Brussels, 19 May 2025

COST 039/25

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action “Psychedelic renaissance: turn on, tune in and drop in” (PSY-NET) CA24130

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action Psychedelic renaissance: turn on, tune in and drop in approved by the Committee of Senior Officials through written procedure on 19 May 2025.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA24130
PSYCHEDELIC RENAISSANCE: TURN ON, TUNE IN AND DROP IN (PSY-NET)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to (1) facilitate the creation of a network of academic institutions, scientific societies, industry, patient/caregivers organisations, advocacy groups and regulatory bodies, working on psychedelics, (2) define new directions for the use of psychedelics in therapy, identify neurobiological biomarkers and predictors of their effects, and develop recommendations for their use.. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
Given the current stagnation in developing new treatments based on traditional drugs and mechanisms in the neurosciences, the resurgence of psychedelics has opened up a new, rapidly expanding field of research into consciousness, mental disorders and their treatment. Psilocybin, LSD, DMT or MDMA have already shown efficacy in the treatment of depression, anxiety and addiction. Recent advances in neuroimaging have made it possible to understand in detail the processes behind their unique effects, and groundbreaking discoveries about the therapeutic effects of psychedelics are finding their way into the world's most prestigious journals. Despite all this, academic psychedelic research still suffers greatly from a lack of coordination at the international level in the areas of developing new molecules and formulations, understanding the underlying neurobiology from the molecular level to neuroimaging, conducting multicentre academic clinical trials, and sharing and standardising data to generate big data. At the same time, it is crucial to address the necessary adjustments to outdated regulatory frameworks to enable their wider therapeutic use. The current project aims to network academic scientific institutions from all these research areas with the pharmaceutical industry and organisations working on the reclassification of psychedelics. The aim is to create a platform for psychedelic research that will pave the way for the submission of large collaborative research projects, multicentre academic clinical trials at European level, open access data sharing, big data analysis and the conditions for the implementation of psychedelics in mental health care.

Areas of Expertise Relevant for the Action	**Keywords**
● Clinical medicine: Psychiatry ● Psychology: Neuropsychology ● Biological sciences: Biological systems analysis, modelling and simulation ● Chemical sciences: Molecular architecture and structure ● Medical biotechnology: Databases, data mining, data curation, computational modelling	● Psychedelic ● Mental disorders ● Neurobiology research ● Academic clinical trials ● Open source data sharing

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Coordination of designing of novel molecules with their pharmacodynamic properties, facilitate development of novel formulations, delivery systems or dosage/administration schemes within the psychoactive psychedelics as well as their non-psychoactive counterparts, in order to make/improve oral bioavailability, better control/titrate the intensity and duration of effects and improve compliance
● Creating guidelines and standard operational procedures for translational animal research that would have yield in a meaningful screening set of behavioural, electrophysiological and neuroimaging methods that would identify the characteristic features of psychedelics and their non-psychedelic analogues for the treatment of depression, anxiety, addiction and existential distress in palliative care
● Propose designs and protocols for novel clinical trials with psychedelics in depression, anxiety related disorders, addiction, and other neuropsychiatric conditions in order to be used in future large- scale collaborative projects. Guidelines for psychedelic assisted therapy and minimal requirements for subjects that will prescribe them.
● Create guidelines, standard operational procedures (SOPs) and recommendations for standardisation of

data collection and advanced analyses in neuroimaging studies, creation of standardised pre-processing pipelines and standardised toolboxes enabling comparable data analyses across sites.
● Coordination and facilitation of the creation of open access databases that would comprise of preclinical as well as anonymised clinical data, prepare common guidelines for creation Informed and GDPR consents that would allow data sharing, creation of web hub with access to all databases and other data.
● Work on political and regulatory domain in order to facilitate future legislative changes on EU level as well as on the United Nations level that would allow wider access to psychedelics and psychedelic assisted therapy.

Capacity Building
● Connect high-quality scientists, research institutes, scientific organisations, patient organisations, industry and regulatory bodies across Europe.
● Make recent knowledge base, technological advances, clinical experiences, drug sources available to the whole network and beyond.
● Fostering and facilitation networking of YRIs within the network and to facilitate the training under supervision of research leaders within the network and beyond.
● Fostering and facilitation of communication between researchers, regulatory authorities and industry towards maximisation of impact of the Action.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

Mental health is becoming an increasingly important societal issue. Long-term stress, such as work pressure and financial insecurity, social isolation or fear of an uncertain future, is one of the major factors that can trigger a variety of mental health problems, such as anxiety, depression and burnout. In addition, stress and mental disorders can aggravate physical health problems, such as cardiovascular problems, as well as neuropsychiatric disorders, such as Alzheimer disease.[1]

Mental disorders are the fifth leading cause of Disability-Adjusted Life Years (DALYs) [2]. According to the World Health Organization (WHO), depression alone is the fourth most common cause of disability worldwide. According to number of sources the average lifetime and 12-month prevalence of major depressive disorder (MDD) are approximately 10.8-14.6% and 5.5-7.2%, respectively [3,4], with one of the highest rates In US, where the lifetime risk of experiencing a single episode of depression is estimated to be 20% [5]. Similarly, anxiety disorders have a lifetime prevalence of 28.8%, according to National Comorbidity Survey Replication in the United States [6] and according to WHO, around 70% of people globally will experience a potentially traumatic event during their lifetime[7] with 5.6% progressing into posttraumatic stress disorder (PTSD) resulting in a cross-national lifetime prevalence of PTSD 3.9% [8].

Mental health has also become a key issue in the wake of the COVID-19 pandemic, and in the post-COVID era as the world struggles to recover from its effects. The pandemic had a further significant negative impact via prolonged social isolation, health concerns and economic insecurity resulting in a devastating increase of 25.6% in incidence of anxiety and 27.6% in MDD[9]. The recent decade has further brought significant stress and uncertainty due to several past and ongoing wars in the Middle East and Europe, at least for European and the Middle East populations[10-12] with unsurprising increases in PTSD among people directly involved in the conflict who have more than three times higher risk than general population[13]. Similarly, prevalence of anxiety and depression within those exposed are also two- to three -fold higher amongst people, with women and children being the most vulnerable[14].

Despite the fact that we have several therapeutic strategies to treat all of these disorders, one of the major issues in psychiatry we are facing today is lack of response and development of treatment resistant disorders[1,15,16]. Treatment resistance affects 20%-60% of patients with psychiatric disorders and is associated with increased healthcare burden and costs up to ten-fold higher relative to patients in general[17] with depression, as one of the leading causes of disability, treatment resistance reaches up to 30%[18]. In US population in 2021 the prevalence of treatment resistant depression (TRD) was 2.8 million out of 8.9 million adults with MDD[19]. Overall, it is extrapolated that more than 100 million people globally meet TRD criteria with more than half of direct and indirect economic costs associated with MDD being attributable to TRD[20]. The situation is similar for anxiety spectrum disorders and, in particular for PTSD [11,21]. Another major clinical area where people often suffer with treatment resistant symptoms of depression and anxiety is linked to existential crisis linked to terminal illnesses[22,23].

The traditional pharmacotherapy is further characterized by delayed onset of treatment response with around 6-8 weeks at a sufficient therapeutic dose. In case of insufficient response, second, third and all subsequent lines of treatment again requires such a long period [24,25]. Moreover, as mental health problems are still stigmatised[26], the time from the onset to seeking a specialist ranges from a few weeks to several months. As a result, for an individual who develops one of these disorders, the suffering, and the associated impairment in work performance, employability and quality of life, can easily last for several months. Additionally, the common psychopharmaceuticals used have significant side effects that include fatigue, blunted experience, sexual dysfunction, weight gain, abnormal heart rhythms and extrapyramidal symptoms and in case of benzodiazepines also addictive potential[24,27,28]. These often lead to premature treatment discontinuation and drug switching, again secondarily prolonging the period to achieve a therapeutic response.

