO 2013/136078 A1 (LEVICEPT LTD [GB]) 19 September 2013 (2013-09-19)
- D6 WO 2020/082048 A1 (KINDRED BIOSCIENCES INC [US]) 23 April 2020 (2020-04-23)
- D7 DATABASE UNIPROT [Online] 14 December 2022 (2022-12-14), Anonymous : "Nerve growth factor receptor L homeolog precursor; p75 neurotrophin receptor a-1; p75 neurotrophin receptor a-2", XP093149849, retrieved from EBI accession no. UNIPROT:Q9PRG7_XENLA; -& HUTSON LARA D. ET AL: "Expression and function of Xenopus laevis p75 NTR suggest evolution of developmental regulatory mechanisms", JOURNAL OF NEUROBIOLOGY, vol. 49, no. 2, 27 September 2001 (2001-09-27), pages 79-98, XP093149848

3 THE APPLICATION

3.1 The present application relates to effective therapies for pain, inflammation and osteoarthritis. The application provides an isolated polypeptide comprising a variant p75 neurotrophin receptor (p75NTR) extracellular domain, in particular,

from human or companion animals, comprising variant amino acids at positions 75, 109, 133 and/or 134. The application also relates to a fusion proteins containing these, especially as Fc fusion proteins. Nucleic acids encoding the proteins are also encompassed as well as methods of using the same, in particular as effective therapies for pain, inflammation and osteoarthritis.

- 3.2 In the application fusion proteins of the ECD of canine p75NTR to canine Fc (named PetML119) were produced in CHO cells, as well as variants thereof with 5 single mutations. Variants with S109Y, S109H and V133R lead to a high affinity molecules while variants with E75T and D134L show lower affinity than the original PetML119 (dog-p75TNR:dog-Fc). Also human p75NTR:Fc fusions were produced. These molecules were tested and compared with a antibody, in vitro for binding to neurotrophins rat NGF, human BDNF, human NT-3, human NT-4 and human proNGF, also for inhibition of TF-1-induced cell proliferation and, tested in vivo in a rat model of osteoarthritis, where the proteins showed efficacy in pain relief.

4 PRIOR ART and NOVELTY (Art. 33(2) PCT)

- 4.1 **D1** (WO2022226170; see complete disclosure above, under unity of invention) discloses mutations in the ECD of human p75NTR which result in changes in the affinity to the p75NTR ligands. Point mutations in the p75NTR protein with SEQ ID NO: 8 F136D, S137A, S137D, E147D, P150A, P150D, L165A, and R182A exhibited significant reduction in binding of the p75NTR protein to B7- 1. Mutations L36D, M95A, D104R, D162A, D162R, and/or E171A mutations can reduce or eliminate hydrogen or electrostatic bonds with NGF, proNGF, or NT3, while maintaining binding to B7-1 (Fig. 3A-D, pages 17-19). The mutation in human p75 neurotrophin receptor **S137A, S137D** (see e.g. Example 4) corresponds to position 109 in present SEQ ID NO: 73 or 7, the ECD of human, dog or other mammalian p75NTR. Mutation **D162A, D162R** in human p74NTR of D1 (page 18, lines 19-35) corresponds to position **D134** in claim 1 and the present application. D1 discloses that these molecules can be used as B7-1 inhibitors e.g. in model animals, like mice, which can be also considered as "companion animals" or pets (e.g. claims 13, 14). Also as animal models for diseases including sclerosis, pain and others (e.g. claims 14-15). However, it appears that D1 does not **specifically** disclose variants of companion animal p75NTR with variant amino acids at positions 75, 109, 133 and/or 134 (of the extracellular domain, corresponding to the numbering in Fig. 1 of the application).

