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RESEARCH ARTICLE

COMPARATIVE STUDY TO EVALUATE EFFICACY, SAFETY AND PHARMACOKINETICS OF FIRST INDIGENOUS BIOSIMILAR SOMATROPIN

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ABSTRACT

Background: Recombinant human GH is used for the treatment of GHD and various conditions of non-GHD short stature and catabolic states. A comparative clinical study was done to evaluate an indigenous biosimilar somatropin in growth hormone deficient children.

Materials and Methods: This was a prospective, multi-centric, randomized, comparative clinical study to evaluate efficacy, safety, pharmacokinetics and pharmacodynamics of biosimilar somatropin (study arm) and innovator reference product (reference arm) in 24 subjects of growth hormone deficient children. Primary objective was to assess the efficacy of study/ reference product and the secondary objectives were to assess change in weight, change in body mass index (BMI), change in bone age, assessment of IGF-1 levels, comparative pharmacokinetics and pharmacodynamics of study and reference products and evaluation of safety.

Result: After 12 months of treatment period, mean change in height at 6 months and 12 months was 7.5 cm and 12.3 cm in study arm and 6.0 cm and 11.4 cm in reference arm with non- significant difference.The mean change in weight at 6 months was 2.6 kg in biosimilar study arm and 1.8 kg in reference arm while the mean change in weight at 12 months was 4.8 kg in study arm and 4.1 kg in reference arm. The difference in both arms was statistically not significant. The mean change in BMI at 6 months and 12 months was also similar without any statistical difference. The mean change in bone age from baseline to month 12 and IGF 1 levels at screening, 3, 6 and 12 months were also similar in both arms without any significant statistical difference. Pharmacokinetic (PK) profile with parameters C_{max}, AUC_{0-24}, $AUC_{0-\infty}$, Ln-transformed pharmacokinetic parameters and t1/2 were similar. A total of 28 adverse events were reported. Six (50.00%) subjects in biosimilar study arm and 8 (66.67%) subjects in the reference arm reported at least one adverse event. Fourteen treatment related adverse events (TEAEs) were reported in the study arm and 13 were reported in the reference arm. Two TEAEs reported in biosimilar somatropin arm were considered to be related to study drug. No deaths or other SAEs were reported during this study. All the samples analysed in this study were negative for anti-drug antibody response with negative immunogenicity.

Conclusion: The biosimilar somatropin showed marked clinical similarity with the reference product in terms of efficacy, pharmacokinetics and safety.

INTRODUCTION

Growth hormone deficiency (GHD) results from inadequate production of growth hormone (GH) and can produce various medical conditions dependent on age. In infancy and childhood, growth failure may be the major effect[1]. Clinical approaches to the treatment of GH deficiency have overcome many difficulties, beginning from where to obtain it or how to synthesize it, to determining the appropriate dosage and availability once inside the body[2]. The advent of recombinant human growth hormone (hGH) marked a paradigm shift in pediatric endocrinology, expanding its scope beyond replacement of deficient and suppression of excess hormones to include pharmacological hormonal augmentation therapy[3]. The introduction of rhGH in 1985 ended the phase of pituitary-derived human growth hormone (pit-hGH) and its associated limitations and risks, opening the possibility of widespread clinical use[2]. Somatropin (recombinant human growth hormone) is recommended as a treatment option for children with growth failure associated with any conditions of GHD like Turner syndrome, Prader–Willi syndrome, chronic renal insufficiency and small for gestational age with subsequent growth failure at 4 years of age or later short stature homeobox-containing gene (*SHOX*) deficiency[4].The syndrome of GHD in children and adulthood has been fully defined and is characterized by decrease in growth in height, weight, bone structure, body mass and alterations in body composition, decreased capacity for exercise and quality of life (QoL), as well as a series of unfavorable changes in cardiovascular function, and lipid and carbohydrate metabolism[5]. Its diagnosis is based on the combination of growth parametres, pituitary disease, hypopituitarism and a decrease in the concentration of IGF-1 or in diminished GH responses to different stimuli[5]. Replacement therapy with recombinant human GH has been available since the 1980s. The experience accumulated since then is extensive, and nowadays there is no doubt that this

therapy improves or reverses most of the signs and symptoms of this hormonal deficiency[5].

