**Achondroplasia (ACH)** is the most common non-lethal form of skeletal dysplasia, affecting between 1 in 10,000 to 1 in 20,000 live births. 

**Clinical features of ACH include:**
- Short stature with short limbs and rhizomelic disproporion.
- Macrocephaly with variable frontal and parietal bossing.
- Thickened and redundant skin folds.
- Midfacial retrusion due to the under-development of cartilaginous bones of the face.
- Thoracolumbar kyphosis and lumbar hyperlordosis.
- Relatively short neck.
- Short fingers and thumb insertion defects.
- Hypermobile hips and knees and limited elbow extension.
- Flat occiput; small foramen magnum.
- Relatively short chest with overly compliant ribs.
- Tibial bowing of the mesial segment of the legs.
- Kyphosis, occurring in most infants with ACH.
- Hypotonia, occurring in most infants with ACH.

Genetically, ACH is an autosomal dominant disorder characterized by gain of function variants in the FGFR3 gene, of which 95% of substitutions in the transmembrane domain of FGFR3. Eighty percent of affected individuals represent de novo events.

Linear growth is stunted in ACH children compared with average stature children (Table 1).

- **Body length at birth** is approximately between 1.4 and 2 SDs for non-ACH reference tables.
- **Infants** and **children** fall progressively and deserves even follow-up from average stature of less than a subject growth start. **Final height** is approximately 151 cm for males and 141 cm for females.

**Table 1. Growth velocity in ACH patients with ACH compared with those having average stature**

<table>
<thead>
<tr>
<th>Age group</th>
<th>ACH growth velocity</th>
<th>Average stature growth velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 year</td>
<td>9.3 cm/year (3.7 cm/month)</td>
<td>10.2 cm/year (4.9 cm/month)</td>
</tr>
<tr>
<td>1-2 years</td>
<td>9.0 cm/year (3.6 cm/month)</td>
<td>10.8 cm/year (5.0 cm/month)</td>
</tr>
<tr>
<td>2-3 years</td>
<td>7.2 cm/year (2.6 cm/month)</td>
<td>9.0 cm/year (2.5 cm/month)</td>
</tr>
</tbody>
</table>

**Figure 1. Medical complications associated with ACH**

- **Cardiac abnormalities:**
  - Ventricular septal defect
  - Patent ductus arteriosus
  - Aortic coarctation
  - Tetralogy of Fallot
  - Hypertrophic cardiomyopathy
  - Mitral valve prolapse

- **Neurosurgical complications:**
  - Meningocele
  - Chiari malformation
  - Hydrocephalus
  - Spinal dysraphism
  - Syringomyelia
  - Arachnoid cyst

- **ENT = ear, nose and throat. Modified from Unger et al. 2017.**

**Figure 2. FGFR3-mediated inhibition of bone growth in ACH**

**PROPEL study design**

**PROPEL** is a prospective, non-interventional clinical assessment study to collect serial assessments in order to characterize the natural history of children with ACH.

The study is designed to evaluate participants over a period of time (minimum of 6 months and maximum of 2 years) and to collect baseline data prior to potential enrolment in a GQ-sponsored interventional phase 2 or 3 trial to assess the safety of daily dosing, evidence of efficacy, and dose finding of infliximab in children with ACH.

**Table 2. Key inclusion/exclusion criteria**

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Signed informed consent by study participant or parent(s) and legally authorized representative (LAR) and signed informed assent by the study participant (when applicable).</td>
<td>1. Hypochondroplasia or short stature condition other than ACH.</td>
</tr>
<tr>
<td>2. Age ≥ 10 years (inclusive) at study entry.</td>
<td>2. Females who have had their menarche.</td>
</tr>
<tr>
<td>3. Diagnosis of ACH (as confirmed by the Principal Investigator).</td>
<td>3. Height ≥ 2 or &gt; 2 standard deviations for age and sex based on reference tables on growth in children with ACH and ACH participating in a study (when applicable).</td>
</tr>
<tr>
<td>4. Annualized height velocity ≤ 1.5 cm/year over a period of 6 months prior to screening.</td>
<td>4. Annualized height velocity &gt; 1.5 cm/year over a period of 6 months prior to screening.</td>
</tr>
<tr>
<td>5. Concurrent disease or condition that, in the view of the investigator and/or study sponsor, may impact growth or where this treatment is known to impact growth.</td>
<td>5. Concurrent disease or condition that, in the view of the investigator and/or study sponsor, may impact growth or where this treatment is known to impact growth.</td>
</tr>
<tr>
<td>7. Treatment with growth hormone, insulin-like growth factor 1 (IGF-1), or interferon-like growth factor in the previous 6 months or long-term treatment (&gt;6 months) at any time.</td>
<td>7. Treatment with growth hormone, insulin-like growth factor 1 (IGF-1), or interferon-like growth factor in the previous 6 months or long-term treatment (&gt;6 months) at any time.</td>
</tr>
<tr>
<td>8. Treatment with A-type natriuretic peptide (ANP), epinephrine, or any other investigational product or investigational medical device for the treatment of ACH or short stature.</td>
<td>8. Treatment with A-type natriuretic peptide (ANP), epinephrine, or any other investigational product or investigational medical device for the treatment of ACH or short stature.</td>
</tr>
</tbody>
</table>

**PROPEL trial: current status**

**Endpoints**

- **Primary objectives:**
  - Collect baseline height velocity measurements of children with ACH biannualized for future enrollment in interventional studies sponsored by QED Therapeutics.
  - Annualized height velocity.

- **Other objectives:**
  - Collect other baseline height measurements of children with ACH biannualized for future enrollment in interventional studies sponsored by QED Therapeutics.
  - Change from baseline in other growth parameters, including but not limited to height, weight, pubertal body area, upper arm fat area, and upper leg fat area.

**PRISMA**

**Figure 3. FGFR3-mediated inhibition of bone growth in ACH**

**Figure 4. FGFR3 inhibition in chondrocytes in vivo**

**References**