2 STUDY SYNOPSIS

Name of Sponsor: PurGenesis Technologies Inc.	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product: Not applicable	Volume:	
Name of Active Ingredient: PUR 0110 rectal enema	Report:	

Title of the study:	A 2-Week Exploratory Randomized, Double-Blind, Parallel-Group, Dose-Ranging, Placebo-Controlled Safety, Tolerability, Biomarker and Efficacy Clinical Study of PUR 0110 Rectal Enema in Mild-to-Moderate Distal Ulcerative Colitis
Coordinating Investigator:	Prof. Dr. Michael Rünzi, Kliniken Essen-Süd, 45239 Essen-Werden, Germany
Study centers:	14 study centers in Germany
Publications (references):	None to date
Period of study:	Study initiation date (first subject signed the informed consent): 28 June 2010 Study completion date (last subject last visit): 18 November 2011
Clinical phase:	Phase IIa
Objectives:	**Primary objective:** To evaluate the safety and tolerability of PUR 0110 rectal enema 250 mg, 500 mg and 1000 mg once daily (OD) versus placebo OD in patients with active mild-to-moderate distal ulcerative colitis. **Secondary objectives:** To explore the effectiveness of PUR 0110 rectal enema 250 mg, 500 mg and 1000 mg OD versus placebo OD in patients with active mild-to-moderate distal ulcerative colitis. To evaluate through an exploratory analyses the effect of PUR 0110 rectal enema on: • serum lutein levels; and • the concentrations of biomarkers of inflammation, in vivo oxidative stress, apoptosis and total cell death, and antioxidant defense mechanisms in the plasma, serum, feces, urine and biopsy tissue of patients with active mild-to-moderate distal ulcerative colitis; the biomarkers include: • C-reactive protein (CRP), high sensitivity CRP (hs-CRP), erythrocyte sedimentation rate (ESR), fecal calprotectin (FCP), and fecal lactoferrin (FL); • T-helper (Th)1 serum cytokines: interleukin (IL)-2, IL-6, IL-8, interferon-gamma (IFN-γ), tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β); • Th2 serum cytokines: IL-4 and IL-10; • Th17 serum cytokines: IL-17 and IL-23; • M30 and M65 apoptosomes in serum and biopsies; • serum levels of human beta-defensin-2 (hβD-2); • plasma and urinary isoprostane levels; • serum lipid peroxidation (malondialdehyde = MDA) levels; • serum lipoxin A_4 (LXA_4) levels;

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	• serum glutathione (GSH) levels; and • leukotriene B_4 (LTB_4) levels in serum and biopsies.
Methodology (design of study):	This was a multicenter, randomized, double-blind, parallel-group, dose-ranging, placebo-controlled safety, tolerability and efficacy study of PUR 0110 rectal enema in subjects with active mild-to-moderate distal ulcerative colitis (modified Mayo score ≥5 to ≤10). The study consisted of a 7-day screening period, followed by a 14-day double-blind treatment period. One week after completing the treatment period, subjects returned for a post-study follow-up visit for final safety and efficacy assessments. Subjects who prematurely terminated from the study had to have all Day 14 efficacy and safety assessments performed and were encouraged to return 1 week later for the Day 21 visit assessments. Subjects were required to record their ulcerative colitis symptoms on a daily basis in a subject diary within 1 hour of going to bed from screening (Visit 1 / Day -7) to Day 21 (Visit 6). All subjects had a flexible sigmoidoscopy performed during screening at Visit 2 (Day -3), extending 10 to 50 cm from the anal margin and within not more than 3 ± 1 days before the baseline (Day 0) visit. To be eligible for study entry, subjects had to have a modified Mayo score (Disease Activity Index) at baseline of ≥5 to ≤10, including sigmoidoscopic inflammation grade and rectal bleeding scores of at least 2 each. Subjects had another sigmoidoscopy within 12 ± 4 hours after the last dose of study medication during Visit 5/Day 14 or early termination. During each sigmoidoscopy, the endoscopist assessed the macroscopic appearance of the most severely inflamed area of mucosa in the sigmoid colon/rectum based on the 4-point scale of the flexible proctosigmoidoscopy sub-score of the Mayo score. In addition, 4 pinch biopsy specimens of the mucosa were obtained during each sigmoidoscopy in the colon at <50 cm from the anal verge and at about the same level in each subject during screening (Day -3) and end of treatment (Day 14) sigmoidoscopies. All pinch biopsies were put in universal fixative (4% formalin) and sent to a central pathology laboratory. Two (2) of the pinch biopsies were used for histological examination/grading and the other 2 pinch biopsies were used for transmission electron microscopy and immunohistologic determinations of tissue biomarker concentrations. Subjects were instructed to avoid the consumption of lutein-rich vegetables and egg yolks, and to maintain a low-lutein diet, from 1 week before baseline to the Day 21 visit.
Number of subjects:	No sample size calculations were performed for this exploratory study. Sample size for the study was selected based on clinical judgment and review of previous studies. A total of 24 subjects (4 groups of 6 subjects) was planned to be enrolled: Twenty-four (24) male and female subjects with active mild-to-moderate distal ulcerative colitis were included and randomized (6 subjects each in the 250 and 1000 mg PUR 0110 groups, 7 subjects in the 500 mg group and 5 subjects in the placebo group); 3 subjects dropped out, thus 21 subjects completed the study as planned. The three subjects that dropped out prematurely included 1 subject each from the 500 mg and 1000 mg PUR 0110 and from the placebo groups. All subjects were included in the safety population and in the intent-to-

