Development of a novel *Drug Delivery System 2 (DDS2)* for colon targeted delivery treatment of ulcerative colitis

Shaoying Nikki Lee, PhD[1]; Jeff Shimizu[1]; Cheryl Stork, PhD[1]; Nelson Quintana[1]; Chris Wahl, MD[1]; Sharat Singh, PhD[1]; Emil Chuang, MD[1]

[1]Progenity, Inc., San Diego, CA

progenity®

Introduction

There remains a significant medical need for safe and effective therapeutics in ulcerative colitis (UC) and Crohn's disease (CD). Drugs that are liquid, peptides, or proteins are difficult to formulate for targeted colonic delivery using existing pH and microbial enzyme-based technologies, often showing low bioavailability, variable release profiles, and systemic toxicity. In addition, enteric-coated and timed-release drug delivery systems depend on the patient's gastrointestinal (GI) physiology for release. However, variations in GI pH and motility, especially in diseases like inflammatory bowel disease (IBD), can cause early or delayed drug release if the capsule experiences a significant lag time in the small GI or rapid GI motility.

Local delivery of liquid drug formulations to the cecum/right colon has the potential to improve local coverage at the site of inflammation by improving drug absorption and concentration to increase both efficacy and bioavailability, while reducing systemic drug levels and associated risks. Pre-clinical proof-of-concept studies showed local delivery of biologics, such as anti-TNF, or small molecules, such as tofacitinib, achieved higher tissue exposure, limited systemic exposure, and extended pharmacodynamic effects. Showing comparable tissue efficacy with less systemic exposure at 10-15X smaller doses can be achieved with intracecal (IC) delivery of tofacitinib compared to oral delivery in animal models.[1]

The Drug Delivery System 2 (DDS2) is an ingestible electronic capsule that can deliver any formulation of a therapeutic compound, including liquids, to a defined location in the gastrointestinal tract. By functioning independently of variable GI pH and motility, the DDS2 system is expected to achieve precise location targeting independent of disease state and thus higher local concentrations at the targeted disease site.

The DDS2 Capsule

- The DDS2 is comprised of a drug reservoir that houses a liquid formulation of the therapeutic compound, a removable cap, and an electronic module (**Figure 1**).
- The electronic module houses the localization system, optical detection, and the gas cell required for releasing the drug formulation in the target location (**Figure 1A**).

Autonomous Capsule Localization

- The autonomous localization technology was developed with a comparable prototype, the Telemetric Localization Capsule (TLC), in 58 subjects across three clinical studies to validate and improve the technology and internal algorithm used for localization.
- The 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 2**).
- Upon detection of entry into the colon (S4), the DDS2 capsule initiates the gas cell actuator for drug release.

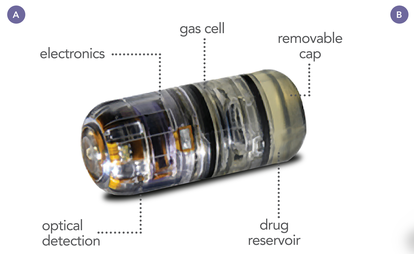

Figure 1. Drug Delivery System 2
(A) Photograph of Drug Delivery System 2 (DDS2); (B) Rendering of planned commercial DDS2.

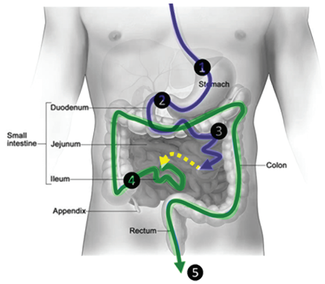

Figure 2. Proprietary localization technology enables precision medicine for targeted therapeutics. The internal algorithm can detect five major anatomical locations to trigger various functions: (1) stomach, (2) pylorus, (3) small intestine, (4) colon, and (5) rectum.

