ACHONDROPLASIA (ACH)

- ACH is the most common short-limbed skeletal dysplasia
- 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
- Global birth prevalence of ACH is approximately 4.6 per 100,000

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 signaling resulting from both ligand-dependent and -independent signaling
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 Defects in Well Understood

CNP does not alter the function of FGF receptors or change endogenous levels of FGFs; hence, reducing FGFs by targeting CNP with normal FGF biology

CURRENT MANAGEMENT OF ACH

- No therapies addressing the underlying pathology of ACH
- Most available treatments are surgical with goals to address the symptoms from specific comorbidities (i.e. foramen magnum and spinal stenosis or recurrent otitis media)

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 followed from birth to 8 years of age
- All 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 comorbidity and their treatments are collected
- The first patient was enrolled in 2019 and a total of 83 children have been enrolled to date

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

• Able to stand without assistance if the child is 24 months or older
• Age 0-8 years old at enrollment
• Clinical diagnosis of ACH
• No therapies addressing the underlying pathology of ACH
• All available treatments are surgical with goals to address the symptoms from specific comorbidities (i.e. foramen magnum and spinal stenosis or recurrent otitis media)

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 6 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 comorbidity 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

Current Status

- The ACHieve study will provide novel insights 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, TransCon CNP (Figure 4)

Methods

- Since the available therapies do not address the underlying etiology, individually 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

Table 1. ACHieve Preliminary Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographic (N = 83)</th>
<th>Baseline Characteristics (N = 83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Median (Min, Max)</td>
<td>8.3 (1.2)</td>
</tr>
<tr>
<td>Age at ACH Diagnosis</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Age Group (years) - n(%)</td>
<td>&lt; 6 months</td>
</tr>
<tr>
<td>6 - 12 months</td>
<td>29 (33.7)</td>
</tr>
<tr>
<td>&gt; 12 months</td>
<td>27 (32.5)</td>
</tr>
<tr>
<td>Sex - n(%)</td>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td>Ethnicity - n(%)</td>
<td>Other</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.2)</td>
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<tr>
<td>Black or African American</td>
<td>1 (1.2)</td>
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<tr>
<td>White</td>
<td>71 (85.5)</td>
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<tr>
<td>Median (Min, Max)</td>
<td>Height (cm)</td>
</tr>
<tr>
<td>Adult</td>
<td>174.2 (56.0)</td>
</tr>
<tr>
<td>Pre-Birth</td>
<td>122 (114.5)</td>
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<tr>
<td>Birth</td>
<td>172 (20.5)</td>
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<tr>
<td>At 0 – 6 Months</td>
<td>45 (54.2)</td>
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<tr>
<td>&gt; 6 Months</td>
<td>83 (9.8)</td>
</tr>
<tr>
<td>Type of Mutation – n(%)</td>
<td>1108G &gt; A or 1186G &gt; C</td>
</tr>
<tr>
<td>Other</td>
<td>9 (11.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>12 (14.5)</td>
</tr>
</tbody>
</table>

Figure Legend

- Upon enrollment of 83 subjects
- Key natural history observations to date include:
  - Frailty within decent
  - Majority diagnosed within 6 months of birth
  - Mean height SDS -4.6
  - 75% have 1138G > A or 1186G > C mutation

References:

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