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treat (ITT) population.

		Treatment group			
		PUR 0110 rectal enema			Placebo
		250 mg	500 mg	1000 mg	
No. of subjects treated	N	6	7	6	5
No. of subjects completing the study	N	6 (100.0%)	6 (85.7%)	5 (83.3%)	4 (80.0%)
No. of subjects with premature termination	N	0 (0.0%)	1 (14.3%	1 (16.7%)	1 (20.0%)
Reason: lack of efficacy	N			1 (16.7%)	
withdrawal criteria	N		1 (14.3%)		
other reasons/lost to follow-up	N				1 (20.0%)

Diagnosis and main criteria for inclusion:	Male and female subjects between ≥18 and ≤75 years, who were newly diagnosed or with ongoing active distal ulcerative colitis of ≥3 months duration. Active disease was confirmed by flexible sigmoidoscopy, performed during screening within not more than 3±1 days before the baseline (Day 0) visit, and showing disease extending 10 to 50 cm from the anal margin. Subjects with ongoing active distal ulcerative colitis of ≥3 months duration had to be on a stable dose of oral mesalamine (5-ASA) for ≥2 months before the baseline (Day 0) visit, except the high strength oral MMX mesalamine, Mezavant®, which was not allowed within 2 weeks of the baseline visit to the Day 21 visit. Subjects newly diagnosed were treated with only the randomized study medication, concurrent oral mesalamine treatment was not allowed. The modified Mayo score (disease activity index) at baseline had to be of ≥5 to ≤10, including sigmoidoscopic inflammation grade and rectal bleeding scores of at least 2 each. Females of child bearing potential had to have a negative serum pregnancy test at screening and had to be either sexually inactive (abstinent) for 3 months prior to dosing and throughout the study or be using an acceptable methods of contraception. Subjects had to have a negative stool test at screening to rule out parasites, bacterial pathogens and *clostridium difficile*.
Test product, dose and mode of administration, batch number:	Test substance: PUR 0110 rectal enema Doses: 3 dose levels were administered: 250 mg/60 g, 500 mg/60 g, and 1000 mg/60 g (60 g is the vehicle) Route: rectal administration of 60 g rectal enema. Batch number of the ready packed material: A04029, A06473 All treatments were administered at about 10:00 PM (bedtime) once-daily. Subjects were provided with 2 bottles. One bottle contained PUR 0110 or matching placebo powder and the other bottle contained 60 g of reconstitution solution. Subjects were instructed to reconstitute the enema, within 3 hours of administration, by adding the reconstitution solution to the powder. Study treatment was self-administered at 10:00 p.m. ± 1 hour once-daily as a 60 g rectal enema, and subjects were instructed to retain it for as long as possible, preferably overnight.
Duration of treatment:	Treatment was applied OD for 14 days.
Reference therapy, dose and mode of	Placebo: PUR 0110 placebo enema Route: rectal administration of 60 g rectal enema that matched the active

