Efficacy of PhenActiv™ on gastrointestinal tract function in otherwise healthy adults. A randomised double blind placebo-controlled study.

FINAL REPORT (n=41 participants)

Protocol Number – WAIKFG-18

Abbreviated study title*: GIT PhenActiv™ study*

Investigators and Qualifications

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Purpose of Study

This study was designed to assess the effectiveness of PhenActiv™ on gastrointestinal tract (GIT) function (including bowel frequency, bloating, flatulence and abnormal pain).

Background Information

Gastrointestinal discomfort including symptoms of bloating, abdominal pain, constipation and diarrhoea is experienced by around one in five Australians (Better Health Channel 2017). Such symptoms can cause distress to the sufferer and can have a significant impact on quality of life. A direct cause of functional gastrointestinal disorders is poorly understood. However, underlying factors includes diet, food allergies, inflammation, dysbiosis, visceral hypersensitivity, genetics, brain-gut axis, and epithelial hyperpermeability (Ench et al 2016).

PhenActiv™ is a freeze-dried kiwifruit concentration powder made from New Zealand grown, GMO free, green kiwifruit (actinidia deliciosa). Kiwifruit contains actinidin, a proteolytic enzyme known to enhance protein digestion and play a role in supporting gut motility (Udani & Bloom 2013). Both of which have a beneficial effect on overall bowel function. Kiwi fruit is also a source of soluble and insoluble fibre as well as prebiotics, which help support the growth of beneficial bacteria and protect against dysbiosis (Udani & Bloom 2013). Furthermore, kiwi fruit is a source of lutein, a carotenoid present in high concentrations in the retina and plays an important role in maintaining the health of the eyes (Lima et al 2016). Specifically, lutein's antioxidant activity protects the retina from oxidative damage by scavenging reactive oxygen species and filtering blue light (Ma et al 2016).

The effect of kiwi fruit extract on functional gastrointestinal disorders in humans has been previously studied. Specifically, Udani and Bloom 2013 evaluated the efficacy of a kiwi fruit extract versus placebo on constipation and overall gut health in 87 adults over 4 weeks. A dose of 5.5g kiwi fruit extract was taken daily. Results of the study showed a significant improvement in spontaneous and complete bowel movements in the treatment group along with reducing abdominal pain and flatulence compared to placebo. Kindleysides et al 2015 trialled 1g/day of encapsulated kiwifruit extract compared to placebo in 40 adults experiencing constipation over 3 weeks. Results of the study showed no improvement in bowel motion frequency or any other parameters. The authors concluded a higher dose may be required to see a beneficial result. Furthermore, Ansell et al 2015 studied the effect of Actazin and Gold, 2 powdered ingredients derived from whole New Zealand green and gold kiwifruit on stool frequency in 19 adults. Along with placebo there were two dosing regimes for the Actazin, specifically 600mg and 2400mg/day and a single dose of 2400mg Gold over 28 days. Results of the study showed both Actazin (2400mg/day) and Gold (2400mg/day) significantly increases daily bowel motions by more than 1 bowel movement per week and was well tolerated.

One possible mechanism by which kiwi fruit extracts its benefit on the GIT may be via increased serotonin production. Although most strongly associated with being a neurotransmitter in the central nervous system, the primary site of serotonin synthesis, storage and release is the GIT. From the mucosa, serotonin is released

within the GIT, where it may activate neural reflexes associated GIT function (secretions, motility and vasodilation). By increasing serotonin levels, beneficial effects on the GIT may be possible. However, the effects kiwi fruit have on serotonin levels to date are unknown. One outcome of this trial was to investigate this effect.

The aim of this study was to evaluate the effect of PhenActiv™ on gastrointestinal tract function in healthy adults over 6 weeks. It was hypothesised PhenActiv™ would enhance GIT function (including bowel movements, abdominal pain, and intestinal permeability) and increase quality of life compared to placebo.

Investigational Product

The investigational product, PhenActiv™, was provided in vegetarian microcrystalline hard shell 2-piece capsules, filled in a GMP compliant manufacturing facility. The investigational product included two active treatment arms; Arm A contained PhenActiv™ 1000mg dose which included 6 x 167mg PhenActiv plus 533mg maltodextrin (total capsule fill weight 700mg), and Arm B contained PhenActiv™ 3000mg dose which included 6 x 500mg PhenActiv + 200mg maltodextrin (total capsule fill weight 700mg). The placebo product contained 6 x 700mg maltodextrin (total capsule fill weight 700mg) and was housed in a capsule identical in appearance to the test product. The daily dose for all treatment arms was 6 capsules taken orally at breakfast time with food and 250ml of water for a period of 6 weeks.

This trial was conducted in compliance with the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), the Therapeutic Goods Administration (TGA), Notice for Guidance on Good Clinical Practice and ethical guidelines outlined in Additional Ethical Considerations. It was approved by Bellberry Limited Human Research and Ethics committee (approval number 201712968) and registered on the Australia New Zealand Clinical Trials Registry ACTRN12618000875202.

