Evaluation of the Pharmacokinetics of Glucagon-Like-Peptide-1 (GLP-1) Receptor Agonist Delivered through the BioJet™ Oral Biotherapeutic Delivery Platform in a Porcine Model

Shaoying Nikki Lee[1], Cheryl Stork[1], Rene Valenzuela[1], Michelle Walker[1], Bryan Smith[1], Jeff Smith[1], Nelson Quintana[1], Chris Wahl[1], Sharat Singh[1]

1. Biora Therapeutics, CA, USA

INTRODUCTION

Glucagon-like-peptide-1 (GLP-1) receptor agonists stimulate insulin secretion and suppress glucagon release. Semaglutide is a GLP-1 agonist currently used to treat type 2 diabetes and for weight management via subcutaneous injection or taken orally.

Needle injection is associated with a 42% higher discontinuation rate versus those starting oral therapy.[1] However, oral administration of protein/peptide therapeutics has proven difficult due to the harsh conditions of the upper gastrointestinal tract (GIT) and poor absorption rates in the small intestine. The currently available technology for oral delivery of semaglutide provides approximately 0.4 – 1% bioavailability when delivered in tablet form.[2]

The BioJet™ systemic oral delivery platform (previously called the Oral Biotherapeutic Delivery system or OBDS) is an ingestible drug-device combination developed to prevent drug degradation in the upper GIT and increase drug bioavailability via needleless jet injection in the proximal small intestine following oral administration.

The BioJet Systemic Oral Delivery Platform

- The BioJet device is comprised of a drug module, which houses a formulation of a therapeutic compound, and a trigger module **(Figure 1)**.
- The BioJet device is intended to deliver a needleless jet injection to deposit the liquid drug payload into the submucosal space of the proximal small intestine for absorption into systemic circulation.

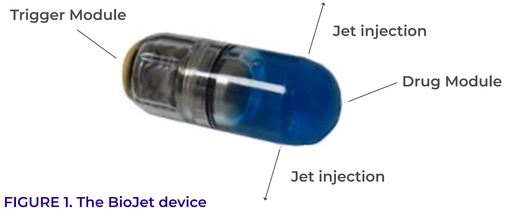

FIGURE 1. The BioJet device

References:

1. Spain CV, Wright JJ, Hahn RM, Wivel A, Martin AA. Self-reported Barriers to Adherence and Persistence to Treatment With Injectable Medications for Type 2 Diabetes. *Clin Ther*. 2016;38(7):1653-1664.e1. doi:10.1016/j.clinthera.2016.05.009
2. Novo Nordisk A/S. Rybelsus (oral semaglutide) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213051s006lbl.pdf. Revised January 2023. Accessed May 31, 2023.
3. Lunney JK, Van Goor A, Walker KE, Hailstock T, Franklin J, Dai C. Importance of the pig as a human biomedical model. *Sci Transl Med*. 2021;13(621):eabd5758. doi:10.1126/scitranslmed.abd5758

Preclinical Animal Model Selection for Human Translation

A *Yucatan* minipig model was chosen to represent the pharmacokinetic properties of submucosal injection of semaglutide in humans due to its similarities in physiology, mucosal immunity, and histology features in the small intestine **(Table 1)** and the similarity of pig insulin to human.[3]

TABLE 1: Comparison of Physiologic and Anatomic Characteristics

	Gastric pH[a]	Duodenum pH[a]	Gastric Emptying Time, Fasted	Small Intestinal Transit Time	Small Intestinal Volume (ml)[a]	Small Intestinal Villi Shape	Length of Intestine per kg of Body Weight[f]
Human	0.4 – 4 (fasted)	5 – 7	0.66 – 1[b]	2 – 4 hrs[a]	212 ± 110	Finger[a]	~ 0.1
Swine	1.4 – 4 (fasted)	6	1 – 4 hrs and up to 20 days[c,d]	3 – 4 hrs[d]; 1 – 2 days[e]	476 ± 253	Finger[a]	~ 0.1

A. Hatton et al., 2015; B. Worsoe et al., 2011; C. Davis et al., 2001; D. Hossain et al., 1990; E. Gregory et al., 1990; F. Lunney et al., 2021.

OBJECTIVES

- To evaluate the ability of the BioJet device to deliver a small-peptide therapeutic, semaglutide, into the submucosal space of the small intestine by needleless injection.
- To evaluate systemic exposure of semaglutide following intraduodenal (ID) endoscopic placement and activation of the BioJet device in the duodenum in a *Yucatan* minipig model.

