Single ascending dose results from a Phase 1 clinical trial of BT-600, a combination product of the NaviCap targeted oral delivery platform and tofacitinib

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INTRODUCTION

Despite approved treatments for UC, outcomes remain sub-optimal with clinical remission rates after induction ranging from 15–30%,[1] and 60% of patients who achieve remission relapse within 12 months.[2] BT-600 is an ingestible drug/device combination product designed for targeted delivery of a liquid formulation of tofacitinib into the colon, and has potential for improved efficacy driven by increased colonic tissue exposure, while reducing systemic-exposure-associated adverse events.

Data for JAK-inhibitors, TNF-inhibitors, and anti-integrins demonstrate that achieving higher drug levels and activity in colon tissue mucosa could improve clinical benefit.[3,4,5] Higher doses of systemic treatments or combination treatments may be needed to achieve sufficient colonic tissue exposure but are limited by systemic safety risks.[6, 7]

BT-600 utilizes the NaviCap™ device **(Figure 1A)**, designed to deliver a liquid drug formulation directly to the colon mucosa, bypassing the upper gastrointestinal (GI) tract. The NaviCap device recognizes specific locations through an internal algorithm designed to evaluate changes in reflected light associated with anatomical features, such as the transition from the ileum to the colon **(Figure 1B)**. The NaviCap device is distinct in its ability to precisely target and coat the entire colon with a liquid formulation of therapeutic, without early delivery.

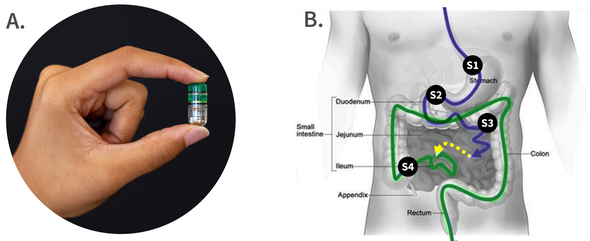

FIGURE 1. Autonomous localization technology enables targeted delivery of therapeutics. A. Photograph of the NaviCap device; B. The internal algorithm can detect five major anatomical locations: (S1) entry into the stomach, (S2) entry into the duodenum (gastric emptying), (S3) entry into the jejunum, (S4) entry into the colon, and (S5) exit from the body.

METHODS

The Phase 1, randomized, double-blind, placebo-controlled, sequential, single and multiple ascending dose (SAD/MAD) clinical trial evaluated the safety and pharmacokinetics (PK) of BT-600 in healthy adult participants **(Figure 2)**. Devices were recovered from feces to verify excretion and analyze device function. A pre-specified interim analysis included results on safety, plasma PK, and evidence of drug in feces during the SAD portion.

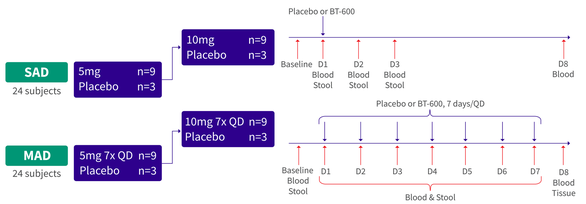

FIGURE 2. Clinical Trial Design

RESULTS

Safety

BT-600 was well tolerated. There were no serious adverse events, and adverse events were transient and similar to those expected in a healthy population **(Table 1)**.

TABLE 1: Treatment-Emergent Adverse Event Frequency, SAD

Treatment-Emergent Adverse Events (TEAEs)	Single Dose			Overall (n=24)
	Pooled Placebo (n=6)	5 mg BT-600 (n=9)	10 mg BT-600 (n=9)	
Abdominal pain	0 (0%)	0 (0%)	1 (11%)	1 (4%)
Diarrhea	0 (0%)	0 (0%)	1 (11%)	1 (4%)
Flatulence	0 (0%)	1 (11%)	0 (0%)	1 (4%)
Pain in extremity	0 (0%)	0 (0%)	1 (11%)	1 (4%)
Headache	1 (17%)	0 (0%)	0 (0%)	1 (4%)
Nipple pain	0 (0%)	0 (0%)	1 (11%)	1 (4%)
Oropharyngeal pain	0 (0%)	1 (11%)	0 (0%)	1 (4%)
Number of Participants with TEAEs	**1 (17%)**	**2 (22%)**	**2 (22%)**	**5 (21%)**

Adverse events are classified according to MedDRA® Version 26.1

Plasma Pharmacokinetics, SAD

All 24 participants showed plasma PK parameters consistent with colonic delivery, in distinction to delivery in the upper GI tract.

