Evaluation of the pharmacokinetics of PGN-OB1 following oral administration of an oral biotherapeutics delivery system (OBDS) in *Yucatan* swine

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INTRODUCTION

Biologics/peptides/nucleic acids are highly effective drugs; however, oral delivery of these therapeutics has proven difficult due to the harsh conditions of the upper gastrointestinal tract (GIT) and the poor absorption rate in the small intestinal mucosa. The current state of-the-art technology for a successful oral protein delivery provides around 1% bioavailability when delivered as an oral tablet (Rybelsus® oral Semaglutide).

We aim to develop an oral biotherapeutic delivery system (OBDS) that prevents drug degradation in the upper GIT and increases bioavailability via submucosal injection. The OBDS device operates autonomously and provides a needleless injection to deposit the liquid drug payload into the submucosal space of the proximal small intestine.

OBJECTIVE

To develop an intraduodenal endoscopic placement method to place a semi-autonomous OBDS device into the small intestine of swine to allow natural transit, triggering, and submucosal injection for better human translation.

PRECLINICAL MODEL

- Although the canine is a preferred model for oral therapeutic evaluation, anatomical differences between the canine and human small intestine make it suboptimal for the evaluation of intestinal injection **(Table 1)**.
- A *Yucatan* minipig model was chosen to better represent the pharmacokinetic properties of submucosal injection in humans. *Ex-vivo* testing results showed similar tissue ink deposition to human (see poster #D0637).

Preclinical Animal Model Selection for Human Translation

Swine model for proof of mechanism of action and performance test for a semi-autonomous device **(Figure 1)**.

Pros
- Similar anatomical and histology features in the small intestine
- Better representation of PK for submucosal injection for human translation

Cons
- Variable GI transit → higher variability
- Prolonged gastric emptying time → cannot fully evaluate autonomous trigger

Canine model for repeatability and consistency of fully autonomous device

Pros
- Similar GI transit and motility to human
- Consistent and controllable gastric emptying
- Ease of oral dosing and repeat dosing for consistency testing

Cons
- May underestimate bioavailability due to less injection volume/deposition (see poster #D0637)

METHODS

In-vivo evaluation of the pharmacokinetics of PGN-OB1 via intraduodenal endoscopy placement in the *Yucatan* Swine

Intraduodenal (ID) endoscopy placement of the OBDS device(s):

- OBDS devices, which were filled with India ink for the *in-vivo* ink deposition test, or with a variant of adalimumab for evaluating the pharmacokinetics of PGN-OB1, were attached to the endoscope via the working channel and endoscope delivery device and inserted orally into fasted animals under anesthesia.
- The device was advanced past the pyloric sphincter and expelled from the placement instrument in the proximal small intestine. The device then transited naturally and autonomously triggered in the GIT.
- Blood samples post-ID dosing were collected to evaluate the injection efficiency of the OBDS compared with the IV control group.

TABLE 1: Physiological and Anatomical Differences Comparison

	Gastric pH[a]	Duodenum pH[a]	Gastric Emptying Time, Fasted (hr)	Gastric Emptying Time, Fed (hr)	Small Intestinal Transit Time (hr)	Small Intestinal Volume Time (ml)[a]	Small Intestinal Villi Shape
Human	0.4 – 4 (fasted) 2 – 4.5 (fed)	5 – 7	0.66 – 1[b]	2 – 5[g]	2 – 4[a]	212 ± 110	Finger[a]
Swine	1.4 – 4 (fasted) 4.4 (fed)	6	Variable; 1.4 and up to 20 days[c,d]	Variable[h,i]	Variable 3 – 4; 1 – 2 days[d,h]	476 ± 253	Finger[a]
Canine	1.5 (fasted) 3 – 5 (fed)	6.2	0.4 – 1[e,f]	Variable; 12 – 13[j]	2 – 3[j]	300	Long and slender[a]

