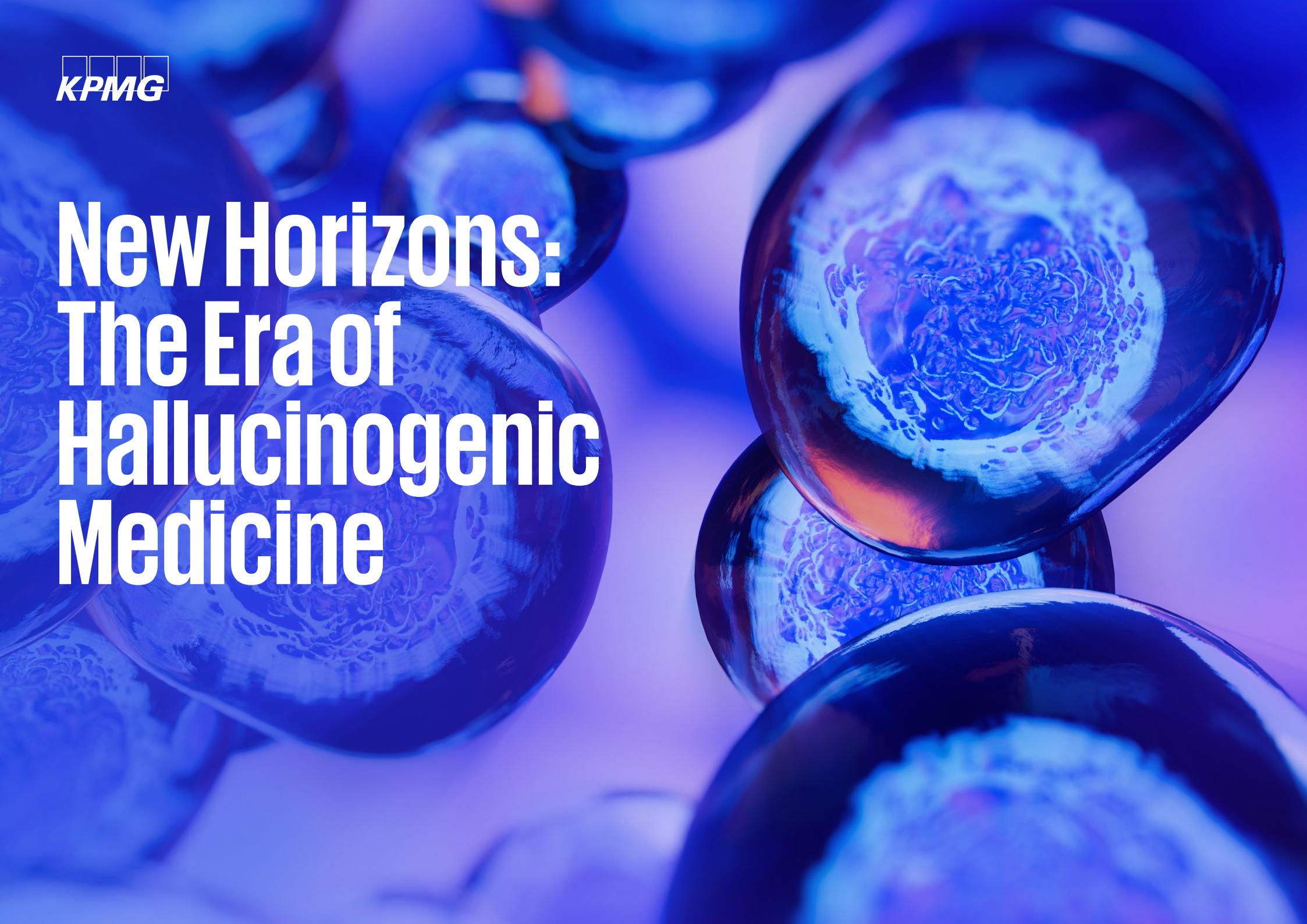
KPMG

New Horizons: The Era of Hallucinogenic Medicine



New Horizons: The Era of Hallucinogenic Medicine

At a time when the leading cause of disability in the world is mental illness, the advent of new treatment options for Health Care Practitioners is overdue (The Lancet., 2020). The number of antidepressant medication prescriptions - the first-line treatment for depression - increases year on year, with the market recently valued at approximately £11bn (PHE., 2020). Prevalence rates of depression have not decreased since records began. One reason suggested for this paradox being that current treatment do not explain why and how depression occurs (Carhart-Harris, 2021). This suggests new breakthrough therapies and research into mechanisms of action are needed.

The last 20 years has seen a significant increase in the number of clinical studies investigating the therapeutic use of hallucinogenic substances for targeted medical indications (Nichols, 2016). Currently, clinical trials with hallucinogenic substances are mostly sponsored by academia. In trials with psilocybin for example only 22 of 99 ongoing and planned Phase I–III trials are sponsored by the industry versus 43 by institutions, according to Global Data's Clinical Trial Database (Clinical Trials Arena., 2022). Following a so-called "dark age" of ~40 years of limited research into these chemicals from the 1960s onwards (as illustrated in Figure 1 below, with relatively little published research), an increase in not only the number of clinical studies, but also positive randomised clinical trials (RCT) with hallucinogenic based therapies, is ushering in a new age of research in this field.

