A Rationally Selected, Orally Administered, Live Biotherapeutic Consortium of Commensal Bacteria for the Treatment of Ulcerative Colitis

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Introduction

Ulcerative colitis (UC) manifests as relapsing-remitting inflammation and ulceration of the colon and rectum. The disease is characterized by innate and adaptive immune inflammation and a damaged gut mucosal barrier. Fecal microbiota transplants have shown limited efficacy in a subset of UC patients, suggesting that a well-defined consortium of bacteria, rationally selected based on disease-relevant mechanisms, could provide meaningful clinical benefit. To this end, we present preclinical results for ABI-M201, a defined, live biotherapeutic consortium currently under evaluation in a Phase 1b clinical trial.

Methods

Rationally Selecting Consortia of Live Microbes with Pharmacological and Biological Functions

 ABI-M201 Consortium Increases Barrier Function in Human Colon Epithelial Cell Assay

 ABI-M201 Consortium Induces Dose-Dependent Increase of the Anti-Inflammatory Cytokine IL-10 in Human Macrophage Cell Line Assay

 ABI-M201 Consortium Increases IL-10 in Human PBMC Assay

 ABI-M201 Consortium Produces Beneficial SCFA and Individual Strains Exhibit Cross-Feeding In Vitro

 ABI-M201 Consortium Enhances Epithelial Barrier Function and Modulates Macrophage Cytokines in Context of Human UC Fecal Microflora

 ABI-M201 Consortium Decreases a Potentially Clinically Relevant Plasma Inflammatory Protein Lipocalin-2 (LCN2), in the DSS Colitis Model

Summary of ABI-M201 Consortium

• Commensal microbes isolated and purified from well-curated healthy human samples were extensively characterized and three consortium bacteria were selected using a biological function-based platform
• The ABI-M201 consortium has reproducible and validated cell-based assays reflecting priority mechanisms of action for ulcerative colitis, including:
  - Increased barrier function
  - Induction of anti-inflammatory cytokines
• Consortium strains produce beneficial short chain fatty acids (SCFA) and exhibit cross-feeding
• The ABI-M201 consortium shows efficacy in a mouse DSS colitis model
• Well-defined CMC processes were established and GMP manufacturing of ABI-M201 Drug Substance & Drug Product was completed
• Lyophilized formulation retains functional activities
• Targeted gastrointestinal tract delivery
• Enrollment ongoing in US & Canada for Phase 1b clinical trial in UC patients

Results

Lyophilized Formulation of ABI-M201 Consortium Maintains In Vitro Activities Demonstrated with Freshly Grown Microbes

 ABI-M201 Consortium Decreases a Potentially Clinically Relevant Plasma Inflammatory Protein Lipocalin-2 (LCN2), in the DSS Colitis Model

• DSS treatment elevates plasma LCN2
• ABI-M201, Anti-IL-12p40, and their combination, respectively, decrease LCN2
• LCN2 levels directly correlate with efficacy measured by body weight

Ongoing Phase 1b Clinical Trial in Ulcerative Colitis Patients

• This work was performed under a partnership with Allergan plc
• JM, JH, and JP are employees, and PA is a former employee, of Assembly Biosciences

Statistics

• p<0.05, Two-stage method of Benjamini, Krieger and Yekutieli for multiple comparison correction by controlling False Discovery Rate
• Student t test for 2 sample comparison, one-way ANOVA for ≥3 sample comparison, two-way ANOVA for comparison across multiple time points
• Results reproducible across multiple independent experiments

Disclosures

• This was performed under a partnership with Allergan plc