ASX Release **21 August 2025**

Landmark agreement to validate a novel EEG-based brain entropy biomarker for precision psychiatry

- **Agreement signed with international key opinion leader Professor Robin Carhart-Harris and Professor Pedro Mediano of the Imperial College London to validate a new EEG-based biomarker platform for use in clinical practice**
- **Agreement leverages real-time cortical entropy research to predict and optimise the therapeutic utility of TRP-8803 and provide a quantitative measure for mental health disorders**
- **Development based on Carhart-Harris' Entropic Brain Hypothesis which predicts psychedelics increase brain entropy, enhancing neural flexibility, and unlocking potential for therapeutic change**
- **EEG data from previous trials has demonstrated that TRP-8803 induces high brain entropy states**
- **Development of the biomarker will commence next month using TYP EEG data from the Phase 1 trial and the upcoming study using TRP-8803 as a treatment for Binge Eating Disorder**

Melbourne, Australia – Tryptamine Therapeutics Limited ('**Tryp**', '**TYP**' or the '**Company**') (**ASX: TYP**), a clinical-stage biotechnology company, is pleased to advise it has entered into an exclusive biomarker development agreement (the 'Agreement') with Professor Robin Carhart-Harris, Chair of TYP's Scientific Advisory Board and Professor Pedro Mediano of the Imperial College London to develop a proprietary electroencephalogram (EEG) based platform to support clinical development of the Company's lead asset, TRP-8803 (IV-infused psilocin).

Under the terms of the exclusive collaboration, Professor Carhart-Harris and Professor Mediano will work alongside the Company to develop a proprietary EEG-based biomarker platform leveraging real-time cortical entropy to predict and optimise therapeutic outcomes before, during and after IV administration of TRP-8803.

The initiative aims to establish new frontiers in biomarker-guided precision psychiatry, building a platform to allow clinicians to identify patients that may best respond to psychedelic intervention and modulate dosing in real time to reach the optimal neuroplasticity window.

Trials of Central Nervous System (CNS) active treatments that use biomarkers have more than a 10-fold higher probability of achieving regulatory approval.[1] Importantly, pricing of new drugs with companion biomarkers is typically greater than drugs without biomarkers and IP is significantly strengthened with the use of a companion diagnostic.

This companion biomarker program is based on the Entropic Brain Hypothesis pioneered by Prof. Carhart-Harris and will integrate machine learning algorithms with closed-loop EEG monitoring to define and modulate the ideal therapeutic zone for TRP-8803 infusion. The resulting diagnostic tool is expected to generate quantitative measures for mental health conditions, providing a new precedent in regulatory-grade physiological markers in psychiatry.

1. Wong, C. H., Siah, K. W. & Lo, A. W. Estimation of clinical trial success rates and related parameters. *Biostatistics* **20**, 273–286 (2019).

Brain Entropy

Professor Carhart-Harris' ground-breaking Entropic Brain Hypothesis proposes that richness and cognitive flexibility of conscious experience are linked to the entropy - or variability - of spontaneous brain activity. In normal waking states, brain entropy is relatively low, supporting stable, ordered cognition. Psychedelic compounds such as TRP-8803 increase brain entropy, moving the system closer to a zone between order and complexity, where connectivity patterns become more flexible and receptive to change. This heightened state may help loosen rigid, maladaptive neural patterns, offering a potential mechanism for therapeutic benefits observed in neuropsychiatric disorders and mental health conditions.[2]

Utilising EEG to measure entropy provides for non-invasive, high resolution and real time brain signalling data by capturing the brain's electrical language by recording voltage fluctuations from neuronal activity across the scalp. These signals reflect synchronised cortical neurons, revealing pattens that encode a person's perceptions, attention, emotion and cognition.

Tryp has already undertaken work to explore psychedelic-induced entropy dynamics, which has delivered promising connective network reorganisation in animal models, as well as undertaking EEG measurements during its Phase 1b trial using TRP-8803. During the Phase 1b trial, spectral power was considerably higher at all EEG electrode points for the loading dose phase, compared to baseline (refer image below). This highlights the significant, biomarker potential for Professor Carhart-Harris' Entropic Brain Hypothesis.

