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CLINICAL CASE STUDY

VIDEO CAMERA ENDOSCOPY (VCE) CLINICAL TRIALS

How to asset the ability of the probiotic strain to attenuate NSAIDs effect in deterioration of small intestinal mucosa tissue

Executive Summary

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are commonly used worldwide, both as prescription-only medicines and as "over-the-counter" preparations. However, low dose use of NSAIDS, is associated with gastrointestinal (GI) injury. Strategies to prevent GI complications associated with NSAID use included are generally associated with undesired side effects, whereas live bacteria formulated as probiotics may offer a safe alternative to prevent or at least decrease negative side effects of NSAIDS. The present clinical trial is aiming to bring a product containing a probiotic strain able to attenuate and/or reverse NSAIDs-induced small intestinal damage and GI symptoms in NSAIDs users.

We established a clinical challenge model aiming at investigating the ability of the probiotic strain in attenuating and/or reversing deterioration in the healthy human gastrointestinal tract

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Keep reading about the challenges and objectives

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About the Sponsor

Probiotic bacteria have been demonstrated to have possible therapeutic effects against intestinal inflammation and the sponsor, a world-class innovative company, focused on bringing to market a treatment. They have previously performed several in vitro screening assays in order to characterize approximately 200 different strains. Five strains were then selected based on their characteristics in vitro, the selected 5 strains were then tested in a rat model of colitis. The present clinical trial was the first in a clinical development program aiming to bring a product containing the selected strain to marked able to attenuate and/or reverse NSAIDs-induced small intestinal damage and GI symptoms in NSAIDs users. The investigational product were vegetable capsules containing the probiotics per daily dose. All capsules were produced in the same batch by the sponsor, which is certified for food production.

Challenges and Objectives

The Sponsor needed a highly experienced research partner able to assess the deterioration of small intestinal mucosa tissue however they needed a method not too invasive in order to overcome the Ethical burdens. The main objectives were:

- To investigate the ability of the probiotic strain to attenuate and/or reverse low-dose, long-term NSAIDs-induced deterioration of small intestinal mucosa tissue as assessed by capsule endoscopy in healthy volunteers
- To investigate the ability of the probiotic strain to attenuate and reverse low-dose, long term NSAIDs-induced GI symptoms as assessed AUC ulcer number as well as assessed by AUC of pain syndrome score for GSRS.
- To investigate co-administration of the probiotic strain to low-dose, long term NSAIDs on changes in multiple biomarkers of general intestinal barrier function in blood and faecal samples.

How Atlantia's Solution Helped

Consequently, we established a clinical challenge model aiming at investigating the ability of the probiotic strain in attenuating and/or reversing deterioration in the healthy human gastrointestinal tract. The deterioration was induced by a chemical agent commonly used and with well-established deteriorating effects on the small intestine. For the primary endpoint, we used the method capsule endoscopy (CE) to assess the small intestinal damage. Capsule endoscopy has been reviewed in a technology status evaluation report by the American society for gastrointestinal endoscopy and it is now the gold standard for assessing occult gastrointestinal bleeding, and indications for its use are continuing to expand. Current uses include exploration and surveillance of bowel pathology such as in Crohn's disease, polyps, small bowel malignancy and drug-induced mucosal injury. Capsule endoscopy (CE) is generally a safe and well tolerated procedure. Atlantia has a highly expert team on managing these technologies when conducting trials and was a perfect fit for the sponsor.

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About the Study

This trial was a single-site, randomised, double-blind, placebo-controlled, two-armed, parallel-group trial in healthy, adult volunteers. It investigated the effect of daily intake of the probiotic strain or placebo when co-administered with daily intake of 300mg of Aspirin.
The trial was conducted in accordance with the ethical principles set forth in the current version of the Declaration of Helsinki (seventh revision; October 2013), the International Conference on Harmonization E6 Good Clinical Practice (ICH-GCP, 10 June 1996) and all applicable local regulatory requirements.
The trial included a run-in period of two weeks duration followed by a six-week intervention period where the probiotic/placebo and NSAIDs were co-administered. After the 6-weeks, the probiotic/placebo was given for two additional weeks to investigate the potential effects of the probiotic on intestinal healing after long-time NSAIDs use. Subjects participated in the trial for a total duration of 10-weeks including the run-in phase.
The primary efficacy variable was to investigate the effect of oral supplement of the probiotic strain versus placebo on small intestinal mucosa damage when co-administered with a NSAIDs challenge for measured as the area-under-the-curve (AUC) for Lewis Score obtained by capsule endoscopy. The sample size of 30 completing participants in each arm was estimated based on a power calculation performed on intervention on percent difference of AUC between two normalized curves (active vs. placebo) as an approximation. To account for a potential drop-out rate of approximately 15%, a total of 35 subjects were randomized in each group. A cclinically significant decrease was seen in the AUC data following treatment with the Probiotic versus placebo.