- 4.2 **D2** (WO2020191289) discloses extracellular domains (ECD) of a TrkA which binds an NGF, especially as fusion proteins with an Fc; the molecule may further comprise the ECD of NGFR (a synonym of p75NTR; see e.g. [0027], [0028], [0032] [0188], claims 50-51). The NGFR/p75NTR may be from an animal, like a canine, feline or equine ([0032]). The Fc domain may also be from animals [0186] or a variant Fc with increased binding affinity to Protein A (e.g. claim 22). These proteins are mainly for uses to treat pain or inflammation, also osteoarthritis, especially in companion animals like canine, feline or equine subjects (e.g. claims 64-68). Variants are mentioned in D2 [0033], [0034], but not specifically at the positions in claim 1 of the application,
- 4.3 **D3** (WO2016146841) discloses improved p75NTR neurotrophin binding protein (NBP)-Fc fusion protein comprising a p75NTR(NBP) portion, especially the ECD, and an immunoglobulin portion, especially Fc (see claims, examples). In certain embodiments, the p75NTR(NBP)-Fc fusion protein is for medical uses in the treatment of pain. The fusion proteins are applicable in human and veterinary medical fields. Preferably, the individual is a mammal, for example a companion animal such as a horse, cat or dog or a farm animal such as a sheep, cow or pig. Most preferably the individual is a human (page 11, lines 27-29). One of the conditions to be treated is osteoarthritis (e.g. claim 5). However, the p75NTR do not have any variant amino acids at positions indicated in claim 1.
- 4.4 **D4** (WO2015040398) discloses p75NTR:Fc fusion proteins, including variants, like truncated variants (Fig. 5) and, some where the dimers show increased affinity (page 6, para. 2). The fusions are to treat pain (claims 9, 12, 17), including also osteoarthritis, e.g. in animal models like, e.g. in rats (page 26, para 6 to p. 27, para. 1). In D4 variants of the fusion proteins are considered to reduce the immunogenicity, like, e.g. a mutant C222S (see p. 20, "EpibaseTM Immune profiling"; page 22 "p75-NTR Fc-Fusion Protein Design"; Fig. 5). The p75NTR ECD of D4 however, does not include variants at the amino acids at positions of claim 1.
- 4.5 **D5** (WO2013136078) discloses p75NTR(NBP):Fc (p75NTR(NBP) SEQ ID NO. 2 coupled to IgG-Fc SEQ ID NO. 12 using the linker of SEQ ID NO 17); see claims, Fig. 11 discloses SEQ ID NO: 2, the Human p75NTR ECD including signal sequence and Fig. 12, SEQ ID NO. 3 Human p75NTR extracellular domain without signal sequence. D5 discloses uses of such molecules for the treatment of pain and osteoarthritis (page 10, lines 28-33, claim 18). The subjects to be treated include human, or companion animals, like cat, dog,

- horse, cow or pig (page 16, lines 20-21). D5 also refers to mutations, but in the Fc part of the fusion protein, e.g. to minimise complement fixation or antibody-dependent cellular cytotoxicity or which improve affinity of binding to the Fc receptor (page 6, lines 13-30).
- 4.6 **D6** (WO2020082048) discloses Fc variants with altered binding to neonatal Fc receptor (FCRN) and/or extended half-life for antibodies and fusion proteins to treat various disorders ([0002], claims) especially for veterinary use, especially in companion animals such as cats, dogs and horses [0005]. This document, suggest fusion to the ECD of many polypeptides, including an ECD of a LNGFR polypeptide (see Claims 25, 27, [0121], [0123]). Such therapeutic polypeptide may be e.g. from canine, equine or feline species. However, D6 does not disclose any p75NTR with variant amino acids at positions indicated in claim 1.
- 4.7 **D7** (XP093149849; UNIPROT:Q9PRG7_XENLA; see also D7a, XP093149848) discloses the sequence of *Xenopus laevis* p75TNR, with 57.8% identity to the extracellular domain (ECD) of human p75NTR of SEQ ID NO: 73 of the application and, comprises a variant amino acid compared to the human sequence at the position corresponding to 133 in human p75NTR, V133R.
- 4.8 Although none of the prior art discloses specific mutations of specific companion animal p75NTR with variant amino acids at positions 75, 109, 133 and/or 134 (interpreted as positions of the extracellular domain, corresponding to the numbering in Fig. 1 of the application), due to the lack of clarity of the wording of the claims, they have to be interpreted broadly. Thus, animals such as amphibians (e.f. *Xenopus*), can be seen as "companion animals" and since, it is also not clear to which reference sequence the variation occurs, and can be interpreted, e.g. as an amino acid different to those of the consensus in Fig. 1 or different to e.g. dog p74NTR, the p75NTR from *Xenopus* falls under the scope of present claims
- 4.9 Thus, the present application does not satisfy the criterion set forth in Art. 33(2) PCT because the subject-matter of at least **claims 1, 4-6, 13** is not new in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

