Semaglutide with salcaprozate sodium (SNAC) – ICH M13A food effect

Case Study

Nuno Silva

Faculty of Pharmacy
Lisbon University

Objectives & key questions

- Clinical pharmacology of Rybelsus (semaglutide + SNAC)
- How SNAC and semaglutide work together to enable absorption
- Water volume and food effects restrictions
- Placing the product in ICH M13A and Q&A 2.4 and 2.5
- Conclusion: fasting+fed in the EU? Or fasting-only with justification?

What is Rybelsus?

- Tablet formulation with peptide drug semaglutide (GLP-1 receptor agonist)
- Co-formulated with absorption enhancer salcaprozate sodium (SNAC)
- Goal: allow a peptide to be absorbed from the stomach after oral dosing
- Submitted to FDA as NDA and to EMA as centralized procedure in March/April 2019

What is semaglutide?

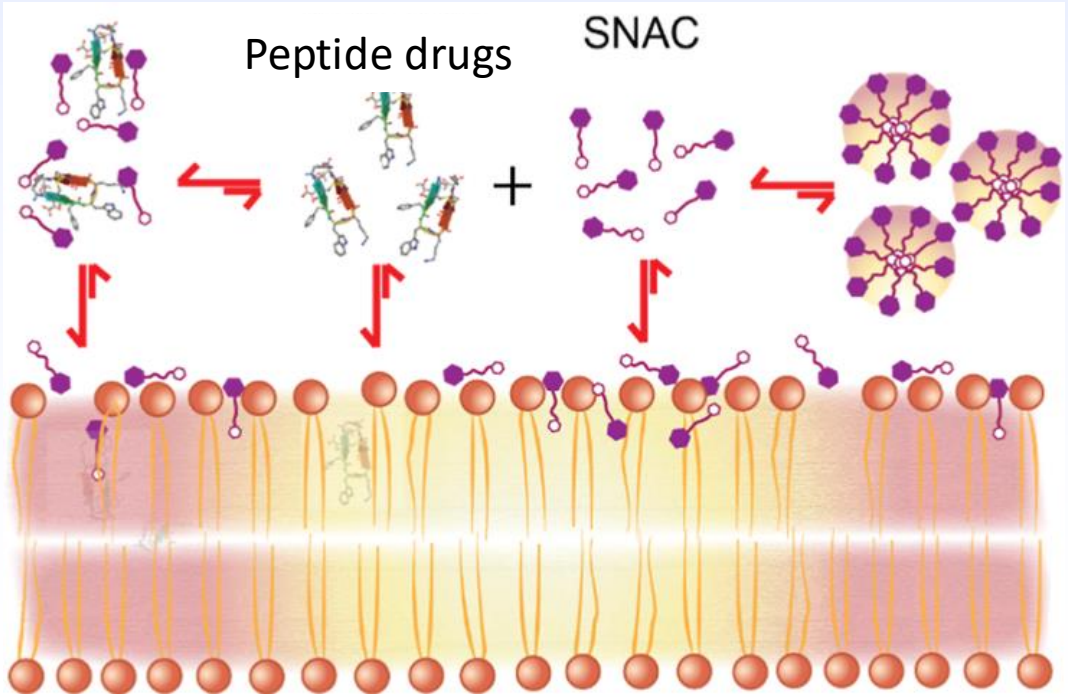
- Is a recombinant long-acting analogue of human glucagon-like peptide-1 (GLP-1) that selectively binds to and activates the GLP-1 receptor

- GLP-1 is an endogenous incretin hormone that stimulates insulin secretion and inhibits glucagon secretion from the pancreatic islets in a glucose-dependent manner

- Semaglutide exhibits a 94% sequence homology to human GLP-1, but with modifications that increase its binding to albumin and turns more resistant to degradation by dipeptidyl peptidase-4, resulting in an extended half-life of approximately 1 week

What is SNAC?

