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

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• Somapacitan is a long-acting GH derivative currently in clinical development.
• Daily injections of growth hormone (GH) replacement therapy can be cumbersome for affected patients and may compromise treatment adherence.
• Somapacitan is a long-acting GH derivative currently in development to enable once-weekly dosing in adults and for affected patients and may compromise treatment adherence.
• 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.

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.
• Somapacitan consists of a human GH (22 kDa) with a single and albumin binder specified position of the tritium atoms, linker sequence and a well-established development to enable once-weekly dosing in adults and for affected patients and may compromise treatment adherence.

Objectives

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

Secondary objectives:
• To assess the pharmacokinetics (PK) of somapacitan and [³H]-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.

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/m². Participants received one single s.c. dose of 6 mg somapacitan containing [³H]-somapacitan (20 MBq) (Figure 2).
• Plasma collected at pre-dose, 8, 16, 32, 48, 96, 168, and 336 h was pooled for each time point prior to metabolism profiling analysis, which was performed using high-performance liquid chromatography (HPLC) and radiochemical detection.
• Plasma concentrations of somapacitan and [³H]-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 with lower challenges with liquid chromatography separation of P1 from endogenous material.

Results

• The plasma metabolites were detected as radioactive HPLC peaks (P1, P2, P3, P4 and P5) and quantitated.
• At time points after 7 days post-dosing, [³H]-somapacitan-related material was the major component, indicating the presence of metabolites 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 [³H]-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 dose [³H]-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.

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


Conflicts of interest disclosure

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