Pre-Clinical Proof of Concept in Beagle Dogs

Methodology

- This study was conducted to demonstrate the functionality of the DDS2 after oral administration (PO) in fasted male beagle dogs pre-treated with pentagastrin (6 µg/kg) (N=5; 8-14 kg).
- The DDS2 drug reservoir was loaded with two marker drugs, acetaminophen (30.4 mg) and sulfasalazine (21.3 mg), the afternoon before administration and stored at room temperature.
- Acetaminophen is rapidly absorbed in the GI and indicates drug release. Sulfasalazine is cleaved by colonic bacteria to sulfapyridine and serves as a colon arrival indicator.
- Blood sampling occurred at the following time points: Pre-dose, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, and 24 hours post-dose to generate plasma concentration curves for both marker drugs (**Figure 3**).
- Fecal samples were carefully monitored up to 72 hours post-dose to recover DDS capsules. The localization data were then extracted from the recovered capsule and analyzed.

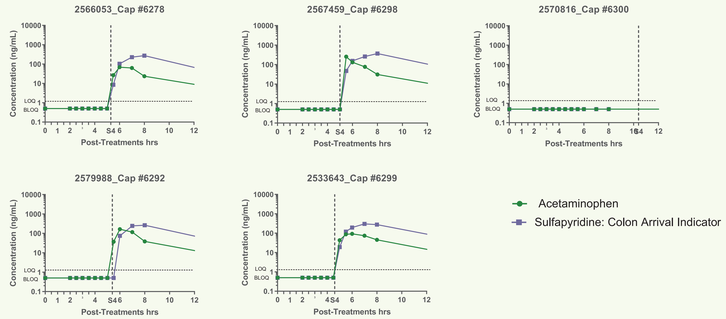

Figure 3. Pharmacokinetics of acetaminophen and sulfapyridine post-dose in beagle dogs. Plots of plasma concentration for acetaminophen and sulfapyridine versus time in five beagle dogs are shown here. The vertical dashed line indicates the timepoint of the capsule S4 event.

Results

- All capsules indicated the S4 trigger (entry into the colon) required for the gas cell actuator to start and stop. The reported event times are indicated in **Table 1**.
- Gas cell start times in 5/5 capsules coincided with the associated S4 trigger times and ended 30 minutes post-starting time.
- Comparison of the pharmacokinetic profile of acetaminophen and sulfapyridine indicated drug release in the colon shortly after self-determined delivery trigger (S4) around 4-5 hours post-dose in 4/5 capsules (**Figure 3**).
- In the one remaining capsule, the drug release was after the first 8-hour post-dose blood sampling schedule but was later detected at the 24-hour timepoint and confirmed that the capsule functioned as intended.

Table 1. Localization and actuator events recorded on DDS2 capsules. The event log was examined to determine the localization event call times of gas cell actuator start and stop. The gas cell is the drug delivery actuator. The reported event times are shown in the table.

Animal #	Capsule #	S4 (min)	Gas Start (min)	Gas End (min)
2566053	6278	318.25	318.25	348.25
2567459	6298	301.5	301.5	331.5
2570816	6300	622.75	622.75	652.75
2579988	6292	326.0	326.0	356.0
253643	6299	278.0	278.0	308.0

Summary and Conclusions

- This pre-clinical study demonstrated that the Drug Delivery System 2 (DDS2) successfully autonomously identified the colonic entry (S4) and delivered the marker drugs to the colon.
- The DDS2 enables more precise dosing and higher local concentrations at the site of inflammation to increase tissue concentration, reduce systemic exposure, and address the need for more efficient colonic delivery of therapeutics for improved safety.
- By leveraging a compound with proven efficacy, such as adalimumab or tofacitinib, in a soluble formulation, the DDS2 has the potential to apply this novel platform technology to address the unmet need of mucosal targeted therapy for inflammatory bowel disease.

Reference

1. Lee SN, et al. Targeted delivery of soluble tofacitinib citrate to the site of inflammation to improve efficacy and safety. Poster presented at Digestive Disease Week virtual conference, May 2021. Poster #Fr488.

Contact

Shaoying Nikki Lee

Progenity Inc.

4330 La Jolla Village Drive, Suite 200
San Diego, CA 92121

Nikki.Lee@progenity.com

 | **progenity.com/research**