- Included in dietary supplements (Vitamin B12)
- Is a small fatty-acid-derivate absorption enhancer



Adapted from: Mol. Pharmaceutics 2025, 22, 459−473

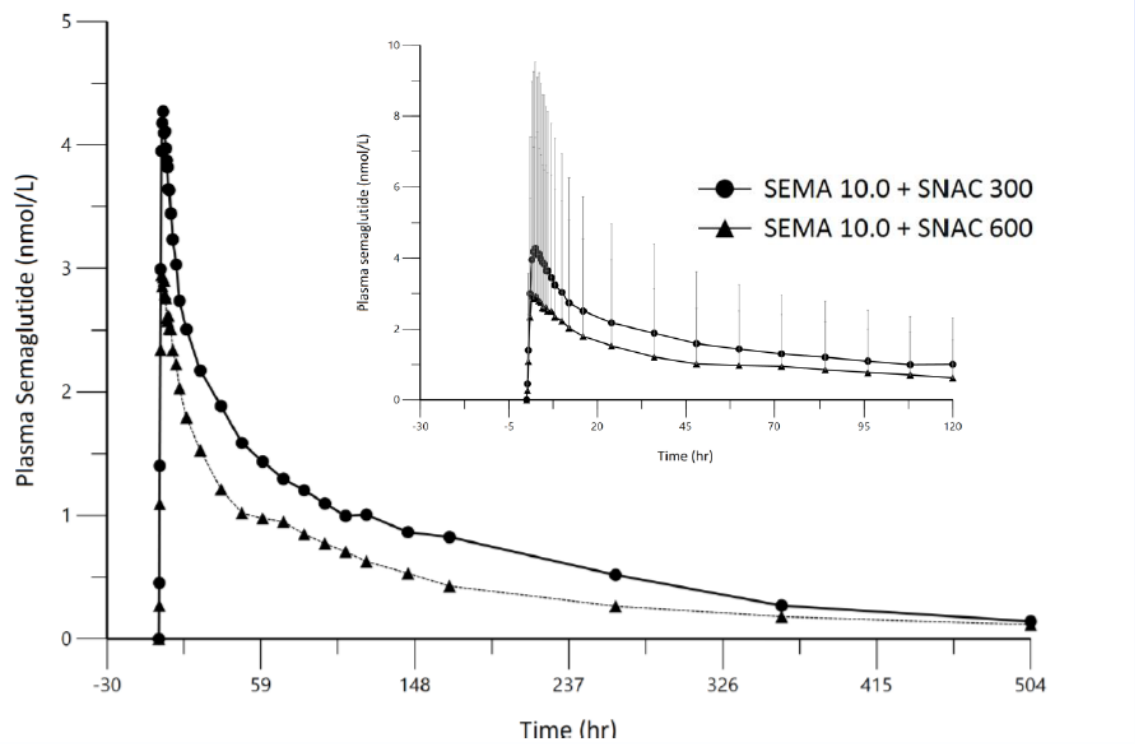
What is SNAC?

- *In vitro* results indicate:
  - ✓ A ~7-fold increase in the apparent permeability (P_{app}) of semaglutide was seen with 80 mM SNAC as compared to no SNAC
  - ✓ The effects on semaglutide P_{app} were transient
  - ✓ Presence of SNAC shift in the oligomeric state of semaglutide towards its monomeric form, favoring absorption
  - ✓ Incubation of oral semaglutide tablets containing SNAC in small volumes (1-30 mL) of simulated human gastric fluid (SGF) revealed that SNAC increased the pH of SGF from acidic to neutral within 5-15 min

How SNAC empowers semaglutide oral absorption?

