BIORA™ Therapeutics

635: 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

Jeff Smith, PhD
Senior Director, Bioanalytical Sciences, Biora Therapeutics

Authors:
Shaoying Nikki Lee, Cheryl Stork, Rene Valenzuela, Michelle Walker, Bryan Smith, Jeff Smith, Nelson Quintana, Chris Wahl, Sharat Singh

NEEDLES ARE ASSOCIATED WITH POOR DISEASE MANAGEMENT

38% of people with diabetes discontinue injectable medications due to injection concerns[1,2]

42% of patients fail to maintain diabetes treatment due to injection concerns when using an injectable GLP-1 agonist[2]

71% higher discontinuation rate for diabetes patients initiating treatment with an injectable GLP-1 agonist vs. those starting oral therapy[2]

1. Palanca A, Ampudia-Blasco FJ, Calderón JM, et al. Real-World Evaluation of GLP-1 Receptor Agonist Therapy Persistence, Adherence and Therapeutic Inertia Among Obese Adults with Type 2 Diabetes. *Diabetes Ther*. 2023;14(4):723-736. doi:10.1007/s13300-023-01382-9
2. 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

BIOJET™ SYSTEMIC DRUG DELIVERY PLATFORM

Needle-free, oral delivery to small intestine

ORAL CAPSULE

- Multivitamin size for ease of swallowing

PRECISE DELIVERY

- Enteric trigger for precise timing of drug delivery into the small intestine submucosal space for absorption into systemic circulation

