Gastrointestinal auto-injectors for the oral delivery of biologics

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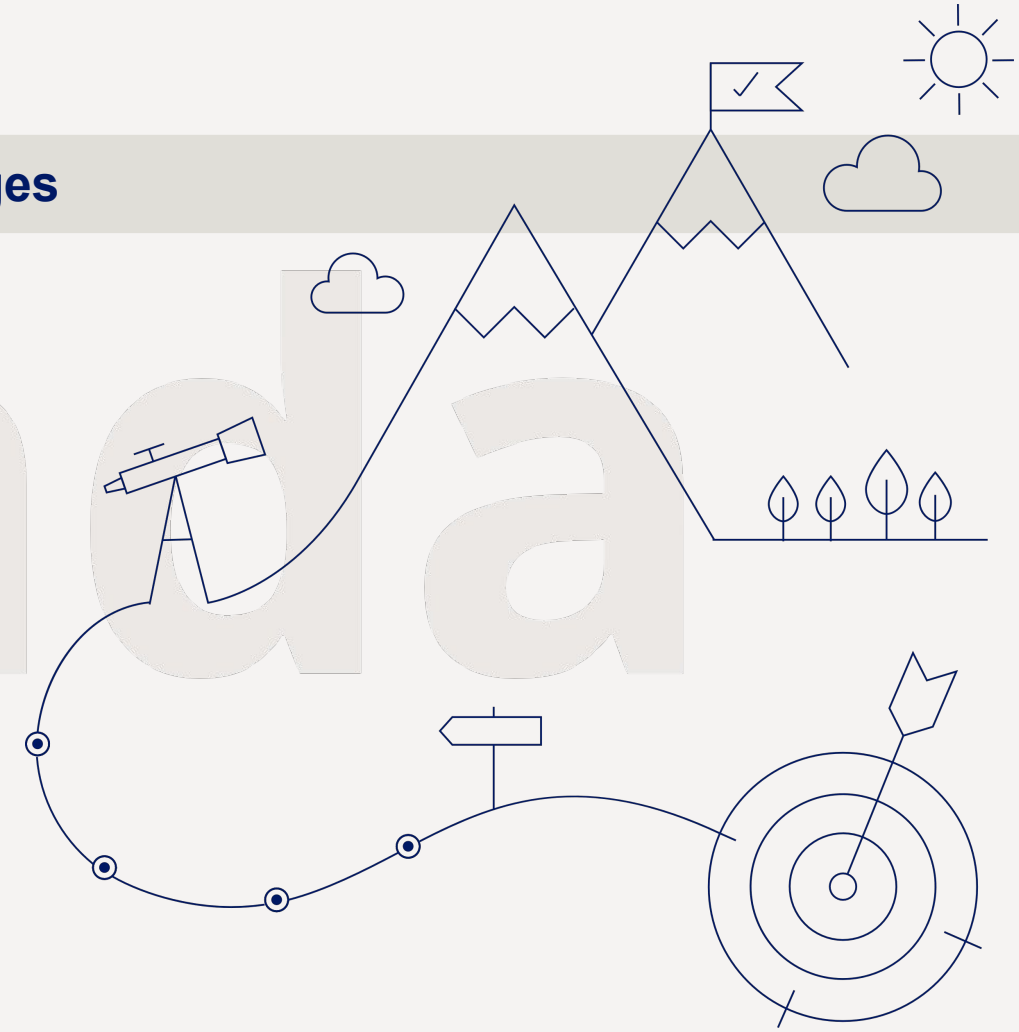
Agenda

1. **Oral biologics delivery | Rationale and challenges**
2. Oral ingestible devices
3. Liquid (L)-SOMA
4. Conclusions



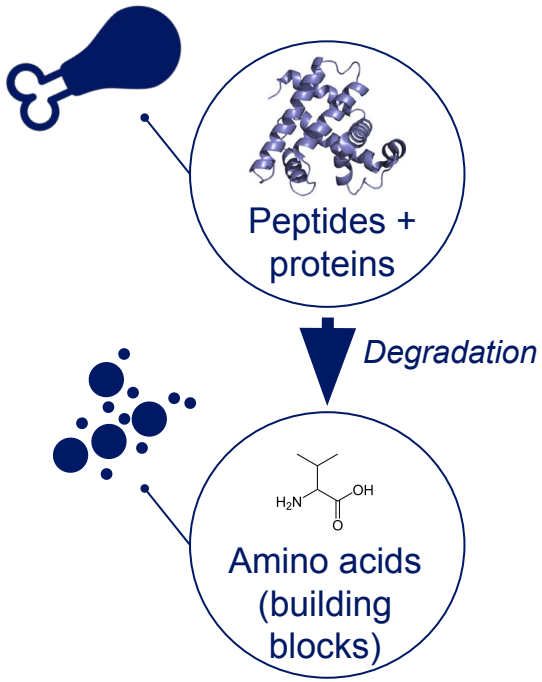
Oral delivery

to facilitate better treatment outcomes

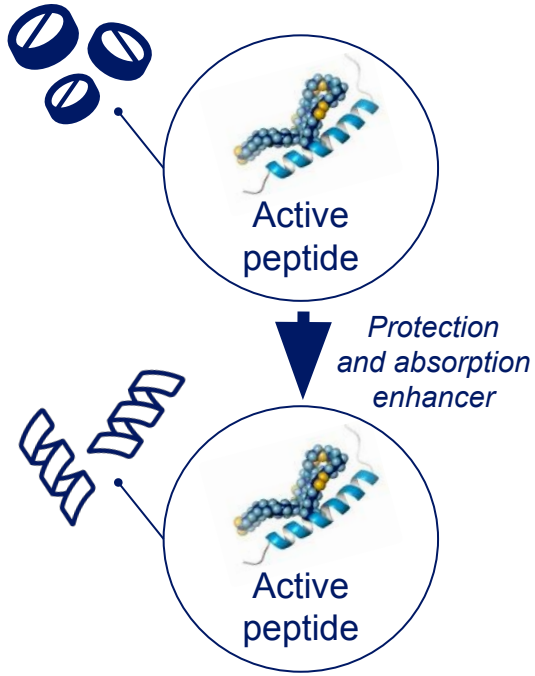
- Improve patient compliance and expand treatment options
- Early commencement of treatment; better patient outcomes
- Address barriers associated with s.c. administration

Oral delivery | Challenges

Food



Oral biologic drugs



Challenges to overcome

Permeability

- Hydrophilicity of peptide/proteins
- Diffusion through mucus & glycocalyx layer
- Tight junctions (prevent paracellular absorption)

Enzymatic stability

- Pepsin, trypsin, chymotrypsin etc.
- pH (hydrolysis peptide bonds)

