

Summary ID# 0817/4419

Clinical Study Summary: Study B9R-CA-GDCT Core Study and Addenda

Humatrope Treatment to Final Height in Turner Syndrome

Date summary approved by Lilly: 24 November 2008

Title of Study: Humatrope Treatment to Final Height in Turner Syndrome	
Investigator(s): This multicenter study included 13 principal investigators.	
Study Center(s): This study was conducted at 13 study centers in 1 country.	
Length of Study: Date of first patient visit: 06 February 1989 Date of last patient visit: 05 December 2007	Phase of Development: Phase 3 at study initiation Phase 4 at study completion
<p>Objectives:</p> <p>Core Study</p> <p><u>Primary Objective:</u> To determine the efficacy of Humatrope in promoting linear growth to final height in girls with Turner syndrome.</p> <p><u>Secondary Objective:</u> To determine the antigenicity and other measures of clinical safety of Humatrope in patients with Turner syndrome.</p> <p>Addendum 1:</p> <p>Objective: To provide to patients who were randomized to the Control group of the Core Study and who discontinued from the study on or after 19 December 1997 the option to receive Humatrope treatment if judged appropriate by their physician.</p> <p>Addendum 2:</p> <p>Objectives: 1) to collect true final height data; 2) to evaluate hearing, tympanic membrane function, and other specific areas of interest with respect to the safety of growth hormone therapy in Turner syndrome; and 3) to evaluate pancreatic beta cell function, as assessed by measurement of parameters of glucose metabolism.</p> <p>Addendum 3:</p> <p>Objectives: to determine the parental origin of the retained X chromosome of an appropriate subset of patients and to determine whether this held any predictive value for spontaneous growth or response to growth hormone therapy.</p>	

Study Design: Study B9R-CA-GDCT (hereafter referred to as the Core Study) was initiated as a Phase 3 outpatient, randomized, parallel, controlled comparison of the outcomes of Humatrope treatment versus non-treatment (hereafter referred to as the Control group, or simply, Control) to final height in patients with Turner syndrome. Patients in the Control group received no injections; patients in the treatment group (hereafter referred to as the Humatrope group) received Humatrope (50 µg/kg/dose) by subcutaneous injection 6 times per week (total weekly dose 0.3 mg/kg). Patients in both groups received ethinyl estradiol (escalating doses from 2.5 to 20 µg daily) after age 13, and medroxyprogesterone acetate (10-mg tablets 10 days each month) after age 15. Patients in both groups were to continue on study until attainment of final height (defined as the last height measurement when the patient's bone age was at least 14 years and height velocity was less than 2.0 cm/year, based on height measurements performed at least 6 months apart; Figure 1).

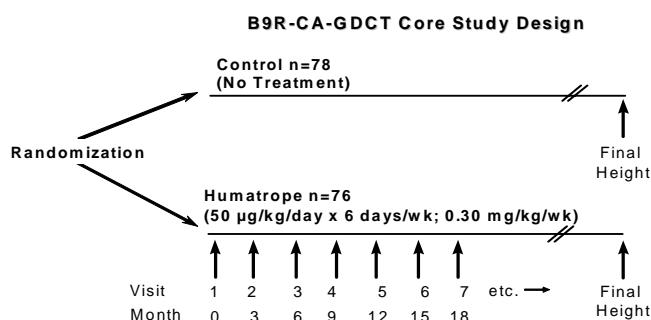
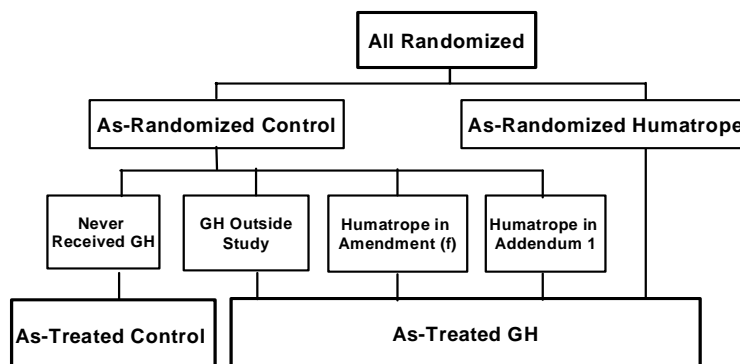


Figure 1. Study design.

Patients who had been randomized to the Control group in the Core Study and who remained in the study until 19 December 1997 were given the option to receive Humatrope through Protocol Amendment (f) or Protocol Addendum 1. In addition, some Control patients discontinued the Core Study and received growth hormone treatment outside the study; a number of these patients participated in follow-up through Protocol Addendum 2 (Figure 2).



Abbreviations: GH = growth hormone.

Figure 2. Participant flow diagram.

Number of Patients:

Planned: 100 (50 Control; 50 Humatrope)
 Randomized: 154 (78 Control; 76 Humatrope)
 Completed Core Study: 104 (43 Control; 61 Humatrope)
 Entered Addendum 1: 2 (2 Control; 0 Humatrope)
 Completed Addendum 1: 2 (2 Control; 0 Humatrope)
 Entered Addendum 2: 76 (28 Control; 48 Humatrope)
 Completed Addendum 2: 49 (18 Control; 31 Humatrope)
 Participated in Addendum 3: 57 (20 Control; 37 Humatrope)

Main Inclusion Criteria:

- Females with a diagnosis of Turner syndrome
- Chronological age 7 years to less than 13 years
- Prepubertal (Tanner stage I breast development)
- Height less than or equal to the 10th percentile for sex and age of the general population (United States National Center for Health Statistics standards, 1976)
- Prestudy height velocity less than 6 cm/year based on measurements obtained at least 6 months apart
- In hypothyroid patients, normal thyroid function tests over the 6-month period prior to enrollment
- Provision of signed informed consent by parent(s) or legal guardian(s)

Main Exclusion Criteria:

- Prior treatment with growth hormone
- Presence of a Y chromosome component in the karyotype with gonads in situ
- Diabetes mellitus or other clinically significant systemic disease
- History of malignancy

Study Drug Dosage and Mode of Administration:

The study drug was Humatrope (somatropin [rDNA for injection]; recombinant human growth hormone [GH]).

As-Randomized Treatment Groups

The **As-Randomized Non-Treatment Control** group (hereafter referred to as the Control group) was randomized to receive no injections (no active growth-promoting treatment). This group includes all patients who were randomized to the Non-Treatment Control group (no Humatrope) at Study GDCT entry, whether or not they subsequently received Humatrope or another brand of GH by any mechanism.

The **As-Randomized Humatrope-Treated** group (hereafter referred to as the As-Randomized Humatrope group, abbreviated when necessary to AR Humatrope) was randomized to receive Humatrope 0.05 mg/kg (50 µg/kg) by subcutaneous injection 6 times per week (0.3 mg/kg total weekly dose). The weekly Humatrope dose was not to exceed 15 mg. This group includes all patients who were randomized to the Humatrope group at Study GDCT entry, whether or not they actually received Humatrope.

As-Treated Treatment Groups

Several patients changed from Control to GH treatment outside the Core Study; in particular, some patients participated in Addendum 1, which provided the option of GH treatment to former Controls. Additionally, some patients who were randomized to Humatrope did not choose to continue in the Core Study and did not ever receive GH but contributed data in follow-up. To facilitate analysis according to treatment actually received, “As-Treated” groups are also defined.

The **As-Treated No-GH** group (abbreviated when necessary to **AT No GH**) group includes all patients who were randomized in the Core Study and received no form of GH either during or outside the study.

(continued)

As-Treated Treatment Groups (concluded)

The ***As-Treated GH-Treated*** group (hereafter referred to as the ***As-Treated GH*** group, abbreviated when necessary to ***AT GH***) group includes all patients, irrespective of their randomization group, who received Humatrope at any time during the study or any brand of GH outside the study.

Additional Study Medications (Both As-Randomized Treatment Groups)

In addition, patients in both treatment groups who had no clinical evidence of ovarian function received orally administered sex hormone replacement therapy (ethinyl estradiol 5.0-µg tablets and medroxyprogesterone acetate 10-mg tablets) on a standardized schedule according to the following criteria:

1. Patients at least 13 years of age who had been followed in the study for at least 12 months began estrogen replacement with ethinyl estradiol 2.5 µg daily;
2. Patients at least 14 years of age, but not yet 15 years of age, received ethinyl estradiol 5.0 µg daily;
3. After 1 year of treatment with ethinyl estradiol 5.0 µg, a cyclic hormone replacement regimen was initiated. The regimen comprised ethinyl estradiol 20 µg daily from Days 1 through 24, accompanied by medroxyprogesterone acetate 10 mg on Days 15 through 24. Both drugs were suspended on Day 24; the cycle was reinitiated on the first day of the following month.

Duration of Treatment or Study Participation: The Core Study was approved in 1988 with an initial treatment (or follow-up) duration of 18 months, to be extended by 12-month blocks to final height, based on interim study results. The protocol was amended in 1992 (Amendment [d]) to provide a definition of final height (annualized growth rate <2.0 cm/year based on at least 6 months' growth data and a bone age ≥14 years) as the criterion to determine patient completion of the Core Study.

Ethinyl estradiol and medroxyprogesterone acetate were to be taken as described above, until study completion (or beyond, at the discretion of the investigator).

Variables:Efficacy:

- Height standard deviation score (SDS; according to general female population standards of the National Center for Health Statistics [NHCS] [Kuczmarski et al. 2000]), hereafter abbreviated as Height SDS [NHCS]
- Change in height SDS [NHCS]
- Height SDS (according to the Turner syndrome standards of Lyon et al. 1985), hereafter abbreviated as Height SDS [Lyon]
- Change in height SDS [Lyon]
- Height (cm)
- Change in height (cm)

Safety:

- Adverse events
- Measures of middle ear and hearing function
- Measures of glucose metabolism (fasting blood glucose, fasting insulin, hemoglobin A_{1C})

Evaluation Methods:**Populations:**

The **All Randomized Population** is defined as all patients randomized in the Core Study, whether or not they received any study drug, or had a post-baseline visit.

