A Study to evaluate the effect of GenF20Plus on IGF-1 levels in Normal to Overweight Adult Volunteers with Poor Quality of Sleep, Decreased Memory, Decreased Libido, and Low Energy Levels

Protocol ID :	DM/100711/GFP/IGF-1
Investigational Product:	GenF20 Plus tablets + liquid
Sponsor :	Leading Edge Marketing
CRO :	Vedic Lifesciences Pvt. Ltd.
Date first patient enrolled :	23/7/2011
Date last patient completed :	7/4/2012
Date study terminated, if any :	NA
Investigator (name and affiliation) :	Dr. Pravin Supe, Dr. Rahul Patil, Dr. Suhas Erande, Dr. Vinayak Kale, Dr. Shivram Bhonagiri
Sponsor's medical officer / representative :	Mr. Douglas MacKay DM Contact Management
Report signatory and contact details :	Dr. Navneet Sonawane Tel.no.: 91-22-42025706
GCP compliance :	This study was conducted in full accordance with the study protocol and all applicable laws and regulations, including but not limited to current ICH-Good Clinical Practices, Schedule Y and the ICMR Ethical Guidelines for Biomedical Research on Human Participants.
Date of report :	Version 1.1 dated: 19-Jul-2012

This report conforms to the ICH-E3 guidelines for structure and content of Clinical Study Reports

1. Synopsis

Name of Sponsor/Company: Leading Edge Marketing **Name of Finished Product:** GenF20 Plus
Name of Active Ingredient: **GenF20 Plus tablets:** L Glutamine, L Arginine HCl , L Glycine, L Tyrosine, Tribulus Terrestris Extract , L Lysine HCl, Astragalus root, Colostrum powder, Deer Velvet Antler powder, GABA, L Isoleucine, Anterior pituitary powder, Phosphatidyl choline, L Valine, L Ornithine, GTF Chromium **GenF20 Plus Liquid:** Alpha GPC Growth Factor Proprietary Blend: GABA, Mucuna Pruriens, Moomiyo Extract Stimulator Factor Proprietary Blend: Ornithine Alpha Ketoglutarate, L-Glutamine, L-Arginine, L-Lysine, L-Valine, L-Isoleucine, L-Tyrosine and Glycine
Title of Study: GenF20 Plus in normal to overweight adult volunteers with poor quality of sleep, decreased memory, decreased libido and low energy levels
Investigators: Dr. Pravin Supe, Dr. Rahul Patil, Dr. Suhas Erande, Dr. Vinayak Kale, Dr. Shivram Bhonagiri
Study centre(s): 6 Supe Hospital, Jeevan Rekha Hospital, Akshay Hospital, Lokmanya Hospital, Medi-Point Clinic

Studied period : 12 weeks Date of first enrolment: 23/7/2011 Date of last completed: 7/4/2012	Phase of development: Exploratory

Objectives:

- To assess the effect of the IP on the quality of life (with respect to libido, sleep, memory, energy, body weight) using QoL questionnaire as compared to placebo
- To assess the safety and tolerability of the IP in study volunteers as compared to placebo

- To assess the effect of the IP on IGF-1 levels as compared to placebo

Methodology:

Normal to overweight subjects between the age group of 35-65 yrs were recruited. The treatment period was 12 weeks from baseline to end of treatment. The total number of visits were 5 including screening visit.

At the screening visit, a thorough explanation was given to each subject about the aims and course of the study, dosage, mode of administration, safety and efficacy of GenF20Plus (Tablets and Liquid).

After signing the informed consent form, medical history was noted and a physical examination was performed. Body Mass Index (BMI) was measured, an ECG was performed and a QoL questionnaire was filled by the subjects. Blood and urine samples were taken to assess laboratory parameters and screen out patients with related exclusion criteria. A Urine Pregnancy Test was performed to rule out pregnancy.

At the baseline visit (day 0), blood test was performed to determine serum IGF-1 levels. All the necessary clinical examinations and the QoL score were recorded. BMI, Waist circumference (WC), Body fat percentage and lean body mass were measured. The IP (124 tablets and 3 bottles of liquid GenF20 plus) was dispensed to subjects.

