4 May 2026

Breakthrough 75% response rate in treatment-resistant IBS patients in Phase 2a TRP-8802 trial

- **Strongest clinical signal ever reported in IBS drug development**
- **Results presented at the prestigious Digestive Disease Week Congress 2026 by researchers from Massachusetts General Hospital and Columbia University**
- **75% response rate achieved in treatment-resistant IBS patients, represents a treatment breakthrough compared to existing therapies that deliver 17-44% response rates**
- **Strong efficacy signal observed in the hardest-to-treat patient population that current available therapies are unable to deliver a consistent patient benefit**
- **Positive clinical outcomes linked to improvements in psychological insight and flexibility, supporting the gut-brain axis mechanism of action hypothesis**
- **Data supports therapy is targeting root-cause neurobiological pathways, not masking symptoms**
- **Results strongly support and derisk development of TRP-8803 (IV-infused psilocin)**
- **TRP-8803 may offer IBS patients with a best-in-class treatment**
- **IBS represents a significant market opportunity with 10.4 million patients spending over US$60Bn annually on IBS treatments in the US alone**
- **Results leave Entropy well placed for partnering discussions, larger trials, potential grant funding opportunities and a clear US-focused development pathway**
- **Investor webinar scheduled for Wednesday, 6 May at 10:30am AEST**

Melbourne, Australia – Entropy Neurodynamics Limited ('**Entropy Neurodynamics**', '**ENP**' or the '**Company**') (**ASX: ENP**), a clinical-stage biotechnology company, is pleased to announce breakthrough clinical results from the Company's Phase 2a Clinical Study of TRP-8802 (oral psilocybin) in patients with treatment-resistant, irritable bowel syndrome (IBS).

The data was presented on 3 May 2026 (US time) at Digestive Disease Week (DDW) 2026, the world's leading gastroenterology congress, by researchers from the original and largest teaching hospital of Harvard Medical School, Massachusetts General Hospital (MGH) and Columbia University. The presentation entitled *"OPEN-LABEL PSILOCYBIN-ASSISTED THERAPY IN TREATMENT-REFRACTORY IBS"* is attached to this announcement.

The results represent a major milestone for the Company and provide compelling evidence that psychedelic-assisted therapy can deliver clinically meaningful and mechanistically coherent benefits in one of the most difficult-to-treat chronic conditions.

Breakthrough clinical outcomes in treatment-resistant IBS

The open-label Phase 2a study evaluated two doses of TRP-8802 (oral psilocybin) administered with structured psychotherapy in 12 patients who had previously failed multiple standard treatments.

Key findings:

- 75% of patients achieved clinically meaningful improvement, meeting the pre-defined IBS-SSS response threshold
- Response was linked to improvements in psychological flexibility and insight, validating the gut-brain axis mechanism
- Subtype responses were highly encouraging:
    - IBS-C: 100% (3/3)
    - IBS-M: 80% (4/5)
    - IBS-D: 50% (2/4)
- Safety profile was consistent with expectations for psychedelic-assisted therapy. One serious adverse event was recorded and resolved with appropriate clinical support, underscoring the importance of standard psychological screening and integration procedures

These results far exceed the 17-44% response rates typically observed with approved IBS therapies[1,2], where treatment failure and relapse are common[3,4].

A comparative summary of existing therapies is included below, highlighting the clear differentiation of TRP-8802.

Therapy:	Mechanism:	Population:	Response:	Notes:
TRP-8802 (oral psilocybin)	**5-HT2A agonist**	**Treatment refractory IBS**	**75%**	**Strongest ever signal reported in refractory IBS**
Linzess (linaclotide)	GC-C agonist	IBS-C	33-34%	Approved, non-refractory population
Trulance (plecanatide)	GC-C agonist	IBS-C	30-33%	Approved, non-refractory population
Amitiza (lubprostone)	Chloride channel activator	IBS-C	17-18%	Approved, modest efficacy
Ibsrela (tenapanor)	NHE3 inhibitor	IBS-C	27-33%	Approved, diarrhoea common
Xifaxan (rifaximin)	Non-absorbed antibiotic	IBS-D	40-44%	Relapse common
Viberzi (eluxadoline)	Mixed opioid modulator	IBS-D	29-33%	Safety limitations, pancreatitis risk
TCAs (e.g. amitriptyline)	Central neuromodulation	IBS-M/D	30-40%	Off-label, tolerability issues
SSRIs / SNRIs	Central neuromodulation	IBS-M/D	20-30%	Off-label, inconsistent benefit