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administration, batch number:	treatment in color and container closure system. Placebo enema was administered once-daily as described for the test product.
Criteria of evaluation:	**Efficacy:** • Clinical remission rate with clinical remission defined as an endoscopy score of ≤ 1, a rectal bleeding score of 0, and an improvement or no change from baseline in the stool frequency score at the end of 2 weeks of treatment / withdrawal visit; • Clinical response rate defined as the percentage of subjects with a drop of ≥3 points from the baseline overall modified Mayo score; • Subject defined response and remission rates; • Change from baseline in the overall modified Mayo score; • Change from baseline in each of the 4 individual sub-scores of the modified Mayo score; • Change from baseline in investigator assessment of ulcerative colitis symptom score; • Change from baseline in inflammatory bowel disease questionnaire (IBDQ) score; • Proportion of subjects with treatment failure; • Change from baseline in serum lutein levels; • Change from baseline in CRP, hs-CRP, ESR, FCP and FL; • Change from baseline in exploratory biomarkers - serum IL-2, IL-6, IL-8, IFN-γ, TNF-α, TGF-β, IL-4, IL-10, IL-17, IL-23, hβD-2, MDA, LXA_4, GSH, M30 and M65 apoptosomes in serum and biopsies, plasma and urinary isoprostane levels, and LTB_4 levels in serum and biopsies. **Safety:** Incidence, nature and severity of adverse events (AEs); and abnormal clinical laboratory test results.
Statistical methods:	**Efficacy:** All efficacy parameters were evaluated using descriptive statistics. The following inferential statistical analyses were performed. For binary outcome variables, a Pearson Chi-squared test was performed to detect the differences between the active doses and placebo. For categorical change from baseline variables, a Pearson Chi-squared test was performed to detect the general associations between the doses and change from baseline variables. To detect the dose-response trends, a Mantel-Haenszel linear trend test was used. For continuous variables, an analysis of variance (ANOVA) model was used to detect the differences between the active doses and placebo with respect to changes from baseline. To detect the dose-response trends, a linear dose effect was tested in the ANOVA model. **Safety:** All safety variables were analyzed descriptively. No statistical tests were used.

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Summary and conclusions:

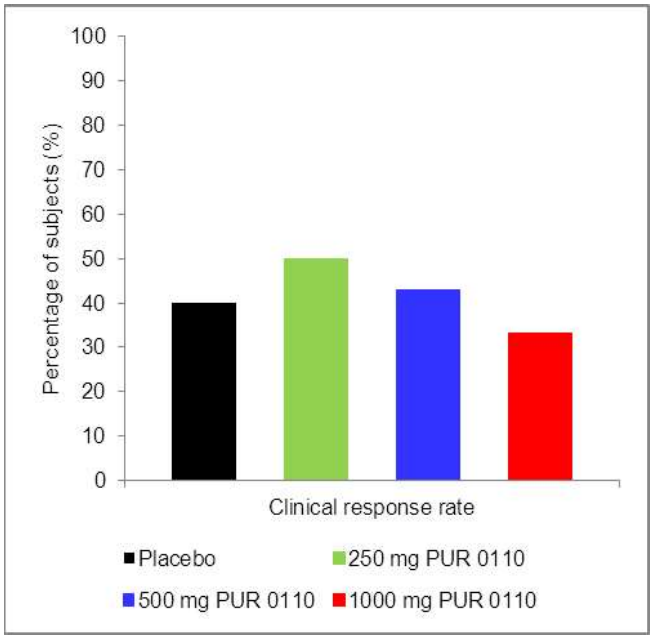
Efficacy

This first-in-patient exploratory study was not powered to assess statistical significance because there is no data from previous studies with this investigational drug product to inform this process, and the study duration was short. Therefore, emphasis should not be placed on statistical significance but on trends in observed effects.

The efficacy evaluation was performed with the ITT population.

Clinical remission: Only 1 subject in the 250 mg PUR 0110 showed a clinical remission. However, a review of the histological examination of biopsy tissue obtained from this subject at baseline (Day -3) and on Day 14, revealed the subject had no active inflammation at both visits, both scores were normal (0). But at the baseline visit, the subject had a score of moderate (1) for chronic inflammation and mild (1) for crypt distortion.

Clinical response rate



Clinical response: Overall, 10 subjects showed a clinical response: 50.0% of the subjects in the 250 mg group, 42.9% of the subjects in the 500 mg group, 33.3% of the subjects in the 1000 mg PUR 0110 group and 40.0% of the subjects in the placebo group. The statistical test revealed no differences between the active treatments and placebo.