GH replacement therapy is associated with beneficial effects on body composition, bone structure, health-related QoL and several cardiovascular risk factors. In patients with childhood-onset GHD it has been shown that the continuation or reinstitution of treatment for two years, in patients who completed growth, induced a significant increase in bone mineral density BMD compared to untreated patients. Therefore, the continuation of GH treatment during the period of transition from childhood to adulthood is recommended to obtain complete bone maturation. GH treatment improves health-related QoL in the majority of adult patients. Most of the improvement in QoL occurs during the first year of treatment, although this beneficial effect persists in the medium and long term. Sustained improvement in QoL scores has been shown to be more marked in women and in patients with low QoL at baseline. Treatment with GH in patients with GHD improves several cardiovascular risk factors, such as lipid profile, endothelial function and cardiovascular inflammatory markers. Morselli *et al*. have shown that four months of GH replacement therapy partly reversed sleep disturbances previously observed in untreated patients. Cardiac size and cardiac performance have been reported to improve with GH replacement therapy. Six months of GH treatment significantly improved anaerobic capacity and physical function in a time-dependent manner in adults with GHD[5].

MATERIALS AND METHODS

This was a prospective, multi-centric, open label, randomized, two-arm, parallel group, active control, comparative clinical study (**CTRI**/2015/06/005907) to evaluate efficacy, safety and pharmacokinetics of biosimilar somatropin (study arm) and innovator reference product (reference arm) in growth hormone deficient children. The study was conducted in compliance with the ethical principles that originated in the declaration of Helsinki andGood Clinical Practice Guideline of the International Conference on Harmonization (ICH-GCP) and Indian Schedule-Y regulations.

The primary objective was to assess the efficacy of study/ reference product in growth hormone deficient children. The secondary objectives were to assess change in weight, change in BMI, change in bone age, assessment of IGF-1 levels, to determine comparative single dose PK and PD of study and reference products and evaluation of safety. A total of 24 patients with height < -2 SD, height velocity below 25th percentile and proven GHD levels (defined as peak level of <7 ng/ml or peak level as defined by central lab for GH deficiency, whichever is higher) by GH stimulation test, as recommended by the Indian academy of paediatricians (IAP) Growth Monitoring Guidelines for Children from birth to 18 years, were enrolled in the study across five centers. Primary end point of the study was mean change in height at 12 months from baseline, after the start of therapy. From the published references, change in height, after treatment of rhGH was in between 6 and 9 with a standard deviation of 2.4. With expected height velocity 7 after treatment with rhGH at the end of one year and considering the standard deviation 2-2.4, alpha as 0.05 and power of 80%, the sample size required was 24.

Clinically suspected GH naïve prepubertal children between 3 -11 years of age for males and 3-10 years of age for females (both inclusive) with height < -2 SD and height velocity below 25th percentile were enrolled in the study. Idiopathic GHD confirmed during the screening period by a standard GH stimulation test, patients with ratio of bone age/chronological age of <0.9 with open epiphysis were enrolled in the study. Patients with a history of resistance to growth hormone therapy, major systemic illness, and/or had known hypersensitivity to study drug, patients having active neoplasia or intracranial tumor or growth retardation attributable to causes other than GHD were excluded. Patients with history of administration of other growth-altering medications, patients with abnormal laboratory parameters like serum creatinine, liver enzymes, blood cell count and Hb were also excluded. Patients with HIV, HBsAg, or HCV test positive or history of clinically significant diseases were also excluded from the study.

Patients were randomized in 1:1 ratio to receive either study or reference somatropin at a dose of 0.033 mg/kg/day (0.23 mg/kg/week) subcutaneously daily for one year. The randomization schedule was generated by the statistician and the centralized randomization provided was followed across all sites and subjects were assigned to the treatment groups according to randomization schedule. Randomization was managed centrally. Subject identification number was a unique number containing site number and patient number.

Baseline evaluation included medical history, physical examination, vital signs, GH stimulation test, ECG, X-ray (Bone age), hemogram, LFT/KFT, blood sugar (Fasting), electrolyte (Na+, K+, Ca++, PO4–), IGF-1, TSH, T3 and T4 levels, anti rhGH antibody assessment and demography [including height of subject before (6-12 month) at screening, height velocity of subject at screening and height of parents]. Subjects visited the study center for screening, randomization (Day 1) and subsequently after every month for 1 year. Subjects/parents were provided with a subject diary to keep a record of every day dose and time of administration to the subject, as per schedule. Parents were also required to record occurrence of adverse events (AEs), if any. Subjects/parents were required to carry the diary at the time of every visit/follow up during the study. During each visit, demographics (height and weight) were measured, following which the total dose to be given was adjusted and explained to the guardian. All subjects were monitored for AEs throughout the study.