The need for safe and efficacious novel treatments against the backdrop of a global mental health crisis was highlighted by Thomas Insel, MD former Director of the National Institute for Mental Health:

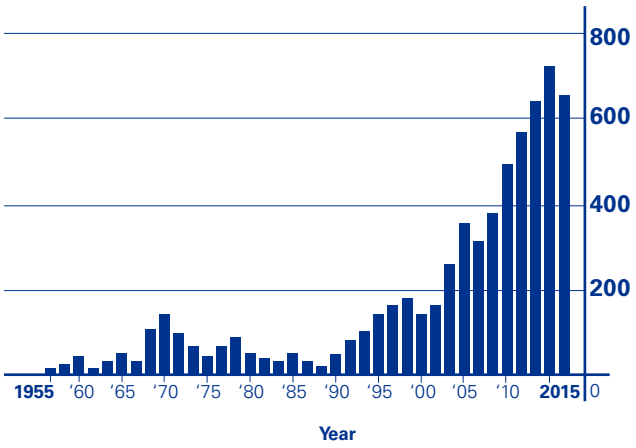
> **"Today there are about 30 different antidepressants, 20 different antipsychotic drugs, seven different mood stabilizers used in bipolar disorder, and [six] different classes of drugs for Attention Deficit Hyperactivity Disorder (ADHD). Almost none of these are more effective than the medications we had [three] decades ago, although newer medications have different and, in some cases, better side-effect profiles (Insel, 2022)."**

There is a need for stakeholders, including payers, Sponsors and Researchers to address an unmet need and exploit the ever-increasing research data indicating the potential for effective hallucinogenic therapies that are safe and relatively inexpensive to develop. The Regulators are prepared to react to the emerging RCT data and support pioneers in this space. Companies should now explore this regulatory landscape providing accessible treatment options for mental health.

Revival of interest in Hallucinogenic and Psychedelic research

Number of papers on psychedelics in the Web of Science database of peer-reviewed publications

Figure 1 - A revival of interest in hallucinogenic / psychedelic research –a web of science review searching for papers mentioning "LSD," "PSILOCYBIN", "PSYCHEDELICS," or "HALLUCINOGENS"



Adapted from (Bloomberg., 2021)

Hallucinogens and Psychedelics? What's the difference?

It's important that the term hallucinogen is defined in clinical practice to allow for homogeneity in comparative trials. Hallucinogenic chemicals are grouped not on their chemical structure (as this can differ greatly between substances in this group) but rather on their pharmacological action where via different biological modes of action they elicit changes in perception, thought, and feeling, ranging from distortions of what is sensed (illusions) to sensing objects where none exist (hallucinations). Figure 2 shows chemicals considered to be hallucinogens in the dark blue circle, with further sub-categorisation into other groups including psychedelics (discussed below).

Hallucinogens are often broadly categorised to include many different psychoactive molecules based on their site of action in the central nervous system (CNS), the receptors they bind to and the effect they elicit.

One sub-group of hallucinogens are psychedelics, which are defined as such by their ability to exert profound subjective alterations in mood, thought and perception, visual and auditory hallucinations, synesthesia, mystical-type experiences, derealization, depersonalization, ego dissolution, etc (Mendes et al., 2022). This subgroup can be further sub-categorised to classic and non-classic psychedelics (also see Figure 3):

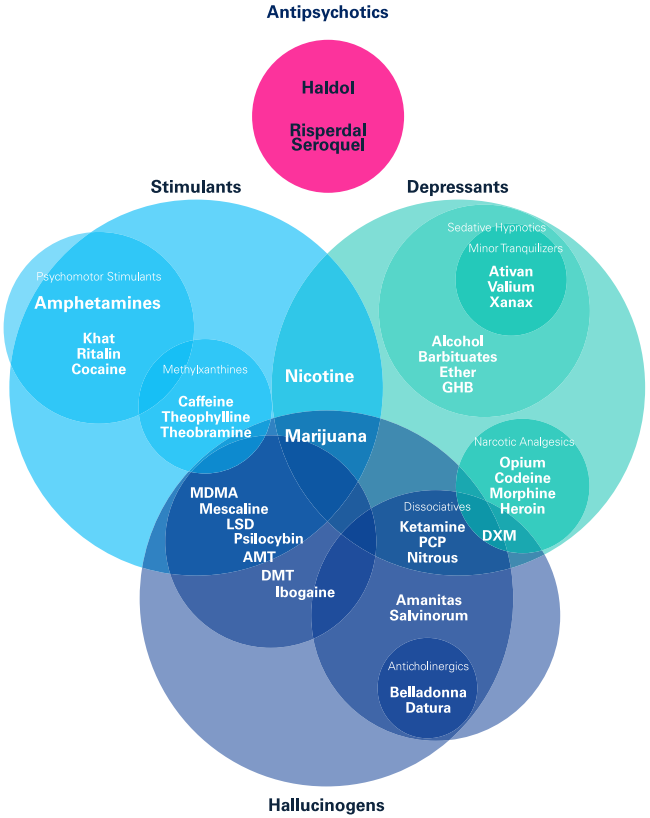
Classic psychedelics:

- Which act as partial or full agonists on the serotonin or (5-HT) 2A receptors – e.g. lysergic acid diethylamide (LSD), dimethyltryptamine (DMT), psilocybin and mescaline (Nichols., 2016)

Non-classic psychedelics:

- Which have varied pharmacological mechanisms. For instance, ketamine is a N-methyl-d-aspartate (NMDA) receptor antagonist; 3,4 methylenedioxymethamphetamine (MDMA) acts as a 5-HT and DA reuptake inhibitor and releaser;
- Ibogaine is an indole alkaloid with multiple targets; salvinorin A is a kappa-opioid receptor agonist; and tetrahydrocannabinol (THC) acts as a cannabinoid receptor partial agonist.
- Whilst these substances can lead to altered states of consciousness with profound changes in somatic and affective processes, perception and cognition, their subjective effects profile is clearly different from those produced by classic psychedelics (Preller and Vollenweider., 2016).

Figure 2 - The categorisation of commonly known controlled substances



Regulatory Challenges Demonstrating the Efficacy of Hallucinogenic Therapies

Whilst the results of recent clinical research are promising, there are regulatory challenges that must be overcome for hallucinogenic substances to be licensed as safe and effective treatment options (Butlen-Ducuing et al., 2023). In an important development for the progression of classic psychedelic compounds to licensed medicines, a number of EU Regulators, including the European Medicines Agency (EMA), the EMA's Central Nervous System Working Party, and the European College of Neuropsychopharmacology (ECNP) have published a joint commentary in The Lancet.

