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/IB2020/053688	17.04.2020	17.04.2019

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/675 A61K31/4045 A61P1/00 A61P25/16 A61P25/30 A61P25/00 A61P25/06 A61P25/22

Applicant
COMPASS PATHWAYS LIMITED

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/IB2020/053688

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. 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 43*bis*.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 43*bis*.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:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 107-110, 112-116, 118-125(completely); 111, 128-162(partially)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international search *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 107-110 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 112-116, 118-125(completely); 107-111, 128-162(partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☒ See Supplemental Box for further details

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. 1-106, 117, 126, 127(completely); 107-111, 128-162(partially)

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	13-15, 19, 23, 24, 28-31, 34-58, 61, 69-73, 75, 81, 85, 95-97, 99, 100, 102, 106(completely); 130-138, 140, 141, 145-162(partially)
	No:	Claims	1-12, 16-18, 20-22, 25-27, 32, 33, 59, 60, 62-68, 74, 76-80, 82-84, 86-94, 98, 101, 103-105, 117, 126, 127(completely); 111, 128, 129, 139, 142-144(partially)
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-106, 117, 126, 127(completely); 111, 128-162(partially)
Industrial applicability (IA)	Yes:	Claims	1-106, 117, 126, 127(completely); 111, 128-162(partially)
	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

Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT; see also Item IV).

2. In accordance with Article 6 PCT, the claims must define the matter of which protection is sought, in particular Rule 6.2(a) states that claims shall not rely on references to the description or drawings. **Thus no opinion will be given for claims 107-110.**

Item IV

Lack of unity of invention

3.The requisite unity of invention (Rule 13.1 PCT) appears to be lacking in the present application.

The problems posed within the present application are the following:

1. Method of treating depression (claims 1-106).

2. Method of treating Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Premenstrual Dysphoric Disorder, Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition, Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, SubstanceMedication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder, Post-Traumatic Stress Disorder (PTSD), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder, Substance/ Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder), Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache, Dysphasia, Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder, Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, or Kleptomania (claim 111).

3. Method of treating Neurocognitive Disorders due to Alzheimer's, Lewy Bodies, Traumatic Brain Injury, Prion Disease, HIV Infection, Parkinson's, or Huntington's; concussion; chronic traumatic encephalopathy (CTE); Language Disorder, Speech Sound Disorder (Phonological Disorder); Childhood-Onset Fluency Disorder (Stuttering); Social (Pragmatic) Communication Disorder;

Tourette's Disorder; Persistent (Chronic) Motor or Vocal Tic Disorder; Amnestic Disorder Due to Known Physiological Condition; Transient Cerebral Ischemic Attack, Cerebral Infarction, Cerebral Bleeding, Progressive Supranuclear Ophthalmoplegia, or Retrograde Amnesia (claim 112)

4. Method of treating Autism Spectrum Disorder, or Antisocial Personality Disorder (claim 113)

5. Method of treating Attention-Deficit/Hyperactivity Disorder, Other Specified Attention-Deficit/Hyperactivity Disorder; or Unspecified Attention-Deficit/Hyperactivity Disorder (claim 114)

4. Method of treating Schizotypal (Personality) Disorder, Delusional Disorder, Schizophrenia, or Schizoaffective Disorder (claim 115)

5. Method of treating Female Sexual Interest/Arousal Disorder, Male Hypoactive Sexual Desire Disorder, or Excessive Sexual Drive (claim 116)

6. Method of treating Bipolar I Disorder, Bipolar II Disorder, or Cyclothymic Disorder (claim 117)

7. Method of treating Insomnia Disorder, Hypersomnolence Disorder, Narcolepsy, or Primary Central Sleep Apnea (claim 118)

8. Method of treating Schizoid Personality Disorder, Schizotypal Personality Disorder, Antisocial Personality Disorder, Borderline Personality Disorder, or Obsessive-Compulsive Personality Disorder (claim 119)

9. Method of treating age-related hearing loss or tinnitus (claim 120)

10. Method of treating Multiple Sclerosis, Cranial Nerve Disorder, Neuromyelitis Optica, Bell's Palsy, Guillain Barre Syndrome, Demyelinating Disease of Central Nervous System, or Chronic Inflammatory Demyelinating Polyneuritis (claim 121)

