Achondroplasia (ACH) is the most common short-limbed skeletal dysplasia. It is caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 (FGFR3) gene and results in impaired development of cartilage and bone, causing dwarfism (Figure 1). FGFR3 regulates chondrocyte development through inhibition of the FGFR3 pathway, which leads to dwarfism and other symptoms in ACH patients (Figure 2). CNP is a potential therapeutic pathway for ACH, as reported by caregivers of children with ACH, there is an impact on symptoms and daily functioning (Figure 3).

**Figure 1. CNP Can Counteract the Pathology of ACH**

Qualitative analysis of impacts of ACH on children aged 2-12 years was undertaken to inform the development of the ACHcomplishH Trial. ACH patients were asked to report subjective symptoms in a 5-point Likert scale, with 1 being ‘not at all affected’ and 5 being ‘very much affected’. The highest symptom burden was observed for trouble sleeping, trouble getting dressed, and trouble eating (Figure 4). In addition, ACH patients reported limited lower body segment ratio (Figure 5). TransCon CNP was designed to provide effective delivery of CNP, starting with a dose of 100 µg/kg, followed by dose escalation to 500 µg/kg (Figure 6). The trial is currently ongoing and will review safety data prior to initiation of a higher dose cohort for 52 weeks of treatment. Four staggered parallel groups will receive weekly TransCon CNP treatment or placebo from the prodrug. The trial is designed to evaluate the efficacy and safety of TransCon CNP in children with ACH, and include valuable long-term data beyond 52 weeks.

**Figure 6. TransCon CNP Phase 3 Trial Design**

**METHODS**

- **Primary Efficacy Endpoints:**
  - Annualized height velocity (AHV), as measured after 52 weeks of weekly TransCon CNP treatment or placebo
  - Other Efficacy Endpoints:
    - Change in upper to lower body segment ratio as measured at 52 weeks of weekly TransCon CNP treatment or placebo

**SAFETY OUTCOMES**

- AEs from the prodrug were characterized by a slow rise to peak plasma concentrations with median Tmax ranging from 45 to 66 h postdose. After the prodrug was characterized by a slow rise to peak plasma concentrations with median Tmax ranging from 45 to 66 h postdose. After the prodrug is metabolized by the liver, the metabolite is excreted in the urine. After the prodrug is metabolized by the liver, the metabolite is excreted in the urine.

**CONCLUSIONS**

- TransCon CNP treatment was well-tolerated and no serious adverse events or discontinuations were reported. Changes were observed across treatment groups for efficacy, safety, and PK of TransCon CNP by weekly TransCon CNP treatment or placebo.