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*

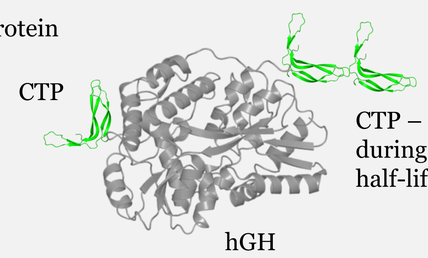
Nataliya Zelinska[1], Yulia Skorodok[2], Oleg Malievsky[3], Violeta Iotova[4], Ron G. Rosenfeld[5], Zvi Zadik[6], Shelly Vander[7], and Aleksandra Pastrak[8]

[1]Ukrainian Children Specialized Clinical Hospital, Kyev; [2]St. Petersburg State Pediatric Medical University, St. Petersburg; [3]Bashkir State Medical University, Ufa; [4]UMHAT, Varna; [5]Oregon Health & Science University, Oregon, USA; [6]Kaplan Medical Center, Rehovot, Israel; [7]OPKO Biologics, Kiryat Gat, Israel; [8]OPKO Health, Miami.

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 of this report 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.

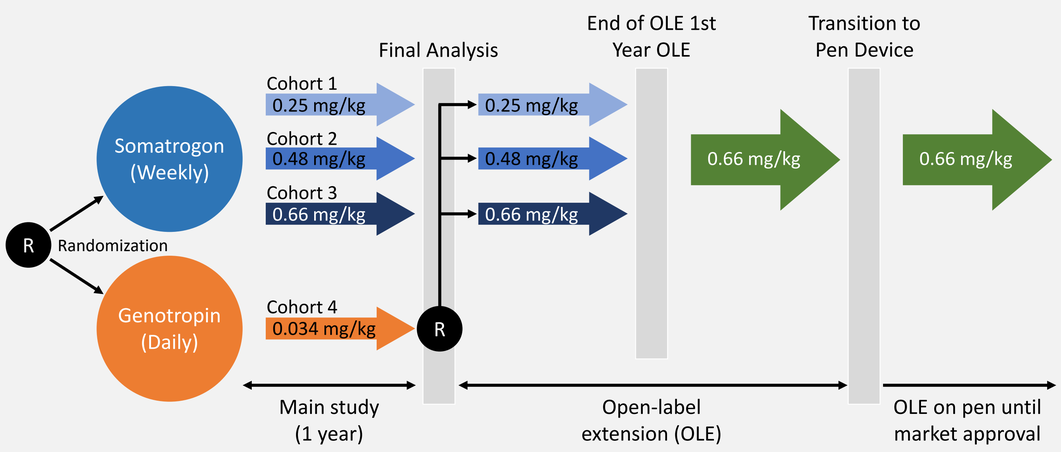
METHODS

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.

Subjects were treated with somatrogon (frozen vial) 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: Demographics at the Start of Open Label Extension

	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: OLE Safety Years 1 to 4

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)

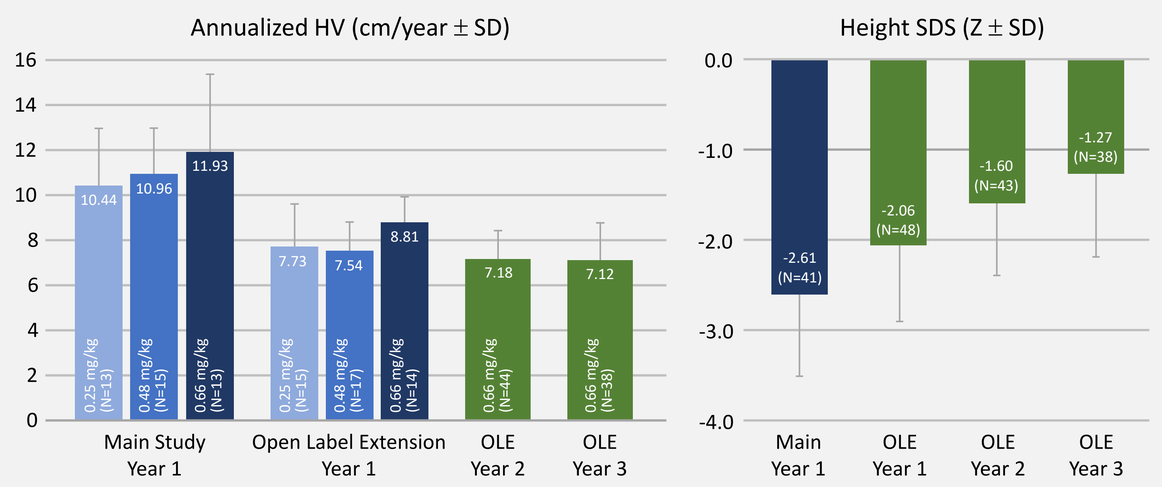
TEAEs > 5% of subjects	All (N=48)
Ear infection	4 (8.3)
Nasopharyngitis	4 (8.3)

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 in the OLE.
- 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 (0.956)	0.65 (1.082)	1.05 (0.819)

- Mean annualized HV over 3 years in the OLE shows that long-term somatrogon treatment resulted in sustained growth rate. Height SDS values showed height normalization over time.
- IGF-1 and IGF-binding protein-3 (IGFBP-3) levels remained within the normal range with ongoing somatrogon therapy.
- Subjects that had developed non-neutralizing Abs demonstrated similar annualized HV (cm/year) to subjects with no detectable Abs [8.43 (1.03) vs. 7.85 (1.66), 7.17 (1.31) vs. 7.19 (1.25), and 6.71 (1.19) vs. 7.36 (1.56)]; and height SDS [-2.31 (1.22) vs. -1.98 (0.70) , -1.71 (1.10) vs. -1.54 (0.63), and -1.47 (1.12) vs. -1.15 (0.80) for OLE year 1, 2, and 3, respectively].

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 levels

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