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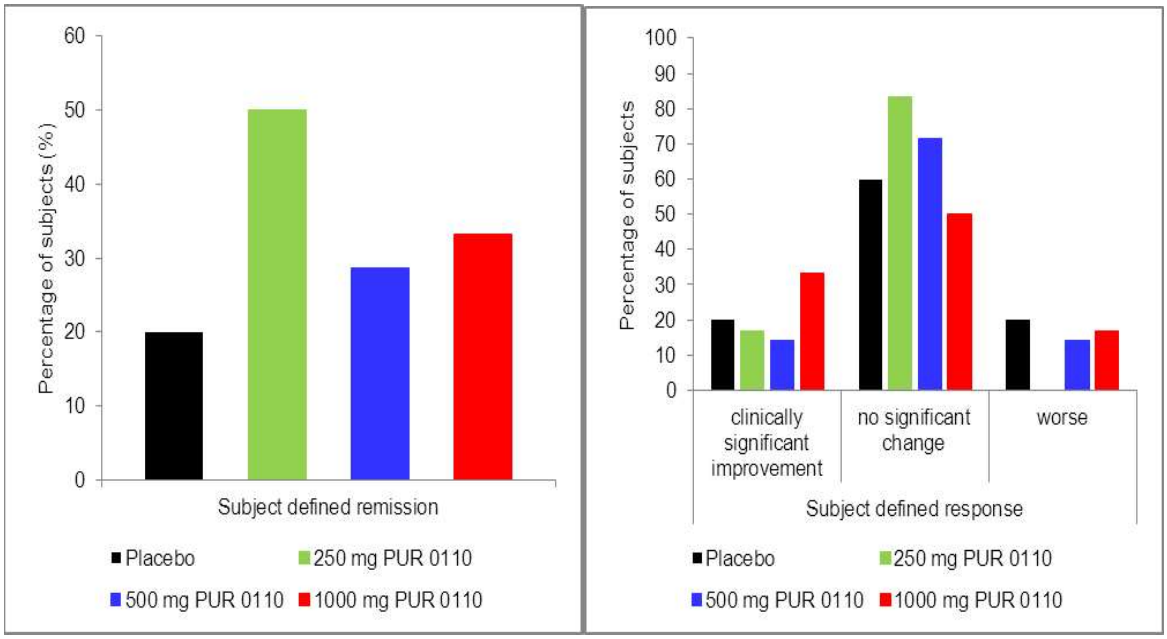
Subject-defined remission and response



Clinically significant improvement = Likert score 1 and 2, no significant change = Likert score 3 to 5, worse = Likert score 6 and 7

Subject-defined remission: was observed in 50.0% of the subjects in the 250 mg group, 28.6% of the subjects in the 500 mg group, 33.3% of the subjects in the 1000 mg PUR 0110 group and 20.0% of the subjects in the placebo group. The statistical test revealed no differences between the active treatments and placebo.

Subject-defined response: the proportion of subjects who responded that they had clinically significant improvement ("much better" or "somewhat better" = Likert scores 1 or 2) following 14 days of treatment were 16.7% in the PUR 0110 250 mg group, 16.7% in the 500 mg group, 33.3% in the 1000 mg group, and 25% in the placebo group. There were no statistically significant differences between the treatment groups and a dose-response trend was not observed.

Overall modified Mayo score: After 14 days of treatment, the mean±SD changes from baseline in the overall modified Mayo score were similar in all treatment groups (PUR 0110 250 mg: -1.7±2.5; 500 mg: -1.5±2.6; 1000 mg: -1.8±1.8; and placebo: -1.5±2.6). The 95% confidence intervals revealed no differences between the treatments.

There were reductions in the mean partial Mayo scores at Day 7 in all treatment groups with further reductions at the Day 21 visit. ANOVA showed no significant differences between the mean reductions observed in the 4 treatment groups at Days 7 and 21. However, on Day 21, the mean reductions showed a trend towards superiority in the PUR 0110 treatment groups over placebo with the 250 mg group showing the largest reduction (PUR 0110 250 mg: -3.2±2.0; 500 mg: -2.3±2.6; 1000 mg: -2.6±2.1; and placebo: -1.8±1.5).

