PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.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.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2018/065107	08.06.2018	09.06.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K39/395 ADD. A61K39/00

Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

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 43*bis*.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 notifed the International Bureau under Rule 66.1*bis*(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
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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2018/065107

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(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 13*ter*.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 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.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. 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 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-27
	No:	Claims	28-32
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	1-32
	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

Re Item IV

Lack of unity of invention

This Authority considers that the application does not meet the requirements of unity of invention and that there are 2 inventions covered by the claims indicated as follows:

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by **Rule 13.1 PCT**, are as follows:

Independent **claim 1** aims at providing an TrkB antibody (or antigen binding fragment thereof) that comprises the claimed CDR sequences of the heavy and light chain variable region.

Independent **claim 28** discloses an anti-TrkB antibody that binds to at least one amino acid residue within the amino acid regions 92-112, 130-143 and/or 205-219 of the extracellular domain of human TrkB with SEQ ID No 54.

Independent **claim 32** aims at providing an anti-TrkB antibody that competes for binding to TrkB with any one of the claimed antibodies.

The common matter linking together the independent claims 1, 28 and 32 is the following:

- Antibodies that bind TrkB

This common matter does not comprise a single general inventive concept, based on the same or corresponding special technical features within the meaning of **Rule 13.2 PCT**, because antibodies that bind TrkB are known in the art, see e.g. **D1-D7:**

WO 2011/103667 (**D1**) discloses agonist anti-TrkB antibodies, such as antibody mAb1D7, binding to the extracellular D2-D3 domain with SEQ ID No 4, which corresponds to amino acids 56-170 of SEQ ID No 54 of present application (p. 30, l. 3-5, l. 12-18). mAb 1D7 conferred significant neuro-protection (p. 33, l. 14-19) and retinal ganglion cell survival in glaucoma (p. 32-33, example 3) and maintained retinal structures in glaucoma and optic nerve axotomy (p. 34, example 5). **D1** teaches that the receptor sites for BDNF binding and activation are not overlapping with the receptor sites for mAb 1D7 binding. and pre-binding of BDNF to cell surface TrkB does not inhibit mAb 1D7 binding to TrkB (p. 30, l. 24-27).

WO 2017/085035 (**D2**) teaches TrkB binding agonist antibodies for use in the treatment of neurological disorders (abstract, p. 51, table 3). The anti-TrkB antibodies bind to epitopes in the D4-D5-JM domain (p. 57, paragraph 3, p.

59, table) (the D4-D5-JM domain corresponds to amino acids 163-399 of SEQ ID No 54 of present application). Antibody 1G11 enhanced survival of spinal cord neurons (p. 64, paragraph 3), ameliorated gait deficits, delayed tremor onsets and improved survival of mice (p. 66, paragraph 2).

WO 2006/133164 (**D3**) describes agonist anti-TrkB antibodies that bind to human and mouse TrkB (p. 2, l. 28-29, p. 4, l. 19-23, p. 35, table 2). Seven TrkB antibodies increased significantly neurite outgrowth with efficacies superior to BDNF (p. 37, l. 16-23, fig. 5A and 5B). Antibody 17D11 recognizes loop-3 of the IgG-2 segment of human TrkB (KNEYGKD, amino acids 364-370 of SEQ ID No 1 of **D3**) (which correspond to amino acids 333-339 of SEQ ID No 54 of present application) and loop-1 of IgG-2 segment of human TrkB (KGNPKP amino acids 308-313 of SEQ ID No 1 of **D3**) (p. 47, l. 26- p. 48, l. 2) (which correspond to amino acids 277-382 of SEQ ID No 54 of present application). Antibodies 29D7, 7F5, 11E1 and 19E12 all recognize loop-3 of the IgG-1 segment of human TrkB (ENLVGED, amino acids 269-275 of SEQ ID No 1 of **D3**) and may also recognize loop-1 of the IgG-1 segment (AGDPVP, amino acids 221-226 of SEQ ID No 1 of **D3** (which correspond to amino acids 238-244 and 190-195 of SEQ ID No 54 of present application, respectively) (p. 48, l. 7-14).

WO 2017/019907 (**D4**) discloses agonist anti-TrkB antibodies (p. 2- p. 3 , [0008]) that recognize an epitope comprising SEQ ID No 118 (p. 47, [00171]), which corresponds to amino acids 257-276 of SEQ ID No 54 of present application.

WO 2010/086828 (**D5**) teaches agonist anti-TrkB antibodies (p. 115, tables 6-7), for instance antibody C2, that increased survival of retinal ganglion cells in an animal model of glaucoma (p. 123, example 7).

