Design and Baseline Demographics of a Five-Year, Multi-National Observational Cohort Study of Children with Achondroplasia (ACHieve)

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BACKGROUND

ACHONDROPLASIA (ACH)

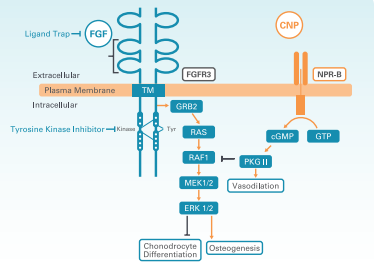
- ACH is the most common short limbed skeletal dysplasia[1]
- Caused by a gain-of-function mutation in the fibroblast growth factor receptor 3 (FGFR3) gene and results in impairment of the endochondral ossification process[2]
- Global birth prevalence of ACH is approximately 4.6 per 100,000[3]

C-TYPE NATRIURETIC PEPTIDE (CNP)

- Promotes chondrocyte development through inhibition of the FGFR3 pathway, specifically through activation of natriuretic peptide receptor type B (NPR-B)
- Potential promising therapeutic pathway for treating growth failure and dwarfism, as it inhibits the overactive signalling resulting from both ligand-dependent and -independent signalling through the mutated FGFR3 receptor causing ACH[4] (Figure 1)
- Due to the very short half-life of native CNP (2-3 minutes), has historically not been a druggable target, as prolonged exposure is required for improved growth

Figure 1. Achondroplasia Signaling Defect[5] is Well Understood

CNP does not alter the function of FGF receptors or change endogenous levels of FGF ligands, hereby reducing the risk of interfering with normal FGF biology



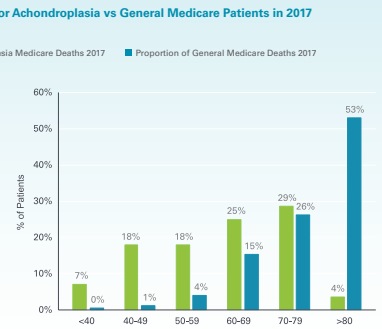
CURRENT MANAGEMENT OF ACH

- No therapies addressing the underlying pathology of ACH
- Most available treatments are surgical with goals to alleviate the symptoms from specific comorbidities (i.e. foramen magnum and spinal stenosis or recurrent otitis media)
- Since the available therapies do not address the underlying etiology, individuals with ACH often undergo multiple surgeries and myriad other forms of supportive care throughout their lives
- Higher mortality rates are recognized in ACH. Although changes in clinical management have improved survival, mortality is still higher than in the general population (Figure 2)

Figure 2. Achondroplasia Mortality

Preliminary analysis among people with achondroplasia indicates a median age of death of 60 years – consistent with published literature

Markedly higher mortality rate in these patients compared to the overall Medicare population, especially among those <70 years



Data on file.

AIMS AND OBJECTIVES

- The precise timing of comorbidity onset and the natural history of ACH are incompletely defined
- Prospective natural history studies are needed to provide important observational insights into the experience of children living with ACH and to inform the design and conduct of pathology-targeted intervention studies
- The goal of this analysis is to describe the design of a natural history study, ACHieve, that targets skeletal morbidity in children with ACH
  - The results of which will serve as a benchmark for comparing clinical outcomes in children with ACH receiving a novel therapeutic, TransCon CNP

METHODS

STUDY DESIGN

- The ACHieve study is a multi-center, longitudinal, non-therapeutic observational cohort study in children with ACH from birth up to 8 years at enrollment
- Children are evaluated every six months for up to 5 years in 25 centers from North America, Europe, and Oceania
- At each assessment, children undergo comprehensive anthropometric studies (including body proportionality measurements and recumbent or standing height) and information on the timing and nature of ACH-related comorbidities and their treatments are collected
- The first patient was enrolled in 2019 and a total of 83 children have been enrolled to date

Primary Outcome Measure

- Annualized height velocity (centimeters/year) in children with ACH, for up to 5 years

Secondary Outcome Measure

- Collection of natural history of achondroplasia symptoms in children with ACH, for up to 5 years

ACHieve STUDY

KEY INCLUSION CRITERIA

- Clinical diagnosis of ACH
- Age 0-8 years old at enrollment
- Able to stand without assistance if the child is 24 months or older

KEY EXCLUSION CRITERIA

- **Prior treatment with:**
  - Human growth hormone (hGH) or other medicinal products intended to affect stature or body proportionality
  - Medicinal products intended to affect stature or body proportionality within the previous 6 months of screening
  - Any investigational medicinal product or device intended to affect stature or body proportionality at any time
- **History or presence of:**
  - Injury or disease of the growth plate(s), other than ACH, that affects growth potential of long bones
  - Bone-related surgery that affects growth potential of long bones. Limb-lengthening with full recovery is allowed with a minimum of 12 months of bone healing
  - Forms of skeletal dysplasias other than ACH or medical conditions that result in short stature or abnormal bone growth
  - Malignant disease, other than basal cell epithelioma/carcinoma or completely resected squamous skin cancer with no recurrence for 12 months per medical records