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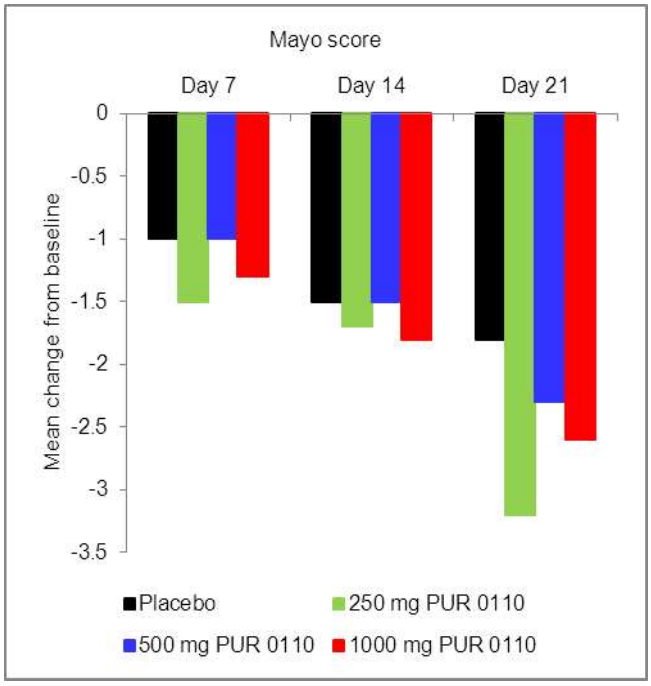
Mean changes from baseline in overall modified (Day 14) and partial (Days 7 and 21) Mayo scores



Individual sub-scores of the modified Mayo score: The mean changes from baseline in the 4 individual sub-scores of the modified Mayo score were only summarized; they were not tested for statistical significance. There were trends toward superiority of the PUR 0110 treatment groups over placebo in the sub-scores for stool frequency and rectal bleeding. The mean change from baseline stool frequency sub-score for the PUR 0110 1000 mg group showed the largest magnitude of reduction compared to an increase in the placebo group (-0.7±1.0 vs. 0.2±1.1; difference 0.9). There were further reductions at the Day 21 visit resulting in the maintenance of the treatment difference of 0.9 between the PUR 0110 1000 mg group and placebo (-1.2±1.3 vs. -0.3±0.5; difference 0.9).

The mean change from baseline in the rectal bleeding sub-scores were numerically larger (mean reductions) particularly in the PUR 0110 250 and 500 mg treatment groups at the Day 14 visit compared to placebo (PUR 0110 250 mg: -1.0±0.6; 500 mg: -1.0±1.2; placebo: -0.4±0.5; Difference vs. placebo 0.6 each). At the Day 21 visit, there were further reductions from baseline in both treatment groups (PUR 0110 250 mg: -1.5±0.8; 500 mg: -1.1±0.7; placebo: -0.5±0.6; Difference vs. placebo 1.0 and 0.6, respectively).

These approximately 1 point placebo-corrected improvements in the stool frequency and rectal bleeding scores following treatment, which corresponds to a shift of symptom severity from moderate at baseline to mild at the primary endpoint (Day 14), suggest PUR 0110 rectal enema has activity against the disease process in active mild-to-moderate distal ulcerative colitis.

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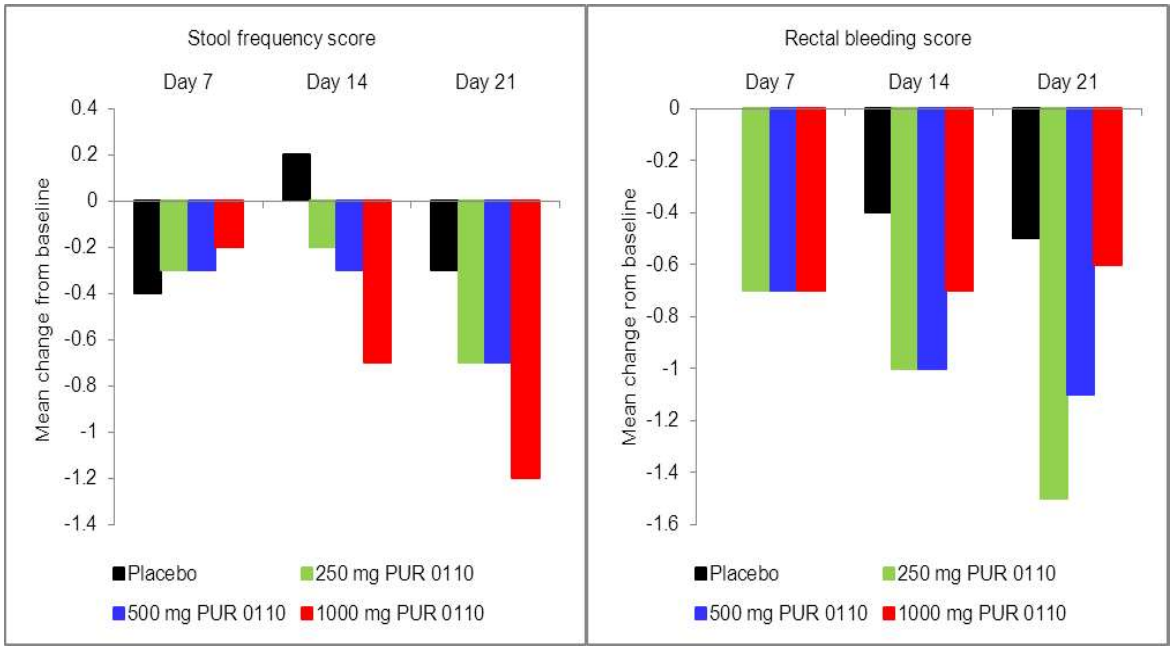
Mean changes from baseline in stool frequency and rectal bleeding modified Mayo sub-scores