The **Final Height Population** is defined as those patients who fulfilled any of the following criteria:

- Had a height measurement available after annualized height velocity had fallen below 2 cm/year, based on measurements at least 6 months apart, *and* after bone age (according to the central reader) was 14 years or greater (protocol completion criteria);
- Declared “Protocol Complete” by the investigator (whether or not formal protocol completion criteria were met); or
- Had a height measurement available after bone age of 15 years or chronological age of 17 years.

Safety Population

Patients in the **All Randomized Population** who either received any study medication or had post-baseline safety data.

Treated-As-Randomized Population

Patients in the **All Randomized Population** who at each observed time point maintained the treatment to which they were assigned at randomization.

Glucose 4-Year Population

Patients in the **Safety Population** who were followed for at least 4 years without GH treatment (if never treated with GH) or who received GH for a total of 4 years (if ever treated with GH).

Statistical Methods, Efficacy: Because the intent of the protocol was to establish both the principle of a GH-treatment effect in patients with Turner syndrome, and its magnitude in patients who completed treatment, the primary efficacy analysis consists of 2 components: intent-to-treat analysis of gain in height in the **All Randomized Population** (to inferentially establish presence of a GH effect) and Final Height analysis in the **Final Height Population** (for estimation of magnitude of GH effect).

Height and change-in-height analyses are performed using SDS, based on the US general population female standards (Kuczmarski et al. 2000) and the published Turner syndrome standards (Lyon et al. 1985). These SDS variables are referred to as Height SDS [NCHS] and Height SDS [Lyon].

Height SDS is calculated on each scale as:

- age-specific values, based on height and age at the time of measurement, and
- adult-standard values (last available height, irrespective of age, converted to SDS for height at 20 years of age [that is, adult height]).

Both height and change in height from baseline to last measurement are assessed with age-specific SDS. For patients in the **Final Height Population**, last measurement of height is additionally assessed in centimeters (cm) and adult SDS.

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Statistical Methods, Efficacy (concluded)

The presence or absence of a treatment effect of Humatrope upon height is determined by an intent-to-treat analysis, contrasting the treatments to which the patients were randomized. Specifically, the **primary inferential analysis** tests for difference between As-Randomized Treatment groups in the mean change in age-specific height SDS [NCHS], from baseline to last available height measurement, in the **All Randomized Population**.

In the presence of a treatment effect, the magnitude of treatment effect is estimated by an analysis of patients for whom true final height data are available, contrasting the treatments actually received by the patients. Specifically, the **primary estimation analysis** computes the difference between As-Treated Treatment Groups in the mean age-specific height SDS [NCHS], at last available height measurement, in the **Final Height Population**.

Primary and secondary efficacy variables are evaluated in an analysis of covariance (ANCOVA) model that includes explanatory variables of baseline height SDS [Lyon], baseline age, treatment, baseline height SDS [Lyon] by treatment interaction, and baseline age by treatment interaction. Baseline height SDS [Lyon] and treatment are retained as design factors; other terms are removed from the model if not significant at $p < 0.05$. P-values are given for the difference of least squares (LS) means between treatment groups based on Type III sums of squares in the ANCOVA model.

Statistical Methods, Safety: Analyses of adverse events are performed using the **Safety Population**, using As-Randomized treatment groups when analyzing the Core Study, and using As-Treated treatment groups when analyzing Addendum 2 data. To avoid confounding the safety data because of the change in treatment assignment of a number of patients after they had completed their participation in the Core Study, the **Treated-as-Randomized Population** is used to summarize the adverse events when analyzing the study as a whole (Core Baseline to Addendum 2 Endpoint). Treatment-emergent adverse events (TEAEs) are summarized at the patient level by counts and percentages of each occurring Medical Dictionary for Drug Regulatory Activities (MedDRA) Lower Level Term (LLT), for terms with prevalence $\geq 5\%$ in either treatment group. In addition, using an a priori classification of events into categories of special interest, occurrences at the patient level are compared between treatment groups, by counts and percentages, in the **Treated-as-Randomized Population** over the study as a whole. Targeted adverse events were collected by questionnaire during Addendum 2; numbers of occurrences at the patient level are compared for each event term by a Fisher Exact test between As-Treated treatment groups.

All middle ear and hearing analyses are performed on patients in the **All Randomized Population** who had a hearing examination performed. Because each patient who ever received GH had been treated by the time her hearing examination was performed, hearing analyses are performed with As-Treated treatment groups. The audiologists' qualitative assessments of normality or abnormality of middle ear and hearing data are evaluated by summarizing the number and percentage of patients with normal versus abnormal (or unknown) results for each of the following: (i) impedance tympanometry, (ii) pure tone audiometry, and (iii) speech audiometry. Additionally, for each of these tests, an analysis is performed of an objectively calculated criterion of normality, based on published references (King et al. 2007; Moscicki et al. 1985). All hearing analyses are evaluated with a Fisher Exact test of the number of abnormal results among evaluable results, between As-Treated treatment groups.

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Statistical Methods, Safety (concluded):

Addendum 2 collected additional targeted safety endpoints and laboratory data that were not collected in the Core Study. Safety data specifically from Addendum 2 (Addendum 2 Baseline to Addendum 2 Endpoint) are analyzed using the **Safety Population**, with the As-Treated treatment groups. When safety data from Addendum 2 are integrated for analysis with safety data from the Core Study, the **Treated-As-Randomized Population** is used.

Analyses of glucose metabolism data presented here focus on patients in the **Glucose 4-year Population**, to address specific questions of interest identified in the protocol. Mean fasting blood glucose, fasting insulin, and hemoglobin A_{1C} are tabulated at multiple analysis time points between Core Baseline and Addendum 2 last measurement. Change from Core Baseline to Addendum 2 Maximum, and Change from Core Last Measurement to Addendum 2 Maximum in each analyte are examined in an analysis of variance (ANOVA) model with a term for treatment. For both the Core Study (during treatment) and the Addendum (post-GH follow-up), the number of patients crossing specific clinically relevant cutpoints is tabulated, and tested between treatment groups by a Fisher Exact test, for glucose metabolism parameters of interest.

Patient Disposition

Table 1 provides the numbers of patients available for analyses of efficacy and safety variables.

**Table 1. Summary of Patient Disposition
All Analysis Populations
As-Randomized Treatment Groups
B9R-CA-GDCT**

	As-Randomized Control	As-Randomized Humatrope	Total
All Randomized Patients	78 (100%)	76 (100%)	154 (100%)
Safety Population	66 (84.6%)	75 (98.7%)	141 (91.6%)
Treated As Randomized	54 (69.2%)	74 (97.4%)	128 (83.1%)
Glucose Safety Population 1-year	60 (76.9%)	73 (96.1%)	133 (86.4%)
Glucose Safety Population 4-year	51 (65.4%)	59 (77.6%)	110 (71.4%)
Final Height Population	58 (74.4%)	72 (94.7%)	130 (84.4%)

The total number of patients randomized was used to calculate the percentages.

Program Location: SMDISA1.sas
Output Location: SMDISA11.txt
Data Location: Analysis_Data_Sets (COMMON)

Table 2 presents patient disposition and reasons for discontinuation. Of the 154 patients randomized in the study, 104 (67.5%) were declared protocol complete by the investigator. The most common reason for study discontinuation prior to protocol completion was patient decision (n=22; 14.3%).

**Table 2. Patient Disposition and Reasons for Discontinuation
All Randomized Population
As-Randomized Treatment Groups
B9R-CA-GDCT**

	As-Randomized Control	As-Randomized Humatrope	Total
All Randomized Population	78 (100%)	76 (100%)	154 (100%)
Declared Protocol Complete	43 (55.1%)	61 (80.3%)	104 (67.5%)
Discontinued Before Completion	35 (44.9%)	15 (19.7%)	50 (32.5%)
Withdrew Before Visit 1	11 (14.1%)	1 (1.3%)	12 (7.8%)
Discontinued at or Beyond Visit 1			
Patient Decision	14 (17.9%)	8 (10.5%)	22 (14.3%)
Entry Criteria Exclusion	3 (3.8%)	1 (1.3%)	4 (2.6%)
Protocol Violation	3 (3.8%)	1 (1.3%)	4 (2.6%)
Lost to Follow-up	3 (3.8%)	0 (0.0%)	3 (1.9%)
Adverse Event	0 (0.0%)	2 (2.6%)	2 (1.3%)
Lack Of Efficacy	0 (0.0%)	2 (2.6%)	2 (1.3%)
Death	1 (1.3%)	0 (0.0%)	1 (0.6%)

Notes:

Frequencies are presented as number (percent). Percentages are calculated relative to total number of randomized patients within treatment group. Reasons for patient discontinuation at or beyond Visit 1 are listed in descending order of frequency for the total patient population.

Program Location: SMDISA2.sas

Output Location: SMDISA21.txt

Data Location: Analysis_Data_Sets (ALL_M)

Of the 130 patients included in the **Final Height Population**, 108 (83.1%) fulfilled the formal protocol definition of final height (Table 3). An additional 22 patients either were declared protocol complete by the investigator, or had height measurements available at or beyond chronological age 17 or bone age 15.

