ASX Release **18 December 2024**

Positive interim results in Phase 2a TRP-8802 IBS trial conducted at the Massachusetts General Hospital

- **Four of up to 10 patients successfully administered treatment in trial being performed at Massachusetts General Hospital (MGH) – Marks the first time MGH has administered psilocybin in a clinical setting**
- **Strong interim results observed across preliminary cohort: 75% of patients reported a clinically meaningful decrease in abdominal pain and anxiety associated with gastro-intestinal inflammation**
- **In addition, patients with pre-existing anxiety and depression also showed positive trends in improvement**
- **Interim results are highly encouraging and indicate that IBS is a viable target condition for TRP-8803 (IV-infused psilocin) treatment**
- **Results now being incorporated into proprietary datasets to further inform the clinical development pathway of TRP-8803 in CY25**
- **TRP-8803 is an innovative and commercially scalable psilocin-based IV-infusion with potential neuroplastic benefits. Pharmaceuticals that achieve a change in neuroplasticity are known to cause adaptive structural and functional changes within the brain that are thought to be responsible for clinical improvements**
- **TRP-8803 has multiple advantages over oral psilocybin dosing including faster onset (under 20 minutes) with precise control of the depth and duration to the psychedelic state in a commercially feasible timeframe**
- **Phase 2a TRP-8802 study at MGH is ongoing, with additional results pending – Study expected to complete on time during H1 CY25**
- **Considering the strong interim results, Tryp is assessing the potential for TRP-8803 to positively impact a broader range of secondary patient-centric outcomes which impact daily quality of life**

Melbourne, Australia – Tryptamine Therapeutics Limited ('**Tryp**' or the '**Company**') (**ASX: TYP**), a clinical-stage biopharmaceutical company, is pleased to provide positive Interim analysis as part of its Phase 2a Clinical Study in patients with Irritable Bowel Syndrome (IBS) being undertaken at Massachusetts General Hospital ('MGH' or 'Mass General') (refer ASX announcement: 24 July 2024). To date, four of up to 10 patients have successfully been administered TRP-8802 (oral psilocybin). This initiative marks the first time that MGH has administered psilocybin in a clinical setting.

The study is evaluating the safety and efficacy of TRP-8802 in conjunction with therapist support, based on clinical rationale involving the 'gut-brain axis' which primarily includes the neurotransmitter, serotonin. The study has been designed to assess the capacity for psilocin, the active metabolite of psilocybin, to bind to serotonin receptors (5HT-2A) in the brain and the gastrointestinal (GI) system, potentially resulting in a viable pathway to positively impact abdominal pain and visceral tenderness – both hallmarks of IBS.

Preliminary results demonstrated that 75% of the patients dosed achieved a reduction in abdominal pain and GI associated anxiety. For those patients with pre-existing anxiety or depression there were also positive trends in improvement. This is greatly encouraging for the Company and highlights the potential for IBS as a viable indication for treatment with TRP-8803.

The Phase 2a study at MGH forms part of Tryp's broader US-based clinical development pipeline, which also includes a completed Phase 2a Study in collaboration with the University of Florida, to assess the application of TRP-8802 to treat Binge Eating Disorder (BED). Strong initial results from the BED trial included an average reduction in binge eating episodes of over 80% in patients compared with baseline, in addition to commensurate reductions in Anxiety and Depression and a durability of effect up to 60 days. The Company's TRP-8802 trial pipeline also included a study with the University of Michigan into Fibromyalgia, which highlighted clinically meaningful improvements in pain reduction in 100% of patients, as well as secondary endpoints (refer ASX announcement: 12 August 2024).

Along with the potential to achieve improved patient health outcomes, results from the Phase 2a trials with TRP-8802 will provide Tryp with important proprietary data to advance the clinical development pathway for TRP-8803, the Company's lead asset. TRP-8803 is an innovative and scalable psilocin-based IV-infusion formulation with potential neuroplastic benefits. Neuroplasticity is the ability of neural networks in the brain to change through growth and reorganisation. Treatments which improve neuroplasticity are known to cause adaptive structural and functional changes within the brain.

The positive preliminary results from the Phase 2a IBS study for TRP-8802 will be incorporated into clinical design program for TRP-8803, including its application for patients suffering from IBS symptoms. IBS is estimated to affect around 20% of Australians[i] and 15% of the total US population[ii], and is a leading cause of work absenteeism[iii].

The IBS data for TRP-8802 follows the recent completion of a detailed Phase 1b trial for TRP-8803, that successfully met all key objectives including safety and optimal dosing rates to achieve target psilocin blood levels in healthy subjects, enabling advancement to Phase 2 clinical trials (refer ASX Announcement: 19 November 2024). An extension to the Phase 1b trial also showed the same key objectives were met for a cohort of obese subjects, that was consistent with those shown in non-obese subjects (refer ASX Announcement: 16 December 2024).

In addition to safety, the primary efficacy endpoint for the Phase 2a IBS study is a reduction in abdominal pain and visceral tenderness. The study is also evaluating the potential for the treatment to positively impact a broad range of secondary patient-centric outcomes that represent debilitating symptoms that impact their daily Quality of Life (QOL). Experimental clinical measurements including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalogram (EEG) scans are presently under evaluation. Tryp looks forward to presenting the results from these secondary endpoints as they become available.

Management commentary:

Chief Executive Officer, Mr. Jason Carroll said: *"These positive interim results from the first four patients within the Phase 2a Clinical Study at MGH provide another strong indication of the broad potential of Tryp's clinically-backed product suite to achieve improved patient health outcomes. In the first instance, it was exciting to see the interim results reporting a clinically meaningful decrease in abdominal pain and anxiety stemming from IBS symptoms. Looking ahead, this interim analysis highlights that IBS is highly likely to be a viable indication for Tryp to pursue for commercialisation with TRP-8803 (IV-infused psilocin).*

"Whilst the MGH team will dose the remaining IBS patients, our work will commence to incorporate these interim results into our expanding proprietary dataset. This will, in turn, underpin the company's future clinical trial pipeline. Tryp's pipeline will be solely focused on TRP-8803, given the significant competitive advantage we see with TRP-8803 when compared to oral psilocybin.

"We look forward to providing additional details from the Phase 2a IBS trial for TRP-8802 as they are received, along with the forthcoming initiation of Phase 2 trials for Tryp's TRP-8803 IV-infused psilocin therapy."

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 biopharmaceutical 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 asset, TRP-8803, is a proprietary, scalable and innovative formulation of IV-infused psilocin (the active metabolite of psilocybin) with neuroplastic benefits. It has the potential to alleviate numerous shortcomings of oral psilocybin including: significantly reducing the time to onset of the neuroplastic state, controlling the depth and duration of the neuroplastic 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 successful 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.

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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.

[i] MJA 207, Diagnosis and management of irritable bowel syndrome: a guide for the generalist: Ecushla C Linedale & Jane M Matthews
[ii] https://gi.org/topics/irritable-bowel-syndrome/#tabs3
[iii] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5010380/