Food effect

- pH & bile salt stimulation
- Gastric emptying & transit time

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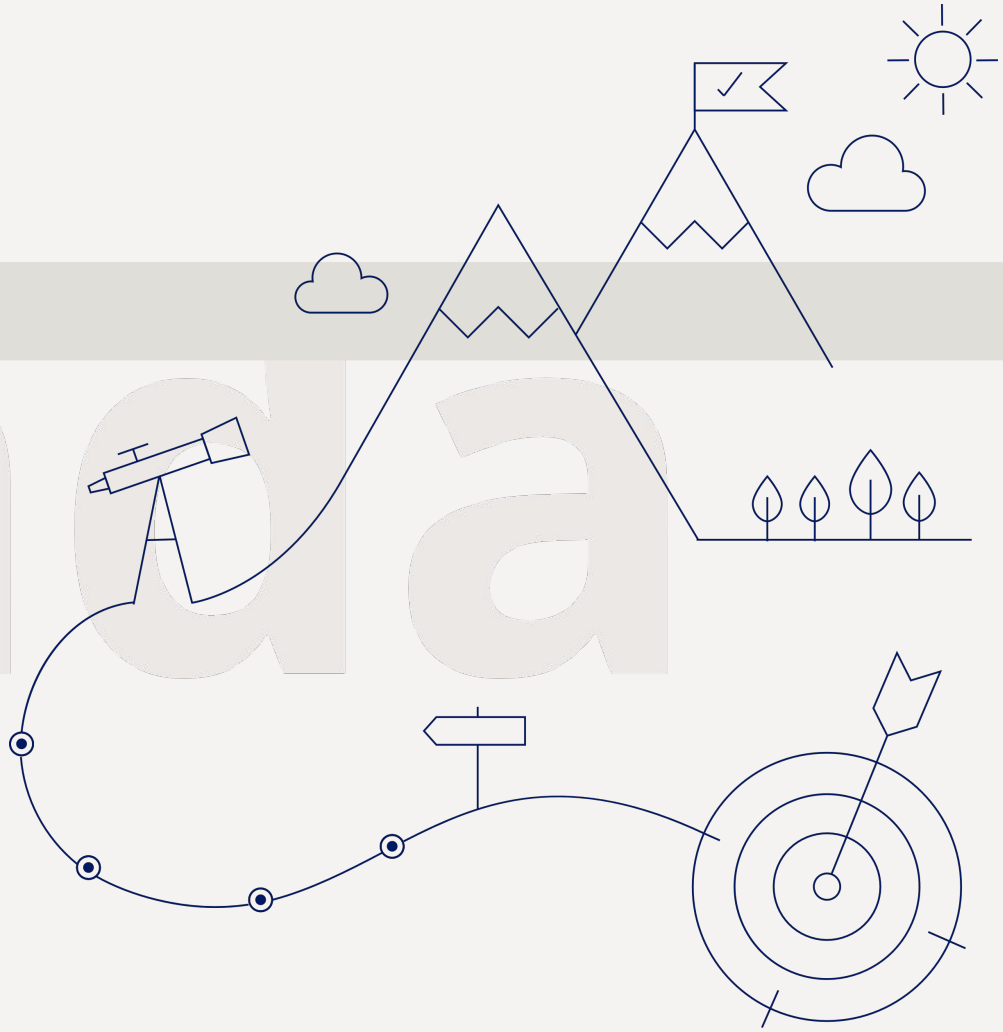
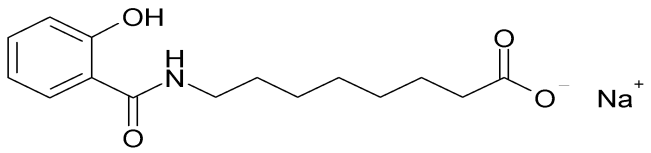
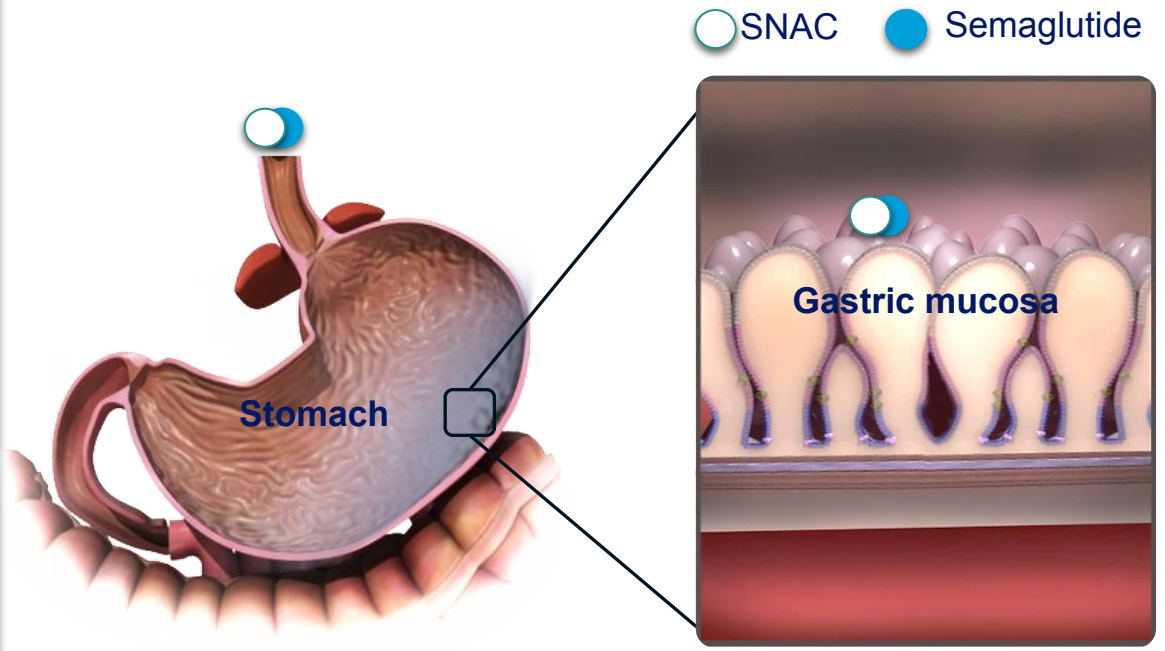


