A Randomized Controlled Study of the Psychedelic RE104 for the Treatment of Adjustment Disorder in Patients With Cancer and Other Medical Illnesses

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CONCLUSIONS

1. AjD in patients with cancer and other medical illnesses, including MS, ALS, PD, and IPF, can be profoundly distressing and disabling; effective treatments for this condition are a significant clinical unmet need
2. Development of an effective, well-tolerated, and rapidly active psychedelic agent may offer an important treatment option for affected patients
3. RE104 is being actively investigated in a Phase 2, double-blind, randomized, controlled trial, and trial results will elucidate whether there is potential for it to treat the underserved population of patients who have AjD associated with medical illness

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BACKGROUND ON ADJUSTMENT DISORDER

PSYCHOLOGICAL DISTRESS OF CANCER AND MEDICAL ILLNESSES

- Cancer and other medical illnesses, such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease (PD), and idiopathic pulmonary fibrosis (IPF), can be distressing for both patients and their caregivers
  - In addition to suffering mounting physical debility as well as the prospect and management of disease-related interventions, patients must deal with the emotional impact of their illness and a potentially poor prognosis[1,2]
  - The psychological distress adversely affects quality of life (QOL) and may negatively influence the clinical course of the disease and lead to poor treatment adherence[2,3]

DEFINITION OF ADJUSTMENT DISORDER

- Adjustment disorder (AjD) is a psychological condition characterized by the development of emotional or behavioral symptoms in response to an identifiable stressor[4] (**Table**)
  - While these stress responses are natural, AjD is characterized by a response that is disproportionate to the severity or intensity of the stressor, or symptoms that cause functional impairment[4]

Table. Diagnostic Criteria for Adjustment Disorder[4]

DSM-5-TR	ICD-11
▪ Onset of emotional or behavioral symptoms occurring in response to an identifiable stressor and within 3 months of the stressor ▪ Symptoms are clinically significant and marked by – Distress that is disproportionate to the severity or intensity of the stressor (accounting for cultural or other contextual factors) – Significant impairments in social, occupational, or other domains of functioning ▪ Disturbance does not meet the diagnostic criteria for another mental disorder and is not an exacerbation of a preexisting disorder ▪ Symptoms do not represent normal bereavement ▪ Symptoms do not last >6 additional months after the stressor or its consequences have been resolved	▪ Presence of an identifiable psychosocial stressor, with symptoms emerging within 1 month of the stressor ▪ Preoccupation related to the stressor or its consequences in the form of ≥1 of the following: – Excessive worry about the stressor – Recurrent and distressing thoughts about the stressor – Constant rumination about the implications of the stressor ▪ Failure to adapt to the stressor that causes significant impairment in personal, family, social, educational, or other important areas of functioning ▪ Symptoms are not of sufficient specificity or severity to justify the diagnosis of another mental or behavioral disorder ▪ Symptoms typically resolve within 6 months, unless the stressor persists for a longer duration

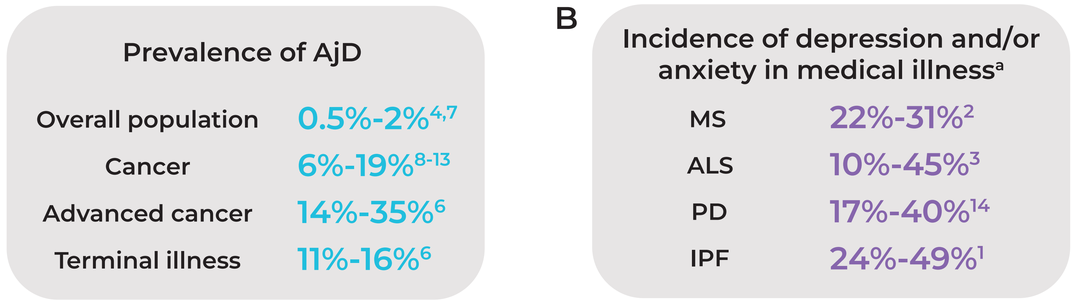
DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision; ICD-11, International Classification of Diseases and Related Health Problems 11th Revision.

- Patients with AjD may experience a range of symptoms that can vary between patients and severely affect QOL[5] (**Figure 1**)
  - There are 6 identified subtypes of AjD: depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, mixed disturbance of emotions and conduct, and unspecified[4]

Figure 1. Symptoms of adjustment disorder.