US 2010/150914 (**D6**) teaches agonist antibody A10, which binds to the ligand binding domain and antibody C20, which does not bind to the ligand binding domain (p. 6, [0070]-[0071], p. 9, ex. 1).

WO 2012/156505 (**D7**) teaches agonist antibodies generated against the first loop of the D5 domain of the TrkB (p12, l. 4 and p. 13, l. 4-5) (corresponding to amino acids of SEQ ID No 54 of present application).

Hence, the following separate inventions or groups of inventions are not so linked as to form a single general inventive concept.

Since the antibodies disclosed in **claim 32** comprise all the 6 CDRs recited in **claim 1**, the examiner considered independent **claim 32** as part of Invention 1.

The inventions are the following:

Invention 1: **claims 1-27** and **32** (in full)

anti-TrkB antibodies comprising HDR1-3 with SEQ ID No 51-53 (definition of CDRs according to Chemical Computing Group (CCG)), 55-57 (definition of CDRs according to Kabat) or 58-60 (definition of CDRs according to Chothia) respectively and LCDR1-3 with SEQ ID No 48-50, respectively and antibodies competing for binding to TrkB with antibodies comprising in their heavy and light chain variable regions the CDRs of **claim 1**.

Invention 2: **claims 28-31** (in full)

anti-TrkB antibodies that bind to at least one amino acid residue within amino acid regions 92-112, 130-143 and /or 205-219 of the extracellular domain of human TrkB with SEQ ID No 54.

All groups of inventions have been searched in the international search report since no extra search effort was required for the additional group of inventions. The present opinion consequently relates to all groups of inventions. However, the above non-unity objections are relevant for the examination of the present application once it enters the regional/national phase.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1 **WO 2011/103667** A1 (6452728 CANADA INC [CA]; SARAGOVI HORACIO URI [CA]) 1 September 2011 (2011-09-01)

D2 **WO 2017/085035** A1 (GLAXOSMITHKLINE IP DEV LTD [GB]; GLAXOSMITHKLINE R&D COMPANY LTD [CN]) 26 May 2017 (2017-05-26)

D3 **WO 2006/133164** A2 (WYETH CORP [US]; CHO SEONGEUN [US]; GILL DAVINDER SINGH [US]; TAN XIAN) 14 December 2006 (2006-12-14)

D4 **WO 2017/019907** A1 (OTONOMY INC [US]; SARAGOVI HORACIO URI [CA]) 2 February 2017 (2017-02-02)

D5 **WO 2010/086828** A2 (RINAT NEUROSCIENCE CORP [US]; LIN CHIA-YANG [US]; CHAPARRO RIGGERS JAV) 5 August 2010 (2010-08-05)

D6 **US 2010/150914** A1 (WANG YAN [US] ET AL) 17 June 2010 (2010-06-17) cited in the application

D7 **WO 2012/156505** A1 (UNIV BASEL [CH]; HOFBAUER KARL [CH]; PETER JEAN-CHRISTOPHE [FR]) 22 November 2012 (2012-11-22)

D8 **DANIEL TODD ET AL**: "A Monoclonal Antibody TrkB Receptor Agonist as a Potential Therapeutic for Huntington's Disease", PLOS ONE, vol. 9, no. 2, 4 February 2014 (2014-02-04), page e87923, XP055339993, DOI: 10.1371/journal.pone.0087923

D9 **WO 2008/078179** A1 (RINAT NEUROSCIENCE CORP [US]; LIN CHIA-YANG [US]; LONG HUA [US]; TSAO) 3 July 2008 (2008-07-03)

D10 **CAZORLA M ET AL**: "Pharmacological characterization of six trkB antibodies reveals a novel class of functional agents for the study of the BDNF receptor", BRITISH JOURNAL OF PHARMACOLOGY, WILEY-BLACKWELL, UK, vol. 162, no. 4, 1 February 2011 (2011-02-01), pages 947-960, XP002679847, ISSN: 0007-1188, DOI: 10.1111/J.1476-5381.2010.01094.X [retrieved on 2011-01-21]

D11 **WO 2009/092049** A1 (IRM LLC; LUEHRSEN KENNETH R [US]) 23 July 2009 (2009-07-23)

Invention 1: claims 1-27 and 32 (in full)

1 Novelty (Art. 33(2) PCT)

1.1 Relating to present **claim 32**: There are numerous antibodies disclosed in the prior art as binding human TrkB, as already discussed for **D1** to **D7** (see below). The applicant has not demonstrated that said antibodies lack cross-reactivity with the claimed antibodies, let alone shown that the epitope of the

claimed antibodies is different from the epitopes of the prior art antibodies. In the absence of any such evidence, the novelty of **claim 32** cannot be acknowledged.