In the publication, the authors highlight the need for safe and effective new treatments for mental disorders, whilst underscoring a range of regulatory and clinical research methodology challenges that require addressing prior to obtaining marketing authorisations with psychedelic therapies. Of note, the authors stipulate that they refer only to research with classic psychedelics (mescaline, DMT, LSD, and psilocybin) with non-classic psychedelics being considered out of scope for the recommendations due to difference in mechanism of action and legal status (see section on The Legal Basis of Hallucinogens).

Stakeholder Regulatory Considerations:

Maintaining double blinding-
Challenges with research methodology need to be addressed to enable valid efficacy estimations in clinical trials. Maintaining a double blind in trials is challenging since placebo can be distinguished from the psychedelic experience by both patients and raters . Alternative RCT protocol designs have been explored, such as low-dose comparators or an active placebo, however the absence of a real placebo group may bias the effect estimate in either direction (Bogenschutz et al., 2022).

Managing positive and negative expectancy-
Positive expectancy is the phenomenon of over-estimating the effect of the treatment based on pre-conceptions around the therapy being given. External influence on expectancy is an important factor in clinical trials with psychedelics where participants are likely to have come across depictions of psychedelics that claim the substances are highly effective (Aday et al., 2022). The same consideration should be given to the role of negative expectancy among trial participants and its effect on symptom worsening or safety issues, also known as the "nocebo" effect (Muthukumaraswamy et al., 2021). It is suggested that researchers utilise independent, external raters, psychedelic naive patients (where possible) and quantify unblinding and expectancy in clinical protocol design.

Dose optimisation-
It is imperative that the optimum dose for psychedelics is investigated, to understand how this dose relates to the characteristics of acute psychedelic experience and clinical efficacy. Understanding the risk of inter-individual variability in drug metabolism and the patient specific pharmacokinetic (PK) profiles relating to factors such as age, sex, ethnicity, and bodyweight are important (Vizeli et al., 2021).

The added value of psychedelics compared to just psychological interventions alone-
Many of the largest and most successful trials with hallucinogens have examined the therapeutic benefit of psychedelics when used in conjunction with psychotherapy or psychological support, with this likely to be captured in any future labelling of approved medicines (Mitchell et al., 2021; Goodwin et al., 2022). However, authors of the Regulatory Perspective Article suggest that trials should confirm that any clinical improvement is not due to the psychotherapy alone (Butlen-Ducuing et al., 2023).

Stakeholder Regulatory Considerations:

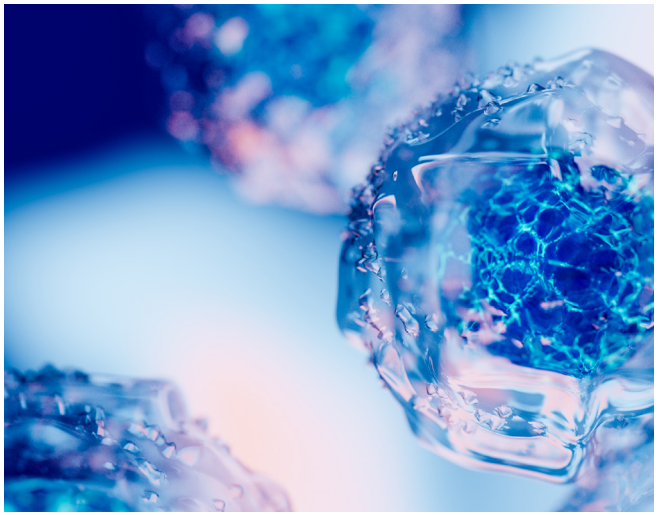
Assessment of preparatory psychotherapy sessions is required-
As mentioned there is a key factor in terms of expectancy and unblinding in trials with psychedelics, therefore it is important to investigate the impact that preparatory psychotherapy prior to administration has on treatment effect. It is also important to have solid methodological basis for evaluating the effects and comparison of effects between different types of psychotherapy and psychological treatment types. This should include the duration of effect, whether repeated sessions are required, any follow up psychotherapy, or the need for adjunctive pharmacological treatment.

Psychedelic therapy safety profiles-
As with any medicine, the safety of psychedelic treatments should be assessed using data generated in clinical trials, as well as by understanding the pharmacological mode of action and the PK properties (e.g half-life) that may influence safety. To date, adverse events (AE's) and serious adverse events (SAE's) that have been noted in RCT with psychedelics include anxiety, derealisation, headaches, increased blood pressure, tachycardia and suicidal ideation and behaviours, require further investigation (Madras., 2022; Breeksema et al., 2022). Additionally, can the short-term psychedelic effects of the treatment be separated from the long-term effects?

Regulatory tools for minimising risk-
It is suggested that safe and effective use of psychedelic treatments can be achieved by using regulatory tools such as the summary of product characteristics (SPC), risk management plans (RMPs) and post approval pharmacovigilance (PV) studies, in conjunction with supporting educational materials for staff and patients. The use of controlled access programmes (CAPs), agreed with national health authorities, have also been successfully implemented in the case of i.e. Esketamine. Esketamine, is a Schedule 2 (considered to have medical value) "non-classical psychedelic" which received approval for use in treating TRD in adults in 2019 (EMA., 2019).

Understanding the risk of drug-
Drug-drug interactions (DDI's), particularly in a population that is most likely to be co-administered other drugs is imperative to the approval process to inform health care professionals. Clear conditions and restrictions for the safe and effective use of any licensed treatment would require defining prior to approval. This should also include monitoring requirements needed to be in place before, during and after the administration of the therapy.