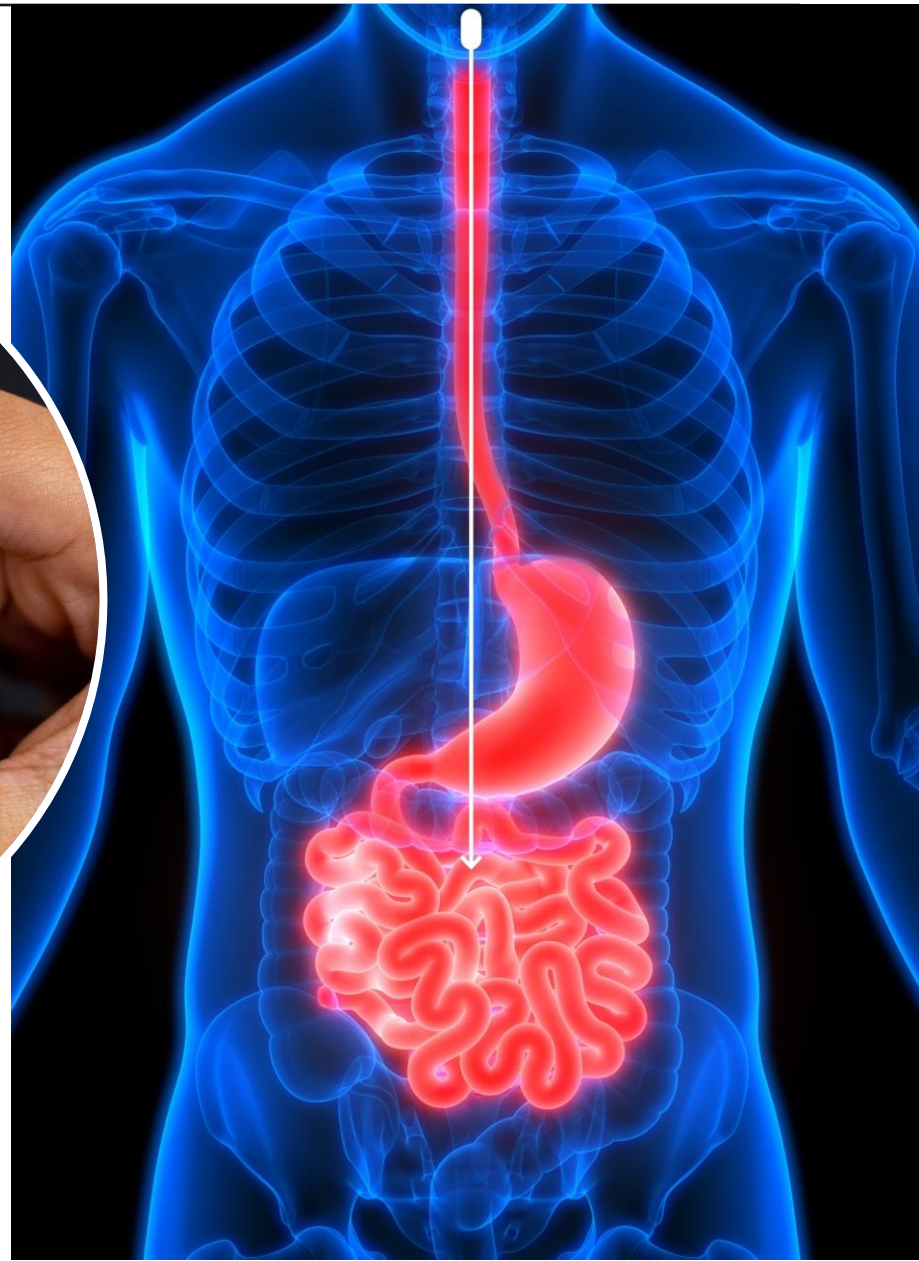
NEEDLE-FREE ADMINISTRATION

- Liquid jet injection to the small intestine to maximize systemic uptake

DELIVERY AT MG-RANGE DOSES SIMILAR TO SUBCUTANEOUS INJECTION

- Antibodies
- Proteins
- Peptides
- Oligonucleotides

SUPPORTS EXISTING LIQUID FORMULATIONS

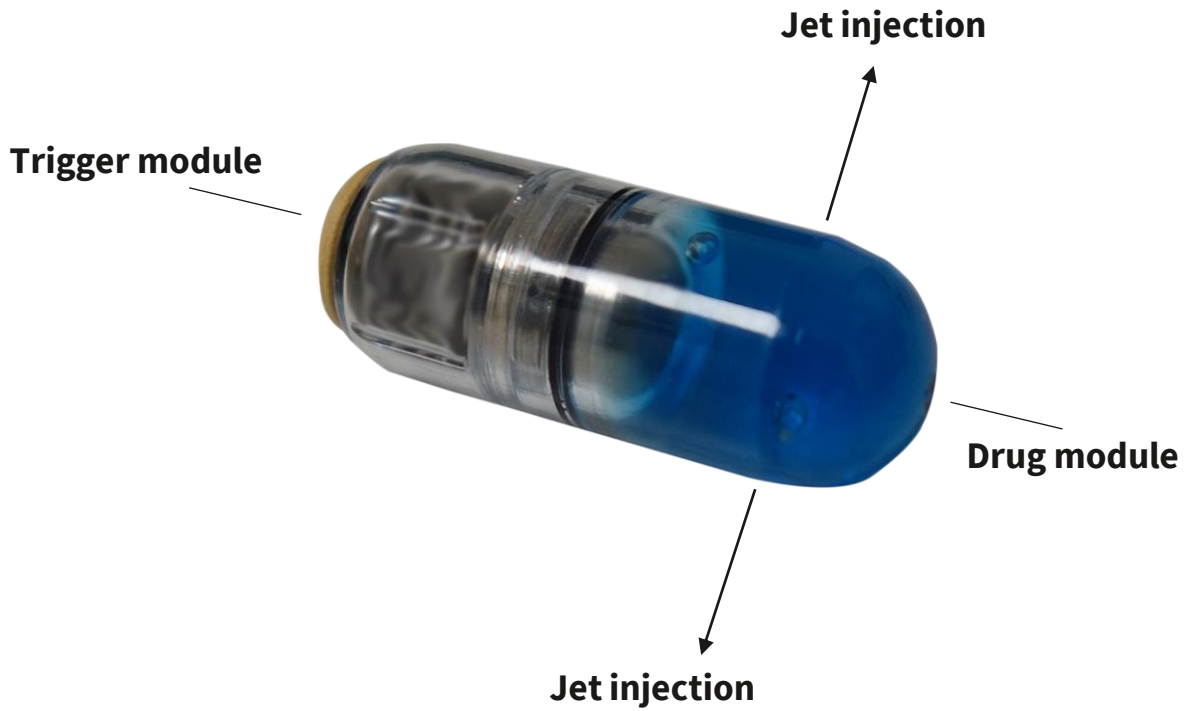


PRE-CLINICAL *IN VIVO* DEVICE PERFORMANCE AND PK STUDIES IN PORCINE MODEL

STUDY PROCEDURE

- Porcine model selected due to similar anatomical and histological features to human
  - BioJet™ device designed for human oral delivery
  - Prolonged and variable gastric residence times in the porcine model require that device be endoscopically placed
- BioJet device filled with ~1mg semaglutide attached to an endoscope and inserted orally into fasted animals under anesthesia