1.2 The prior art documents at hand do not disclose an anti-TrkB antibody comprising the 6 CDRs as disclosed in present independent **claim 1**, or its use in medicine. Therefore, the subject matter of **claims 1-27** is novel (**Art. 33(2) PCT**).

2 Inventive Step (Art. 33(3) PCT)

2.1 **D1** may be considered to represent the closest prior art document for the subject matter of **claim 1**. Alternatively, any of **D2** to **D7** are suitable as the closest prior art document.

2.2 The subject matter of **claim 1** differs from **D1** in that the **CDR** sequences are different.

2.3 There does not appear to be a technical effect associated with this difference, since the properties of CDRs outside the context of a full-length light and heavy chain antibody (or antibody antigen-binding domain) have not been demonstrated in present application. It is common knowledge that the framework regions, in addition to the CDRs, affect affinity and avidity. Furthermore, it is widely recognized, especially in case of recognition of conformational epitopes, that antibody framework regions are required for proper paratope structure and antibody binding, and complete functional paratopes are formed only when CDR and framework regions are structurally organized into VH and VL domains that together form a functional binding unit.

2.4 The objective technical problem may thus be regarded as the provision of an alternative anti-TrkB antibody.

2.5 The procedure to obtain, screen and produce monoclonal antibodies specifically recognizing well known proteins such as TrkB, is considered routine procedure for the skilled artisan. Therefore, the production of monoclonal antibodies directed against TrkB is considered to represent a routine procedure (see for example **D1-D7**) and, in the absence of evidence to the contrary, the antibodies as defined in the claims do not solve a previously unforeseeable technical problem and do not lead to an unexpected and surprising technical effect.

2.6 It is considered that the presence of a prior art antibody and the common knowledge which guides the skilled person to produce similar ones, having similar functional properties, is in general sufficient to deny inventive step, in spite of noticeable structural differences at CDR level and/or framework or constant region level. It is true that structure can support inventive step (e.g. particularly original constructs such as bi-functional antibodies whose structure is not derivable from the prior art). However, manipulation of residues at the variable binding regions and/or other regions are usually not enough to acknowledge inventive step unless the differences give rise to an unexpected technical effect.

2.7 Therefore, the subject matter of **claims 1-27** does not involve an inventive step in view of **D1**, or any of **D2-D7**, and common general knowledge (**Art. 33(3) PCT**).

2.8 It might be possible to recognise inventive step for the antibodies for which a technical effect has been shown, provided the applicant can show that this technical effect cannot be observed with the antibody of the closest prior art and is, therefore, surprising. In this context, it would be helpful if the applicant could explain the advantages linked to the antibodies of the present application versus the antibodies described in the prior art **D1-D7**.

2.9 **Claim 1** encompasses antibodies that have the 3 CDRs of the VL and the 3 CDRs of the VH in all possible configurations, since the notation of features (such as L-CDR-1) within parenthesis means that these features are optional, i.e. that they are not necessarily part of the claimed subject-matter and as such they do not limit the scope of protection. Importantly the application does not teach any other antibodies comprising these CDRs in other configurations, leading to a lack of support (**Art. 6 PCT**).

2.10 Even if **claim 32** was considered novel, it would not be regarded as involving an inventive step for the following reasons. There are not effects associated with the antibodies of **claim 32**. They do not have to exhibit any of the activities attributed to or shown for defined antibodies disclosed in the application, since the antibodies may compete and yet do not share functional properties. For instance, the antibodies may bind overlapping epitopes, or even distinct epitopes and merely sterically hinder binding of each other.

Invention 2: **claims 28-31** (in full)

3 **Novelty (Art. 33(2) PCT)**

3.1 **D1** discloses agonist anti-TrkB antibodies, such as antibody mAb1D7, which binds to the extracellular D2-D3 domain with SEQ ID No 4, which corresponds to amino acids 56-170 of SEQ ID No 54 of present application (p. 30, l. 3-5, l. 12-18). mAb 1D7 conferred significant neuro-protection (p. 33, l. 14-19) and retinal ganglion cell survival in glaucoma (p. 32-33, example 3) and maintained retinal structures in glaucoma and optic nerve axotomy (p. 34, example 5).