5 **INVENTIVE STEP (Art. 33(3) PCT)**

- 5.1 **D1** (WO2022226170) see disclosure above, can be considered to represent the **closest prior art** because it specifically addresses mutations in p75NTR that alter the affinity of the receptor for some of its ligands (see passages referred to above under unity of invention).
- 5.1.1 The technical **difference** can be seen as the specific positions where the variant amino acid occurs, namely, 75, 109, 133 and/or 134 (in respect to specific sequences of the p75NTR-ECD as shown in Fig. 1 and SEQ ID NO: referred therein) and, possibly, on the sequence of the "companion animal" p75NTR before the variation is introduced.
- 5.1.2 These features provide the alleged **technical effect** that the variant p75NTR has an altered affinity to the p75NTR ligands as compared to the original/wild type "companion animal" sequence. This was shown in the application for very few substitutions at these positions in canine p75NTR-ECD. There is no technical effect over the whole scope claimed, which covers any possible variants at these positions and covering any undefined "companion animals". The **technical problem** is thus, seen as providing polypeptides comprising variants of "companion animal" p75NTR extracellular domain. The **solution** of the sub-inventions is to alter positions selected from 75, 109, 133 and/or 134 in the companion animal p75NTR.
- 5.1.3 This solution is not inventive because, as discussed above, in **D1** there is a clear disclosure of variants/mutants of human p75NTR at some of the positions indicated in claim 1, namely, **S137A, S137D, D162A, D162R** (Ex. 4, page 18, lines 19-35) which correspond to positions S109 and D134 in p75NTR from human, dog, cat, horse and others (see Fig. 1 of the application and SEQ ID NO:s referred therein). D1 discloses that these molecules can be used as B7-1 inhibitors in model animals, like mice, which can be considered as "companion animals" or pets (e.g. claims 13, 14).
- 5.1.4 The skilled person who wanted to provide variants of the ECD of the p75NTR of certain companion animals to use them as therapeutic molecules, would have the information from D1, that some mutations, even at the same residues of the application, lead to changes in the affinity of the p75NTR receptor to some of its ligands. Thus, the provision of further mutations at these or, even other residues, with the purpose to either increase or decrease partially the affinity to some ligands, would appear obvious or mere alternatives for the skilled person in the technical field of the invention.

- 5.1.5 The provision of fusions of the p75NTR to Fc, even animal Fc, would be obvious to improve the properties and reduce immunogenicity, and the skilled person would choose Fc from the same species as the p75NTR, depending on the species to be treated. Moreover, mutations in animal Fc to improve the properties were known (see e.g. D6). Use of such molecules for treating pain, inflammation and even osteoarthritis, and uses to inhibit NGF activity, were standard in the field of the invention and disclosed in the prior art (D1-D6, passages referred to above; D2 [0129]).
- 5.2 Thus, the solution of **claims 1-34** does not involve an inventive step, especially over the teachings of D1 or D1 in combination with any of D2-D6 (Art. 33(3) and Rule 65(1)(2) PCT).
- 5.3 At present, it is unclear whether specific variants of canine p75NTR, shown in the examples, have any properties which would not be obvious or merely arbitrary alternatives in view of those of the prior art. For limited, specifically defined variants, e.g. some of those of claim 11 and the examples, an inventive might be acknowledged, but not for all of those in the claim. If the application enters the (international/regional) examination, the Applicant could then provide arguments as to the possible inventive step of specific variants

6 PATENTABILITY

- 6.1 For the assessment of present **claims 25-31, 33-34** on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for use in a medical treatment.

Item VIII

7 CLARITY, SUPPORT and DISCLOSURE (Art. 6, 5 PCT)

- 7.1 The term "**companion animal**" is used in several claims; in the application it appears that it is mainly meant to include mammalian companion animals, such as dogs, cats, horses, camels or cattle, but in general, companion animals are also known to include other species, like birds (e.g. chicken), fish, small reptiles, insects and others; human p75NTR would not be included. For instance, those of Fig. 1 have at least 92% sequence identity in their extracellular domain but

e.g. chicken p75TNR has only about 73% and this would be even lower for other taxons. Thus, the p75NTR from companion animals is not clearly defined and lacks clarity (Art. 6 PCT).

- 7.2 In addition, there is no specific sequence and no specific companion animal thus, the term "**variant**" includes natural variations of p75NTR; another possible interpretation is that the term also includes a variant compared to the consensus sequence, e.g. as shown in Fig. 1 of the application. Also the numbering of the positions **positions 75, 109, 133 and/or 134** in the claims and the application seems to be in reference to specific SEQ ID NOs as in Fig. 1, but this is not specified in claim 1 and no basis sequence is mentioned. These correspond to positions E103, S137, V161, D162 in full length human p75NTR or, positions E103, S139, V163, D164 of dog p75NTR. The numbering should be rendered clear in the claims. Thus, the specific amino acid positions indicated by such numbers are not clear (Art. 6 PCT).
- 7.3 In the examples, only variants of a fusion protein of **canine p75NTR** with an Fc domain from **canine IgG-B**, referred to as **PetML119** and variants thereof were tested. It is possible that the effects of the mutations, especially an increased or decreased affinity to ligands of p75NTR could be present for variants of a very high sequence identity, and, also for the ligands of specific species, but not for the broad subject-matter claimed (Art. 6 PCT). The effect of mutations in dog p75NTR, as in the application, could work for other mammalian companion animals, which have a high degree of identity, but no evidence of this has been provided. Thus, the subject-matter claimed is not supported over the broad scope claimed (Art. 6 PCT).
- 7.4 The present set of claims does not comply with the requirements of Art. 6 PCT because it lacks conciseness. The **multiplicity of independent claims**, some in the same category and having an overlapping scope, is not justified and does not comply with the requirements of PCT (see Appendix to Chapter 5 of the ISPE Guidelines, GL/ISPE A5.16[2], A5.42[1],[2]).