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Effect of GenF20 Plus Supplementation on hGH Levels of Aging Adults-A Double-blind, Randomized, Placebo-Controlled, Crossover Study

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ABSTRACT

The present study was aimed to evaluate the human Growth Hormone (hGH) stimulatory potential of GenF20 Plus in aging adults. This was a double blind, randomized, crossover, placebo-controlled study and a total of 30 otherwise healthy participants were stratified to either receive GenF20 Plus or placebo in a cross-over manner. On day 3 and 11 of assessment, blood samples were collected before and after study product administration, and hGH levels were assessed using electro-chemiluminescence immunoassay. Treatment exposure across time was determined using area under concentration-time curve, whereas fatigue severity was evaluated by a visual analogue scale. Results indicated that GenF20 Plus levels peaked at 30 minutes and further at 90 minutes, and hGH levels in GenF20 Plus arm were significantly higher than placebo; $p<0.05$. Furthermore, a higher mean area under curve was observed for GenF20 Plus arm (18.78) as compared to the placebo (10.38) group at the end of study period; $p=0.056$. The VAS score though reduced in GenF20 group of participants was not significant; $p=0.06$.

Keywords: Human growth hormone (hGH), GenF20 plus, Immunoassay.

Abbreviation:

hGH: Human Growth Hormone; AUC: Area Under Curve; GH: Growth Hormone; IGF 1: Insulin-like Growth Factor-1; WHO: World Health Organization; GHD: Growth Hormone Deficiency; rhGH: recombinant human Growth Hormone; GABA: Gamma-Aminobutyric Acid; FDA: Food and Drug Administration; GCP: Good Clinical Practice; FBS: Fasting Blood Sugar; TSH: Thyroid Stimulating Hormone; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; IP: Investigational Product; GTF: Glucose Tolerance Factor; GPC: Glyceryl Phosphorylcholine; TMF: Trial Master File; VAFS: Visual Analogue Fatigue Scale; AEs: Adverse Events; SAEs: Seropis Adverse Events; ECLIA: Electro Chemiluminescence Immunoassay; PP: Per-Protocol; ICH-GCP: International Council of Harmonisation-Good Clinical Practice; SPSS: Statistical Package for the Social Sciences; SD: Standard Deviation; CI: Confidence Interval.

INTRODUCTION

Due in large part to the declining mortality, the average life expectancy of humans has continuously increased around the globe [1]. Although extended living brings a plethora of opportunities, it is very much dependent on individuals maintaining good health [2]. As a result, whether the additional life years are being enjoyed in healthy wellness or spent in sufferance has become a topic of intense research [1]. The World Health Organization (WHO) defines healthy ageing as "as the process of developing and maintaining the functional ability that enables wellbeing in older age" [1,2]. Functional ability refers to the capabilities that enable an individual to perform functionings that he or she values. It is unfortunate that the current evidence is contradictory and most of the elderlies experience poorer health

trajectories in latter part of their life [3]. As people age, some experience abnormal declines in physical and cognitive functioning. Both factors are detrimental and have major effect on one's ability to function adequately and efficiently [4]. Today, the world's older population is continually growing at an unprecedented rate. Thus, maintaining physical function and cognitive vitality in ageing population is one of the key challenges for the present healthcare system [5].

Growth Hormone (GH), also called as somatotropin is a 191 amino acid single chain polypeptide produced and secreted by the anterior pituitary gland. It has several critical roles throughout the human life span such as, maintaining lean body and bone mass, limiting visceral adiposity, regulating cardiovascular system as well as cognitive functions. Recent reviews of literature reports that with advancing age the GH production and concentrations in adults starts diminishing rapidly and after 30s, and reduction is by ~14% for every 10 years. Furthermore, this decrease in GH parallels the reduction in levels of Insulin-like Growth Factor-1 (IGF-1) that has endocrine, paracrine and autocrine effects [5,6]. As a result, this gradual decline or complete loss in GH production leads to body composition abnormalities, metabolic complications, disruption of GH/IGF-1 axis, immune deficiencies and psychological impairments [7,8]. With advancing age being linked to falling GH levels, most of the aforementioned changes resemble that of Growth Hormone Deficiency (GHD) syndrome. The treatment for GHD is GH replacement by 'recombinant human Growth Hormone (rhGH) ' and It has been effectively used for reversing many of these abnormalities [9,10]. The current rhGH treatment requires individuals to take daily subcutaneous injections over long periods of time, which especially in the elderly may be for life. This routine is considered to be too infrequent in reproducing multiple daily pulses of normal endogenous GH secretion. Moreover, ensuing treatment adherence is a burden for patients and their families alike [11]. Further, number of adverse events such as edema, arthralgia, gynecomastia, impaired fasting glucose, and diabetes have been reported in people undergoing GH injectable therapy [12]. With daily requisite injections, route inconvenience and high treatment costs limiting hGH therapy efficacy, there is a growing demand for developing natural, simpler, evidence-based alternatives that could not only be used as a stand-alone therapy but also as an addition to conventional treatments.