11. Method of treating pain (claim 122)

12. Method of treating Myelopathy, Traumatic Brain Injury, Intellectual Disabilities, Mania, Neurodegeneration, Paraphilic disorders, Suicidal Behavior Disorder, Nonsuicidal Self-Injury, Persistent Complex Bereavement Disorder, GI Tract Related Diseases, Epilepsy, Sickle Cell Disease, locked-in syndrome, restless leg syndrome, stroke, or Amyotrophic Lateral Sclerosis (ALS) (claim 123)

13. Method of improving in cognition (claim 124)

14. Method of treating Treatment Resistant Depression (TRD) (claim 126)

15. Method of treating Major Depressive Disorder (MDD) (claim 127)

16. Method of providing a dosage form comprising psilocybin in the form of Polymorph A (claim 145).

4. Carhart-Harris et al (2016;2018) report that psilocybin showed efficacy in treatment-resistant major depression combined with psychological support.

WO2018135943 is directed to the combination of psilocybin and cannabidiol for treating depression and bipolar I and II disorders. Example 1 provides data when psilocybin is administered alone. It is disclosed that some patients reported improved mood after administration of psilocybin alone at 30mg.

De Veen et al provides an overview of the existing and potential therapeutic role of psilocybin for treating substance use disorders. Several references are made to findings on the use of psilocybin in treating e.g. alcohol and tobacco dependence.

WO2018148605 discloses the use of two psilocybin derivative for treating depressive disorders, addiction, obsessive compulsive disorder, anxiety disorders.

Kaelen et al discloses that patients with treatment-resistant major depressive disorder treated with psilocybin showed reductions in depression when combined with music therapy.

Sewell et al investigated the response of cluster headache to psilocybin. A positive effect is reported in patients with chronic cluster headache with either an improvement or termination.

5. Accordingly, some of the above mentioned problems appear to be already solved in the prior art.

The ISA is unable to find/identify ANY NOVEL INVENTIVE CONCEPT linking the problems identified in the sense of Rule 13.2 PCT.

6. The present application is therefore considered to cover at least the following 15 different subject matters (NB some problems have been linked together for convenience):

1. claims: 1-106, 117, 126, 127(completely); 107-111, 128-162(partially)

   Method of treating depression,Disruptive Mood Dysregulation Disorder, Major Depressive Disorder (MDD), Bipolar I Disorder, Bipolar II Disorder, or Cyclothymic Disorder;Treatment Resistant Depression, Persistent Depressive Disorder (Dysthymia), Substance/Medication-Induced Depressive Disorder, Post-Partum depression, or Depressive Disorder due to Another Medical Condition comprising administering an effective amount of psilocybin or an active metabolite thereof

2. claims: 107-111, 128-162(all partially)

Method of treating Separation Anxiety Disorder, Selective Mutism, Specific Phobia, Social Anxiety Disorder (Social Phobia), Panic Disorder, Panic Attack, Agoraphobia, Generalized Anxiety Disorder, Substance Medication-Induced Anxiety Disorder, Anxiety Disorder Due to Another Medical Condition, Somatic Symptom Disorder, Illness Anxiety Disorder (hypochondriac), Adjustment Disorders, Acute Distress Disorder, Obsessive-Compulsive Disorder, Body Dysmorphic Disorder, Substance/Medication-Induced Obsessive-Compulsive and Related Disorder, Obsessive-Compulsive and Related Disorder due to Another Medical Condition, Post-Traumatic Stress Disorder (PTSD), Hoarding Disorder, Trichotillomania (Hair-Pulling) Disorder, Excoriation (Skin-Picking) Disorder,Conversion Disorder (Functional Neurological Symptom Disorder), Factitious Disorder comprising administering an effective amount of psilocybin or an active metabolite thereof

3. claims: 107-111, 128-162(all partially)

Method of treating treating Substance-Related Disorders, Alcohol-Related Disorders, Cannabis-Related Disorders, Hallucinogen-Related Disorders, Inhalant-Related Disorders, Cocaine-Related Disorders, Opioid-Related Disorders, Sedative-, Hypnotic-, or Anxiolytic-Related Disorders, Stimulant-Related Disorders, Tobacco-Related Disorders, Non-Substance-Related Disorders (Gambling or Gaming Disorder) comprising administering an effective amount of psilocybin or an active metabolite thereof

