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Effect of Very Early Growth Hormone (GH) Treatment on Long-term Growth in Girls with Turner Syndrome (TS): A Multicenter, Open-Label, Extension Study

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BACKGROUND

- Girls with turner syndrome (TS) have progressive postnatal linear growth failure [1], and if untreated, attain an average adult height ~20 cm shorter than women in general population and their mid-parental height [2].
- Late initiation of growth hormone (GH) therapy may result in suboptimal adult height.
- In a, randomized, controlled, clinical trial 88 girls with karyotype-proven TS, aged 1.98 ± 1.00 y, were randomized to receive either GH (50 µg/kg/day; early treated; ET) for 2y, or to remain as untreated controls (early untreated; EUT) ("Toddler Turner" study).
- Height SDS (standard deviation score) increased in ET group: -1.4 ± 1.0 to -0.3 ± 1.1, while it decreased in the control group: -1.8 ± 1.1 to -2.2 ± 1.2 SDS (between-group difference of **1.6 ± 0.6 SDS** (p<0.0001[1]).
- It was uncertain whether these early height gains in ET group would translate to taller adult heights.

OBJECTIVES

Patients from the original study were invited to participate in this extension study to adult height to determine differences between ET and EUT for:

- Near-adult height standard deviation score (SDS);
- Age at onset of puberty (thelarche);
- Age at attainment of adult height;
- Safety of long term exposure to GH;
- Hearing and middle ear function (data not shown)

METHODS

- US multicenter (9 centers), open-label, study.
- 88 patients were eligible to participate.
- Medical history, including history of GH treatment in ~2-year period between end of original study and start of extension collected.
- GH treatment in the extension was at the discretion of investigator and subject's local physician.
- Auxology, bone age x-ray, laboratory, and safety assessments obtained annually.
- Near-adult height (NAH) = first height measurement obtained when height velocity was ≤ 2.0 cm/y / bone age was ≥ 14.5 y.

Statistical Methods

- A priori 80% power (assuming SD of 1.22 for height SDS in either group) to detect between-group difference in NAH if 10, 25, or 43 subjects reached NAH, assuming between group Δ height SDS of 1.66, 1.00 and 0.75 respectively.
- Safety population = all subjects who entered the extension
- Intent-to-treat (ITT) Population = subjects with at least 1 post-baseline visit
- NAH Population = subjects who reached NAH (defined above)
- Fixed-effects analysis of covariance (ANCOVA) model, using height SDS at original study entry and age at original study entry as covariates used to compare Δ height SDS (2-sided; 5% level of significance) at NAH
- Age at attainment of Tanner 2 breast development (thelarche) and at attainment of NAH analyzed using Kaplan-Meier estimator and Cox proportional hazard model with group (ET vs. EUT) and quintile of propensity to enter extension study as covariates.

RESULTS

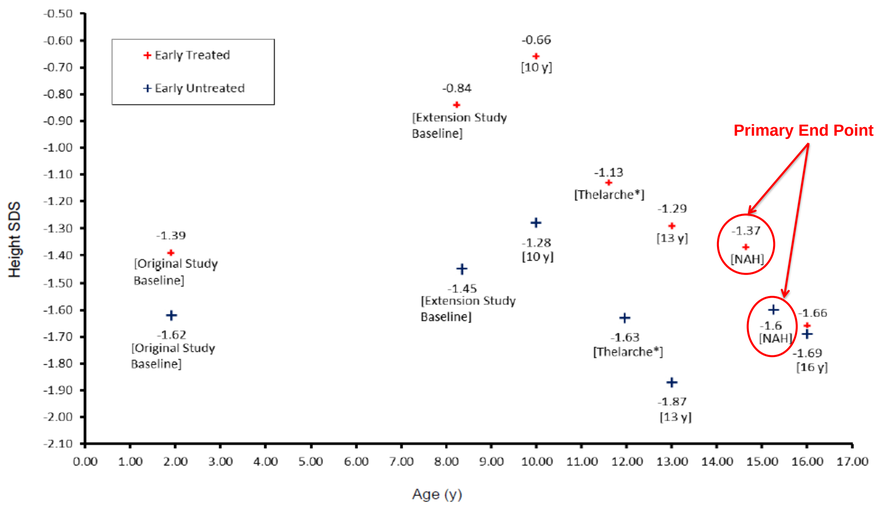
- 69 subjects enrolled; 19 subjects either declined participation or could not be contacted.
- 2-year gap between end of original study and start of extension (inter-study period)
- 28 of 36 (78%) vs. 30 of 33 (91%) subjects from ET vs. EUT group received GH treatment in inter-study period.
- At extension study closure, 42 of 69 subjects fulfilled protocol-defined completion criteria (height velocity ≤ 1.0 cm/y and bone age ≥ 15y); 12 subjects were still active on study, 9 had discontinued due to subject/ parent/ caregiver decision, 5 were lost to follow up and 1 subject had died. NAH was available for 51 subjects.