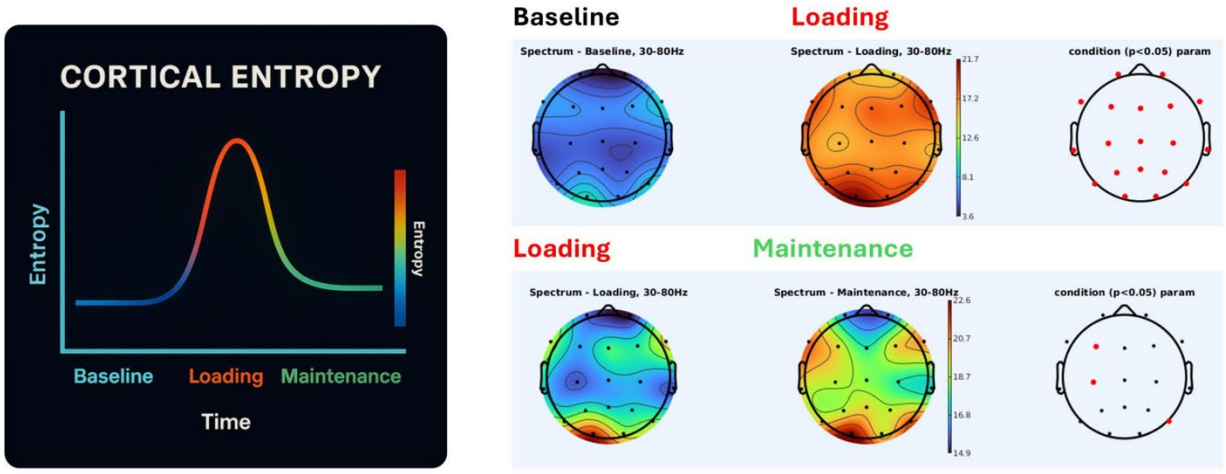

Image: Real time EEG measurements from administration of TRP-8803 during TYP's Phase 1b trial

Platform development initiatives will commence from next month with all data from the Company's previously undertaken animal modelling and Phase 1b trial to be used. This data set will be bolstered by additional EEG data from Tryp's upcoming clinical trial using TRP-8803 to treat Binge Eating Disorder (ASX announcement: 10 April 2025) and additional, pending clinical studies. Development will be funded from Tryp's pro forma cash balance of $5.63m which includes cash at bank at 30 June and its R&D loan facility (refer ASX announcement: 12 August 2025). This will be further strengthened by receipt of pending FY24 R&D Tax Incentives this quarter, valued at ~$800,000.

2. Carhart-Harris, R. L. *et al.* The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Front. Hum. Neurosci.* **8**, 20 (2014).

Collaborators

Professor Carhart-Harris is a globally recognised leader in psychedelic science, renowned for pioneering research that has advanced the understanding of how psychedelic compounds affect the brain and their potential therapeutic applications. Founding the Centre for Psychedelic Research at Imperial College London and now holding the Ralph Metzner Distinguished Professorship in Neurology and Psychiatry at the University of California, San Francisco, he has led ground-breaking neuroimaging and clinical studies exploring the use of psychedelics in treating depression, addiction, and other mental health conditions. His theoretical contributions, including the Entropic Brain Hypothesis, have provided influential frameworks for explaining the neurobiological and psychological mechanisms underpinning psychedelic-assisted therapy.

Professor Mediano is a Physicist and a leading figure in the emerging field of computational neuroscience of altered states of consciousness, with his work having advanced the theoretical and empirical understanding of how psychedelics can reshape consciousness. His work blends informational theory, complexity science, and neuroimaging, as well as building models explaining neural entropy increase under psychedelic influence, to the quantitative effects of external context on psychedelic brain dynamics. He is seen to be at the forefront of scientifically rigorous, mathematically grounded psychedelic research.

Management commentary

Chair of TYP's Scientific Advisory Board, Professor Robin Carhart-Harris, said: *"The entropic brain hypothesis highlights how shifts in brain dynamics can shape mental health and wellbeing. To have secured an agreement with Tryp to develop a specific biomarker anchored in this framework has the potential to transform psychiatry and marks an important step in translating complex neuroscience into practical tools for real-world care. By creating a measurable signal of brain entropy, we unlock the possibility for personalising treatments and predicting therapeutic response – allowing for more effective interventions for patients in need."*

Tryp Chief Executive Officer, Jason Carroll, said: *"This agreement, with two of the world's foremost experts in the field of neural entropy and psychedelic research, marks a transformational step in advancing mental health care. By linking precision IV-infusion and entropy to clinical response, we aim to combine traditional, subjective patient efficacy endpoints with dynamic, data-driven biomarkers to generate true quantitative outcomes of efficacy and safety."*

