

Pediatric Phase 2 Data Demonstrate That TransCon hGH Has An Anti-hGH Immunogenic Profile That is Comparable to Daily hGH

David Gilfoyle¹, PhD; Susanne Pihl¹; Pierre Chatelain², MD; Michael Beckert¹, MD

¹Ascendis Pharma A/S, Hellerup, Denmark; ²Div. Endocrinologie Pédiatrique – Hôpital Mere-Enfant, University Claude Bernard Lyon 1, Lyon, France
This study was sponsored by Ascendis Pharma A/S

Background

TransCon Growth Hormone is a sustained-release prodrug of recombinant human Growth Hormone (hGH) that releases fully active, unmodified hGH into the blood compartment (Figure 1).

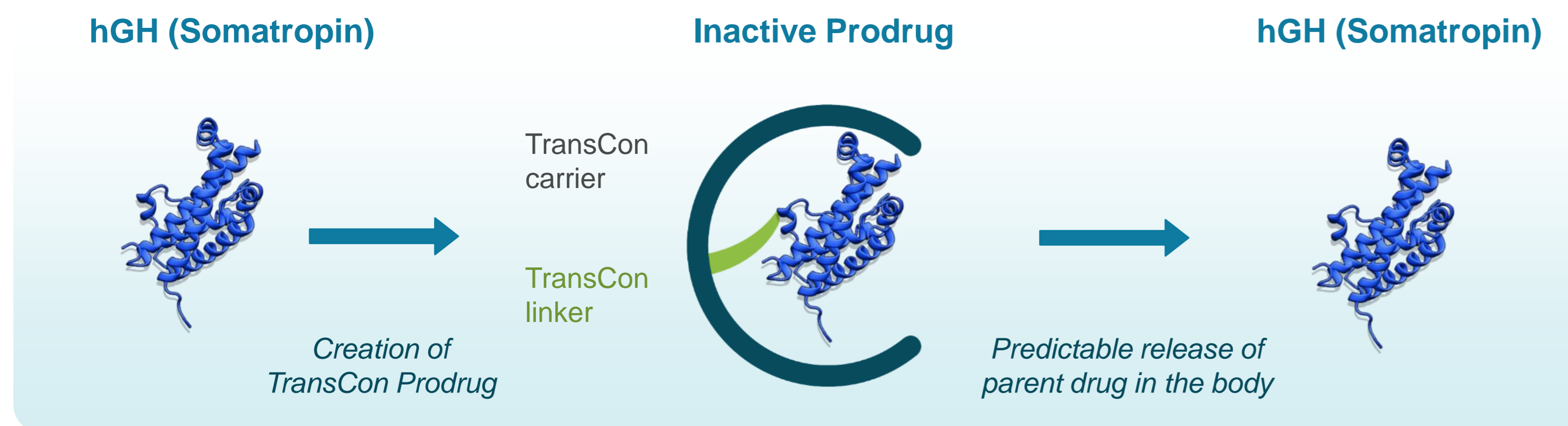


Figure 1: The TransCon hGH prodrug consists of hGH transiently bound to a polyethylene glycol carrier via a TransCon linker. The released hGH is unmodified, and designed to maintain the same mode of action and distribution in the body as daily hGH.

Daily administered hGH replacement therapy:

- Well tolerated, without significant anti-hGH immunogenicity
- Low titer, non-neutralizing anti-hGH antibodies detected in 8% (7 of 87) of pediatric Growth Hormone Deficient (GHD) subjects treated with Genotropin [1]
- Patients with neutralizing anti-hGH antibodies, may not respond to hGH therapy, and may require long-term IGF-I therapy to facilitate growth
- New sustained-release therapies should maintain a comparable safety profile

TransCon hGH has been shown in a Phase 2 study in GHD children, to be safe and well tolerated, demonstrating an anti-hGH immunogenicity profile comparable to that reported for daily administered hGH.

Objectives

While permanent conjugation of carrier molecules to protein therapeutics has the potential to reduce immunogenicity through epitope shielding [2], the protein-carrier interface can also elicit unwanted immunogenicity [3].

TransCon hGH is designed to leverage the inherent low immunogenicity of recombinant hGH:

- In the prodrug form, the carrier shields both the protein and the protein-carrier interface
- Following release of unmodified hGH, the potentially immunogenic protein-carrier interface is removed

Sensitive anti-hGH binding and neutralizing antibody assays have been developed, validated and utilized to assess anti-hGH immunogenicity in a Phase 2 clinical study of GHD children and consequently support the TransCon hGH product concept.