- Device advanced past the pyloric sphincter and manually or autonomously triggered in the proximal small intestine (ID dosing)
- Blood PK sampling at 0 – 240 hours post-dose was evaluated compared to IV administration

THE BIOJET DEVICE

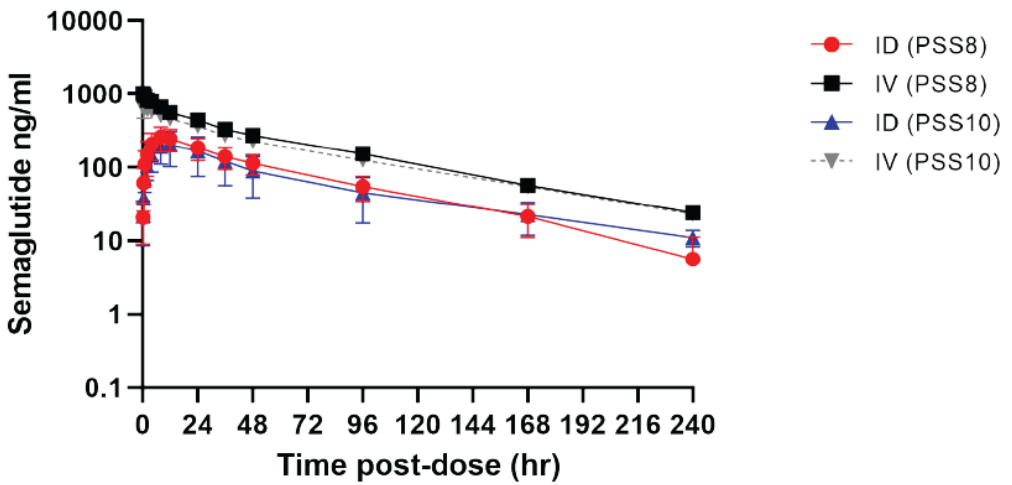


BIORA Therapeutics

PHARMACOKINETICS OF SEMAGLUTIDE DELIVERED VIA THE BIOJET™ DEVICE IN A PORCINE MODEL

RESULTS

- Average oral bioavailability vs IV administration of 37% ± 15% (N=7; CV:40%), ranging up to 60%†
- A repeat study (PSS10) showed similar results with average oral bioavailability of 37% (N=5; CV:57%)
- All dosed animals showed detectable drug levels up to ten days post-dosing
- No significant clinical signs observed in any of the animals for up to 10 days



	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%)
$AUC_{0\text{-}240}$ (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%)