- Tofacitinib was first detected in plasma at ≈6 hours following administration.
- The median time to reach maximum plasma concentration (Tmax) was 8–10 hours vs 0.5–1.0 hours for conventional oral tofacitinib.
- BT-600 was associated with 3–4x lower systemic absorption of tofacitinib compared with conventional oral tofacitinib **(Table 2)**.
- Plasma exposures were dose proportional from BT-600 5 mg to 10 mg.
- While the true systemic elimination rate is the same regardless of delivery method, calculated t½ with BT-600 was longer and more variable (range 3.04–12.5 hours) than for conventional tofacitinib due to later and variable drug release time in the colon, resulting in a higher apparent elimination rate.
- Tofacitinib was present in fecal samples of all participants, further confirming device function.

Plasma concentration over time is shown in **Figure 3** for BT-600 and for conventional tofacitinib following single doses.

TABLE 2: Plasma Tofacitinib Pharmacokinetic Parameters Following Administration of Single Oral Doses of BT-600

Pharmacokinetic Parameters[a]	BT-600 (n=9)		Conventional Tofacitinib[b]
Dosing Regimen	**5 mg Single Dose**	**10 mg Single Dose**	**10 mg Single Dose**
T_{first} (hours)	6 (6–10)	6 (4–8)	NR
T_{max} (hours)	8 (6–16)	10 (6–16)	0.5 (0.25–1.0)
$t_{½}$ (hours)	4.9 (1.59)	7.8 (3.24)	2.61 (0.633)
C_{max} (ng/mL)	14 (4.2)	26 (14.8)	88 (10.2)
AUC_{24} (ng·hr/mL)	114 (34)	218 (119)	283 (80)

a. Values for T_{first} and T_{max} represent median (range). Values for C_{max}, AUC_{24} and $t_{1/2}$ represent arithmetic mean (SD).
b. Krishnaswami S, Boy M, Chow V, Chan G. Safety, tolerability, and pharmacokinetics of single oral doses of tofacitinib, a Janus kinase inhibitor, healthy volunteers. *Clin Pharmacol Drug Dev.* 2015;4(2):83-88. Data are from different clinical trials; no head-to-head clinical trials have been conducted.

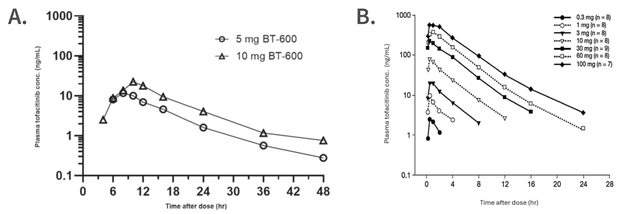

FIGURE 3. Mean Plasma Tofacitinib Concentration-Time Curves for A. BT-600 and B. Conventional Tofacitinib*

*Krishnaswami S, Boy M, Chow V, Chan G. Safety, tolerability, and pharmacokinetics of single oral doses of tofacitinib, a Janus kinase inhibitor, healthy volunteers. Clin Pharmacol Drug Dev. 2015;4(2):83-88. Data are from different clinical trials; no head-to-head clinical trials have been conducted.

UPDATE SINCE ABSTRACT SUBMISSION

The study has completed. Results from once daily dosing for 7 days (MAD) are summarized below.

Safety

- Safety profile was consistent with SAD, with no serious adverse events.
- No evidence of device or drug colon toxicity was observed; colon tissue histology was within normal limits.
- There were no notable changes or differences in safety laboratory parameters between groups.