Mechanistic Validation – Targeting Root-Cause Gut-Brain Neurobiology

The study demonstrated that symptom improvement was strongly associated with changes in psychological drivers, including insight and flexibility. This confirms that the therapy is:

- Acting on central brain pathways, not merely masking symptoms
- Engaging the gut-brain axis, a core driver of IBS
- Aligned with Entropy's mechanism-based development strategy

This mechanistic coherence significantly de-risks the program and supports progression to larger controlled studies.

Strategic implications for TRP-8803 (IV-infused psilocin)

The TRP-8802 program was designed to inform the development of TRP-8803, Entropy's proprietary IV-infused psilocin formulation.

TRP-8803 offers several advantages over oral psilocybin, including faster onset of action, precise control over the dose, depth and duration of therapeutic effect, an improved patient and therapist experience and a more commercially scalable treatment model.

Importantly, the Phase 2a trial provide direct mechanistic validation for the use TRP-8803 in IBS and significantly enhance its commercial and partnering profile.

Entropy will continue to review its IBS dataset and commence planning for new clinical trials and pursue non-dilutive grant funding to advance further US-based clinical trials using TRP-8803 in IBS.

Large, underserved market with high commercial potential

IBS affects:

- 10.4m patients in the US[5], where annual spend exceeds US$60Bn[6]
- Over 1m patients in Australia[7], with high unmet need in treatment-resistant populations

IBS patients commonly cycle through up to 10 therapies[8], incur substantial out-of-pocket costs[9], and demonstrate a strong willingness to adopt new treatments[10].

IBS is characterised by persistent, intrusive physical symptoms including pain, bloating, urgency, constipation and diarrhoea, often occurring daily and significantly impairing quality of life[11,12], sleep and social functioning. Patients seek treatment more frequently than many other chronic conditions[13]. Importantly, IBS is also free from the stigma associated with psychiatric conditions, supporting rapid adoption of effective therapies[14,15].

Entropy believes TRP-8803 has the potential to deliver a best-in-class therapeutic profile in this multi-billion-dollar global market.

Management commentary

CEO, Mr Jason Carroll said: *"These results represent a breakthrough moment for Entropy and for the treatment of IBS. To deliver a 75% response rate in a treatment-resistant population, where existing therapies typically achieve only modest outcomes, is clinically unprecedented.*

Importantly, the dataset is mechanistically coherent. We are seeing clear alignment between clinical outcomes and improvements in psychological drivers, reinforcing that we are targeting the root cause of disease through the gut-brain axis.

TRP-8802 has now de-risked both the indication and the mechanism, while TRP-8803 is designed to unlock

the full commercial potential of this opportunity. We see a clear pathway to building a leading, differentiated franchise in gut-brain disorders."

Investor webinar

The Company advises a webinar will be held at 10:30am AEST (8:30am AWST) on Wednesday, 6 May 2026, hosted by CEO Mr Jason Carroll.

The webinar will be followed by a Q&A session. Questions can be submitted to henry.jordan@sdir.com.au prior to, or in written form, during the webinar. Anyone wishing to attend the webinar must register via the following:

- https://us02web.zoom.us/webinar/register/WN_i8Pyaq-KRAWpiJkPOHmq9g

A recording of the presentation will be made available following the webinar.

Q&A

What is TRP-8802?

TRP-8802 is oral psilocybin administered with structured psychotherapy, used as a mechanistic and clinical de-risking tool for Entropy's lead program, TRP-8803.

What is TRP-8803?

TRP-8803 is Entropy's proprietary IV-infused psilocin formulation, designed to overcome the limitations of oral psilocybin.