Research conducted during the last decade provided a considerable amount of new evidence for the role of GH in human aging [13]. Research efforts are now seeking products of natural origin that can stimulate the *in-situ* production of serum hGH levels. Rick Alleman conducted a study to evaluate the effectiveness of *Chlorophytum borivilianum* and *Mucuna pruriens* for enhancing the circulating GH levels of strength-trained individuals. Results demonstrated that the investigational product supplementation significantly increased the serum GH levels in study participants [14]. In addition, several studies have utilized amino acids or their isoforms for stimulating serum GH levels. Oral supplement -ation of Arginine [15], L-tryptophan, and Gamma Amino Butyric Acid (GABA) [16] have also shown potential in increasing endogenous GH levels in humans.With multiple effects of GH gaining global recognition, GenF20 Plus was developed as a novel alternative for improving treatment convenience and compliance in middle and older aged adults seeking GH therapy. In our previous double-blind, placebo-controlled study, we evaluated potential of GenF20 Plus in stimulating IGF-1 levels in 61 study volunteers. In the age group of ≥ 40 years, GenF20 Plus increased the levels of IGF-1 as compared to placebo (GenF20 Plus versus placebo IGF-1 levels: 28.57% vs-0.55%) [17]. Based on the promising results and evidence of our previous clinical trial, the present double blind, randomized, crossover, placebo-controlled study was conducted to evaluate the potential of GenF20 Plus supplementation in stimulating hGH levels of otherwise healthy middle to older aged individuals.

MATERIALS AND METHODS

Trial design and ethical considerations

The study was approved by an independent ethics committee-ACEAS, registered with the Office for Human Research Protections in the U.S. Department of Health and Human Services (IRB00006475). Written informed consents were voluntarily obtained from all participants and the study was registered on public clinical trials registry of U.S. National Library of Medicine (clinicaltrials.gov; NCT03658187). The study was performed in compliance with the Helsinki Declaration and ICH-GCP guidelines.

Study population

The study population included male and female participants aged between 40-60 years having hGH levels in the range of ≤ 0.94 and ≥ 0.12 ng/mL.Participants were included if they were in general good health, Body Mass Index (BMI) in the range of ≥ 25.0 and ≤ 29.9 kg/m^2, agreed to conform to overnight fasting and practice a consistent sleep wake schedule for the trial period. Participants were eligible if thyroid hormone levels were of euthyroid nature and Fasting Blood Sugar (FBS) was of non-diabetic nature. Study volunteers were excluded if they satisfied any of the

following criteria: ongoing or history of systemic conditions, showing symptoms of acute or chronic infections, use of beta-blockers, antibiotics, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids or psychotropic drugs. Abstinence from alcohol (≤ 24 hours) and caffeine products (≤ 12 hours) prior to any assessment visit was mandatory. Furthermore, a urine pregnancy test was performed in females of childbearing potential at assessment visits and those pregnant, planning pregnancy, or breastfeeding were not included.

