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Metabolism of somapacitan, a long-acting growth hormone derivative, in human subjects

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Objectives

Primary objective:

- To investigate the absorption, metabolism and excretion of tritium [^{3}H]-labelled somapacitan after a single s.c. injection in healthy male subjects.

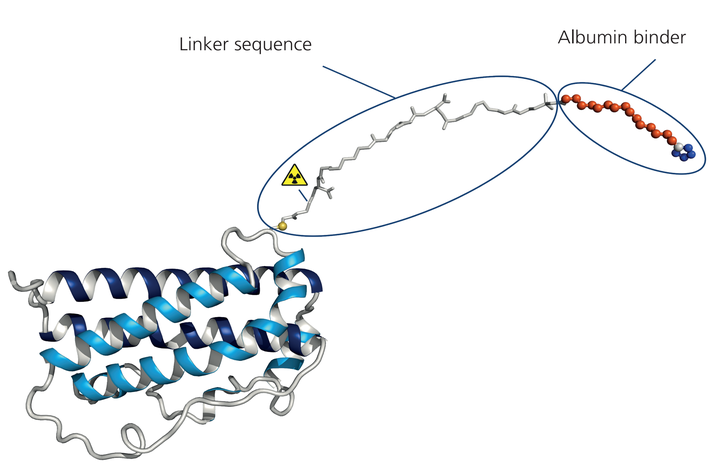
Secondary objectives:

- To assess the pharmacokinetics (PK) of somapacitan and [^{3}H]-labelled somapacitan-related materials.
- To determine the metabolite profile of somapacitan and the structure of the main metabolites in plasma and urine from healthy human subjects.

Introduction

- Daily injections of growth hormone (GH) replacement therapy for growth hormone deficiency (GHD) can be burdensome for affected patients and may compromise treatment adherence.[1]
- Somapacitan is a long-acting GH derivative currently in development to enable once-weekly dosing in adults and children with GHD,[2,3] designed with a well-established protraction method proven to extend half-life in insulin and glucagon-like peptide-1 therapies.
- Somapacitan consists of a human GH (22 kDa) with a single amino acid substitution Leu101Cys (not involved in binding to the GH receptor) and an albumin-binding moiety (1.3 kDa), which delays elimination and prolongs half-life (**Figure 1**).
- An absorption, metabolism, and excretion trial was carried out as part of the clinical development programme. The absorption, excretion and pharmacokinetic results were presented previously.[4]

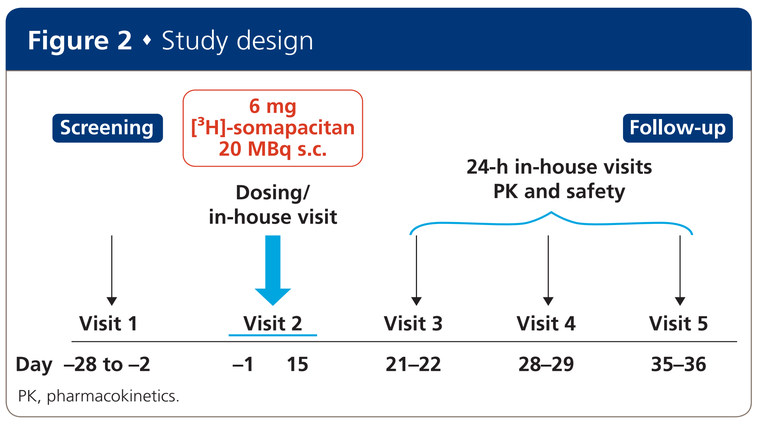
Figure 1 ♦ Structure of radiolabelled somapacitan with specified position of the tritium atoms, linker sequence and albumin binder



Methods

- This was a single-centre, open-label trial, with seven healthy male subjects aged 45–62 years with a body mass index 22.8–27.1 kg/m^2. Participants received a single s.c. dose of 6 mg somapacitan containing [^{3}H]-somapacitan (20 MBq) (**Figure 2**).
- Plasma collected at pre-dose, 8, 16, 32, 48, 96, 168, 336, and 504 h was pooled for each time point prior to metabolite profiling analysis, which was performed using high-performance liquid chromatography (HPLC) and radiochemical detection.
- Plasma concentrations of somapacitan and [^{3}H]-somapacitan-related materials were measured from pooled samples and the PK parameters were determined.
- The radioactive peaks of the most abundant plasma and urine metabolites were identified using HPLC fractionation.
- Fractions with individual plasma and urine components were analysed with Ultra Performance Liquid Chromatography -mass spectrometry and radioactivity monitoring to identify the structure of two plasma metabolites (M1 and M1B) and two urine metabolites (M4 and M5).
- Several attempts were made to identify peak P1. This was not possible owing to challenges with liquid chromatography separation of P1 from endogenous plasma compounds.

Figure 2 ♦ Study design



PK, pharmacokinetics.

