Long-Term Safety of a Once-Weekly Somatrogon (hGH-CTP): *4-Year Results of a Phase 2 Extension Study in Children with Growth Hormone Deficiency*

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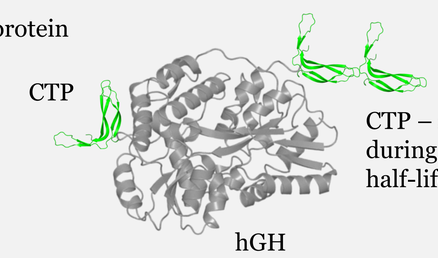
BACKGROUND

Once-daily growth hormone (GH) therapy is an effective treatment for children with growth hormone deficiency (GHD), but a decrease in compliance with prolonged treatment can reduce the treatment benefits. Somatrogon, also known as MOD-4023, is a long-acting recombinant protein consisting of human growth hormone (hGH) and three copies of C-terminal peptide (CTP). It is a new molecular entity with receptor binding properties and a mechanism of action analogous to hGH. A once-weekly somatrogon (hGH-CTP), is being developed to reduce the treatment burden of daily dosing for children and caregivers and potentially improve compliance and long-term efficacy [1].

Figure 1. Long-acting CTP-hGH protein



CTP – a natural peptide created during evolution to enhance the half-life of hCG

OBJECTIVES

The objective of the open-label extension (OLE) Phase 2 study was to demonstrate the long-term impact of once-weekly somatrogon treatment beyond the initial 12 months of the primary study. Key objectives included evaluation of safety, local tolerability, growth outcome and immunogenicity in patients treated with somatrogon for a period of up to 4 years in the OLE.

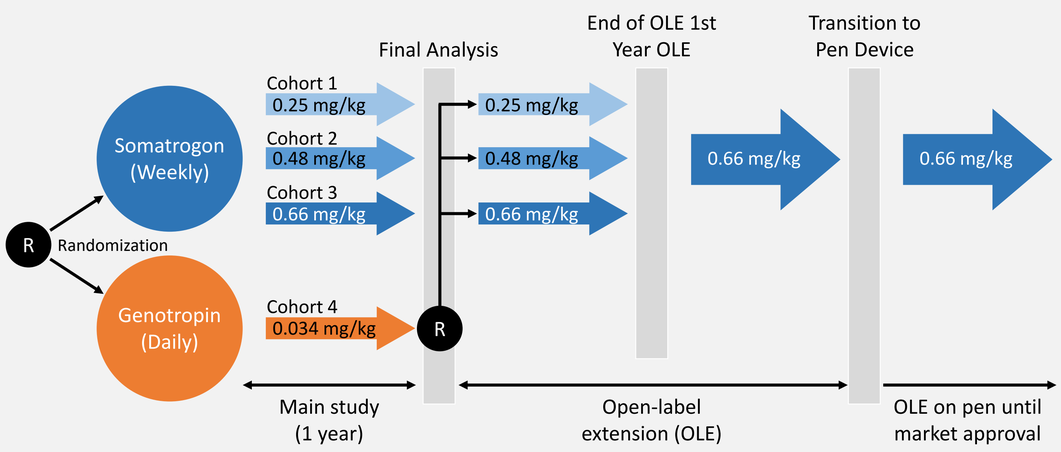
METHODS

The OLE phase 2 study was a continuation of a randomized 12-month study that investigated the efficacy, safety, and tolerability of 3 dose levels of somatrogon, administered weekly (0.25, 0.48, or 0.66 mg/kg/week) compared to daily r-hGH (Genotropin® 0.034 mg/kg/day) in pre-pubertal pediatric patients with GHD [2].

Forty-eight children with GHD that completed the main Phase 2 study continued in the OLE. Subjects who were randomized to somatrogon in the main study continued with the same dose of somatrogon; subjects who were originally assigned to daily Genotropin® were randomly re-assigned to one of the three somatrogon dose levels. Following the first 12-months of treatment in the OLE all subjects were transitioned to 0.66 mg/kg/week.

Subject were treated with somatrogon for up to 4 years until transfer to a somatrogon pen device. Forty subjects (83%) are continuing in OLE on pen device (Figure 2). Top line results for up to 4 years of treatment in the OLE are reported.

Figure 2. Study design (*ClinicalTrials.gov: NCT01592500*)



RESULTS: Demographic Characteristics

	All (N=48)
Mean age (SD), years	7.65 (2.104)
Gender, male (%)	32 (66.7)
Race, white (%)	45 (93.8)
Pubertal status Tanner I (%)	47 (97.9)

	All (N=48)
Mean weight (SD), kg	20.39 (5.150)
Mean height (SD), cm	112.6 (11.07)
Mean BMI (SD), kg/m^2	15.82 (1.740)
Mean IGF-1 SDS (SD), Z	0.03 (1.176)

RESULTS: Safety

Treatment-emergent adverse events (TEAEs)	All subjects (N=48), n (%) [AEs]
Any TEAEs	38 (79.2) [190]
Serious TEAEs	3 (6.3) [4]
TEAEs related to study drug	4 (8.3) [11]
TEAEs leading to study discontinuation	1 (2.1) [1]