Investigational products

Two different formulations of the Investigational Product (IP) were administered. The first in the form of tablets and the second in the form of liquid. The GenF20 Plus composition is detailed below:

- Composition of GenF20 Plus tablet: L-glutamine, L-arginine HCl, L-glycine, L-tyrosine, tribulus terrestris extract (40%), L-lysine HCl, astragalus root, colostrum powder, deer velvet antler powder, Gamma-Amino Butyric Acid (GABA), L-isoleucine, anterior pituitary powder, phosphatidylcholine choline 40%, L-valine, L-ornithine, and Glucose-Tolerance Factor (GTF) chromium
- Composition of GenF20 Plus (berry flavored) sublingual spray: Alpha Glyceryl Phosphorylcholine (GPC), GABA, mucuna pruriens, moomiyo extract, ornithine alpha ketoglutarate, L-glutamine, L-arginine, L-lysine, L-valine, L-isoleucine, L-tyrosine, and glycine

Matching placebo tablets were made up of carboxymethyl cellulose. Similarly, its liquid component was made up of berry-flavored distilled water with sodium saccharin and sucralose. The IP and placebo were indistinguishable in terms of color, flavor, size, weight and viscosity, and were dispensed in matching amber-colored glass bottles. Participants first took two tablets orally with water followed by 2 ml of sublingual liquid spray every day before lunch and dinner. Table 1 and Table 2 provides the composition of Investigational product.

Table 1: Composition of investigational product-GenF20 plus tablet

Sr. no.	Active ingredients	Quantity (mg)
1	L-Glutamine	115
2	L-Arginine HCl	130
3	L-Glycine	115
4	L-Tyrosine	100
5	Tribulus terrestris Ext 40%	80
6	L-Lysine HCl	100
7	Astragalus root	60
8	Colostrum Ext.	50
9	Deer antler velvet	50
10	Gamma Amino Butyric Acid (GABA)	50
11	L-Isoleucine	40
12	Anterior pituitary substance	30
13	Phosphatidyl Choline 40%	25
14	L-Valine	40
15	L-Ornithine	25
16	GTF chromium (yeast)	0.1
Total		1010.1
Other ingredients		
Dicalcium phosphate, Cellulose, Croscarmellose sodium, Silicon dioxide, Stearic acid, Magnesium stearate, Sodium alginate, Food glaze, Acetylated monoglycerides, Polysorbate 80-coating agent		

Table 2: Composition of investigational product-GenF20 plus syrup

Sr. no.	Active ingredients	Quantity/2 ml
1	Alpha GPC	350 mg
2	Growth factor proprietary blend: GABA (Gamma Amino Butyric Acid), Mucuna pruriens (seed), Moomiyo extract (in equal proportion of each)	2000 ng
3	Stimulator factor proprietary blend: Ornithine Alpha Ketoglutarate, L-Glutamine, L-Arginine, L-Lysine, L-Valine, L-Isoleucine, L-Tyrosine and Glycine (in equal proportion of each)	1000 ng
	Excipients	
4	Other Ingredients: filtered water, glycerin, citric acid, stevia, berry flavor, sodium benzoate, and potassium sorbate.	Quantity sufficient

Randomization and blinding

Study volunteers were randomized in blocks of 4 using Stats direct software-2.7.9 (Stats Direct Ltd, Altrincham, U.K) to either receive GenF20 Plus followed by placebo or vice versa. The blinding codes were secured in tamper-evident, sealed envelopes and access was limited to authorized personnel as per Vedic Lifesciences standard operating procedures.

Study conduct

Participants satisfying the inclusion/exclusion criteria on screening visit (-5 to -3day) were enrolled in the doubleblind, randomized, crossover, placebo-controlled study. Eligible participants were randomized on the baseline visit (day 0) in either of the study groups and a Visual Analog Fatigue Scale (VAFS) diary was provided [18] that was to be completed at the end of the day. On the evening prior to 1st IP assessment visit (day 3), study volunteers consumed 1st dose of IP and visited the clinical site in the morning in a fasting state. During this 1st IP assessment visit, 2nd dose of IP was administered on clinical site and blood samples were withdrawn before study product consumption (0 minutes) and every 30 minutes after study product consumption (30 minutes, 60 minutes, 90 minutesand 120 minutes) and a VAFS diary was provided that was to be completed at the end of the day. Participants were crossed over to the next sequence post wash out period of 7 days. Again, on the evening prior to 2nd IP visit, volunteers consumed the IP and visited the site in the morning in a fasting state. IP was then administered and blood samples as detailed before were withdrawn pre-study and post-study product consumption. Participant was also provided a VAFS diary that was to be completed at the end of the day.

