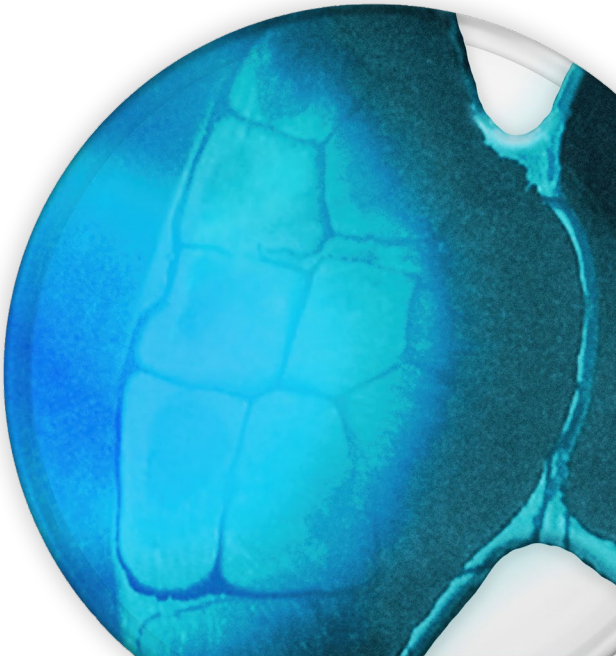
PrecisionBiotics®

Clinical Evidence Summary

Paediatric Gut Health & the 35624™ Probiotic Strain



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Clinical Evidence Summary

Paediatric Gut Health & the 35624™ Probiotic Strain

The pathophysiology of irritable bowel syndrome (IBS) is not fully understood[1]. However, in both adults and children, alterations in the composition of the gut microbiome may play a role in the development of functional gastrointestinal disorders (FGIDs), an umbrella term which includes IBS[2-7]. FGIDs are also referred to as 'disorders of gut-brain interaction'[2].

The influence of the gut microbiome on gut health and function has prompted research into the potential of probiotics for IBS[8, 9]. This has resulted in international clinical guidelines recommending the use of specific probiotic strains for managing symptoms of IBS[8, 10]. Clinical and real-world data in adults and children show the *Bifidobacterium longum* **35624**™ probiotic strain may be effective in managing the global symptoms of IBS and may also improve the impact of IBS symptoms on quality of life[11-18].

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.

Note: The **35624**™ strain, formerly classified as *Bifidobacterium infantis*, has been reclassified as belonging to the species *Bifidobacterium longum*.

Key Points:

- FGIDs in children are common, with IBS being among the most common FGID in children over the age of four[19]
- Gut bacteria profiles of children with IBS may differ from those without[5-7]
- Low-grade inflammation may be a component of IBS in some paediatric cases[20-22]
- Probiotics have been recognised in the management of IBS in children[10, 21, 23, 24]
- The *Bifidobacterium longum* **35624**™ strain has demonstrated systemic immunomodulatory properties[25]
- In adults, clinical and real-world data has shown *Bifidobacterium longum* **35624**™ to be associated with improvements in the management of IBS symptoms and quality of life, reduction in the severity of IBS[12-18] and modulation of inflammatory biomarkers[13]
- In children, a real-world, open-label clinical study found that *Bifidobacterium longum* **35624**™ can help reduce the severity of IBS symptoms, and reduce the impact of IBS symptoms on life[11]
- 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 in Children

The composition of the gut microbiome, which is established early in life, is influenced by various factors such as mode of delivery at birth, breastfeeding, geographic location, household exposures (e.g. to pets) and nutrition[26]. In the first two years of life, the gut microbiome develops and changes, usually stabilising by the age of three years[26]. A rich diversity of microbial species in the gut is considered healthy[27,28].

Whilst it is difficult to modify the composition of the gut microbiome beyond early life[26,29], aging, illness, use of medications such as antibiotics, lifestyle and diet may all have an effect[30,31]. 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 microbiome[32]. Additionally, supplementation of the gut microbiome with certain probiotics to confer potential health benefits has been recognised in children[23,24].

