



Precision
Biotics

Clinical Evidence Summary

Gut Health
& the 35624[®]
Probiotic
Strain



CLINICAL EVIDENCE SUMMARY

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The importance of the gut microbiome in human health and disease is now well established and our knowledge of its complex composition and potential is growing. The gut microbiome influences human physiology, immune function, metabolism and nutrition, with emerging evidence of an underlying link to the pathophysiology of functional gastrointestinal disorders (FGIDs), including irritable bowel syndrome (IBS).

The key influence of the gut microbiome on gut health and function has prompted research into the potential of probiotics for IBS. This has resulted in international clinical guidelines recommending the use of strain specific probiotics for managing symptoms of IBS. Clinical data shows the **35624[®]** probiotic strain may be effective in managing the global symptoms of IBS and may also improve quality of life.

Definitions:

Microbiota:

All microscopic organisms (e.g. bacteria, archaea, viruses, fungi, some eukaryotes) living in a defined habitat or environment (such as the human gut).

Microbiome:

All microorganisms living in a defined habitat (the microbiota), including:

- Their internal molecules (e.g. nucleic acids, proteins, lipids, polysaccharides, etc)
- The metabolites they produce (e.g. short chain fatty acids, toxins, etc)
- Their surrounding host environment (e.g. the cells and nutrients in the human gut)

While the microbiome contains microbiota, the microbiome is more than just microbiota alone.

Key Points

- ▶ The gut microbiome plays a key role in human health and disease, influencing immunity, metabolism and nutrition, gut health and function¹.
- ▶ Gut bacteria profiles of people with IBS differ from those of people without IBS².
- ▶ The gut microbiota may contribute to the pathophysiology of IBS³ and is therefore a potential therapeutic target in the management of symptoms of IBS and other FGIDs.
- ▶ FGIDs are common, with IBS being the most common, affecting around 1 in 10 people globally⁴.
- ▶ International clinical guidelines highlight the potential strain-specific benefit of *Bifidobacterium longum* **35624**[®] for managing the symptoms of IBS.
- ▶ Robust clinical trials have demonstrated that the *Bifidobacterium longum* **35624**[®] strain leads to significant improvements in^{2,5,6}:
 - ✓ Symptom scores for all IBS symptoms, irrespective of bowel habit subtype
 - ✓ Abdominal pain/discomfort
 - ✓ Bloating/distension
 - ✓ Bowel habit satisfaction
 - ✓ Inflammatory biomarkers
- ▶ The **35624**[®] strain has been carefully selected for its safety and efficacy by PrecisionBiotics, who have over 20 years' experience of scientific research and expertise in this field.



The Gut Microbiome

The gut microbiome is more than just microorganisms. It refers to all of the microorganisms that live in the gut (such as bacteria, fungi, archaea and some protists – collectively known as microbiota) and also⁷:

- ▶ Their internal molecules
- ▶ The metabolites they produce
- ▶ The cells and nutrients that surround them

An adult gastrointestinal tract harbours a vast, complex and dynamic microbial population of more than 10^{14} (one hundred trillion) microorganisms⁸. A rich diversity of microbial species in the gut is considered a healthy sign^{1,9}.

The composition of the gut microbiome is established in early life, influenced by various factors such as mode of delivery at birth, geographic location, household exposures, e.g. to pets and nutrition. Whilst it is difficult to modify the composition of the gut microbiome beyond early life^{10,11}, aging, illness, use of medications such as antibiotics, lifestyle and diet may all have an effect^{12,13}. Long-term and consistent dietary changes, such as eating a diet rich in fruits, vegetables and wholegrains, may have a positive effect on the composition of the gut microbiome¹⁴. Additionally, supplementation of the gut microbiome with specific probiotics has been shown to have a number of strain-specific health benefits¹⁵.

The Gut Microbiome in Health

The gut microbiome plays a key role in the regulation of human health¹⁶. It is involved in many functions in the body including¹⁶:

- ▶ Maintenance of normal gut physiology and health, through regulation of epithelial cell proliferation and differentiation
- ▶ Protection against pathogens, through colonisation of mucosal surfaces and production of antimicrobial substances
- ▶ Regulation of a number of systems and processes including the immune system, digestion, metabolism, insulin sensitivity and secretion
- ▶ Modulation of gut-brain communication, in turn affecting mental and neurological functions

The Gut Microbiome in Illness

An altered gut microbiome has been associated with a number of diseases¹³. Whilst it is not fully understood whether this is a cause or consequence, there is speculation that gut dysbiosis may trigger a proinflammatory state which could contribute to the onset of diseases, including metabolic, immunological, cardiovascular, neuropsychiatric and gastrointestinal conditions¹⁶.

