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Safety, tolerability and pharmacokinetics of BT051, an oral inhibitor of neutrophil migration and activation in clinical development for Inflammatory Bowel Disease

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Background

Introduction

- Ulcerative colitis (UC) is a progressive autoimmune disease, causing inflammation and tissue damage in the lining of the colon
- Patients with ulcerative colitis can experience constant symptoms that disrupt daily life, and despite currently available therapies, up to one-third of patients with UC will ultimately require surgery due to incomplete efficacy
- BT051 is an oral, non-systemic, MRP2/FPR1 antagonist that was designed to specifically target gut neutrophil activity and is in clinical development for the treatment of UC

Aims

- The objectives of this first-in-human study were to evaluate the safety, tolerability and pharmacokinetics (PK)/pharmacodynamics (PD) of single ascending doses of BT051 in healthy subjects

Methods

- This was a Phase 1, randomized, double-blind, single ascending dose in healthy adult male and female subjects
- Fifty subjects were enrolled in 5 sequential, ascending dose cohorts of 10 subjects per cohort randomized to BT051 or placebo (8 BT051:2 placebo) and followed until Day 30 post-dose
- Safety assessments included monitoring of adverse events (AEs), clinical laboratory testing, vital signs, physical examinations and ECGs; a safety review committee evaluated dose-limiting AEs through Day 3 before dose escalation
- Samples for PK analysis were collected from blood, stool and urine pre-dose and up to 48 hours post-dose; stool samples for PK analysis were also collected on Day 7
- Systemic immunosuppression was assessed by measuring cytokine secretion induced from T-cells in peripheral blood mononuclear cells up to 7 days post-dose

Results

- Overall, 40 healthy subjects received BT051 and 10 subjects received placebo
- Subjects had a mean age of 35.0 years (range: 19-49 years), a mean weight of 80.33 kg, and a mean BMI of 26.76 kg/m^2; there were more male (66.0%) subjects enrolled than female (34.0%), and the majority were white (56.0%) and not Hispanic or Latino (84.0%)
- 11 of 50 subjects (22.0%) reported at least 1 AE, with 22.5% and 20.0% of subjects reporting AEs after receiving BT051 and placebo, respectively (**Table 1**)
- No dose-limiting toxicities, serious AEs or study discontinuations due to AEs were observed
- Systemic exposure to BT051 was not quantifiable; in 2 subjects, only 1 blood sample out of their entire profile was quantifiable, and 1 of these 2 samples was within 2-fold of the LLOQ (i.e., <10 ng/mL)
- Mean %dose excreted in stool from partial collection ranged between 10.2-23.7% (**Table 2**)
- At all doses tested, concentrations of BT051 in the large intestine were estimated to exceed >20x the threshold for inhibition of neutrophil transmigration and activation in vitro (1 µM) and continued to be detected out to 7 days post-dose
- Mean %dose excreted in urine through 48 hours post-dose ranged between 0.01-0.03% (**Table 3**)
- No evidence of circulating T-cell immunosuppression was observed at any dose level

Table 1. Treatment Emergent Adverse Events (TEAEs) by Preferred Term

Preferred Term	BT051 100mg (N=8)	BT051 300mg (N=8)	BT051 700mg (N=8)	BT051 1500mg (N=8)	BT051 3500mg (N=8)	BT051 Combined (N=40)	Placebo (N=10)
Number of subjects with at least 1 TEAE, n(%)	1 (12.5)	0	2 (25.0)	4 (50.0)	2 (25.0)	9 (22.5)	2 (20.0)
Vessel puncture site pain	0	0	1 (12.5)	2 (25.0)	2 (25.0)	5 (12.5)	0
Fatigue	0	0	0	0	0	0	1 (10.0)
Constipation	0	0	0	2 (25.0)	0	2 (5.0)	0
Abdominal pain	1 (12.5)	0	0	0	0	1 (2.5)	0
Headache	0	0	1 (12.5)	0	0	1 (2.5)	1 (10.0)
Dizziness	0	0	0	0	1 (12.5)	1 (2.5)	0
Syncope	0	0	0	0	1 (12.5)	1 (2.5)	0
Blood creatinine increased	0	0	1 (12.5)	0	0	1 (2.5)	0
Hyperhidrosis	0	0	0	0	1 (12.5)	1 (2.5)	0
Pallor	0	0	0	0	1 (12.5)	1 (2.5)	0