Table 1. Demographics and Subject Characteristics (ITT Population)

	ET (N=35)	EUT (N=32)	Total (N=67)	p-value
Karyotype group, n (%)				-
45,X	23 (65.7)	23 (71.9)	46 (68.7)	-
45,X/46,XX	7 (20.0)	4 (12.5)	11 (16.4)	-
Other	5 (14.3)	5 (15.6)	10 (14.9)	-
Original Study (Baseline)				
Chronological age (y)	1.90 ± 0.94	1.92 ± 1.02	1.91 ± 0.97	0.918
Bone age (y)	1.93 ± 0.85	1.79 ± 0.95	1.87 ± 0.89	0.518
Height (cm)	78.05 ± 8.07	77.33 ± 8.92	77.71 ± 8.43	0.733
Height SDS	-1.39 ± 1.10	-1.62 ± 1.08	-1.50 ± 1.09	0.390
Extension Study (Baseline)				
Chronological age (y)	8.23 ± 1.18	8.35 ±1.27	8.29 ± 1.22	0.692
Bone age (y)	8.76 ± 1.57	8.28 ± 1.56	8.53 ± 1.57	0.219
Height (cm)	124.02 ± 10.05	120.99 ± 9.91	122.58 ± 10.02	0.219
Height SDS	-0.84 ± 1.24	-1.45 ± 1.23	-1.13 ± 1.27	0.048

cm = centimeters; N = number of subjects in population; SDS = standard deviation score; y = years

Figure 1. Mean Height SDS and Age at Various Milestones (ITT Population)



SDS = standard deviation score; y = year.

Table 2. GH Exposure (ITT Population)

	ET (N=36)	EUT (N=32)
Average GH dose in extension (µg/kg/day)	39.5 ± 14.6	42.4 ± 13.2
Duration of GH treatment [original study baseline to extension study end (y)]	11.99 ± 3.54	10.79 ± 2.66

Statistical testing was not performed for between-group differences

Figure 2. Kaplan Meier Curve of Chronological Age at Thelarche (NAH population)

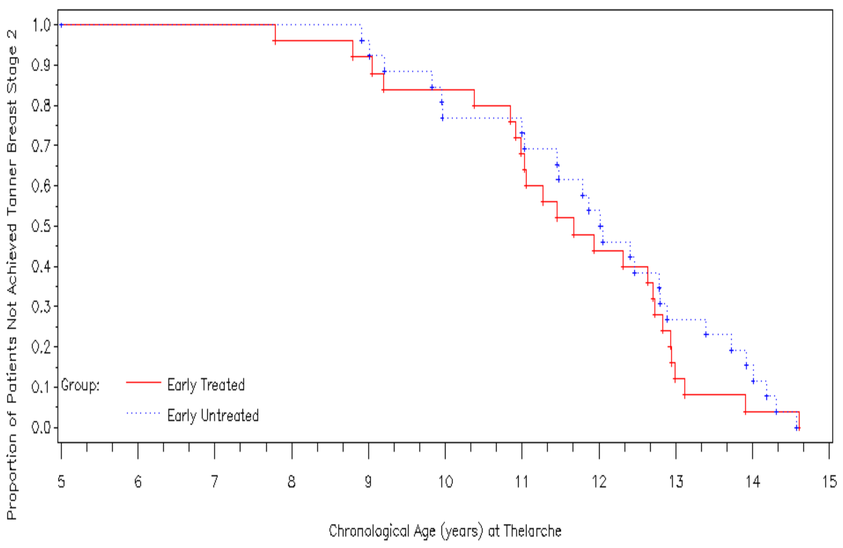
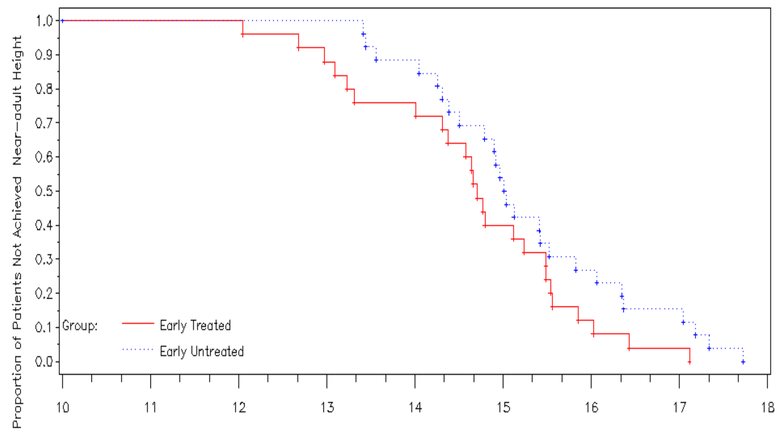