**Table 3. Final Height Population
As-Randomized Treatment Groups
Completion Criteria Summary
B9R-CA-GDCT**

	As-Randomized Control	As-Randomized Humatrope	Total
Final Height Population	58 (100%)	72 (100%)	130 (100%)
Declared Protocol Complete by Investigator	43 (74.1%)	61 (84.7%)	104 (80.0%)
Fulfilled Protocol Definition of Protocol Completion	43 (74.1%)	65 (90.3%)	108 (83.1%)
Height Measurement Available at CA 17 or BA 15	53 (91.4%)	66 (91.7%)	119 (91.5%)

CA = Chronological Age, BA = Bone Age.

Program Location: SMDISA3.sas

Output Location: SMDISA31.txt

Data Location: Analysis_Data_Sets (COMMON)

Of the 154 patients who entered the Core Study, 76 (49.4%) returned for long-term follow-up in Addendum 2, and 49 (31.8%) completed Addendum 2 (Table 4).

**Table 4. Patient Participation in Core Study and Addenda
All Randomized Population
As-Randomized Treatment Groups
B9R-CA-GDCT**

Number of Patients	As-Randomized Control	As-Randomized Humatrope	Total
Core Study			
Started	78 (100%)	76 (100%)	154 (100%)
Completed	43 (55.1%)	61 (80.3%)	104 (67.5%)
Addendum 1			
Started	2 (2.6%)	NA	2 (1.3%)
Completed	2 (2.6%)	NA	2 (1.3%)
Addendum 2			
Started	28 (35.9%)	48 (63.2%)	76 (49.4%)
Completed	18 (23.1%)	31 (40.8%)	49 (31.8%)
Addendum 3			
Participated	20 (25.6%)	37 (48.7%)	57 (37.0%)
Hearing Examination Test Performed	25 (32.1%)	47 (61.8%)	72 (46.8%)

Program Location: SMDISA4.sas
Output Location: SMDISA41.txt
Data Location: Analysis_Data_Sets (ALL_M)

Efficacy Analyses

There were no statistically significant differences in baseline characteristics between treatment groups for either the **All Randomized Population** (Table 5) or the **Final Height Population** (Table 6).

Table 5. Summary of Patient Characteristics at Core Study Baseline All Randomized Population As-Randomized Treatment Groups B9R-CA-GDCT

Characteristics	As-Randomized Control	As-Randomized Humatrope	p-value
Age (years)	10.46 ± 1.77	10.36 ± 1.80	0.709
Height (cm)	120.06 ± 8.26	119.84 ± 8.45	0.872
Height SDS [NCHS] ¹	-3.25 ± 0.82	-3.21 ± 0.82	0.796
Height SDS [Lyon] ²	-0.13 ± 0.86	-0.10 ± 0.88	0.809
Pre-treatment height velocity (cm/year)	4.08 ± 1.01	4.23 ± 1.10	0.418
Pre-treatment height velocity SDS [Ranke] ²	0.27 ± 0.69	0.35 ± 0.74	0.509
Target height ³ (cm)	160.02 ± 6.04	161.42 ± 6.06	0.172
Target height ³ SDS NCHS [adult]	-0.51 ± 0.93	-0.29 ± 0.93	0.173
Bone age (years)	8.57 ± 1.51	8.79 ± 1.42	0.373
Bone age delay (years)	-1.89 ± 1.28	-1.57 ± 1.16	0.134
Weight (kg)	27.03 ± 7.78	26.69 ± 7.78	0.788
Weight SDS	-1.75 ± 1.16	-1.80 ± 1.30	0.789
Body mass index (kg/m ²)	18.44 ± 3.37	18.24 ± 3.35	0.713
Body mass index SDS	0.27 ± 0.82	0.18 ± 0.97	0.547
Karyotype 45,X (%)	61.5	59.2	0.702
Caucasian / Asian / other (%)	80.6 / 10.4 / 9.0	88.0 / 8.0 / 4.0	0.111
Stature stratum: lower / middle / upper (%)	21.8 / 39.7 / 38.5	23.7 / 36.8 / 39.5	0.936

Abbreviations: SDS = standard deviation score; NCHS = National Center for Health Statistics.

¹US general population female reference standard [Kuczmarski et al. 2000]

²Turner syndrome reference standard for height [Lyon et al. 1985] and height velocity [Ranke et al. 1988]

³Target height is the sex-adjusted average of parents' heights (also referred to as midparental height).

Frequencies of categorical variables are analyzed using a Fisher Exact test for the distribution across all categories in the data; means of continuous variables are analyzed using a type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.

Program Location: SMBSCA1.sas

Output Location: SMBSCA11.txt

Data Location: Analysis_Data_Sets (EFFICACY)

**Table 6. Summary of Patient Characteristics at Core Study Baseline
Final Height Population
As-Randomized Treatment Groups
B9R-CA-GDCT**

Characteristics	As-Randomized Control	As-Randomized Humatrope	p-value
Age (years)	10.57 ± 1.72	10.39 ± 1.80	0.557
Height (cm)	120.48 ± 7.74	119.84 ± 8.49	0.657
Height SDS [NCHS] ¹	-3.23 ± 0.84	-3.24 ± 0.83	0.988
Height SDS [Lyon] ²	-0.13 ± 0.87	-0.12 ± 0.89	0.967
Pre-treatment height velocity (cm/year)	4.18 ± 1.00	4.22 ± 1.12	0.823
Pre-treatment height velocity SDS [Ranke] ²	0.35 ± 0.68	0.34 ± 0.75	0.955
Target height ³ (cm)	160.14 ± 5.94	161.34 ± 6.14	0.268
Target height ³ SDS NCHS [adult]	-0.49 ± 0.92	-0.31 ± 0.95	0.268
Bone age (years)	8.64 ± 1.46	8.80 ± 1.43	0.538
Bone age delay (years)	-1.95 ± 1.37	-1.55 ± 1.18	0.089
Weight (kg)	27.38 ± 8.04	26.86 ± 7.84	0.712
Weight SDS	-1.74 ± 1.16	-1.78 ± 1.33	0.834
Body mass index (kg/m ²)	18.58 ± 3.64	18.36 ± 3.37	0.726
Body mass index SDS	0.27 ± 0.84	0.22 ± 0.97	0.778
Karyotype 45,X (%)	60.3	58.3	0.453
Caucasian / Asian / other (%)	78.6 / 10.7 / 10.7	87.5 / 8.3 / 4.2	0.072
Stature stratum: lower / middle / upper (%)	22.4 / 41.4 / 36.2	25.0 / 34.7 / 40.3	0.750

Abbreviations: SDS = standard deviation score; NCHS = National Center for Health Statistics.

¹US general population female reference standard [Kuczmarski et al. 2000]

²Turner syndrome reference standard for height [Lyon et al. 1985] and height velocity [Ranke et al. 1988]

³Target height is the sex-adjusted average of parents' heights (also referred to as midparental height).

Frequencies of categorical variables are analyzed using a Fisher Exact test for the distribution across all categories in the data; means of continuous variables are analyzed using a type III Sum of Squares analysis of variance (ANOVA): PROC GLM model=treatment.

Program Location: SMBSCA1.sas

Output Location: SMBSCA12.txt

Data Location: Analysis_Data_Sets (EFFICACY)

Table 7 presents a summary of the primary efficacy analyses. In the intent-to-treat analysis, a statistically significant difference was demonstrated for Change in Height SDS [NCHS] between As-Randomized treatment groups in the **All Randomized Population** (p<0.001, primary inferential analysis). In the efficacy analysis, for the **Final Height Population** according to As-Treated treatment groups, final Height SDS [NCHS] was 1.0 SDS (95% confidence interval [CI]: 0.9, 1.2) greater for the GH group than for the No GH group (primary estimation analysis).

**Table 7. Summary of Primary Efficacy Analyses, Height SDS [NCHS]
Inferential Analysis in All Randomized Population with As-Randomized Treatment Groups
Estimation Analysis in Final Height Population with As-Treated Treatment Groups
B9R-CA-GDCT**

Intent-to-Treat Analysis (Primary Inferential Analysis)						
Change in Height SDS [NCHS], Baseline to Last Measurement						
All Randomized Population						
As-Randomized Control			As-Randomized Humatrope			p-value
n	LS Mean	SE	n	LS Mean	SE	
78	0.09	0.07	76	0.97	0.07	0.9 (0.7, 1.1)
LS Means Difference and 95% CI						
						<0.001 ^a
Efficacy Analysis (Primary Estimation Analysis)						
Height SDS [NCHS], Last Measurement After Attainment of Final Height						
Final Height Population						
As-Treated No GH			As-Treated GH			p-value
n	LS Mean	SE	n	LS Mean	SE	
48	-3.30	0.07	82	-2.25	0.05	1.0 (0.9, 1.2) ^b
LS Means Difference and 95% CI						<0.001

Abbreviations: ANCOVA = analysis of covariance; SDS = standard deviation score; NCHS = National Center for Health Statistics; LS = least squares; SE = standard error; CI = confidence interval; GH = growth hormone.

Each analysis uses an ANCOVA model that includes explanatory variables of baseline height SDS [Lyon], baseline age, treatment, baseline height SDS [Lyon] by treatment interaction, and baseline age by treatment interaction. Baseline height SDS [Lyon] and treatment are retained as design factors; other terms are removed from the model if not significant at $p < 0.05$. P-values are given for the difference of LS means between treatment groups based on Type III sums of squares in the ANCOVA model.

^aThe p-value from the primary inferential analysis is used to establish existence of a treatment effect. Source: SMEFFA13.

^bThe LS means difference from the primary estimation analysis is the principal estimate of magnitude of treatment effect. Source: SMEFFA12.

The average age of the patients at final height was 20 years for the As-Randomized Control group and 21 years for the As-Randomized Humatrope group, after approximately 4.7 and 5.3 years of participation in the Core Study, respectively. Eleven (19%) of the patients randomized to Control ultimately received GH (Table 8).