All subjects were considered for single-dose PK and PD analysis with an objective of understanding the comparative PK and PD after two treatments. The parameters such as C_{max}, AUC_{0-24} and IGF-1 were estimated based on the drug level in the serum after first dose. Total twelve samples (1 ml each) were collected for pharmacokinetic analysis. Blood samples were taken at 60 minutes prior to drug administration with eleven post dose samples. Evaluation of safety was based on incidence of TEAEs, abnormal clinical as well as laboratory results from baseline to end of the study. Anti rhGH antibody assessment was carried out at baseline, 3 months, 6 months and 12 months.

The study and reference somatropin was administered at a dose of 0.033 mg/kg/day (0.23 mg/kg/week), 7 times a week, subcutaneously at night, (at bed time) approximately at the same time each day. During follow up in every month, demographics (height and weight) was measured, following which the total dose to be given was adjusted in accordance with the individual's weight. Subjects/parents were provided with a subject diary to keep a record of every day dose and

time of administration to the subject, as per schedule and were also be required to record occurrence of adverse event if any. Statistical analysis plan (SAP) was prepared to describe the statistical methods to be employed in the study and the data presentations required for this study. Statistical analyses were performed using the SAS® statistical software (Version: 9.3; SAS® Institute Inc., USA).

RESULTS

A total of 24 subjects were enrolled in the study across 5 centers. Subjects were randomized in a 1:1 ratio to receive study or reference somatropin i.e. 12 subjects in each arm. All randomized subjects received study medication as per study protocol and were considered for intent to treat (ITT)/safety population. All randomized subjects completed the study evaluations as per protocol without major deviations. Hence all subjects were considered for per-protocol (PP) population. The details of patient disposition are presented in table 1.

Table 1 Summary of subject disposition

	Study arm (N=12) n (%)	Reference arm (N=12) n (%)	Total (N=24) n (%)
Per protocol population	12 (100.00%)	12 (100.00%)	24 (100.00%)
Intent-To-Treat population	12 (100.00%)	12 (100.00%)	24 (100.00%)
Pharmacokinetic population	12 (100.00%)	12 (100.00%)	24 (100.00%)
Patients who completed study	12 (100.00%)	12 (100.00%)	24 (100.00%)
Patients who discontinued study	0 (0.00%)	0 (0.00%)	0 (0.00%)

In study somatropin arm, the mean age of the subjects was 7.4 years, mean height was 101.9 cm and mean weight was 16.1 kg. Out of 12 subjects randomized in study arm, 4 (33.33%) subjects were female and 8 (66.67%) subjects were males. In reference arm, the mean age of the subjects was 7.8 years, mean height was 96.9 cm and mean weight was 14.2 kg and out of 12 subjects, 7 (58.33%) subjects were female and 5 (41.67%) subjects were males. The demographic characteristics of the subjects enrolled in both arms for age, gender, height and weight at screening were matching[6].

Analysis of Efficacy

The mean height of subjects at screening was 101.9 cm in study arm compared to 96.9 cm in reference somatropin arm. After 12 months of treatment period, mean height was 114.2 cm in study arm compared to 108.2 cm in the reference arm. The mean change in height at 6 months and 12 months was 7.5 cm and 12.3 cm in study arm and 6.0 cm and 11.4 cm in reference arm. The difference between the two arms was statistically not significant at month 12. (Table 2)

Table 2 Summary statistics of Height [Intent To Treat population (ITT)]