Adverse/Serious Adverse Events (AEs/SAEs) and vitals (heart rate and blood pressure) were monitored throughout the study period. Participants were specifically asked to avoid changing their diet and exercise while partaking in the clinical study. The study was conducted from July through October 2018.

OUTCOME MEASURES

Primary efficacy outcome

The hGH level was analyzed using Electro-Chemiluminescence-Immunoassay (ECLIA) using COBAS 6000 (Roche Diagnostics, Mannheim, Germany). Fasting blood samples were collected on day 3 and 11 at 0 (defined as last available measurement prior to study product consumption), (30 minutes, 60 minutes, 90 minutes and 120 minutes (defined as measurement post study product consumption). Area under the plasma concentration curve (AUC) calcula tions were made as per standard trapezoidal rule [19]. Change in hGH serum concentration of IP and placebo was compared at each time points.

Secondary efficacy outcome

The self-perceived feelings of fatigue were evaluated using VAFS [18]. The participants reported fatigue experienced on a 0-10 cm horizontal line with '0' representing 'No fatigue' and '10' denoting 'Worst possible fatigue' experienced. The score was obtained by measuring the line from "No Fatigue" to the point indicated by the participant representing their level of fatigue. Lower the score, lesser was the state of fatigue. Fatigue severity was self-assessed by the participant at the end of day 0, 3 and 11.

Safety assessment

Safety was determined in terms of clinical AEs/SAEs occurrences and evaluation of vital signs (blood pressure and heart rate) throughout the study duration.

QUALITY ASSURANCE

The study was conducted in compliance with the ICH-GCP guidelines laid down in E6 (R2) as per pre-approved monitoring and auditing plan by a Vedic Lifesciences team, independent of the clinical operations team.

STATISTICAL ANALYSIS

This sample size was chosen arbitrarily considering the exploratory nature of the study. Efficacy and safety analysis was performed for the Per-Protocol (PP) population inclusive of participants without any major protocol deviations. Shapiro-Wilk test was used for testing the normality of data and baseline characteristics were compared using paired t-test (continuous variables) and chi-square test (categorical variables). The AUC for hGH levels (0-120 minutes) was calculated using the standard trapezoidal rule and statistically analyzed using paired t-test. The between and within group significance for VAFS was assessed by Independent t-test and paired t-test. A result of '$p<0.05$' was considered to be statistically significant and all statistical analysis was performed using SPSS Python 3.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 60 participants were screened and 32 participants were enrolled in the present study. Study volunteers were randomized in two sequences (Sequence I: 1st dose GenF20 Plus and 2nd dose placebo and Sequence II: 1st dose Placebo and then 2nd dose GenF20 Plus). Total number of screening failures was 25, and 3 participants withdrew consent prior to dose administration. Post randomization, 1 participant each was lost to follow-up and withdrawn (due to presence of co-morbidities) on the discretion of study investigator. The PP analysis consisted of 30 participants with 15 in each arm. The participant disposition been provided in Figure 1.

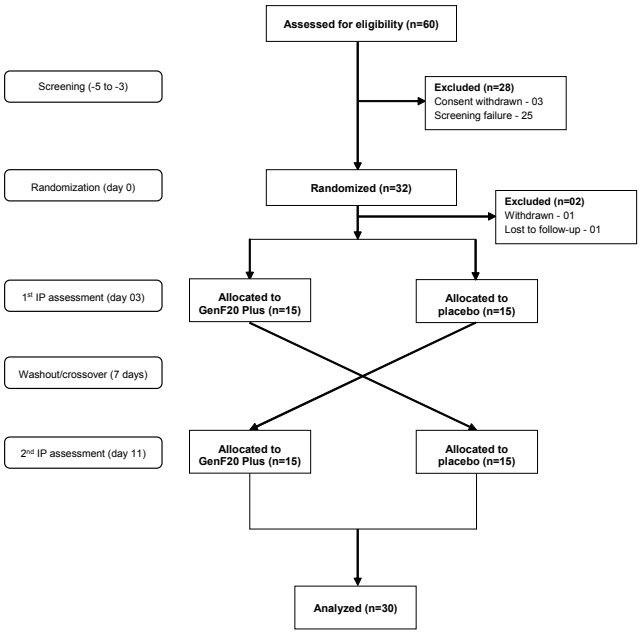

Figure 1. Participant disposition.