The Gut Microbiome in Health and Illness

The gut microbiome plays a key role in the regulation of human health[33]. It is involved in many functions in the body including[33]:

- Maintenance of normal gut physiology and health, through regulation of epithelialcell proliferation and differentiation
- Protection against pathogens, through colonisation of mucosal surfaces and production of antimicrobial substances
- Regulation of multiple 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

An altered gut microbiome has been associated with numerous health conditions[31]. Whilst it is not fully understood whether this is a cause or consequence, there is speculation that alteration of the gut microbiome may be related to a variety of diseases, including metabolic, immunological, cardiovascular and neuropsychiatric conditions, as well as gastrointestinal (GI) conditions, such as IBS[33].

IBS in Children

IBS is a relapsing and long-term condition that affects the digestive system[34]. A diagnosis of IBS is made based on patient-reported symptoms, in the absence of other detectable diseases[9,35]. In the paediatric population, the Rome IV criteria define IBS as a functional abdominal pain disorder, within the umbrella term of FGID[20].

The Rome IV criteria[20] state that the diagnostic criteria* for IBS in children must include all of the following:

- Abdominal pain at least four days per month that is either related to defecation and/or a change in stool frequency and/ or a change in stool form
- In children with constipation, the pain does not resolve with resolution of the constipation
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

*Criteria fulfilled for at least 2 months before diagnosis

IBS is amongst the most common FGID in children over four years of age[19]. FGIDs are frequently encountered in healthcare settings and may account for up to 50% of paediatric gastroenterology consultations[36]. In addition to increased healthcare expenditure, FGIDs in children are linked with reduced quality of life, low mood, anxiety, school absenteeism, and missed work for caregivers[19,36]. Both the psychosocial factors and gastrointestinal symptoms associated with FGIDs can persist into adulthood[19,36].

The aetiology and pathophysiology of IBS in children

The aetiology and pathophysiology of IBS in children (and adults) are not completely understood, however, different mechanisms have been suggested regarding the development of IBS[37]. Some potential predisposing factors occur outside of the gut, for example, genetic predisposition, environmental influences and psychosocial disturbances[1, 22]. Diet is often attributed as a contributory factor for IBS, however, the exact relationship between diet and IBS has not been determined[22]. In addition, there may be a relationship between early life conditions (such as umbilical hernia, pyloric stenosis and cow's milk protein allergy) and IBS, although further studies are needed to confirm this[22].

Some of the potential pathophysiological changes occurring in paediatric IBS within the gut are outlined below.

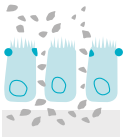
Inflammation and infection

- Studies of children with IBS have shown an accumulation of inflammatory cells in the intestinal mucosa[22]
- There may be an infectious trigger for IBS in some paediatric cases[20, 37]
- Increased incidence of IBS has been reported after an episode of bacterial gastroenteritis in children (post-infectious IBS)[22, 38]

Visceral hypersensitivity

- Visceral hypersensitivity (i.e. the increased perception of stimulus to the intestine, manifesting as pain or discomfort), is believed to have a key role in the pathogenesis of IBS[39]
- Visceral hypersensitivity has been documented in paediatric populations with IBS[40]
- Chronic inflammation of the intestinal mucosa combined with stress factors can cause visceral hypersensitivity in the lower GI tract[39]

Increased intestinal permeability



- The gut-brain axis, gut microbiota and the intestinal barrier work together to provide nutrients and are involved in the development of the immune system[36]
- A dysregulation of this system may lead to increased intestinal permeability and GI transit time, which can, in turn, cause symptoms such as abdominal pain and bloating[36]
- There is some evidence that children with functional abdominal pain/ IBS have increased permeability in the proximal GI tract and colon[41]

Alterations in gut microbiome composition

- Studies in paediatric populations have found differences between the gut microbiome of those with IBS and those without[5-7]
- Processes that are known to cause alterations in the gut microbiome may be associated with an increased risk of developing IBS, such as courses of antibiotics[42] or small intestinal bacterial overgrowth[43]