Investigator's assessment of ulcerative colitis symptom score: The mean changes from baseline in Investigator's Assessment of Ulcerative Colitis Symptom score (IAUCSS) showed no statistically significant differences as indicated by the 95% confidence intervals for the comparisons between active treatment and placebo performed for Days 7, 14 and 21. Although the PUR 0110 500 mg treatment group consistently showed a trend toward superiority over placebo at the Day 14 visit for the mean total score, the sum of all 4 symptoms' scores (-0.7±0.8 vs. -0.1±1.1; difference 0.6), diarrhea score (-0.9±0.9 vs. -0.0±0.7; difference 0.9), rectal bleeding score (-0.9±0.9 vs. -0.0±1.4; difference 0.9), and the abdominal pain score (-0.9±1.2 vs. -0.4±0.5; difference 0.5). These observed trends resulting in approximately 1 point placebo-corrected improvements for diarrhea and rectal bleeding symptoms' severity at the Day 14 visit further suggest PUR 0110 rectal enema, particularly the 500 mg dose, has activity against the disease process in active mild-to-moderate distal ulcerative colitis.

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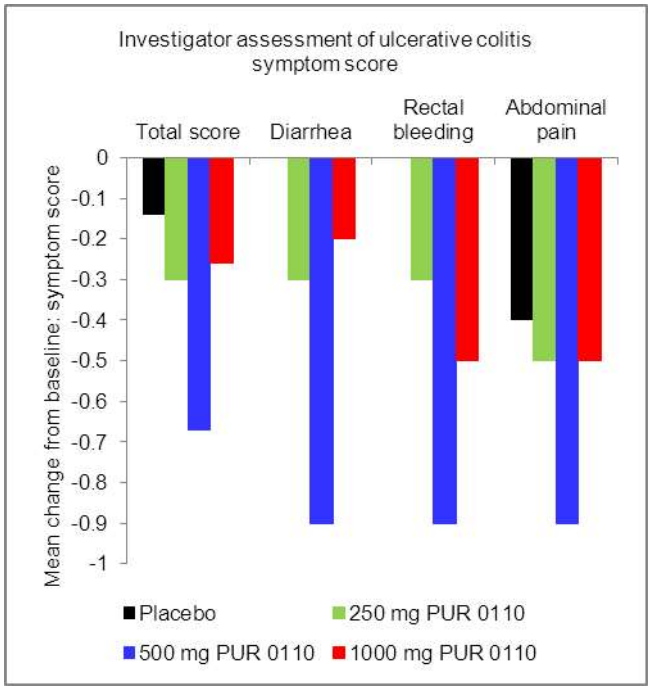
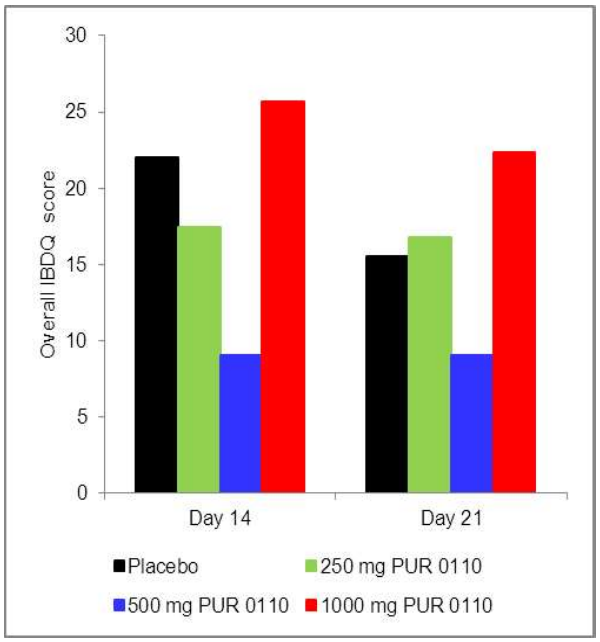
Mean changes from baseline in investigator's assessment of ulcerative colitis symptom score



Inflammatory bowel disease questionnaire (IBDQ): The mean changes from baseline for the overall IBDQ score and for the 4 dimensions of IBDQ were similar following treatment on Day 14. The largest mean change from baseline (increase) in the overall IBDQ score was observed in the 1000 mg PUR 0110 group, however, the 95% confidence intervals revealed no treatment differences.

