26 August 2026

US Phase 2 clinical trial of TRP-8803 against leading antidepressant treatment in Major Depressive Disorder

- **Pre-CTA secured with the University of California, San Francisco (UCSF) to develop a Phase 2 head-to-head trial of TRP-8803 against escitalopram (Lexapro®)**
- **Escitalopram is the most widely prescribed antidepressant in the US, providing an established benchmark to directly evaluate TRP-8803**
- **There were ~37m prescriptions to 8.8m patients of Escitalopram administered to patients in the US alone in 2023[1] while 21m US adults experience a major depressive episode annually, with prevalence highest among 18–25-year-olds at 18.6%[2]**
- **Trial will recruit young adults in the US with Major Depressive Disorder and assess depression severity over eight weeks and six months**
- **Study aims to explore earlier treatment with TRP-8803 in the depression treatment pathway rather than after failure of conventional therapies**
- **Trial expected to commence in H1 CY27 and be led by Professor Robin Carhart-Harris, the world's foremost psychedelic researcher**
- **With 52,000+ citations, Professor Carhart-Harris is the world's most influential psychedelic neuroscientist and one of the most cited figures in modern neuropsychopharmacology**
- **Entropy sponsors the FDA IND and progress the required regulatory activities to support FDA clearance of the proposed trial**
- **Subject to FDA acceptance, an IND for TRP-8803 may establish a broader US regulatory pathway, capable of supporting a US clinical development program**
- **Trial to be funded from existing cash reserves, option conversions and pending R&D Tax Incentives**
- **Investor webinar to be held on Friday, 28 August at 11:00am AEST (9:00am AWST)**

Melbourne, Australia – Entropy Neurodynamics Limited ('**Entropy Neurodynamics**' or the '**Company**') (**ASX: ENP**), a clinical-stage biotechnology company developing precision-controlled psychedelic therapies, is pleased to advise it has signed a pre-Clinical Trial Agreement ("pre-CTA") with the University of California, San Francisco ("UCSF") to undertake a Phase 2 clinical trial to compare the Company's proprietary TRP-8803 (IV-infused psilocin) with escitalopram (Lexapro®), the most widely prescribed antidepressant in the US, in up to 80 young adults with Major Depressive Disorder ("MDD").

The proposed trial is an important expansion of the clinical development program for TRP-

8803, establishing a pathway into the US and evaluating the treatment directly against an established antidepressant treatment, and the current standard of care in young adults with MDD.

This innovative head-to-head comparative trial is to be led by Professor Robin Carhart-Harris as Principal Investigator. Dr. Carhart-Harris is the Ralph Metzner Distinguished Professor of Neurology and Psychiatry at UCSF and one of the world's foremost researchers in psychedelic therapies. His research has played a significant role in advancing the modern scientific understanding of psychedelic therapies, including as lead author of the landmark New England Journal of Medicine ("NEJM") trial directly comparing psilocybin therapy with escitalopram in patients with moderate-to-severe MDD.

Under the pre-CTA agreement, Entropy and UCSF will work closely to develop the clinical trial protocol, informed consent and establish the electronic data capture forms for the proposed trial. The Company will act as the US Food and Drug Administration (FDA) Investigational New Drug ("IND") sponsor and, with UCSF's support, progress the required regulatory activities to support commencement of the trial in the United States.

Importantly, establishing an FDA IND for TRP-8803 provides a broader US regulatory foundation for the clinical development program, including those informed by results from Entropy's ongoing 72-patient, eight-indication Phase 1b/2a Basket-design Study with Swinburne University of Technology (refer ASX announcement: 4 August 2026).

The MDD trial directly complements Entropy's existing Australian clinical programs while advancing a US development pathway capable of supporting the broader clinical development of TRP-8803.

Phase 2 trial overview:

Major Depressive Disorder is standardly treated with selective serotonin reuptake inhibitors ("SSRIs"), such as escitalopram. While SSRIs are widely used, treatment typically involves ongoing daily dosing and their use can be associated with emotional blunting, sexual dysfunction and other tolerability issues that may affect quality of life and treatment adherence. Response to SSRIs can also vary widely between patients, creating a need for alternative treatment approaches that can deliver meaningful and durable outcomes without reliance on continuous daily medication.

The proposed Phase 2 trial is intended to investigate whether a limited course of precision-controlled TRP-8803 treatment can deliver meaningful clinical and functional outcomes to patients when compared directly with conventional daily SSRI treatment in young adults experiencing MDD using established measures of depression together with treatment adherence, tolerability and key safety assessments. Secondary measures will be included to assess patient wellbeing, meaning and connectedness, work, social functioning and longer-term outcomes. The trial is also expected to incorporate EEG measures, including complexity, spectral power and network dynamics, to investigate potential mechanistic differences between precision-controlled IV psilocin and conventional SSRI treatment.