Clinical Guidelines for Probiotics in Paediatric IBS

- The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Special Interest Group on Gut Microbiota and Modifications and the World Gastroenterology Organisation (WGO) Global Guideline on probiotics both recognise the benefit of using certain specific strains of probiotics in children with IBS[10, 23]
- An Italian guideline for the management of IBS in children has given conditional recommendations for certain probiotics to treat global IBS symptoms[21]
- An expert consensus recommended certain probiotics for improving the symptoms of IBS in children[24]
- A systematic review of the use of probiotics in functional abdominal pain disorders (incorporating IBS) concluded that probiotics may provide better pain relief (compared to placebo) for children with functional abdominal pain[44]

Mechanism of Action of the 35624™ strain

The immunomodulatory properties of the *Bifidobacterium longum* **35624**™ strain have been demonstrated in three double-blind, randomised, placebo-controlled trials in people with ulcerative colitis, chronic fatigue syndrome and psoriasis[25]. These studies demonstrated that the **35624**™ strain significantly reduced C-reactive protein and the proinflammatory cytokines TNF-α and IL-6, suggesting a systemic immunoregulatory mechanism of action[25].

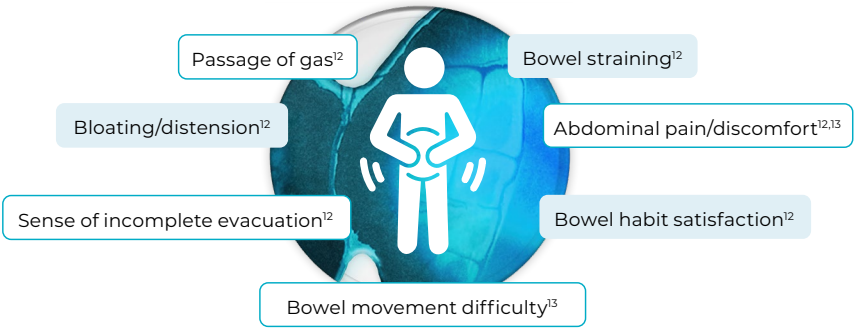
- Downregulating proinflammatory cytokines (e.g. IL-12 and TNF-α)
- Upregulating anti-inflammatory cytokines (e.g. IL-10, TGF-β)
- Activating regulatory T-cells

Additionally, results from pre-clinical models suggest that the unique exopolysaccharide (EPS) coating of the **35624**™ strain mediates some of its immunoregulatory properties, playing a key role in the inhibition of proinflammatory cytokines (e.g. IL-17)[48, 49]. This multifaceted mode of action is thought to prevent symptoms and tissue damage caused by chronic low-grade inflammation[45].

Clinical and Real-World Evidence for the 35624™ strain in IBS

Clinical trials in adults[12, 13] and children[11, 50] have demonstrated that *Bifidobacterium longum* **35624**™ is a safe and well tolerated probiotic strain.

Randomised, placebo-controlled trials have demonstrated benefits in adults with IBS following supplementation with the **35624**™ strain, including significant improvements ($p<0.05$ vs placebo) in overall IBS symptom scores[12, 13] and in certain inflammatory biomarkers[13]. In addition, there were significant improvements ($p<0.05$ vs placebo) in specific symptoms of IBS, including:



Real-world, open-label studies of *Bifidobacterium longum* **35624**™ have shown similar positive effects on GI symptoms, as well as improvements to quality of life[14-17].*

More recently, an open-label, single-arm clinical study demonstrated positive effects of 12 weeks of supplementation with the **35624**™ strain in children and adolescents with IBS, including[11]:

- Significant decreases in composite IBS severity scoring system (IBS-SSS) scores ($p<0.0001$ vs baseline)
- 96.6% of participants experienced a clinically meaningful** improvement in their composite IBS-SSS score
- Significant improvements in all IBS-SSS domains ($p<0.0001$ vs baseline; Figure 1)
- Numerical improvements in at least three IBS-SSS domains experienced by 98.3% of participants