Table 3. Ages - Thelarche, Attainment of NAH and Start of Estrogen Replacement (NAH Population)

Chronological Age at	ET (N=25)	EUT (N=26)	p-value
Thelarche (y)	11.60 ± 0.33	11.96 ± 0.34	0.038
Attainment of NAH (y)	14.64 ± 0.25	15.26 ± 0.23	0.330
Start of estrogen replacement (y)	12.11 ± 0.96 (n=21)	12.66 ± 1.34 (n=20)	0.140

Figure 3. Kaplan Meier Curve of Chronological age at Attainment of Near-Adult Height (NAH population)



Safety

- Neoplasia – 4 cases (3 *de novo*) reported in 3 subjects in ET group
  - Acute myeloblastic leukemia (AML) following medulloblastoma in same patient
    - Received ~12 months of GH treatment only during the original study;
    - Medulloblastoma diagnosed ~8.5y after discontinuation of GH, treated with surgery, chemotherapy and cranial irradiation;
    - AML diagnosed ~2.5y after diagnosis of medulloblastoma and treated with chemotherapy but patient died of complications;
  - Primary mediastinal ganglioneuroma: age at diagnosis ~6.6y, duration of GH treatment ~0.7y.
  - Primary colon adenoma: age at diagnosis ~11.7y after ~10y of GH treatment .
- At least 1 non-serious adverse event:: 34 (94.4%) subjects in ET group and 32 (97.0%) in EUT group.
- Most commonly reported adverse events were in MedDRA classes - infections and infestations (n=54); gastrointestinal disorders (n=36); surgical and medical procedures (n=36).

Table 4. Occurrence Rates of SAEs (Safety Population)

Event	Early Treated (N=36)	Early Untreated (N=33)	Total (N=69)
Scoliosis	2 (5.6%)	0 (0.0%)	2 (2.9%)
Pneumonia	0 (0.0%)	2 (6.0%)	2 (2.9%)
Cellulitis	0 (0.0%)	1 (3.0%)	1 (1.4%)
Gastroenteritis	1 (2.8%)	0 (0.0%)	1 (1.4%)
Gastrointestinal hemorrhage	1 (2.8%)	0 (0.0%)	1 (1.4%)
Headache	1 (2.8%)	0 (0.0%)	1 (1.4%)
Mediastinal mass (ganglioneuroma)	1 (2.8%)	0 (0.0%)	1 (1.4%)
Medulloblastoma	1 (2.8%)	0 (0.0%)	1 (1.4%)
Surgery for anomalous pulmonary venous connection	0 (0.0%)	1 (3.0%)	1 (1.4%)
Surgery for atrial septal defect	1 (2.8%)	0 (0.0%)	1 (1.4%)
Surgery for pterygium colli	0 (0.0%)	1 (3.0%)	1 (1.4%)
Number of patients with SAE	6 (16.7%)	5 (15.2%)	

N = number of subjects in safety population, which included all participants

DISCUSSION AND CONCLUSIONS

- There were modest, non-significant differences in height SDS between ET and EUT groups at ages 10 y and 13 y.
- Mean NAH SDS was similar for ET and EUT and both groups attained NAH ~10 cm (ET 153.3 ± 6.7; n=25; EUT 152.1 ± 7.7; n=26) greater than if untreated, based on historical data [2].
- Study was not powered to detect between-group differences at interim time points, and based on number of subjects with NAH available, was only powered to detect a between-group difference of 1.0 SDS.
- GH treatment for EUT group was relatively early compared to standard practice (i.e. around age 4-6 y vs. 9 y [3]).
- Most ET subjects attained thelarche somewhat earlier than EUT subjects. However, there was no significant difference in age at initiation of estrogen replacement and attainment of NAH.
- In view of 3 cases of *de novo* neoplasia, it is important to provide long-term follow-up of GH-treated patients with TS, particularly those whose GH treatment is initiated at a very young age.

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References:

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