Oral semaglutide | Tablet co-formulation with SNAC

SNAC Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate



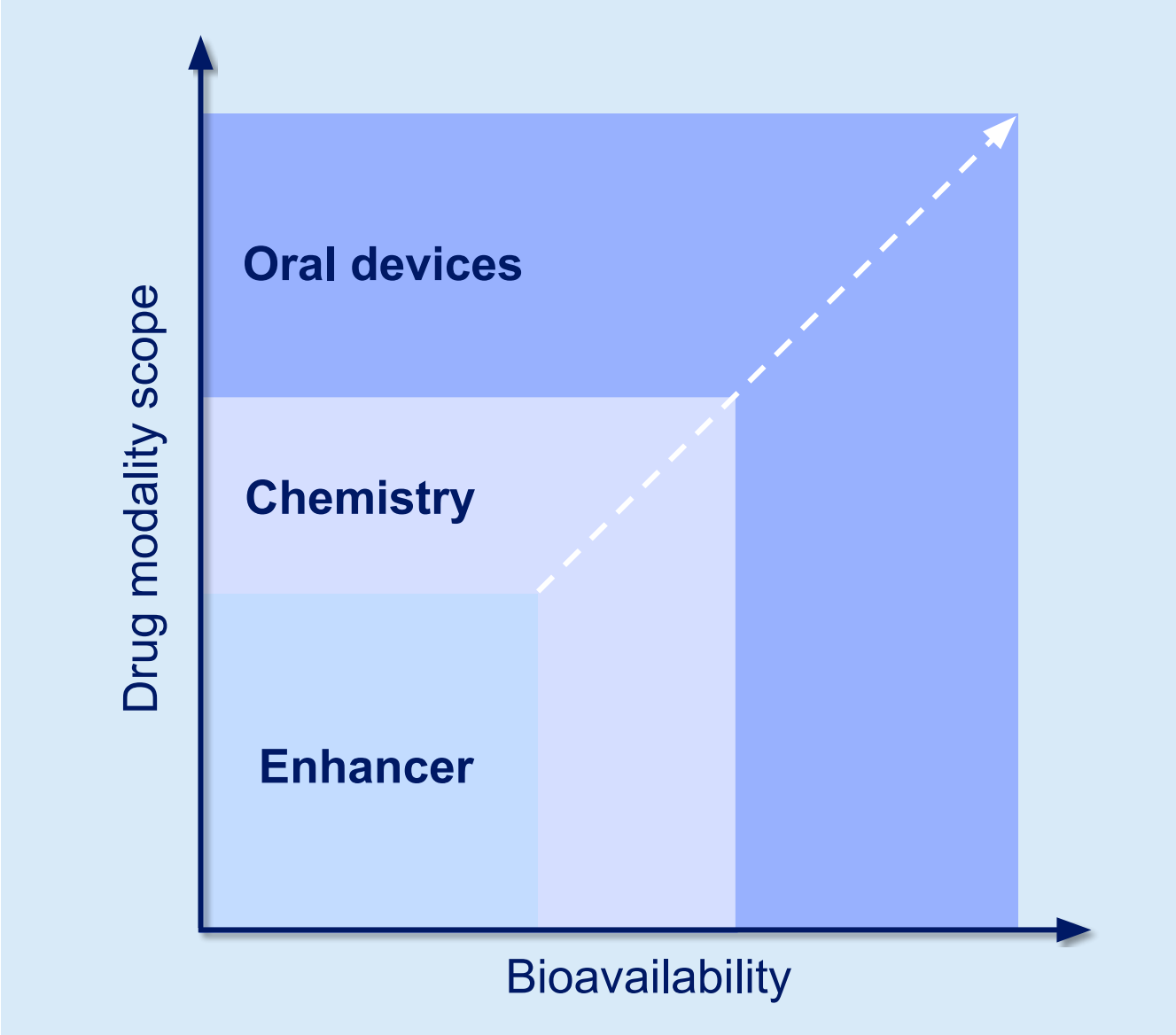
- SNAC, a small fatty acid derivative, is an absorption enhancer that facilitates absorption
- The available data for semaglutide co-formulated with SNAC support that absorption takes place in the stomach in a localised buffered environment
- The effect is strictly time-dependent and occurs primarily via transcellular route



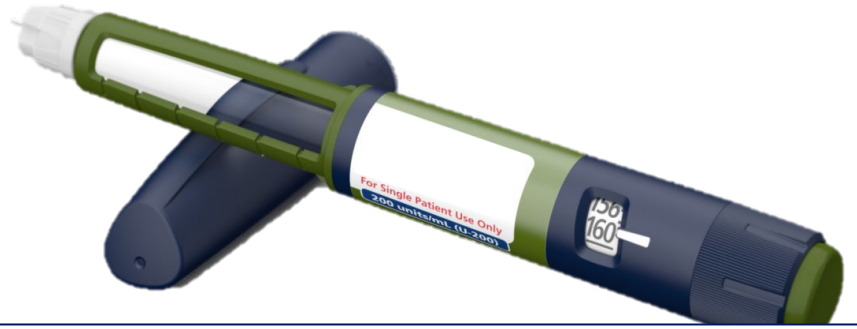
Buckley ST *et al.* Sci Transl Med. 2018;10(467)

Oral delivery of any biologic

Enable oral delivery of any biologic therapy to remove the burden of treatment for patients with serious chronic diseases



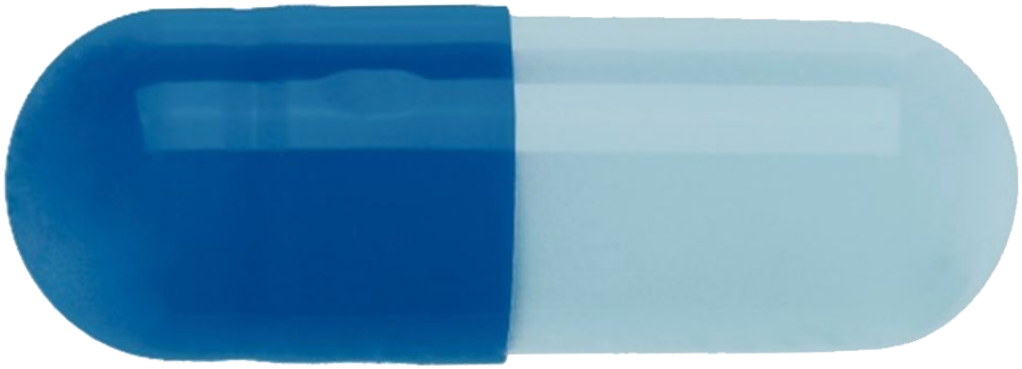
Injection device



- High bioavailability
- Low variation
- Broad therapeutic application

- Non-compliance
- Fear of needles
- Device handling

Oral



- No needle handling
- Easy to use
- Discreet

- Very low bioavailability
- High variation
- Food interactions
- Narrow therapeutic application

Oral ingestible device

- Broad therapeutic application
- High bioavailability
- Low variation
- No needle handling

- No available technology
- Unknown regulatory pathway
- Unknown safety profile

Aspirational device profile

- PK & dose
  - Dose several mg
  - High bioavailability
  - Low variation
  - Limited dosing restrictions
- Device properties
  - GRAS materials
  - Two year stability
  - No major safety risks
- Scalable for manufacturing
  - As few assembly steps as possible
  - Use of known high volume manufacturing principles