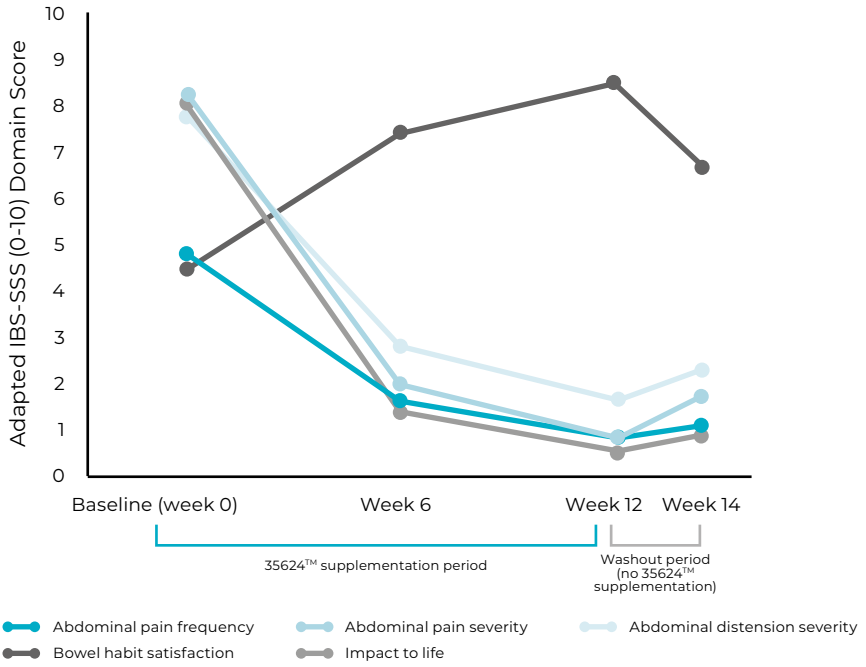


Figure 1: IBS-SSS domain scores during 35624™ supplementation period

*Please refer to Clinical Evidence Summary: Gut Health & the **35624**™ Probiotic Strain for further details of the studies conducted in adults.

**≥50-point decrease in IBS-SSS score

- Improvements in the distribution of IBS severity categories, with decreases in the number of participants with severe or moderate symptoms, and increases in those either mild symptoms or in remission (Figure 2)

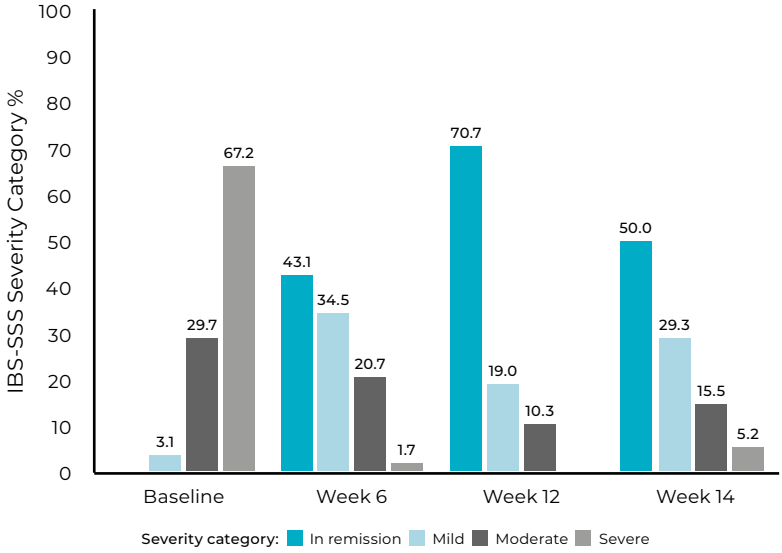


Figure 2: Percentage of participants in each IBS-SSS severity category by time-point

