

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

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/EP2022/080020

International filing date (day/month/year)
26.10.2022

Priority date (day/month/year)
28.10.2021

International Patent Classification (IPC) or both national classification and IPC
INV. C12N15/86 A61P1/00

Applicant
UCB BIOPHARMA SRL

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:



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Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

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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.
 - 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. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43bis.1 and 64.1) is the claimed priority date.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.
3. Additional observations, if necessary:

see separate sheet

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 | |
| | No: Claims | <u>1-16</u> |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | <u>1-16</u> |
| Industrial applicability (IA) | Yes: Claims | <u>1-16</u> |
| | No: Claims | |
2. Citations and explanations
- see separate sheet**

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)
and / or
2. Non-written disclosures (Rules 43*bis*.1 and 70.9)
see form 210

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

Reference is made to the following documents:

- D1 WO 2018/187363 A1 (ENCODED THERAPEUTICS INC [US]) 11 October 2018 (2018-10-11)
- D2 WO 2010/020642 A1 (BRAINCO BIOPHARMA S L [ES]; GUERRERO MARTINEZ MARIA JOSE [ES] ET AL.) 25 February 2010 (2010-02-25)
- D3 WO 2009/084472 A1 (PUBLIC UNIVERSITY CORP YOKOHAM [JP]; MATSUMOTO NAOMICHI [JP] ET AL.) 9 July 2009 (2009-07-09)
- D4 WO 2022/011390 A1 (BAYLOR COLLEGE MEDICINE [US]) 13 January 2022 (2022-01-13)
- D5 WO 2022/214635 A1 (STICHTING VU [NL]) 13 October 2022 (2022-10-13)
- D6 WO 2021/089856 A1 (HORAMA [FR]) 14 May 2021 (2021-05-14)

The present application concerns a nucleic acid encoding a syntaxin binding protein 1 (STXBP1) isoform as well as adeno-associated virus (AAV) vectors comprising the nucleic acid for use in the treatment of early onset epileptic encephalopathies.

Re Item II:

The current assessment is based on the assumption that all claims enjoy the priority rights from the filing date of the priority document (28.10.2021), i.e. D4 and D5 mentioned in the International Search Report (ISR) as P-documents are not taken into account. D4 and D5 might become relevant in the regional phase as conflicting earlier documents.

Re Item IV:

The application does not comply with the requirements of unity (**Article 34(3), Rule 13 PCT**) since the eight groups of subinventions mentioned in the International Search Report (ISR) are not so linked as to form a single general inventive concept.

The only concept which is common to all compounds of claim 1 is the provision of a nucleic acid encoding a STXBP1 isoform. Said concept is neither novel nor inventive since nucleic acids encoding STXBP1 and comprising e.g. SEQ ID NO. 7 of the present application as well as their use in AAV vectors for gene therapy are already known (e.g. D1-D3, see item 2).

The common matter of all groups of claims including its technical effect is thus known from the prior art and cannot comprise a single general inventive concept based on same or corresponding special technical features.

The technical problem underlying all groups of subinventions is formulated as the provision of a further nucleic acid encoding a STXBP1 isoform which may be inserted into a viral vector and used in therapy. The application solves this technical problem by providing different transcript variants encoding eight different STXBP1 isoforms.

The technical feature representing the difference over the non-inventive common matter mentioned above is the individual STXBP1 isoform sequence. Each specific feature may have the potential to make a contribution over the prior art but is not common to all claimed inventions and therefore cannot provide the required technical relationship.

In view of the different structures and properties of said STXBP1 sequences, it is not apparent which is the common same or corresponding special technical feature among the eight specified sequences defining an inventive contribution over the above mentioned prior art.

As a consequence, each of the eight subgroups of claims listed in the International Search Report has to be regarded as a separate invention, even if they could be searched as a whole without unreasonable extra effort.

NB: The naturally-occurring variants of claim 1.iii are considered as being covered by the definitions of claim 1.ii. Otherwise, an individual subgroup would had to be formulated for each of the variants shown in table 7.