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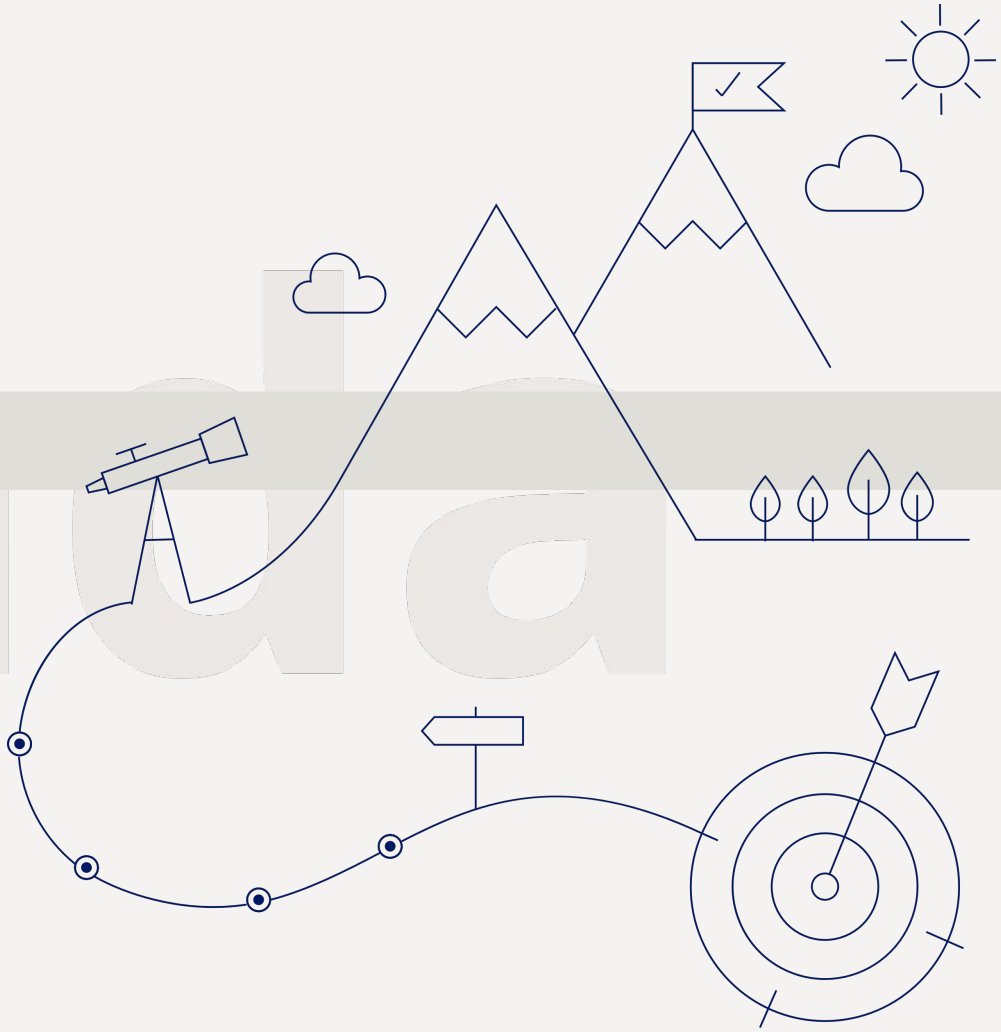
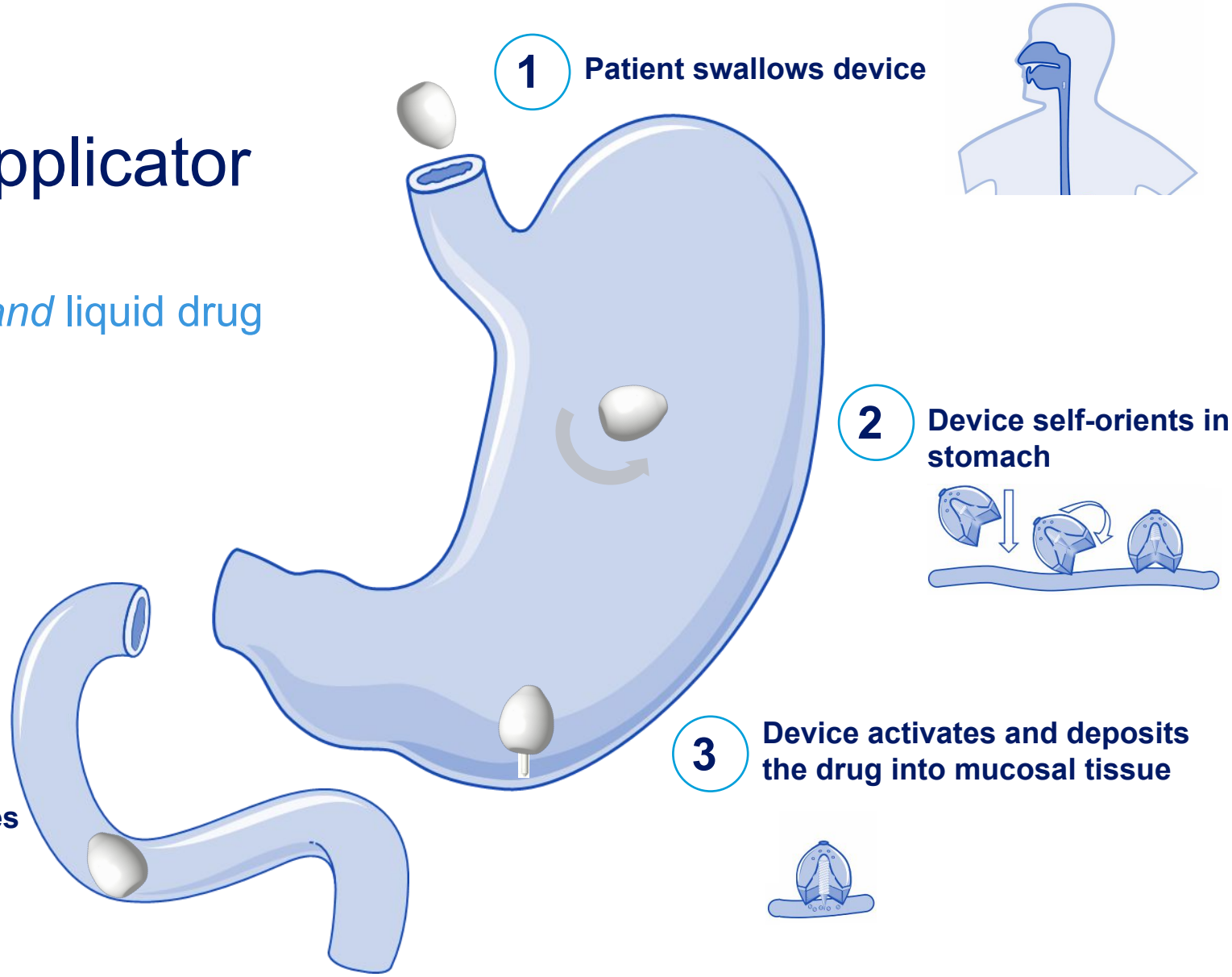


Self-orienting millimeter-scale applicator (SOMA)

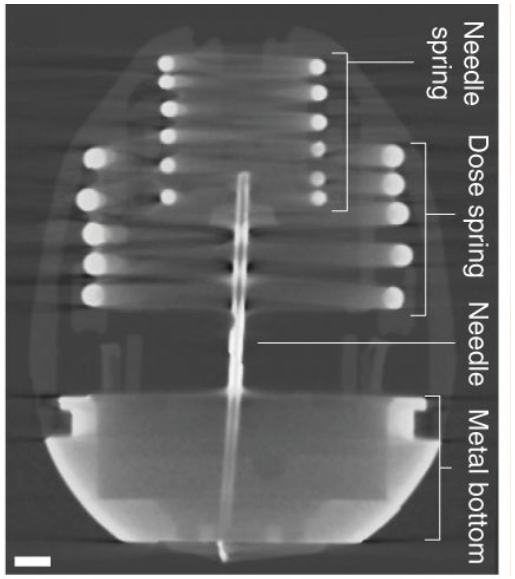
Stomach delivery of a solid *and* liquid drug products