Methods

Participants

Following preliminary screening via telephone, 41 eligible potential participants attended the clinic for an information session and provided consent for inclusion into the trial. Enrolment in the trial to receive product occurred only after all inclusion criteria were met. Male and female participants were included if they were over 18 years of age, had normal dietary habits, agreed not to change their diet and exercise regime, agreed not to use other dietary supplements targeted to gut health, were able to provide informed consent and experienced three or more of the following symptoms for at least 3 days in the 3 months before enrolment into the study: bloating, flatulence, diarrhoea, constipation, reflux, heart burn, and abdominal pain/discomfort. Participants were excluded if they had significant medical conditions, had a history of inflammatory bowel disease or gastrointestinal tract surgery, pregnant or lactating women, smoked, consumed more than 2 standard alcoholic drinks daily, allergic to kiwi fruit, had a history of infection, worked nightshifts, or suffered acute or chronic inflammation.

Eligible participants provided consent and undertook a health assessment which included lifestyle questionnaires, blood pressure, heart rate, current medications, medical history, body composition, dietary intake, GIT function (questionnaire), and quality of life (fatigue). Participants further undertook a macular pigment optical density (MPOD) test, and blood collection, which will be analysed for zonulin concentration.

Participants were asked to take the allocated product according to the prescribed dose and attended the study site at weeks 3 and 6 for further body composition assessment, and questionnaires. Between visits, participants recorded the number of daily bowel movements in a stool frequency diary. During the final appointment at week 6, assessment identical to baseline was conducted.

Outcome Measures

The primary outcome measure of this study was change in GIT function with stool frequency as the primary focus. Secondary outcome measures included change in GIT function (The Patient Assessment of Constipation Quality of Life Questionnaire, Gastrointestinal Symptom Rating Scale, IBS Symptom Scoring System, Bristol Stool Chart), change in GIT permeability (plasma zonulin), change in quality of life and fatigue (SF36 questionnaire), change in plasma lutein, change in MPOD score (MPS II Macular Pigment Screener), change in sleep quality (Pittsburgh Sleep Quality Assessment), and adverse reactions and gastrointestinal tolerance (GIT Tolerance questionnaire).

Results

The data analysed is for two treatment groups only, Placebo (n=20) and the higher dose of 3000mg PhenActiv per day (n=21) at baseline and final appointments only.

Table 1: Demographic data

	Baseline		Week 3		Week 6	
	PhenActiv	Placebo	PhenActiv	Placebo	PhenActiv	Placebo
Age	50.0 ± 12.8	46.4 ± 14.8	N/A	N/A	N/A	N/A
Waist circumference (cm)	92.6 ± 15.4	89.1 ± 11.3	92.7 ± 15.5	88.6 ± 12.2	92.3 ± 16.5	87.8 ± 12.0
Hip circumference (cm)	107.2 ± 12.1	104.6 ± 9.9	107.6 ± 12.3	105.0 ± 10.4	107.2 ± 12.4	104.5 ± 11.2
Waist to hip ratio	0.86 ± 0.07	0.85 ± 0.07	0.86 ± 0.07	0.84 ± 0.06	0.86 ± 0.08	0.84 ± 0.06
Systolic blood pressure (mmHg)	121.1 ± 13.0	125.3 ± 17.1	N/A	N/A	123.1 ± 15.6	124.1 ± 20.0
Diastolic blood pressure (mmHg)	81.0 ± 11.0	80.6 ± 14.5	N/A	N/A	81.8 ± 10.5	79.4 ± 12.8
Heart rate (bpm)	70.4 ± 7.31	65.1 ± 10.2	N/A	N/A	69.8 ± 6.0	67.3 ± 10.0
Height (cm)	167.9 ± 6.7	167.3 ± 11.5	N/A	N/A	168.0 ± 6.7	167.2 ± 11.2
Weight (kg)	77.8 ± 16.5	74.7 ± 18.5	78.4 ± 16.7	75.2 ± 19.0	78.2 ± 16.8	75.0 ± 19.2
Body mass index (m/kg^2)	27.7 ± 6.5	26.4 ± 4.7	N/A	N/A	27.8 ± 6.6	26.6 ± 5.1

Table 2: Stool consistency and frequency

	Baseline		Week 3		Week 6	
	PhenActiv	**Placebo**	**PhenActiv**	**Placebo**	**PhenActiv**	**Placebo**
Stool number per week	12.0 ± 7.3	10.6 ± 4.6	11.1 ± 5.6	11.2 ± 4.2	11.7 ± 6.4	11.2 ± 4.9
Stool average number per day	1.7 ± 1.0	1.5 ± 0.7	1.6 ± 0.8	1.6 ± 0.6	1.6 ± 0.9	1.6 ± 0.7
Stool consistency (Bristol stool chart)	3.9 ± 1.9	3.3 ± 1.4	4.0 ± 1.2	3.7 ± 1.0	3.9 ± 1.4	3.5 ± 1.2

	Baseline		Week 6	
	PhenActiv	**Placebo**	**PhenActiv**	**Placebo**
Zonulin (ng/mL)	8.6 ± 3.5	7.8 ± 3.8	8.8 ± 3.0	7.9 ± 3.3