Based on these facts one of the major challenges is the search for effective ways of reducing the time between the onset of symptoms and the achievement of adequate improvement or remission while having low risk of side effects. Unfortunately, current development of novel drugs for the treatment of mental disorders was marked by many failures and a significant disparity between the resources invested and successful new treatment alternatives. However, during the last decade mainly, historically highly controversial and controlled substances, psychedelics, have gained attention as drugs with very promising fast acting profile. The main representatives include LSD (*N,N-diethyllysergamide*),

psilocybin, ayahuasca, DMT (*N,N-dimethyltryptamine*), 5-MeO-DMT (*5-methoxy-N,N-diethyltryptamine*), ketamine and also MDMA (*3,4-methylenedioxymethamphetamine*) or ecstasy[21,29-32]. In the past, under political pressure, these substances have been placed in Schedule I, in a category without any medical use, under the 1971 United Nations Convention on Psychotropic Substances. This is despite the fact that at the time there was no adequate scientific evidence of their dangerousness or addictive potential. On the contrary, the therapeutic potential of psychedelic drugs can be found across studies as early as in 1950´s; e.g within 19 studies for mood disorders published between 1949 and 1973, 79% of patients showed 'clinically judged improvement' post treatment[33]. Recent research demonstrates the therapeutic potential of various psychedelics in mental health treatment, particularly for individuals with treatment-resistant conditions. Ketamine, psilocybin, DMT, Ayahuasca, 5-MeO-DMT all have shown sustained antidepressant and anxiolytic effects in patients with TRD, GAD and existential distress with improvements lasting from 2 weeks to 12 months post-treatment. Similarly MDMA-assisted therapy has been highly effective in reducing PTSD symptoms, and has shown promise in addressing related issues such as eating disorders and sleep disturbances (for extensive review see [34,35]). The uniqueness of psychedelic therapy lies in the fact that often a single administration of these substances in a controlled environment leads to immediate symptom relief, i.e. reduction in the duration of suffering and incapacity to work, and a substantial improvement in the quality of life of patients, even in patients who were resistant to previous treatments. Because their therapeutic effects were firstly described for depression, they are currently classified as "rapid-onset or fast-acting antidepressants" [36-38]. The interest in these substances in the last decade has been so high in the professional community that publications on this topic have appeared in the world's most prestigious journals[21,36-39]. In contrast to historical research, modern clinical trials with psychedelics are better designed, and new research methods, particularly advances in neuroimaging and advanced data analysis, have led to a better understanding of the mechanisms behind their unique effects. However, larger, more rigorous studies are essential to confirm and expand upon these promising findings

There is limited research on the cost-effectiveness of psychedelic-assisted therapies, but initial findings suggest they offer substantial potential compared to standard treatments for PTSD and TRD. MDMA-assisted therapy shows a cost reduction of about 30% over the long term, delivering significant health benefits while breaking even on costs in under four years. Psilocybin-assisted therapy is projected to cost more than conventional medication alone, but it delivers the highest quality-adjusted life years (QALYs) among available therapies[40]. Cost-effectiveness is further improved by reducing therapist support and drug costs, making psilocybin-assisted therapy particularly promising from a societal perspective[41]. Given the limited data on long-term outcomes and the lack of comprehensive economic evaluations, further research into the cost-effectiveness of psychedelic therapies is critical[42]. The underlying neurobiology of psychedelics rapid therapeutic effects could involve four potential mechanisms: **1)** direct pharmacological influence on the receptor-level signaling through which they act and which play a key role in these disorders (particularly serotonin 5-HT_{2A} receptors), **2)** induction of neuroplasticity, **3)** alteration of brain functional state, and **4)** influence on psychological aspects that may be directly related to the disorder. Because of their ability to indicate changes in neuroplasticity, they are also referred to as neuroplastogens or psychoplastogens [29,43-47].

Recent advances in academia as well as industry sponsored research focuses on extending the knowledge and identification underlying neurobiological mechanisms in preclinical (neuroplasticity, translational studies, neuroimaging) as well as clinical experiments (phenomenology, neuroimaging), identification new target patient populations and target disorders, development of novel analogues of traditional psychedelics and new delivery systems for clinical application (sustained release forms of medication, with advantageous use e.g. in patients who do not want to experience psychedelic effects, nasal administration, vaporization etc.).

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Based on the data above we have identified several knowledge and practical gaps that this COST Action aims to address. First, in contrast to industry sponsored research, academic research carries with specific limitations, greatly bound by the funding possibilities, resulting in inability to recruit large numbers of patients/volunteers. As a result, there is often relatively low statistical power of the studies, not only for clinical effect, but especially in relation to exploratory aims, e.g. in analyses of neuroimaging data. It also impacts the number of novel candidates or formulations to be evaluated. Second issue is the low standardisation of data collection and often of data structure, pre-processing and even of the actual analytical methods across different institutions. It is sometimes difficult to compare data, resulting in high variability of published results, especially in neuroimaging data. For example, recent study compared different methods of entropy analysis that have been previously used across different psychedelic studies, on their own psilocybin dataset, with 7 out of 12 not giving the expected results[48].

For preclinical data, standardisation is even less common. Finally, it is also the translational validity of preclinical research, i.e. the validity of data found in preclinical models in clinical reality, where preclinical findings are often not confirmed in clinical setting or clinical populations. Thus, this Action aims to bridge these problems and facilitate creation of guidelines in order to standardize data collection, validate translational research methods, create shared databases, and pooling data so we can shift to methods that work with big data and to generate consortia projects collecting data on high number of subjects in a standardized way in multicentre trials. This, however, to a fundamental extent also runs into ethical issues and the related GDPR (General Data Protection Regulation), where different countries have different challenges in setting such parameters. Extreme emphasis will be given to the protection of patient data in the digital space, which is regulated by European legislation and the Data Governance Act, which provides a framework to enhance trust in voluntary data sharing for the benefit of the industry and the general public. Sharing e.g. neuroimaging data between academic studies and industry sponsored studies is a major challenge today. For this reason, among others, the "ECNP Psychedelic research Network" is currently launching an initiative to prepare a large multicentre study on hundreds of patients with MDD, with the participation of most of the clinical centres in the EU working with psychedelics, which should make it possible to collect such data.An equally crucial question in the case of psychedelics is their legislative status. Most classical psychedelics are Schedule I substances with no therapeutic potential under international conventions, which in practice means that they can only be handled in very limited situations, such as research or clinical trials, and those handling them must have the appropriate special authorisation to do so. This makes it very difficult to run clinical trials, and at the same time, this it is impossible in most countries around the world to market them as conventional medicines [49]. At present, some solutions already happened in Australia, US and Canada, albeit, for the time being, at least to a limited extent. EU is however not at this stage yet.