[a]Hatton et al. 2015; [b]Worsoe et al. 2011; [c]Davis et al. 2001; [d]Hossain et al 1990; [e]Mahar et al 2012; [f]Kolziek et al 2019; [g]Lee et al 2014; [h]Gregory 1990; [i]Treacy 1990; [j]Linbury et al 2012

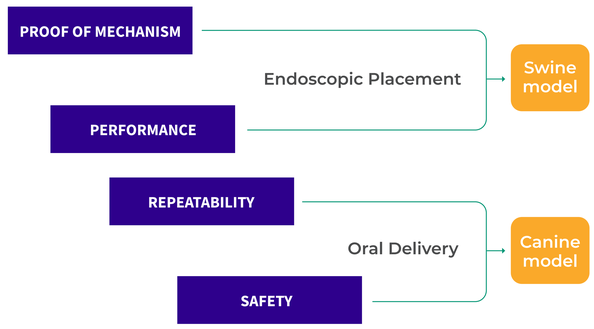

FIGURE 1. Preclinical Model Selection

RESULTS

In-vivo OBDS ink deposition in swine

- OBDS devices filled with India ink were placed in proximal small intestine and manually triggered **(Figure 2, A-C)**.
- At 24 hours post-dose, the animal was sacrificed and ink deposition was observed in the small intestine **(Figure 2, D)**.

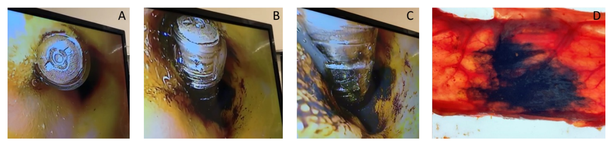

FIGURE 2. Endoscopic placement of OBDS device *in vivo*.
A. placement of OBDS device in the duodenum; **B.** manual triggering of device; **C.** Close-up look at the tissue ink deposition; **D.** Ink deposition at terminal necropsy of swine duodenum at 24hr post-deployment.

Pharmacokinetics via endoscopic placement in swine

- All OBDS devices were successfully advanced through the pyloric sphincter, without early deployment, and were released in the proximal duodenum to naturally transit and deploy *in vivo*.
- Eight animals showed detectable drug levels **(Figure 3)** and an oral bioavailability average of 25% (range from 7-55%), excluding an animal showing a late deployment at 72hr post-dose.

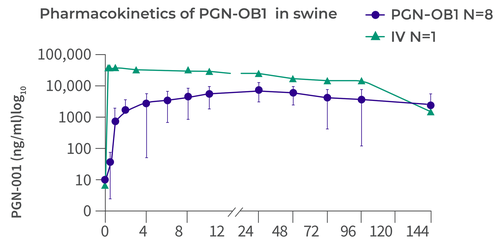

FIGURE 3. Plasma concentration of PGN-OB1 delivered via ID and IV over time

CONCLUSION

In this study, we have demonstrated that PGN-OB1 can achieve as high as 55% bioavailability of a variant of adalimumab, which is a magnitude greater than current oral protein or peptide delivery technology in the market, and at levels much closer to the subcutaneous route of administration estimated in human trials.

Limitations

Swine represents a good model to understand the potential human pharmacokinetics (PK) of submucosal injection, however, variability is expected with an autonomous trigger device due to variable small intestine transit time, motility, gas, and water pockets when compared to the human or canine model **(Table 1)**.

- An OBDS prototype device with tethered triggering in the fixed location in the proximal small intestine showed similar bioavailability but less inter-animal variability (~26% ± 7%).

Consistency and repeatability of a fully autonomous device will be further examined in the canine model.

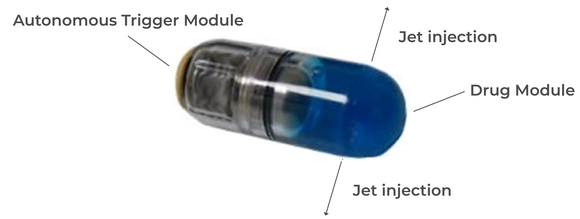

FIGURE 4. Image of autonomous OBDS device

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