Collaborator, Professor Pedro Mediano added: *"Tryp's data offers an unprecedented opportunity to apply our research and maximise the benefits of psychedelic therapy. I'm thrilled to work with Jason and the team to push the boundaries of computational neuropsychiatry and accelerate this very necessary research."*

Terms:

The agreement has an initial one-year term with an option to extend for a further year, under which the Company will pay US$100,000 per annum for the services provided. In addition, the Company will grant, subject to shareholder approval, 1,000,000 options each to Professor Robin Carhart-Harris and Professor Pedro Mediano, exercisable at $0.08 and expiring two years from the date of issue.

Q&A:

What is brain entropy?

Brain entropy is a measure of the complexity and unpredictability of brain activity. Higher entropy reflects more flexible, dynamic neural states.

Why does brain entropy matter in mental health?

Mental illnesses often involve overly rigid brain networks. Increasing entropy may help 'reset' these patterns, enabling patient improvement.

What is a biomarker?

A non-subjective measurable indicator of some biological state or condition.

What is EEG entropy biomarker?

It's a real-time signal derived from the electrical brainwaves recorded by placing electrodes on the scalp of the patient that can detect changes in brain entropy during a treatment. It provides non-subjective data that a treatment may be working or not.

How does this relate to TRP-8803?

TRP-8803 is an IV-administered psychedelic. The entropy biomarker may help identify which patients will respond best to treatment and if there is a need to adjust dosing for a particular patient.

What makes this EEG biomarker unique?

It's dynamic, real-time dose-responsive, and mechanistically anchored measure of brain activity — unlike traditional symptom scores that are highly subjective and static.

Are biomarkers important for regulatory approval?

Yes. They are increasingly important for regulatory approval of all new treatments. In psychiatry most mental health conditions are diagnosed using subjective measures that lack precision and accuracy. The use of biomarkers may provide objective proof of treatment effect ensuring patients get the right treatment for their illness.

Is the Entropy biomarker accepted by regulators?

Brain entropy is emerging as a promising physiological marker of brain health and activity. This collaboration aims to generate the clinical data needed for regulatory validation.

Will this biomarker be used in future clinical trials?

Yes. It will guide dosing, predict outcomes, and support regulatory submissions for TRP-8803 and future compounds.

Is this technology IP protected?

Yes. Tryptamine owns all the IP developed under the agreement, including algorithms and device designs.

Can this biomarker be applied beyond TRP-8803?

Potentially. Entropy biomarkers may be relevant in depression, PTSD, schizophrenia, and cognitive decline – any condition involving network rigidity.

How could this affect the valuation of Tryp?

It positions Tryp as a psychiatric platform company, not just a single drug developer and may unlock premium valuation multiples.

What is next?

The Biomarker development program begins on 1 September 2025 and all existing and new EEG data that will be generated by TRP-8803 clinical studies will be included - the results of which are expected to shape future clinical strategy for TRP-8803 in neuropsychiatric disorders.

This announcement has been authorised for release by the Board of Tryptamine Therapeutics Limited.

-ENDS-

About Tryptamine Therapeutics Limited

Tryp Therapeutics 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. Tryp'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. The Company has completed a Phase 2a clinical trial for the treatment of binge eating disorder at the University of Florida, which demonstrated an average reduction in binge eating episodes of greater than 80%.

The Company also has also just completed a Phase 2a clinical trial for the treatment of fibromyalgia in collaboration with the University of Michigan and has initiated a Phase 2a clinical trial in collaboration with Massachusetts General Hospital for the treatment of abdominal pain and visceral tenderness in patients suffering from irritable bowel syndrome.

Each of the studies is utilising TRP-8802 (synthetic, oral psilocybin) to demonstrate clinical benefit in these indications. Where a positive clinical response is demonstrated, subsequent studies are expected to utilise TRP-8803 (IV-infused psilocin), that has the potential to further improve efficacy, safety, and patient experience.

For more information, please visit www.tryptherapeutics.com.

Investor & Media Contact

Jason Carroll
Chief Executive Officer
Tryptamine Therapeutics Limited
jcarroll@tryptherapeutics.com

Henry Jordan
Six Degrees Investor Relations
+61 (0) 431 271 538
henry.jordan@sdir.com.au

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 regimens 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 Tryp 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 Tryp'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 Tryp; 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 Tryp 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.