METHODS

- Animals were fasted overnight and anesthetized using inhalation of isoflurane via an anesthetic mask during the entire procedure.
- BioJet devices filled with India ink or semaglutide (~1mg) were administered by intraduodenal (ID) endoscopic placement in the proximal small intestine of female *Yucatan* swine **(Table 2)**.
- Following confirmation of the location, the BioJet device(s) were externally triggered to inject either India ink or semaglutide into the proximal small intestine.
- Animals dosed with India ink were sacrificed at 20 – 24 hours post-dose to confirm the deployment of the device in the proximal small intestine.
- Pharmacokinetic blood sampling was performed from 0 to 240 hours post-dose on animals dosed with semaglutide **(Table 2)**.
- Systemic concentrations of semaglutide were measured using LC-MS/MS to evaluate the injection efficiency of the BioJet device compared with the IV control group.

TABLE 2: Pharmacokinetic Study Design for Delivery of Semaglutide using the BioJet Device

Group	Dose Route	Test Article	Dose Conc. mg/mL	Dose	Blood Collection Time Points
1	ID	BioJet device filled with semaglutide	3.2 mg/mL	~1 mg	Pre-dose, 30 min, 1 hr, 2 hr, 4 hr, 12 hr, 24 hr, 48 hr, 96 hr, 168 hr, and 240 hr post-dose
2	IV	semaglutide	3.2 mg/mL	~1 mg	

RESULTS

In Vivo Ink Deposition in Porcine Model

- BioJet devices filled with India ink were placed in the proximal small intestine and endoscopically triggered. Animals were sacrificed at 20 – 24 hours post-dose and ink deposition was observed at the injection site **(Figure 2A & 2B)**.

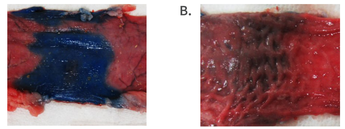

FIGURE 2. Deposition of India Ink in Proximal Small Intestine
A. Outer view of small intestine at the injection site; B. luminal view of small intestine at the injection site.

Pharmacokinetics of Semaglutide Delivered via the BioJet Device in a Porcine Model

- Seven of eight (7/8) devices (PSS8) were successfully activated in the duodenum; one device did not activate due to procedural errors.
- All seven dosed animals (PSS8) showed detectable drug levels up to ten days post-dosing and had an oral bioavailability average of 37% ± 15% (CV: 40%), ranging from 19% – 60% compared to IV control **(Table 3, Figure 3)**.
- A repeat study (PSS10) showed similar results with an average oral bioavailability of 37% (N=5; CV:57%), demonstrating the repeatability of the results **(Table 3, Figure 3)**.
- No significant clinical signs were observed in any of the animals before or after dosing for up to 10 days.

TABLE 3: Pharmacokinetics Parameters of Semaglutide Delivered via BioJet Device

	PSS8	PSS10
Route	ID	ID
Test Article	Semaglutide	Semaglutide
N	7	5
T_{max} (hours)	9.71 ± 2.14 (22%)	9.6 ± 3.2 (33%)
C_{max} (ng/mL) ± STDEV (CV%)	253.4 ± 105.1 (41%)	214.96 ± 95.55 (44%)
$AUC_{0\text{-}240}$ (hours*ng/mL) ± STDEV (CV%)	16,275.7 ± 6,539.4 (46%)	13,386.2 ± 7,614.99 (57%)
Bioavailability ± STDEV (CV%)	37% ± 15% (40%)	37% ± 21% (57%)

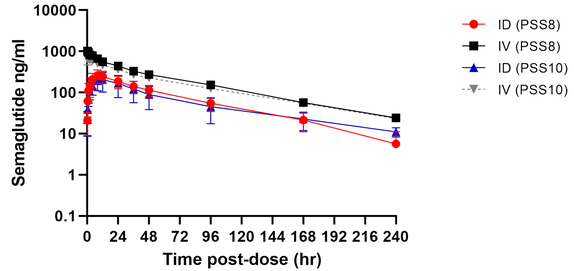

FIGURE 3. Systemic Exposure to Semaglutide following Intraduodenal Administration of the BioJet Device

CONCLUSION

- **This study demonstrated that the BioJet platform has the potential to achieve an average of 37% and as high as 60% bioavailability of a GLP-1 receptor agonist in animals.**
- **This is a magnitude greater than the currently marketed oral tablet, which has less than 1% bioavailability estimated in human trials.[2]**
- **The BioJet platform could provide an alternative for the oral administration of large molecules and may improve patient compliance vs. needle-based administration.**

© 2023 Biora Therapeutics, Inc. All rights reserved. Biora Therapeutics™ and BioJet™ are trademarks of Biora Therapeutics, Inc.

Poster #80-LB
Presented at the American Diabetes Association 83rd Scientific Sessions, San Diego, California, June 23-26, 2023.

CONTACT INFO
Shaoying Nikki Lee, PhD
Director, Clinical and Translational Science
nikki.lee@bioratherapeutics.com
bioratherapeutics.com

Scan the code to view an electronic version of this poster, or visit bioratherapeutics.com/publications