- AjD is more common in individuals with serious illness[6] relative to the general population[4,7] and is the most commonly diagnosed psychiatric disorder in patients with cancer[6,8-13] (**Figure 2**)
  - Other serious illnesses, such as MS, ALS, PD, and IPF, can be associated with depression and anxiety, which are prevalent symptoms of AjD[1-3,14]

Figure 2. (A) Prevalence of adjustment disorder. (B) Incidence of depression and/or anxiety in medical illness.



AjD, adjustment disorder; ALS, amyotrophic lateral sclerosis; IPF, idiopathic pulmonary fibrosis; MS, multiple sclerosis; PD, Parkinson's disease. [a]AjD is not well characterized in these populations, but depression and/or anxiety is common.

TREATMENT FOR ADJUSTMENT DISORDER

- Despite AjD being a common diagnosis, there is a gap in research regarding treatments for the disorder, which translates to a lack of evidence-based treatment guidelines[15,16]
  - This is partly due to the transient nature of the disorder (depending on the duration of the stressor), symptoms present in other psychiatric disorders, and, until recently, lack of clear diagnostic criteria[4]
- Current standard of care for AjD includes both psychotherapeutic and pharmacologic treatments[17]
  - However, both treatment types are variably effective, and there are currently no US Food and Drug Administration–approved pharmacotherapies or evidence-based combined pharmacologic-psychosocial interventions to treat AjD[17]
  - Although the use of pharmacotherapy in cancer-related or other illness-related psychiatric conditions is common, a meta-analysis failed to show superiority of antidepressants over placebo, and there was insufficient evidence to substantiate the effectiveness of anxiolytic treatment for AjD[17]
  - Moreover, with many currently prescribed pharmacotherapies, the onset of clinical improvement is delayed, relapse rates are high, and significant side effects compromise treatment adherence[18]
- The unmet need for effective treatments for AjD has stimulated interest in exploring the therapeutic potential of psychedelic medicines, particularly for resistant forms of the disorder
  - A rapid-acting psychotropic medication with favorable safety would allow patients to better employ available coping strategies and prevent progression into a more severe mental disorder
- The psychedelic psilocybin has been shown to rapidly improve anxiety and depression symptoms, improve demoralization and overall QOL, and provide durable outcomes without serious adverse events in patients with cancer[19-22]
  - While psychedelics have not been systematically studied for treatment of AjD in patients with medical illnesses, there are phenomenological and mechanistic similarities between AjD and anxiety and depression that support the clinical potential of psychedelics to treat AjD[23]

BACKGROUND ON RE104

- RE104 (4-Glutaroyl-3-[2-diisopropyl-aminoethyl]-1H-indole hydrochloride) is a prodrug of the synthetic psychedelic drug 4-OH-DiPT, a molecule that is unique from, but structurally related to, psilocin, the active metabolite of psilocybin[24]
  - RE104 is being developed as a subcutaneous injection to enable rapid conversion to the active metabolite, promote optimal absorption, and ensure a relatively short and reproducible psychedelic experience[24]