In sum we define six main areas of interest on which the network will collaborate and on which the research areas and working groups (WG) will be further defined:

WG1 - Chemistry & biophysics: make accessible pharmaceutical grade substances (active pharmaceutical ingredients (API)) for academic studies, design of novel drug candidates, delivery systems and dosing schemes, pharmacological characterization of these drugs/systems

WG2 – Preclinical: molecular and cellular pharmacology, integrative neuropharmacology (behaviour, electrophysiology, neuroimaging), translational validity of data

WG3 - Clinical: designs of healthy volunteer trials (neurobiology, neuroimaging, phase I studies etc), clinical trials in patient populations (depression, anxiety, addictions, palliative care etc.), role of placebo and unblinding and psychotherapy, cost effectiveness and cost benefit analyses

WG4 - Advances in Neuroimaging: implementing novel approaches, standardisation of data collection, prescreening, designation and standardisation of advanced analyses such as hyperscanning, simultaneous EEG/fMRI

WG5 - Data sharing and databases: implementation of shared databases in order to work with big data, standardisation, legal issues, including ethical concerns and protection of personal data

WG6 - Policy regulations: legal framework of psychedelics in relation to clinical use, lobbying on national and international level in order to facilitate legislative changes that would enable their use in clinical populations

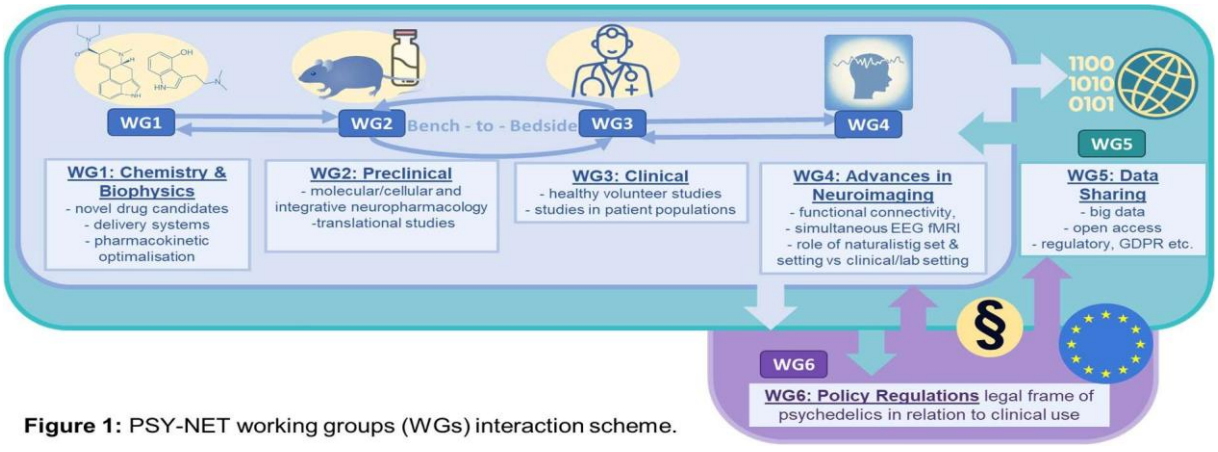

Figure 1: PSY-NET working groups (WGs) interaction scheme.

Therefore, the main objective of PSY-NET COST Action is to integrate these areas and to facilitate the creation of a **network of academic institutions with scientific societies, industry, patient/caregivers organisations, advocacy groups and regulatory bodies. These stakeholders** together will define new directions for the **use of psychedelics in therapy**, identify **neurobiological biomarkers** and **predictors** of their effects, and develop **recommendations** and **guidelines for their use**, including **recommendations for a regulatory framework** to enable their future adequate availability and accessibility to patient populations. As part of the programme, we will emphasise **the promotion of networking and training of Young Researchers and Innovators (YRIs), as well as young career clinicians**, who will define future trends in the field.

1.2. PROGRESS BEYOND THE STATE OF THE ART

1.2.1. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART

The key issues stated above are non-standardization of the scientific data, small sample sizes and lack of translational validity of preclinical to clinical context, and lack of coordination of tasks resulting in regulatory changes. This COST Action thus aims to bring new possibilities of improving these areas with experts from all these research areas across European countries who joined PSY-NET. The collaboration will result to the development of recommendations, guidelines or proposals for standard operating procedures (SOPs), consortia clinical trial protocols, database enabling the analysis of large data sets, and the sharing of optimised and standardised tools (scripts) for digital data analysis. In order to make this happen we have identified three main pillars:

The first major **pillar** of the PSY-NET Action will link preclinical research and development with clinical research by generating data and methods with high translational validity. For example, one of the key aspects of psychedelics effects, the alteration of perception and emotionality, are not even described in animals. The only animal biomarker that is used to label drug as potential psychedelic induction of head twitching behaviour, which is believed to be a marker of agonist activity at 5-HT2A receptors. However, such a fundamental effect of psychedelics as visual perceptual distortions, have not been proved in rats until recently[50]. As in humans it is the intensity of the psychedelic experience, or its mystical dimension, that appears to be one of the main factors determining the therapeutic response, we must improve phenomenological validity of animal experiments. Last but not least, the current models of neuropsychiatric disorders have significant weaknesses in terms of their construct and predictive validity. It is therefore crucial to start thinking more broadly and to look for better/specific biomarkers that will allow us to assess the psychedelic and therapeutic potential of psychedelics in animal models, but also to use new models/methods that involve long-term monitoring of the population of interest, including social interaction between individuals in as natural setting as possible, using complex systems based on artificial intelligence (AI) principles. For example, to study behaviour beyond the state-of-the-art, we will implement advanced computer vision and machine learning-based tracking systems, in combination with artificial neural network models to (1) cluster animal behaviours based on similarity; (2) detect anomalous behavioural differences between groups; or (3) identify previously undefined or unnoticed behaviours [51]. Similarly, we will implement clustering algorithms to classify high density animal EEG in order to find characteristic patterns of psychedelics with therapeutic potential, and develop a tool that might facilitate the recognition of novel drug candidates within this class. In addition, cortical monitoring of brain activity using telemetry, and ultrasound-based measuring of brain blood flow will also be implemented. Such data should then be compared with clinical data, considering the translational validity of the findings. PSY-NET will therefore build on and significantly expand existing collaborations by involving experts in the fields of preclinical models, clinical trials and neuroimaging. The aim is to design and define as many optimised ways as possible to assess the effects of psychedelics with maximum translational validity of the data collected. With the participation of partners in the field of medicinal chemistry and experts in the field of monoaminergic neurotransmission and animal modelling, PSY-NET will then improve the testing of new candidate molecules.

The second pillar is the effective networking in clinical research focusing on therapeutic response and evaluation of neurobiology of the effects. First, the necessity of generating large data sets needs to form consortia projects with multicentre clinical trials, that collect both clinical and neurobiological data. These trials will primarily address key questions that were recognized at the "European Medicinal Agency (EMA) multi-stakeholder workshop on psychedelics" that took place April 2024 in Amsterdam, such as blinding of psychedelic studies, role of psychotherapy vs psychological support, single vs

repeated dosing, dose escalation, role of the duration of the experience etc. In conjunction with that this project will also include economic aspects of psychedelic therapies, including costs, cost-effectiveness, cost-benefit analyses, and the potential economic impact of broader implementation into clinical practice.

Second, many of the partners involved already have large amounts of data, but often struggle with the capacity of experts to competently analyse it. At the same time, it is difficult to find experts who can bridge biological and technical disciplines to avoid misunderstandings and misinterpretations of data. This kind of bridging will enable effective work on standardising data collection methods, developing standardised procedures for pre-processing and data analysis, and ultimately sharing open access scripts/modules for data analysis. At the same time, this collaboration will lead to the definition of rules for data sharing, treatment of ethical aspects and legal frameworks (GDPR), and will facilitate the development of shared open access databases and big data analysis from already available as well as newly collected within novel clinical trials.