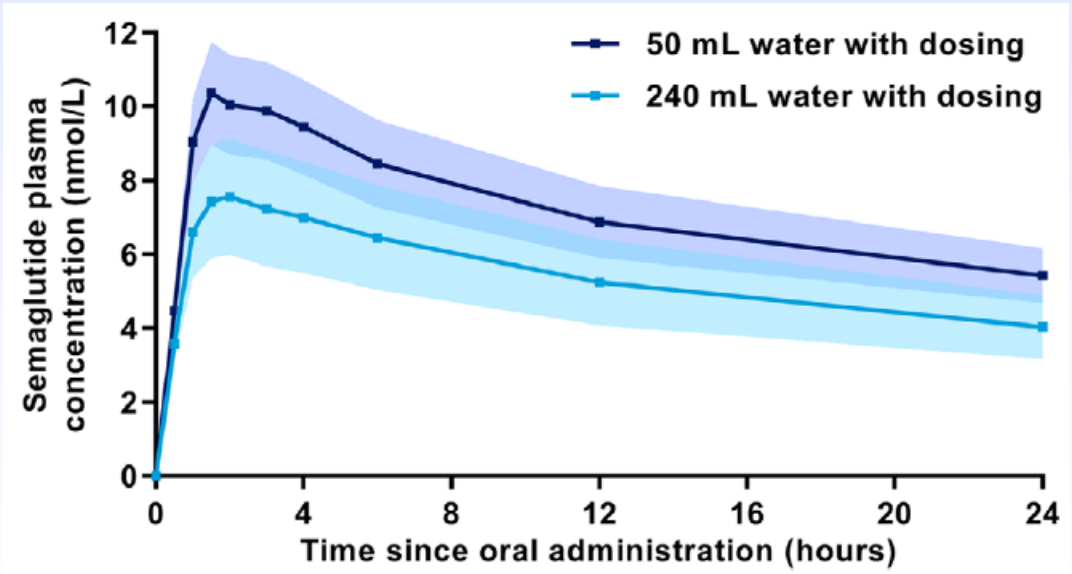
- Local protection in stomach
  - ✓ SNAC creates a brief high-pH micro-environment under the tablet (buffering action)
  - ✓ This protects semaglutide from acid/enzymes
- Increase temporarily transcellular permeability in gastric cells
- Does not modify semaglutide biological activity
- A fixed amount of 300 mg SNAC is used in all strengths, based on clinical studies

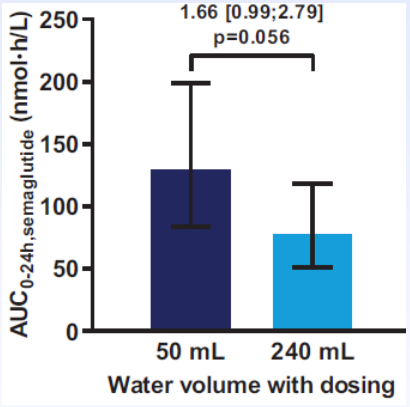
SNAC dose selection to optimize semaglutide absorption

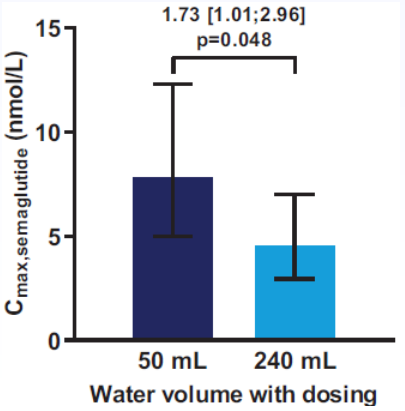


Source: Rybelsus FDA Clinical Pharmacology Review (Study 3691)