**Table 8. Temporal Characteristics at Last Measurement
Final Height Population
As-Randomized Treatment Groups
B9R-CA-GDCT**

Characteristics	As-Randomized Control		As-Randomized Humatrope	
	n	Mean \pm SD	n	Mean \pm SD
Age (years)	58	20.05 \pm 3.62	72	20.97 \pm 3.42
Time on Core Study (years)	58	4.72 \pm 2.34	72	5.31 \pm 1.95
Total follow-up time (years)	58	9.48 \pm 3.79	72	10.58 \pm 3.61
Duration of GH (years) ^a	8	3.64 \pm 0.94	71	5.38 \pm 1.86

Abbreviations: SD = standard deviation; GH = growth hormone.

^aEleven patients who were randomized to Control ultimately received GH; duration of GH treatment is unknown for 3 patients.

Program Location: SMEFFA1.sas

Output Location: SMEFFA11.txt

Data Location: Analysis_Data_Sets (EFFICACY)

Analysis of the **Final Height Population** according to the As-Randomized treatment groups showed a difference of 0.8 SDS in the mean in adult Height SDS (NCHS). The corresponding difference between treatment groups for mean attained height was 5.4 cm. Mean bone age was approximately 15 years for both groups (Table 9).

**Table 9. Auxological Characteristics at Last Measurement
Final Height Population
As-Randomized Treatment Groups
B9R-CA-GDCT**

Characteristics	As-Randomized Control			As-Randomized Humatrope			LS Means Difference and 95% CI	p-value
	n	LS Mean	SE	n	LS Mean	SE		
Height (cm)	58	143.11	0.50	72	148.51	0.44	5.4 (4.1, 6.7)	<0.001
Height SDS [NCHS AS]	58	-3.08	0.08	72	-2.25	0.07	0.8 (0.6, 1.0)	<0.001
Height SDS [NCHS adult]	58	-3.10	0.08	72	-2.28	0.07	0.8 (0.6, 1.0)	<0.001
Height SDS [Lyon AS]	58	0.17	0.08	72	0.93	0.07	0.8 (0.6, 1.0)	<0.001
Height SDS [Lyon adult]	58	0.02	0.07	72	0.82	0.07	0.8 (0.6, 1.0)	<0.001
Height (cm), change from baseline	58	23.00	0.49	72	28.39	0.44	5.4 (4.1, 6.7)	<0.001
Height SDS [NCHS AS], change from baseline	58	0.15	0.08	72	0.99	0.08	0.8 (0.6, 1.1)	<0.001
Height SDS [Lyon AS], change from baseline	58	0.29	0.08	72	1.05	0.07	0.8 (0.6, 1.0)	<0.001
Bone Age (years)	57	14.83	0.15	72	14.89	0.13	0.1 (-0.3, 0.5)	0.775
Weight (kg)	56	49.36	1.70	72	56.81	1.50	7.5 (3.0, 11.9)	0.001
Weight SDS	56	-1.23	0.18	72	-0.30	0.16	0.9 (0.4, 1.4)	<0.001
BMI (kg/m ²)	56	24.45	0.68	72	25.78	0.60	1.3 (-0.5, 3.1)	0.142
BMI SDS [NCHS AS]	56	0.59	0.10	72	0.81	0.09	0.2 (-0.1, 0.5)	0.125
BMI SDS [NCHS AS], change from baseline	56	0.35	0.09	72	0.59	0.08	0.2 (-0.0, 0.5)	0.056

Abbreviations: LS = least squares; SE = standard error; CI = confidence interval; SDS = standard deviation score; NCHS = US general population female reference standard [Kuczmarski et al. 2000]; AS = age-specific; Lyon = Turner syndrome reference standard [Lyon et al. 1985]; BMI = body mass index.

Each analysis uses an ANCOVA model that includes explanatory variables of baseline height SDS [Lyon], baseline age, treatment, baseline height SDS [Lyon] by treatment interaction, and baseline age by treatment interaction. Baseline height SDS [Lyon] and treatment are retained as design factors; other terms are removed from the model if not significant at $p < 0.05$. P-values are given for the difference of LS means between treatment groups based on Type III sums of squares in the ANCOVA model. Source: SMEFFA11.

The average age of the patients at final height was 20 years for the As-Treated No GH group and 21 years for the As-Treated GH group after approximately 5.1 and 5.0 years of participation in the Core Study, respectively (Table 10).

**Table 10. Temporal Characteristics at Last Measurement
Final Height Population
As-Treated Treatment Groups
B9R-CA-GDCT**

Characteristics	As-Treated No GH		As-Treated GH	
	n	Mean \pm SD	n	Mean \pm SD
Age (years)	48	19.94 \pm 3.64	82	20.92 \pm 3.43
Time on Core Study (years)	48	5.08 \pm 2.27	82	5.03 \pm 2.09
Total follow-up time (years)	48	9.14 \pm 3.80	82	10.65 \pm 3.57
Duration of GH (years) ^a	0	NA	79	5.21 \pm 1.86

Abbreviations: SD = standard deviation; GH = growth hormone; NA = Not applicable.

^aEleven patients who were randomized to Control ultimately received GH; duration of GH treatment is unknown for 3 patients.

Program Location: SMEFFA1.sas

Output Location: SMEFFA12.txt

Data Location: Analysis_Data_Sets (EFFICACY)

Analysis of the **Final Height Population** according to the As-Treated treatment groups showed a difference of 1.0 SDS in the mean age-specific Height SDS (NCHS), and a difference of 1.1 SDS in mean adult Height SDS (NCHS). The corresponding difference between groups for mean attained height was 6.9 cm. Mean bone age was approximately 15 years for both groups (Table 11).

**Table 11. Auxological Characteristics at Last Measurement
Final Height Population
As-Treated Treatment Groups
B9R-CA-GDCT**

Characteristics	As-Treated No GH			As-Treated GH			LS Means Difference and 95% CI	p-value
	n	LS Mean	SE	n	LS Mean	SE		
Height (cm)	48	141.63	0.47	82	148.52	0.36	6.9 (5.7, 8.1)	<0.001
Height SDS [NCHS AS]	48	-3.30	0.07	82	-2.25	0.05	1.0 (0.9, 1.2) ^a	<0.001
Height SDS [NCHS adult]	48	-3.33	0.07	82	-2.27	0.05	1.1 (0.9, 1.2)	<0.001
Height SDS [Lyon AS]	48	-0.02	0.08	82	0.92	0.06	0.9 (0.7, 1.1)	<0.001
Height SDS [Lyon adult]	48	-0.20	0.07	82	0.82	0.05	1.0 (0.9, 1.2)	<0.001
Height (cm), change from baseline	48	21.53	0.47	82	28.38	0.36	6.8 (5.7, 8.0)	<0.001
Height SDS [NCHS AS], change from baseline	48	-0.09	0.08	82	0.99	0.06	1.1 (0.9, 1.3)	<0.001
Height SDS [Lyon AS], change from baseline	48	0.10	0.08	82	1.05	0.06	0.9 (0.7, 1.1)	<0.001
Bone age (years)	47	14.87	0.17	82	14.86	0.13	0.0 (-0.4, 0.4)	0.992
Weight (kg)	46	49.10	1.89	82	56.05	1.42	7.0 (2.3, 11.6)	0.004
Weight SDS	46	-1.37	0.20	82	-0.33	0.15	1.0 (0.5, 1.5)	<0.001
BMI (kg/m ²)	46	24.16	0.75	82	25.78	0.56	1.6 (-0.2, 3.5)	0.084
BMI SDS [NCHS AS]	46	0.52	0.11	82	0.82	0.09	0.3 (0.0, 0.6)	0.042
BMI SDS [NCHS AS], change from baseline	46	0.41	0.11	82	0.52	0.08	0.1 (-0.2, 0.4)	0.440

Abbreviations: GH = growth hormone; LS = least squares; SE = standard error; CI = confidence interval; SDS = standard deviation score; NCHS = US general population female reference standard [Kuczmarski et al. 2000]; AS = age-specific; Lyon = Turner syndrome reference standard [Lyon et al. 1985]; BMI = body mass index.

^aThe LS Means difference from this primary estimation analysis is the principal estimate of magnitude of treatment effect.

Each analysis uses an ANCOVA model that includes explanatory variables of baseline height SDS [Lyon], baseline age, treatment, baseline height SDS [Lyon] by treatment interaction, and baseline age by treatment interaction. Baseline height SDS [Lyon] and treatment are retained as design factors; other terms are removed from the model if not significant at p<0.05. P-values are given for the difference of LS means between treatment groups based on Type III sums of squares in the ANCOVA model. Source: SMEFFA12.

Safety Analyses

Table 12 provides an overview of adverse events reported in this study for patients in the **Treated-As-Randomized Population**. One Control patient for whom a serious adverse event was reported is not included in Table 12, because the patient received GH after participating in the Core Study and is therefore excluded from the **Treated-As-Randomized Population**; this patient's serious adverse event occurred during the Core Study, prior to GH therapy. In addition, 1 patient had an event of shortness of breath (dyspnea) that was not designated as serious when initially reported by the study site. The diagnosis for this event was later changed to asthma and the event outcome was changed to serious on the basis of threat to life; however, this change was not reflected in the study database, and this patient is therefore not included in the data provided below for serious adverse events.