4. claims: 107-111, 128-162(all partially)

Method of treating Migraines, Cluster Headaches such as Chronic Cluster Headaches, Cyclical Vomiting, Tension-Type Headache comprising administering an effective amount of psilocybin or an active metabolite thereof

5. claims: 107-111, 128-162(all partially)

Method of treating Pica, Anorexia Nervosa, Bulimia Nervosa, Binge-Eating Disorder comprising administering an effective amount of psilocybin or an active metabolite thereof

6. claims: 107-111, 128-162(all partially)

Method of treating Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Antisocial Personality Disorder, Psychopathy, Pyromania, or Kleptomania comprising administering an effective amount of psilocybin or an active metabolite thereof

7. claims: 113, 114, 118(completely); 107-112, 123, 128-162(partially)

Method of treating Neurocognitive Disorders due to Alzheimer's, Lewy Bodies, Traumatic Brain Injury, Prion Disease, HIV Infection, Parkinson's, or Huntington's; Language Disorder, Dysphasia (laguage disorder from brain disease or damage); Speech Sound Disorder (Phonological Disorder); Childhood-Onset Fluency Disorder (Stuttering); Social (Pragmatic) Communication Disorder; Tourette's Disorder; Persistent (Chronic) Motor or Vocal Tic Disorder; Amnestic Disorder Due to Known Physiological Condition; Retrograde Amnesia; Insomnia Disorder, Hypersomnolence Disorder, Narcolepsy, or Primary Central Sleep Apnea.; Intellectual Disabilities; Suicidal

Behavior Disorder, Nonsuicidal Self-Injury, Persistent Complex Bereavement Disorder; Epilepsy or Amyotrophic Lateral Sclerosis (ALS); Autism Spectrum Disorder or Antisocial Personality Disorder; Attention-Deficit/ Hyperactivity Disorder, Other Specified Attention-Deficit/Hyperactivity Disorder; or Unspecified Attention-Deficit/ Hyperactivity Disorder comprising administering an effective amount of psilocybin or an active metabolite thereof

8. claims: 107-110, 112, 123, 128-162(all partially)

Method of treating concussion; chronic traumatic encephalopathy (CTE); Transient Cerebral Ischemic Attack, Cerebral Infarction, Cerebral Bleeding; Progressive Supranuclear Ophthalmoplegia; stroke ; Traumatic Brain Injury, Neurodegeneration, locked-in syndrome comprising administering an effective amount of psilocybin or an active metabolite thereof

9. claims: 115, 119(completely); 107-110, 123, 128-162(partially)

Method of treating Schizotypal (Personality) Disorder, Delusional Disorder, Schizophrenia, or Schizoaffective Disorder; Schizoid Personality Disorder, Schizotypal Personality Disorder, Antisocial Personality Disorder, Borderline Personality Disorder, Obsessive-Compulsive Personality Disorder; Mania comprising administering an effective amount of psilocybin or an active metabolite thereof

10. claims: 116(completely); 107-110, 123, 128-162(partially)

Method of treating Female Sexual Interest/Arousal Disorder, Male Hypoactive Sexual Desire Disorder, or Excessive Sexual Drive; Paraphilic disorders comprising administering an effective amount of psilocybin or an active metabolite thereof

11. claims: 120(completely); 107-110, 128-162(partially)

Method of treating age-related hearing loss or tinnitus comprising administering an effective amount of psilocybin or an active metabolite thereof

12. claims: 121(completely); 107-110, 123, 128-162(partially)

Method of treating Multiple Sclerosis, Cranial Nerve Disorder, Neuromyelitis Optica, Bell's Palsy, Guillain Barre Syndrome, Demyelinating Disease of Central Nervous System, or Chronic Inflammatory Demyelinating Polyneuritis; Myelopathy, comprising administering an effective amount of psilocybin or an active metabolite thereof

13. claims: 107-110, 123, 128-162(all partially)

Method of treating GI Tract Related Diseases, Sickle Cell Disease, restless leg syndrome comprising administering an effective amount of psilocybin or an active metabolite thereof

14. claims: 122(completely); 107-110, 128-162(partially)

Method of treating pain administering an effective amount of psilocybin or an active metabolite thereof

15. claims: 124,125 (completely); 107-110, 128-162(partially)

Method of treating a subject to improve cognition comprising administering an effective amount of psilocybin or an active metabolite thereof

Searching of the additional 14 inventions would require a significant additional searching effort.