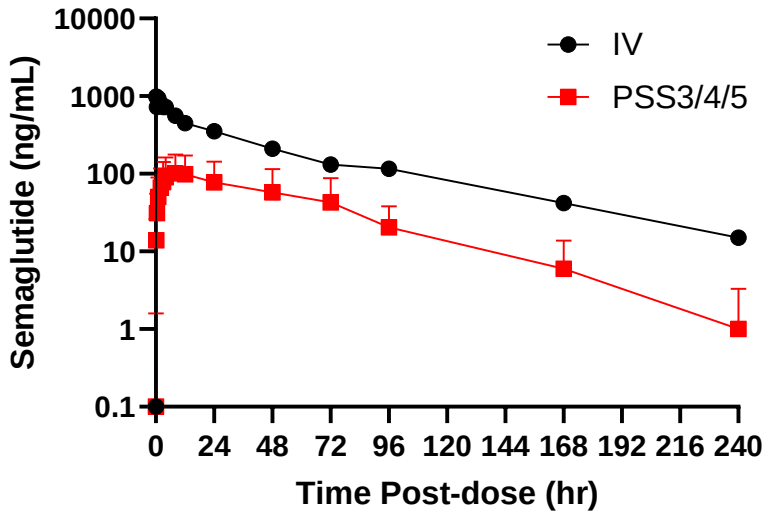
† Bioavailability is relative to intravenous administration.

‡ 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.

UPDATE: RECENT EXPERIMENTS WITH NEXT-GENERATION AUTONOMOUS DEVICE CONFIRM CONSISTENT PERFORMANCE

RESULTS

- Device was advanced past the pyloric sphincter into the proximal duodenum for autonomous triggering
- Average oral bioavailability vs IV administration of 20.5% ± 15.3% (N=22; CV = 74.6%)
- 96% of animals (22/23) showed semaglutide in systemic circulation at clinically relevant levels



ABSOLUTE BIOAVAILABILITY 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%**

† PSS4: 7 out of 8 devices functioned. Data are shown for animals with functional devices.

CONCLUSIONS

- 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, Rybelsus®, which has less than 1% bioavailability estimated in human trials.[1]
- Bioavailability with semaglutide confirm results previously observed with delivery of anti-TNF monoclonal antibodies in the swine model.[2]
- The BioJet platform could provide an alternative for the oral administration of large molecules and may improve patient compliance vs. needle-based administration.

1. 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.
2. Lee SN, Stork C, Smith J, et al. Assessing the performance of an oral biotherapeutic delivery system (OBDS) using intra-duodenal endoscopy delivery in *Yucatan* minipigs. Poster presented at: *Controlled Release Society Annual Meeting*, July 13-14, 2022, Montreal, Canada.

BIORA Therapeutics

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.

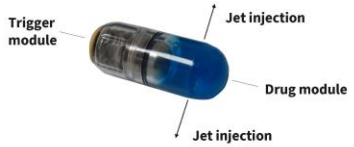


FIGURE 1. The BioJet device

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			

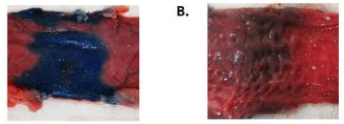


FIGURE 2. Deposition of India Ink in Proximal Small Intestine
A. Outer view and B. luminal view of small intestine at the injection site.

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%)
$AUC_{0\text{-}240}$ (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%)

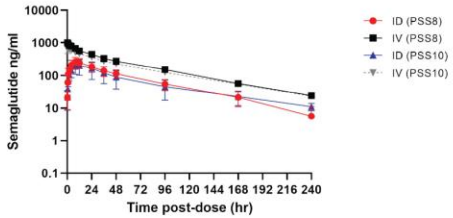


FIGURE 3. Systemic Exposure to Semaglutide following Intraduodenal Administration of the BioJet Device

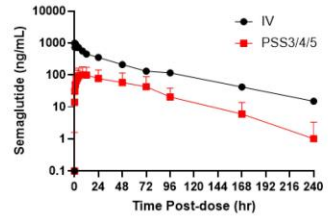


FIGURE 4. Systemic Exposure to Semaglutide following Autonomous Triggering of the BioJet Device

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.**

Poster presented at the 59th Annual Meeting of the European Association for the Study of Diabetes, October 2-6, 2023, Hamburg, Germany.

Contact Info
Jeffrey Smith, PhD, Senior Director, Bioanalytical Sciences
jeffrey.smith@bioratherapeutics.com

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