The subsequent 3 visits were scheduled at intervals of 4 weeks each. Subjects were called for follow up visits on day 28, 56 and 84 during which history and physical examination (including the measurement of BMI, waist circumference, Body fat percentage and lean body mass) was performed, QoL score was noted, IP was dispensed (except on day 84)and IP compliance was documented. AE and SAE monitoring was done at all visits except the screening visit.

On day 84, in addition to the measurements performed on the previous visits, safety blood and urine testing and ECG recording was done. An additional blood test was performed to determine change in the serum IGF-1 levels from the baseline. Global assessment of efficacy by subject was also noted at this last visit.

Diagnosis and main criteria for inclusion:

a. Adults with complains of any 2 from the following conditions: poor quality of sleep, decreased memory, decreased libido and low energy levels with grade scored 1 or 2 on a Likert scale 1-5. The conditions were present since at least 1 month and for not more than 6 months.)
b. Age between 35 to 65 years
c. Body Mass Index between 18.5 to 29.9 kg/m^2
d. Subjects willing to give written informed consent and abide with trial procedures and come for the follow up visits.
e. Women willing to practice suitable contraception (except oral contraceptives) during the study.
f. Subjects willing to continue current lifestyle practices with no modifications (in diet and exercise) during the study period

Test product, dose and mode of administration, batch number:

GenF20Plus tablets - 2 tablets twice a day, one hour before meals, route of administration – oral, batch no- 110621

GenF20Plus liquid (4 ml/day) – 2 ml to be held under the tongue for 30 seconds and then to be swallowed, twice a day before meals, batch no- 110622

Duration of treatment: 12 weeks/ subject

Reference therapy, dose and mode of administration, batch number:

Placebo Tablets - Carboxymethyl cellulose 2 tablets twice a day, one hour before meals, route of administration – oral, batch no- 110621

Placebo liquid – Berry flavoured distilled water with sodium saccharin and sucralose -2 ml to be held under the tongue for 30 seconds and then to be swallowed, twice a day before meals, batch no- 110622

Criteria for evaluation:

Efficacy parameters:

a. QoL questionnaire
b. Serum IGF-1 levels
c. BMI
d. Waist circumference
e. Body fat and lean body mass

f. Global Assessment by subject as excellent, good, fair & poor

Safety parameters:

a. CBC
b. SGPT
c. Serum Creatinine
d. Urine- routine
e. ECG
f. AE and SAE

Statistical methods:

The efficacy analysis was conducted on the PP population consisting of 61 subjects who completed the study strictly in accordance with the protocol. Of these 31 belonged to the active treatment group. Analysis of vital parameters and incidence of adverse events was described in the intention-to-treat (ITT) population consisting of subjects (n=70) who were randomized, received at least one dose of study medication and reported for at least one post-baseline measurement. Changes in laboratory parameters were analyzed in an ITT subset of subjects (n=52) for whom screening and end-of-treatment laboratory data were available.

Changes in IGF-1 values, BMI, waist circumference, body fat percentage, lean body mass and QoL parameters from baseline to Day 84 was compared across the two groups using ANOVA. Sub group analysis based on age (age≥40 & age<40) done by ANOVA and the effects of covariates on the change were adjusted for IGF-1 values. Responses to global assessment were analyzed using Pearson's chi square test.

Efficacy Results:

Efficacy analysis was conducted on the PP population (n=61).

GenF20 Plus was postulated to stimulate anterior pituitary gland to secrete HGH and thereby increase serum IGF-1 levels. HGH when released into the blood stream stimulates the liver to produce IGF-1 which is the primary mediator of HGH. Most of the indirect effects are mediated by induction of IGF-1 expression in the liver and in peripheral tissues. Thus levels of HGH and IGF-1 go hand in hand. Measuring levels of serum IGF-1 was included as one of the efficacy variables to indirectly assess HGH levels. Increase in serum IGF-1 levels due to consumption of GenF20 Plus during the study period would translate vis-a-vis as an increase in HGH secretion.

