Safety and Tolerability of Once-Weekly Administration of CTP-Modified Human Growth Hormone (MOD-4023): Phase 2 Study in Children with Growth Hormone Deficiency

Introduction

OPKO Biologies developing bio better longer acting versions of existing therapeutic proteins utilizing a technology called CTP.

The technology involves fusion of the C terminus peptide of hNG to one or both ends of the target protein. The technology was clinically validated and proven as a safe and efficient way for increasing the half-life of several therapeutic proteins while maintaining their biological activity. MOD-4023 (hNG-CTP) is a long acting hGH with the following competitive advantages:

- Non Viscous, high concentration formulation
- Consists of ~75% native hGH content
- hGH-CTP is injected by pen device with 30 - 31G needle

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Study Outline

A randomized, comparator-controlled Phase 2 study was conducted in up to 53 pre-pubertal, naïve GHD children receiving one of three MOD-4023 doses as once-weekly regimen (0.25, 0.48, 0.66mg/kg per week) or daily Genotropin (0.24mg/kg per week / 0.834mg/kg per day) as comparator arm in SC injections. In order to introduce naïve patients to the allocated MOD-4023 dose in a gradual manner, a stepwise dose increase approach was implemented. All patients randomized to receive one of the three MOD-4023 doses started treatment for 2 weeks with the low MOD-4023 dose and based on the patient's dose allocation, followed by a dose increase to the next dose level every two weeks until the final allocated dose was reached. Height velocity (HV), safety, PK and PD were routinely assessed over 12 months. Safety evaluations included monitoring of adverse events (AEs), injection-site reactions, physical condition and vital signs. Laboratory assessments included glucose and lipid metabolism, blood biochemistry and immunology.

Overall Study Design

Baseline Characteristics [n=52]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>Mean 12</td>
<td>Mean 12</td>
<td>Mean 12</td>
<td>Mean 12</td>
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<tr>
<td>Height SDS</td>
<td>-0.84</td>
<td>0.59</td>
<td>0.63</td>
<td>0.81</td>
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<tr>
<td>HV SDS</td>
<td>0.32</td>
<td>0.05</td>
<td>0.05</td>
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<tr>
<td>AEs</td>
<td>9.8%</td>
<td>12.0%</td>
<td>12.0%</td>
<td>14.7%</td>
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<tr>
<td>Hypoglycemia</td>
<td>0.1%</td>
<td>0.0%</td>
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</tbody>
</table>

PK-PD

MOD-4023 weekly Pharmacokinetics profile

IGF-I SDS Profile Following 12m of MOD-4023 Administration

Efficacy

Mean Height Velocity Following 12 Months of Treatment

Delta Height SDS Following 12 Months of Treatment

Height Velocity SDS Following 12 Months of Treatment

Safety

Conclusions

- MOD-4023 confirmed to be a long-acting GH with extended half-life, enhanced exposure and reduced clearance for all patients.
- IGF-I seems to be normalized and stabilized within the normal range during 12 months of treatment, reaching IGF-I SDS values around 0 for the two higher MOD-4023 cohorts comparable to the daily hGH arm.
- All four treatment groups demonstrated adequate "catch-up" growth, as reflected by HV, HVSDS and AHSDS, following 12 months of treatment.
- The two higher doses of MOD-4023 showed a comparable Height SDS and Height velocity values as daily r-hGH with no difference between MOD-4023 and daily comparator.
- The 12 months analysis study confirms a significant and promising profile including the following:
  - No serious adverse events
  - No reported lipoatrophy or clinically significant local tolerability issues
  - No clinically significant local tolerability issues
  - Comparable rate of AEs between MOD-4023 groups and control group
  - Neither Anti-CTP ADA nor Neutralizing Antibodies were detected.

The PK-PD, efficacy and safety data support the initiation of a Phase 3 study in GHD pediatric population using a single weekly injection of MOD-4023.