**Table 12. Summary of Adverse Events for Overall Study
Treated-As-Randomized Population
As-Randomized Treatment Groups
B9R-CA-GDCT Core Baseline to Addendum 2 Endpoint**

	As-Randomized Control	As-Randomized Humatrope	Total
Treated-As-Randomized Population	54 (100%)	74 (100%)	128 (100%)
Type of Adverse Event			
Death	1 (1.9%)	0 (0.0%)	1 (0.8%)
Serious	10 (18.5%)	22 (29.7%)	32 (25.0%)
Resulted in Discontinuation from Study	0 (0.0%)	2 (2.7%)	2 (1.6%)
Event of Special Interest	47 (87.0%)	73 (98.6%)	120 (93.8%)
Treatment-emergent	53 (98.1%)	74 (100%)	127 (99.2%)

N = number of patients in treatment group; n = number of patients in treatment group for whom event was reported. Frequencies are presented as number (percent). Percentages are relative to Treated-As-Randomized population, within column.

A serious event was defined as an event that resulted in any of the following outcomes; death; threat to life; severe or permanent disability; hospitalization or prolongation of hospital stay if the event occurred while the patient was already hospitalized; other severe outcome (including cancer).

An event of special interest was defined as an event that either is known to occur with increased frequency in patients with Turner syndrome, or is listed in the product labeling for Humatrope.

A treatment-emergent adverse event was defined as any event that began after baseline (Visit 1) or increased in severity after baseline. The numbers represent patients for whom at least one treatment-emergent adverse event was reported.

Program Location: FQAESA1.sas
Output Location: FQAESA11.txt
Data Location: Analysis_Data_Sets (EVENT)

Serious Adverse Events

One patient in the As-Randomized Control group died as a result of a cardiac arrest following rupture of an aortic aneurysm. Forty-three other serious adverse events were reported for 33 patients: 11 patients in the As-Randomized Control group (including the patient who later died, and 1 patient who received GH treatment after leaving the Core Study) and 22 patients in the As-Randomized Humatrope group. These 43 events, which were serious on the basis of hospitalization, are summarized below in 5 broad categories. Because 5 of 33 patients had multiple hospitalizations, they are included in 2 distinct categories; the remaining 28 patients are included in 1 category only.

- Fifteen patients were hospitalized for 17 events that represented acute illnesses, infections, injuries, or surgeries (Control, n=5: 2 patients, appendicitis and appendectomy; 1 patient, ruptured aortic aneurysm; 1 patient, possible thrombophlebitis; 1 patient, pneumonia; Humatrope, n=10: 2 patients, arm fractures; 2 patients, viral gastroenteritis/“stomach flu”; 1 patient, acute psoriasis/pustular psoriasis [2 separate episodes]; 1 patient, cellulitis; 1 patient, pyelonephritis; 1 patient, viral meningitis; 1 patient, dehydration and wrist fracture [2 separate events]; and 1 patient, otitis media).
- Seven patients were hospitalized for 10 events of surgery related to ear, nose, and throat conditions (Control, n=1: 1 patient, teeth extraction; Humatrope, n=6: 1 patient, adenoidectomy; 1 patient tympanoplasty and mastoid operation [2 separate events]; 1 patient, mastoidectomy; 1 patient, tympanoplasty, mastoidectomy, and nasal surgery; 1 patient, tympanoplasty [1 event] and cholesteatoma resection [3 separate events]; and 1 patient, dental surgery).
- Six patients were hospitalized for elective surgeries (Control, n=4: 1 patient, ureteral reimplantation; 1 patient, pectus excavatum repair; 1 patient, plastic surgery for pterygium colli; 1 patient, plastic surgery for keloid scar removal; Humatrope, n=2: 1 patient, gonadectomy; and 1 patient, plastic surgery for pterygium colli).
- Six patients were hospitalized for other surgeries or procedures (Control, n=1: 1 patient, unspecified surgical procedure; Humatrope, n=5: 1 patient, gastroscopy and colonoscopy; 1 patient, cystoscopy and pyelogram; 1 patient, strabismus repair; 1 patient, coarctation repair; and 1 patient, ventriculo-peritoneal shunt revision).
- Four patients were hospitalized for events that were significant for other reasons (Control, n=1: 1 patient, idiopathic thrombocytopenic purpura; Humatrope, n=3: 1 patient, iron deficiency anemia; 1 patient, hypochromic, microcytic anemia; and 1 patient, cerebellar cyst).

Treatment-Emergent Adverse Events

Table 13 presents TEAEs reported in $\geq 5\%$ of patients in either group.

**Table 13. Treatment-Emergent Adverse Events (MedDRA LLT)
Reported for at least 5% of Patients in Either Group
Treated-As-Randomized Population, Events for Overall
Study
As-Randomized Treatment Groups
B9R-CA-GDCT Core Baseline to Addendum 2 Endpoint**

Treated-As-Randomized Population	As-Randomized Control 54 (100%)	As-Randomized Humatrope 74 (100%)	Total 128 (100%)
Any Adverse Event	53 (98.1%)	74 (100%)	127 (99.2%)
Cold	39 (72.2%)	42 (56.8%)	81 (63.3%)
Headache	25 (46.3%)	46 (62.2%)	71 (55.5%)
Sore throat	28 (51.9%)	37 (50.0%)	65 (50.8%)
Fever	20 (37.0%)	36 (48.6%)	56 (43.8%)
Flu	20 (37.0%)	36 (48.6%)	56 (43.8%)
Vomiting	21 (38.9%)	29 (39.2%)	50 (39.1%)
Otitis media	13 (24.1%)	32 (43.2%)	45 (35.2%)
Cough	14 (25.9%)	27 (36.5%)	41 (32.0%)
Ear infection	12 (22.2%)	27 (36.5%)	39 (30.5%)
Rhinitis	11 (20.4%)	17 (23.0%)	28 (21.9%)
Head cold	9 (16.7%)	18 (24.3%)	27 (21.1%)
Upper respiratory infection	14 (25.9%)	13 (17.6%)	27 (21.1%)
Nasal congestion	8 (14.8%)	17 (23.0%)	25 (19.5%)
Diarrhea	11 (20.4%)	12 (16.2%)	23 (18.0%)
Flu syndrome	6 (11.1%)	15 (20.3%)	21 (16.4%)
Hypothyroidism	7 (13.0%)	13 (17.6%)	20 (15.6%)
Otitis externa	6 (11.1%)	13 (17.6%)	19 (14.8%)
Pharyngitis	8 (14.8%)	11 (14.9%)	19 (14.8%)
Abdominal pain	9 (16.7%)	9 (12.2%)	18 (14.1%)
Nausea	5 (9.3%)	13 (17.6%)	18 (14.1%)
Ear pain	3 (5.6%)	14 (18.9%)	17 (13.3%)
Upper respiratory tract infection	9 (16.7%)	8 (10.8%)	17 (13.3%)
Ear ache	6 (11.1%)	10 (13.5%)	16 (12.5%)

(continued)

**Table 13. Treatment-Emergent Adverse Events (MedDRA LLT)
Reported for at least 5% of Patients in Either Group
Treated-As-Randomized Population, Events for Overall
Study
As-Randomized Treatment Groups
B9R-CA-GDCT Core Baseline to Addendum 2 Endpoint
(Continued)**

Treated-As-Randomized Population	As-Randomized Control 54 (100%)	As-Randomized Humatrope 74 (100%)	Total 128 (100%)
Rash	8 (14.8%)	8 (10.8%)	16 (12.5%)
Intermittent headache	3 (5.6%)	12 (16.2%)	15 (11.7%)
Throat infection	7 (13.0%)	8 (10.8%)	15 (11.7%)
Dental treatment	8 (14.8%)	6 (8.1%)	14 (10.9%)
Menstrual cramps	7 (13.0%)	7 (9.5%)	14 (10.9%)
Scoliosis	8 (14.8%)	6 (8.1%)	14 (10.9%)
Stomach ache	7 (13.0%)	7 (9.5%)	14 (10.9%)
Chickenpox	5 (9.3%)	8 (10.8%)	13 (10.2%)
Earache	5 (9.3%)	8 (10.8%)	13 (10.2%)
Stomach flu	6 (11.1%)	7 (9.5%)	13 (10.2%)
Streptococcal sore throat	4 (7.4%)	9 (12.2%)	13 (10.2%)
Bronchitis	5 (9.3%)	7 (9.5%)	12 (9.4%)
Eye infection	3 (5.6%)	9 (12.2%)	12 (9.4%)
Sinus congestion	5 (9.3%)	7 (9.5%)	12 (9.4%)
Cold symptoms	4 (7.4%)	7 (9.5%)	11 (8.6%)
Dizziness	4 (7.4%)	7 (9.5%)	11 (8.6%)
Tonsillitis	5 (9.3%)	6 (8.1%)	11 (8.6%)
Depression	4 (7.4%)	6 (8.1%)	10 (7.8%)
Impetigo	4 (7.4%)	6 (8.1%)	10 (7.8%)
Sinusitis	3 (5.6%)	7 (9.5%)	10 (7.8%)
Common cold	4 (7.4%)	5 (6.8%)	9 (7.0%)
Dry skin	1 (1.9%)	8 (10.8%)	9 (7.0%)
Gastroenteritis	2 (3.7%)	7 (9.5%)	9 (7.0%)
Hearing loss	2 (3.7%)	7 (9.5%)	9 (7.0%)
Knee pain	1 (1.9%)	8 (10.8%)	9 (7.0%)

(continued)

**Table 13. Treatment-Emergent Adverse Events (MedDRA LLT)
Reported for at least 5% of Patients in Either Group
Treated-As-Randomized Population, Events for Overall
Study
As-Randomized Treatment Groups
B9R-CA-GDCT Core Baseline to Addendum 2 Endpoint
(Continued)**

