EP845

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

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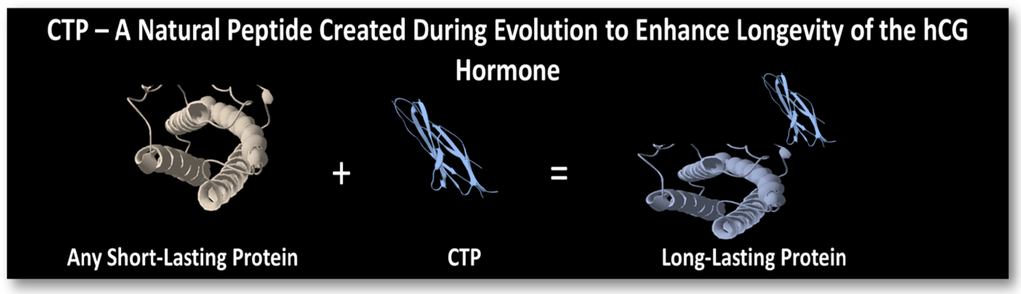
Introduction

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



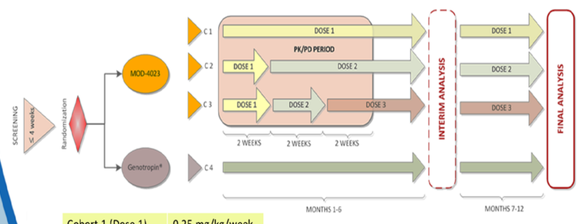
The technology involves fusion of the C terminus peptide of hCG to one or both ends of the target protein. The technology was clinically validated and proven as a safe and efficient way for increasing the half-life of several therapeutic proteins while maintaining their biological activity. MOD-4023 (hGH-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**

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 / 0.034µg/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 immunogenicity.

Overall Study Design



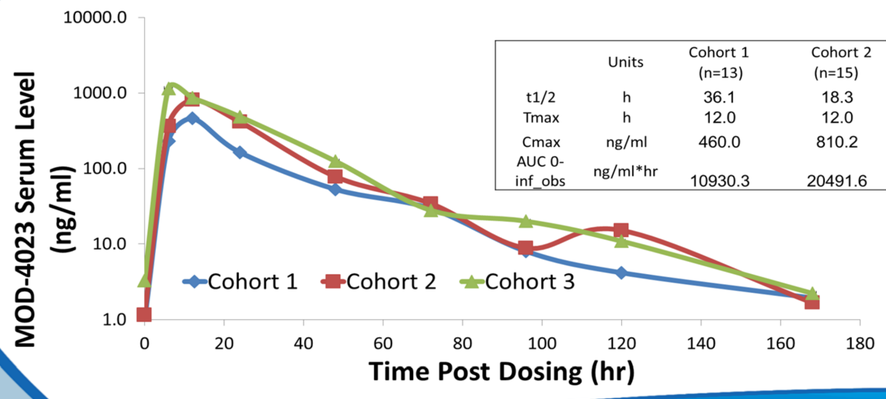
Cohort 1 (Dose 1)	0.25 mg/kg/week
Cohort 2 (Dose 2)	0.48 mg/kg/week
Cohort 3 (Dose 3)	0.66 mg/kg/week
Cohort 4 Genotropin	0.24 mg/kg/week

Baseline Characteristics (n=52)

	Cohort 1 (n=13)		Cohort 2 (n=15)		Cohort 3 (n=13)		Cohort 4 (n=11)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age at V1	6.92	2.19	6.53	2.20	7.08	2.40	6.43	1.79
HT SDS	-3.64	0.97	-3.72	0.87	-4.21	1.45	-4.22	1.58
HtSDS - THSDS	-3.22	0.95	-3.00	0.70	-3.36	1.54	-3.68	1.70
HV SDS	-2.93	1.42	-2.68	1.00	-3.01	1.42	-3.29	1.91
Peak GH	3.93	3.15	4.13	2.64	3.97	2.97	3.82	2.78
SCREENING IGF-I SDS	-2.13	0.85	-2.13	0.77	-1.97	0.83	-2.15	0.94

PK-PD

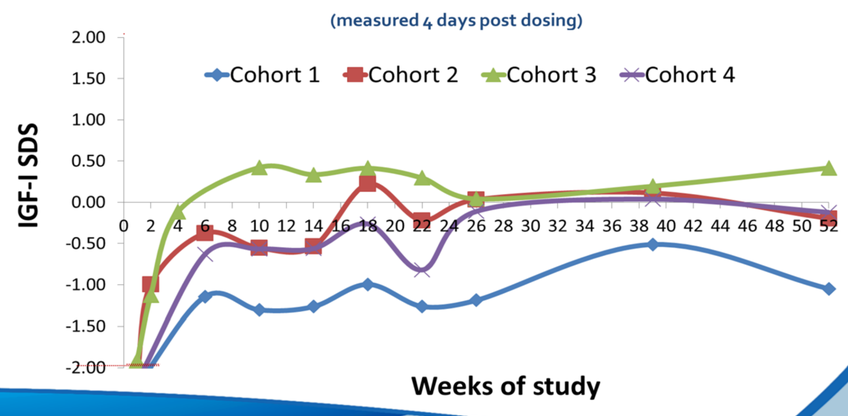
MOD-4023 weekly Pharmacokinetics profile