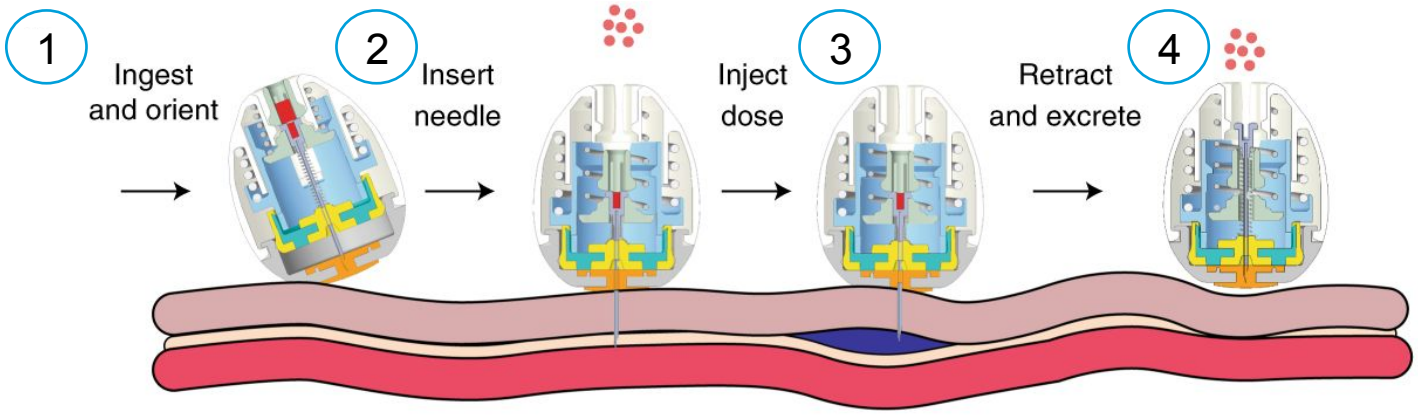


An ingestible self-orienting system for oral delivery of macromolecules. Abramson A et al. Science 2019; 611-615

Liquid (L)-SOMA | Orally dosed liquid auto-injector

Liquid (L)-SOMA

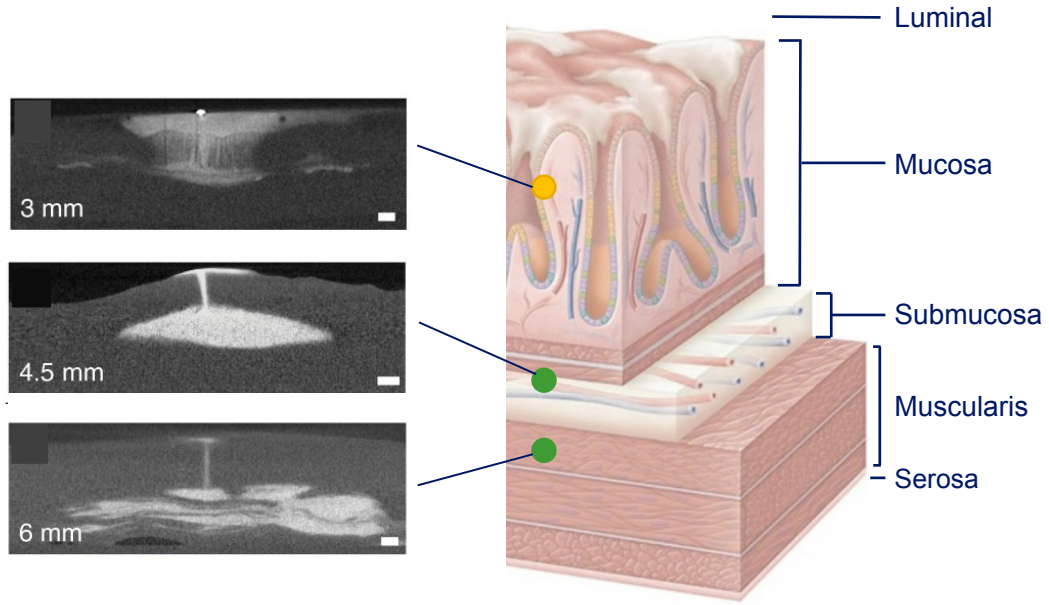




Staged and sequence controlled multi-spring actuation system that injects a hypodermic needle beneath the gastric mucosa and, thereupon, delivers 80 µl of liquid drug formulation into the submucosal space.

Optimal needle penetration depth secures delivery to the stomach submucosa

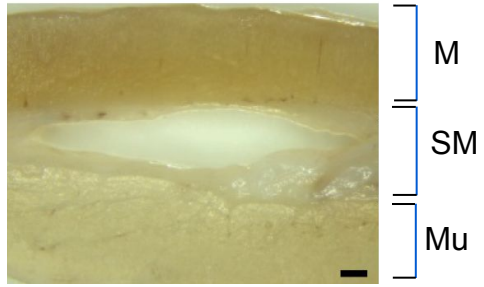
Consistent delivery of entire dose into sub-mucosa

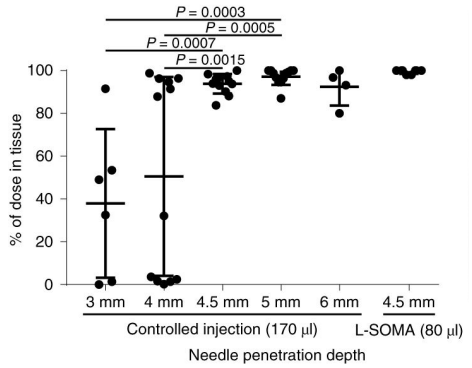


Extending the needle insertion depth to 4.5 mm or greater, the device consistently delivered the entire liquid dose into the tissue

Sub-mucosal depot injection achieved

Microtome image of fixed swine stomach tissue after an injection with the L-SOMA



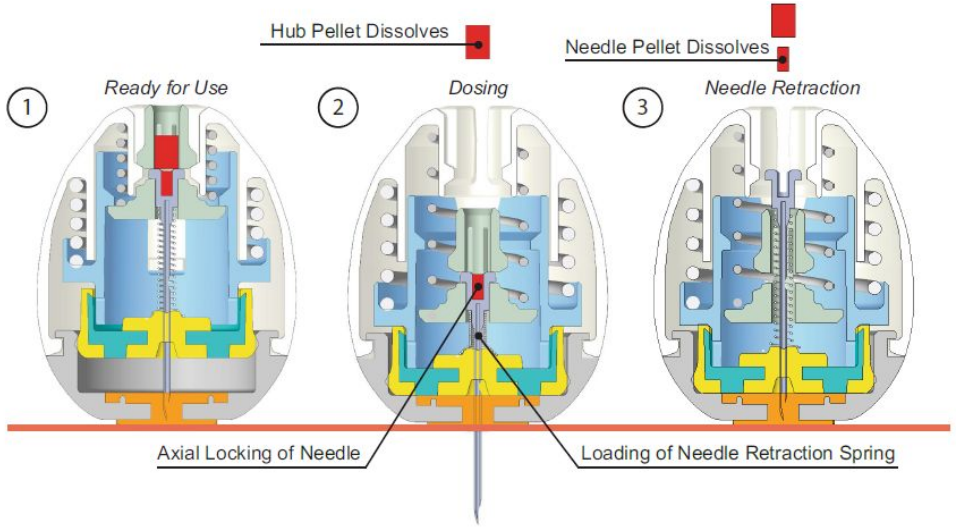


Percent of contrast dye that remained in tissue after injection calculated using 3D reconstructions of MicroCT images

