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Nonclinical pharmacokinetic and pharmacodynamic characterisation of somapacitan: A reversible non-covalent albumin-binding growth hormone

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ABSTRACT

Objective: Somapacitan is an albumin-binding growth hormone derivative intended for once weekly administration, currently in clinical development for treatment of adult as well as juvenile GH deficiency. Nonclinical in vivo pharmacological characterisation of somapacitan was performed to support the clinical trials. Here we present the pharmacokinetic and pharmacodynamic effects of somapacitan in rats, minipigs, and cynomolgus monkeys.

Methods: Pharmacokinetic studies investigating exposure, absorption, clearance, and bioavailability after single intravenous (i.v.) and subcutaneous (s.c.) administration were performed in all species. A dose-response study with five dose levels and a multiple dose pharmacodynamic study with four once weekly doses was performed in hypophysectomised rats to evaluate the effect of somapacitan on growth and IGF-I production.

Results: Pharmacokinetic profiles indicated first order absorption from the subcutaneous tissue after s.c. injections for somapacitan in all three species. Apparent terminal half-lives were 5–6 h in rats, 10–12 h in minipigs, and 17–20 h in monkeys.

Somapacitan induced a dose-dependent growth in hypophysectomised rats ($p < 0.001$) and an increase in plasma IGF-I levels in rats ($p < 0.01$), minipigs ($p < 0.01$), and cynomolgus monkeys ($p < 0.05$) after single dose administration. Multiple once weekly dosing of somapacitan in hypophysectomised rats induced a step-wise increase in body weight with an initial linear phase the first 3–4 days in each dosing interval ($p < 0.001$).

Conclusion: The nonclinical pharmacokinetic and pharmacodynamic studies of somapacitan showed similar pharmacokinetic properties, with no absorption-limited elimination, increased clearance and increased and sustained levels of IGF-I in plasma for up to 10 days after a single dose administration in all three species.

Somapacitan induced a dose-dependent increase in body weight and IGF-I levels in hypophysectomised rats. Multiple dosing of somapacitan in hypophysectomised rats suggested a linear growth for the first 3–4 days in each weekly dosing interval, whereas daily hGH dosing showed linear growth for approximately two weeks before reaching a plateau level.

1. Introduction

Since the introduction of recombinant human growth hormone (hGH) in the mid-1980's, numerous paediatric and adult patients with hGH deficiency have received hGH replacement therapy with positive clinical outcomes. However, current hGH treatment implies frequent administration. This represents a burden for patients as well as for parents of children undergoing hGH treatment. Notably, it affects the overall treatment adherence [1–4] and has prompted a number of companies to explore and develop alternative treatment regiments primarily focused on reducing injection frequency [5,6].

Novo Nordisk is currently developing somapacitan for treating growth hormone deficiency in adults and children. Somapacitan is as a long-acting reversible non-covalent albumin-binding hGH derivative for once weekly clinical administration. The albumin binding moiety is covalently attached to growth hormone via a specific linker.

Abbreviations: hGH, human growth hormone; IGF-1, insulin-like growth factor 1; μCT scanning, micro computed tomography scanning

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Somapacitan is 99% identical to native growth hormone in terms of amino acid sequence and 95% identical in terms of molecular weight.

This paper presents the nonclinical pharmacokinetic and pharmacodynamic data of somapacitan conducted in rats, minipigs and cynomolgus monkeys. The pharmacokinetic studies were performed to investigate the exposure, absorption, clearance and bioavailability after single intravenous (i.v.) and subcutaneous (s.c.) administration. The pharmacodynamic studies were conducted in order to investigate the effect of once weekly administration of somapacitan for one or four weeks on growth, body composition and IGF-I induction in growth hormone deficient hypophysectomised rats. IGF-I production was also investigated in minipigs and cynomolgus monkeys after single dose administration of somapacitan.

Hypophysectomised rats are the golden standard animal model for studying growth hormone pharmacology. Minipigs were included to study the absorption of somapacitan from the subcutaneous tissue and cynomolgus monkeys were used due to the similar response of hGH as observed in humans [7], hence a more realistic reflection of somapacitans pharmacological potential in humans.

2. Materials and methods

2.1. Drug

Somapacitan and hGH were dissolved in buffer (Glycine 20 mg/mL, Mannitol 2 mg/mL, $NaHCO_3$ 2.4 mg/mL, pH 8.2). Relevant concentrations are described under the individual experiments.

2.2. Animals

The nonclinical characterisation of somapacitan was performed in normal and hypophysectomised Sprague Dawley rats, Göttingen minipigs and cynomolgus monkeys. All animal experiments in Denmark were conducted in accordance with the EU Directive 2010/63/EU for animal experiments, the Protection of Animals Act, the Act on Experiments on Animals and the Standard Operating Procedures for Experiments on Animals at BioAdvice A/S and Novo Nordisk A/S. The experiments were performed under the supervision and approval of the Danish Government Animal Experiments Inspectorate, and the Novo Nordisk Ethical Review Committee. The study at Covance, UK was performed in accordance with the EU Directive 2010/63/EU for animal experiments, The Animals (Scientific Procedures) Act and Covance Standard Operating Procedures and approved by the Novo Nordisk Ethical Review Committee.