Effect of water volume in the pharmacokinetics of semagludide

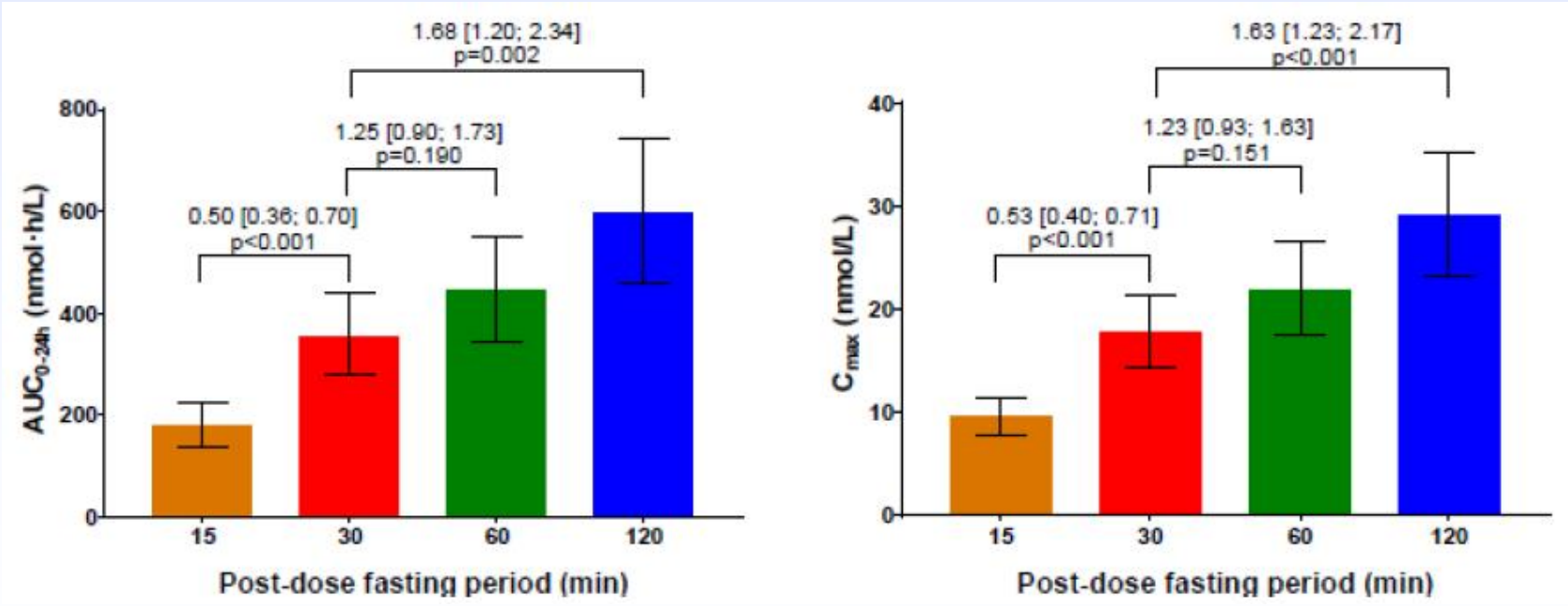






Source: Clin Pharmacol Drug Dev. 2021 May;10(5):453-462

Effect of post-dose fasting time in the pharmacokinetics of semagludide



Source: Rybelsus FDA Clinical Pharmacology Review (Study 3794)

How to take Rybelsus?

Rybelsus is a tablet for once-daily oral use.

- ✓ This medicinal product should be taken on an empty stomach after a recommended fasting period of at least 8 hours
- ✓ It should be swallowed whole with a sip of water (up to half a glass of water equivalent to 120 mL). Tablets should not be split, crushed or chewed, as it is not known whether this impacts absorption of semaglutide
- ✓ Patients should wait at least 30 minutes before eating, drinking or taking other oral medicinal products. Waiting less than 30 minutes decreases the absorption of semaglutide

Source: Rybelsus SmPC (EMA)

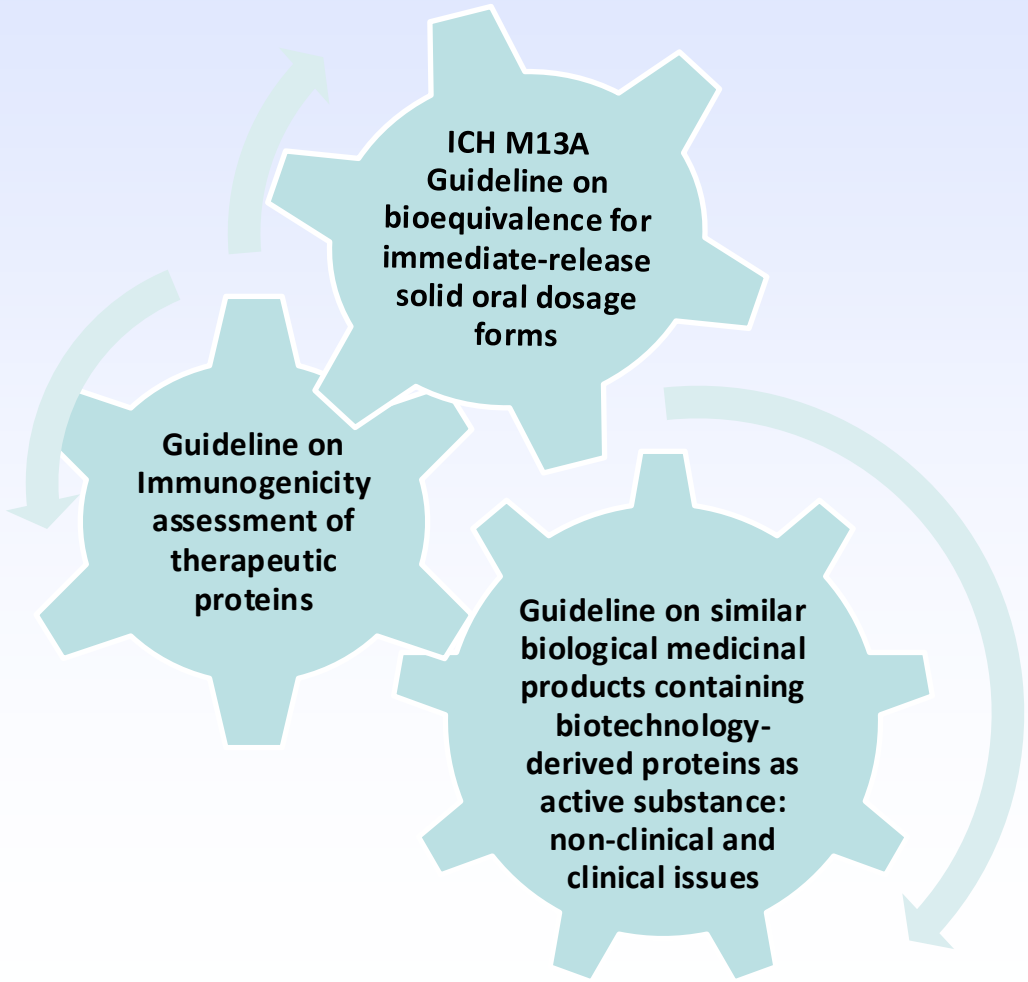
Food effect (what actually happens)

