Anatara
LIFESCIENCES

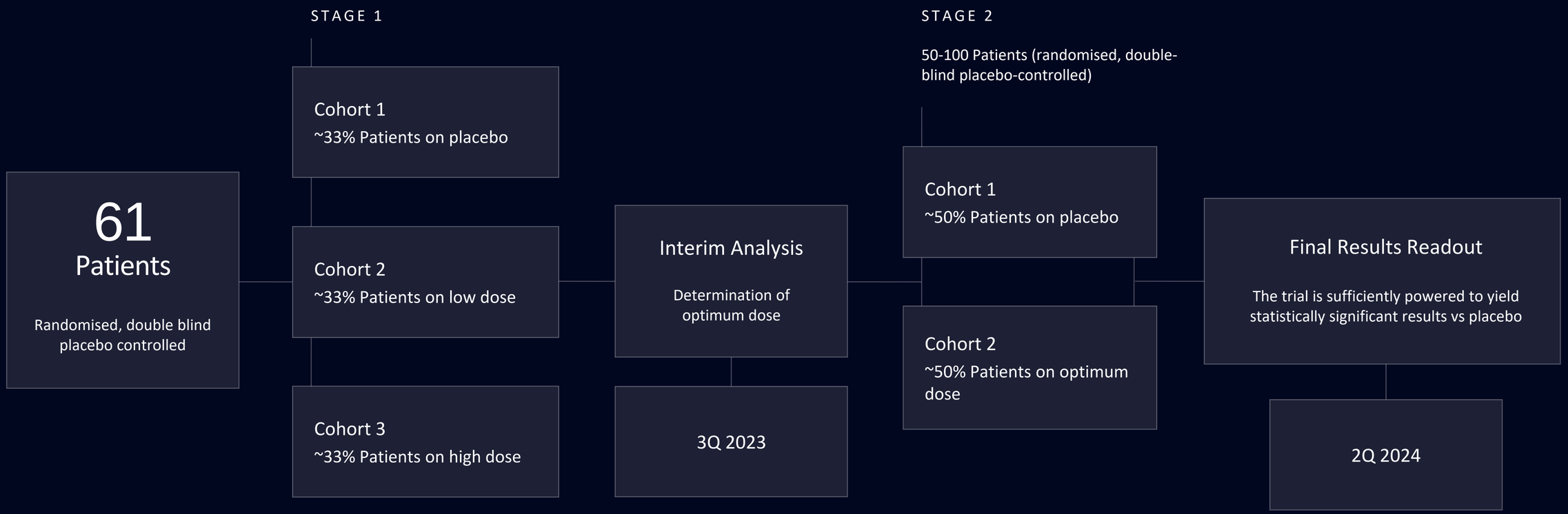
NOVEMBER 2023

GaRP Clinical Trial Discussion

ANATARA LIFESCIENCES LTD

Clinical trial - Irritable Bowel Syndrome

ROBUST CLINICAL TRIAL TO VALIDATE THE EFFECTIVENESS OF GARP



GaRP

ONE PRODUCT, MULTIPLE BENEFITS

Patent Protected

Scientifically designed for the relief and management of background IBS symptoms and the rejuvenation of GIT dynamics

ANR-Bromelain - Anatara know how & innovation

Anatara has in-house knowledge of Bromelain protease activity and the associated QA required for clinical benefits.

Everyday Option

Designed as an everyday option to manage the causes and relieve symptoms of IBS (pain, cramping, gas, bloating, diarrhoea & constipation).

Effective Relief

Coated components released to the target areas for effective and sustained relief -2 components release in the small intestine and 3 components have additional coating for delivery in the large intestine (colon).

Natural Components

Combines bromelain extract from pineapple stems in a patent pending formulation with other synergistic coated GRAS components. These components have specialist roles when delivered into specific regions of the GIT. *For MOA (Mechanism of Action) to be effective these components are coated for delivery into colon/large intestine.

GaRP

ANR-Bromelain

Reduces pro-inflammatory cytokines & serotonin; promotes healing via mucin genes; reduces attachment some bacteria.

Menthol

Antispasmodic for smooth muscle GITract.

Vitamin D*

Improves mucosal barrier homeostasis and assists microbiome; down- regulation of pro-inflammatory factors.

Threonine*

Amino acid that stimulates colonic healing & mucin synthesis.