The Current Research Landscape



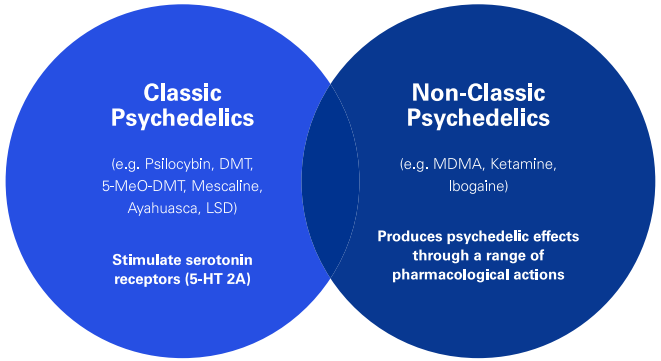
There is a global public health need for effective and safe new medicines to treat mental health disorders. In the EU, impaired mental health affects more than one in six people which is associated with significant individual, societal and economic cost (OECD., 2018). **In 2022 it was reported that the UK economic cost of mental health problems is equivalent to ~ 5% of the country's GDP (McDaid et al., 2022).**

Mental health problems account for 23% of the UK disease burden but only 11% of NHS budget is allocated to mental health services. This disparity is not restricted to the UK; and there is no surprise that in the last 20 years there has been a renewed interest in using hallucinogenic substances for the treatment of a range of mental health disorders including: post-traumatic stress disorder (PTSD), alcohol and substance abuse disorders,TRD and end of life psychological distress (Mitchell et al., 2021; Johnson et al., 2017; Goodwin et al., 2022; Agin-Liebes et al., 2020; Holze et al., 2023).

Hallucinogenic substances as mentioned, can have a range of effects on sensory perception and consciousness but when used in conjunction with psychotherapy and other interpersonal support it is anticipated that patients might expect improved treatment outcomes. Figure 4 shows the different actions and effects of a range of hallucinogenic substances. Research with the medicinal use of hallucinogenic chemicals is showing significant promise, with several high profile and positive outcomes reported from RCTs with well-known chemicals.

For the purposes of this paper, unless a specific derogation is stated, the word **"hallucinogen"** will be used to indicate any chemicals that elicit profound alterations in sensory and perceptual experiences, **with the key property of hallucinogenic chemicals being their ability to change the way people see, hear, taste, smell, feel and affect mood and thought (CAMH., 2022).**

Figure 3 - The difference between classical and non-classic psychedelics.



Classification and Mechanism of Action of Hallucinogens

Figure 4 - Classification and Mechanism of Action of Hallucinogens

Class	Pharmacologic mechanisms	Pharmacologic mechanisms	Drugs
Classic hallucinogens Entactogens	5-HT2A agonists	Visual and auditory hallucinations	LSD, DMT, Psilocybin MDMA
Dissociatives	Monoamine releasers and reuptake inhibitors	Evoke a sense of openness and connection	Ketamine DXM Phency clidine Scopolamine
Muscarinic receptor antagonists	NMDA antagonists	Hallucinations with mooda and Cognitive disturbances	NMDA antagonists

Adapted from (Ford et al., 2022)

The Legal Basis of Psychedelics

One of the main hurdles of undertaking research with some hallucinogenic substances relates to their legal status in the country where the research is performed. **The UN 1971 Convention on Psychotropic Substances** was an international treaty aimed at limiting drug use to scientific and medical purposes, with many national drug laws being passed to implement the convention, for example the **UK's Misuse of Drug Act 1971** and the **US Controlled Substances Act** (UN., 1971). See Figure 5.

The UN convention categorised chemicals such as **Psilocybin, DMT, LSD, MDMA and others as Schedule 1** drugs, meaning they have 1) no therapeutic potential, 2) a high potential for abuse/dependence and cause serious adverse effects (Dos Santos et al., 2021). Whilst **research is still possible with Schedule 1 drugs,** this often translates to costly and **time-consuming bureaucratic processes** to perform both pre-clinical and human studies with these drugs.

For example, **in the UK, Schedule 1 drugs cannot be stored, prescribed, or researched without possession of a controlled drugs (CD) licence from the UK Home Office** (Howard et al., 2021). In a survey of members of the UK's leading psychopharmacology organisation, the British Association for Psychopharmacology (BAP), **the most reported barriers to research were found to be the cost of Schedule 1 CD** licences, storage and security requirements, transportation difficulties and penalties for not adhering to guidelines (Freeman et al., 2018).

Despite the classification of classic psychedelics as Schedule 1 drugs – meaning they are categorised as having "no currently accepted medical use" and high potential for abuse. Research has now shown classic psychedelics demonstrate no potential for addiction, alongside a growing abundance of evidence of their therapeutic potential in psychedelic assisted therapies (Vollenweider et al., 1999).

Figure 5 – Drug schedules in the USA

Schedule	Medical use?	Potential for abuse	Potential for addiction	Examples
Schedule I	✕	!	!	Ecstasy, methaqualone, peyote, heroin, LSD, cannabis
Schedule II	✓ !	!	!	Adderall, Vicodin, Cocaine, Fentanyl, Ritalin, Dexedrine, Oxycodone, Methamphetamine, Methadone, Vyvanse, Hydromorphone,Concerta, Meperidine
Schedule III	✓	!	!	Ketamine, Tylenol with codeine, Anabolic Steroids, Testosterone
Schedule IV	✓	!	!	Xanax, Soma,Ambien, Tramadol, Valium, Ativan, Darvocet, Darvon,Talwin
Schedule V	✓	✕	✕	Robitussin AC, Lomotil, Motofen, Lyrica, Parepectolin

! Has medical uses, but is strictly regulated

! High risk for abuse/ addiction

! Moderate risk for abuse/addiction

✕ High risk for abuse/ addiction

Schedule I according to federal USA regulations; however, it is legal in many states

Adapted from (DEA.gov)

MDMA-Assisted Therapy for Post-Traumatic Stress Disorder (MAPP2- Trial)

In the world's first FDA Phase III trial using MDMA, a randomized, double blind, placebo controlled, multicentre clinical trial to investigate the efficacy and safety of MDMA-assisted psychotherapy, for the treatment of PTSD, was conducted in 100 trial participants (Mitchell et al., 2021). See Figure 6 for an explanation of how MDMA-Assisted Therapy may help treat PTSD.

In this study, the primary study endpoint (18 weeks after baseline), 28 of 42 (67%) of the participants in the MDMA group no longer met the diagnostic criteria for PTSD, compared with 12 of 37 (32%) of those in the placebo group after three sessions. Additionally, 14 of 42 participants in the MDMA group (33%) and 2 of 37 participants in the placebo group (5%) met the criteria for remission after three sessions. Figure 7 is a graphic representation of the study results.