	Units	Cohort 1 (n=13)	Cohort 2 (n=15)	Cohort 3 (n=13)
t1/2	h	36.1	18.3	22.4
Tmax	h	12.0	12.0	6.0
Cmax	ng/ml	460.0	810.2	1150.9
AUC 0-inf_obs	ng/ml*hr	10930.3	20491.6	28084.9

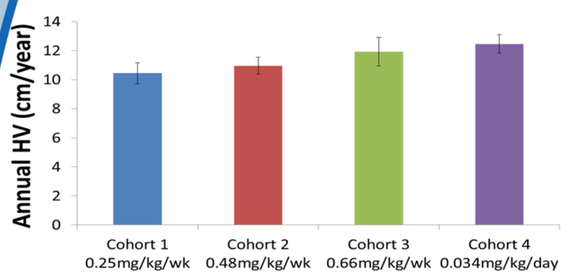
IGF-I SDS Profile Following 12m of MOD-4023 Administration

(measured 4 days post dosing)

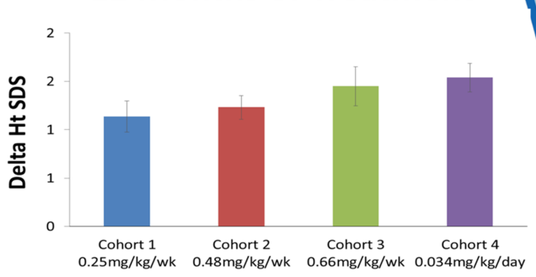


Efficacy

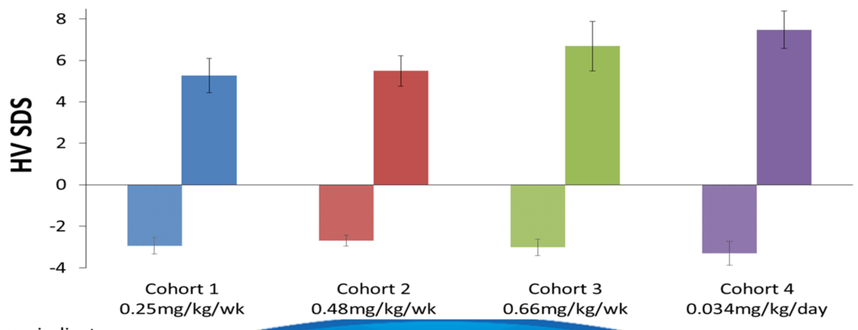
Mean Height Velocity Following 12 Months of Treatment



Delta Height SDS Following 12 Months of Treatment



Height Velocity SDS Following 12 Months of Treatment



* Error bars indicate +/- 1St Error

Safety

	MOD-4023 Treatment				r-hGH Treatment
	Cohort 1 N=13	Cohort 2 N=15	Cohort 3 N=14	Total (1-3) N=42	Cohort 4 N=11
Patients reporting at least one AE; n (%)	9 (69.2%)	10 (66.7%)	10 (71.4%)	29 (69.0%)	8 (72.7%)
Total number of AEs; n	67	22	23	112	33
Adverse events unrelated or unlikely related to study drug	65	19	15	99	33
Adverse events possibly, probably, or definitely related to study drug	2	3	8	13	0

The safety of MOD-4023 was demonstrated during the study:

- The most common AEs reported were anemia, hypothyroidism, varicella, bronchitis, respiratory tract infection and headache
- There were no severe AEs during MOD-4023 treatment
- There were no deaths during the study
- Laboratory assessments supported the tolerability of MOD-4023 treatment:
  - No significant findings attributed to MOD-4023 were observed in glucose metabolism (glucose, HbA1c and insulin). All values across cohorts were within normal values . Fluctuations in values between visits, and from baseline, were with no apparent dose-dependent or time-dependent trends, and were not considered clinically significant.
  - No significant changes were observed for the lipid profile.
  - No adverse effects attributed to MOD-4023 were observed in TSH, fT4, fT3 and cortisol levels
  - The majority of mean blood chemistry and hematology values were within normal limits, with the exception of relative eosinophil and relative lymphocyte levels. These levels were also high at screening, and in line with previous published clinical studies conducted with hGH (Rekers-Mombarg et al, 1995).
  - No significant overall changes were observed in mean vital signs
  - No injection site-related AEs were reported.

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 ΔHtSDS, 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 safety analysis suggests a clean 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.

ECE 2016 845-EP
Paediatric endocrinology
Gili Hart
Poster presented at: ECE2016 28 – 31 May 2016 MUNICH, GERMANY 18th EUROPEAN CONGRESS OF ENDOCRINOLOGY
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