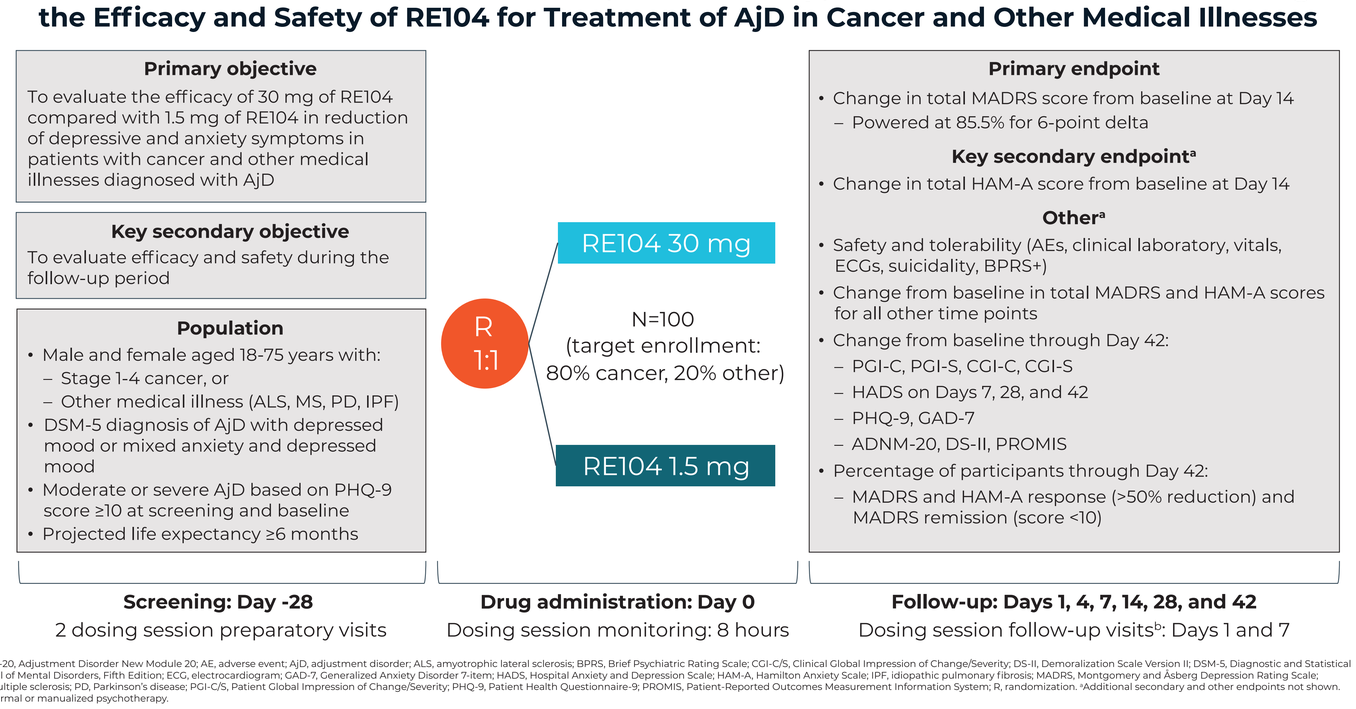
PRIOR STUDIES OF RE104

- Preclinical studies of RE104 demonstrated a strong relationship between the pharmacokinetic profile of RE104 (and the active metabolite 4-OH-DiPT) and pharmacodynamic effects, with antidepressant effects observed in rodent models[24]
- A Phase 1 study in healthy adult volunteers who had prior psychedelic experience found that a subcutaneous injection of RE104 was well tolerated, with a similar safety profile to psilocybin[25]
  - Dose-dependent increases in psychoactive effects were observed in participants treated with RE104[25]
  - Most participants treated with ≥30 mg of RE104 experienced a "complete mystical experience"[25]
  - Peak effect was reached in 1.2 hours, with a mean duration of 3.6 hours, which was notably shorter than the typical duration of psilocybin[25]
  - These results support the potential clinical benefit of RE104 and warrant further investigation of RE104 in Phase 2 trials

REKINDLE: A PHASE 2 TRIAL OF RE104 FOR ADJUSTMENT DISORDER DUE TO CANCER AND OTHER MEDICAL ILLNESS

- A Phase 2, double-blind, randomized, controlled trial is currently being initiated to investigate whether a single dose of RE104 will provide durable benefit for participants with multidimensional psychiatric distress associated with AjD due to cancer or other medical illness (**Figure 3**)
  - Results from this trial are expected to expand knowledge about the clinical potential of psychedelics for treatment of AjD associated with medical illness and begin filling the gap related to the lack of high-quality research in this underserved patient population

Figure 3. Phase 2 REKINDLE trial overview.



ADNM-20, Adjustment Disorder New Module 20; AE, adverse event; AjD, adjustment disorder; ALS, amyotrophic lateral sclerosis; BPRS, Brief Psychiatric Rating Scale; CGI-C/S, Clinical Global Impression of Change/Severity; DS-II, Demoralization Scale Version II; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECG, electrocardiogram; GAD-7, Generalized Anxiety Disorder 7-item; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Anxiety Scale; IPF, idiopathic pulmonary fibrosis; MADRS, Montgomery and Åsberg Depression Rating Scale; MS, multiple sclerosis; PD, Parkinson's disease; PGI-C/S, Patient Global Impression of Change/Severity; PHQ-9, Patient Health Questionnaire-9; PROMIS, Patient-Reported Outcomes Measurement Information System; R, randomization. [a]Additional secondary and other endpoints not shown. [b]Not formal or manualized psychotherapy.