Potential effects of food on a novel Drug Delivery System (DDS) to deliver therapeutic compound into the colon

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INTRODUCTION

Despite multiple approved and novel therapies for the management of moderate to severe ulcerative colitis (UC), outcomes remain sub-optimal, with clinical remission rates between 15-30% after induction. Research has shown that an inadequate amount of drug at the disease site may be responsible for limited clinical benefit.

The Drug Delivery System (DDS) is an ingestible electronic targeted delivery device containing a proprietary localization system designed to autonomously identify colon entry based on gastrointestinal (GI) anatomy, independent of variable GI physiological conditions. The DDS is designed to deliver a dose of a liquid drug formulation to the colon mucosa to improve efficacy and reduce systemic toxicity. In previous studies, we have shown that the DDS device was well-tolerated and functioned as intended in identifying colon entry and releasing payload in the colon, regardless of variable GI motility or disease status in both normal healthy volunteers and active UC patients.

In this study, we aim to evaluate the safety, tolerability, and functionality of repeat doses of DDS devices in fasted and fed states in normal healthy volunteers (NHV).

THE DDS DEVICE

- The DDS device comprises a drug reservoir that houses a liquid formulation of the therapeutic compound and an electronic module **(Figure 1A)**.
- The electronic module houses the localization system, electronics, and the gas cell required for displacing the drug reservoir from the device at the target location **(Figure 1A)**.

Autonomous Localization

- The proprietary autonomous localization system identifies different anatomical regions by emitting colored light that interacts with the local GI environment and returns to spatially separated detectors. Measured light levels are analyzed by the algorithm to detect changes associated with different anatomical features **(Figure 1B)**.
- Upon detection of entry into the colon (S4), the device initiates the gas cell actuator for drug release **(Figure 1B)**.

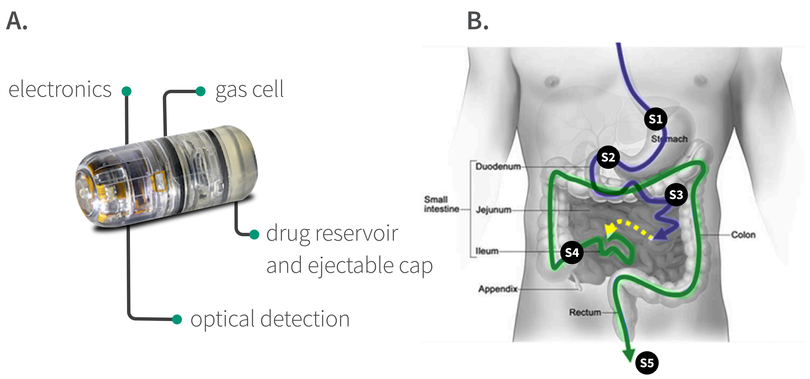

FIGURE 1. DDS with autonomous localization technology enables targeted delivery of therapeutics. A) Photograph of DDS device; B) The internal algorithm can detect five major anatomical locations: (S1) entry to stomach, (S2) pylorus(gastric emptying), (S3) small intestine, (S4) colon, and (S5) exit from body.

OBJECTIVE

- To assess the safety and tolerability of repeat dosing of DDS devices in a fasted state and with different fed schedules by measuring the number, severity, expectedness, and type of device-related adverse events (AE).
- To evaluate the localization and delivery function of DDS devices by recovering the device and analyzing the internal algorithm data in a fasted state and with different fed schedules.

METHODS

Clinical Study Designs and Intervention

- NHV were enrolled and administered a single DDS device at each weekly visit in either a fasted state or in 1 of 3 possible fed schedules over ~4 weeks.
- Subjects were fasted overnight and dosed in the morning (fasted schedule).
- Subjects were fasted overnight and consumed a light breakfast with equivalent calories and protein/fat content of egg-beater meal either:
  - immediately before dosing of DDS device (fed schedule #1),
  - 30 minutes post-dose of DDS device (fed schedule #2), or
  - 2 hours before dosing of DDS device (fed schedule #3).
- DDS devices were recovered from the feces, and data were extracted from the devices to confirm the function of the colon entry call and activation of payload release by the internal algorithm.