The third pillar of PSY-NET will aim to link academia with advocacy groups and regulatory authorities, mental health patient organisations and industry partners. The aim of these activities will be to facilitate the development of new therapeutic approaches based on psychedelics and to define their availability to those in need. These approaches will include the necessary training of specialists, such as legal experts, in order to work with regulatory authorities to prepare the ground for the introduction of psychedelics as controlled substances for various types of therapeutic interventions. The project will aim to engage with the EU policymakers, the European Parliament, the Council of the EU and the European Commission as well as the relevant EU agencies such as EMA or EUDA to advocate for the medical use of psychedelics while connecting them to the legislative agenda (e.g. in relation to health, pharmaceuticals, mental health, war in Ukraine) and to develop recommendations for changes in legislation that would allow such use without violating international conventions. As a proof that such changes are possible, the Czech Republic can be an example, where based on the collaborative work of Czech experts with lawyers and politicians an update of the scheduled drugs law has been recently accepted by both chambers of parliament. This law newly defines the category of psychomodulatory and psychoactive substances[52]. Additional changes that recognize “medicinal psilocybin”, in a similar manner as in Australia or to “medicinal cannabis”, are currently under evaluation. Significant attention also deserves current activities that would facilitate connections between European and Ukrainian policymakers through conferences and events to explore potential pathways for implementing psychedelic assisted therapy for people suffering PTSD in Ukraine. Several such events already happened in European Parliament and in Prague (e.g. Resilient Mental Health in the European Union, Innovating Mental Health in the EU Pharma Legislation: Regulatory Pathways for Psychedelic Therapies, The Potential of PAT in Mitigating War-Induced Trauma: The Case of Ukraine, Novel Mental Health Treatments and Sustainability of Healthcare Systems: Czechia as a Leader of the EU?) and projects/clinical trials in support of Ukraine are currently being designed. A multidisciplinary team of different stakeholders and experts will thus be formed, in order to define the priorities based on (EMA’s recent recommendations[53,54]). The recent experience of “medicinal cannabis” in many European countries will be used, as an example, in order to propose a revised legislative framework. Experts serving on committees in National Organisations of Medicines will be leading this initiative and will work closely with administrator’s, legal and ethics experts to define the needs and strategic plan. Moreover, an effort to work on a strategic plan that goes beyond approval of new psychedelics and include Health-Technology Assessment will be made.

1.2.2. OBJECTIVES

The objectives are specified according to **SMART** principle (**S**pecific, **M**easurable, **A**chievable, **R**elevant and **T**ime-bound):

1.2.2.1. Research Coordination Objectives

1) S: Coordination of designing of novel molecules with their pharmacodynamic properties, facilitate development of novel formulations, delivery systems or dosage/administration schemes within the psychoactive psychedelics as well as their non-psychoactive counterparts, in order to make/improve oral bioavailability, better control/titrate the intensity and duration of effects and improve compliance. ***M:*** *the number of novel compounds, delivery systems etc. proposed, publications.* ***A:*** *the members of consortium are experts with the area and are also involved in the psychedelic research, having several joint publications,* ***R:*** *identification of these novel drugs/systems will generate novel therapeutic candidates and approaches,* ***T:*** *across the lifespan of the Action*

2) S: Coordination of creating guidelines and standard operational procedures (SOPs) for

translational animal research that would have yield in a meaningful screening set of behavioural, electrophysiological and neuroimaging methods that would identify the characteristic features of psychedelics and their non-psychedelic analogues for the treatment of depression, anxiety, addiction and existential distress in palliative care. ***M:*** *the number of publications, guidelines and SOPs published.* ***A:*** *the members of consortium are leading experts exploring the monoaminergic systems and psychedelics and novel psychoactive substances, having several joint publications,* ***R:*** *identification of underlying mechanisms of action, standardisation of methods and sharing data analytical tools,* ***T:*** *across the lifespan of the Action*

3) S: Propose designs and protocols for novel clinical trials with psychedelics in depression, anxiety related disorders, addiction, and other neuropsychiatric conditions in order to be used in future large-scale collaborative projects. Create guidelines/recommendations on how to deal with unblinding of studies with psychoactive doses with psychedelics and propose appropriate standardisation with selecting placebo´s or active comparators. Guidelines for psychedelic assisted therapy and minimal requirements for subjects that will prescribe them. Currently as an example, a multicentric trial focusing on the role of psychotherapy in conjunction with psilocybin in the treatment of MDD is under preparation within the ECNP Psychedelic research Network. Pave paths for compassionate use. ***M:*** *the number of protocols designed, recommendations and guidelines published,* ***A:*** *the members of consortium are leading experts in performing clinical trials within the psychedelic domain and neuropsychiatric disorders, having several joint publications,* ***R:*** *Testing efficacy in candidate disorders where psychedelics might be effective and decrease suffering of patients, evaluation of the role of psychotherapy, blinding etc.),* ***T:*** *across the lifespan of the Action*

4) S: Create guidelines, standard operational procedures (SOPs) and recommendations for standardisation of data collection and advanced analyses in neuroimaging studies, creation of standardised pre-processing pipelines and standardised toolboxes enabling comparable data analyses across sites. ***M:*** *the number of publications, guidelines and SOPs published* ***A:*** *the members of consortium are leading experts in neuroimaging, creating novel methods, and innovative approaches, having several joint publications,* ***R:*** *identification of underlying mechanisms of action, standardisation of methods and sharing data analytical tools,* ***T:*** *across the lifespan of the Action*

5) S: Coordination and facilitation of the creation of open access databases that would comprise of preclinical as well as anonymised clinical data, prepare common guidelines for creation Informed and GDPR consents that would allow data sharing, creation of web hub with access to all databases and other data. ***M:*** *web-based hub containing links to open access databases ready for sharing clinical, neuroimaging and preclinical data, number of informed consents and GDPR templates* ***A:*** *the members of consortium are already collecting data and have already started discussions on data sharing and made some of the data already available for joint collaborations,* ***R:*** *big data analyses on standardised samples of phenomenology, EEG and fMRI data collected through multicentric trial or shared between institutions,* ***T:*** *across the lifespan of the Action*

6) S: Work on political and regulatory domain in order to facilitate future legislative changes on EU level as well as on the United Nations level that would allow wider access to psychedelics and psychedelic assisted therapy. ***M:*** *meetings and workshops with regulatory bodies, EU parliament etc., and relevant documents that have impact on political formations* ***A:*** *the members of consortium are already organising events in European Parliament, have experience in discussions with regulator bodies such as EMA (European Medicines Agency),* ***R:*** *Need for legislative changes and definition of the legal framework, in order to make psychedelics that show therapeutic efficacy accessible to patients,* ***T:*** *across the lifespan of the Action*

1.2.2.2. Capacity-building Objectives

1) S: To connect high-quality scientists, research institutes, scientific organisations, patient organisations, industry and regulatory bodies across Europe.
M*: The number of researchers, institutions and other bodies within the network.* **A**: *There is already a substantial number of major partners that have joined the project in its preparatory phase and others will follow* **R:** *Collaboration between experts from such a wide area ensures the biggest impact.* **T:** *Four annual meetings across the lifespan of the Action*
2) S: To make recent knowledge base, technological advances, clinical experiences, drug sources available to the whole network and beyond.
M: *Number of collaborations, workshops, webinars, training schools, short-term internships.* **A:** *Sharing existing knowledge, scripts, anonymous data, joint analyses of datasets* **R:** *generation of novel hypotheses, advanced data analyses, experimental designs* **T:** *meetings as well as Short-Term*

Scientific Missions (STSMs) will be organised across the lifespan of the Action

3) **S:** Fostering and facilitation networking of YRIs within the network and to facilitate the training under supervision of research leaders within the network and beyond.