Treated-As-Randomized Population	As-Randomized Control 54 (100%)	As-Randomized Humatrope 74 (100%)	Total 128 (100%)
Myringotomy	1 (1.9%)	8 (10.8%)	9 (7.0%)
Primary ovarian failure	4 (7.4%)	5 (6.8%)	9 (7.0%)
Eczema	4 (7.4%)	4 (5.4%)	8 (6.3%)
Hay fever	1 (1.9%)	7 (9.5%)	8 (6.3%)
Hypertension	1 (1.9%)	7 (9.5%)	8 (6.3%)
Stomach cramps	4 (7.4%)	4 (5.4%)	8 (6.3%)
Stomach pain	2 (3.7%)	6 (8.1%)	8 (6.3%)
Upset stomach	3 (5.6%)	5 (6.8%)	8 (6.3%)
Urinary tract infection	3 (5.6%)	5 (6.8%)	8 (6.3%)
Bladder infection	3 (5.6%)	4 (5.4%)	7 (5.5%)
Chest cold	0 (0.0%)	7 (9.5%)	7 (5.5%)
Congestion nasal	2 (3.7%)	5 (6.8%)	7 (5.5%)
Coughing	2 (3.7%)	5 (6.8%)	7 (5.5%)
Low back pain	4 (7.4%)	3 (4.1%)	7 (5.5%)
Mole excision	2 (3.7%)	5 (6.8%)	7 (5.5%)
Multiple allergies	1 (1.9%)	6 (8.1%)	7 (5.5%)
Myopia	3 (5.6%)	4 (5.4%)	7 (5.5%)
Naevus	2 (3.7%)	5 (6.8%)	7 (5.5%)
Throat sore	1 (1.9%)	6 (8.1%)	7 (5.5%)
Tympanoplasty	0 (0.0%)	7 (9.5%)	7 (5.5%)
Conjunctivitis	2 (3.7%)	4 (5.4%)	6 (4.7%)
Cramps menstrual	2 (3.7%)	4 (5.4%)	6 (4.7%)
Dysmenorrhea	2 (3.7%)	4 (5.4%)	6 (4.7%)
Nose bleed	1 (1.9%)	5 (6.8%)	6 (4.7%)
Osteopenia	4 (7.4%)	2 (2.7%)	6 (4.7%)

(continued)

Table 13. Treatment-Emergent Adverse Events (MedDRA LLT) Reported for at least 5% of Patients in Either Group Treated-As-Randomized Population, Events for Overall Study As-Randomized Treatment Groups B9R-CA-GDCT Core Baseline to Addendum 2 Endpoint (Concluded)

Treated-As-Randomized Population	As-Randomized Control 54 (100%)	As-Randomized Humatrope 74 (100%)	Total 128 (100%)
Sinus infection	1 (1.9%)	5 (6.8%)	6 (4.7%)
Tooth extraction	3 (5.6%)	3 (4.1%)	6 (4.7%)
Accidental overdose	0 (0.0%)	5 (6.8%)	5 (3.9%)
Chest pain	4 (7.4%)	1 (1.4%)	5 (3.9%)
Dental surgery NOS	1 (1.9%)	4 (5.4%)	5 (3.9%)
Ear tube insertion	1 (1.9%)	4 (5.4%)	5 (3.9%)
Epistaxis	3 (5.6%)	2 (2.7%)	5 (3.9%)
Fatigue	4 (7.4%)	1 (1.4%)	5 (3.9%)
Head injury	3 (5.6%)	2 (2.7%)	5 (3.9%)
Ingrown toe nail	3 (5.6%)	2 (2.7%)	5 (3.9%)
Leg pain	1 (1.9%)	4 (5.4%)	5 (3.9%)
Nasal discharge	3 (5.6%)	2 (2.7%)	5 (3.9%)
Ache stomach	0 (0.0%)	4 (5.4%)	4 (3.1%)
Aortic dilatation	3 (5.6%)	1 (1.4%)	4 (3.1%)
Asthma	0 (0.0%)	4 (5.4%)	4 (3.1%)
Blood pressure high	3 (5.6%)	1 (1.4%)	4 (3.1%)
Ear discharge	0 (0.0%)	4 (5.4%)	4 (3.1%)
Pain	0 (0.0%)	4 (5.4%)	4 (3.1%)
Psoriasis	0 (0.0%)	4 (5.4%)	4 (3.1%)
Spotting vaginal	4 (7.4%)	0 (0.0%)	4 (3.1%)
Sensorineural hearing loss	3 (5.6%)	0 (0.0%)	3 (2.3%)
Tympanosclerosis	3 (5.6%)	0 (0.0%)	3 (2.3%)

N = number of patients in treatment group; n = number of patients in treatment group for whom event was reported. Frequencies are presented as number (percent). Percentages are relative to Treated-As-Randomized population, within column.

Events are listed in order of overall frequency of occurrence for total population.

MedDRA = Medical Dictionary for Regulatory Affairs, LLT = Lower Level Term.

A treatment-emergent adverse event was defined as any event that began after baseline (Visit 1) or increased in severity after baseline. The numbers represent patients for whom at least one treatment-emergent adverse event was reported.

Program Location: FQAESA2.sas
Output Location: FQAESA22.txt
Data Location: Analysis_Data_Sets (EVENT)

Addendum 2 employed a targeted questionnaire to solicit the occurrence of certain adverse events of special interest to patients with Turner syndrome or to those receiving GH. There were no statistically significant differences between treatment groups for any of these events (Table 14).

**Table 14. Targeted Adverse Events Collected by Questionnaire during Addendum 2
Safety Population with Addendum 2 Data
As-Treated Treatment Groups
B9R-CA-GDCT**

Safety Population	As-Treated No-GH 21 (100%)	As-Treated GH 55 (100%)	Total 76 (100%)	p-value
Diabetes	0 (0.0%)	1 (1.8%)	1 (1.3%)	>0.999
High blood sugar	0 (0.0%)	1 (1.8%)	1 (1.3%)	>0.999
Middle ear infection	2 (9.5%)	13 (23.6%)	15 (19.7%)	0.212
Ear surgery	0 (0.0%)	3 (5.5%)	3 (3.9%)	0.556
Hearing loss	5 (23.8%)	17 (30.9%)	22 (28.9%)	0.778
Other ear problem	0 (0.0%)	3 (5.5%)	3 (3.9%)	0.556
Heart surgery	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Other heart problem	4 (19.0%)	5 (9.1%)	9 (11.8%)	0.251
High blood pressure	3 (14.3%)	8 (14.5%)	11 (14.5%)	>0.999
Edema	2 (9.5%)	10 (18.2%)	12 (15.8%)	0.492
New diagnosis of scoliosis	1 (4.8%)	0 (0.0%)	1 (1.3%)	0.276
Worsening of scoliosis already present	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Surgery of scoliosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Limp	1 (4.8%)	1 (1.8%)	2 (2.6%)	0.479
Hip pain	1 (4.8%)	3 (5.5%)	4 (5.3%)	>0.999
Slipped capital femoral epiphysis	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Other bone or joint problem	3 (14.3%)	12 (21.8%)	15 (19.7%)	0.538
Pressure/fluid on the brain	0 (0.0%)	2 (3.6%)	2 (2.6%)	>0.999
Frequent headache	2 (9.5%)	6 (10.9%)	8 (10.5%)	>0.999
Hyperthyroidism	0 (0.0%)	1 (1.8%)	1 (1.3%)	>0.999
Hypothyroidism	4 (19.0%)	10 (18.2%)	14 (18.4%)	>0.999
Development of new moles on the skin	4 (19.0%)	7 (12.7%)	11 (14.5%)	0.484
Darkening or enlargement of moles already present on the skin	1 (4.8%)	7 (12.7%)	8 (10.5%)	0.432
Other surgery	3 (14.3%)	13 (23.6%)	16 (21.1%)	0.533
Other health problem	10 (47.6%)	19 (34.5%)	29 (38.2%)	0.306

N = number of patients in treatment group; n = number of patients in treatment group for whom event was reported. Frequencies are presented as number (percent). Percentages are relative to Safety Population with Addendum 2 data, within column.

P-values calculated using Fisher Exact test.

Program Location: FQAESA3.sas
Output Location: FQAESA31.txt
Data Location: Analysis_Data_Sets (EVENT)

An additional analysis of spontaneously reported TEAEs was performed to aid in detection of any potential safety signals. For this analysis, custom classifications were prospectively defined for events that may have clinical significance for patients with Turner syndrome or that may be associated with GH treatment (Table 15).

**Table 15. Events of Special Interest for Overall Study
Treated-As-Randomized Population
As-Randomized Treatment Groups
B9R-CA-GDCT Core Baseline to Addendum 2 Endpoint**

	As-Randomized Control	As-Randomized Humatrope	Total
Treated-As-Randomized Population	54 (100%)	74 (100%)	128 (100%)
Event of Special Interest	47 (87.0%)	73 (98.6%)	120 (93.8%)
Headache	25 (46.3%)	50 (67.6%)	75 (58.6%)
Otitis Media	22 (40.7%)	52 (70.3%)	74 (57.8%)
Ear Disorder	10 (18.5%)	35 (47.3%)	45 (35.2%)
Joint Disorder	9 (16.7%)	23 (31.1%)	32 (25.0%)
Menstrual Disorder	13 (24.1%)	19 (25.7%)	32 (25.0%)
Thyroid Disorder	12 (22.2%)	17 (23.0%)	29 (22.7%)
Cardiovascular Disorder	9 (16.7%)	18 (24.3%)	27 (21.1%)
Change in Cutaneous Nevi	8 (14.8%)	19 (25.7%)	27 (21.1%)
Hearing Disorder	5 (9.3%)	15 (20.3%)	20 (15.6%)
Scoliosis	8 (14.8%)	8 (10.8%)	16 (12.5%)
Back Pain	7 (13.0%)	8 (10.8%)	15 (11.7%)
Ear Tubes	3 (5.6%)	12 (16.2%)	15 (11.7%)
Edema	4 (7.4%)	10 (13.5%)	14 (10.9%)
Tympanic Membrane Disorder	4 (7.4%)	10 (13.5%)	14 (10.9%)
Fracture	4 (7.4%)	9 (12.2%)	13 (10.2%)
Bone Disorder	4 (7.4%)	4 (5.4%)	8 (6.3%)
Tonsillectomy and/or Adenoidectomy	1 (1.9%)	7 (9.5%)	8 (6.3%)
Liver Disorder	3 (5.6%)	2 (2.7%)	5 (3.9%)
Lymphoid Tissue Hyperplasia	1 (1.9%)	4 (5.4%)	5 (3.9%)
Diabetes Mellitus and Related	1 (1.9%)	2 (2.7%)	3 (2.3%)
Lipid Disorder	0 (0.0%)	3 (4.1%)	3 (2.3%)
Neoplasia	0 (0.0%)	1 (1.4%)	1 (0.8%)
Raised Intracranial Pressure	0 (0.0%)	1 (1.4%)	1 (0.8%)

N = number of patients in treatment group; n = number of patients in treatment group for whom event was reported. Frequencies are presented as number (percent). Percentages are relative to Treated-As-Randomized population, within column.