Recruitment	Number of subjects
Planned	75
Screened	140
Randomized	75
Dropouts	17
Completed	66

Throughout the entire trial, subjects were instructed to maintain their habitual life style with regard to diet, physical activity level and sleep habits. Intake of probiotic products as well as food and food supplements containing probiotics were not allowed from the screening visit and until the end of the intervention period. Subjects were not withdrawn from the trial due to single violations, but violations were recorded as protocol deviations.
Small intestine mucosa deterioration was evaluated using video capsule endoscopy as well as indirect biomarkers in feaces and blood samples At these visits, subjects also filled out the GSRS questionnaire which assessed GI symptoms and pain.
Each subject underwent a video capsule endoscopy over the course of the 8 week intervention. Capsule endoscopy was deemed to be a relevant and acceptable method to evaluate both mild and severe intestinal damage caused by low dosage of Aspirin measured as area-under-the-curve for damage.

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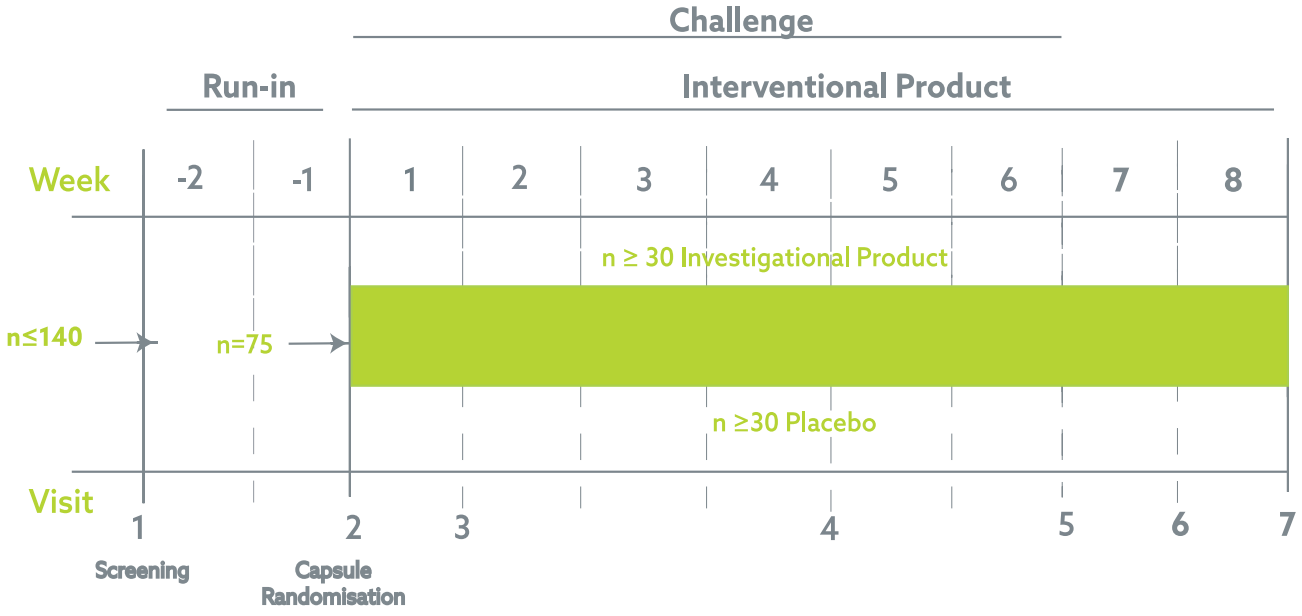

Future plans and Return on Investiment

Our findings support that capsule endoscopy is a robust and reliable method for measuring intestinal damage. The GSRS questionnaire showed a response in some of the categories, but the challenge signal was in general very small and no effect of the intervention was observed in the overall data. While fecal calprotectin and blood I-FABP responded to the NSAIDs challenge, VCE should remain the preferred method used for all clinical activities above any biomarkers or questionnaires. The AUC approach allowed the sensitivity required to observe intervention effects and should be used again in future clinical activities relating to this project. Further studies are necessary to determine if probiotics can aid in reversal of GI damage in the period after NSAIDs intake (recovery). A number of statistically significant findings in exploratory endpoints related to ulcers, further support further clinical development of the pobiotio selected.

This clinical trial demonstrates that subjects who were randomized to receive the probiotic responded significantly better to the Aspirin challenge model in relation to the primary outcome measure, as well as a number of the secondary and exploratory outcomes related to ulcers. The dataset was robust with few protocol violations and excellent product accountability. This study was published in a high impact journal after completion.

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Contact our experts today!

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