7. The present written opinion will cover the first identified subject matter, namely claims 1-106, 126, 127(completely); 107-111, 128-162(partially)

Item V

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

8. Claims 1-106,111,126-144 relate to a subject-matter considered by this Authority to be covered by the provision 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 tothe 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.

9.The documents cited in the International Search Report are consecutively numbered D1-D9 in this communication;this numbering will be adhered to in the rest of the procedure. The cited passage(s) for each citation will be considered unless otherwise specified.

Novelty (Article 33(2) PCT)

10.The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,7-12,16-18,20,26,32,33,59,60,62-65,67, 74,76-79,111, 126-129,142-144 are not new in the sense of Article 33(2) PCT vis-a-vis D1.

Carhart-Harris et al (2016) reports that psilocybin showed efficacy in treatment-resistant major depression combined with psychological support.

11. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,7-12,16-18,20,21,32,33,59,60, 62-65,67,74,76, 77,78-80,82-84,86-92,94,98,101,103-105,111,126-129,142-144 are not new in the sense of Article 33(2)PCT vis-a-vis D2.

Carhart-Harris et al (2018) reports efficacy at 6 months.

12. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-6,8,9,20,32,33,59,60,63-68,74,77-79, 111,117, 128,129 are not new in the sense of Article 33(2) PCT vis-a-vis D3.

WO2018135943 is directed to the combination of psilocybin and cannabidiol for treating depression and bipolar I and II disorders. Example 1 provides data when psilocybin is administered alone. It is disclosed that some patients reported improved mood after administration of psilocybin alone at 30mg.

The wording of claim 1 "comprising" does not exclude further active agents being present in the composition.

13.The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-4,8,9,21,22,32,33,59,64,65, 78,79,127-129,139 are not new in the sense of Article 33(2) PCT vis-a-vis D4.

WO2018148605 discloses the use of two psilocybin derivative for treating depressive disorders including bipolar, major depressive, premenstrual dysphoric disorders. A further antidepressant may be administered. The derivatives include psilocybin itself and the metabolite psilocin.

14. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,7-11,21,25,26,27,32,33,59,60,62, 63,64,65,67,74,76-80,82-84,86-94,111,126-129 are not new in the sense of Article 33(2) PCT vis-a-vis D5.

Kaelen et al discloses that patients with treatment-resistant major depressive disorder treated with psilocybin showed reductions in depression when combined with music therapy.

15. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-3,7-11,32,33,59,111,126-129 are not new in the sense of Article 33(2) PCT vis-a-vis D6.

Patra et al concerns the use of psilocybin for treatment resistant depression and refers to other literature disclosing other therapeutic effects such as reducing suicidal thoughts, Phase II studies on treating obsessive compulsive disorders, depressive disorders and substance abuse. In addition, Patra et al. discloses the inhibitory effect of psilocybin on amygadal.

16. The remaining claims 13-15, 19, 23, 24, 28-31, 34-58, 61, 69-73, 75, 81, 85, 95-97, 99, 100, 102, 106, 130-138, 140, 141, 145-162 are considered to fulfill the requirements of Article 33(2) PCT.

De Veen et al (D7) provides an overview of the existing and potential therapeutic role of psilocybin for treating substance use disorders. Several references are made to findings on the use of psilocybin in treating e.g. alcohol and tobacco dependence.

Sewell et al (D8) investigated the response of cluster headache to psilocybin. A positive effect is reported in patients with chronic cluster headache with either an improvement or termination.

Inventive Step (Article 33(3) PCT)

17. The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 13 and 14 does not involve an inventive step in the sense of Article 33(3)PCT.