What is IBS?

Irritable Bowel Syndrome (IBS) is a chronic gut-brain disorder characterised by pain, bloating, constipation, diarrhoea, urgency and impaired quality of life.

What is the difference between IBS-C, IBS-M and IBS-D?

All three are subtypes of Irritable Bowel Syndrome and share the same core features:

• Chronic abdominal pain

• Bloating or discomfort

• Symptoms linked to bowel movements

• No structural disease on testing

Patients diagnosed with IBS-C (Constipation-predominant) is where a patient's bowel movements are infrequent and hard, IBS-D (Diarrhoea-predominant) patients have bowel movements that are loose and urgent whereas an IBS-M (Mixed) diagnosis occurs when a patient alternates between constipation and diarrhoea, with both hard and loose stools making up ≥25% of bowel movements.

Despite these differences, all three subtypes can experience significant abdominal pain and impaired quality of life and all are included within the broader category of disorders of gut–brain interaction.

What is the IBS-SSS and how is it used to assess product efficacy?

The IBS Symptom Severity Score (IBS-SSS) is a validated clinical scale measuring pain, distension, bowel

habit dissatisfaction and quality of life.

A “clinically meaningful improvement” is defined by a ≥50-point reduction, which was the pre-defined response threshold in the study.

How strong are these results compared to existing IBS treatments?

Exceptionally strong. Approved IBS drugs typically deliver 17–44% response rates in non-refractory populations. TRP-8802 achieved 75% in treatment-resistant patients — the hardest group to treat.

Why is a 75% response rate considered a breakthrough?

Because no approved IBS therapy has ever approached this level of efficacy, especially in refractory patients.

How many patients were in the study, and why is the sample size appropriate?

The Phase 2a study included 12 treatment-resistant IBS patients.

Early-phase mechanistic studies are typically small and the magnitude and consistency of the signal (75% response) is unusually strong for this stage.

What does “mechanistically coherent” mean in this context?

It means the clinical improvements aligned with measurable changes in psychological flexibility and insight, supporting the gut-brain axis mechanism.

Why is the gut-brain axis important in IBS?

IBS is increasingly understood as a brain-driven disorder involving dysregulated pain processing, stress responses and autonomic imbalance.

How does the study result de-risk TRP-8803?

TRP-8802 validates the IBS indication, the gut-brain axis modulation mechanism, the therapeutic approach and directly supports TRP-8803’s development in IBS

Why is TRP-8803 expected to outperform TRP-8802?

Because IV psilocin avoids first-pass liver metabolism, it removes the dose and efficacy variability seen with oral psilocybin. As TRP-8803 is delivered via a patented two-phase psilocin infusion, it will be expected to provide a precise, consistent and controlled therapeutic dose when compared to TRP-8802.

Why is the treatment-resistant IBS population commercially attractive?

IBS is a valuable and unique indication as, unlike typical neuropsychiatric disorders, IBS has no “psychiatric stigma”. IBS is a condition with a high unmet clinical need and has between 3.1-4.2m patients in the US that are currently classified as treatment-resistant – this means that these patients are looking for a new treatment option right now. These patients already spend between US$6,000 and US$11,000 per year (out-of-pocket) on medicines to treat their IBS so they are very open in pursuing new treatment options.

This is one of the most urgent and commercially valuable patient groups in chronic disease.

How does this position Entropy for partnering?

The results provide Entropy with a clear efficacy signal, mechanistic validation and a differentiated product

profile within a very high-value market

How does this impact Entropy's valuation?

Whilst there is no valuation inferred, a breakthrough in a US$60B market with a best-in-class profile is typically viewed as a major value inflection point. To put this into perspective, the IBS addressable market in the US is larger than that for Depression.

References

1. Zhou Z, Li Y, Tu Y, et al. Efficacy and safety of Guanylyl cyclase C agonists in IBS-C: systematic review and meta-analysis. Front Pharmacol. 2026.