					Change From Baseline	
Parameter	**Visit**	**Statistic**	**Study arm (N=12)**	**Reference arm (N=12)**	**Study arm (N=12)**	**Reference arm (N=12)**
Height (cm)	Screening	N	12	12		
		Mean	101.9	96.9		
		Std Dev	13.63	15.45		
		Median	100.0	100.7		
		Range	(77.0 , 117.5)	(76.0 , 117.0)		
	Month 6	N	12	12	12	12
		Mean	109.4	102.9	7.5	6.0
		Std Dev	13.49	14.64	1.39	1.57
		Median	107.5	106.3	7.0	6.2
		Range	(84.0 , 125.0)	(82.0 , 122.8)	(5.8 , 9.6)	(2.5 , 8.2)
		P value			0.0232	
	Month 12	N	12	12	12	12
		Mean	114.2	108.2	12.3	11.4
		Std Dev	13.51	14.13	2.85	2.46
		Median	113.3	110.4	11.9	12.2
		Range	(88.1 , 129.0)	(87.4 , 126.3)	(7.8 , 17.3)	(6.0 , 14.5)
		P value			0.3865	

The mean weight at baseline was 16.1 kg in study arm compared to 14.2 kg in reference arm. The mean change in weight at 6 months was 2.6 kg in biosimilar study arm and 1.8 kg in reference arm (p = 0.1947) while the mean change in weight at 12 months was 4.8 kg in study arm and 4.1 kg in reference arm (p=0.4598). The difference in both arms at 6 months and 12 months was statistically not significant. (Table3)

Table 3 Summary of Weight (ITT Population)

					Change From Baseline	
Parameter	**Visit**	**Statistic**	**Study arm (N=12)**	**Reference Arm (N=12)**	**Study arm (N=12)**	**Reference arm (N=12)**
Weight (kg)	Screening	N	12	12		
		Mean	16.1	14.2		
		Std Dev	5.08	5.68		
		Median	15.4	13.6		
		Range	(7.9 , 24.0)	(7.0 , 23.4)		
	Month 6	N	12	12	12	12
		Mean	18.7	16.0	2.6	1.8
		Std Dev	6.20	6.31	1.85	1.07
		Median	18.2	15.7	2.4	1.8
		Range	(9.2 , 28.9)	(8.7 , 27.6)	(0.2 , 5.9)	(0.0 , 4.2)
		P value			0.1947	
	Month 12	N	12	12	12	12
		Mean	20.8	18.3	4.8	4.1
		Std Dev	6.41	6.80	2.62	1.42
		Median	20.4	17.0	4.9	3.7
		Range	(11.1 , 32.0)	(9.6 , 30.2)	(1.7 , 10.3)	(2.2 , 6.8)
		P value			0.4598	

Change in BMI was also assessed at 6 and 12 months.The mean BMI at baseline was 15.1 kg/m^2 in study arm compared to 14.5 kg/m^2 in reference arm. The mean change in BMI at 6 months was 0.1 kg/m^2 and in study arm and 0.0 Kg/m^2 in reference arm (p = 0.7443). The mean change in BMI at 12 months was 0.5 kg/m^2 in both treatment arms (p = 0.9746). The difference in both arms at 6 months and 12 months was statistically not significant. (Table 4)

Table 4 Summary Statistics of BMI (ITT Population)

					Change From Baseline	
Parameter	**Visit**	**Statistic**	**Study arm (N=12)**	**Reference (N=12)**	**Study arm (N=12)**	**Reference (N=12)**
BMI (kg/m^2)	Screening	N	12	12		
		Mean	15.1	14.5		
		Std Dev	2.27	2.32		
		Median	15.1	13.5		
		Range	(11.7 , 18.3)	(12.1 , 20.8)		
	Month 6	N	12	12	12	12
		Mean	15.3	14.5	0.1	-0.0
		Std Dev	2.70	2.53	1.26	0.95
		Median	15.0	13.9	-0.0	-0.2
		Range	(11.5 , 20.5)	(11.9 , 21.6)	(-2.2 , 2.3)	(-1.9 , 1.5)
		P value			0.7443	
	Month 12	N	12	12	12	12
		Mean	15.6	15.0	0.5	0.5
		Std Dev	2.39	2.44	1.52	0.75
		Median	15.0	14.1	0.7	0.5

					Change From Baseline	
Parameter	Visit	Statistic	Study arm (N=12)	Reference (N=12)	Study arm (N=12)	Reference (N=12)
		Range	(12.4 , 19.9)	(12.6 , 21.4)	(-2.5 , 3.4)	(-0.7 , 2.4)
		P value			0.9746	