For analysis of Events of Special Interest, custom classifications were prospectively defined for events that may have clinical significance for patients with Turner syndrome or that may be associated with GH treatment.

Events are listed in order of overall frequency of occurrence for total population.

Program Location: FQAESA4.sas
Output Location: FQAESA41.txt
Data Location: Analysis_Data_Sets (EVENT)

Middle Ear and Hearing Assessments

There were no statistically significant differences between treatment groups in audiologists' assessments of any of 3 middle ear and hearing evaluations (Table 16).

**Table 16. Audiometric Examination Normality, Audiologist Assessed
All Randomized Patients with Hearing Examination
As-Treated Treatment Groups
B9R-CA-GDCT**

	As-Treated No GH	As-Treated GH	Total	p-value
Hearing Examination Performed	19	53	72	
Audiometric Examination Normality Questions Answered	19 (100%)	53 (100%)	72 (100%)	
Abnormal Pure Tone Audiometry, Hearing Threshold	10 (52.6%)	29 (54.7%)	39 (54.2%)	>0.999
Abnormal Speech Audiometry	3 (15.8%)	12 (22.6%)	15 (20.8%)	0.744
Abnormal Impedance Tympanogram	2 (10.5%)	18 (34.0%)	20 (27.8%)	0.073

Each p-value is from a Fisher Exact test of the proportion of patients whose result was reported abnormal among patients for whom the audiologist completed the normality assessment questions for 'Pure Tone Audiometry, Hearing Threshold', 'Speech Audiometry', and 'Impedance Tympanogram'.

Program Location: FQHEAA1.sas

Output Location: FQHEAA11.txt

Data Location: Analysis_Data_Sets (AUDEXAM_NORM_AA)

There was no statistically significant difference between treatment groups in the audiologists' overall assessment of hearing loss (Table 17).

**Table 17. Overview of Hearing Loss, Audiologist Assessed, By Type
All Randomized Patients with Hearing Examination
As-Treated Treatment Groups
B9R-CA-GDCT**

	As-Treated No GH	As-Treated GH	Total	p-value
Hearing Examination Performed	19	53	72	
Hearing Examination Normality Question Answered	19 (100%)	52 (100%)	71 (100%)	
No Hearing Loss, Audiologist Assessment	7 (36.8%)	20 (38.5%)	27 (38.0%)	
Hearing Loss, Audiologist Assessment	12 (63.2%)	32 (61.5%)	44 (62.0%)	>0.999
Conductive Hearing Loss	1 (5.3%)	7 (13.5%)	8 (11.3%)	
Sensorineural Hearing Loss	8 (42.1%)	15 (28.8%)	23 (32.4%)	
Conductive and Sensorineural (Mixed) Hearing Loss	2 (10.5%)	9 (17.3%)	11 (15.5%)	
Unspecified Hearing Loss	1 (5.3%)	1 (1.9%)	2 (2.8%)	

The p-value on 'Hearing Loss, Audiologist Assessment' is from a Fisher Exact test, upon the proportion of patients for whom the audiologist responded to an omnibus question regarding normality of the audiometric examination.

Program Location: FQHEAA1.sas

Output Location: FQHEAA12.txt

Data Location: Analysis_Data_Sets (HEARLOSS_TYPE_AA)

There was no statistically significant difference between treatment groups in calculated determinations of test normality for pure tone audiometry (Table 18), impedance tympanometry (Table 19), or speech audiometry (Table 20).

**Table 18. Overview of Hearing Loss, Calculated from Pure Tone Audiometry, By Type
All Randomized Patients with Hearing Examination
As-Treated Treatment Groups
B9R-CA-GDCT**

	As-Treated No GH	As-Treated GH	Total	p-value
Hearing Examination Performed	19	53	72	
Evaluable Pure Tone Audiometry Data	17 (100%)	44 (100%)	61 (100%)	
No Hearing Loss, Calculated	7 (41.2%)	20 (45.5%)	27 (44.3%)	
Hearing Loss of Any Type, Calculated	10 (58.8%)	24 (54.5%)	34 (55.7%)	>0.999
Sensorineural Hearing Loss (SNHL)	5 (29.4%)	7 (15.9%)	12 (19.7%)	
Conductive Hearing Loss (CHL)	0 (0.0%)	5 (11.4%)	5 (8.2%)	
Mixed Hearing Loss Type I (MHL1)	2 (11.8%)	6 (13.6%)	8 (13.1%)	
Mixed Hearing Loss Type II (MHL2)	1 (5.9%)	5 (11.4%)	6 (9.8%)	
Unspecified Hearing Loss (UHL)	4 (23.5%)	7 (15.9%)	11 (18.0%)	
Abnormal Pure Tone Average, Calculated	5 (29.4%)	19 (43.2%)	24 (39.3%)	0.391

Pure Tone Audiometry data was considered evaluable if air conduction values were available for all frequencies from 250 to 8000 Hz for both ears, and the difference in hearing threshold between air conduction and bone conduction was ≥ -5 dB HL in those cases in which bone conduction was tested. Abnormal hearing: air conduction > 20 dB HL at two adjacent frequencies or air conduction > 30 dB HL at any individual frequency; sensorineural hearing loss (SNHL): air conduction threshold > 20 dB HL and air-bone gap ≤ 10 dB HL; conductive hearing loss (CHL): air conduction threshold > 20 dB HL, bone conduction threshold ≤ 20 dB HL and air-bone gap > 10 dB HL; mixed hearing loss type 1 (MHL1): air conduction threshold > 20 dB HL and bone threshold > 20 and air-bone gap > 10 dB HL; mixed hearing loss type 2 (MHL2): evidence of SNHL as defined in (2) and CHL as defined in (3) in the same ear; unspecified hearing loss (UHL): abnormal hearing with none of SNHL, CHL, MHL1, or MHL2 present.

The p-values on 'Hearing Loss Of Any Type, Calculated' and 'Abnormal Pure Tone Average' are from a Fisher Exact test, as a proportion of patients with evaluable Pure Tone Audiometry data. In this table, an individual ear may have only one Type of Hearing Loss. However, Type of Hearing Loss may be different in each ear of an individual patient, and so categories are not mutually exclusive at the patient level.

Program Location: FQHEAA2.sas
Output Location: FQHEAA21.txt
Data Location: Analysis_Data_Sets (PURETONE_CALC)

**Table 19. Overview of Impedance Tympanometry, Calculated
All Randomized Patients with Hearing Examination
As-Treated Treatment Groups
B9R-CA-GDCT**

	As-Treated No GH	As-Treated GH	Total	p-value
Hearing Examination Performed	19	53	72	
Evaluable Tympanogram	16 (100%)	42 (100%)	58 (100%)	
Normal Tympanogram, Calculated	10 (62.5%)	17 (40.5%)	27 (46.6%)	
Tympanogram Abnormality Of Any Type, Calculated	6 (37.5%)	25 (59.5%)	31 (53.4%)	0.153
Reduced Equivalent Ear Canal Volume (ECV)	1 (6.3%)	0 (0.0%)	1 (1.7%)	
Increased Equivalent Ear Canal Volume (ECV)	3 (18.8%)	15 (35.7%)	18 (31.0%)	
Reduced Tympanometric Peak Pressure (TPP)	0 (0.0%)	6 (14.3%)	6 (10.3%)	
Reduced Static Admittance/Compliance (SA/C)	2 (12.5%)	8 (19.0%)	10 (17.2%)	
Increased Static Admittance/Compliance (SA/C)	0 (0.0%)	6 (14.3%)	6 (10.3%)	

Impedance Tympanometry data is Evaluable if, in both ears, values are available for each of Equivalent Ear Canal Volume (ECV), Tympanometric Peak Pressure (TPP), and Static Admittance/Compliance (SA/C). Types of tympanometry abnormality are not mutually exclusive; therefore, an individual patient may be included in more than one category.

The p-value for 'Tympanogram Abnormality Of Any Type, Calculated' is from a Fisher Exact test, as a proportion of patients with abnormal findings among the patients with evaluable Impedance Tympanometry data.

Program Location: FQHEAA2.sas

Output Location: FQHEAA22.txt

Data Location: Analysis_Data_Sets (TYMPANOMETRY_CALC)

**Table 20. Overview of Speech Audiometry, Calculated
All Randomized Patients with Hearing Examination
As-Treated Treatment Groups
B9R-CA-GDCT**

	As-Treated No GH	As-Treated GH	Total	p-value
Hearing Examination Performed	19	53	72	
Evaluable Speech Audiometry	19 (100%)	50 (100%)	69 (100%)	
Normal Speech Audiometry, Calculated	16 (84.2%)	41 (82.0%)	57 (82.6%)	
Speech Audiometry Abnormality Of Any Type, Calculated	3 (15.8%)	9 (18.0%)	12 (17.4%)	>0.999
Abnormal Speech Reception Threshold	3 (15.8%)	9 (18.0%)	12 (17.4%)	
Abnormal Speech Discrimination	1 (5.3%)	1 (2.0%)	2 (2.9%)	

Speech Audiometry data is Evaluable if, for both ears, values are available for Speech Reception Threshold and Speech Discrimination.