MDMA was found to elicit a statistically significant reduction in Clinician-Administered PTSD Scale (CAPS-5) when compared against placebo ($P < 0.0001$, $d = 0.91$) as well as to significantly reduce the scores in the Sheehan Disability Scale (SDS) when compared against placebo ($p = 0.0116$, $d = 0.43$).

MDMA did not induce adverse events of abuse potential, suicidality or QT prolongation. Overall, the data points indicate potential for MDMA- assisted therapy being effective in the treatment of PTSD, with the treatment being safe and tolerable, even in patients with co-morbidities.

What is MDMA-Assisted Therapy?

Figure 6 - showing how MDMA Assisted Therapy may assist treating PTSD

MDMA is a synthetic compound that **decreases fear and defensiveness,** making it easier for patients to engage with dificult material.

MDMA increases the release of **oxytocin** and **prolactin** (hormones associated with trust and bonding), allowing patients to discuss their memories openly.

MDMA decreases activity in the **amygdala**, associated with fear and traumatic memories, and may **increase interpersonal trust.**

MDMA is a tool for the therapist and patient that can augment the therapeutic process by fostering openness and communication.

No drug is without risks. MDMA has been administered to over **1775 people in clinical studies** with one serious adverse reaction reports, with no lasting harms.

MDMA is not "ecstasy". Substances sold in unregulated markets as "ecstasy" are of unknown strength, may not contain MDMA, and may contain harmful adulterants.

Adapted from (MAPS., 2021)

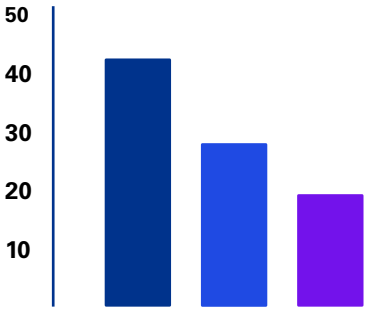
Treatment of PTSD with MDMA Assisted Therapy

Figure 7 - Phase 3 MAPP2 Trial Results – Treating PTSD with MDMA Assisted Therapy **(MAPS., 2021)**

67% of participants in the MDMA assisted therapy group no longer had a PTSD diagnosis after 3 sessions

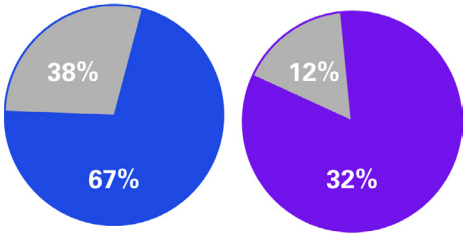
32% of participants in the placebo with therapy group no longer had a PTSD diagnosis 3 sessions

Average Severity of PTSD Symptoms (CAPS-5 Score)



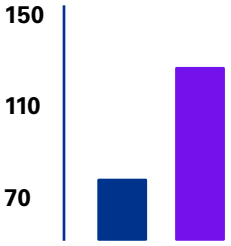
- **Before treatment**
- **Placebo with therapy**
- **MDMA-assisted therapy**

Participants with Clinically Meaningful Response



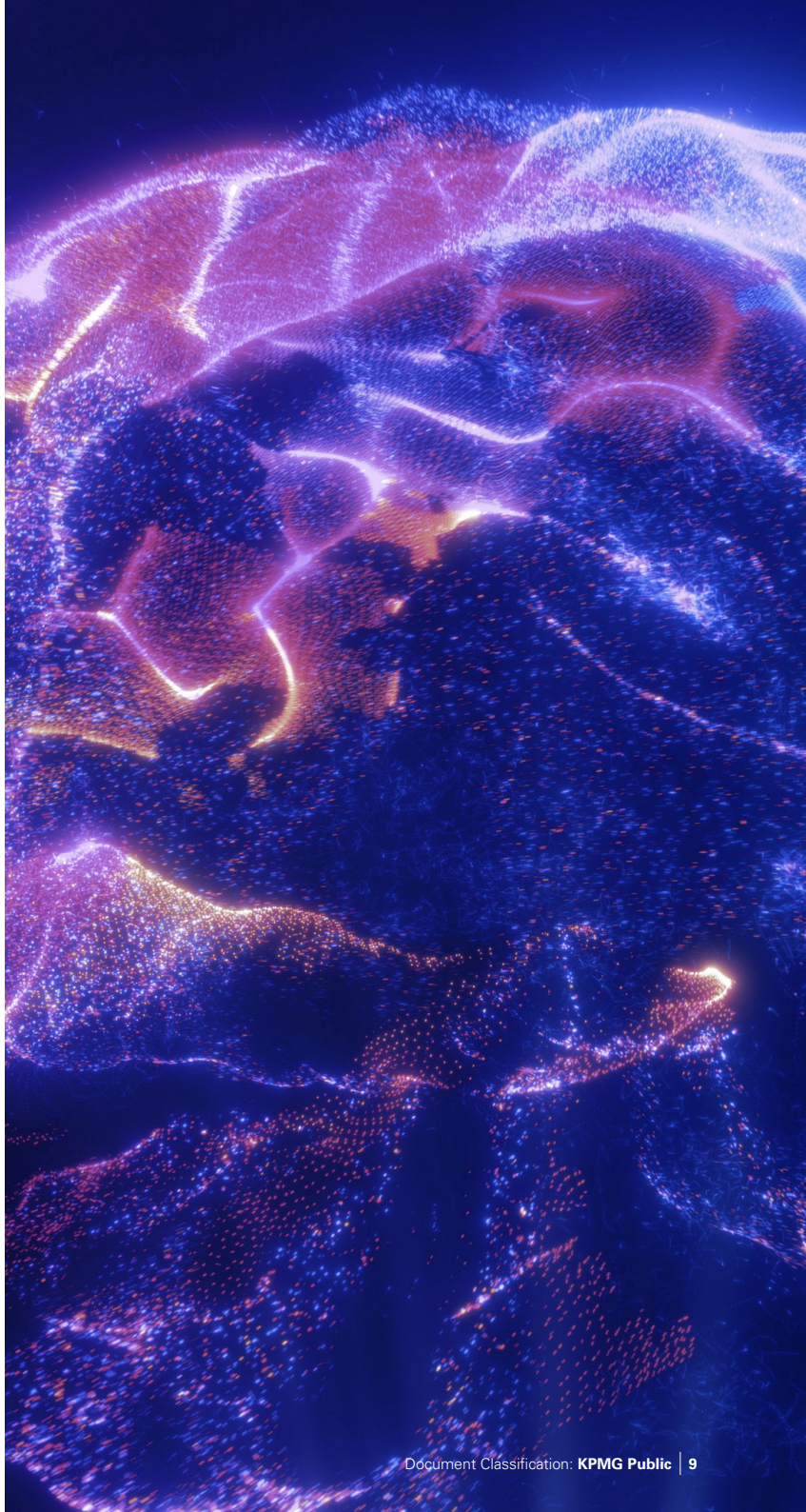
- **Placebo with therapy**
- **MDMA-assisted therapy**
- **No treatment response**