The subject matter of these claims would appear to be directed to established methods of assessing depression (cf. Patra et al)

18. The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claim 15 does not involve an inventive step in the sense of Article 33(3)PCT.

The prior art documents D1 and D2 would appear to only assess the improvement in depression after 1 week. However, in the absence of any teaching to the contrary, the skilled person could have expected an effect after 1 day. Examples 4-6 would not appear top provide any data demonstrating an unexpected effect after 1 day.

19. The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 23 and 24 does not involve an inventive step in the sense of Article 33(3)PCT.

Combination therapy is a common approach to treat disorders and the subject matter of claims 13 and 14 merely provide obvious dosing regimes without demonstrating any special technical effect in the application as filed to provide a basis for an inventive step.

20. The subject matter of claims 28-31 define patients being treated with psilocybin or active metabolite thereof already defined in the prior art, but further having a comorbidity.

Prior art documents WO2018135943 (Parkinson's and Alzheimer's disease); De Veen et (alcohol dependence); WO2018148605 (obsessive compulsive disorder, anxiety disorders) already disclose efficacy of psilocybin and psilocin against some of the morbidities claimed (non-exhaustive), therefore in the absence of data demonstrating a special technical effect, the subject matter is not considered inventive but rather an arbitrary selection based on prior art disclosures.

21. The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 61,69-73,75,140,141, does not involve an inventive step in the sense of Article 33(3)PCT.

The subject matter of these claims are directed to a dosing regime without demonstrating any special technical effect that would provide a basis for an inventive step.

22. The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 34-58,130-138 and 145-162 does not involve an inventive step in the sense of Article 33(3)PCT.

Either D1-D6 may be considered the closest prior art art.

The subject matter of claims 34-58; 130-138, and 145-162 differ in that psilocybin in the form of polymorph A is used.

The application as filed does no appear to provide any comparative or data concerning the use of psilocybin in the form of polymorph A.

Thus the objective technical problem solved by the subject-matter of claims 34-58 and 145-162 is seen as the provision of a further polymorphic form of a known compound having the same technical effect.

The biological activity of a compound depends primarily on its molecular structure. To reach this target it will be at some point in solution, e.g. in body fluids, where all differences among polymorphs disappear. The skilled person would thus expect that all polymorphs of psilocybin are useful in treating depressive disorders.

From common general knowledge it is known that the systematic investigation of a compound to determine whether it is prone to polymorphism is routine practice in the pharmaceutical industry. Furthermore, the methods for screening polymorphs are well known in the art.

The skilled person being interested in the therapeutic application of a specific compound would thus routinely screen for polymorphs of the said compound. If such routine work yields another polymorph, e.g. the present polymorph A then its provision is an obvious solution of the problem as defined above. In the absence of any substantiated unexpected properties of the claimed polymorph A, which are relevant for their technical application, in comparison with the closest related (crystalline) form of the present compound, no inventive step would be acknowledged for present polymorphs.

23. The features of dependent claims 81, 85, 95-97, 99, 100, 102, 106 are considered obvious methods of providing psychological support and remote therapeutic support with established means to implement. Thus an inventive step cannot be acknowledged for these claims in the sense of Article 33(3)PCT.

Item VI

Certain documents cited

24. Although D9 is not a document pursuant to Rule 64.1 PCT, it discloses some features of claims 1-3, 7, 8, 32-34, 36-38, 40-46, 48-53, 56-63, 111, 128-130, 132-141,145-149,160-162.

WO2019073379 provides crystalline psilocybin in the form polymorph A and formulations thereof, for treating drug resistant depression.

This document may be taken into account in the regional phase for the assessment of novelty and/or inventive step.

Item VIII

Certain observations on the international application

25. The crystal form claimed in claims 34-47,54,55,145,159 is only arbitrary defined by means of the label polymorph. However, no standard nomenclature for polymorphic crystal forms exists. It is therefore unclear which product is covered by the definition in claims (Article 6 PCT). The crystal form should be defined by reproducible physiochemical parameters. If the values of the parameters depend on the conditions under which they were measured, these conditions should be included in the wording of the claim to meet the requirements of Article 6 PCT.

26. Claim 65 is dependent upon claim 65 thus lack clarity contrary to A. 6 PCT.