IBS is one of the most common FGIDs, and has been associated with altered stability and diversity of gut bacteria¹⁷. Placebo-controlled randomised trials have demonstrated that targeting the gut microbiota, such as through supplementation with certain probiotic strains, can alleviate symptoms of IBS¹⁷. This has led to FGIDs, such as IBS, being re-defined as disorders of the microbiome-gut-brain-axis^{17,18}.

Bifidobacterium longum 35624®

The use of a daily probiotic supplement, in addition to changes in diet and lifestyle, may help individuals to maintain a healthy digestive system¹⁹. In particular, probiotics containing *Bifidobacterium longum* 35624® can be taken as a dietary supplement to help “promote and support a healthy digestive system in individuals interested in promoting their digestive well-being”¹⁹.

Clinical Guidelines for the 35624® strain in IBS

International clinical guidelines highlight the potential strain-specific benefit of *Bifidobacterium longum* 35624® for managing the symptoms of IBS.

In 2015, the World Gastroenterology Organisation guidelines highlighted that *Bifidobacterium longum* 35624® had the best evidence base for efficacy in IBS²⁰.

The 2018 European Society of Primary Care Gastroenterology Guidelines outlined that this specific strain helps to:

- ▶ Relieve overall symptom burden in some patients with IBS (Grade of evidence: High; Agreement: 100%)
- ▶ Relieve overall symptom burden in some patients with IBS-D (Grade of evidence: Moderate; Agreement: 100%)
- ▶ Reduce abdominal pain in some patients with IBS (Grade of evidence: High; Agreement: 100%)
- ▶ Reduce bloating/distension in some patients with IBS (Grade of evidence: Moderate; Agreement: 80%)
- ▶ Improve frequency and/or consistency of bowel movements in some IBS patients (Grade of evidence: Moderate; Agreement: 100%)

HIGH - Probiotics with supportive evidence for benefit should be tried;

MODERATE - Probiotics with supportive evidence for benefit could be tried.

Clinical Evidence for the 35624® strain in IBS & Inflammatory Conditions

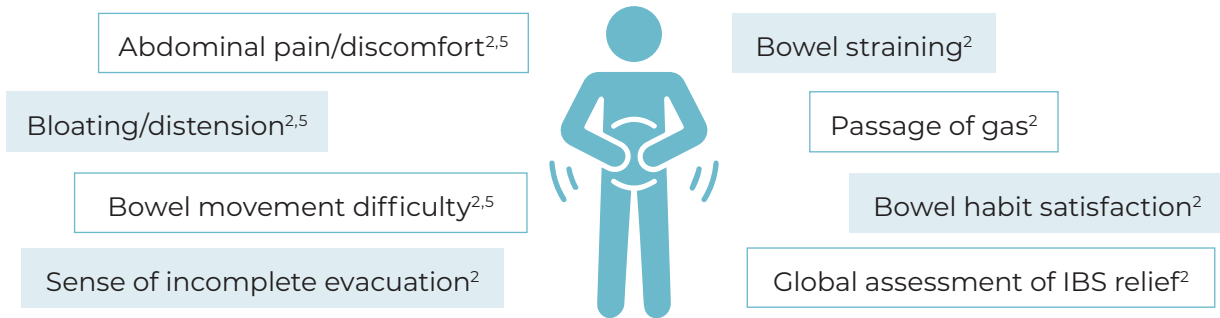
Placebo-controlled, randomised clinical trials^{2,5} comparing the 35624® strain to controls have demonstrated significant benefits in people with IBS including:

- ▶ Significant improvements in overall IBS symptom scores ($p < 0.05$)^{2,5}

Table: Significant improvements observed in composite IBS symptoms (visual analogue scale) vs placebo⁵

		Supplementation period (weeks)								Follow up (weeks) No probiotic supplement			
		1	2	3	4	5	6	7	8	9	10	11	12
Overall symptoms	35624®	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✗
	Other probiotic	✗	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗

- ▶ Significant improvements ($p < 0.05$) in:



- ▶ Modulation of dysregulated cytokine profiles to be similar to that of healthy people, which was not achieved with controls⁵