Main Inclusion and Exclusion Criteria

- Male and non-pregnant female subjects between ≥18 and ≤75 years of age who were willing to adhere to contraception and sperm donation criteria.
- Subjects who could swallow 000 size capsule.
- Subjects diagnosed with Crohn's disease, indeterminate colitis, or clinical findings suggestive of Crohn's disease (e.g., stricture, fistula, or granulomas on biopsy) were excluded.
- Subjects who had fulminant colitis (e.g., toxic megacolon or bowel perforation), evidence or history of colonic dysplasia, who needed to undergo surgery, or who had other histories of increased risk of bowel obstruction were excluded.

RESULTS

Safety and Tolerability of DDS

- A total of twelve NHV (N=12) were enrolled, and eleven (N=11) subjects completed all four dosing fasted/fed schedules over 4 weeks.
  - One subject was withdrawn due to non-compliance with device recovery.
- Overall, the DDS devices were well-tolerated in all enrolled subjects dosed (N=46 devices).
- No serious device-related AEs were reported in this study.
- Mild AEs were reported as possibly related to the device in two subjects, including vomiting (N=1) and nausea (N=1) following device administration, which was resolved on the same day.

Localization Validation and Delivery Performance

- Out of 44 devices administered to 11 subjects, 43 were successfully recovered, and device data was successfully recovered from 39 devices for device function evaluation.
- All 39 devices had successfully identified colon entry calls (S4) **(Table 1)**.
  - The internal algorithm, which analyzes the 3-color LED RGB light measurement over time, demonstrated minimum effects of the three fed schedules on S4 determination **(Figure 2)**.
- All 39 devices had successfully activated H2 gas cells for delivery in all fasted/fed schedules (100%).
- Thirty-eight out of 39 recovered devices (97.4%) had successfully activated the payload release function, and one did not **(Table 1)**.

SUMMARY

- **The study demonstrated that the DDS device was well-tolerated and functioned as intended in NHV subjects in these four fasted/fed dosing schedules.**
- **The study confirmed that the potential effect of food on the function of the DDS device is minimal.**

TABLE 1: Device performance in fasted and fed states (analysis population N=11 subjects)

Parameter	Fasted State (D = 9)*	Fed State			All (D = 39)*
		Schedule #1 (D = 11)*	Schedule #2 (D = 11)*	Schedule #3 (D = 8)*	
S4 Call					
Correct call (%)	9 (100.0%)	11 (100.0%)	11 (100.0%)	8 (100.0%)	39 (100.0%)
Wilson-Score 95% CI	(70.1%, 100.0%)	(74.1%, 100.0%)	(74.1%, 100.0%)	(67.6%, 100.0%)	(91.0%, 100.0%)
H2 Cell Activation					
Activated (%)	9 (100.0%)	11 (100.0%)	11 (100.0%)	8 (100.0%)	39 (100.0%)
Wilson-Score 95% CI	(70.1%, 100.0%)	(74.1%, 100.0%)	(74.1%, 100.0%)	(67.6%, 100.0%)	(91.0%, 100.0%)
Payload Release Activation					
Delivered (%)	9 (100.0%)	11 (100.0%)	10 (90.9%)	8 (100.0%)	38 (97.4%)
Wilson-Score 95% CI	(70.1%, 100.0%)	(74.1%, 100.0%)	(62.3%, 98.4%)	(67.6%, 100.0%)	(86.8%, 99.5%)

*Total number of successfully retrieved devices with recoverable data

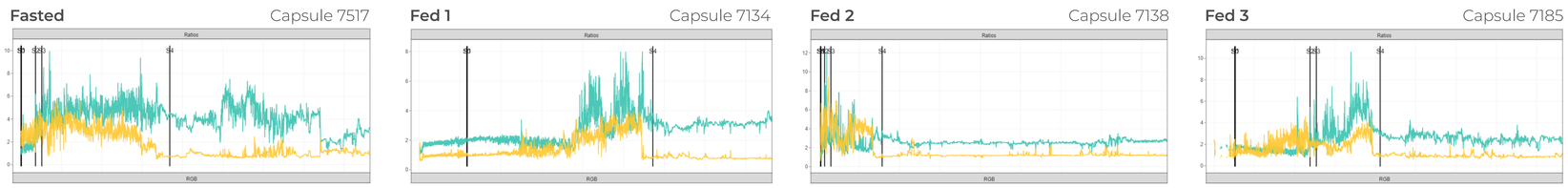

FIGURE 2. Examples of RGB light measurement and ratio over time in different fasting and fed schedules. Variable: Green/Blue Ratio Red/Green Ratio

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