Abramson A *et al*., Oral delivery of systemic monoclonal antibodies, peptides and small molecules using gastric auto-injectors. *Nat Biotechnol*. 2022; 40(1):103-109.

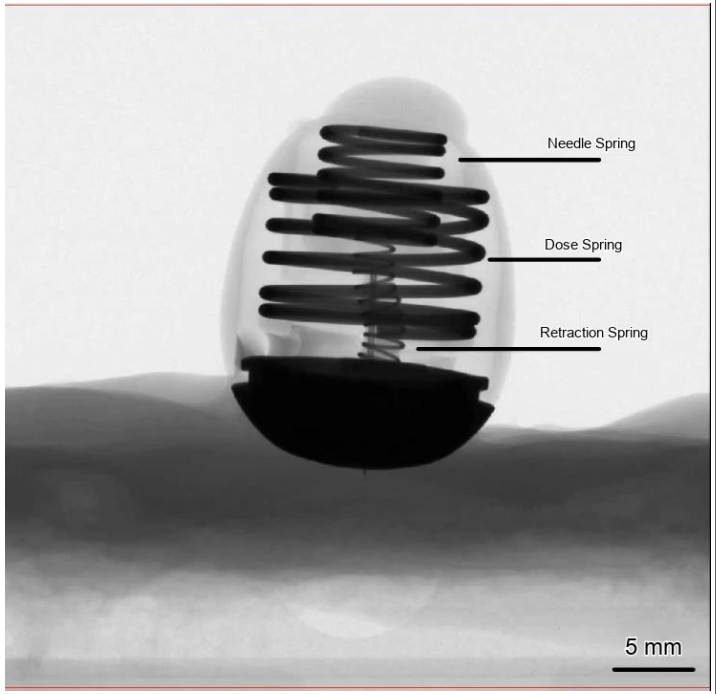
A retractable needle system for gastric injections

L-SOMA needle retraction mechanism design



The device first actuates after the hub pellet (red) dissolves and allows the latching mechanism at the top of the pill to release. The retraction spring, located axially around the needle shaft, compresses after the first stage of actuation due to the inherent movement of the needle during injection. The dissolution of the second pellet, which is exposed only after the first pellet dissolves, frees the spring to expand and draw the needle back into the capsule.

MicroCT of retractable L-SOMA



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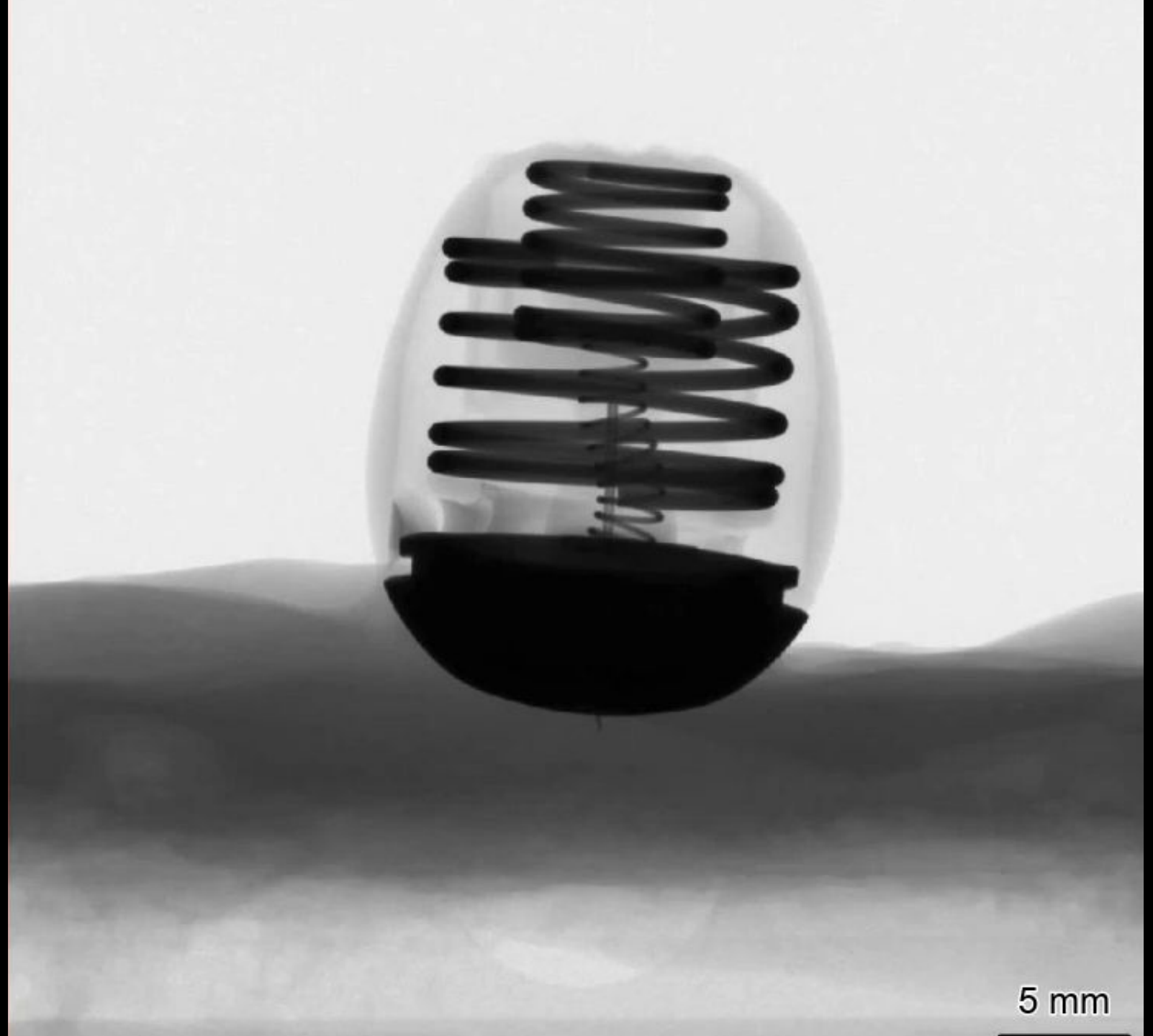
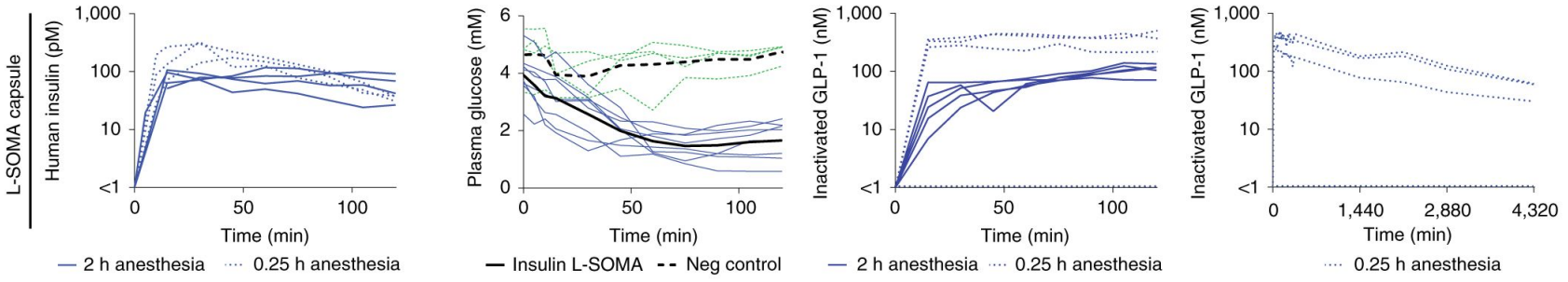
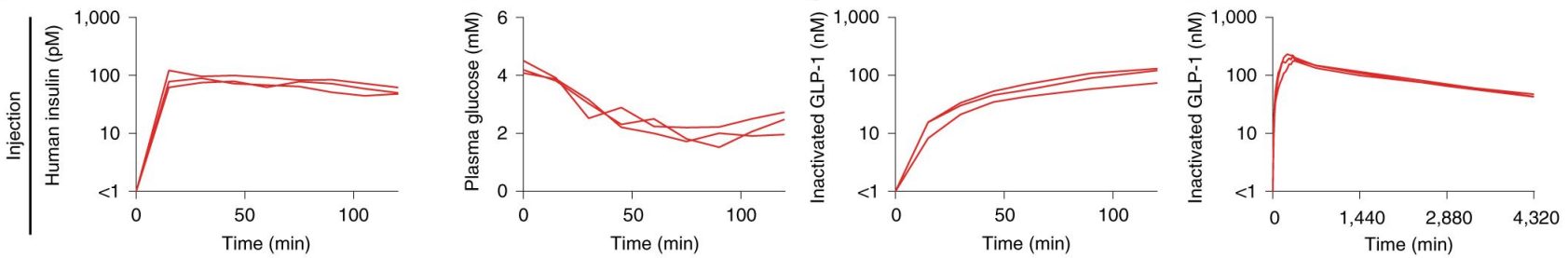


