TransCon Growth Hormone is designed as a once-weekly sustained-release prodrg of recombinant human growth hormone (hGH, somatropin) (Figure 1). Based on the inert TransCon prodrg technology unmodified native hGH is released with a C\text{max} and AUC comparable to daily therapy. TransCon Growth Hormone leverages the known pharmacology of daily hGH and is being developed for the treatment of Growth Hormone Deficiency (GHD) in children and adults.

### Objectives

The objective is to develop a safe and efficacious sustained-release hGH resulting in both hGH and IGF-1 serum concentrations within the therapeutic range, leveraging the safety, efficacy, tolerability and immunogenicity of daily hGH dosing, which has been established for use over decades.

### Design and Methods

TransCon Growth Hormone was investigated in a total of two Healthy Volunteer (HV) Phase 1 and two Phase 2 studies in adults and children with GHD. Daily hGH with an equivalent dose-level was included in most trials to enable comparison of hGH-levels, IGF-1 levels; and efficacy by height velocity in GHD.

### Phase 1 HV and Phase 2 AGHD Studies

A total of 68 healthy adult subjects were included in two Phase 1 single-dose pharmacokinetic and pharmacodynamic studies, investigating TransCon hGH dose-levels from 0.04 mg hGH/kg/week up to 0.36 mg hGH/kg/week. In these Phase 1 studies, TransCon hGH was shown to:

1. Be safe and well tolerated.
2. Be suitable for a once-weekly dosing regimen.
3. Provide a pharmacokinetic hGH and pharmacodynamic IGF-1 response comparable to daily hGH treatment throughout the dosing period (Figure 2 and 3).

In a Phase 2 study including 37 subjects with Adult Growth Hormone Deficiency (AGHD), with four repeated dosings, TransCon hGH demonstrated dose-linearity over a dose-range of 0.02 mg hGH/kg/week up to 0.08 mg hGH/kg/week and comparable efficacy (IGF-1) to the daily hGH control group on exactly the same weekly dose-level (0.04 mg hGH/kg/week).

### Results – Phase 2 Pediatric GHD Study

This pediatric Phase 2 clinical study was designed to investigate the safety, efficacy, pharmacokinetics and pharmacodynamics of TransCon hGH compared to daily hGH over a treatment period of six months. The results of this Phase 2 study in 53 pediatric patients with GHD confirmed the safety, tolerability and the suitability of TransCon hGH for once-weekly dosing. An equivalent dose-level to daily hGH demonstrated slightly numerically higher growth rates compared to daily hGH treatment (Figure 4). Maximum hGH blood concentration was also comparable between equivalent weekly doses of TransCon hGH and daily hGH (Figure 5). No drug-related SAEs occurred, no lipoatrophy, nodule formation or anti-hGH neutralizing antibodies were seen. IGF-1 changes suggest a dose response and levels were in the expected range (P. Chatelain et al., ENDO 2016, Boston; NCT01947907).

### Recently Initiated – Phase 3 Pediatric GHD Study

This is a Phase 3, randomized, open-label, active-controlled trial investigating the safety, tolerability and efficacy of TransCon hGH as compared to standard daily growth hormone, over 52 weeks in prepubertal children with GHD.

It was initiated in August 2016 and will be conducted in North America, Europe, the Middle East, North Africa and Oceania. A brief description of this clinical study is available on www.heighttrial.com (NCT02781727).

### Conclusion

To date, the TransCon Growth Hormone has demonstrated efficacy and safety comparable to that observed with daily hGH. Injection site reactions were generally mild and similar to daily hGH injections, with no nodule formation or lipoatrophy noted. In addition, no neutralizing anti-hGH antibodies occurred.

TransCon hGH was shown to be dose-linear across different dose-levels (hGH and IGF-1) and demonstrated the same therapeutic effect (annualized height velocity) to daily hGH on the same weekly dose-level (pediatric GHD study; 0.21 mg hGH/kg/week).

TransCon hGH can be administered in small volumes with a fine (30G or smaller) needle at comparable weekly dose-levels to daily hGH. The product can be stored at room temperature.

The completed clinical studies support Phase 3 development with TransCon hGH. A Phase 3 study in pediatric GHD, the heGHT Trial, was recently initiated.

Disclosure Statement: All authors listed above are employees and shareholders of Ascendis Pharma.