# Meeting Unmet Needs: The Sustained-Release of Protein and Peptide Drugs

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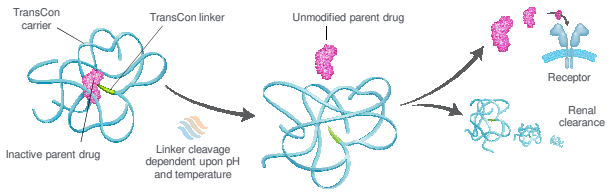
## BACKGROUND

Drug candidates often suffer from suboptimal properties such as poor bioavailability and inadequate circulation half-life due to rapid renal and/or receptor-mediated clearance. Additionally, optimal efficacy may be difficult to achieve due to poor compliance associated with frequent dosing or undesired side effects related to suboptimal pharmacokinetics.

Ascendis Pharma utilizes its sustained-release prodrug TransCon technology to address significant unmet medical needs. The TransCon technology enables transient conjugation of a parent drug to an inert carrier through a proprietary TransCon linker to create a prodrug. Following injection, the TransCon linker autohydrolyzes, releasing unmodified and fully active parent drug, while the carrier-linker moiety is cleared primarily by renal excretion.




## TRANSCON CARRIER AND LINKER

**The TransCon systemic carrier** is based on soluble polymers designed to extend circulation time of a given parent drug (in the form of a small molecule, peptide, or protein) through a shielding effect that minimizes renal excretion, proteolytic degradation, and receptor-mediated uptake of the parent drug. Systemic carrier systems are utilized in the current Ascendis Pharma endocrinology pipeline.

**The TransCon linker** connects a carrier to a parent drug and is designed to sustainably release the parent drug at a predictable rate dependent only on pH and temperature. The release of parent drug from the linker thus follows first-order kinetics and is independent of enzymatic contribution.

**The TransCon carrier-linker-drug** combination is a prodrug absorbed into the bloodstream as a circulating depot. As the linker autohydrolyzes, the parent drug is predictably released, with excellent in vitro/in vivo correlation and allowing for daily to more than 6 month administration frequencies. The released parent drug distributes and acts on its target site(s) while the hydrolyzed TransCon linker and carrier (by design, still bound together) undergo predominantly renal clearance.

Since parent drug is released in its unmodified form, its pharmacology is well established, with the same biodistribution, receptor affinity, and mode-of-action as the parent drug.

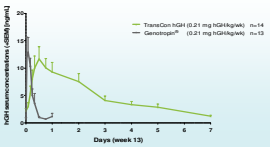
## TRANSCON GH RESULTS

The goal of TransCon GH is to provide human growth hormone (hGH; somatropin) over a 7-day period. Based on the pharmacokinetics (PK) of somatropin and a TransCon linker with a 4-day half life, a PK model was created and used to design a sustained release prodrug, TransCon GH.

**Figure 1: Predicted and actual mean GH serum levels in healthy volunteers administered TransCon GH**

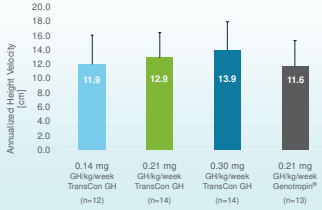
In a 6-month phase 2 study of a pediatric growth hormone deficient population (n=53), GH exposure (maximum concentration and area under the curve) after administration of TransCon GH or daily Genotropin at comparable weekly doses was similar.[1]

**Figure 2: GH serum concentration after weekly administration of TransCon GH or daily Genotropin.**



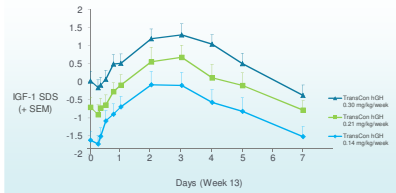

The phase 2 trial confirmed the safety, efficacy, tolerability, and lack of immunogenicity of weekly TransCon GH; an equivalent dose of TransCon GH to daily GH demonstrated slightly higher annualized height velocity (HV).

**Figure 3: Annualized height velocity in GHD pediatric subjects after 26 weeks of TransCon GH vs. Genotropin**




In addition to showing dose-dependent exposure and dose-dependent annualized HV, this phase 2 study demonstrated dose-dependent normalization of IGF-1 SDS, which remained within the normal range over 7 days.

**Figure 4: IGF-1 SDS after weekly administration of 3 different doses of TransCon GH.**




## APPLICATION OF THE TRANSCON TECHNOLOGY

The TransCon technology has been used to develop a pipeline of rare endocrinology disease programs.

| Product Candidate | Primary Indication | Development Stage | Dosing Frequency |
|---|---|---|---|
| TransCon GH | Growth hormone deficiency | Phase 3 | Weekly |
| TransCon PTH | Hypoparathyroidism | Phase 1 (completed) | Daily |
| TransCon CNP | Achondroplasia | Phase 1 | Weekly |

## CONCLUSION

The TransCon technology provides a unique carrier-linker-drug platform to sustainably deliver small molecules, peptides, or proteins in their native form. Using a soluble polymer, the rare endocrinology disease pipeline of systemic prodrugs are in clinical development for growth hormone deficiency, hypoparathyroidism, and achondroplasia.

These clinical studies of TransCon GH provide proof-of-concept for the TransCon platform, demonstrating a strong correlation between in-vitro linker half-life, nonclinical in vivo half-life, and clinical in vivo half-life. Further, the clinical safety, efficacy, tolerability, and lack of immunogenicity of the parent drug has been maintained.

Like TransCon GH, TransCon CNP provides CNP over 7 days with a single weekly injection.

In contrast, the optimal treatment of hypoparathyroidism is to provide a flat, infusion-like profile of PTH within the physiological range.[2] Thus, TransCon PTH utilizes daily dosing with 60-hour half-life linker, which was predicted by translation from preclinical data and has demonstrated the desired PK profile in a phase 1 study.

Given a large library of linkers and carriers and the ability to optimize drug-release rates to accommodate desirable dosing frequencies for both local and systemic administration, the technology may be applied to many therapeutic areas.

**REFERENCES:**
[1]Chatelain, P., et al., *A Randomized Phase 2 Study of Long-Acting TransCon GH vs Daily GH in Childhood GH Deficiency.* J Clin Endocrinol Metab, 2017. 102(5): p. 1673-1682.
[2]Winer, K.K., et al., *Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism.* J Clin Endocrinol Metab, 2012. **97**(2): p. 391-9.

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