The proposed trial will build on Dr Carhart-Harris' landmark NEJM trial comparing oral psilocybin with escitalopram, which demonstrated encouraging clinical outcomes for psilocybin, including higher remission rates and improvements across a range of

secondary measures to evaluate whether the precision, predictability and control offered by TRP-8803 can further enhance the potential of psychedelic therapy when compared directly with an established SSRI.

Strategic rationale:

The proposed trial advances two key elements of Entropy's development strategy for TRP-8803: evaluating the treatment at an earlier timepoint in the depression treatment pathway and establishing a broader clinical and regulatory pathway in the US.

While much of the development of novel therapies for depression has focused on treatment-resistant patients, the trial will evaluate TRP-8803 in young adults experiencing earlier stages of MDD. The head-to-head design provides an opportunity to assess whether a limited, precision-controlled intervention can provide an alternative to ongoing daily antidepressant therapy, while directly comparing TRP-8803 to an established SSRI treatment.

TRP-8803 has been designed to address key limitations associated with oral psilocybin administration. By delivering psilocin through IV-infusion, the platform delivers rapid onset, precise control over treatment duration, intensity and predictability of the psychedelic experience. This precision-controlled approach has the potential to improve treatment consistency and clinical management while offering a more reproducible and scalable treatment model.

The proposed US regulatory pathway is also strategically important beyond this trial. Subject to FDA clearance, establishing an IND for TRP-8803 provides a regulatory foundation to support additional US clinical development, including other Phase 2b/3 studies in selected indications informed by data from the Company's ongoing 72-patient, eight-indication Phase 2 Basket-design Study with Swinburne University of Technology (refer ASX announcement: 4 August 2026).

Together, the proposed UCSF trial, Australian clinical program and future US IND are intended to generate a broad body of clinical evidence from which Entropy can prioritise indications and subsequent development pathways for TRP-8803.

BioCina will manufacture the GMP-grade TRP-8803 and matched placebo vials for the US clinical program, providing the scalable manufacturing capabilities to support future clinical development (refer ASX announcement: 19 August 2026).

Management commentary:

UCSF Ralph Metzner Distinguished Professor of Neurology and Psychiatry and Principal Investigator, Professor Robin Carhart-Harris said: *"Our previous trial comparing psilocybin with escitalopram provided encouraging evidence for the potential of psychedelic therapy in MDD and raised important questions about how these different treatment approaches compare clinically and mechanistically.*

"TRP-8803 provides an opportunity to build on that work using an IV formulation of psilocin designed to offer greater precision, predictability and control over the treatment experience. These characteristics are particularly interesting from a research perspective because they may enable us to examine the effects of psilocin with a level of control that is difficult to achieve with oral psilocybin.

"The proposed trial will also examine an important patient population. By studying young adults experiencing major depression, we have an opportunity to investigate psychedelic therapy earlier in the course of the condition and directly compare a limited intervention with conventional daily antidepressant treatment.

"I look forward to working with Entropy and the team at UCSF to develop and undertake a rigorous trial that can advance our understanding of both the clinical and mechanistic potential of precision-controlled psilocin therapy."

Entropy CEO and Executive Director, Mr Jason Carroll said: *"This is a bold and revolutionary step forward for TRP-8803 and significantly expands the clinical and regulatory pathway we are building around the program. Working with UCSF and Professor Carhart-Harris provides us with the opportunity to evaluate TRP-8803 directly against the most widely prescribed antidepressant in the US and the world, in a patient population where treatment decisions made early in the course of depression can have long-term implications.*

"What is particularly compelling about this trial is that we are moving upstream in the treatment pathway. Until now, the development of novel therapies for depression have focused on patients who have already failed years on conventional treatments. We want to understand whether a limited number of precision-controlled TRP-8803 treatments can provide an effective alternative treatment in young adults experiencing major depression much earlier in the condition progression.

"The trial also has strategic importance beyond MDD. Subject to FDA clearance, establishing an IND for TRP-8803 would provide Entropy with a US regulatory foundation that could support the broader development of the platform. As data emerges from our 72-patient Basket-design Study in Australia, this may support a pathway to advance selected indications into subsequent Phase 2b/3 studies in the US.

"We've been building these pieces very carefully and deliberately over the last 18 months. We now have a broad Australian clinical program underway, a proposed US trial with the world's leading psychedelic researcher, a pathway towards an IND with the FDA and a manufacturing relationship with BioCina, designed to support TRP-8803 as the program advances. Together, these initiatives are intended to generate the clinical evidence required to determine where TRP-8803 may have the greatest therapeutic potential and open the Company to commercial partnership discussions."