TEAEs > 5% of subjects	All (N=48)
U. resp. tract infection	13 (27.1)
Bronchitis	9 (18.8)
Rhinitis	5 (10.4)

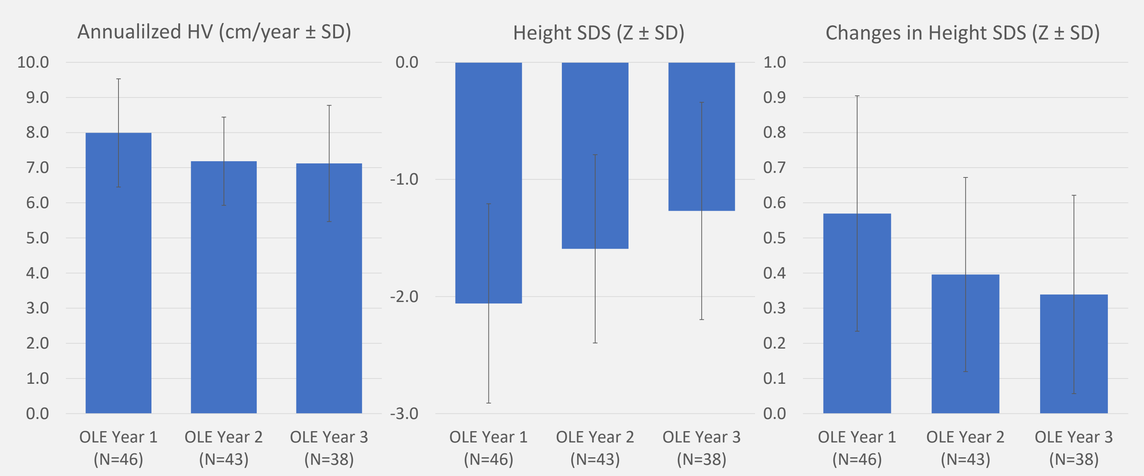
TEAEs > 5% of subjects	All (N=48)
Ear infection	4 (8.3)
Nasopharyngitis	4 (8.3)

Parameter, Mean (SD)		OLE Y1	OLE Y2	OLE Y3/Y4
HbA1c, %	N	45	43	40
	Mean	5.12 (0.282)	5.16 (0.309)	5.17 (0.343)
Fasting glucose, mmol/L	N	44	42	40
	Mean	4.65 (0.598)	4.45 (0.433)	4.68 (0.447)

Anti-Somatrogon antibody, n (%)	Overall (N=48)	OLE Y1 (N=48)	OLE Y2 (N=44)	OLE Y3 (N=43)
Anti-somatrogon Ab	17 (35.4)	12 (25.0)	11 (25.0)	11 (25.6)
Neutralizing Ab	0	0	0	0

- The safety and tolerability from the OLE study were comparable to that observed in the 12-month Phase 2 study [2] and the reported safety profile of daily r-hGH. Most AEs were of mild severity (75.8%) and no local tolerability issues were identified.
- There were 3 non-related serious AEs, and one probably related serious AEs of exacerbation of thoracic scoliosis that led to discontinuation.
- There were no changes in HbA1c, fasting glucose, or insulin over the 4 years of treatment
- Low titers of anti-somatrogon antibodies were detected in 17 subjects, of which 3 subjects had transient antibodies. All samples were negative for neutralizing Ab.

RESULTS: Efficacy



Parameter, Mean (SD)		OLE Y1	OLE Y2	OLE Y3
IGF-1 SDS, Z	N	43	41	38
	Mean	0.64 (0.996)	0.65 (1.082)	1.05 (0.819)

- Mean annualized HV over 3 years shows that long-term somatrogon treatment resulted in sustained growth rate. Height SDS values over time showed height normalization over time.
- Somatrogon treatment showed that IGF-1 and IGF-binding peptide-3 (IGFBP-3) levels were maintained within the normal range with ongoing somatrogon therapy.
- Subjects that had developed Abs demonstrated similar annualized height velocity (cm/year) [8.43 (1.03), 7.17 (1.31), and 6.71 (1.19), respectively] and height SDS ranges [-2.31 (1.22), -1.71 (1.10), and -1.47 (1.12), respectively], suggesting that the presence of non-neutralizing Abs had no effect on somatrogon efficacy. There was no effect of Abs on IGF-1 and somatrogon PK.

CONCLUSION

- Somatrogon treatment demonstrated a favorable safety profile and local tolerability after four years of dosing in GHD pediatric subjects
- Serum IGF-1 SDS values were maintained within the normal range, and a growth rate comparable to that reported for daily hGH was observed
- Low titers of non-neutralizing Abs did not affect growth parameters and IGF-1

REFERENCES

1. Calo D et al. Precis Med 2015, (2) e989: 1-8
2. Zelinska N et al. J. Clin. Endocrin. Metab. 2017, (102) 1578-1587