As the levels of serum IGF 1 decreases with increasing age, sub group analysis based on age (age≥40 and age<40) was done to get better understanding of the change in serum IGF-1 levels. In the subgroup (age≥40 years), the mean increase in IGF-1 values after ANCOVA was

statistically significant (p = 0.02) in GenF20 Plus group [22.69] as compared to the placebo group [-4.31]. The percentage increase of the same subgroup was 28.57% in GenF20 plus group and -0.55% in the placebo group with statistical significance (p=0.017). However in the subgroup (age<40), the mean increase in IGF 1 values after ANCOVA in GenF20 Plus group [12.71] and in placebo group [9.46] was not statistically significant (0.84).

The significant increase in the serum IGF-1 levels in the subgroup age ≥ 40 in the GenF20 plus group as compared to the placebo group is attributable to the consumption of GenF20 plus. In the sub group age<40, sustained inherent mechanism of the body of secreting normal levels of serum IGF-1 levels might be the reason of not showing considerable increase. Also the serum IGF-1 levels of the whole group increased from baseline to end-of-treatment in both the groups. The mean (SD) change occurred more in the GenF20 plus group 13.46(36.12) than in the placebo group 6.35(36.56). However it failed to reach statistical significance (p=0.45).

There was statistically significant improvement in Quality of Life variables; memory, energy level, and sleep from baseline to end of treatment in both the active and the placebo group. But the change was not statistically significant between the two groups. The short duration of 12 weeks was probably insufficient to assess improvement in the parameters. Scientific literature has shown positive effects of IGF-1 and HGH on improvement of sleep quality, energy levels, memory and libido. Thus longer study duration would have probably showed noteworthy improvement.

At the end of 12 weeks of treatment, the BMI, waist circumference, body fat and lean body mass did not show a significant reduction as compared to baseline in both, the active and placebo groups. Pearson's Chi square test on global assessment by subjects did not show a significant difference (p=0.80) between GenF20 Plus and placebo groups.

Safety Results:

There were a total of 12 adverse events reported; acidity (n=8), pain in abdomen (n=2), headache (n=1) and skin eruptions (n=1). Most of the adverse events were mild in severity. All AE's were not related to the study drugs and were successfully resolved. No serious adverse event occurred in the study.

Laboratory measurements were analyzed in subset of 52 subjects in whom complete laboratory data was available and vitals in ITT population (n=70). There were no significant changes observed in the hematology variables or vitals or urine routine test within each group and between the two groups.

Conclusion:

GenF20 Plus was well-tolerated and did demonstrate a significant increase in serum IGF-1 levels in the people aged 40 years and above but failed to show substantial efficacy in reducing weight and other parameters of Quality of Life in short duration of 12 weeks. As increase in HGH and IGF 1 by GenF20 plus is postulated to combat ageing and increase physical stamina, lean muscle mass, improve libido, quality of sleep and memory, a long term study to assess changes in the other parameters may help to substantiate the above postulation. The fact that serum IGF-1 levels have increased in 12 weeks, fosters the probability of improvement in all other parameters as well with consumption of GenF20 plus for longer duration.

Date of the report: Version 1.1 dated:19-July-2012

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2. List of Abbreviations

Abbreviations	Full form
AE	Adverse Event
ANCOVA	Analysis Of Covariance
ANOVA	Analysis Of Variance
BMI	Body Mass Index
CBC	Complete Blood Count
CRF	Case Report Form
CRO	Contract Research Organization
EC	Ethics Committee
ECG	Electro Cardio Gram
FDA	Food and Drug Administration
GI	Gastro Intestinal
HbA1C	Glycated Hemoglobin
HGH	Human Growth Hormone
ICH-GCP	International Conference on Harmonization
ICMR	Indian Council of Medical Research
IEC	Independent Ethics Committee
IGF	Insulin like Growth Factor
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent To Treat
LOCF	Last Observation Carried Forward
PP	Per Protocol
QA	Quality Assurance
QoL	Quality of Life

SAE	Serious Adverse Event
SGPT	Serum Glutamic Pyruvic Tranaminase
TIA	Transient ischemic attack
TMF	Trial Master File
TSH	Thyroid Stimulating Hormone
UPT	Urine Pregnancy Test
CV	Concomitant Variable
DV	Dependent Variable
WC	Waist Circumference

