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

BIORA™ Therapeutics

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.
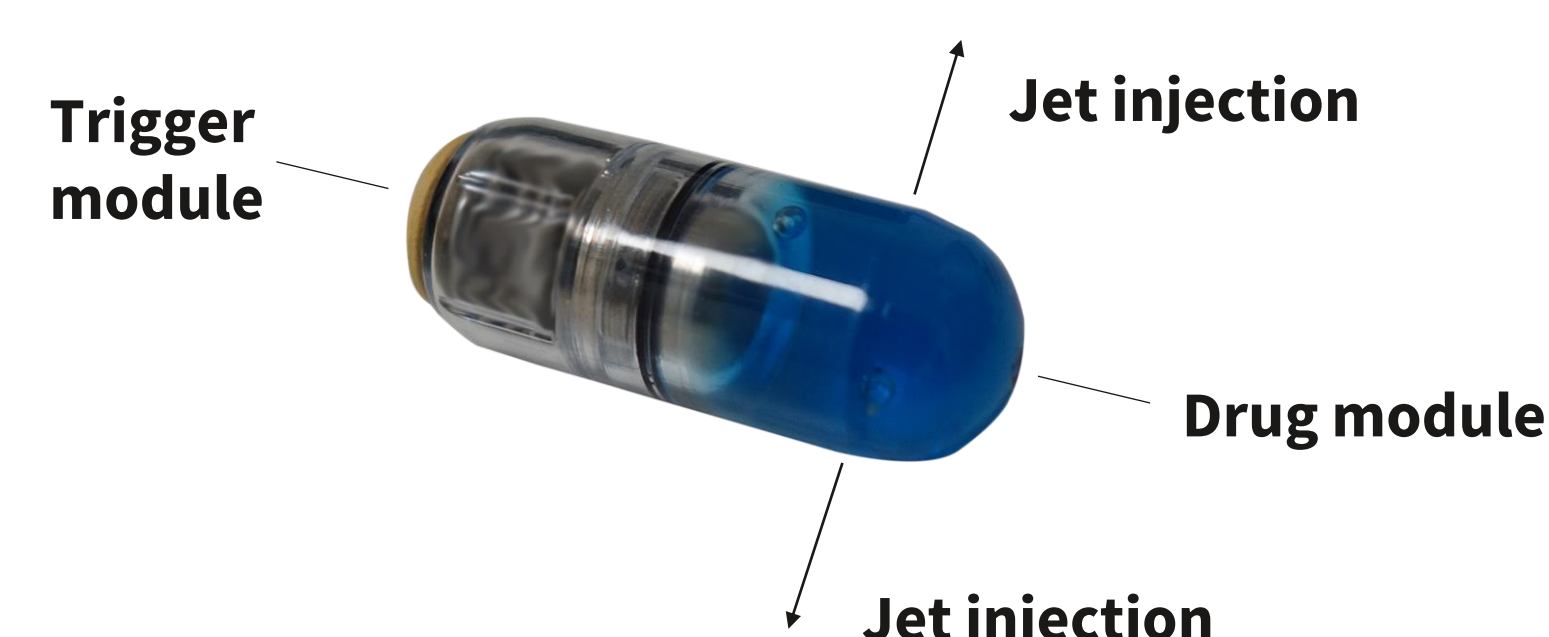

FIGURE 1. The BioJet device

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 either manual or autonomous activation of the BioJet device in the duodenum in a porcine model.

† PSS8: 7 out of 8 devices were successfully activated in the duodenum; one device did not activate due to procedural errors. Data are shown for animals with activated devices.
‡ PSS4: 7 out of 8 devices functioned. Data are shown for animals with functional devices.

METHODS

A porcine model was selected due to the similarities in physiology, mucosal immunity, histology features in the small intestine, and insulin between porcine and human. However, prolonged and variable gastric residence times in the porcine model require that the device be endoscopically placed.

- BioJet devices filled with either India ink or semaglutide (~1mg) were attached to an endoscope and inserted orally into fasted female *Yucatan* minipigs under anesthesia **(Table 1)**.
- Devices were advanced past the pyloric sphincter and were either manually triggered or released for autonomous triggering in 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.
- For animals dosed with semaglutide, pharmacokinetic blood sampling was performed from 0 to 240 hours post-dose **(Table 1)**.
- Systemic concentrations of semaglutide were measured using LC-MS/MS to evaluate the injection efficiency of the BioJet device compared with an IV control group.