2. Busam JA, Batta N, Shah ED, et al. The Safety of Pharmacotherapy for Irritable Bowel Syndrome: Systematic Review and Meta-Analysis. Am J Gastroenterol. 2025;121(3):745–753.

3. Pimentel M, Lembo A, Chey WD, et al. Rifaximin Therapy for IBS without Constipation. N Engl J Med. 2011;364:22–32.

4. Linedale EC, Andrews JM. Diagnosis and management of irritable bowel syndrome: a guide for the generalist. Med J Aust. 2017;207(7):309–315.

5. Rome Foundation Global Epidemiology Study. IBS prevalence in the United States (~10%).

6. Peery AF, Murphy CC, Anderson C, et al. Burden and Cost of Gastrointestinal Diseases in the United States: Update 2024. Gastroenterology. 2025;168(5):1000–1024.

7. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. JAMA. 2015;313(9):949–958.

8. Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to IBS. J Clin Med. 2017;6(11):99.

9. Lacy BE, Weiser K, De Lee R. The treatment of irritable bowel syndrome. Therap Adv Gastroenterol. 2009;2(4):221–238.

10. Black CJ, Ford AC. Global burden of IBS. Nat Rev Gastroenterol Hepatol. 2020;17:473–486.

11. Canavan C, West J, Card T. The epidemiology of IBS. Clin Epidemiol. 2014;6:71–80.

12. Lacy BE, Mearin F, Chang L, et al. Bowel Disorders. Gastroenterology. 2016;150:1393–1407.

13. Peery AF, Crockett SD, Murphy CC, et al. Burden and Cost of GI Disease in the U.S.: Update 2024. Gastroenterology. 2025;168(5):1000–1024.

14. Fukudo S. Stress and visceral pain. Neurogastroenterol Motil. 2013;25(9):792–799.

15. Drossman DA. Functional gastrointestinal disorders and Rome IV. Gastroenterology. 2016;150:1262–1279.

This announcement has been authorised by the Board of Entropy Neurodynamics

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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.

DDW2026 Digestive Disease Week®
MAY 2–5, 2026 | CHICAGO, IL
EXHIBIT DATES: MAY 3-5, 2026

OPEN-LABEL PSILOCYBIN-ASSISTED THERAPY IN TREATMENT-REFRACTORY IBS

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PURPOSE / OBJECTIVES

Irritable bowel syndrome (IBS) affects about 4% (using Rome IV criteria) of adults worldwide; a significant proportion are refractory to standard care including diet, pharmacotherapy, and gut-brain behavioral therapy. Effective options for this population are needed.

Psilocybin-assisted therapy (PAT) acts via 5-HT2A signalling and modulates the default mode network among other pathways implicated in visceral hypersensitivity. PAT has demonstrated durable efficacy in the treatment of depression, with emerging evidence for pain disorders like migraine headache. No clinical trial has examined PAT in IBS.

Objective: To assess the safety and efficacy of two 25 mg oral doses of psilocybin delivered in concert with structured psychotherapy in adults with treatment-refractory IBS (IND 163994).

METHODS

Design: Phase 2a open-label pilot, randomized 3:1 (immediate:delayed treatment).

Population: Rome IV IBS (all subtypes), treatment-resistant (tried pharmacotherapy and diet), n=12.

Intervention: Oral psilocybin 25mg × 2 doses ~3 weeks apart with structured psychotherapy (2 prep + 2 integration sessions per dose).

Key Assessments:

- GI: IBS-SSS (primary efficacy: ≥50 pt reduction), Visceral Sensitivity Index, daily pain and stool diaries.
- Psych: Hospital Anxiety and Depression (HADS) Questionnaire, Visceral Sensitivity Index, Acceptance and Action Questionnaire, Mystical Experience Questionnaire, Challenging Experiences Questionnaire
- Exploratory: inflammatory biomarkers, fMRI pre-/post-, heart rate variability

Psilocybin-assisted therapy produced **clinically meaningful symptom improvement in 75%** of patients with treatment-refractory IBS.

Response was associated with reduction in psychological inflexibility and improved psychological insight.