3. Ethics

3.1 Independent Ethics Committee (IEC)

In order to assure the safety and rights of the human volunteers who would enroll in the study, approval from central Ethics Committee (as mentioned below) was sought before initiating the trial. The name and address of the Ethics Committee for this study is as follows:

Independent Ethics Committee- Aditya,
ACEAS Clinical research,
001, Aradhya Apartments,
Behind Hero-Honda showroom,
Under Shreyas flyover, Ambawadi,
Ahemdabad, 380015, India.
Contact- +91-79-26460930, +91-93279 24927, +91-9377576768, +91 9377576769
Email-aceas@rediffmail.com

3.2 Ethical conduct of the study

This study has been conducted according to US and international standards of Good Clinical Practice and International Conference on Harmonization guidelines, the Declaration of Helsinki, the ICMR Ethical Guidelines for Biomedical Research on Human Participants, Schedule Y, applicable government regulations and Institutional research policies and procedures.

The protocol and any amendments were submitted to a properly constituted Independent Ethics Committee (IEC), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study was made in writing to the investigator and a copy of this decision was provided to the sponsor before commencement of this study.

3.3 Patient information and consent

All patients for this study were provided a consent form describing the study and providing sufficient information for patients to make an informed decision about their participation in this study. These consent forms were submitted with the protocol for review and approval by the EC/IRB for the study. The written consent of a patient, using the EC/IRB-approved consent form, was obtained before that patient was submitted to any study procedure. The patient and an impartial witness (incase the subject is illiterate) and the investigator-designated research professional obtaining the consent, had to sign this consent form. A signed copy of the consent form was provided to the patients.

4. Investigators and study administrative structure

The study's administrative structure has been tabulated in Table 1 below.

Table 1: Administrative Structure of Study Members

Contract Research Organization (CRO)		Vedic Lifesciences Pvt. Ltd. (VLPL) 118 Morya House, Off Link Road, Andheri (W), Mumbai-400053, India
Project Manager		Ms. Seema Damakale
Monitors		Mr. Ganesh Shresta Mr. Chetan Metha
Site	**Investigator**	**Study Coordinators**
1 – Nashik	Dr. Pravin Supe	Ms. Amandeep Kaur
2 – Nashik	Dr. Rahul Patil	Ms. Sonal Kulkarni
3 – Pune	Dr. Suhas Erande	Dr. Vinod Nagure.
4 – Pune	Dr. Vinayak Kale	Dr. Navnath Raut, Dr. Yashodhara Kasabe
5 - Pune	Dr. Shivram Bhonagiri	Dr. Vishal Oswal
Central Laboratory		Metropolis Healthcare Pvt. Ltd. Metropolis Healthcare Ltd. 250-D, Udyog Bhavan, Hind Cycle Marg, Behind Glaxo, Worli. Mumbai – 400030.
Bio-statistician		Dr. Arun Nanivadekar
Data Manager		Ms. Ashwini Mate
Medical Writer		Dr. Anuradha Kulkarni
Clinical Trial Supply Manufacturer (Active)		Mr. Sanjay Kukreja, Adroit Pharmaceuticals Pvt. Ltd. 46, Garo Maidan, Itwari, Nagpur – 440002
Clinical Trial Insurance Company		The Oriental Insurance Co. Ltd., Mumbai city divisional office no 18, Magnet house, 2nd floor, Narottam Morarji marg, Ballard Estate, Mumbai 400001

5. Introduction

Human Growth hormone (HGH) has growth promoting effects on the body, especially skeletal muscle, cartilage, bone, liver, kidney, nerves, skin, hematopoietic cell, and lungs. HGH production reaches its peak till adolescence and then gradually decreases with increasing age, an estimated 14% decrease per decade of adult life[1,2]. HGH when released into the blood stream stimulates the liver to produce Insulin-like growth factor 1 (IGF-1) which is the primary mediator of HGH. Most of the indirect effects are mediated by induction of IGF-1 expression in the liver and in peripheral tissues[3]. Thus levels of HGH and IGF-1 go hand in hand. Prolonged reduction of HGH and IGF 1 levels gets reflected through reduction in lean body mass, increase in body fat and rise in low-density lipoprotein (LDL) cholesterol[4].