Temporary Blood Pressure Increase with MDMA



- **Systolic Blood Pressure(BP) with MDMA**
- **Diastolic Blood Pressure(BP) with MDMA**

Adapted from (MAPS., 2021)



Psylocybin

- Psylocybin is a naturally occurring compound found in more than 200 species of fungi. Psylocybin is metabolised in the body to psilocin, where it then acts on the serotonin (5-HT) receptors eliciting psychedelic effects. The therapeutic potential of psylocybin has been investigated for over 60 years, however as illustrated in Figure 8 there has been a considerable increase in interest in using psylocybins in clinical research over the last 10/15 years.

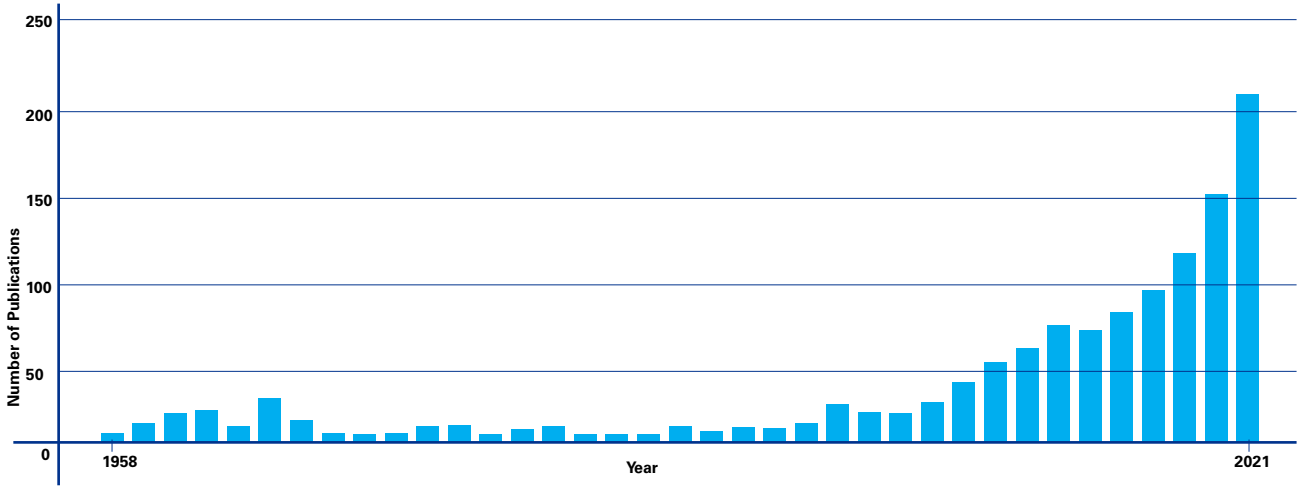
Treatment Resistant Depression
The outcome of these studies with psylocybin is a demonstration of varying degrees of efficacy in the treatment of depression, general anxiety, cancer related anxiety and addiction. Here we will present some of the case studies covering these indications.

COMP360 – Phase 2b Study
In a 2021 Phase II RCT sponsored by COMPASS Pathways, 233 patients with treatment resistant depression (TRD) received a single dose of psylocybin (either 1mg (control), 10mg, or 25mg) in combination with psychological support from therapists (Goodwin et al., 2022).

Approximately 30% of patients in the 25mg group were in remission (Montgomery–Åsberg Depression Rating Scale (MADRS) total score ≤10) at week 3 (29.1%). The 25mg group when in combination with psychological support experienced a statistically significant reduction in symptoms of depression after three weeks when compared to the 1mg control group. The difference between the 25mg group and 1mg group was -6.6 on the MADRS depression scale at week 3 (P < 0.001). See Figure 9 for an illustration of the results.

The results of this study showed that psilocybin at a single dose of 25 mg, but not 10 mg, reduced depression scores significantly more than a 1-mg dose over a period of 3 weeks, but was associated with adverse effects.