Adverse events were classified according to MedDRA Version 23.0

Table 2. Summary of Mean (CV%) [Min, Max] Cumulative Percentage of BT051 Dose Excreted in Feces

Parameter	BT051 100mg (N=7)[a]	BT051 300mg (N=7)[a]	BT051 700mg (N=8)	BT051 1500mg (N=8)	BT051 3500mg (N=8)
$CumAef_{0\text{-}12}$ (%)	NA (NA) [0, 0]	1.974 (180.0) [0, 8.86]	2.698 (282.8) [0, 21.6]	4.423 (244.4) [0, 31.0]	0.9356 (185.2) [0, 3.86]
$CumAef_{0\text{-}24}$ (%)	NA (NA) [0, 0]	3.137 (130.4) [0, 8.86]	3.370 (225.4) [0, 21.6]	4.425 (244.3) [0, 31.0]	0.9364 (185.0) [0, 3.86]
$CumAef_{0\text{-}48}$ (%)[b]	12.34 (65.5) [0, 20.5]	18.03 (107.4) [0.000405, 46.7]	21.14 (86.9) [0.000297, 55.5]	11.07 (92.9) [0, 31.0]	9.979 (96.9) [0.0967, 28.9]
$CumAef_{0\text{-}72}$ (%)[b,c]	13.29 (54.1) [0, 20.5]	20.70 (92.5) [0.000405, 49.1]	23.58 (82.2) [0.000297, 55.6]	15.00 (72.1) [1.36, 31.3]	10.13 (96.7) [0.0967, 28.9]
$CumAef_{0\text{-}Day\ 7}$ (%)[b,d]	13.39 (52.9) [0, 20.5]	21.31 (86.5) [2.45, 49.1]	23.69 (81.8) [0.0284, 55.6]	15.18 (70.5) [1.59, 31.3]	10.19 (95.8) [0.0993, 28.9]

Abbreviation: $CumAef_{0\text{-}t}$ (%), Cumulative percentage of dose excreted in feces from time 0 through the end time of each collection interval; Min, Minimum; Max, Maximum
[a] One subject had no quantifiable fecal concentrations of BT051
[b] Fecal excretion is underestimated for the 100-mg cohort: no weight was recorded for stool provided by Subject 1006 during the 24-48h interval despite quantifiable analyte concentrations
[c] The actual upper limit of the 0-72-hour time interval was 55.10 hours
[d] Because no stool was collected on Days 4-6, this cumulative value is underestimated

Table 3. Summary of Mean (CV%) Cumulative Percentage of BT051 Dose Excreted in Urine

Parameter	BT051 100mg (N=8)	BT051 300mg (N=7)	BT051 700mg (N=8)	BT051 1500mg (N=7)	BT051 3500mg (N=8)
$CumAeu_{0\text{-}4}$ (%)	0.0008284 (112.0)	0.003623 (89.3)	0.0009847 (177.7)	0.0006669 (137.4)	0.0004534 (80.6)
$CumAeu_{0\text{-}8}$ (%)	0.007378 (61.6)	0.008319 (29.1)	0.004800 (85.0)	0.002763 (46.2)	0.002405 (53.6)
$CumAeu_{0\text{-}24}$ (%)	0.01644 (27.2)	0.01523 (26.6)	0.01103 (47.3)	0.007940 (99.5)	0.005434 (47.7)
$CumAeu_{0\text{-}48}$ (%)	0.01948 (15.2)	0.01803 (35.3)	0.03316 (150.7)	0.01255 (59.9)	0.009561 (53.2)

Abbreviation: $CumAeu_{0\text{-}t}$ (%), Cumulative percentage of dose excreted in urine from time 0 through the end time of each collection interval

Conclusions

- Single doses up to 3500 mg of BT051 were safe and well-tolerated in healthy subjects
- PK data suggest BT051 has very limited systemic exposure and is primarily excreted in the feces, demonstrating limited gut absorption after oral dosing with no evidence of circulating T-cell immunosuppression
- Findings from this first-in-human study support the continued development of BT051 as a gut-targeted therapy for patients with IBD

Disclosures of Interest

C Stevens, C Murphy, E Hershberger, M Quintas, B Miller are employees of Bacainn Therapeutics.
P Ghahramani is a paid consultant to Bacainn Therapeutics.

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