Or

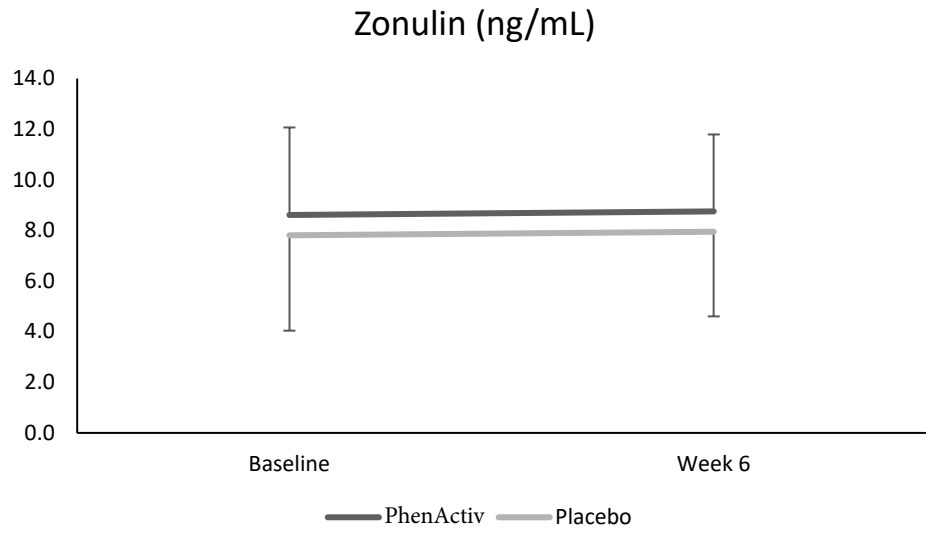

Table 3: Gastrointestinal symptom rating scale and irritable bowel symptom severity score

	Baseline		**Week 3**		**Week 6**	
	PhenActiv	**Placebo**	PhenActiv	**Placebo**	**PhenActiv**	**Placebo**
GSRS total	7.7 ± 2.5	7.5 ± 2.0	4.6 ± 2.8*	5.8 ± 2.8*	4.9 ± 2.9*	6.2 ± 3.2*
IBSSS total	12.5 ± 5.1	11.8 ± 4.1	**7.0 ± 4.2***	9.4 ± 5.5	**7.9 ± 5.1***	10.7 ± 5.7

*denotes a difference from baseline ($p < 0.05$)

Table 4: Macula pigment optical density testing

	Baseline		**Week 6**		Δ	
	PhenActiv	**Placebo**	PhenActiv	**Placebo**	PhenActiv	**Placebo**
MPOD left eye	0.44 ± 0.21	0.40 ± 0.17	0.40 ± 0.15	0.42 ± 0.15	-0.04 ± 0.12	0.02 ± 0.15
MPOD right eye	0.41 ± 0.20	0.42 ± 0.20	0.43 ± 0.19	0.43 ± 0.15	0.02 ± 0.09	0.02 ± 0.15

PAC-QOL

Both groups had a similar reduction in number of participants who no longer reported constipation from baseline to week 6 (n=6 per group), however, the placebo group had a larger proportion of participants who reported no constipation at baseline (n=6 - placebo, n=3 - PhenActiv). One person in the placebo group developed constipation over the trial period. This did not occur in the Actiphen group. The following table provides PAC-QOL total scores, however, as there are a limited number of participants who completed the PAC-QOL at both baseline and week 6 (either due to not having constipation or having relief of constipation), the results must be interpreted with caution

	Baseline		**Week 3**		**Week 6**	
	PhenActiv	**Placebo**	PhenActiv	**Placebo**	PhenActiv	**Placebo**
PAC-QOL total	32.8 ± 15.7	42.1 ± 7.8	25.5 ± 15.9	40.1 ± 19.7	**29.2 ± 10.7***	44.8 ± 17.2

* denotes a significant difference from baseline

Discussion

There were no differences in any demographic data from baseline to week 3 or week 6.
The number of stools per week and day, and consistency of stools did not change from baseline to week 6 in either group, however, this is difficult to analyse on a group basis. Individual results varied with some participants improving both consistency and frequency.

Both PhenActiv and placebo significantly improved responses to the gastrointestinal symptom rating scale at both week 3 and week 6. Only PhenActiv was able to reduce total irritable bowel syndrome severity score at week 3 and week 6. PhenActiv was also associated with a ~40% reduction in IBSSS total. IBSSS rates symptoms such as abdominal pain, abdominal distension, satisfaction with bowel movements, and how bowel habits interfere with everyday life. Furthermore, only PhenActiv was able to reduce total PAC-QOL score at week 6 compared to baseline. This suggests that PhenActiv was able to reduce the symptoms of constipation, however, the placebo group reported a greater number of participants who had a complete reduction of constipation.

There was no difference in MPOD score between groups. The same was true for plasma zonulin concentration. Gastrointestinal disturbances did not differ from baseline to week 6 suggesting that the product was well tolerated by participants with no side-effects.

Conclusion

These initial results indicate that PhenActiv (3000mg /day) significantly reduced the severity of IBS symptoms and constipation as compared to placebo with no side-effects reported.