Re Item V:

- 1 D1 discloses AAV or lentiviral vectors encoding STXBP1 for selective expression in the CNS in order to treat e.g. epilepsy or Dravet syndrome. In particular, an AAV9 vector with AAV2 ITRs is disclosed which comprises regulatory elements resulting in selective transgene expression in parvalbumin neurons. Control vectors comprise the transgene under control of e.g. a CAG promoter (D1, e.g. claims, examples, paragraph [00173], [0191]). The expression cassette may further contain e.g. a hSynI promoter or a SV40 polyA signal (D1, e.g. paragraph [0090]). The STXBP1 protein with SEQ ID NO. 40 of D1 (GSP:BFS85876) is e.g. 100% identical in a 603 aa overlap to SEQ ID NO: 9 of the present application, 99.14 % identical in a 583 aa overlap to SEQ ID NO: 10 of the present application, 98.46 % identical in a 583 aa overlap to SEQ ID NO: 11 of the present application, 100 % identical in a 589 aa overlap to SEQ ID NO: 12 of the present application, 99.12 % identical in a 569 aa overlap to SEQ ID NO: 13 of the present application, 100 % identical in a 568 aa overlap to SEQ ID NO: 14 of the present application, 100 % identical in a 567 aa overlap to SEQ ID NO: 15 of the present application and 94.03 % identical in a 603 aa overlap to SEQ ID NO: 16 of the present application. D1 is novelty-destroying for claims 1, 4-16.

D2 discloses a mouse model expressing human STXBP1 under control of a brain-specific promoter, in particular under control of an EAAT3 promoter which is specific for glutamatergic neurons (D1, e.g. claims, examples). The human STXBP1 transcript variant 1 with SEQ ID 3 of D2 (GSN:AXV66348) is e.g. 100 % identical in a 1812 bp overlap to SEQ ID NO: 7 of the present application, 100 % identical in a 3868 bp overlap to SEQ ID NO: 22 of the present application, 100 % identical in a 3716 bp overlap to SEQ ID NO: 25 of the present application, 100 % identical in a 3716 bp overlap to SEQ ID NO: 26 of the present application, 100 % identical in a 1925 bp overlap to SEQ ID NO: 27 of the present application or 100 % identical in a 1925 bp overlap to SEQ ID NO: 28 of the present application. The human STXBP1 protein sequence with SEQ ID 4 of D2 (GSN:AXV66349) is e.g. 100 % identical in a 594 aa overlap to SEQ ID NO: 10 of the present application, 99.14 % identical in a 583 aa overlap to SEQ ID NO: 9 of the present application, 99.33 % identical in a 594 aa overlap to SEQ ID NO: 11 of the present application, 99.12 % identical in a 569 aa overlap to SEQ ID NO: 12 of the present application, 100 % identical in a 580 aa overlap to SEQ ID NO: 13 of the present application, 100 % identical in a 568 aa overlap to SEQ ID NO: 14 of the present application, 100 % identical in a 567 aa overlap to SEQ ID NO: 15 of the present application and 92.97 % identical in a 583 aa overlap to SEQ ID NO: 16 of the present application. D2 is novelty-destroying for claims 1-3 and 5.

D3 discloses nucleic acids encoding STXBP1 isoforms (D3, e.g. sequences). The human STXBP1 variant 1 gene with SEQ ID 1 of D3 (GSN:AXD39428) is 100 % identical in a 1812 bp overlap to SEQ ID NO. 7 of the present application. The human STXBP1 variant 1 protein with SEQ ID NO. 2 of D3 (GSP:AXD39429) is e.g. 100 % identical in a 603 aa overlap to SEQ ID NO. 9 of the present application. The human STXBP1 variant 2 protein with SEQ ID NO. 4 of D3 (GSP:AXD39431) is e.g. 100 % identical in a 594 aa overlap to SEQ ID NO. 10 of the present application. The human STXBP1 sequence with SEQ ID 65 of D3 (GSN:AXD39492) is 100 % identical in a 1925 bp overlap with e.g. SEQ ID NO: 22 of the present application. D3 is novelty-destroying for claims 1-3 and 5

None of claims 1-16 thus meets the requirements of **Article 33(2) PCT**.

- 2 Any document disclosing a nucleic acid construct encoding a STXBP1 isoform, for example any of D1-D3, is equally suitable as closest prior art.

The technical problem is formulated as the provision of further nucleic acids encoding STXBP1 isoforms. The application solves this problem by providing STXBP1 isoforms consisting of SEQ ID NOS: 9-16 or being encoded by SEQ ID NOS: 7 or 22-33. Said nucleic acids are inserted into AAV vectors for use in the gene therapy of disorders associated with severe early onset epileptic encephalopathies.