Participant demographics and characteristics

Participant demographic and baseline characteristics are detailed for randomized population. Group A and B had a mean ± SD age of 46.06 ± 6.04 and 46.8 ± 4.86 years and their mean ± SD BMI was 26.93 ± 1.29 and 27.54 ± 1.99 Kg/m^2, respectively. Majority of the participants were non-diabetic and mean hGH level reported for sequence I was 0.87 ± 0.10 ng/mL and 0.07 ± 0.04 ng/mL for sequence II. Apart from the hGH and TSH levels, the two sequences were comparable in other characteristics. A summarized description of demographics and baseline characteristics has been described in Table 3.

Table 3: Participants demographics and characteristics for enrolled population

Parameters	Group A (Sequence AB) (n=17)	Group B (Sequence BA) (n=15)	p-value
Age (years)			
Mean (SD)	46.06 (6.04)	46.8 (4.86)	0.71*
95% CI	42.96-49.16	44.11-49.49	
Gender			
Female-n (%)	2 (11.76)	3 (20)	0.52**
Male-n (%)	13 (88.24)	12 (80)	
Body mass index (kg/m^2)			
Mean (SD)	26.93 (1.29)	27.54 (1.99)	0.31*
95% CI	26.27-27.59	26.44-28.64	
Systolic blood pressure (mmHg)			
Mean (SD)	122.35 (13.08)	120 (14.22)	0.63*
95% CI	115.63-129.08	112.12-127.88	
Diastolic blood pressure (mmHg)			
Mean (SD)	85.88 (9.99)	83.87 (9.52)	0.57*
95% CI	80.75-91.02	78.6-89.14	
Pulse Rate (per minute)			
Mean (SD)	75.59 (7.05)	76.6 (9.08)	0.73*
95% CI	71.97-79.21	71.57-81.63	
Fasting Blood Glucose (mg/dl)			
Mean (SD)	91.12 (11.14)	98.07 (13.18)	0.12*
95% CI	85.39-96.85	90.77-105.36	
Thyroid stimulating hormone (mIU/ml)			
Mean (SD)	1.65 (0.73)	2.29 (1.09)	0.06*
95% CI	1.27-2.03	1.68-2.90	
Serum hGH (ng/mL)			
Mean (SD)	0.87 (0.10)	0.07 (0.04)	0.58*
95% CI	0.03-0.14	0.05-0.09	

n: number of participants; SD: Standard Deviation; CI: Confidence Interval; Sequence AB: GenF20 Plus-Placebo; Sequence BA: Placebo-GenF20 Plus.

Notes: p value: Paired sample t-test*; p value: Chi-square test**

Mean serum hGH levels

At 0 minutes, the mean ± SD hGH serum concentration was 0.15 ± 0.25 and 0.09 ± 0.09 for GenF20 Plus and placebo group respectively. Post administration, the hGH levels peaked at 30 minutes' in the GenF20 Plus group that were 0.19 ± 0.42 (↑ 0.04). In comparison, hGH levels of the placebo group were marginally increased to 0.10 ± 0.11 (↑ 0.01). Though reduced, at 90 minutes, hGH levels were notably higher in the GenF20 Plus arm (0.13 ± 0.15) as compared to placebo (0.07 ± 0.06). Percentage difference between the two groups was ~60 percent and a statistically significant difference was observed between the two groups at 90 minutes intervel; p=0.049. The group wise summary of serum hGH (0-120 minutes) concentration for GenF20 Plus and placebo is provided in Table 4.