Mean changes from baseline in the overall IBDQ score



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Treatment failure: The number of subjects defined as treatment failures was lowest in the 1000 mg group (16.7%), compared to 33.3%, 42.9% and 40.0% of the subjects in the 250 mg, 500 mg and placebo groups, respectively.

Serum Lutein Concentrations: Mean changes from baseline in serum lutein concentrations after treatment with PUR 0110 were small indicating little or no systemic absorption. The highest concentration was observed in the PUR 0110 250 mg treatment group at Day 21.

Established biomarkers of Active Inflammation: The mean changes from baseline in the concentrations of the 5 established biomarkers of active inflammation, CRP, hs-CRP, ESR, FC and FL were only summarized; they were not tested for statistical significance. Some notable trends toward the superiority of the PUR 0110 treatment groups over placebo were observed and included:

- There was a consistent and marked increase in the magnitude of the mean reductions from baseline for the PUR 0110 250 mg treatment group during all post-baseline visits compared to an increase on Day 14 for placebo. The magnitude of the reductions steadily increased starting from the Day 7 visit and at the Day 14 visit were -48%, -52.5%, -28.9%, -41.5% and -63.6% for CRP, hs-CRP, ESR (mean for 1 h & 2 h), FC and FL, respectively.
- There were further reductions to -77.6%, -80.9% and -82.9% for CRP, hs-CRP, and FL, respectively, at the Day 21 visit. The reductions were maintained for ESR and slightly reduced for FC at the Day 21 visit.
- In contrast, in the placebo group, there were increases in the mean concentrations of these biomarkers which varied from 18.8% for ESR to 98.1% and 120.5% for FC and FL, respectively.
- The PUR 0110 1000 mg treatment group showed a similar trend toward superiority over placebo but for only ESR, FC and FL.

There was no dose-response. These consistent and marked reductions in the levels of these established biomarkers of active inflammation are an objective evidence of the biological activity of PUR 0110 on the intestinal inflammation in ulcerative colitis. Since reductions in the response to these biomarkers can only occur as a result of the effect of PUR 0110 on the underlying mucosal inflammation. The activity was highest with the PUR 0110 250 mg dose and less with the 1000 mg treatment group.

Exploratory biomarkers: Only IL-8, TGF-beta, MDA, GSH, M30 and M65 apoptosomes and LTB_4 in serum, 8-isoprostane in urine and M30 and M65 apoptosomes in biopsy tissue were measurable in this study. The rest of the biomarkers were below the lower limit of quantitation. The concentrations of the exploratory biomarkers were highly variable, even mean values at baseline varied considerably between treatment groups. The results were only summarized; they were not tested for statistical significance. The most notable trends toward the superiority of PUR 0110 over placebo seen with these biomarkers included:

- Serum LTB_4 levels – for the PUR 0110 250 mg treatment group mean change from baseline were Day 7: -61.5%; Day 14: -31.4%; and Day 21: -85.0% versus increases for placebo at Day 7: 67.1%; and Day 14: 29.0% followed by a reduction at the Day 21 visit (Day 21: -37.3%).
- Similar reductions for PUR 0110 500 mg treatment group were also observed but of a smaller magnitude (Day 7: -27.2%; Day 14: -28.0%; and Day 21: -46.9%); and at Days 14 and 21 visits in the 1000 mg treatment group (Day 7: 4.3%; Day 14: -22.2%; and Day 21: -21.6%).
- Mean reductions in the serum levels of the following biomarkers at all post-baseline visits compared to increases in the corresponding values for placebo: PUR 0110-500 mg treatment group for transforming growth factor-beta (TGF-β); and PUR 0110-250 mg and PUR 0110-1000 mg treatment groups for M30 apoptosome level.

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- A 42.5% mean reduction in the M30 apoptosome level in colonic biopsy tissue for the PUR 0110 rectal enema 250 mg and 500 mg treatment groups compared to an increase of 28.6% in the placebo group. M30 apoptosome is a biomarker of apoptosis.