2.1 Claims 1-16 are neither novel nor inventive in view of D1-D3.

2.2 In general, the provision of just another STXBP1 isoform and/or encoding nucleotide for use in viral vector-mediated gene therapy is not inventive *per se*.

Since it is known that AAV or lentiviral vectors encoding STXBP1 can be used for selective expression in the CNS in order to treat e.g. epilepsy or Dravet syndrome (e.g. D1) and since the various isoforms of STXBP1 are generally known, a skilled person would obtain with a reasonable expectation of success products close or identical to those claimed in the present application by use of routine techniques. The arbitrary selection of STXBP1 proteins comprising a sequence selected from SEQ ID NO: 9-16 as protein of interest is merely one of several straightforward possibilities from which the skilled person would select without the exercise of inventive skill, in order to solve the problem posed.

Preparing such a polypeptide, generating encoding nucleic acids, insertion said encoding nucleic acids into a viral vector as well as its use for the treatment of e.g. epilepsies is considered as routine technique for a skilled person. It would be obvious to the person skilled in the art, namely when the same result is to be achieved, to apply these features with corresponding effect to a STXBP1 isoform comprising any of SEQ ID NOS: 9-16.

2.3 The dependent claims do not appear to contain any additional features which, in combination with the features of any claim to which it refers, justify the acknowledgement of an inventive step. Features like using CNS-specific promoters, SV40 polyadenylation signals, AAV2 3' and 5' ITRs or AAV serotypes with CNS tropism are modifications which are within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can be readily contemplated in advance.

For example, D6 discloses AAV vectors for transducing a cell in the CNS. The transgene may be STXBP1, the AAV vectors may be for the treatment of e.g. Ohtahara syndrome, West syndrome or Dravet syndrome. The promoter may

be selected e.g. from hSyn, MECP3, hNSE or CamKII promoters. The vector may be an AAV9 vector and/ or may comprise AAV2 ITRs (D6, e.g. claims, examples, page 32, line 1-16).

- 2.4 Finally, the examples do not disclose any surprising and reproducible technical effect for the specific STXBP1 nucleic acids of claim 1 or 2. The examples only use STXBP1 proteins comprising SEQ ID NO. 9 or 10 which were already used in D1. No unexpected effect is shown for proteins comprising or consisting of SEQ ID NO. 11-16 which are therefore considered as arbitrary alternatives.

To establish inventive activity, the provision of a sequence must be justified by the technical purpose, i.e. by a hitherto unknown or unexpected technical effect, caused by those technical features which distinguish the claimed protein from those available from the closest prior art.

- 2.5 Consequently, claims 1-16 are not considered as involving an inventive step (**Article 33(3) PCT**) in view of e.g. D1 in combination with D6 and/or general knowledge, even if the above mentioned objections as to lack of novelty are not taken into account.

- 3 Claims 15 and 16 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.

Re Item VIII:

- 4 Claim 1.iii is neither sufficiently disclosed nor technically supported over its whole scope (**Article 5/6 PCT**). The only naturally-occurring STXBP1 variants which are disclosed in the application are the specific variants of table 7.
- 5 The present application only provides adequate guidance to use AAV vectors as ITR-containing viral vectors. The teaching from the examples cannot be extrapolated to any other viral vector. Hence, the present specification fails to technically support the whole area claimed. Claims 6-9 and 12-16 are neither enabled (**Article 5 PCT**) nor technically supported by the description (**Article 6 PCT**) since their scope is broader than justified by the description and drawings.
- 6 The wording "...*retaining functionality as STXBP1*..." in claim 1.ii is open to interpretation and thus unclear (**Article 6 PCT**). Any protein can exhibit non-specific biological activities, e.g. it can function as an antigen. Moreover, a residual functionality may be found in pathogenic STXBP1 mutants. As a

consequence, the pathogenic or likely pathogenic variants of tables 5 and 6 are considered as falling under the definitions of claim 1.ii. It is however unclear, how a pathogenic variant might be used for gene therapy.

- 7 The subject-matter of claims 13, 15 and 16 is unclear since it is open to interpretation which specific disorders are associated with severe early onset epileptic encephalopathy, loss of STXBP1 functional activity or associated with any pathological STXBP1 variant (**Article 6 PCT**).