Similar exposures for insulin and GLP-1 dosed using L-SOMA or subcutaneously

L-SOMA administration



Subcutaneous administration



- Plasma drug exposure observed **within 15 min** after L-SOMA administration
- Insulin-dosed swine experienced **immediate hypoglycemic onset** in both groups
- Swine dosed with inactivated GLP-1 in both groups displayed measurable plasma drug levels for >3 d after dosing, consistent with its half-life
- **Bioavailabilities** of **51%** and **78%** for insulin and GLP-1 dosed by L-SOMA

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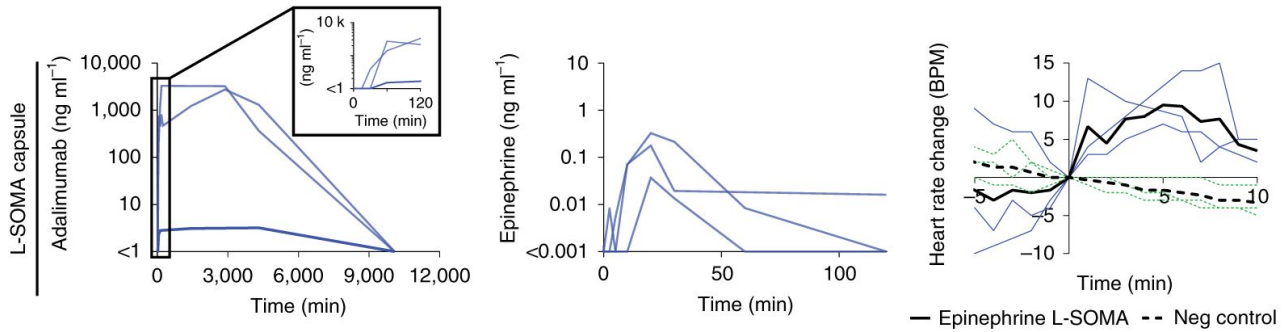
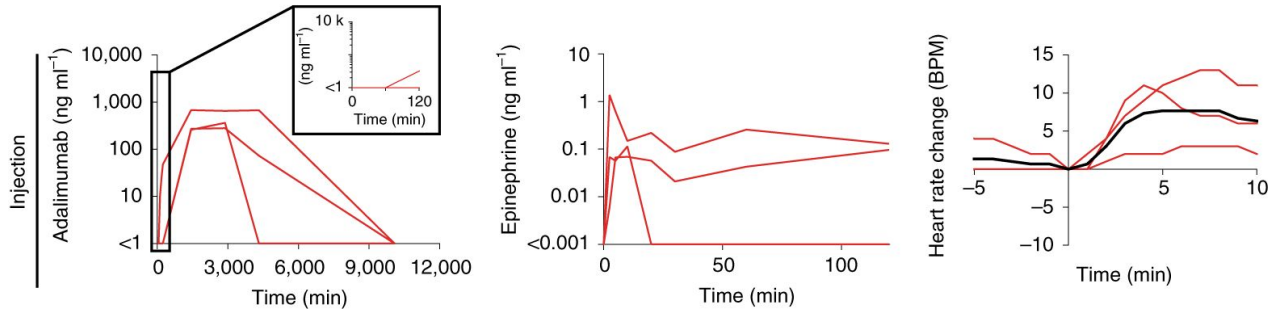
L-SOMA delivers clinically relevant doses of adalimumab and epinephrine in swine

L-SOMA administration



Subcutaneous or intramuscular administration



L-SOMA devices were placed into swine stomachs using an endoscope and allowed to independently actuate. **Actuation** occurred within **4:05 ± 1:17 min**

Exposure profiles were **completely similar** between L-SOMA dosing and intramuscular or subcutaneous dosing for epinephrine (small molecule) and adalimumab (monoclonal antibody)

Adalimumab was observed in the serum within 1 h after L-SOMA administration. Epinephrine-dosed swine experienced a rapid rise in heart rate and blood glucose in both the injection and L-SOMA groups