Butyrate*

Supports colonocytes as a barrier; reduces pro-inflammatory cytokines & restores homeostasis of microbiome.

Phase II Clinical trial
Irritable Bowel Syndrome

ROBUST CLINICAL TRIAL TO VALIDATE THE EFFECTIVENESS OF GARP

Title

Dose Determination and Efficacy Evaluation of the Gastrointestinal ReProgramming (GaRP) Dietary supplement in IBS patients: A Randomized, Double-blind, Placebo controlled virtual clinical trial

Population

Males and females 18-65 years of age with irritable bowel syndrome (IBS-SSS score of 175-350 and categorised as IBS on ROME IV criteria), two stages with interim analysis between stages with approx. 60 in Stage 1 and 50-100 anticipated in Stage 2.

Key Milestones & Messages

Stage 1 Complete – 3Q CY2023

Stage 2 Completion – 2Q CY2024

Endpoints

- ✓ No Treatment-Related Adverse Events.
- ✓ Change in IBS-Severity Scoring System (IBS-SSS) compared to placebo.
- ✓ Change in IBS quality of life (IBS QoL) points compared to baseline.
- ✓ Hospital Anxiety and Depression (HAD) Scale comparing to baseline.
- ✓ IBS Adequate Relief (IBS-AR) compared to baseline.
- ✓ Safety markers.

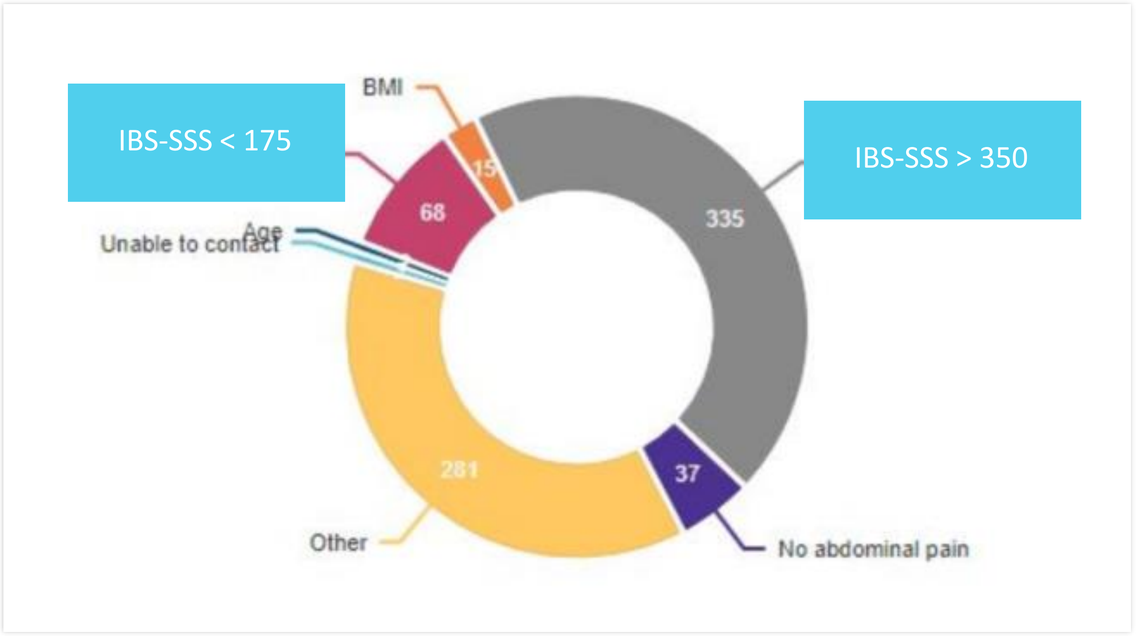
Exploratory Endpoints

- ✓ Plasma levels of specific inflammatory markers.
- ✓ Use of rescue medication across the study group.
- ✓ Alterations in gut microbiota with respect to diversity, perceived balance and correlation to IBS symptoms including overall wellness.