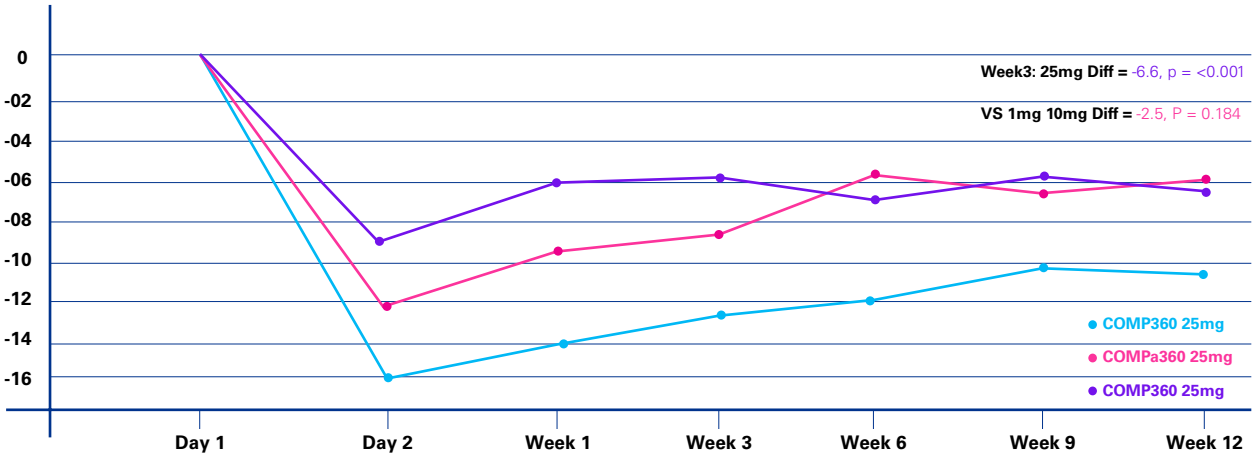
Figure 8 – Psylocybin Research Activity (1958-2021) Number of Studies



Adapted from (Brain Futures., 2022)

Figure 9 - COMP360 trial: The effect of Psylocybin treatment and Psychological Support on TRD

Primary endpoint - change from baseline in MADRS total score
Statistically significant primary endpoint (p<0.001) at week 3 (25mg vs 1mg). There was a rapid onset of action and durable effects with treatment differences between the 25mg vs 1mg group apparent from the day after COMP360 psilocybin administration



Baseline mean (SD): 25mg (n=79) = 31.9 (5.41); 10mg (n=75) = 33.0 (6.31); 1mg (n=79) =32.7 (6.24)

Adapted from (COMPASS Pathways)

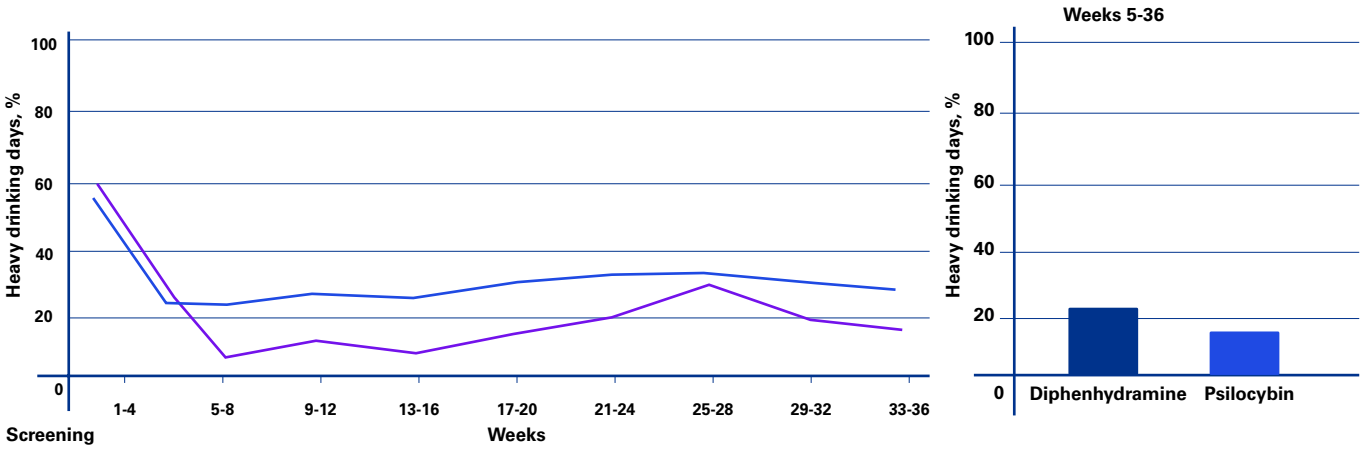
Psylocybin for Treating Addiction – Alcohol Use Disorder (AUD)

A team of scientists conducted a multisite RCT to evaluate the efficacy of psylocybin-assisted psychotherapy for the treatment of AUD (Bogenschutz et al., 2022). The aim was to evaluate whether two administrations of high-dose psylocybin could improve the percentage of heavy drinking days in patients with AUD undergoing psychotherapy compared to outcomes observed with active placebo medication (diphenhydramine) and psychotherapy.

In total, 95 people took part in the study. 49 received the psylocybin study medication and 46 received the diphenhydramine. The percentage of heavy drinking days during the 32-week period was 9.7% for the psylocybin group and 23.6% for the diphenhydramine group, representing a mean difference of 13.9%. The mean daily alcohol consumption was also lower in the psylocybin group. Overall, no serious adverse events were recorded for participants who received psylocybin.

It was also shown that administration of psilocybin together with psychotherapy lead to a more considerable decrease in percentage of heavy drinking days compared to the results derived from the use of an active placebo in combination with psychotherapy. These are summarised in Figure 10.

Figure 10 - Psilocybin Assisted Therapy (PAT) for AUD
Percent heavy drinking days during the 32-week double-blind period was lower in the psilocybin group compared with the diphenhydr-amine group



Percent heavy drinking days
Psilocybin =9.7% | Diphenhyramine = 23.6% | Mean difference, 13.9 (95% CI, 3.0-24.7;P=.01)

Adapted from (Bogenschutz et al, 2022)

The Regulatory Landscape – A Paradigm Shift

Despite the scale of some of the considerations here, the regulatory landscape is more supportive then ever for applicants to develop novel therapies.

The UK MHRA have already granted Innovation Passports (IP) for hallucinogenic therapies as part of their Innovative Licensing and Access Pathway (ILAP) Scheme.

The EMA has already stated its willingness to support stakeholders to address regulatory challenges associated with developing psychedelic therapies, along with providing consultations in parallel with the European Network for Health Technology Assessment (EUnetHTA) (Butlen-Ducuing et al., 2023). EMA support has also included revising guidelines to support researchers, for example updating the guideline on the clinical investigation of medicinal products in the treatment of depression (EMA., 2023).
1971). See Figure 10.

