Liraglutide is a glucagon-like polypeptide-1 (GLP-1) receptor agonist used clinically to treat type 2 diabetes mellitus. It is composed of 32 amino acids and palmitic acid, and has a M₆ of 3751 Da. Liraglutide is currently marketed as a once-daily subcutaneous administered solution, with each mL containing 6 mg of active drug, and daily maintenance doses of 1.2 mg or 1.8 mg. The development of an injectable depot formulation of liraglutide with a dosing interval extended to 7 or 14 days could provide several benefits:

- Fewer injections
- Lower likelihood of missed doses
- Less fluctuation in plasma concentrations, possibly resulting in more stable plasma glucose levels

### Conclusion

We achieved 5 days to 2 weeks duration of liraglutide delivery from aqueous suspensions of peptide-polymer complexes injected subcutaneously.

- The best-performing formulation had a peak-to-rough ratio of 4
- The polymer complexes extended liraglutide MRT from 2- to almost 10-fold relative to an SC IR bolus aqueous solution of peptide
- Initial results suggest that liraglutide-polymer complex is radiation stable against a sterilizing dose of y-irradiation and hence terminal sterilization of liraglutide polymer complexes by y-irradiation is possible
- Reaction of the dermis to injection of the formulations (data not presented here), as assessed by histopathology was quite mild
- Preparation of the peptide powder used in the suspension involved a short sequence of simple operations
- Absolute bioavailability from these formulations was 5%-15%

### Abstract

**Objective:** To investigate the development of injectable depot formulations of liraglutide.

**Methods:** In vitro dissolution studies were performed to evaluate the dissolution profiles of various polymer complexes. Additionally, animal PK studies were conducted to assess the in vivo performance of the formulations.

**Results:** The polymer complexes extended liraglutide to almost 10-fold compared to aqueous formulations. Initial results suggest that liraglutide-polymer complex is radiation stable against a sterilizing dose of y-irradiation, indicating potential for terminal sterilization process.

**Conclusion:** The development of injectable depot formulations of liraglutide with dosing intervals of 7 or 14 days could provide significant benefits over current once-daily dosing regimens.

### Study Results

- **Group 1:** Dose (dt): 0.5 g, Polymer 1, Absolute bioavailability: 5%
- **Group 2:** Dose (dt): 0.5 g, Polymer 2, Absolute bioavailability: 100%
- **Group 3:** Dose (dt): 0.5 g, Polymer 3, Absolute bioavailability: 15%
- **Group 4:** Dose (dt): 0.5 g, Polymer 4, Absolute bioavailability: 20%

### Summary / Conclusions

- MRT for individual animals in each treatment group:
  - **Group 1:** MRT = 14.2 ± 2.2
  - **Group 2:** MRT = 25.3 ± 2.8
  - **Group 3:** MRT = 17.1 ± 2.4
  - **Group 4:** MRT = 17.7 ± 2.6

- By comparing mean residence times (MRT) between treatment group 1 (SC IR bolus, MRT(Animal)) and groups 2-4, one can define the contribution of each polymer to extended delivery of liraglutide (MRT(Complex)).
- Polymer-2 also produced plasma levels at 28 days that were well above the 0.5 ng/mL quantitation limit (not shown in the graph).

### Rat PK Study Design

- Male Sprague Dawley rats, 5 animals / treatment group
- Each treatment group administered one of the following as a single subcutaneous injection:
  - Aqueous solution of liraglutide (20 mg/mL)
  - Aqueous suspension of liraglutide-polymer complex with target liraglutide concentration of 20 mg/mL, incorporating one of 3 polymers:
    - Zn/Protamine
    - Polymer-1
    - Polymer-2

- Injection volume = 100 µL; target dose was 5 mg/kg

- Bioanalytical method:
  - An ELISA / EIA protocol
  - GlP-1 (residues 1-37) (human, bovine, guinea pig, mouse, rat)

- Working range for plasma (liraglutide) ≤1200 ng/mL