Male normal and hypophysectomised Sprague Dawley rats, 5–6 weeks of age, were obtained from Charles River, Germany. The rats were housed in Macrolon Type IV cages with saw dust bedding and free access to standard rodent chow (Altromin) and tap water. During a two week acclimatisation period the rats were examined and weighed weekly in order to secure animal well-being. The rats were 7–8 weeks old and weighing approximately 250 g (normal rats) and 100 g (hypophysectomised rats) at the start of the study and group housed with 2–5 animals per cage in an air conditioned room providing a minimum of 8 air changes/h. The temperature in the room was set to 18–24 °C and the relative humidity to 30–70%. During the entire study a 12-h light (07.00–19.00) and 12-h dark cycle was maintained. At the start of the experiments each group of rats were randomly allocated to the respective treatment groups.

A cynomolgus monkey experiment was conducted at Covance Laboratories Ltd., Harrogate, England. Six healthy purpose bred male cynomolgus monkeys (*Macaca fascicularis*) were obtained from Bioculture, Mauritius and kept at Covance laboratories during the experiment. The animals were housed in an air conditioned room, providing a minimum of 10 air changes/h. The temperature and relative humidity ranges were 18–30 °C and 30–80% respectively. A 12 h light (07.00–19.00) and 12 h dark cycle was maintained during the experiment. The animals were housed in pens that conformed to the 'Code of practice for the housing and care of animals used in scientific procedures' (Home Office, London, 1989). Wood shavings and/or corn cob were used for bedding. Where possible, animals of the same group were housed in the same pen. Food was offered communally. Each animal was offered 100 g of SQC Mazuri Primate Diet (Special Diets Services Ltd., Witham) and a 25 g bonio biscuit (Spillers). Domestic quality drinking water was provided ad libitum via bottles. Subject to availability, the animals were given a daily supplement of diluted mixed fruit juice drink (Booker, Wellingborough) and one of the following: Fresh fruit, fresh vegetables, Forage mix (B & K Hull), Peanuts (B & K Hull), Raisins (B & K Hull), Sunflower seeds (B & K Hull), Bonio shapes (Stottards Harrogate). Whilst at the breeder premises all animals were tested for tuberculosis. On arrival, all animals were given a clinical inspection for ill health and tested for tuberculosis if necessary. On occasion and prior to allocation to the experiment, animals were bled for plasma sampling purposes. The animals were acclimatised to the study room for a period of at least two weeks. A veterinary inspection was performed before the start of dosing to ensure their suitability for the experiment. The animals were acclimatised to procedures, including sham dosing and any necessary restraint. Allocation into treatment groups was based, where possible, on existing social groupings. After allocation the mean body weight distribution between groups was checked. If unacceptable the animals were re-distributed whilst keeping social disruption to a minimum. The animals were individually identified by a subcutaneous electronic transponder/tattoo. Cages were appropriately identified with experiment information.

Göttingen minipigs were studied at BioAdvice A/S, Denmark. Eight male Göttingen minipigs were obtained from Ellegaard Göttingen Minipigs A/S, Denmark. An acclimatisation period of approximately 7 days was allowed. At the start of the acclimatisation period, the minipigs were about 5 months old and in the weight range of 10–12 kg. The animals were housed in an air conditioned room providing a minimum of 10 air changes/h. The temperature in the room was set to 21–23 °C and the relative humidity to 30–70%. A cycle of 12 h light (07.00–19.00) and 12 h darkness was maintained during the study. The animals were housed in a single pen with straw as bedding. All animals were fed with a commercially available minipig diet, "Altromin 9023" (Chr. Petersen A/S, DK-4100 Ringsted, Denmark) 150 g per animal twice daily. The animals were given pieces of apple by hand and had plenty of straw for bedding and balls as environmental enrichment. The animals had free access to domestic quality drinking water. The animals were randomly allocated to two groups, each of four minipigs. Each animal was identified from the supplier by an individual number tagged to the pinna of one ear. In addition they were marked on the skin, using a fatty ink marker, with animal number in the study. Each pen was marked with experiment number, group number and animal numbers. The animals were weighed on arrival and on the day of dosing. Furthermore the animals were weighed weekly during the study.

2.3. Pharmacokinetic studies

Deconvolution analysis was applied for estimating the absorption rate and bioavailability of the s.c. administered somapacitan across the animals species using PCDON [8]. This is based on the following convolution equation:

$$C(t) = \int_0^t r(t-\tau)I(t)d\tau \quad (1)$$

where r(t) is the plasma concentration produced by an intravenous bolus input of unit amount, I(t) is the unknown subcutaneous systemic input rate and C(t) is the plasma concentration produced by the unknown subcutaneous systemic input rate. For the deconvolution analysis, C(t) is approximated by an interpolating spline function and the deconvolution used the analytical approach of Veng-Pedersen [8,9] and