Plasma Pharmacokinetics, MAD

Results were consistent with those seen in SAD. Consistent PK with precise colonic delivery was demonstrated. Steady state was reached by Day 1. Examples of two single-subject concentration time curves are shown in **Figure 4**.

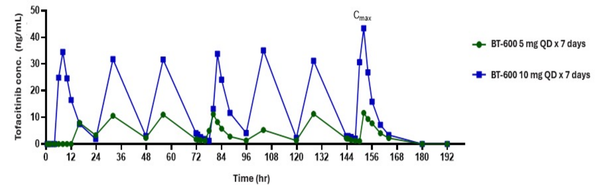

FIGURE 4. Plasma Tofacitinib Concentration Over Time Following Administration of Multiple Oral Doses of 5 mg and 10 mg BT-600 QD in Two Healthy Subjects

Colon Tissue Exposure (MAD)

- Sigmoidoscopy was performed at approximately 24 hours post last dose. Bowel prep included oral MiraLAX and Fleet's enema at 8 and 18 hours post dose, respectively.
- Plasma drug concentrations were near or below trough values (low or BLQ) during biopsy (last measurement at 20 hours).
- Despite dose-to-biopsy latency and bowel prep, 15/18 subjects had quantifiable concentrations in distal regions above estimated IC50, suggesting pan-colonic delivery **(Figure 5)**:
  - Mean (95% CI): splenic flexure 338 ng/g (28, 649); descending colon 159 mg/g (96, 223); and sigmoid colon 161 ng/g (72, 251).
- A log-linear regression model based on correlations between last plasma and tissue concentration predicted exposure above IC90 through at least 16 hours post-dose **(Figure 6)**.
  - Projected levels for BT-600 10 mg at 16 hours: descending colon ≈4705 ng/g, sigmoid colon ≈3094 ng/g.

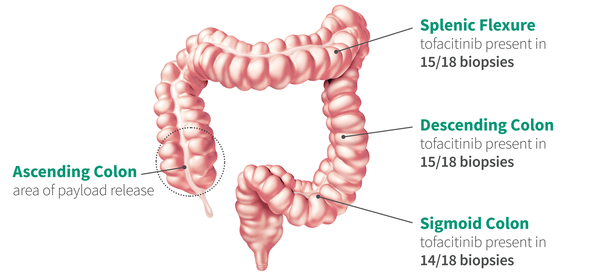

FIGURE 5. Tofacitinib Across Biopsy Sites in Distal Colon

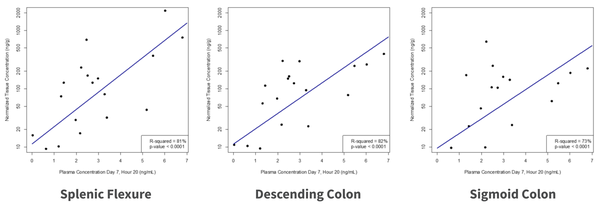

FIGURE 6. Correlation Between Tissue and Plasma Tofacitinib Concentrations at Multiple Colonic Biopsy Sites

Device Function (SAD and MAD)

Software analysis performed on retrieved devices showed that 100% of devices (24/24) in SAD and 96% of devices (156/162) in MAD detected colon entry. Colon entry detection occurred approximately one hour before Tfirst, indicating a tight correlation between device function and PK **(Table 3)**.

TABLE 3: Software Analysis of Retrieved NaviCap Devices

	SAD	MAD
Devices retrieved that identified colon entry	24/24 (100%)	156/162 (96%)
Mean time of colon entry, hours post dose (SD)	5.6 (2.1)	6.6 (3.2)
Mean T_{first}, hours post dose (SD)	6.9 (2.6)	6.9 (2.0)

CONCLUSION

The Phase 1 clinical trial in healthy adult participants showed that BT-600 (tofacitinib delivered via the NaviCap device) was well tolerated and achieved consistent colonic drug delivery with lower systemic exposure than with conventional tofacitinib. Tissue exposure was achieved to the distal colon.

BT-600 has potential for improved efficacy driven by increased colonic tissue exposure, while reducing systemic-exposure-associated adverse events. Future clinical trials will assess safety and efficacy in patients with ulcerative colitis.

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