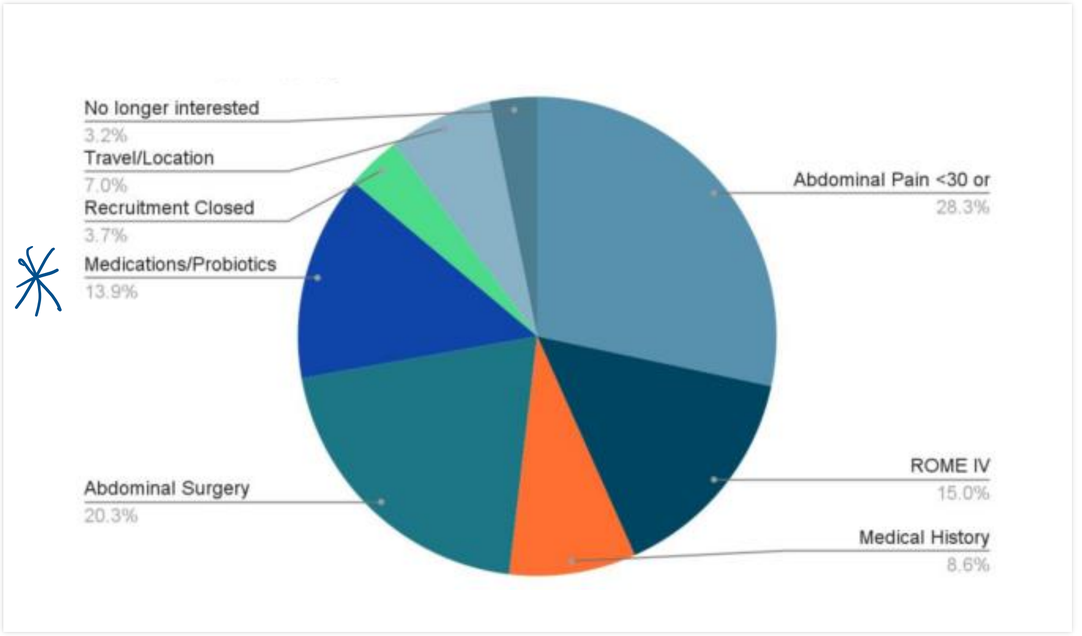
Recruitment - Stage 1

The most prevalent exclusion criterium was the IBS-SSS score

> 45% of participants deemed ineligible during pre-screening



Other exclusion factors

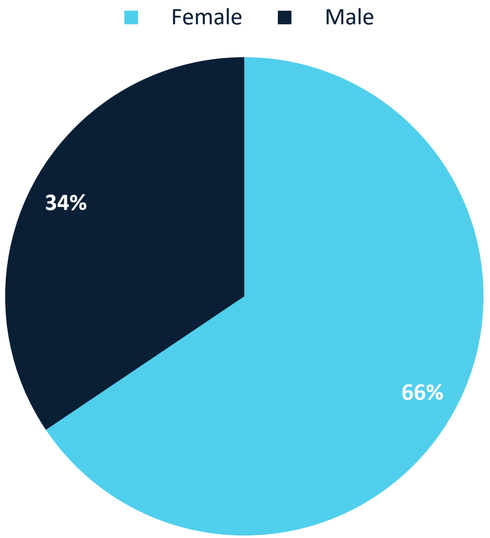


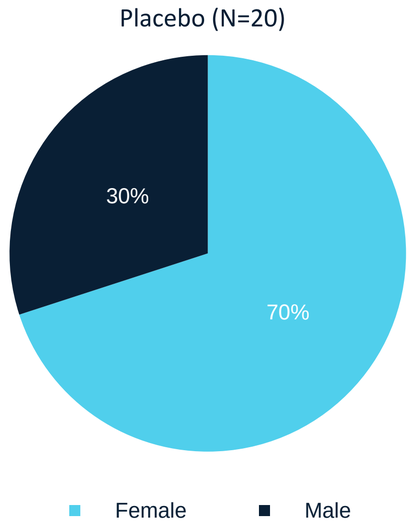
Stage 1- Clinical Trial Results

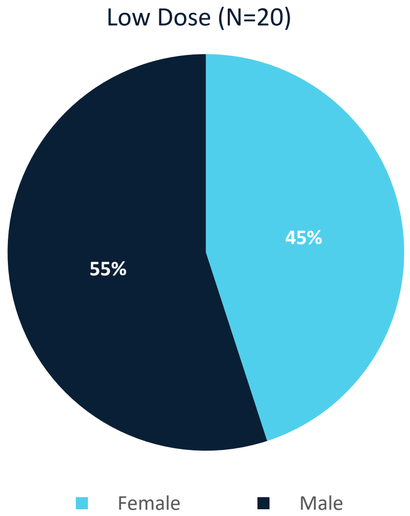
DEMOGRAPHICS

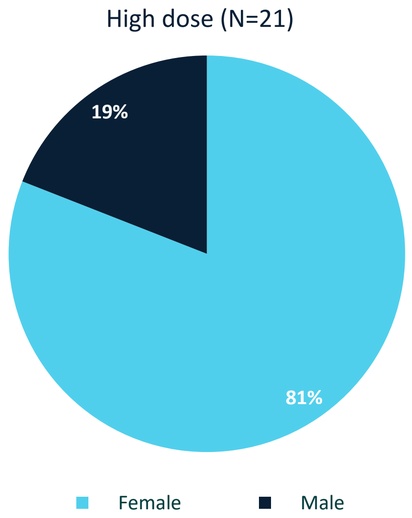
Median Age
37

N: 61
Female: 40
Male: 21









Stage 1- Clinical Trial View

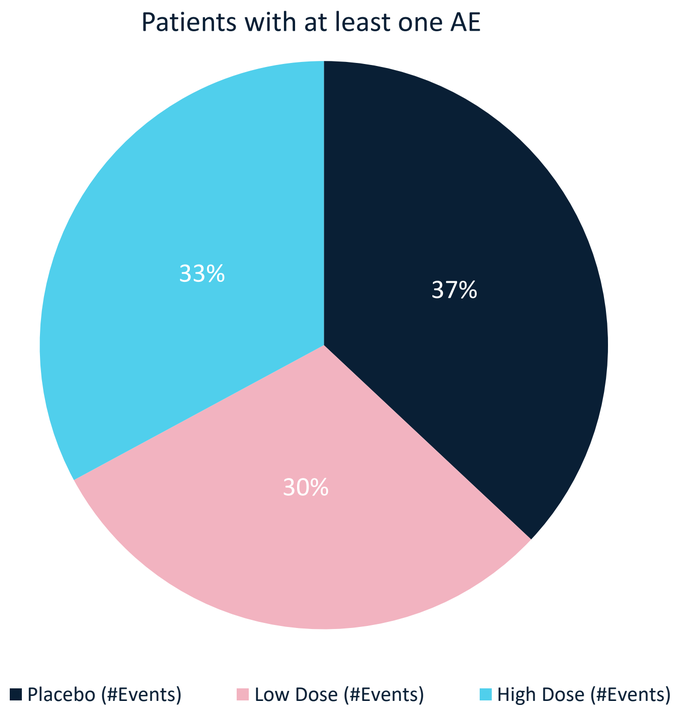
ADVERSE EVENTS

"Low Dose" was the predicted , recommended dose from pre-clinical work.

“High Dose" is double the Low Dose /Recommended Dose .The High Dose cohort was added to ensure that the dose of complementary medicine was not sub-therapeutic in the IBS trial and so that important information on the drug’s therapeutic window could be obtained.

	Placebo			Low Dose			High Dose		
Adverse Event	#Subjects	%	#Events	#Subjects	%	#Events	#Subjects	%	#Events
Ear and labyrinth disorders	0	0.00%	0	1	-5.00%	1	0	0.00%	0
Gastrointestinal disorders	5	-25.00%	16	3	-15.00%	5	2	-9.50%	3
General disorders and administration site conditions	0	0.00%	0	1	-5.00%	1	2	-9.50%	2
Immune system disorders	0	0.00%	0	1	-5.00%	1	0	0.00%	0
Infections and infestations	5	-25.00%	6	6	-30.00%	7	7	-33.30%	10
Musculoskeletal and connective tissue disorders	1	-5.00%	1	1	-5.00%	1	2	-9.50%	2
Nervous system disorders	0	0.00%	0	1	-5.00%	1	4	-19.00%	4
Renal and urinary disorders	1	-5.00%	1	0	0.00%	0	0	0.00%	0
Respiratory, thoracic and mediastinal disorders	0	0.00%	0	2	-10.00%	4	2	-9.50%	2
Skin and subcutaneous tissue disorders	3	-15.00%	3	1	-5.00%	1	1	-4.80%	1