M: *The number of YRIs involved in the management and research structures.* **A:** YRIs will become part of the network and the management, creation of a network within, organisation of training schools and workshops. **R:** *young career scientists and clinicians will improve their networking skills and the knowledge within the psychedelic domain* **T:** *across the lifespan of the Action*

4) **S:** Fostering and facilitation of communication between researchers, regulatory authorities and industry towards maximisation of impact of the Action

M: *Number of meetings between scientific team and partners from other areas, such as patient organisations, industry, research organisations etc.* **A:** *Partners of this project consist of members of leading research institutions within the psychedelic domain, psychiatric clinics, neuroimaging, chemistry and molecular biology, patient organisations, scientific associations and industry across the whole Europe.* **R:** *Translation of the knowledge between academic partners, and closer collaboration with industry* **T:** *across the lifespan of the Action*

2. NETWORKING EXCELLENCE

2.1. ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

PSY-NET is a transdisciplinary and multidisciplinary Action that addresses the use of psychedelics and related compounds-based therapies in the treatment of mood disorders, addiction, PTSD, and towards other possible applications. There are initiatives in Europe devoted to psychedelics including the research on psychedelics (ECNP Psychedelic Research Network), Psychedelics Europe, Psychedelic Access and Research European Alliance (Parea), Osmond Foundation, Drug Science, ITPRI, Beckley foundation to cite a few. Members of PSY-NET have existing collaborations with such networks. Several associations are collecting data to communicate on the use of these compounds as alternative treatments, and act as policy makers. The research aspect that suits the PSY-NET initiative is beyond the current initiatives because it includes research forces that cannot emerge from isolated associations. It offers an institutional framework to better share the preclinical and clinical procedures, the progress of pharmacology and lead concepts, the overture to other fields of medicine beyond the current use of these compounds, and a source of inspiration for younger researchers. PSY-NET is a research-based, unbiased Action that tangentially capitalises on previous and recent efforts at the European level including the study of monoaminergic drugs in the treatment of brain diseases (CM1103), multi-scale medicine (CA15120), the architecture of consciousness (NeuralArchCon), GLISTEN (CM1207 - GPCR-Ligand Interactions, Structures, and Transmembrane Signalling), automated behaviour monitoring in the animal home-cage (TEATIME, CA20135) or Psilocybin Therapy for Psychological Distress in Palliative Care Patients (PsyPal, Horizon 2020 grant no. 101137378). The multidisciplinary approach is required to address specific questions from the bench to the clinic and vice versa.

PSY-NET develops a unique network to address the scientific questions inherent to the use of the psychedelics including 1) their mechanism of action in preclinical and humans studies, 2) the development of agents that could be efficacious without inducing psychotomimetic effects, 3) the research on the clinical approaches of the psychedelics at large scale with brain imaging 4) the data sharing from preclinical and human research, 5) the legislation aspects for both preclinical and clinical research.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS, EXPERTISE AND GEOGRAPHICAL BALANCE WITHIN THE COST MEMBERS AND BEYOND

The research on psychedelics has been growing fast during these last years. Several researchers in Europe have manifested interest in these compounds and most European countries house, at diverse degrees researchers working in this field (pre-clinic and/or clinic) including ITCs, and connected fields. The launch of a COST Action is an extraordinary opportunity to develop initiatives between groups, teaching, exchanges via STSMs, and share the know-how across European countries. In its initial start, 83 partners from 21 European countries (and one cooperating member) are included in the proposal. They include academic, non-academic (private companies, associations) agents including half ITCs.

The gender balance is in the range of 50/50%. Several talented and motivated YRIs, PhD and postdocs are also securing critical mass and expertise and creating 30% of the PSY-NET and are believed to grow in the future.

The Action networking paid attention to include researchers who are not strictly involved in the field of psychedelics as well as people involved in regulatory processes (legislators, attorneys, etc.) and epidemiology. Even if all represented countries include someone directly working on psychedelics, it is also important to include researchers/clinicians/epidemiologists who are specialised in the neurobiology of mood disorders, addiction, PTSD, and other diseases that could be advantageously targeted by psychedelics (neurodegenerative diseases for instance). This enlarged network is valuable for the Action, and should favour interactions between ongoing Action at the European level.

YRIs, postdocs and PhD students from the partner institutions will be involved in the PSY-NET to benefit from the Workshops, Meetings, Training Schools and STSMs. These events will be announced by a call within the partner institutions and the PSY-NET's website. These young researchers will have the possibility to take responsibilities within the PSY-NET. A special interest on Diversity, Equity and Inclusivity measures will be given through all actions.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

PSY-NET is a transdisciplinary Action covering multiple R&D aspects for human health and legislation. The stakeholders are numerous including basic research scientific community, clinicians, industries, foundations and associations, patient and caregiver groups, policymakers and advocacy groups. The organisation of the Action will allow for implementing the stakeholders in and out the existing identified WGs. Stakeholders involved in PSY-NET will collaborate to promote the medical use of psychedelic-assisted therapies. For instance, the process will involve sharing research data with policymakers to ensure that any potential legislative advancement in this regard is science and evidence based. In addition, there will be a dialogue between patient organisations, researchers and policymakers to understand the needs of those who need psychedelic-assisted therapies the most, such as treatment-resistant patients suffering from mental disorders or those in palliative care. The initiative will also aim to build partnerships with industry to foster innovation and drive progress in this field.

The scientific community is involved from basic research to translational and clinical research. The Action will cover preclinical scientific domains as large as computational biochemistry, biophysics, medicinal chemistry, molecular biology, molecular pharmacology, bioengineering, epigenetics, in vitro/in vivo electrophysiological recordings, neurochemistry, integrative pharmacology, behavioural studies including studies on sex differences, pharmacokinetics, and modern approaches to analysing big data. The Action will include academic/industrial researchers.

The clinical community includes psychiatrists, neurologists, pharmacologists, psychologists and epidemiologists in Europe. They will also interact with other clinicians worldwide who have developed expertise in the use of psychedelics. Most of them are involved in the treatment of mood disorders (depression, anxiety), cessation of drugs of abuse (mostly tobacco, alcohol, cannabis use), PTSD, and will share their progress during Action meetings (dedicated WG for human's research, and whole Action meetings). The consortium will help develop specific protocols, collect data across several medical centres, ultimately leading to launch recommendations, guidelines and SOPs for practitioners. This group will also interact with WG2 (preclinical research) and WG4.

The PSY-NET will interact with industry partners. The industry partners in the area of psychedelics such as Compass Pathways, Cybin, MAPS, MindMed Avextra, Usona etc. will be invited to be part of the PSY-NET if accepted and/or be invited to the meetings of the Action (Industry, private company and/or clinic). It will include SMEs and world-leading companies that have strong interest to develop novel pharmacological agents in the field of brain disorders. The interest will be for them to follow the initiatives of the PSY-NET thanks to the website of the Action developed in the very beginning of the action. The high consideration of the industry is also to promote formal partnerships in academia/industry and develop entrepreneurship among younger researchers. Of note, other applications will also be considered as psychedelics also have other properties that could have benefit in various conditions, e.g cluster headaches, palliative care, and neurodegenerative disorders.

The numerous associations in the field of psychedelics will be informed via the PSY-NET's dissemination activities and benefit from the new knowledge, new concepts, and treatment strategies. The dissemination activities will include regular newsletters, social media posts, webinars and hybrid meetings with subtitles and translations in different languages when this is needed. Some members of this PSY-NET are involved in routine clinical practice or clinical trial activities, having good connections with local, national, or international patient/caregiver organisations and healthcare professionals. Additionally, some researchers are scientific referees for some of the associations at the international and/or national levels.

Meanwhile, the Action will clearly involve policymakers to ensure active strategies to involve members of government healthcare advisory boards. Pertinent achievements of this Action (e.g., novel clinical treatment recommendations, procedures, guidelines) could change the healthcare system and modify national and European healthcare guidelines. Some members of this PSY-NET are involved in drug approval at the national level and serve at respective evaluation committees and advisory boards. They also have experience on Health-Technology Assessment that is very relevant to this Action.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAKTHROUGHS

3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

This Action is expected to make a significant scientific and socioeconomic impact, particularly in the field of mood and anxiety disorders, which affect millions of people worldwide and impose enormous social and economic costs[55]. Depression, especially in women, is the leading cause of disease burden among neuropsychiatric disorders[56]. This COST-Action is poised to impact in the long-term patients suffering from TRD, anxiety, PTSD, existential distress, substance use disorders and other severe neuropsychiatric disorders - areas identified as priorities by the WHO.