Adult growth hormone deficiency is a well researched and documented endocrinological condition. The various signs and symptoms of adults with decreased growth hormone deficiency includes abnormal body composition with increased fat mass (especially central adiposity), decreased lean muscle mass, diminished muscle strength, physical energy and stamina, lack of motivation, lethargy, changes in mood, depression, and impairment of cognitive functions. The only treatment option available to diagnosed cases of adult growth hormone deficiency is HGH injections. Though not all adults are suffering from adult growth hormone deficiency, many have some of the symptoms due to subclinical levels of HGH. A new group of patients with disturbances in the HGH/IGF system are defined who are characterized by a relative deficiency in optimal HGH secretion[5]. Moreover, aging is associated with a reduction in plasma HGH and IGF-1 levels. There are no known safe and efficacious treatment options available for subclinical secretion of HGH. Thus GenF20 Plus was intended to provide a safe option to naturally replenish HGH levels in the body and improve quality of life.

GenF20plus contains essential amino acids and other ingredients which are known to stimulate anterior pituitary gland to secrete HGH. GenF20plus is a natural product with no known serious side effects. GenF20Plus is postulated to stimulate anterior pituitary to secrete HGH and thereby increase serum IGF-1 levels. It is postulated to combat ageing and boosts up bodily functions. GenF20Plus is postulated to increase physical stamina and lean muscle mass, improve libido, quality of sleep and memory. This study was designed to evaluate the effect of GenF20Plus on IGF-1 levels in normal to overweight adult volunteers with poor quality of sleep, decreased memory, decreased libido and low energy levels. As increased HGH levels with consumption of GenF20 Plus would translate as increased IGF-1 levels, serum IGF-1 levels was measured to prove the hypothesis. Thus measuring levels of serum IGF-1 levels was included as one of the efficacy variables.

Restoring normal levels of HGH and IGF-1 by consumption of GenF20 Plus should improve one's quality of life with regards to sleep, energy levels, memory and libido. There is no single study in literature which has assessed improvement in all the above parameters together with improvement in HGH or IGF-1 levels. The present study is a pilot study to assess the effects of increased HGH and IGF-1 levels on quality of life. Individual studies have shown efficacy of restoring normal HGH levels to improve sleep quality, increase energy levels, and improve memory and libido. Thus consumption of GenF20 plus should hypothetically increase HGH and IGF-1 levels and manifest improvement in the parameters. Quality of life questionnaire was used as an efficacy variable to assess change in sleep quality, improvement in memory, libido and energy levels. Also subject's global assessment for efficacy was recorded based on their perception about the improvement in the overall health to get a better understanding.

The present study was conducted to test the hypothesis and assess the safety of GenF20 Plus. The present report is a description of a study undertaken to evaluate the role of GenF20Plus, a proprietary blend of herbs, dietary and nutritional ingredients that appear to play a role in improvement of various physiological functions that are associated with normal levels of serum IGF-1 and HGH.

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6. Study objectives

a) To assess the effect of the IP on IGF-1 levels as compared to placebo

b) To assess the effect of the IP on the quality of life (with respect to libido, sleep, memory, energy, body weight) using QoL questionnaire in normal to overweight adult volunteers as compared to placebo

c) To assess the safety and tolerability of the IP in study volunteers as compared to placebo

7. Investigational plan

7.1 Overall Study Design and Plan – Description

Double blind, randomized, placebo controlled, exploratory study of GenF20Plus in normal to overweight adult volunteers with poor quality of sleep, decreased memory, decreased libido and low energy levels.