Consistent findings were observed in a large, real world cohort study, showing improvements in all subtypes of IBS, particularly those with more severe forms of IBS²¹, including:

- ▶ Significant reduction in IBS severity ($p < 0.001$), equating to a 31% reduction in overall IBS symptom severity scores (SSS)
- ▶ Significant reduction in overall disease severity (>50-point decrease in IBS-SSS) in 66% of patients
- ▶ Specific improvements ($p < 0.001$) in:
 - ▶ Abdominal pain
 - ▶ Abdominal distension
 - ▶ Bowel habit satisfaction
 - ▶ Interference with life
 - ▶ Quality of life

Additionally, three double-blind, placebo-controlled, randomised controlled trials demonstrated that the **35624**[®] strain significantly reduces C-reactive protein and proinflammatory cytokines in people with inflammatory conditions including ulcerative colitis, chronic fatigue syndrome and psoriasis⁶.

Overview of Clinical Study Methods

The efficacy of the **35624**[®] strain has been assessed in two placebo-controlled clinical trials in people with IBS^{2,5}, three double blind placebo-controlled trials in people with inflammatory conditions⁶, and more recently, a real world evidence study²¹.

Clinical Trial in IBS (1): The **35624**[®] strain may reduce symptoms of IBS, irrespective of bowel habit subtype⁵

A randomised, double-blind, placebo-controlled study of 77 IBS patients. Participants were randomised to receive either the **35624**[®] strain at 1×10^{10} (one billion) colony forming units (CFU), *Lactobacillus salivarius* UCC4331 at 1×10^{10} (one billion) colony forming units or a placebo, every day for 8 weeks. The cardinal symptoms of IBS were recorded daily and assessed each week, whilst assessment of quality of life and stool microbiology were performed at baseline and at the end of the treatment phase.

Clinical Trial in IBS (2): The **35624**[®] strain may alleviate symptoms of IBS²

A double-blind, placebo-controlled, multi-centre (20 centres) study of 362 IBS patients with any bowel habit subtype. Following a 2 week baseline assessment, participants were randomised to receive either placebo or the **35624**[®] strain at a dose of 1×10^6 , 1×10^8 and 1×10^{10} CFU daily for 4 weeks. IBS symptoms were monitored daily and scored on 6-point Likert scale with primary outcome variable being abdominal pain or discomfort. Other outcome measures included a composite IBS symptom score, the subject's global assessment of IBS symptom relief and measures of quality of life.

Real-World Observational Cohort Study: The **35624**[®] strain may reduce IBS severity and improve quality of life²¹

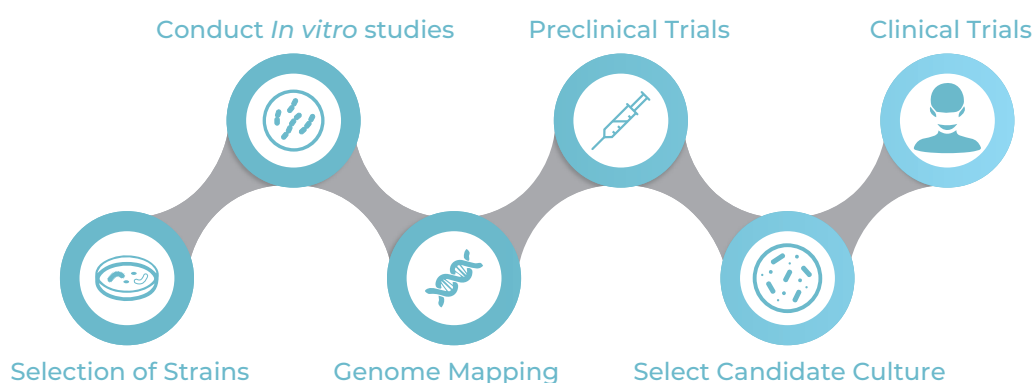
Real world data was collected in a prospective, open-label, multi-centre observational study with 278 patients diagnosed with IBS according to latest Rome IV criteria. Participants received 1 capsule of **35624**[®] at a dose of 1×10^9 colony forming units daily for 30 days. Disease severity using the IBS severity scoring system, and patient quality of life using the IBS quality of life questionnaire were assessed at baseline and at the end of the 30 day treatment.