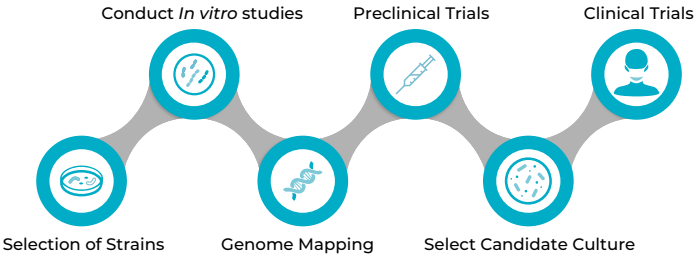
Overview of Research Methods

Effects of *Bifidobacterium longum* 35624 in children and adolescents with irritable bowel syndrome (Cruchet Muñoz et al, 2024)[11]

A real-world, open-label, single-arm study, conducted in 64 children and adolescents (8-18y) with IBS as per the Rome IV criteria, with or without another FGID. Participants received $1x10^9$ colony-forming units of *Bifidobacterium longum* **35624**™ daily for 12 weeks. The IBS symptoms of the participants were measured by the study physician at baseline (one week before intervention period), week 6 and 12 of the intervention period and week 14 (washout period with no supplementation for two weeks after the intervention period). An adapted IBS-SSS measured five domains (abdominal pain frequency [number of days with pain]; abdominal pain severity; abdominal distension severity; bowel habit satisfaction; and impact to life). The Wong-Baker FACES® and numeric pain rating scales were used to obtain children's responses. Diaries were also provided to participants, to record parent and child perspectives of the number of IBS symptoms present via the adapted Questionnaire on Paediatric Gastrointestinal Symptoms (QPGS) and stool consistency via the Bristol Stool Form Scale during the intervention period.

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.

Summary

Alterations in the gut microbiome composition may occur in children with symptoms of IBS compared to those without[5-7]. Clinical guidelines recognise the potential role of probiotics in the management of the symptoms of IBS in children[10, 21, 23]. Results from clinical studies and real-world evidence have previously demonstrated that supplementation with the **35624**™ strain helps to significantly improve GI symptom severity and bowel habits in adults with IBS[12-18]. More recently, the **35624**™ strain has been shown to significantly improve IBS symptoms including abdominal pain, abdominal distension, bowel habit satisfaction and impact to life, in children and adolescents with IBS[11].

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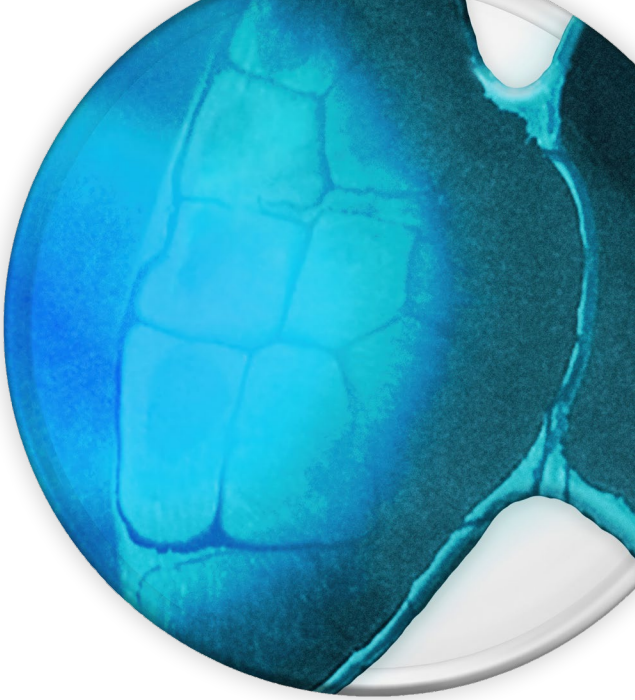

Learn how *Bifidobacterium longum* **35624**™ may help in the management of IBS symptoms in adults and children by visiting our CPD Learning Hub:

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