Pharmacokinetic Modelling predicts native hGH levels following administration of a sustained-release prodrug, TransCon hGH, to children with GHD

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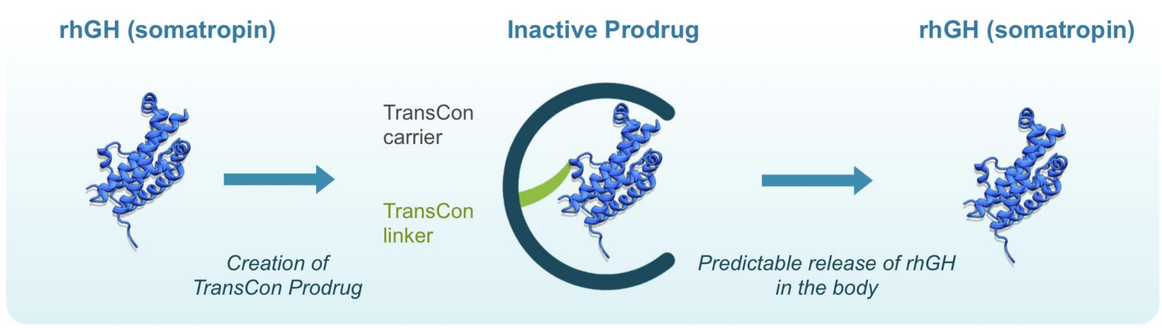
This study was sponsored by Ascendis Pharma A/S.

Background

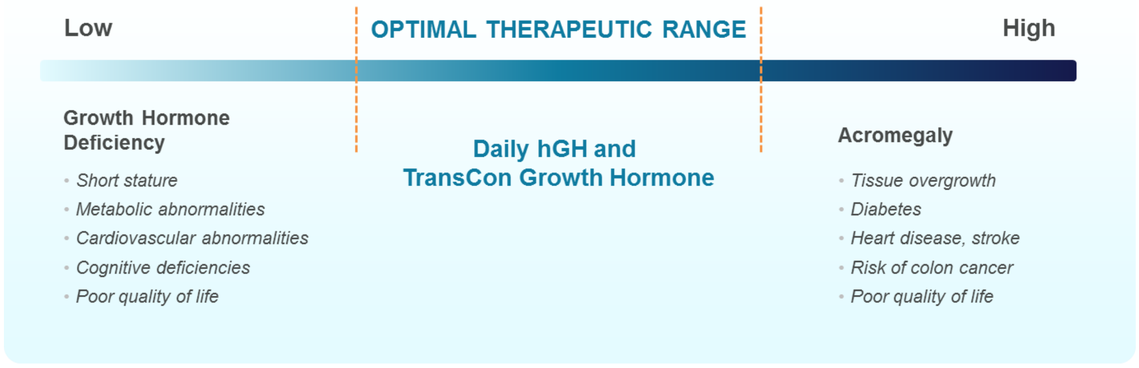
Ascendis Pharma is developing TransCon Growth Hormone, a once-weekly sustained-release prodrug of recombinant human growth hormone (hGH, somatropin) for the treatment of Growth Hormone Deficiency (GHD) in children and adults. hGH is transiently bound to the TransCon carrier molecule *via* the TransCon linker, and hGH is released in its native and unmodified form after administration through predictable hydrolysis of the TransCon linker.



The TransCon hGH prodrug consists of hGH transiently bound to a polyethylene glycol carrier molecule *via* a TransCon linker. The released hGH is unmodified, and designed to maintain the same mode of action and distribution in the body as endogenous hGH.

Objectives

A U-shaped relationship is reported for growth hormone's effect on the cardiovascular system, with both deficiency (GHD) and excess (acromegaly) being associated with increased morbidity[1].



TransCon hGH is designed as a sustained-release prodrug that avoids supraphysiological growth hormone levels in the blood following administration, while retaining efficacious drug levels throughout the dosing interval.

In the following, the construction and confirmation of a pharmacokinetic (PK) model used to design the optimal release profile of native hGH from the prodrug is described.