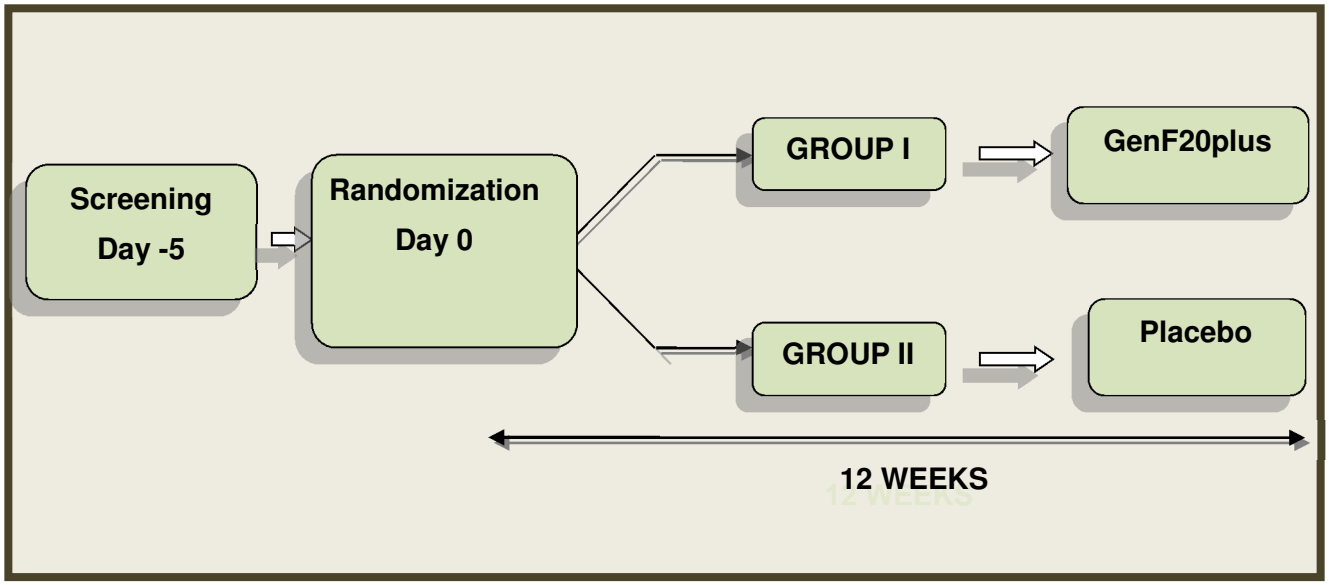

Fig 1.Schematic representation of study design

The 5 visit schedule was as follows:

Visit 1 at day -5: Screening

Visit 2 at day 0: Randomization

Visit 3 at day 28: Follow up

Visit 4 at day 56: Follow up

Visit 5 at day 84: End of Treatment

The visit specific schedule is set out in the table below.

Table 1: Visit Specific Schedule

PARAMETERS	Day -5	Day 0	Day 28	Day 56	Day 84
Informed Consent	✓	-	-	-	-
History	✓	✓	✓	✓	✓
Physical examination + vitals	✓	✓	✓	✓	✓
BMI / WC / body fat / lean muscle mass	✓ (only BMI)	✓	✓	✓	✓
HbA1c	✓	-	-	-	-
CBC	✓	-	-	-	✓
SGPT	✓	-	-	-	✓
Serum Creatinine	✓	-	-	-	✓
Urine- routine	✓	-	-	-	✓
UPT	✓	-	-	-	-
ECG	✓	-	-	-	✓
TSH, T3, T4	✓	-	-	-	-
Serum IGF-1 levels	-	✓	-	-	✓
QoL questionnaire	✓	✓	✓	✓	✓
Global assessment by subject	-	-	-	-	✓
Dispensing of IP	-	✓	✓	✓	-
IP Accountability	-	-	✓	✓	✓
Monitoring of AE/SAE	-	✓	✓	✓	✓

7.2 Selection of Study Population

7.2.1 Inclusion Criteria

a) Adults with any 2 of the following conditions : poor quality of sleep, decreased memory, decreased libido and low energy levels – with the affected parameters (of sleep, memory, libido and energy levels) perceived to be of grade 1 or 2 on a Likert scale of 1-5 where 1 = poor, 2=fair, 3=good, 4=very good and 5=excellent. The above conditions were present since at least 1 month and for not more than 6 months. (This criterion was fulfilled at baseline also)
b) Age between 35 to 65 years
c) Body Mass Index between 18.5 to 29.9 kg/m2
d) Subjects willing to give written informed consent and abide with trial procedures and come for the follow up visits.
e) Women willing to practice suitable contraception (except oral contraceptives) during the study.
f) Subjects willing to continue current lifestyle practices with no modifications (in diet and exercise) during the study period