Table 4: Summary of serum hGH (0-120 minutes) in GenF20 plus and placebo

Time points (minutes)	Statistics	GenF20 Plus (n=30)	Placebo (n=30)	p-value
0	Mean (SD)	0.15 (0.25)	0.09 (0.09)	0.074
	95% CI	0.06-0.25	0.06-0.12	
	Median	0.06	0.56	
	p25-p75	0.04-0.12	0.03-0.11	
30	Mean (SD)	0.19 (0.42)	0.10 (0.11)	0.419
	95% CI	0.04-0.35	0.06-0.14	
	Median	0.06	0.06	
	p25-p75	0.04-0.15	0.04-0.10	
60	Mean (SD)	0.18 (0.28)	0.09 (0.08)	0.16
	95% CI	0.07-0.28	0.06-0.12	
	Median	0.05	0.06	
	p25-p75	0.03-0.12	0.03-0.12	
90	Mean (SD)	0.13 (0.15)	0.07 (0.06)	0.049
	95% CI	0.07-0.18	0.05-0.10	
	Median	0.06	0.05	
	p25-p75	0.03-0.13	0.03-0.09	
120	Mean (SD)	0.08 (0.07)	0.07 (0.05)	0.525
	95% CI	0.06-0.11	0.05-0.09	
	Median	0.04	0.05	
	p25-p75	0.03-0.09	0.03-0.10	

n: number of participants; SD: Standard Deviation; CI: Confidence Interval; p25-p75: Percentile Notes: p value: Paired sample t-test

Area under concentration-time curve

The GenF20 Plus had an AUC of 18.78 which was higher than the AUC curve of 10.38 for the placebo. Though not significant, the difference in the AUC of the two groups indicates superiority of GenF20 Plus group as compared to placebo; p=0.056. Table 5 provides the mean AUC for GenF20 Plus and placebo group.

Table 5: Mean AUC (0-120 minutes) for GenF20 plus and placebo

Statistics	GenF20 Plus (n=30)	Placebo (n=30)	p-value
Mean (SD)	18.78 (26.95)	10.38 (8.16)	0.056
95% CI	8.71-28.84	7.34-13.43	
Median	7.16	8.62	
p25-p75	4.52-18.00	5.44-12.49	
n: number of participants; SD: Standard Deviation; CI: Confidence Interval; p25-p75: Percentile; Notes: p value: Paired sample t-test			

Fatigue severity

Overall mean ± SD VAFS score at baseline was recorded as 4.27 ± 2.50. Inter group comparison revealed reduction in GenF20 Plus arm with VAFS scores of 3.87 ± 2.54 whereas, placebo group scores were increased to 4.50 ± 2.75. Though the comparison was not significant, results do indicate an improvement in fatigue levels of GenF20 Plus participants versus placebo group; p=0.06. Table 6 provides the summary of VAFS score for GenF20 Plus and placebo groups when compared to baseline.

Table 6: VAFS score for GenF20 plus and placebo

Categories	Baseline VAFS score	GenF20 plus VAFS score	Placebo VAFS score
Mean (SD)	4.27 (2.50)	3.87 (2.54)	4.53 (2.75)
95% CI	3.33-5.20	2.92-4.82	3.47-5.53
Median	5	4	5
p25-p75	2-6	2-5	2-7
p value: GenF20 Plus vs Placebo		0.06	
n: Number of participants; SD: Standard Deviation; CI: Confidence Interval; p25-p75: Percentile; Notes: p value: Paired sample t-test			

Safety evaluation

Throughout the study duration, a total of 3 AEs was reported by the study population. Out of these, 2 events- increase in blood pressure and heartburn were reported in GenF20 Plus arm and in placebo group a single participant experien -ced elevated blood pressure. There were no serious adverse events, and AEs were mild in nature, resolved without the need for medical intervention. We would also like to mention the 3 events were reported by the investigator as 'doubtfully related to study product'.Further, BP and HR responses during the trial period did not indicate any clinica -lly significant change in both the study arms.

DISCUSSION

As the debate over the value of rhGH in GHD continues, one possibility that is receiving growing interest for promoting pituitary health and function is the use of GH secretagogues [20]. Examples include orally active GH releasing peptides or analogues of naturally occurring GH releasing hormone as their activity has been shown to decrease due to aging [21,22]. GenF20 Plus is one such novel compound and in the present randomized double-blinded, crossover study, we evaluated its potential to stimulate hGH in otherwise healthy aging adults.