Patients with at least one TEAE	11	-55.00%	27	10	-50.00%	22	12	-57.10%	24



Stage 1- Clinical Trial Results

PRIMARY ENDPOINTS

Stage 1 IBS Clinical Trial

- Number of Patients: Placebo: 20 / Low Dose: 20 / High Dose: 21

Primary Endpoints

✓ Determine optimum Dose: Low Dose

✓ Safety: No serious adverse advents

✓ Improvement in Irritable Bowel Severity Scoring System (IBS-SSS

1. 56% reduction after 8 weeks of treatment
2. Outperformed placebo by ~20%

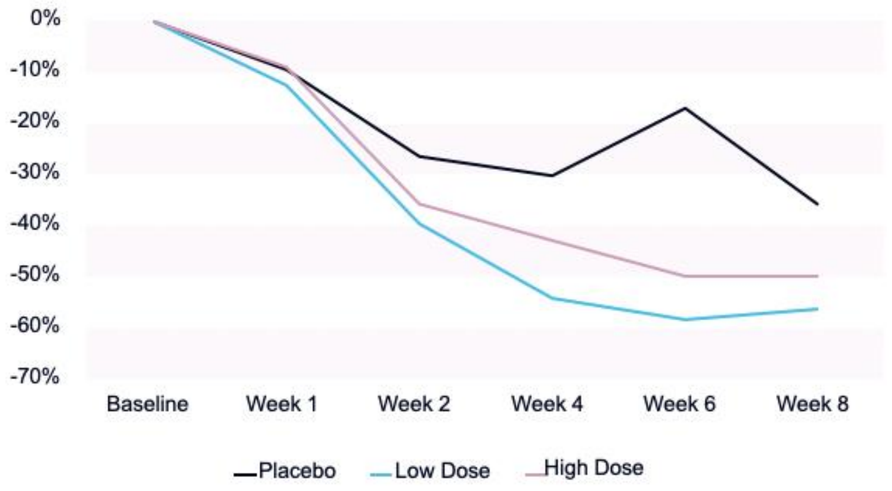
1

MEDIAN IBS-SSS SCORE – BASELINE TO WEEK 8

	Placebo	Low Dose	High Dose
	n=20	n=20	n=21
Baseline	265	240	280
Week 1	240	210	255
Week 2	195	145	180
Week 4	185	110	160
Week 6	220	100	140
Week 8	170	105	140
Difference in baseline score to week 6 score	45	140	140
% Change	-17%	-58%	-50%
Difference in baseline score to week 8 score	95	135	140
% Change	-36%	-56%	-50%

2

MEDIAN REDUCTION IN IBS-SSS SCORE - PLACEBO VS. LOW & HIGH DOSE



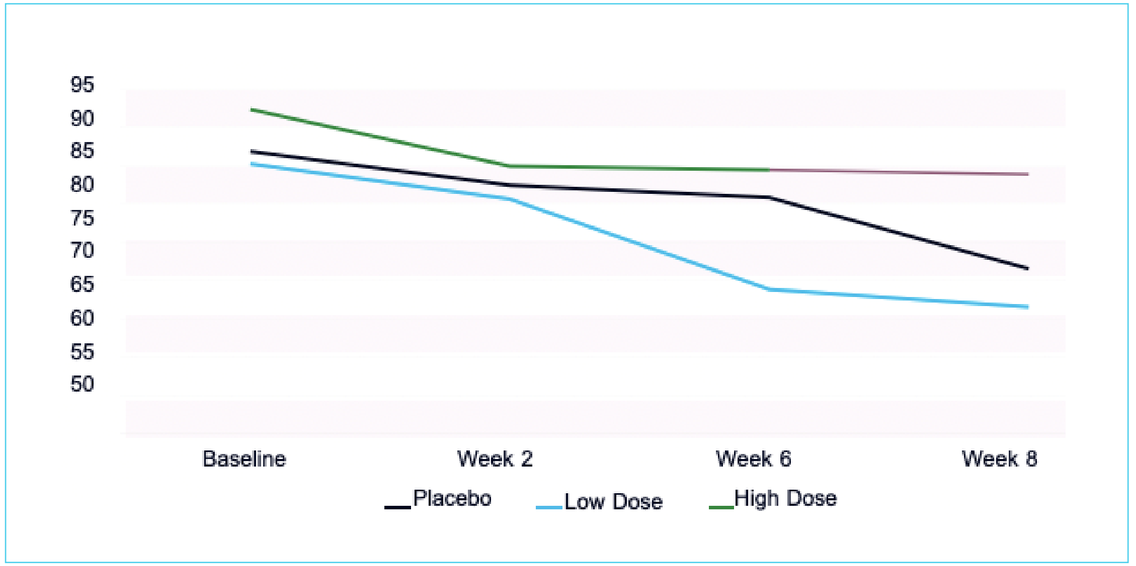
Stage 1- Clinical Trial Results

SECONDARY ENDPOINTS

Improvement in IBS Quality of Life (IBS-QoL) Score

- Low Dose resulted:
  - ✓ A 10 pt + reduction is considered clinically meaningful