The p-value for 'Speech Audiometry Abnormality Of Any Type, Calculated' is from a Fisher Exact test, as a proportion of patients with evaluable Speech Audiometry data. Types of speech audiometry abnormality are not mutually exclusive; therefore, an individual patient may be included in more than one category.

Program Location: FQHEAA2.sas

Output Location: FQHEAA23.txt

Data Location: Analysis_Data_Sets (SPEECHAUD_CALC)

Measures of Glucose Metabolism

Fifty-six patients in the **Safety Population** who were followed for at least 4 years without GH treatment (if never treated) or who received GH for a total of 4 years were included in this analysis of glucose metabolism data. Average values for fasting glucose and hemoglobin A_{1C} were within the normal range (ADA 2007) at all time points and were similar for both treatment groups (Table 21).

**Table 21. Glucose Metabolism – Descriptive Statistics
Treated-As-Randomized Patients in Glucose 4-Year Population
As-Randomized Treatment Groups
B9R-CA-GDCT Patients with Glucose Metabolism Data at Core Baseline and during Addendum 2**

	Core Baseline		Core Last Measurement		Addendum 2 Baseline		Addendum 2 Last Measurement		Addendum 2 Maximum	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD

Fasting Glucose (mg/dL)										
Control	20	79.8 ± 10.6	19	77.0 ± 9.4	20	83.4 ± 7.0	11	81.1 ± 7.3	20	85.3 ± 6.8
Humatrope	36	81.1 ± 10.3	36	80.4 ± 9.2	35	78.9 ± 13.4	26	83.0 ± 8.5	36	84.1 ± 8.3
Fasting Glucose (mMol/L)										
Control	20	4.4 ± 0.6	19	4.3 ± 0.5	20	4.6 ± 0.4	11	4.5 ± 0.4	20	4.7 ± 0.4
Humatrope	36	4.5 ± 0.6	36	4.5 ± 0.5	35	4.4 ± 0.7	26	4.6 ± 0.5	36	4.7 ± 0.5
Hemoglobin A _{1C} (%)										
Control	20	4.8 ± 0.5	19	4.9 ± 0.6	20	5.0 ± 0.5	11	4.6 ± 0.5	20	5.0 ± 0.5
Humatrope	36	4.8 ± 0.5	36	5.0 ± 0.4	34	5.0 ± 0.4	24	4.8 ± 0.4	36	5.0 ± 0.4

Core Last Measurement - last post-baseline measurement in core study
Addendum 2 Last Measurement - last measured value at Visit 202 or 203
Addendum 2 Maximum - maximum value measured at Visit 201, 202, or 203

Program Location: SMLABA1.sas
Output Location: SMLABA13.txt
Data Location: Analysis_Data_Sets (GLUMET)

There were no statistically significant differences between treatment groups for changes in fasting blood glucose or hemoglobin A_{1C} (Table 22).

**Table 22. Glucose Metabolism – Inferential Statistics
Treated-As-Randomized Patients in Glucose 4-Year Population
As-Randomized Treatment Groups
B9R-CA-GDCT Patients with Glucose Metabolism Data at Core Baseline and during Addendum 2**

	Change from Core Baseline to Addendum 2 Maximum		Change from Core Last Measurement to Addendum 2 Maximum	
	Treatment Effect ¹ and 95% CI	p-value ²	Treatment Effect and 95% CI	p-value ³
Fasting Glucose (mg/dL)	-2.492 (-8.631, 3.646)	0.419	-5.071 (-11.324, 1.183)	0.110
Fasting Glucose (mMol/L)	-0.138 (-0.479, 0.202)		-0.281 (-0.628, 0.066)	
Hemoglobin A _{1C} (%)	-0.007 (-0.199, 0.186)	0.945	-0.004 (-0.167, 0.160)	0.966

¹ Treatment effect is difference in least squares means (Humatrope minus Control) from an ANOVA model with a term for treatment

² p-value for treatment effect on change from Core Baseline to Addendum 2 Maximum

³ p-value for treatment effect on change from Core Last Measurement to Addendum 2 Maximum.

Program Location: SMLABA1.sas

Output Location: SMLABA14.txt

Data Location: Analysis_Data_Sets (GLUMET)

Eight Control patients and 9 Humatrope-treated patients had abnormal fasting blood glucose values (≥ 100 mg/dL) at some time during the study. One patient in the Humatrope group had fasting blood glucose of ≥ 126 mg/dL, consistent with the American Diabetes Association (ADA) definition of diabetes (ADA 2007). Two of 16 Humatrope-treated patients who underwent modified oral glucose tolerance tests had 2-hour post-prandial glucose values consistent with the ADA definition of impaired glucose tolerance (≥ 140 mg/dL). There were no statistically significant differences between treatment groups for the proportion of patients with values above the defined cutpoints (Table 23).

Table 23. Glucose Metabolism Cutpoint Analysis, Core Study Safety Population As-Randomized Treatment Groups B9R-CA-GDCT Patients who Participated in Core Study for at Least 4 Years

Laboratory Test	Treatment	N	n (%)	p-value
Fasting Glucose ≥ 100 mg/dL	Control	43	8 (18.6%)	>0.999
	Humatrope	54	9 (16.7%)	
Fasting Glucose ≥ 100 , ≤ 125 mg/dL	Control	43	8 (18.6%)	-
	Humatrope	54	8 (14.8%)	
Fasting Glucose ≥ 126 mg/dL	Control	43	0 (0.0%)	-
	Humatrope	54	1 (1.9%)	
2-Hour Post-Prandial Glucose ≥ 140 mg/dL	Control	17	0 (0.0%)	0.227
	Humatrope	16	2 (12.5%)	
Hemoglobin A1C	Control	43	0 (0.0%)	0.504
	Humatrope	56	2 (3.6%)	

Abbreviations:

N = number of subjects with normal baseline data for Fasting Glucose and Hemoglobin A1C

N = number of subjects with test performed for 2-Hour Post-Prandial Glucose

n = number of subjects with abnormal post-baseline at any time during Core Study

All p-values are from Fisher Exact test.

For Hemoglobin A1C, cutpoint until 11 May 1998 $\geq 6.8\%$, from 19 May 1998 cutpoint was $\geq 6.1\%$.

Program Location: SMLABA5.sas

Output Location: SMLABA52.txt

Data Location: Analysis_Data_Sets (GLUMET)

Of the 60 patients evaluated in long-term follow-up in Addendum 2 (at least 1 year after treatment discontinuation for those who had received GH), 3 of 39 patients previously treated with GH had fasting blood glucose values consistent with the ADA definition of impaired fasting glucose (≥ 100 mg/dL; ADA 2007). Table 24 presents patients with values above or below the defined clinically significant cutpoints for each glucose metabolism parameter.

**Table 24. Glucose Metabolism Cutpoint Analysis, Post-GH Follow-up
Glucose 4-Year Population
As-Treated Treatment Groups
B9R-CA-GDCT Patients with Glucose Metabolism Data
during Addendum 2**

Laboratory Test	Treatment	N	n (%)	p-value
Fasting Glucose ≥ 100 mg/dL	AT No-GH	21	0 (0.0%)	0.545
	AT GH	39	3 (7.7%)	
Fasting Glucose ≥ 100 , ≤ 125 mg/dL	AT No-GH	21	0 (0.0%)	-
	AT GH	39	3 (7.7%)	
Fasting Glucose ≥ 126 mg/dL	AT No-GH	21	0 (0.0%)	-
	AT GH	39	0 (0.0%)	
Fasting Insulin Laboratory ≥ 35 μ IU/mL	AT No-GH	21	1 (4.8%)	>0.999
	AT GH	40	2 (5.0%)	
Fasting Insulin Clinical ≥ 20 μ IU/mL	AT No-GH	21	1 (4.8%)	>0.999
	AT GH	40	2 (5.0%)	
Fasting Glucose/Insulin Ratio ¹ ≤ 4.5 mg/ 10^{-4} U	AT No-GH	21	1 (4.8%)	>0.999
	AT GH	38	3 (7.9%)	
QUICKI ² ≤ 0.30	AT No-GH	21	1 (4.8%)	>0.999
	AT GH	39	2 (5.1%)	
Hemoglobin A1C	AT No-GH	21	0 (0.0%)	-
	AT GH	40	0 (0.0%)	

Abbreviations: N = number of subjects with any Addendum 2 data, n = number of subjects with an abnormal result at any time during Addendum 2

AT No-GH = As-Treated No-GH, AT GH = As-Treated GH

Fasting Insulin Laboratory = Cutpoint is laboratory-provided high limit of normal range

Fasting Insulin Clinical = Exceeding cutpoint yields clinical suspicion of insulin resistance

¹ Calculated only for patients with fasting blood < 100 mg/dL (< 5.6 mMol/L)

² QUICKI = Quantitative Insulin Sensitivity Check Index [Katz et al. 2000]

All p-values are from Fisher Exact test.

For Hemoglobin A1C, cutpoint until 11 May 1998 $\geq 6.8\%$, from 19 May 1998 cutpoint was $\geq 6.1\%$.

Program Location: SMLABA6.sas

Output Location: SMLABA62.txt

Data Location: Analysis_Data_Sets (GLUMET)

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