TABLE 1: Pharmacokinetic Study Design for Delivery of Semaglutide using the BioJet Device

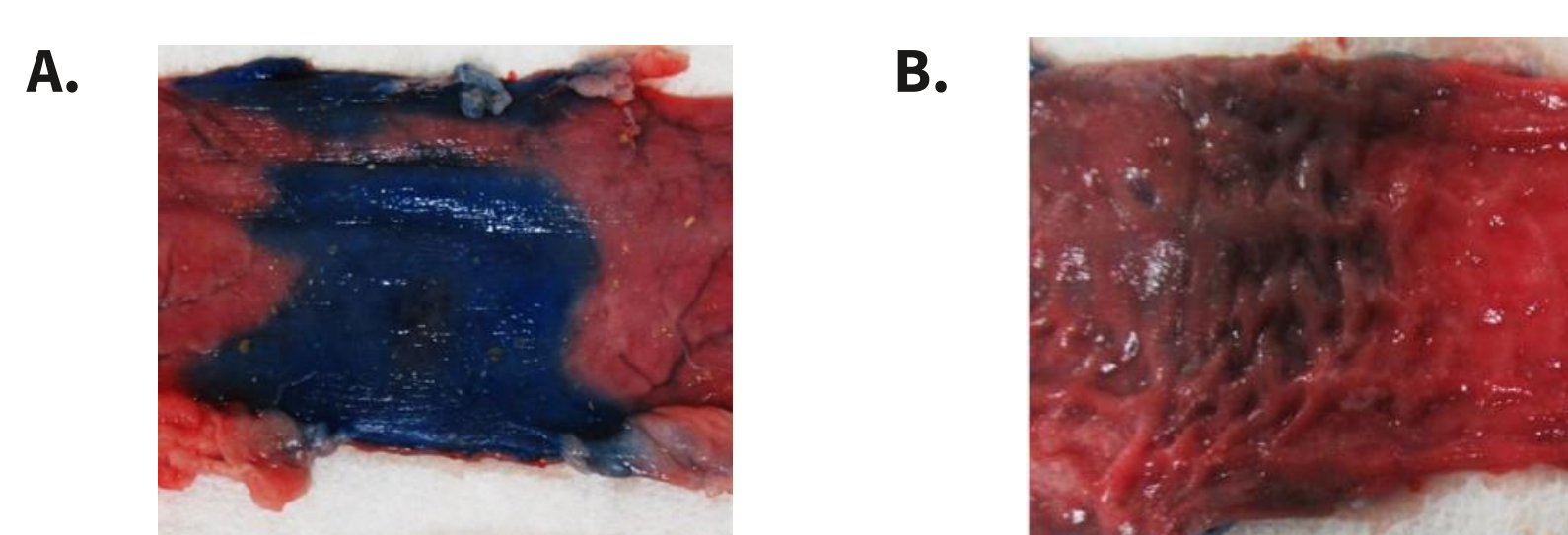| Group	Dose Route	Test Article	Dose Conc. mg/mL	Dose	Blood Collection Time Points
1	intraduodenal	BioJet device filled with semaglutide	3.2 mg/mL	≈1 mg	Pre-dose; 30 min, 1hr, 2hr, 4hr, 12hr, 24hr, 48hr, 96hr, 168hr, and 240hr post-dose
2	intravenous	semaglutide			

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

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. 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). doi:10.1126/scitranslmed.abd5758

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)**.

Pharmacokinetics of Semaglutide Delivered via the Manually Triggered BioJet Device

- 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. Oral bioavailability averaged 37% ± 15% (CV: 40%), ranging from 19% – 60% compared to IV control **(Table 2, Figure 3)**.
- A second study (PSS10) showed similar results with an average oral bioavailability of 37% (N=5; CV:57%) **(Table 2, Figure 3)**.
- No significant clinical signs were observed in any of the animals before or after dosing for up to 10 days.

Pharmacokinetics of Semaglutide Delivered via the Autonomously Triggered BioJet Device

- Additional studies were performed to test the autonomous trigger function of the next-generation BioJet device (PSS3, PSS4, and PSS5).
- Across the three studies, 96% of animals (22/23) showed semaglutide in systemic circulation (one device did not function).
- Oral bioavailability for animals with functional devices averaged 20.5% ± 15.3% (CV: 74.6%), ranging from 4% – 59% compared to IV control **(Table 3, Figure 4)**.
- No significant clinical signs were observed in any of the animals before or after dosing for up to 10 days.