Clinical Study Design

Pre-pubertal, treatment-naïve, children with GHD (53 treated patients) received:

- Weekly s.c. injections of TransCon hGH (0.14, 0.21 or 0.30 mg hGH/kg/week [n=12, 14 and 14, respectively]) or
- Daily s.c. injections of Genotropin® (0.21 mg hGH/kg/week [n=13])
- Six-month treatment period

Serum samples were collected and assessed for anti-hGH binding and, if appropriate, neutralizing antibodies at:

- Screening, pre-dose at Weeks 1, 5 and 13 and 1 week after the last dose (Week 27)

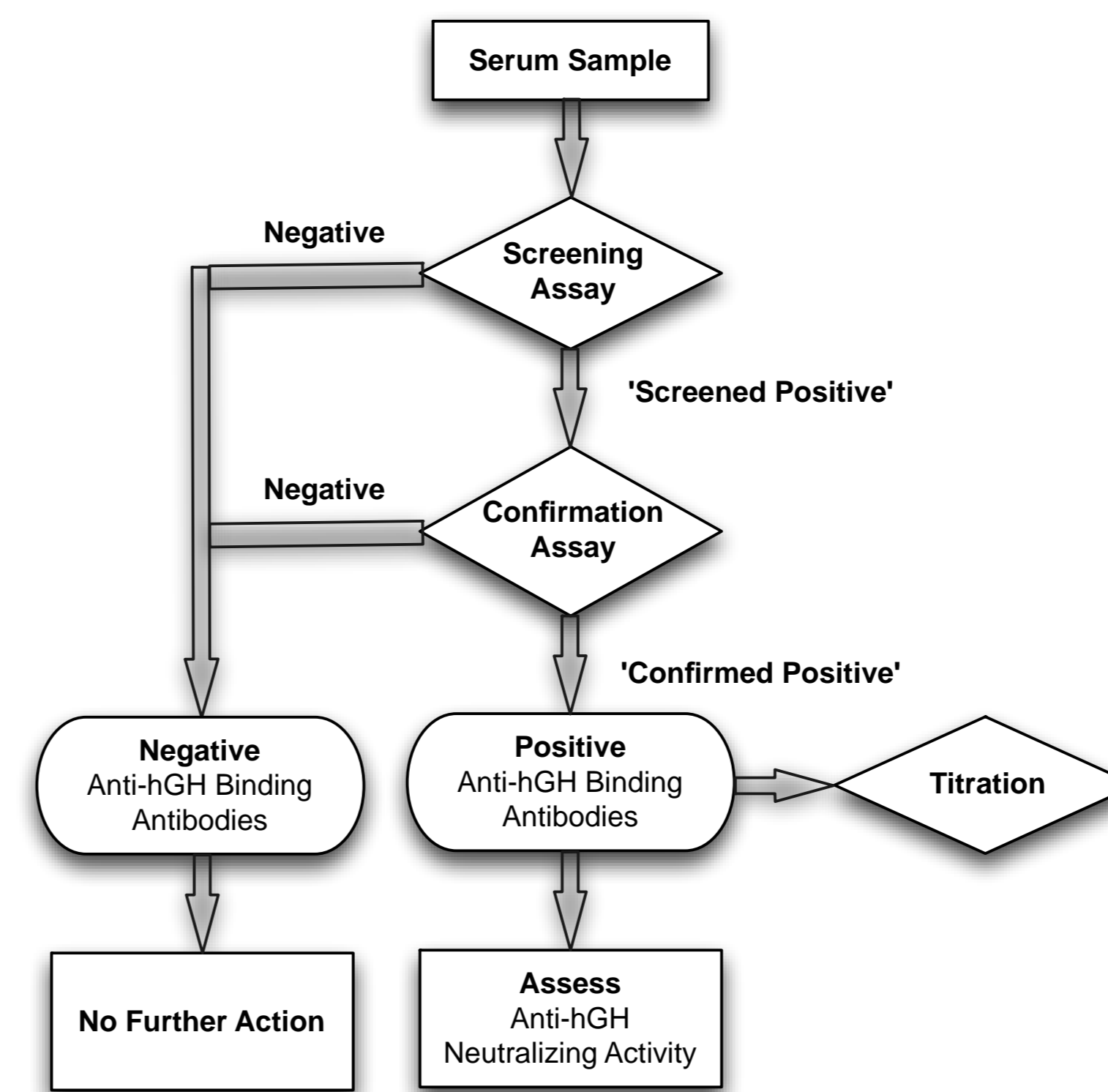
References:

- [1] Assessment Report, Somatropin Biopartners, European Medicines Agency, EMA/CHMP/229458/2013, 30 May 2013
- [2] FDA Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products, August 2014
- [3] Immunogenicity of Biopharmaceuticals, Weert, M. and Moller, E. H. (Eds.) ISBN: 978-0-387-75840-4 (2008)
- [4] FDA Guidance for Industry, Assay Development for Immunogenicity Testing of Therapeutic Proteins, December 2009 (Draft Guidance)
- [5] EMEA/CHMP Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins, April 2008
- [6] Mire-Sluis, A. R. et al, J Immunol Methods, 289, 1 – 16 (2004)
- [7] Shankar, G. et al, J. Pharm Biomed Anal, 48 (5), 1267-1281 (2008)
- [8] Gupta, S. et al, J. Pharm Biomed Anal, 55 (5), 878-888 (2011)

Immunogenicity Assessment

The potential presence of anti-hGH antibodies were assessed in serum using assays developed and validated in accordance with appropriate regulatory and industry guidelines [4 – 8, inclusive]:

Assay Parameter	Binding Assay	Neutralizing Assay
Assay Format	Bridging ELISA	Cell-based (Nb2-11) proliferation assay
Antibody Evaluation Stages	Screening, confirmation and titration (as appropriate)	Screening and confirmation (as appropriate)
Confirmation Principle	Immunodepletion with hGH	Alternative stimulus with prolactin
Isotype Detection	Any hGH-specific Ig isotype based on bridging assay format	IgG, IgM and IgA
Assay Cut-point Determination	Plate specific cut-point derived from normalization factors which assumed a 5% false positive rate (screening assay) based on assessment of 50 male and female children with GHD	
Sensitivity	< 500 ng/mL (based on a control antibody)	
Interference	Hemolysed and lipemic serum assessed	
Drug Tolerance	Assessed for TransCon hGH and hGH - confirmed acceptable at typical C _{trough} concentrations in the presence of currently observed treatment-emergent responses	



Serum samples were assessed in a multiple stage process initially to detect anti-hGH binding antibodies (refer to left figure). Samples confirmed positive for anti-hGH binding antibodies, and with an appropriate assay response were titrated by dilution with negative control serum until the assay response fell below the screening assay cut-point.

All samples confirmed positive for anti-hGH binding antibodies were assessed for anti-hGH neutralizing antibody activity.

Results – Immunogenicity

One subject (0.14 mg hGH/kg/week; 2.5% of subjects administered TransCon hGH [n=40]) developed a treatment-emergent anti-hGH immune response:

- Detected initially at Week 13
- Titration at Week 27 indicated the presence of very low levels of anti-hGH binding antibodies
- Antibodies confirmed to be non-neutralizing
- Drug levels at Week 27 were confirmed to be below levels considered to significantly interfere with the antibody assays

The presence of anti-hGH antibodies did not appear to impact:

- Pharmacokinetic (TransCon hGH and hGH) or pharmacodynamic (IGF-I) profiles compared to antibody negative subjects
- Annualized height velocity (19.0 cm, in the upper half of the treatment cohort)

Conclusion

TransCon hGH has demonstrated an immunogenicity profile in a pediatric population comparable to that observed with daily administered hGH:

- Confirms immunogenicity data for TransCon hGH in two Phase 1 clinical studies in healthy volunteers and a Phase 2 clinical study in adults with GHD (AGHD)
- Detection of anti-hGH binding antibodies at a frequency comparable to that observed for Genotropin® indicates that analytical methodology are fit for purpose to support future clinical development of TransCon hGH

Based on the promising clinical results, the global Phase 3 heiGHt Trial in GHD children has been initiated in mid-2016.

Disclosure Statement (Conflicts of Interest): Authors marked 1 above are employees of Ascendis Pharma A/S. The author marked 2 above was the Coordinating Investigator for Ascendis Clinical Study ACP-001_CT-004.