Bone age was assessed by X-ray of non-dominant hand & wrist at screening and 12 months. The mean bone age at screening was 4.7 years in study arm and 5.0 years in reference arm. The mean bone age at 12 months was 7.2 years in study arm and 6.7 years in reference arm. The mean change in bone age from baseline to month 12 was 2.5 years in biosimilar study arm and 1.7 years in reference arm. The difference in both arms was statistically not significant (p = 0.1262). (Table 5)

Table 5 Summary statistics of Bone Age (ITT Population)

					Change From Baseline	
Parameter	Visit	Statistic	Study arm (N=12)	Reference (N=12)	Study arm (N=12)	Reference (N=12)
Bone Age (years)	Screening	N	12	12		
		Mean	4.7	5.0		
		Std Dev	1.68	2.21		
		Median	5.0	5.4		
		Range	(2.0 , 7.0)	(2.0 , 8.0)		
	Month 12	N	12	12	12	12
		Mean	7.2	6.7	2.5	1.7
		Std Dev	2.79	2.10	1.56	0.52
		Median	7.0	7.1	2.5	2.0
		Range	(3.0 , 11.0)	(4.0 , 9.1)	(0.0 , 6.0)	(0.8 , 2.5)
		P value			0.1262	

Activation of growth hormone receptors stimulates synthesis and secretion of IGF-1. The IGF-1 levels were measured at screening, 3, 6 and 12 months. As expected, the mean IGF1 level increased steadily from baseline to month 12 with growth hormone therapy. The results are presented in Table 6.

Table 6 Summary statistics of IGF-1 (ITT population)

					Change From Baseline	
Parameter	Visit	Statistic	Study arm (N=12)	Reference (N=12)	Study arm (N=12)	Reference (N=12)
IGF-1	Day 1	N	12	12		
		Mean	38.5	18.6		
		Std Dev	67.55	26.43		
		Median	7.4	8.7		
		Range	(1.3 , 231.4)	(2.1 , 97.0)		
	Month 3	N	11	12	11	12
		Mean	155.1	95.8	115.3	77.2
		Std Dev	72.38	74.81	71.44	71.55
		Median	171.9	75.3	103.3	55.8
		Range	(50.1 , 279.6)	(16.3 , 251.6)	(-10.9 , 198.7)	(7.9 , 216.4)
		P value			0.2165	
	Month 6	N	11	12	11	12
		Mean	119.5	115.9	79.1	97.3
		Std Dev	48.21	88.82	60.92	73.56
		Median	104.5	92.1	75.8	83.5
		Range	(72.7 , 208.7)	(16.3 , 271.1)	(-62.7 , 163.4)	(9.5 , 235.8)
		P value			0.5251	
	Month 12	N	12	12	12	12
		Mean	162.1	143.0	123.6	124.5
		Std Dev	69.80	99.85	74.26	88.14
		Median	155.8	122.1	131.0	113.5
		Range	(36.5 , 335.9)	(17.6 , 338.4)	(-57.3 , 228.6)	(5.5 , 303.2)
		P value			0.9799	

Pharmacokinetic blood sampling was performed in all the 24 subjects (12 in each arm). Statistical analysis was performed on the pharmacokinetic parameters by using SAS®, statistical software (Version: 9.3; SAS® Institute Inc., USA). Ratio analysis was performed for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-24} and $AUC_{0-\infty}$. Ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-24} and $AUC_{0-\infty}$ were evaluated considering the 90% confidence interval. For study and reference product, mean C_{max} was 28.04 and 28.49 ng/mL, AUC_{0-24} was 215.15 and 259.33 (ng X hr/mL) and $AUC_{0-\infty}$ was 229.8 and 272.87 (ng X hr/mL) respectively. The median T_{max} observed for study and reference formulations was 3.83 and 4 hours respectively. The median $t_{1/2}$ observed for study and reference formulation was 3.83 hrs and 2.94 hrs respectively[6].

In this study, a total of 28 adverse events were reported. 6 (50.00%) subjects in biosimilar study arm and 8 (66.67%) subjects in the reference arm reported at least one adverse event. Out of these 28 adverse events, 27 were treatment emergent adverse events. 14 TEAEs were reported in the study arm and 13 were reported in the reference arm. Two TEAEs reported in study armwere considered to be related to study drug. No deaths or other serious adverse events (SAEs) were reported during this study. The summary of all adverse events reported during this study is presented below in Table 7.