TABLE 2: Pharmacokinetic Parameters of Semaglutide Delivered via Manually Triggered BioJet Device

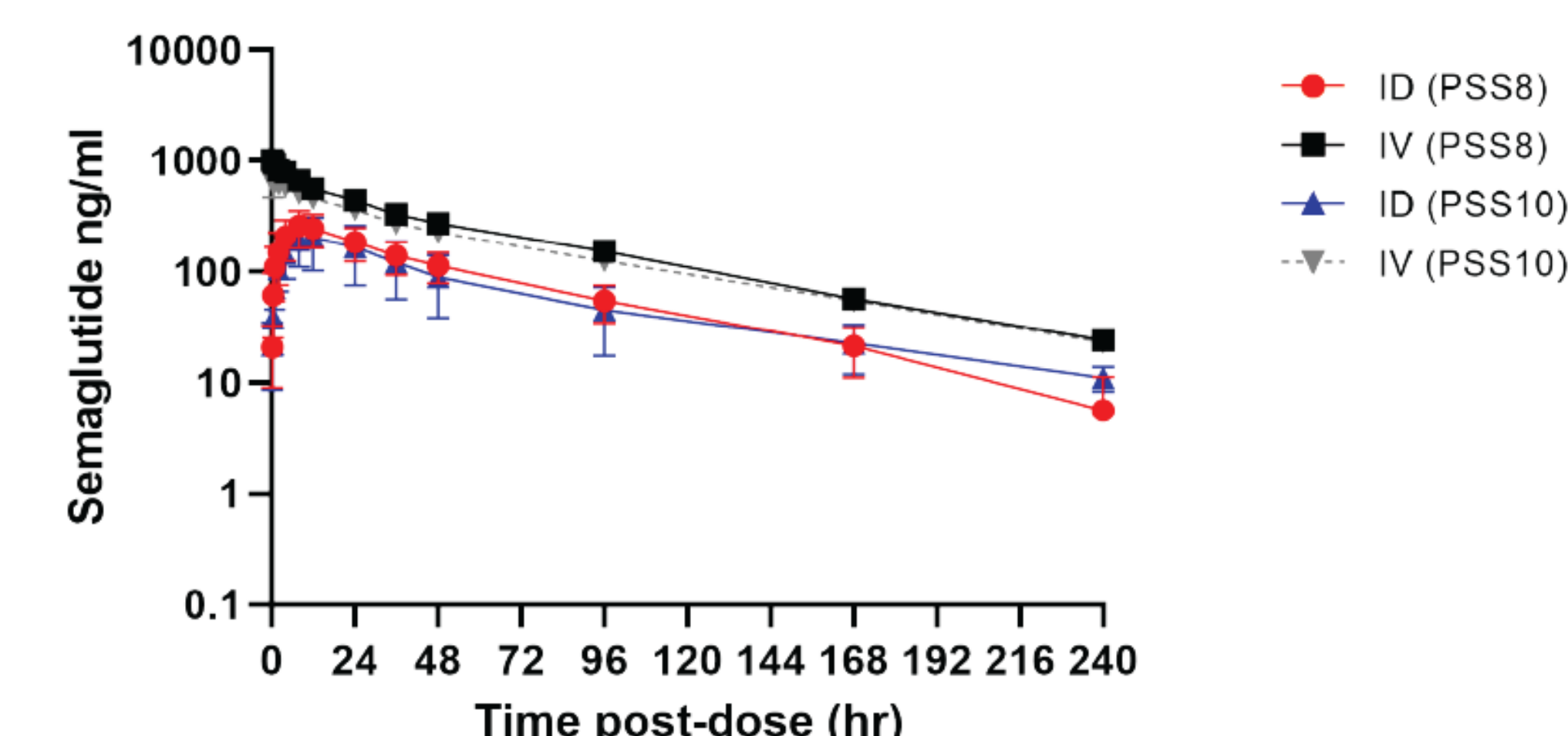|	PSS8	PSS10
Route of Administration	Intraduodenal	Intraduodenal
Test Article	Semaglutide	Semaglutide
N	7†	5
T_{max} (hours)	9.71 ± 2.14 (22%)	9.6 ± 3.2 (33%)
C_{max} (ng/mL) ± STDEV (CV%)	253.4 ± 105.1 (41%)	214.96 ± 95.55 (44%)
AUC_{0-240} (hours*ng/mL) ± STDEV (CV%)	16,275.7 ± 6,539.4 (46%)	13,386.2 ± 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
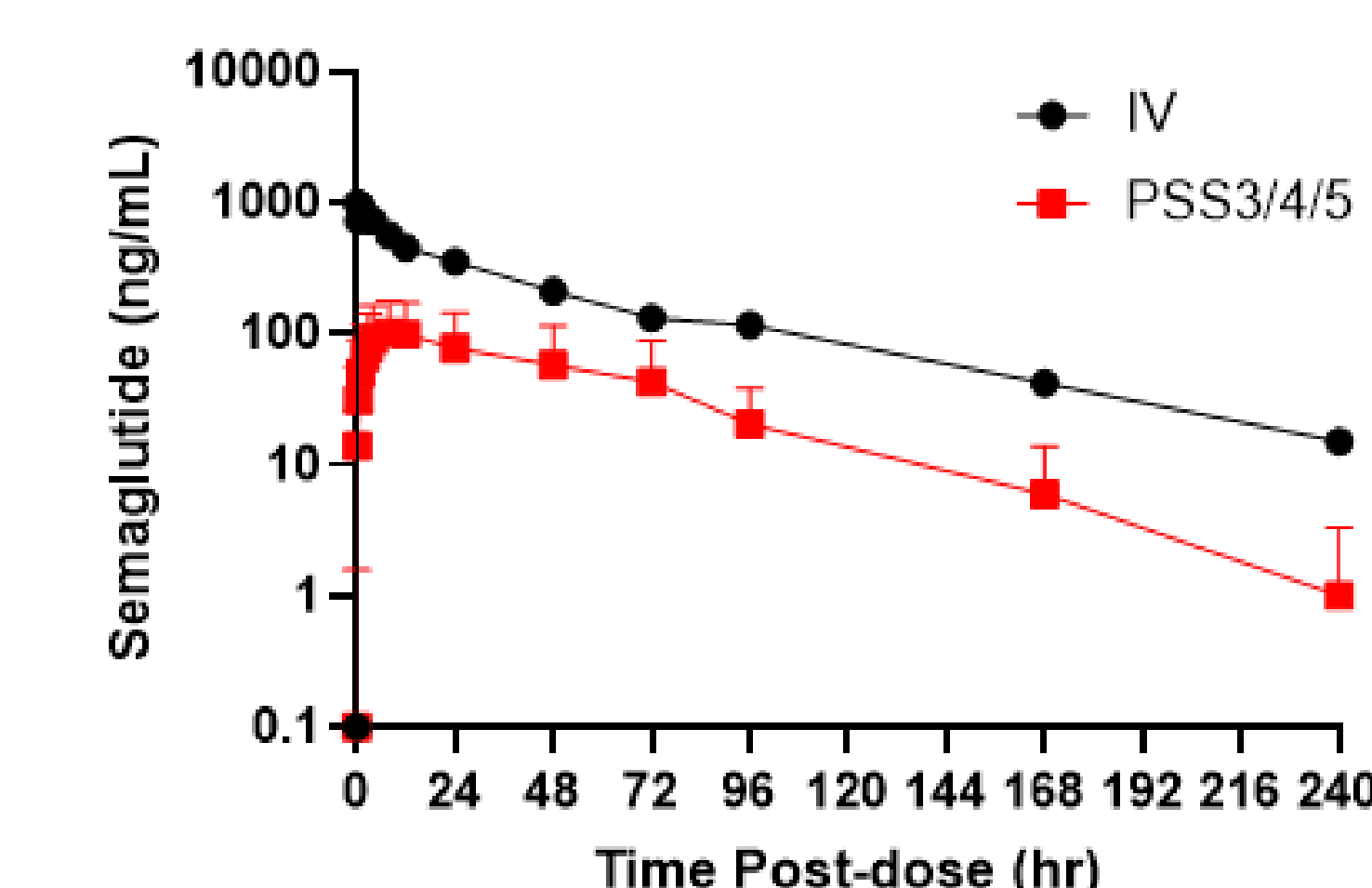

FIGURE 4. Systemic Exposure to Semaglutide following Autonomous Triggering of the BioJet Device

TABLE 3: Absolute Bioavailability of Semaglutide over IV AUC

	PSS3	PSS4	PSS5	PSS3/4/5
N	8	7‡	7	22
Mean ± STDEV	22.4 ± 14.5	19.9 ± 13.4	18.8 ± 19.5	20.5 ± 15.3
Range	4 – 50%	4 – 36%	6 – 59%	4 – 59%
95% CI of mean	10.3 – 34.6%	7.5 – 32.3%	0.8 – 36.9%	13.7 – 27.3%
CV	64.80%	67.50%	103.70%	74.60%

CONCLUSION

- **Oral administration of the BioJet device achieved averages of 20-37% and as high as 60% bioavailability of a GLP-1 receptor agonist in animal experiments.**
- **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.**

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