01

The Innovation Passport is the first step in the ILAP and is open to developers of a wide range of medicines. Innovation Passport holders, the MHRA and partners will next work together to create a product-specific Target Development Profile (TDP) for the new medicine.

02

The TDP will define key regulatory and development features, identify potential pitfalls, offer access to specialist toolkits and create a roadmap for delivering early patient access.

03

The TDP will also outline how the Innovation Passport holder can work together with other UK stakeholders to achieve coordinated, efficient evidence generation and evaluation, and address considerations regarding patient access.

04

Companies that have received an Innovation Passport include MAPS for its MDMA-assisted therapy for PTSD, COMPASS Pathways for COMP360 psilocybin therapy for treatment-resistant depression, and to Small Pharma for SPL026, its DMT formulation to treat patients suffering from Major Depressive Disorder (PSYCH., 2023).

MAPS is granted Innovation Passport in United Kingdom for MDMA as an adjunct to therapy for PTSD

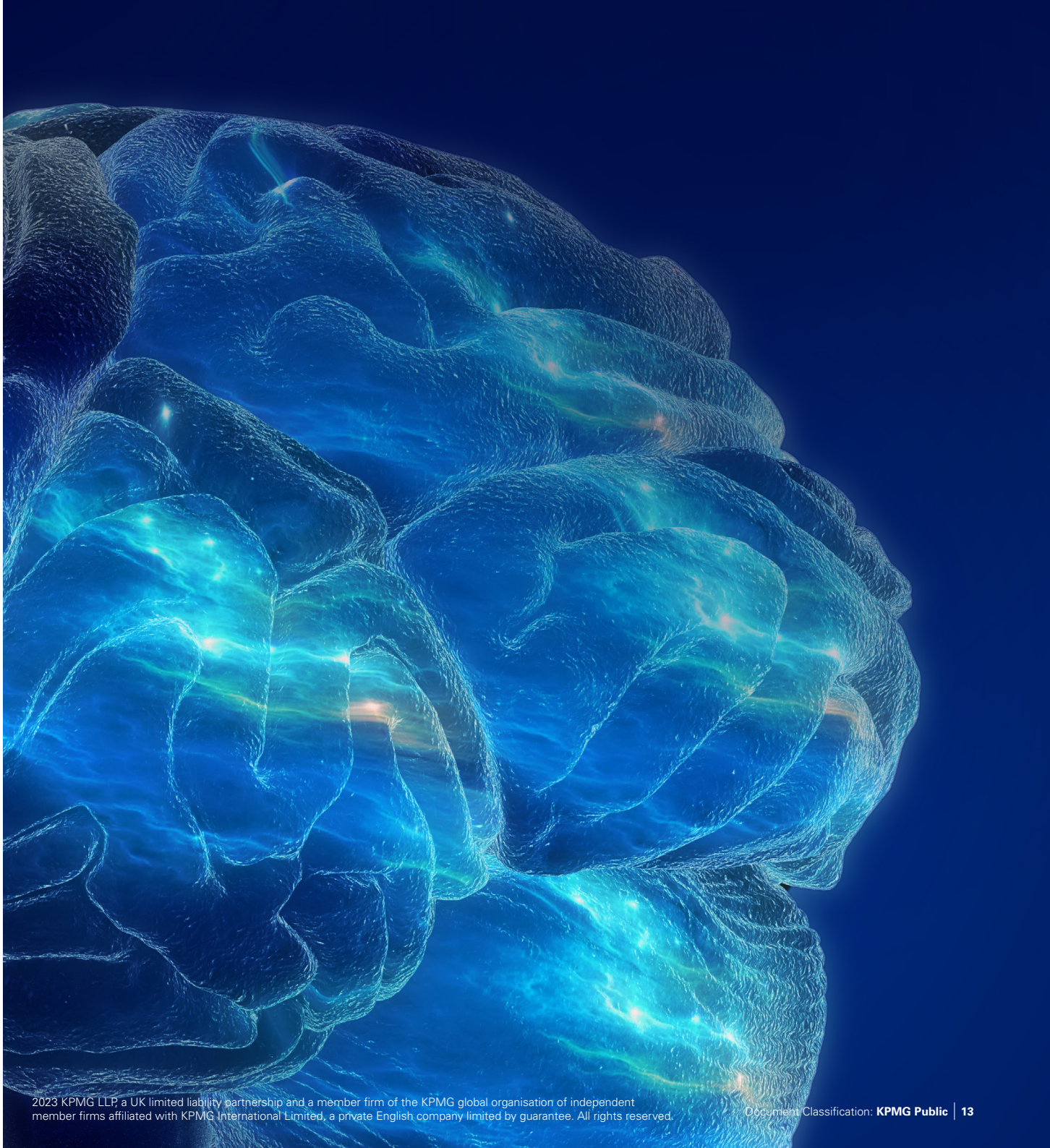
25 January 2022

Future Regulatory Landscape for Psychedelics

Evidence from an ever-expanding clinical data set highlights the promise of hallucinogenic/psychedelic assisted therapies for the treatment of serious mental health disorders. The current research and development landscape is wider reaching, with dozens of potential therapeutic products at preclinical/clinical stages of development. This indicates a licensed therapy with a Schedule 1 hallucinogen may be available in the near future.

How KPMG can help

The KPMG Life Science Regulatory Solutions team has expertise in the field of pharmaceutical and medical device regulations, and can provide advice in terms of understanding potential implications associated with changing policy landscape. In addition, the team offer strategic regulatory advice to life science organisations throughout key product development stages, from early phase planning to launch and compliance for approved products across critical markets internationally.



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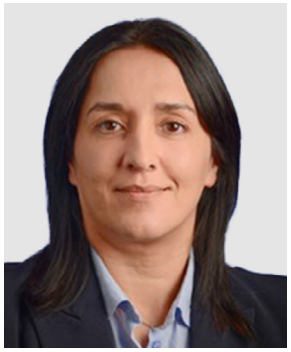

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