The results of our study confirm the rationale that, GenF20 Plus stimulates hGH release in aging individuals. Post GenF20 Plus supplementation, hGH levels peaked at 30 minutes and there was also a significant difference detected between the two groups at 90 minutes' interval: $p<0.05$. A recent study evaluating the effect of an amino acid-based hGH secretagogue on GH levels reported a 682% increase in GH levels. The consequent mean changes in GH level (0 to 120 minutes) was 1.15 ng/mL for the IP whereas-0.48 ng/mL for the placebo group [23]. It is very important to

have a sound scientific rationale for adults seeking synthetic or natural GH therapies. As per literature, excessive secretion of hGH and persistent levels of IGF-1 can have detrimental effects on health of an individual. Ninety-five percent of acromegaly cases are associated with hypertension, joint disorders and episodes of cardiac or respiratory failure [24]. In the present study, a selective and controlled release of hGH was observed with hGH levels getting restored to baseline values at the end of evaluatory period.

Untreated GHD can have serious consequences on psychological, physical, cognitive, and energy aspects of life [25]. Reduced cardiorespiratory fitness, low physical activity accompanied with extreme fatigue and exhaustion are prevalent in adults with GHD [26]. We evaluated the impact of GenF20 Plus on fatigue levels of study participants using a highly sensitive VAF scale. The self-reported energy levels of GenF20 Plus group of participants were increased with reduction in VAFS score as compared with baseline and placebo group. Though inter-group analysis did not reach statistical significance, the findings are important as GenF20 plus cohort experienced reduction in fatigue severity that can have a positive effect on quality of life. Furthermore, AEs were non-severe and did not require any medical care. Although there was a remote chance of events being possibly related to the IP however, no hypothesis in was deducible. During the entire trial period, heart rate and blood pressure were normal with no abnormalities being reported for either groups. Additionally, no SAEs were reported during the course of the study duration. To sum up, GenF20 plus group displayed excellent tolerability and safety characteristics.

There are several reports stating that IGF-1 mediates anabolic as well as linear growth promoting effect of pituitary GH [27,28]. If not in entirety, some of the important effects of GH are facilitated by the IGF-1 hormone [29]. This correlation is also evident in the advancing age where the decline in GH levels of older adults corresponds to an identical reduction in their IGF-1 levels. In our previous study [17], the hypothesis of GenF20 Plus having an effect on the IGF-1 levels of individuals over the age of 40 was established. Whereas, in the present trial, GenF20 Plus was able to increase the hGH levels in participants of the age group 40-60 years. Therefore, study results reaffirm and demonstrate a positive correlation between GH and IGF-1 and also substantiated the potency of GenF20 Plus in stimulating GH levels in ageing population.

Even though, the efficacy of GenF20 plus was postulated, the study does have a few limitations. Being an exploratory study, the sample size was small. However, it was considered to be adequate for the study primary efficacy variable. A larger sample size could have assisted further in extrapolating the present study results. It is also difficult to achieve significant effect in each of the study parameters with a restricted sample size and shorter trial period. Longer duration could have attributed to GenF20 Plus demonstrating significant difference in study parameters however, the same was beyond the scope of the present study. We would also like to mention that the levels of GH in the study were reduced from baseline in both study groups. We believe this can be due to inter-participant variability in terms of age, sex, BMI, diet, blood-glucose levels, or stress [30-33]. Another reason for reduced baseline levels can be the circulatory half-life of the formulation but the same cannot be currently confirmed. Longer studies with broader and stricter trial design will aid in determining more exactly the visible efficacy, pharmacokinetics, and possible contraindications. To summarize, GenF20 Plus can be a viable addition to the current hGH treatment nevertheless, additional studies are patently needed to further extrapolate and extend the present study findings.

CONCLUSION

The results reported in this study confirm the rationale that, GenF20 Plus has potential in stimulating hGH levels of ageing adults and provides further evidence in validating its safety and efficacy. Further large-scale studies are warranted.

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AUTHORS' CONTRIBUTION

Individual contributions are as follows: Study conceptualization, methodology and supervision, Shalini Srivastava; Original draft preparation, writing and editing Ankul Kokate; review, Shalini Srivastava and Ankul Kokate. All auth -ors have read and approved the manuscript.

DECLARATION OF CONFLICTING INTERESTS

Shalini Srivastava and Ankul Kokate are employees of Vedic Lifesciences, Pvt, Ltd., that performed the study.

ETHICS APPROVAL

ACEAS Ethics committee (USA FDA registration No IRB00006475) reviewed the study protocol and approved the study (NCT03658187). The trial was registered retrospectively.

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