QoL	Scoring		
	Placebo	Low Dose	High Dose
Baseline score	86.8	85.2	92.3
Week 2	82.4	80.6	84.9
Week 6	80.8	68.8	84.4
Week 8	71.5	66.5	83.8



Stage 1- Clinical Trial Results

SECONDARY ENDPOINTS

Improvement in Hospital Anxiety & Depression Score (HADS)

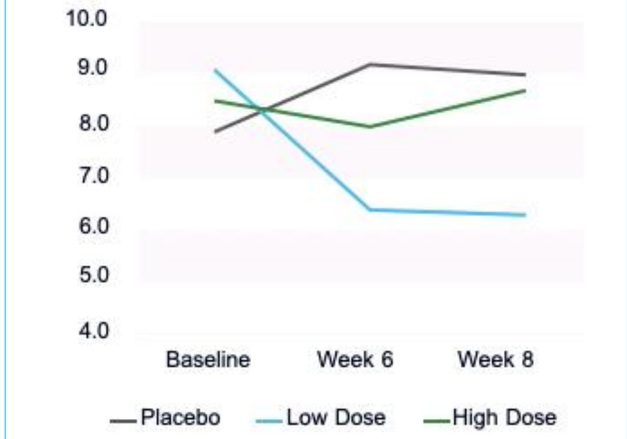
- Low Dose Resulted in:
  - ✓ Anxiety Score: from borderline abnormal to normal
  - ✓ Depression Score: remained normal throughout
  - ✓ Placebo group deteriorated to abnormal range

Anxiety	Scoring (mean)		
	Placebo	Low Dose	High Dose
Baseline	7.9	9.1	8.5
Week 6	9.2	6.4	8.0
Week 8	9.0	6.3	8.7

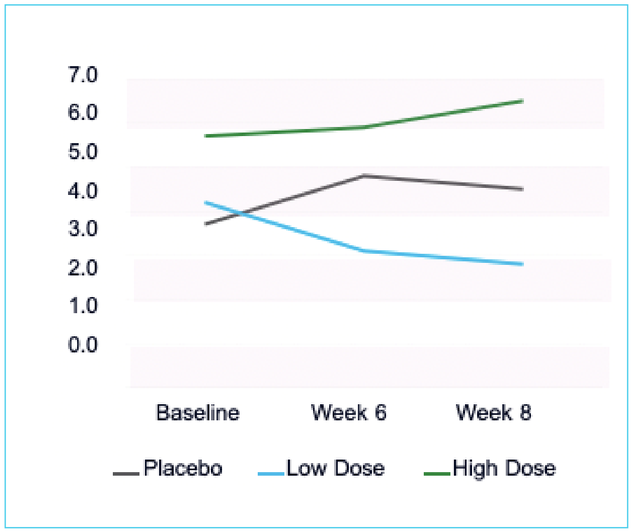
Scoring: (for Depression and anxiety)

0-7	Normal
8-10	Borderline abnormal (borderline case)
11-21	Abnormal (case)

ANXIETY SCORE



DEPRESSION SCORE



Stage 1 Clinical Trial Discussion

Why does anxiety improve?

Direct and indirect effects are easily postulated because of the MOA (Mechanism of Action of the drug). Firstly, improved symptoms as measured by IBS-SSS lessens concern over day –to –day control and management leading to a reduction in background anxiety, with reduction in potential inconvenience and embarrassment. Secondly, the restoration and maintenance of the gastrointestinal tract lining as a barrier is a treatment target and GaRP's MOA is designed to address such "leaky gut" considerations. It is less likely that adverse factors will cross into the blood stream with the potential to influence metabolism within neurons (the brain) and negatively impact psycho- emotive conditions.