Design and Methods

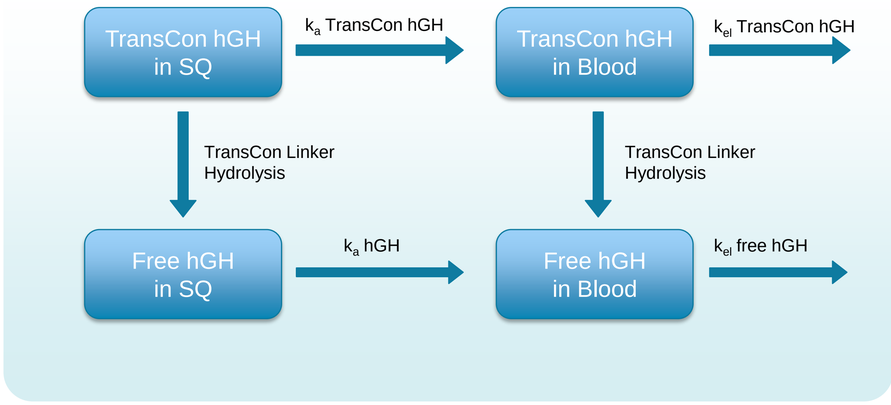
A PK model to predict serum concentrations of hGH following subcutaneous (SQ) administration of TransCon Growth Hormone was constructed.

First-order kinetics for TransCon linker release, absorption from the injection site and elimination of hGH and TransCon hGH were used to construct the model.

Pharmacokinetic parameters for hGH (somatropin) were obtained from the literature. Pharmacokinetic parameters for TransCon hGH and linker release rate were estimated and subsequently confirmed by *in vitro* and *in vivo* experiments (data on file; Ascendis Pharma).

Confirmation of the model was obtained by comparing predicted hGH levels with the PK profile of released native hGH in children with growth hormone deficiency (n=53) (NCT01947907).

PK Model



Pharmacokinetic parameters for hGH	
$T_{½}$ Linker Hydrolysis	92 hours
K_a hGH	0.198 hours^{-1}
K_{el} free hGH	1.7 hours^{-1}
V_D hGH	0.063 L/kg

Results

In pediatric patients with growth hormone deficiency the measured serum concentrations of released hGH were well predicted by the PK model.

The model enabled the design of a sustained-release prodrug of growth hormone, providing safe and efficacious hGH concentrations in the body, at maximum and overall exposure comparable to those observed with daily hGH administered at the same cumulative weekly dosage.

The model was successfully used to design the ideal release profile for unmodified hGH from TransCon Growth Hormone.

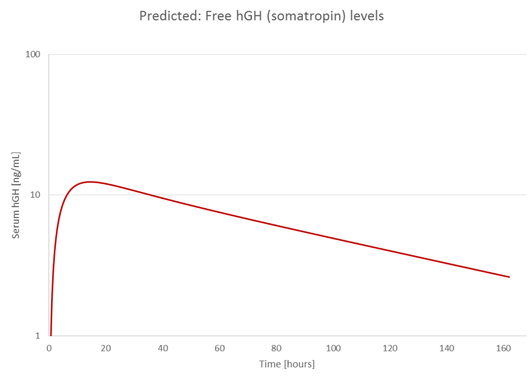


Figure 2: Predicted hGH (somatropin) serum levels for TransCon hGH (0.21 mg hGH/kg/week)

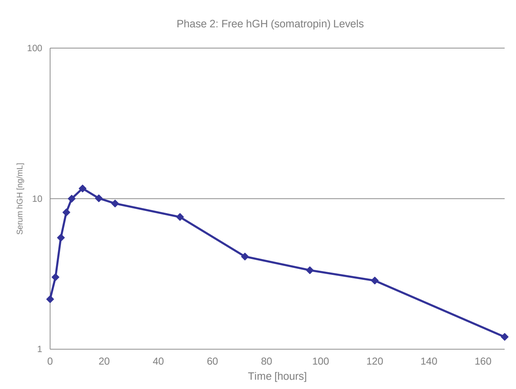


Figure 3: Actual hGH serum levels (mean) measured in GHD Children for TransCon hGH (0.21 mg hGH/kg/week; n=13)

Conclusion

The PK model accurately predicts serum levels of native hGH in the clinical setting, and can be used to predict hGH (somatropin) exposure in patients.

The PK model enabled design a sustained-release growth hormone that avoids high peak exposure (C_{max}) of hGH and IGF-1 to prevent acromegalic-type cardiomyopathies that may be associated with persistent hGH overexposure

TransCon Growth Hormone has the potential to offer patients requiring growth hormone therapy a once-weekly alternative to daily injections, designed to maintain the same safe and efficacious growth hormone and IGF-1 levels in the body as daily hGH.

The completed clinical studies support Phase 3 development with TransCon hGH – a Phase 3 study in GHD, the heiGHt Trial was recently initiated.

[1] Lombardi et al. Is growth hormone bad for your heart? Cardiovascular impact of GH deficiency and of acromegaly. Journal of Endocrinology, 1997, 155, S33-37

Disclosure Statement (Conflicts of interest): KS, MB, EDC, DG, TW are employees and shareholders of Ascendis Pharma