BASELINE DEMOGRAPHICS

Table 1. ACHieve Preliminary Demographics and Baseline Characteristics

Demographic (N = 83)	
Age (years)	
Mean (SD)	3.7 (2.5)
Median (Min, Max)	3.0 (0.3, 9.0)
Age Group (years) – n(%)	
< 2	28 (33.7)
2 - < 5	28 (33.7)
> = 5	27 (32.5)
Sex – n(%)	
Female; Male	45 (54.2); 38 (45.8)
Race – n(%)	
American Indian or Alaska Native	1 (1.2)
Asian	5 (6.0)
Black or African American	1 (1.2)
White	71 (85.5)
Other	5 (6.0)
Ethnicity – n(%)*	
Hispanic or Latino; Not Hispanic or Latino	6 (7.2); 76 (91.6)

Baseline Characteristics (N = 83)	
Height (cm)	
Mean (SD)	78.3 (13.2)
Median (Min, Max)	78.4 (52.5, 102.4)
Height SDS	
Mean (SD)	-4.6 (1.25)
Median (Min, Max)	-4.5 (-7.5, -1.6)
Weight (kg)	
Mean (SD)	13.0 (4.7)
Median (Min, Max)	13.2 (4.6, 22.4)
Age at ACH Diagnosis – n(%)**	
Pre-Birth	12 (14.5)
At Birth	17 (20.5)
≥ 0 – 6 Months	45 (54.2)
> 6 Months	8 (9.6)
Type of Mutation – n(%)**	
1138G > A or 1138G > C	62 (74.7)
Other	8 (9.6)
Unknown	12 (14.5)

* 1 subject with unknown/not reported ethnicity; ** 1 subject with missing data

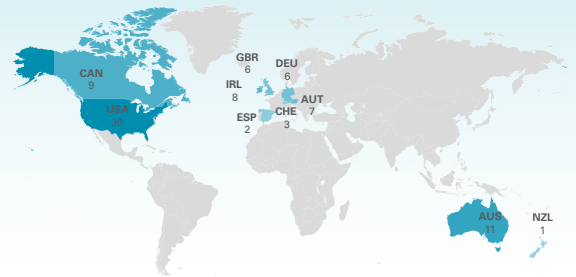
Figure Legend:

Upon enrollment of 83 subjects:

- Key natural history observations to date include:
  - Primarily white descent
  - Mean height SDS -4.6
  - Majority diagnosed within 6 months of birth
  - 75% have 1138G > A or 1138G > C mutations

STUDY STATUS AND FUTURE DIRECTIONS

Figure 3. ACHieve Study Status



CURRENT STATUS

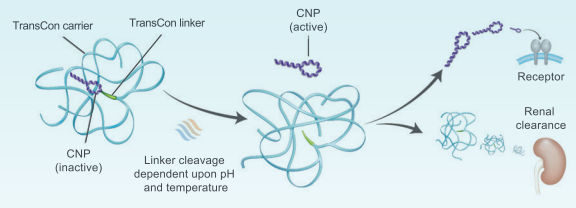
- Open and enrolling, 83 enrolled to date* across 10 countries
- 5 year timeframe to characterize the natural history of ACH. A total of 200 children are targeted for enrollment, which is anticipated to last until 2024

FUTURE DIRECTIONS

- The ACHieve study will provide novel insight into the timing, frequency, and characteristics of linear growth patterns, body proportionality, and comorbidities in children with ACH
- These observations will serve as a benchmark for future intervention trials targeting the pathology of the underlying skeletal dysplasia with the novel therapeutic agent, TransCon CNP (Figure 4)

*analysis as of 18Nov2020

Figure 4. TransCon CNP Design



- TransCon technology is designed to provide effective shielding of CNP[6]:
  - From neutral endopeptidase degradation in subcutaneous tissue and blood compartment
  - Minimize binding of TransCon CNP to the NPR-C receptor
  - Reduce binding of TransCon CNP to the NPR-B receptor in vasculature to avoid hypotension
- CNP liberated from TransCon CNP maintains small enough size to allow penetration into growth plates

Figure Legend:

- TransCon CNP is a sustai ned-release prodrug of CNP. CNP is transiently bound via the TransCon Linker to a chemically inert carrier that prolongs the peptide's overall circulatory half-life. This is achieved by minimizing renal clearance of the TransCon CNP prodrug and shielding of the CNP molecule from proteolytic degradation and from binding to its primary activating and clearance receptors, NPR-B and NPR-C
- Following cleavage of the TransCon Linker under physiological pH and temperature, active CNP peptide is slowly and continuously released
- The Phase 1 clinical trial with TransCon CNP demonstrated that single doses up to 150 µg CNP/kg were well-tolerated in healthy adult male volunteers, with no clinically significant trends observed in clinical laboratory assessments, vital sign measurements, ECG parameters, or physical examination findings[7,8]

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