Results

Metabolite profiling and structural identification of metabolites

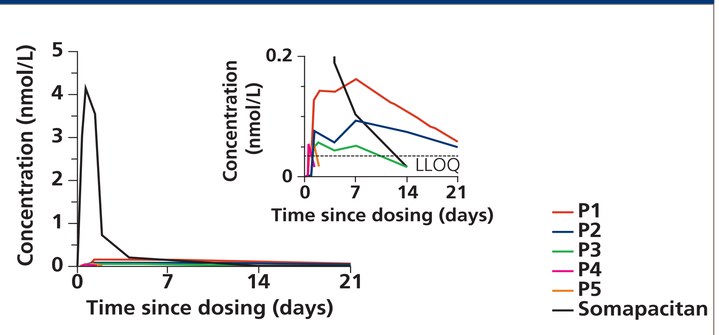
- The plasma metabolites were detected as radioactive HPLC peaks (P1, P2, P3, P4 and P5) and quantified.
- At time points after 7 days post-dosing, [^{3}H]-somapacitan-related material was the major component, indicating the presence of metabolite(s) with longer t½ than somapacitan (**Figure 3**).
- The area under the curve (AUC) of intact somapacitan accounted for 59% of the total AUC of all [^{3}H]-somapacitan-related material in plasma. P1 accounted for 21%, and M1 plus M1B for 12%. The remaining metabolites accounted for <3% of the total AUC (**Table 1**).
- Three abundant plasma (P1, M1 and M1B) and two abundant urine metabolites (M4 and M5) were identified.
- The urine metabolites, M4 and M5, accounted for 37% and 8%, respectively, of the dosed [^{3}H]-somapacitan-related material.
- M1, M1B, M4 and M5 were identified as metabolites formed after extensive degradation of the peptide backbone of somapacitan (**Figure 4**).
  - P1 was not structurally identified, but is likely to be identical to M4 or a conjugate thereof.
  - No intact somapacitan was found in excreta, suggesting full degradation of somapacitan prior to excretion of small residual fragments.

Table 1 ♦ Results of the non-compartmental analysis of somapacitan and metabolites in plasma

HPLC peak	*T_{max} (h)*	*C_{max} (nmol/L)**	*T_{last} (h)*	*C_{last} (nmol/L)**	*AUC_{last} (h x nmol/L)*	*AUC_{last} (% of total)**
P1	168	0.162	504	0.0596	57.8	21
P2 (M1 and M1B)	168	0.0941	504	0.0503	34.9	12
P3	48	0.0574	168	0.0523	7.22	2.6
P4	16	0.0552	16	0.0552	0.221	0.078
P5	32	0.0511	32	0.0511	0.920	0.33
Somapacitan	16	4.16	168	0.104	167	59
Total†	16	4.26	504	0.110	282	-

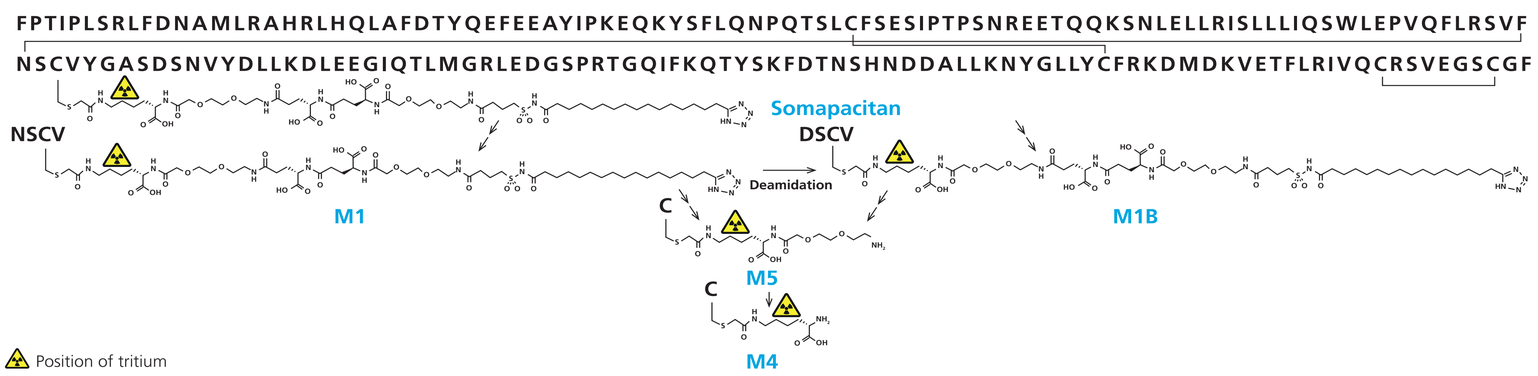
*Values are stated as number of significant digits; †[^{3}H]-somapacitan-related material.
AUC_{last}, last area under the curve; C_{last}, last concentration; C_{max}, the maximum concentration of the drug achieved in the plasma following dose administration; T_{last}, time of last non-zero concentration; T_{max}, the time taken to reach the maximum concentration.

Figure 3 ♦ Plasma concentration of somapacitan and metabolites vs time following single s.c. dosing of [^{3}H]-somapacitan in healthy (male) subjects



Insert represents a magnification of the low concentration part of the curve.
LLOQ, Lower Limit of Quantification.

Figure 4 ♦ Proposed metabolic pathways for plasma (M1, M1B) and urine (M4, M5) metabolites following s.c. dosing of somapacitan in healthy male subjects



The double arrows mark transformation pathways with several cleavages.

Conclusions

- Somapacitan was the principal component in human plasma up to 168 h after dosing and accounted for 59% of the total exposure of plasma components.
- Three abundant somapacitan plasma metabolites were identified (P1, M1 and M1B).
- In healthy subjects, somapacitan is extensively degraded prior to excretion of small residual fragments.

References

1. Christiansen *et al. Eur J Endocrinol* 2016;174:C1–8; 2. Rasmussen *et al. J Clin Endocrinol Metab* 2014;99:E1819–29; 3. Battelino *et al. Clin Endocrinol (Oxf)* 2017;87:350–8; 4. Rasmussen *et al.* Presented at ENDO 2018:SUN-569.

Conflict of interest disclosure

All authors are employees of Novo Nordisk A/S and own shares in the company.

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