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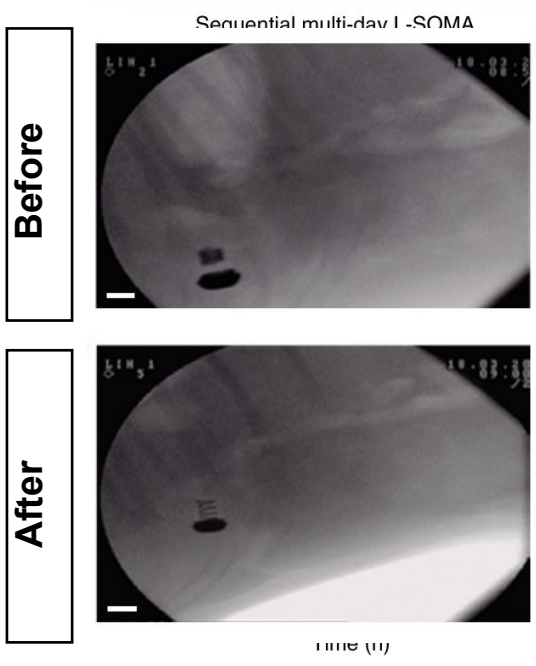
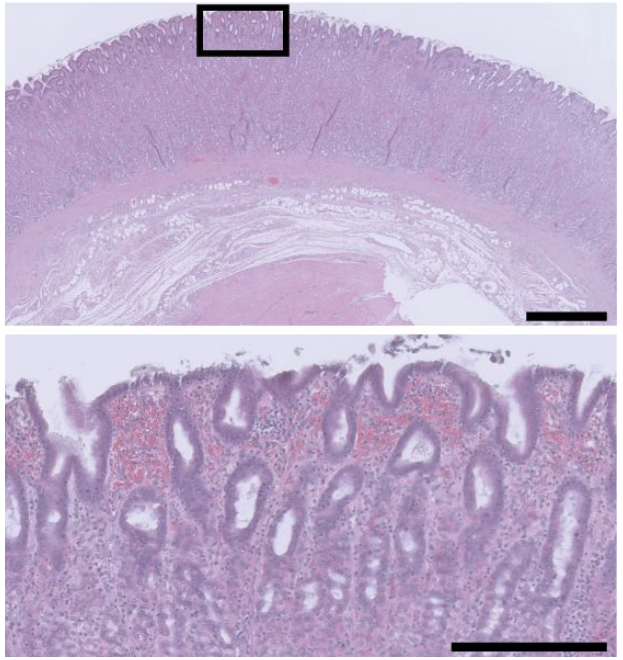
Multi-day dosing using L-SOMA is safe and feasible



Swine dosed with insulin-loaded L-SOMA devices on three subsequent days showed repeated and **consistent systemic uptake** and subsequent plasma glucose drops over the dosing period

Dosing in **awake dogs** demonstrated that the capsule reached the stomach, activated and subsequently passed completely through the gastrointestinal tract

Multi-day dosing experiment supports the **translational potential** of the system



Minimal acute superficial haemorrhage with intact epithelial lining. This area was likely the location of the injection that occurred 6 h before euthanasia.

No other macroscopic abnormalities were found in the stomach from devices fired more than 1 d before euthanasia

Findings suggest that some L-SOMA devices might generate **minimal tissue damage** that heals rapidly

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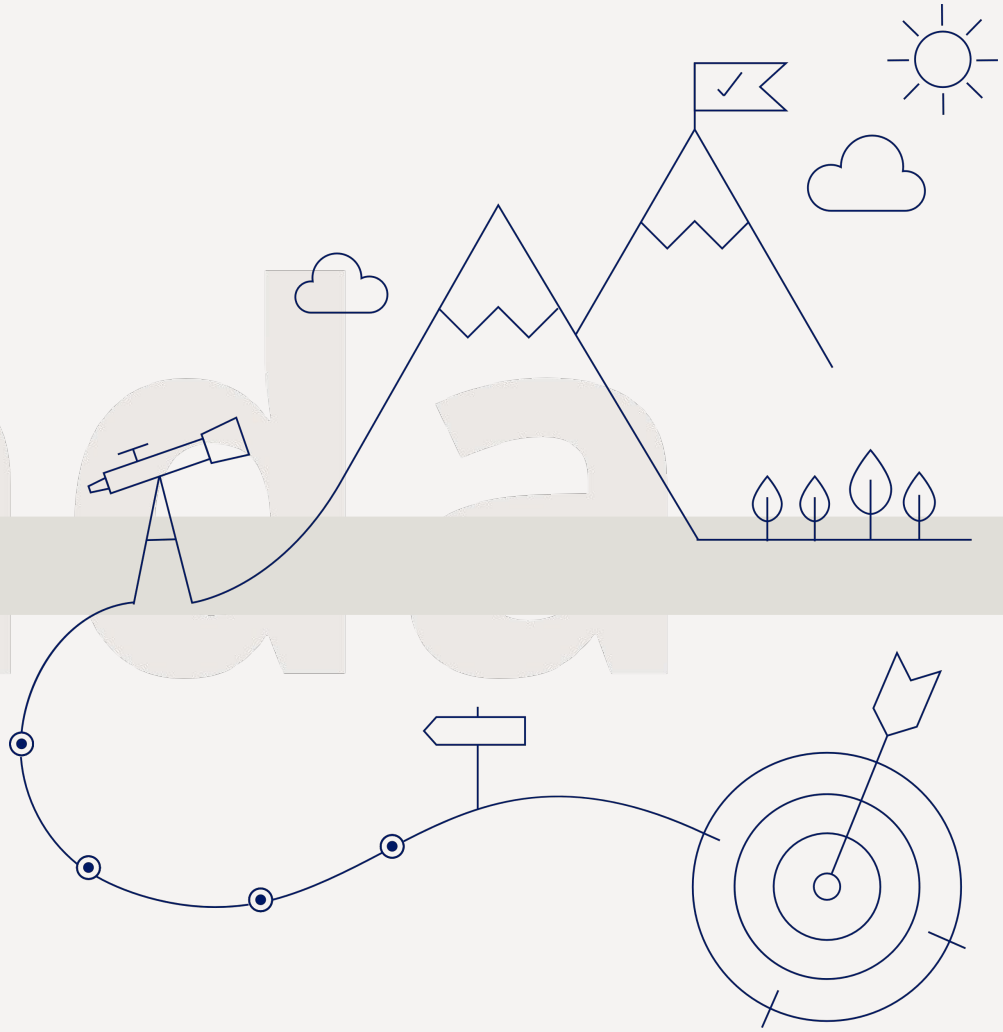

Conclusions

- **Biologics** are challenging compounds and typically require engineering to optimize their *in vivo* performance
- **Oral bioavailability** is a key parameter which determines the viability of investigational oral biologics as drug products
- **Oral ingestible devices** represent the next generation of oral delivery technologies and can potentially realise bioavailabilities on par with sub-cutaneous administration
- **L-SOMA** delivers up to 4-mg doses of a bioavailable drug with the rapid pharmacokinetics of an injection, reaching an absolute bioavailability of up to 80% and a maximum plasma drug concentration within 30 min after dosing
- Broader availability of oral-based biologics can afford **greater convenience** to patients with serious chronic diseases and help achieve **better outcomes**