- In a food interaction study, semaglutide exposure is very low or negligent (concentrations <LOQ) when administered with 240 mL of water, 30 min after a high-fat meal
  - ✓ Food and excess water dilute SNAC and semaglutide
  - ✓ Harder to build the local gradient needed for protection and absorption
- Food does not affect SNAC exposure

Main pharmacokinetic properties of oral semaglutide

- Very low oral bioavailability (~0.4–1%)
- t_{max} ~1 hour
- Highly albumin-bound (>99%); small apparent V_d (~8 L)
- Elimination half-life ~1 week
- SNAC: fast absorption, no accumulation with daily dosing

Regulatory framework for oral semaglutide generics



Risk classification under ICH M13A

- Definition (M13A §2.1.5): High-risk products include complex/specialised technologies
  - e.g., lipid-based, nanotech, solid dispersions… and other specialised technologies to manage food/gastric pH

- Oral semaglutide case
  - Uses SNAC to modify gastric micro-environment and permeability (specialized tech)
  - Marked, formulation-dependent sensitivity to GI conditions (meal, water volume, co-ingested tablets)

Strong scientific basis to treat as HIGH-RISK ⇨ **BE studies on Fasting and Fed condition required**

What HIGH-RISK implies (ICH M13A Q&A)

- Q&A 2.4 (Why fasting & fed?):
  - Formulation/manufacturing differences can interact with variable GI conditions affecting the pharmacokinetics of low soluble drug substances
  - A single condition (fasting or fed alone) may miss inequivalence

- Q&A 2.5 (Even if reference product label says fasting-only?):
  - Yes - still need to do both fasting and fed to cover real-world GI variability

"As there is substantial variability in GI conditions following different meals and there can be significant variability in the degree to which patients are truly in the fasting state when drug products are administered, it is not possible to assess the potential differences in performance of a high-risk product under fasting or fed conditions alone."

Semaglutide is classified as BCS class 4 in FDA's product quality review

The US divergence (FDA PSG for Rybelsus)

- Draft PSG (2019/2021 updates) recommends FASTING-ONLY BE (single-dose)

- Rationale in practice
  - Label mandates fasting; fed exposure often below LLOQ → fed BE impractical and clinically irrelevant for intended use

- Result: Practical ANDA pathway avoids fed study—contrast with ICH M13A's risk-based two-study expectation

Alternative path to discuss with EMA (fasting study only)

- Seek scientific advice proposing FASTING-ONLY for this product (EMA engagement)

- Scientific rationale to assemble
  - Mechanistic: stomach-only absorption via SNAC; fed decreases exposure to near-zero for both products
  - Tight Q1/Q2 similarity including SNAC; relevant Q3 tests

- Could lead to an EMA product-specific guidance for oral semaglutide tablets

Important caveat - EU pathway selection

- Semaglutide is rDNA-derived (biological). In the EU this typically triggers the BIOSIMILAR, not generic, pathway.
  - the BE package becomes part of a broader biosimilarity exercise
  - Plan early classification dialogue; adjust program scope (comparative PK/PD, immunogenicity) accordingly

- BE conclusions still apply to the PK comparability piece, but dossier/legal basis may differ