Next steps:

Entropy and UCSF will now progress the activities required to develop the proposed Phase 2 trial in the US, including:

- Develop and finalise the clinical trial protocol and informed consent with UCSF
- Schedule a pre-IND meeting with FDA to confirm the protocols acceptability;
- Submit an IND application to the US FDA for TRP-8803 for the proposed trial; and

- Following FDA clearance of the trial protocol, finalise the Clinical Trial Research Agreement ("CTRA") with UCSF

Investor webinar:

CEO and Executive Director, Mr Jason Carroll will host an investor webinar at 11:00am (9:00am AWST) on Friday, 28 August to provide additional information about the Company's pending MDD trial, as well as the Company's broader TRP-8803 development program.

The brief will be followed by a Q&A session. Questions can be submitted to henry.jordan@sdir.com.au prior, or during the webinar.

Investor can register via the following link:

- https://us02web.zoom.us/webinar/register/WN_iYnFo3IpR0aka9tFHn42Dw

The webinar will be recorded, with a reply to be made available on the Company's website and social media channels following the event.

This announcement has been authorised by the Board of Entropy Neurodynamics Limited.

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About Entropy Neurodynamics Limited

Entropy Neurodynamics is a clinical-stage biotechnology company focused on developing proprietary, novel formulations for the administration of psilocin in combination with psychotherapy to treat diseases with unmet medical needs. The Company's lead program, TRP-8803, is a proprietary formulation of IV-infused psilocin (the active metabolite of psilocybin) with potential to alleviate numerous shortcomings of oral psilocybin including: significantly reducing the time to onset of the psychedelic state, controlling the depth and duration of the psychedelic experience, and reducing the overall duration of the intervention to a commercially feasible timeframe. Development of TRP-8803 follows a number of Phase 2a clinical trials using oral psilocybin for the treatment of Binge Eating Disorder, Irritable Bowel Syndrome and Fibromyalgia. Results from each of these trials demonstrated the clinical benefits of psychedelic therapy and will be used to further enhance the development of TRP-8803.

Register for updates

The Company encourages investors to register their details with Automic Group investor portal. This also provides shareholders with the opportunity to elect communication methods to electronic only. This can be done via the following steps:

- *Go to investor.automic.com.au*

- *If you're an existing user, log in with your username and password*
- *If you're a new user, click 'register', select 'Entropy Neurodynamics Limited'. Enter your Holding Number and postcode of the registered address on your holding. If your address is outside Australia, select the country. Follow the prompts to set up a username and password.*
- *Once you have created your account, you will need to update your communication method by clicking 'my details' under the 'profile' section of the investor portal account, then navigating to 'communication preferences' and select 'electronic only'.*

Risks associated with Psilocin

All medicines carry risks and specialist prescribers, such as registered psychiatrists are best placed to assess the suitability of a new medication against a patient's individual circumstances and medical history before proceeding. Adverse effects of psilocybin and similar compounds, such as psilocin, can include temporary increase in blood pressure and a raised heart rate. There may be some risk of psychosis in predisposed individuals. These effects of psilocybin and its derivatives are unlikely at low doses and in the treatment regimen used in psychedelic-assisted psychotherapy and appropriately managed in a controlled environment with direct medical supervision.

Forward-Looking Information

Certain information in this news release, constitutes forward looking information. In some cases, but not necessarily in all cases, forward-looking information can be identified by the use of forward-looking terminology such as "plans", "targets", "expects" or "does not expect", "is expected", "an opportunity exists", "is positioned", "estimates", "intends", "assumes", "anticipates" or "does not anticipate" or "believes", or variations of such words and phrases or state that certain actions, events or results "may", "could", "would", "might", "will" or "will be taken", "occur" or "be achieved". In addition, any statements that refer to expectations, projections or other characterizations of future events or circumstances contain forward-looking information. Statements containing forward-looking information are not historical facts but instead represent management's expectations, estimates and projections regarding future events. Forward-looking information is necessarily based on a number of opinions, assumptions and estimates that, while considered reasonable by Entropy Neurodynamics as of the date of this news release, are subject to known and unknown risks, uncertainties, assumptions and other factors that may cause the actual results, level of activity, performance or achievements to be materially different from those expressed or implied by such forward looking information, including but not limited to the factors described in greater detail in the "Risk Factors" section of the Company's Replacement Prospectus available at www.asx.com.au These factors are not intended to represent a complete list of the factors that could affect Entropy Neurodynamics; however, these factors should be considered carefully. There can be no assurance that such estimates and assumptions will prove to be correct. The forward-looking statements contained in this news release are made as of the date of this news release, and the Company expressly disclaims any obligation to update or alter statements containing any forward-looking information, or the factors or assumptions underlying them, whether as a result of new information, future events or otherwise, except as required by law.

[1] *https://clincalc.com/drugstats/Drugs/Escitalopram*

[2] https://www.nimh.nih.gov/health/statistics/major-depression