The proposed project aims to focus on a class of substances with rapid-acting properties that could significantly improve the quality of life for millions of patients. Specifically, the scientific community is investigating the potential of psychedelics, especially psilocybin, as treatments for mental health conditions such as TRD, addiction, and PTSD[37,39,57]. Several have been already labelled as “break through therapy” by the US FDA. Moreover, there is ongoing research exploring the use of psychedelics in conditions such as chronic pain, obsessive-compulsive disorder, eating disorders and even in neurodegeneration such as Alzheimer’s disease[31,58]. Psychedelic substances, particularly psilocybin, are also being studied for their application in palliative care, where they may help alleviate distress in terminally ill patients, including those with cancer. It is also highlighted by a breakthrough project “PsyPal” from Horizon 2020 call in anxiety, depression and existential distress comorbid with severe neurological conditions like multiple sclerosis, multisystem atrophy (MSA) and amyotrophic lateral sclerosis (ALS) [22,59].

Therefore, research in the field of psychedelics is currently a focal point in Pharmacology and Psychiatry, with scientific interest rapidly growing worldwide. This interest is increasingly evident among patient groups (such as PAREA and the Hellenic Society for Endogenous Drugs), whose active involvement has led to a surge in media coverage, as well as interventions in the European Parliament. In 2023, several Members of the European Parliament authored a letter emphasizing the need for further research into psychedelics to address severe mental health disorders, such as TRD. The issue is also attracting attention from respected regulatory bodies. Psilocybin prescriptions, under very specific conditions, are allowed by qualified psychiatrists in countries such as Switzerland, Australia, and Canada.

The PSY-NET will have to address some essential questions such as the extent to which the antidepressant/anxiolytic effect of psychedelics requires the psychedelic experience, the way to conceive pertinent controls (unblinding issue) in future clinical trials, the appropriateness of one psychedelic over another one (non-inferiority studies or superiority studies) for specific cases, the set and setting improvement, the durability of effect (addressing single vs repeated dosing) or the identification of possible side effects. The organisation of PSY-NET mixing neuroscientists and clinicians and patient advocacy groups will allow for faster internal dissemination of the clinical experience. The impact should be considerable in terms of clinical expertise and this knowledge will advantageously be transposed to the other diseases targeted by the PSY-NET (addiction, PTSD, neurodegenerative diseases). Meanwhile, very close to the question of the origin of the therapeutic benefit of these compounds, there will be tremendous advances regarding the mechanisms of action of these drugs and possible sex-differentiated effects, which are very often neglected.[63,64]

As far as the neurobiological corollary of the clinical situation is concerned, it has to be clearly stated whether the mechanisms triggered by these drugs inducing psychedelic effects and antidepressant benefit are the same, distinct but overlapping, or very distinct. It would be of great **interest for industry and academia to design new chemical, innovative compounds with higher efficacy, lower psychotomimetic side-effects, and with long-lasting effects**. Therefore, the ultimate goal of this Action will be to develop safe and effective treatments that do not cause dependence or resistance, which would be of significant benefit to patients, their families and society at large.

Specifically, psychedelic-assisted therapy would have considerable consequences on healthcare systems, with **a drastic reduction of treatment duration compared to the current situation with classical antidepressant/anxiolytic drugs**.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

This research-based Action will produce knowledge, notably as regards the mechanisms of action of the different classes of compounds that could enter the psychedelic class. It will also create new perspectives on the use of the different compounds of the psychedelic armamentarium to refine the clinical procedures according to the diagnosis. The creation of knowledge will occur via the meetings, lab/clinic exchanges, interaction with the different stakeholders. The PSY-NET will develop the availability of the data with the data sharing, especially large databases that could be obtained with human/animal imaging, electrophysiology, and large, multi-scale cohort of patients. The Action will create a favourable environment to promote collaborations within the consortium, and beyond, in respect to the Diversity, Equity, Inclusivity (DEI) principles that have been set by the ALBA network towards diversity and equity for brain sciences. The multidisciplinary approach of the Action will permit postulating to national and international specific calls aimed at combining distinct and distant fields of research. The transfer of knowledge will occur via the meetings of the whole Action, together with the STSMs, and training schools organised by the Action.

Career development will be ensured by training and STSMs for early career investigators with special focus on DEI. They will also be invited to have roles in the Management Committee (MC) or Core Group (see 4.1), WG leadership and other coordination roles (organising meetings, follow-up of the website, conferences). The lab exchanges will also enrich the career of PhD students and eventually master students.

Beyond sharing the know-how procedures at the preclinical and clinical level, it will leverage the ability of researchers to communicate, and harmonise research in the field in Europe. One of the impacts should be the facilitation of developing clinical and preclinical protocols in an easier way across Europe, a point that is still a limiting factor in several countries. The development and the standardisation of some procedures with psychedelics should highly impact the treatment of TRD, general anxiety disorders, PTSD, neurodegenerative disorders and offer a better-recognized alternative to medical practitioners. In other words, it is expected to transform the organisation of neuropsychiatric centres specialised in the above-mentioned diseases.

3.2.2. PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

The dissemination will have several aspects coordinated in the management of the Action. The scientific dissemination will go through the publications in peer-reviewed journals, such as Neuroscience applied, the Journal of Neuroscience methods, European Journal of Neuroscience, European Neuropsychopharmacology with open access possibilities and press releases. It is anticipated to publish at least 5 joint publications/year involving several Action members. Special issues will also be created to maintain high level of peer-reviewed publications. The Action will favour reports and guidelines involving the members of the Action. The dissemination will also occur via the meetings of the Action, involving associations that act in the direction of policy makers, practitioners, and the general public. It will take place through social media and networks, such as ResearchGate, LinkedIn, X (Twitter), Facebook, Instagram and others. An interactive website created at the start of the Action will constantly report the progress of the Action at both scientific, clinical levels, and lay audience. Scientific, clinical and/or lay- language conferences will be organised in different universities and medical centres. It will be based on the participation of national associations/international associations that constantly work towards the different publics. Since the Action involves different countries with distinct languages, specific actions such as conferences/video uploaded on the website in the language of the country will be developed. These will take place during the Brain Awareness Week in March, the World Mental Health Day and will be disseminated through the media with press releases and interviews. Furthermore, the results will be shared at workshops and public forums, including events like the World Human Forum, to engage the broader public. Specific information is given in the Deliverables Table. The dissemination will also include academia via the availability of shared resources for teaching to undergraduate students of various tracks in various universities, and book releases. Similarly, as in the past, events organised at the governmental level including the EU parliament, EMA level, and possibly also WHO will maximise the political impact.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

The Core Group of the Action will be most likely elected during the first Management Committee meeting. Among others, it will be composed of a Chair, a Vice-Chair, a Science Communication Coordinator and a Grant Awarding Coordinator, the leaders and co-leaders (preferentially YRIs) of each WG. Each WG will have bi-annual face-to-face meetings except WG5 and WG6 (one/year, and two the last year); the Action will promote combined WG meetings. Attention on the composition of the Core Group and leadership positions will be given to representativeness based on DEI criteria including gender, status, and function (Researchers, clinicians, YRIs, stakeholders).

The Action is anticipating the enrolment of other researchers, clinicians, YRIs including students (master 2, PhD), and stakeholders during its life. It will be discussed by the MC to keep ensuring balanced across the WGs for gender representation, representation from ITCs, YRIs status, and scheduled activities and objectives. The MC will meet twice each year of the Action (either face to face or in hybrid or online mode), with in-person meetings coordinated with other COST Action activities (e.g. Workshops and Conferences). The MC will also pay attention to the conflict of interest inherent to the large panel of individuals and fields encompassing the Action.