Why does QoL seem to separate for the High Dose?
(i.e. the use of double the predicted therapeutic dose, which is the "Low Dose")

The High Dose had a beneficial effect on the IBS-SSS but did not improve or influence the participant's harmony or psycho-emotive well- being as measured by QoL and HADS . For this discussion we can ignore the "depression" score as the participants were not clinically depressed and remained in similar normal score range (sig. depression being an exclusion from the trial).However, the Low Dose participants improved with scores reducing from borderline abnormal anxiety to normal whereas the High Dose (Double Dose) demonstrated no such effect on psycho-emotive scores. This suggests the MOA in improvement is multifactorial and that more of the drug to an intestinal region is not necessarily a benefit ,with the therapeutic dose curve over saturated with possible deleterious effects on the microbiome harmony .

Stage 1 Clinical Trial Discussion

How does GaRP (to be known as “Anajuve”) restore and maintain the integrity of the gastrointestinal lining as a barrier? How does GaRP/Anajuve therefore have a beneficial effect on the gut-brain axis?

The MOA is complex and regional with reduction of cytokines and other factors that are pro-inflammatory (Bromelain in small intestine; Butyrate,Cholecalciferol/VitD3 in large intestine or colon)), and the reinforcement of mucosal surface homeostasis by upregulating mucin genes and stimulating synthesis and healing of lining cells (L-Threonine ,Cholecalciferol/Vit D3). The homeostasis of the microbiome is assisted (Butryate beneficial for favourable bacteria: Bromelain reduces attachment unfavourable bacteria) and the translocation of adverse factors is reduced (Cholecalciferol/VitD3 in colon). An improved GIT lining barrier combined with microbiome homeostasis assists the gut-brain axis balance by reducing adverse factors being absorbed for release into the blood stream.

What is the gut-brain axis?

This is the two-way biochemical signalling that takes place between the CNS (Central Nervous System consisting brain & spinal cord) and the GIT. The bidirectional communication is complex , multifactorial and includes neural connections such as the autonomic nervous system and enteric nerves with the vagal 10th cranial nerve interacting, immune system factors , and neuroendocrine systems. As well there are the products and factors from GIT (or the gut) secretions, absorptions and the microbiota environment . These complex and wide-ranging products can be absorbed for release in the blood stream or, in a situation of “leaky gut”, escape through the GIT barrier into the blood circulation. These many factors , including cytokines, neurotransmitters and metabolites of the microbiome, then influence the metabolic processes of the neurophysiology of the brain if able to cross the blood –brain barrier.

What is the placebo effect?

This shows the brain’s influence on health where participants are dosed with an identical looking substance of no therapeutic use yet there is an improvement in the targeted condition for treatment . Involvement in a process with a support network, doing something for a difficult to manage complaint and being in communication around the discipline involved in monitoring lifestyle, diet and observations all contribute to perception. It is likely to be more than the positive thinking and conditioning in expectation of an improved outcome to a troublesome long-term complaint ,with a possible contribution of natural endorphin release providing further benefit .

IBS in America Survey

USE OF TREATMENTS FOR IRRITABLE BOWEL SYNDROME AND PATIENT SATISFACTION, BASED ON IBS IN AMERICA SURVEY

Trial Details

Use and satisfaction of various IBS treatments

3,254
IBS sufferers (Rome III criteria)

302
Physicians and gastroenterologists

GaRP

The publication “Highlights the need for further effective IBS treatments”

Significant opportunity for an effective, evidenced based OTC product

OTC is Preferred Treatment Method

77% of individuals with IBS have used OTC treatment for IBS symptoms

15% of individuals with IBS have used prescription medications

Low Treatment Satisfaction

15% of IBS-C sufferers were ‘very satisfied’ with OTC treatments

20% of IBS-D sufferers were ‘very satisfied’ with OTC treatments

Ineffectiveness of Prescription Options

19% of IBS-C sufferers were very satisfied with an FDA approved medication

11% of IBS-D sufferers were very satisfied with an FDA approved medication

SOURCE: HTTPS://WWW.NCBI.NLM.NIH.GOV/PMC/ARTICLES/PMC7212496/

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Contact Us

ANATARA LIFESCIENCES LTD

David Brookes
Executive Chair

+61 0411 712 579
www.anataralifesciences.com

Dirk van Dissel
Investor Relations

Candour Advisory
dirk@candouradvisory.com.au