Table 7 Overall summary of adverse events (ITT population)

	Study product (N=12) n (%) e	Reference product (N=12) n (%) e
At least one AE	6 (50.00%) 15	8 (66.67%) 13
At least one TEAE	6 (50.00%) 14	8 (66.67%) 13
At least one TEAE Related to study drug	1 (8.33%) 2	0 (0.00%) 0
At least one TESAE	0 (0.00%) 0	0 (0.00%) 0
Death	0 (0.00%) 0	0 (0.00%) 0
At least one TEAE leading to discontinuation	0 (0.00%) 0	0 (0.00%) 0

In biosimilar study arm, the most commonly reported adverse event was pyrexia 4 (33.33%). Other adverse events included anaemia, ear pain, vomiting, injection site atrophy, fore-arm fracture and alopecia areata. In reference arm, the most commonly reported adverse event was anaemia 5 (41.67%) followed by upper respiratory tract infection 3 (25.00%). Other adverse events included hypothyroidism, pyrexia, nasopharyngitis and calcium deficiency. Most of the adverse events reported during the study were not related to study drug. Injection site atrophy and one case of pyrexia reported in study armwere considered as possibly related to the study drug whereas causality of vomiting was reported as unknown.

In this study, antibody assessment was done in all subjects at baseline, 3 months, 6 months & 12 months. Immunogenicity assessment was done for anti-drug antibody against Human Growth Hormone (HGH) using in-house developed ELISA. All the samples analysed in this study were negative for anti-drug antibody response and no new immunologically mediated major clinical observations related to safety or efficacy were reported[6].

DISCUSSION

GHD encompasses a group of different pathologies, all with failure of or a reduction in GH secretion. It may occur singly or in combination with other pituitary hormone deficiencies and may be sporadic or familial. It may be congenital or acquired as a result of trauma, infiltrations, tumor or radiation therapy[7]. The era of molecular genetics, recombinant technology and the generation of genetically modified biological systems has expanded our understanding of the regulation and role of the growth hormone/insulin-like growth

factor (GH–IGF) axis. Today, recombinant human GH is used for the treatment of GHD and various conditions of non-GHD short stature and catabolic states[8]. More recent data suggest that a greater proportion of GH-treated patients with GHD are currently achieving an adult height within the normal range than reported in earlier studies. In particular, an analysis from International Growth Study Database (KIGS) of the effect of GH treatment on final height outcomes in children with idiopathic GHD showed that it is possible to achieve an adult height within the mid-parental height range[9]. In children with isolated GHD, younger age at treatment start was associated with improved near adult height (NAH) standard deviation score (SDS) compared with older age at treatment start[9]. The present study was designed to evaluate efficacy safety and PK of indigenous biosimilar somatropin as study arm with that of reference innovator somatropin in growth hormone deficient children. The demographic characteristics of the subjects enrolled in study and reference arms were comparable for age, height and weight. The primary endpoint of the study i.e. mean change in height at 6 months and 12 months from baseline, after start of the therapy was comparable in study and reference treatments arms. Both treatments were also comparable with respect to other efficacy parameters including mean change in weight, BMI and bone age. The mean IGF1 level also increased steadily from baseline to month 12 with growth hormone therapy. These finding support the comparable efficacy profile of study and reference products along with matching pharmacokinetic profile. In study arm, the most commonly reported adverse event was pyrexia with other AEs including anaemia, ear pain, vomiting, injection site atrophy, fore-arm fracture and alopecia areata. Most of the AEs reported during the study were not related to study drug.

A biosimilar product must demonstrate that it has "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product". The biosimilar somatropin showed clinical biosimilarity to reference innovator somatropin in the treatment of GHD in children with established therapeutic equivalence to the reference product. The use of an easily accessible biosimilar somatropin with equivalent safety will provide an added thrust for patient convenience and compliance.

CONCLUSION

In the present study considering the clinical response rate using primary and the secondary endpoint and safety assessments, the study data showed comparable response in both the treatment arms with equivalent safety. Hence, the two treatments were considered clinically equivalent for the treatment of GHD subjects. Therapy and use of biosimilar somatropin will be an equivalent and easily accessible alternative.

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Conflicts of Interest

There are no conflicts of interest.

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