These marked reductions in serum LTB_4 levels confirm the previous findings in animal pharmacology studies that PUR 0110 reduces the production and release of lipid mediators of inflammation including prostaglandins and leukotrienes. The results further provide objective evidence of the biological activity of PUR 0110 rectal enema on the intestinal inflammation in active mild-to-moderate distal ulcerative colitis.

Safety

Administration of 250 mg, 500 mg and 1000 mg PUR 0110 rectal enema once daily was safe and well tolerated in subjects with active mild-to-moderate distal ulcerative colitis. Overall, only 3 subjects (12.5%) reported any adverse event at all. One patient in the PUR 0110 500 mg treatment group had acute tonsillitis (14.3%), another patient in the same group had muscle spasms (14.3%) and a third patient from the PUR 0110-1000 mg treatment group had leukocyturia (16.7%). None of these adverse events were considered drug-related by the investigator. There were no withdrawals due to adverse events, no serious adverse event and no death.

Safety laboratory parameters, vital signs and ECG assessment were mainly normal, no clinically relevant time- or treatment-related changes were observed.

Conclusions

- The primary objective of this short 2-week study was met. Administration of 250 mg, 500 mg and 1000 mg PUR 0110 rectal enema once daily was safe and well tolerated in subjects with active mild-to-moderate distal ulcerative colitis. These results are consistent with the results of the previous Phase 1 study in which single doses of PUR 0110 rectal enema 187.5 to 1500 mg were safely and tolerably administered to healthy volunteers and a maximum tolerated dose was not observed.
- As expected there were no statistically significant differences between PUR 0110 rectal enema 250 mg, 500 mg and 1000 mg and placebo as the study was not adequately powered and was of a short duration. No dose-response trends were observed in any of the investigated parameters.
- However, notable trends towards the superiority of PUR 0110 rectal enema over placebo were observed in the mean reductions in the cardinal symptom of ulcerative colitis, rectal bleeding (250 mg and 500 mg) and the stool frequency (1000 mg) sub-scores of the modified Mayo score. The placebo-corrected improvements of approximately 1 point represent a shift of symptom severity from moderate at baseline to mild at endpoint. These results are suggestive of its biological activity.
- Similarly, a consistent trend towards the superiority of PUR 0110 rectal enema 500 mg, over placebo were observed in the mean reductions in total, rectal bleeding, diarrhea and abdominal pain scores of the investigator's assessment of ulcerative colitis symptom score. Again, the placebo-corrected improvements of approximately 1 point represent a shift of symptom severity from moderate at baseline to mild at endpoint. These results are further suggestive of its biological activity.
- The marked and consistent -29 to -83% reductions in the serum CRP and hs-CRP levels, ESR, FC and FL in response to PUR 0110 treatment with further reductions to -77.6 to -82.9% for CRP, hs-CRP and FL at the Day 21 visit compared to 18.8 to 120% increase in the placebo group are objective evidence of its biological activity on the intestinal inflammation in ulcerative colitis.

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- The marked -31.4% reductions in serum LTB_4 levels reaching up to -85.0% by Day 21 in the PUR 0110 250 mg treatment group compared to a 29% increase in the placebo group at the Day 14 visit plus the smaller magnitude of reductions in serum LTB_4 levels in the 500 mg (-28.0%) and 1000 mg (-22.2%) groups are all further objective evidence of the biological activity of PUR 0110 rectal enema on the intestinal inflammation in ulcerative colitis. These results are consistent with the results of previous animal pharmacology studies that demonstrated PUR 0110 reduces the production and release of lipid mediators of inflammation, including prostaglandins and leukotrienes.
- In addition, the -42.5% reduction in the concentration of M30 apoptosome, a biomarker of apoptosis, in colonic mucosal biopsy tissue observed for PUR 0110 250 mg and 500 mg treatments compared to an increase of 28.6% in the placebo group is further objective evidence of its biological activity.
- Changes from baseline lutein levels were small indicating little or no systemic absorption of PUR 0110.
- The excellent safety profile of PUR 0110 rectal enema to-date, marked reductions in the levels of biomarkers of inflammation and the trends toward superiority over placebo observed in the relief of the key symptoms of ulcerative colitis suggests that it is reasonably likely that the key attributes for success are present at this point in its development.
- This establishes the feasibility of conducting a larger Phase 2 study with longer duration of treatment with PUR 0110 rectal enema.