Clinical Trial in Inflammatory Conditions: The **35624**[®] strain reduces systemic inflammatory biomarkers in people with inflammatory conditions⁶

Three separate randomised, double-blind, placebo-controlled interventions in patients with ulcerative colitis (UC) (n=22), chronic fatigue syndrome (CFS) (n=48) and psoriasis (n=26). Additionally, a group of healthy subjects (n=22), were included as baseline references for the patients with inflammatory disorders. Participants were randomised to receive either the **35624**[®] strain or placebo for 6-8 weeks. At baseline, assessment of disease severity and obtained blood for standard laboratory assessments, including measurements of C-reactive protein, IL-6 and TNF- α were performed.

The Precise Approach to Probiotic Development

For over twenty years, PrecisionBiotics has discovered and developed unique probiotic strains in partnership with scientists and clinical experts from a world-leading centre of research into the microbiome and gut-brain axis - the APC Microbiome Institute, University College Cork, Ireland. This follows a robust process to develop targeted probiotics:



The result has been the development of safe, effective, evidence-based probiotic supplements with strains selected for their specific action for specific conditions.

References

1. Marchesi JR, Adams DH, Fava F, et al. The gut microbiota and host health: a new clinical frontier. *Gut*. 2016;65(2):330-339.
2. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 35624 in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006;101(7):1581-1590.
3. Schmulson MJ, Drossman DA. What Is New in Rome IV. *J Neurogastroenterol Motil*. 2017;23(2):151-163.
4. Black CJ, Ford AC. Global burden of irritable bowel syndrome: trends, predictions and risk factors. *Nat Rev Gastroenterol Hepatol*. 2020;17(8):473-486.
5. O'Mahony L, McCarthy J, Kelly P, et al. *Lactobacillus* and *Bifidobacterium* in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128(3):541-551.
6. Groeger D, O'Mahony L, Murphy EF, et al. *Bifidobacterium infantis* 35624 modulates host inflammatory processes beyond the gut. *Gut Microbes*. 2013;4(4):325-339.
7. Berg G, Rybakova D, Fischer D, et al. Microbiome definition re-visited: Old concepts and new challenges. In: *Microbiome*. Vol 8. 2020:103.
8. Sender R, Fuchs S, Milo R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. *PLoS Biol*. 2016;14(8):e1002533.
9. Thursby E, Juge N. Introduction to the human gut microbiota. *Biochem J*. 2017;474(11):1823-1836.
10. Stewart CJ, Ajami NJ, O'Brien JL, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. *Nature*. 2018;562(7728):583-588.
11. Yao Y, Cai X, Ye Y, Wang F, Chen F, Zheng C. The Role of Microbiota in Infant Health: From Early Life to Adulthood. *Front Immunol*. 2021;12:708472.
12. Hasan N, Yang H. Factors affecting the composition of the gut microbiota, and its modulation. *PeerJ*. 2019;7:e7502.
13. Rinninella E, Raoul P, Cintoni M, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms*. 2019;7(1).
14. Leeming ER, Johnson AJ, Spector TD, Le Roy CI. Effect of Diet on the Gut Microbiota: Rethinking Intervention Duration. *Nutrients*. 2019;11(12).
15. Hill C, Guarner F, Reid G, et al. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat Rev Gastroenterol Hepatol*. 2014;11(8):506-514.
16. Gomaa EZ. Human gut microbiota/microbiome in health and diseases: a review. *Antonie Van Leeuwenhoek*. 2020;113(12):2019-2040.
17. Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Irritable bowel syndrome: A microbiome-gut-brain axis disorder? *World Journal of Gastroenterology*. 2014;20(39):14105-14125.
18. De Palma G, Collins SM, Bercik P. The microbiota-gut-brain axis in functional gastrointestinal disorders. *Gut Microbes*. 2014;5(3):419-429.
19. Lyseng-Williamson K. *Bifidobacterium infantis* 35624 as a probiotic dietary supplement: a profile of its use. *Drugs & Therapy Perspectives*. 2017;33.
20. Quigley EM, Fried M, Gwee KA, et al. World Gastroenterology Organisation Global Guidelines Irritable Bowel Syndrome: A Global Perspective Update September 2015. *J Clin Gastroenterol*. 2016;50(9):704-713.
21. Sabaté JM, Iglicki F. Effect of *Bifidobacterium longum* 35624 on disease severity and quality of life in patients with irritable bowel syndrome. *World J Gastroenterol*. 2022;28(7):732-744.