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

WG1: Chemistry & Biophysics: This team is composed of experts from several scientific domains including Medicinal chemists, Organic chemists, Analytical chemists, Computational chemists and Bioinformaticians; each contributing their knowledge to the drug design process. The WG1 will focus on finding suitable chemical structures and/or formulas. Throughout the duration of the project, novel drug candidates will be discussed and then predicted based on computational models of interaction between drug candidates and their respective targets (Computer-Aided Drug Design (CADD) techniques will be used, i.e. “Pharmacophore modelling and Molecular docking”). Partners involved in the PSY-NET have already experience with evaluations of (Quantitative) Structure-Activity Relationship Study ((Q)SAR), multiple targeting profiles, preclinical screenings and have ongoing projects dedicated to these areas. Based on the pharmacokinetic and pharmacodynamic properties, a suitable drug delivery system that optimises drug stability, bioavailability or focuses on targeted delivery, e.g. a lipid-based drug delivery system for known substances with low or minimal oral bioavailability (e.g DMT or 5-MeO-DMT) and related analogues, will be also proposed for evaluation. Partners within WG2 will subsequently follow up on this work with preclinical research while cooperating on metabolic, pharmacokinetic and pharmacodynamic studies. WG1 will also tightly collaborate with WG5 in data sharing. Yearly reports containing lists of candidate molecules, delivery systems etc. will be published within the consortium and ultimately in peer reviewed journals.

WG2: Preclinical Research: this multidisciplinary group includes experts on pharmacology, behavioural pharmacology, tissue cultures, immunohistochemistry, electrophysiology, will focus on translational evaluation of therapeutic potential and classical psychedelics and related novel compounds psychoplastogens (interaction with WG1). The goal is to decipher the mechanisms of their action, and assess their safety and therapeutic efficacy in the central nervous system without discarding their peripheral effect based on *in vitro* and *in vivo* studies.

The studies will include:

1) ***in vitro* studies** using the iPSCs, primary cell cultures isolated from patients, brain extracts from animal models of both sexes to evaluate old and newer psychedelic compounds (and derivatives) pharmacological profile (receptology and signaling in different neuronal cell systems, efficacy including bias agonism) and study their potential to:

- induce cell proliferation, apoptosis/necrosis (all cellular models),
- spinogenesis, branching, synaptogenesis in cortical neuronal cultures and brain organoids,
- induce immune cells to reassume anti-inflammatory and pro-regenerative functions,
- induce therapeutic mechanisms based on to date unexplored receptors in psychedelic studies such as: 5-HT_{1A}, 5-HT_{2C}, Sigma-1, TAAR1, TAAR2,
- apply in novel phospholipid-based drug delivery systems to improve their therapeutic effects

2) ***in vivo* studies on psychedelic compounds**' effects to evaluate in appropriate animal models of both sexes:

- impact on the electrophysiological and neurochemical properties of neurobiological networks,
- potential use in mood disorders, addiction, post-traumatic stress disorders (PTSD),
- benefit to revert brain injury such as traumatic brain injury (TBI) and stroke,
- possible use in neurodegenerative diseases (e.g. Alzheimer's Disease, Parkinson's Disease,

Amyotrophic Lateral Sclerosis).

The role of WG2 is also to provide suggestions on how to use easy-collectable human-material (wg. urine, blood,) to answer specific questions regarding the influence of psychedelics on various biomarkers in populations of healthy volunteers and neuropsychiatric patients of on-going or planned clinical- trials by the members of WG3.

WG3 - Clinical: The team consists of clinicians experienced in leading clinical trials as principal investigators, psychiatrists, psychologists, neurologists, palliative care specialist, pharmacologists and experts involved in clinical trial management who are consolidating knowledge and resources in order to guarantee that innovative clinical trials become realistic. WG3 aims to rely on international researchers' collaboration and development of most adequate study designs for clinical trials to answer the emergent research questions (e.g. as defined by EMA) and overcome major challenges specific to psychedelic research, such as:

1) Propose multicentre clinical trials in patients with neuropsychiatric disorders, such as MDD, end-of-life anxiety and depression, substance use and possibly also focus on novel challenging areas such neurodegenerative disorders (e.g. Alzheimer) and on possible implementation of compassionate use for patients who were involved in studies with psychedelics and benefited. The present working group is well positioned to contribute toward the standardisation of protocols for psychedelic treatments, such as dosage, administration setting and participating health professionals, in addition to a generalised use of the 'Risk management plan' (RMP) by EMA, to guarantee extensive risk evaluation and best implementation of mitigation strategies.

2) Focus on the neurobiological mechanisms of action of psychedelic compounds both in studies in healthy as well as patient populations. For neuroimaging studies, it is to create and use identical protocols and analysis pipelines to ensure comparable datasets for pooled analyses across centres.

3) To evaluate the role/contribution of psychological support vs psychotherapy intervention, and appropriate number of preparatory and integrative sessions and the role of set and setting. Future research needs to join efforts across countries, to test the impact of the different forms and levels of psychological interventions on the efficacy of psychedelic treatments. As already mentioned above a multicentre study in MDD that should address the role of psychedelic assisted psychotherapy vs psychological support along with psilocybin is currently under preparation.

4) Focus on optimal designs of studies, that might get regulatory approval afterwards, that count 1) with unblinding due to the nature of psychedelic experience, implementing factorial designs and low dose or active placebo, 2) studies where psychedelics are used as add on to standard therapy, thus focusing on safety when co-administered with standard treatments and 3) superiority/inferiority comparative studies with other treatments and or active comparators (e.g. ketamine, such as in existing trials PSIKET001 and PSIKET002, EudraCT no: 2018-004480-31 and 2020-005037-32).

WG4 - Advances in Neuroimaging: Experts on all types of neuroimaging methods in psychedelics (EEG, fMRI, PET) and on computational methods are parts of the team. These methods help understanding neurobiological mechanisms involved in treatment response, in phenomenology of acute experience, and can be used to study the effects of external variables on brain processing during psychedelic experience, e.g. music. As stated above, due to the nature of psychedelic experience human studies are critical as it cannot be as effectively ascertained in animal models. So there is also a need to develop translational models, using the same tools for evaluating changes in animals as in humans. As highlighted above functional brain imaging methodology can be quite variable across sites which generates high variability of findings. Thus WG4 will work on standardization of recording protocols, data analyses and will benefit from data coming from multicentric trials enabling future big data analyses. Coordination and communication between sites can facilitate alignment on paradigms to use, which supports reproducibility of research findings and more quickly converges upon robust biomarkers of drug effects. WG4 will collaborate with WG2 and WG3 in order to increase the opportunity to integrate functional and/or molecular brain imaging into clinical study designs or projects that may not otherwise include these techniques. It will facilitate for starting research groups to collaborate on research projects, share information about brain scan sequence information, task parameters, and data processing strategies.

WG5 - Data Sharing / Databases: Experts across all WGs will contribute to this part. Data sharing is undoubtedly an optimal strategy to significantly accelerate research methods, to use shared computing capacity, to build files with a larger number of subjects and thus to increase the likelihood of finding statistically significant differences. On the one hand, data sharing and the creation of joint databases, especially those that are as openly accessible as possible, are supported by European funding agencies, but on the other hand, especially in the case of human/patient data, they face major challenges in terms of the legal and ethical framework for data protection. Despite the necessary consent of the subjects who have provided the data for its use by third parties, there are a number of pitfalls in ensuring the anonymity of these data and their digital protection. There are also situations

where data that is anonymised today may be de-anonymised in the future, for example, thanks to advanced technologies. Therefore, one of the main objectives of the group will be to produce documents that, on the one hand, serve as recommendations or guidelines for the design of experiments to enable future sharing of anonymised data and, on the other hand, prepare templates for informed consent and GDPR consent that can be used in each EU country and comply with EU and local regulations. At the same time, a web portal will be created within PSY-NET where this information will be accessible, with links to existing (e.g. Public nEUro or OpenNeuro PET) or emerging over time.