RESULTS

- **Demographics (n = 12)**
- Sex: 75% female, 25% male
- Race: 8.3% Asian, 8.3% Black, 83% White. Ethnicity: 25% Hispanic
- IBS-Subtype (% Responder): 3 IBS-C (100%), 4 IBS-D (50%), 5 IBS-M/IBS-U (80%)
- **AE**: One serious adverse event (SI). Transient blood pressure and heart rate elevations during dosing resolved without intervention.
- Greater **reductions in IBS symptom severity (IBS-SSS)** were significantly associated w/ **increased psychological insight** (PIQ: Spearman ρ = −0.69, p = 0.014) and **reduced psychological inflexibility** (AAQ-II: ρ = 0.695, p = 0.026)
- Depth of **mystical experience** (MEQ-30) showed a trend toward greater IBS-SSS improvement (Spearman ρ = −0.54, p = 0.07)
- **Prior psychedelic experience**: 100% responders (5/5) vs 57% (4/7) naive.
- **Visceral sensitivity** (VSI, gut-specific anxiety) demonstrated non-specific minimal change at EOT (mean Δ −0.4), trend toward improvement at 6 months (mean Δ −2.8), EOT p = 0.68, 6-month p = 0.43 (n=5 at 6 months)

SUMMARY / CONCLUSION

In this Phase 2a pilot of psilocybin-assisted therapy for treatment-refractory IBS, 75% of patients met the validated clinical response threshold (IBS-SSS ≥50-pt reduction) at end of treatment.

Psychological mechanisms appear to mediate response. Improvements in psychological insight (PIQ) and psychological flexibility (AAQ-II) were each significantly associated with symptom improvement, while gut-specific anxiety (VSI) showed minimal change at EOT. This dissociation suggests PAT acts through acceptance-based central mechanisms rather than direct extinction of gut-specific anxiety.

IBS-C showed the strongest subgroup response (3/3, 100%), consistent with a possible direct 5-HT2A prokinetic effect. IBS-D showed the greatest heterogeneity, warranting subtype-stratified investigation in future trials.

The safety profile was acceptable. One serious adverse event (transient suicidal ideation) occurred, highlighting the need for robust psychological screening and integration support in future trials. Elevations in blood pressure and heart rate during dosing were self-limited.

These preliminary findings support the feasibility and potential efficacy of PAT for treatment-refractory IBS and provide mechanistic hypotheses for larger, controlled trials with subtype stratification.

RESULTS (CONTINUED)

Figure 1. Psilocybin-assisted therapy reduces IBS symptom severity.

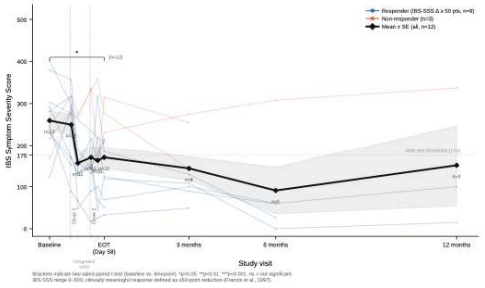
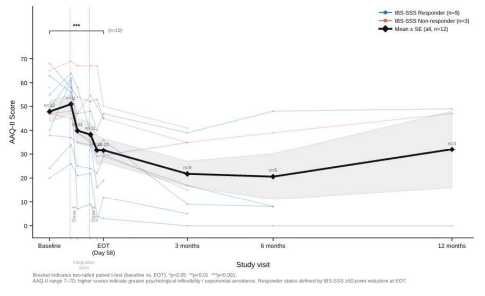


Figure 2. Psilocybin-assisted therapy reduces psychological inflexibility.



REFERENCES

Arif TB, et al. *Am J Gastroenterol*. 2024;119(10S):S517.
Oka P, et al. *Lancet Gastroenterol Hepatol*. 2020;5(10):908–17.
Francis CY, Morris J, Whorwell PJ. *Aliment Pharmacol Ther*. 1997;11:395–402.
Castellanos JP, et al. *Reg Anesth Pain Med*. 2020;45:486–94.

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