D1 anticipates the subject matter of **claims 28-29** (**Art. 33(2) PCT**).

D8 describes commercially available anti-TrkB antibodies47/TrkB, mAb 38B8 and mAb 29D7 directed against the extracellular region of human TrkB, which show partial antagonistic, partial agonistic or agonistic activity (p. 5, table 1). Antibodies 38B8 and 29D7 protect primary striatal neurons from mHTT-induced cell death (p. 5, left col., paragraph 2-right col., paragraph 1).

D9 discloses the TrkB agonist antibody 38B8 (p. 38, ex. 6), which was effective in reducing morbidity in autoimmune disease (p. 39, ex. 7).

D10 teaches three commercial agonist (pAb-UB1, pAb-SA3 and mAb-AA7) and two commercial antagonist antibodies (mAb-BD5 and pAb-BD5) binding to the extracellular domain of TrkB (p. 953, table 2, p. 959, left col., paragraph 2).

D11 discloses agonist anti-TrkB antibodies derived from originating monoclonal antibody A10F18.2 (p. 43, example 1, p. 51, [0189]-[0190]).

Since it cannot be excluded beyond reasonable doubt that the antibodies of **D1, D8, D9, D10** or **D11** bind to at least one amino acid residues within the amino acid regions as recited in present **claims 28-31**, the novelty of said claims cannot be presently acknowledged.

It is noted that the burden of proof to show that the antibodies described in the prior art do not bind to the claimed epitope lies with the applicant. It was the applicant's choice to define the antibody by the parameter of binding to the same epitope. This parameter is new and cannot be considered to be a usual parameter, therefore the burden of proof cannot be shifted to the search/examining division.

4 Inventive Step (Art. 33(3) PCT)

In case the applicant submits a new set of claims overcoming the above objections under **Art. 33 PCT**, the subject matter of **claims 28-31** does not appear to involve an inventive step within the meaning of **Art. 33(3) PCT**, the reasons being following:

Claims 28-31 aim at providing anti-TrkB antibodies, which can be either agonists or antagonists (or neutral in their function), and bind to at least one amino acids within the claimed amino acid stretches of the extracellular region of human TrkB.

There does not appear to be a technical effect of the claimed antibodies to the antibodies of **D1** or any of **D8-D11**.

The objective technical problem would be regarded as the provision of alternative anti-TrkB antibodies.

The procedure to obtain, screen and produce monoclonal antibodies specifically recognizing well known proteins such as TrkB, is considered routine procedure for the skilled artisan. Therefore, the production of monoclonal antibodies directed against TrkB is considered to represent a routine procedure (see for example **D1, D8-D11**) and, in the absence of evidence to the contrary, the antibodies as defined in the claims do not solve a previously unforeseeable technical problem and do not lead to an unexpected and surprising technical effect.

Therefore, the subject matter of **claims 28-31** does not involve an inventive step (**Art. 33(3) PCT**).

Re Item VIII

5 **Certain observations on the international application**

5.1 **Claims 15-19** relate to subject-matter considered by this Authority to be covered by the provisions of **Rule 39.1(iv) / 67.1(iv) PCT**:

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 15-19** has been assessed on the basis of a purpose-limited product claim taking into account the alleged effects of the compound/composition.

5.2 **Claim 21** is unclear as it appears to be a product claim, however refers to the route of administration (i.e. relating to a medical use).

5.3 **Claims 28-31** are directed to anti-TrkB antibodies characterized by functional epitopes comprising residues which appear to be part of a conformational epitope. The present application however does not disclose how to produce antibodies against a conformational epitope comprising the recited residues of TrkB. The application uses standard methods for producing monoclonal antibodies, but does not disclose any methods to produce antibodies against a three-dimensional epitope comprising the recited residues. While preparing an antibody that binds a continuous amino acid sequence is well-known in the art and routine, preparation of an antibody that binds to a conformational epitope is not conventional. Thus, the provision of antibodies binding to defined residues of a conformational epitope would require extensive screening of newly isolated antibodies, followed by epitope mapping which is considered to represent an undue burden (**Art. 5 PCT**).

5.4 Contrary to the requirements of Rule 5.1(a)(ii), PCT, the relevant background art disclosed in **D1-D5, D7** and **D8-D11,** is not mentioned/discussed in the description, nor are these documents identified therein (Guidelines 4.05).

5.5 In a later European regional phase objections might be raised against any expression within the description such as "...incorporated by reference..." as the regional patent law requires that the application is self-contained.