WG6 - Policy Making: Policy recommendations and stakeholder engagement/education for psychedelics in relation to clinical use, lobbying at national and international level to facilitate legislative amendments that would allow their use in clinical populations. The objective of this group is to promote a revised legal framework that supports psychedelic research and psychedelic-assisted therapies (PATs) at both EU and national levels. Advocacy for legislative change will be based on data from clinical trials as well as the latest scientific evidence including building on the work of WG3, WG4 and WG5. The main objectives of WG6 are:

1) Advocating for continued prioritisation of mental health on the EU agenda. Specifically, educate policymakers on the scientific potential of psychedelic compounds.
2) Raising awareness of the medical use of psychedelic substances and destigmatising the issue at national, European and international levels. Considering actions for rescheduling psychedelics and changing their legal classification in different European countries.
3) Encouraging increased provision of EU and national funding programmes for psychedelic research to underpin the evidence of its medical potential and further support these therapies.
4) Advocating for the use of psychedelic substances according to the principle of compassionate use of psychedelic substances.
5) Collaborating with national and EU regulators and agencies to accelerate marketing authorisation and Health-Technology Assessment. Specifically, provide evidence-based policy recommendations for their implementation into clinical practice.
6) Integrating the medicinal use of psychedelic substances into EU health initiatives, such as the comprehensive EU approach to mental health or the review of EU pharmaceutical legislation.
7) Engaging with health systems to facilitate the inclusion of new types of psychedelic-assisted therapies.

This is planned to be achieved in coordination with dissemination activities through workshops, educational forums (e.g. organisation of an event in the European Parliament composed of lawmakers and relevant stakeholders to inform policy), as well as formal publications and white papers.

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

NO	title deliverable	WG	format	time frame / months
D1	molecular structures as hot candidates for future development into clinical studies	1	report	one yearly
D2	strategies on development of innovative delivery systems for psychedelics	1	report	one yearly
D3	recommendations for animal psychedelic research focusing on translational validity	2	report on SOPs/publication	40M
D4	molecular and neuroplastic mechanisms underlying therapeutic effects	2	review publication	24M
D5	guidelines and recommendations how to design clinical trials with psychedelics	3	guidelines	24M
D6	multicenter clinical trial protocols	3	at least 2 clinical trial protocols	1 biannually

NO	title deliverable	WG	format	time frame / months
D7	recommendations for education and training of clinicians working with psychedelics	3	report	24M
D8	strategies for optimised and standardised neuroimaging data collection for comparative studies or big data analyses	4	report	48M
D9	a webpage/portal that implements open access databases of scripts for data analyses of psychedelic neuroimaging data and links for available databases	5	web page	12M
D10	a web based hub/portal with access to all documents generated within the PSY-NET	5	web page	12M
D11	recommendations on how to prepare informed consent and GDPR consents in order to enable data sharing	5	public report	36M
D12	open access templates of Informed and GDPR consents	5	templates in editable text format	36M
D13	public reports from events with European and international regulatory authorities	6	report	one yearly
D14	research papers incl. open access with dedication to the PSY-NET	all	Ca. 5 publications a year + report	on yearly basis

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

Risk	Contingency Plan
misunderstandings between partners	Although the Action is highly multidisciplinary and includes experts from a wide variety of disciplines, all face very similar challenges, which ultimately brought them into this network. Moreover, there is already a mutually fruitful collaboration between many of the partners. Action will be managed by people who are experienced in communicating at international level, while also having experience in managing international projects, including COST Action. In case of disagreements and misunderstandings, they will use their diplomatic skills and experience to facilitate a solution. Given the overload of conventional email communications of most researchers today, emphasis will be given to resolving these issues through face-to-face or online structured meetings based on the holacracy principle.
poor engagement of partners	The team has very effective coordinator and YRIs that are involved in coordination activities, so they will pro-actively manage other senior members. Action will use modern communication channels such as social networks or mobile platform groups to further exchange information outside of planned meetings, enabling additional meetings at major international conferences, integrating new YRIs into the community, building professional relationships and establishing new collaborations. For those who cannot join, meetings will be always made hybrid so online participation on meeting will be also an option.
lower involvement of YRIs	There are currently fewer YRIs in the network compared to senior researchers. However, given the fact that the topic of psychedelics is very attractive to young people, we can expect an increase in this population of researchers and clinicians. Moreover, groups of young researchers are already actively forming, such as the young scientists' network on psychedelics within the ECNP´s Psychedelic Research Network. Recruitment of new members of PSY-NET is planned during events, like ECNP thematic meeting in 2026, dedicated to young researchers.
delays with deliverables	The Action Chair and members of the CG will oversee compliance with deliverables and proactively communicate with WG leaders to achieve these goals. The CG and WG leaders will create a detailed implementation plan that comprises detailed Gantt diagrams with clear accountable/measurable tasks assigned between WG members for faster analysis of the achievements, and decision making in case of delay with scheduled tasks.
withdrawal of individual members or member institutions	Considering the fact that psychedelics are now a hot topic in neuropsychiatry, it is more likely that more potential members will be added. The CG and WG leaders will on the one hand proactively create new contacts and opportunities for additional partners to join and in case of withdrawal of either individuals or the whole institution will look for adequate replacements so that the objectives of the Action are fulfilled.
low interest of industry and public partners	Although it is possible that commercial partners will not want to actively participate, the current situation suggests otherwise, because the new pharmaceutical companies that are involved in the psychedelics are very active and support a number of young researchers and participate in various working groups and international conferences actively with researchers from basic or applied research. Analogously to academics, their studies face problems with defining placebo and unblinding, the concept of psychedelic-assisted therapy vs. pure pharmacological effect, etc. The involvement of authorities such as the European Medicines Agency is also likely, as they are already actively involved in addressing psychedelic issues (see EMA workshop on psychedelics). Their involvement is in most cases only possible in an already approved project due to their internal policy (as was communicated with them). The Action will proactively maintain communication in this area at all levels and will invite representatives to PSY-NET meetings even if they are unable to become Action participants, e.g. due to internal agency politics.
unpredictable events (pandemics, war, terrorism, strikes etc.)	Due to several years of experience with the COVID19 pandemic, we will be running most events in hybrid form.

4.1.4. GANTT DIAGRAM

	group/event/activity	Year 1				Year 2				Year 3				Year 4			
	Meetings	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	Management Committee (MC) and Core Group	x		x		x		x		x		x		x			x
working groups	WG1*		x		x		x		x		x		x		x		x
	WG2*		x		x		x		x		x		x		x		x
	WG3*		x		x		x		x		x		x		x		x
	WG4*		x		x		x		x		x		x		x		x
	WG5*		x				x				x				x		x
	WG6*		x				x				x				x		x
	deliverables																
D1	molecular structures				x				x				x				x
D2	delivery systems				x				x				x				x
D3	translational validity														x		
D4	molecular and neuroplastic mechanisms								x								
D5	how to design clinical trials								x								
D6	clinical trial protocols				x								x				
D7	education and training of clinicians								x								
D8	optimised and standardised neuroimaging																x
D9	a webpage of open access databases of scripts				x												
D10	a web based hub/portal				x												
D11	recommendations on how to prepare informed consent and GDPR consents												x				
D12	templates of Informed and GDPR consents												x				
D13	reports from events with European and international regulatory authorities				x				x				x				x
D14	research papers				x				x				x				x

** most of the meetings of working groups will be joined/shared between two or three WG*
x: scheduled

References:

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