7.2.2 Exclusion Criteria

a) Adults with uncontrolled conditions of diabetes, hypertension, hypothyroidism and hyperthyroidism.
b) Hepatic or renal impairment
c) Women on oral contraceptives, estrogen supplements and corticosteroids
d) Significant cardiovascular co-morbidities, e.g. symptomatic heart failure, a history of ischemic heart disease (as evident from ECG), history of stroke and/or TIA
e) Women who were known cases of estrogen sensitive disorders like breast cancer, uterine cancer, ovarian cancer, endometriosis and uterine fibroids
f) Debilitating neurological or psychiatric disorders including seizure disorders and depression and drugs used in these conditions.
g) Known hypersensitivity or allergy to one or more of the ingredients of the IP
h) Known history of allergy to milk and milk products
i) Recent (< 1 month) participation in a clinical trial
j) Any condition likely to hinder the compliance with the protocol
k) Heavy smoking (more than 10 cigarettes per day) or chronic alcoholics
l) Intake, in the preceding 1 month, of any drugs / supplements for decreasing body fat, increasing libido and energy levels, and improving quality of sleep and memory
m) Pregnant and lactating women

n) Subjects who had started an exercise and/or diet regimen within 30 days of the screening visit
o) Known cases of acromegaly
p) Patients with metallic implants (like rods/plates/screws) in any part of their body as well as implants with electronics like artificial pacemakers and cochlear implants

7.2.3 Removal of Patients from Therapy or Assessment

Withdrawal Criteria

Subjects had the right to withdraw from the study at any time for any reason. A subject who was withdrawn from the study for any reason was not allowed to re-enroll. Withdrawn subjects were not replaced. If the reason for removal of a subject from the study was an adverse event (AE), the same was recorded on the relevant data forms.

Subject was deemed as Withdrawn from the Study:

a) On earnest request of the subject assigning a reason for the same.
b) At the discretion of the Investigator
c) Any single major protocol deviation occurring more than once during the study
d) Serious adverse events where continuation of study posed serious risk to the patient
e) Subject consumed any other medicines for problems related to sleep, libido, energy levels, memory or weight control
f) Subject who did not get his/her laboratory testing done within 7 days of end of study visit (Day 84)
g) Subject got pregnant during the course of the study

Lost to follow up

Subject will be considered as lost to follow up if he/she did not come for follow up at all and could not be contacted during the study period.

Protocol Deviation

Following were deemed as major protocol deviations:

a) Subject with an IP compliance of < 85 % at any visit [applicable separately for both tablets and liquid].

b) Subject who did not come for follow up visit within ± 5 days but before 7 days of their scheduled visit. [This does not apply for the end-of-study visit]

NOTE: Subject were withdrawn from the study if any of the above deviations were repeated more than once during the study.

7.3 Treatments

7.3.1 Treatments Administered

Investigational Product: GenF20 Plus enteric coated tablets and GenF20Plus liquid

Placebo: Carboxy methyl cellulose tablets and berry flavored distilled water with sodium saccharin and sucralose

Presentation: 124 tablets in each white plastic container (bottle) and 60 ml amber colored plastic bottle filled up to 50 ml.

7.3.2 Identity of Investigational Product(s)

The specification of GenF20Plus tablets was as follows:
Size: 0.350”×0.750”; **Average weight:** 1200 mg; **Thickness:** 0.330”;
Description: Gray, speckled, clear enteric coated tablets.

Table 2: Composition of IP

Active ingredients per GenF20Plus tablet in mg are:	
L Glutamine	115
L Arginine HCl	130
L Glycine	115
L Tyrosine	100
Tribulus Terrestris Extract 40%	80
L Lysine HCl	100
Astragalus root	60
Colostrum powder 10%	50
Deer Velvet Antler powder	50
GABA – Gama amino butaric acid	50
L Isoleucine	40
Anterior pituitary powder	30
Phosphatidyl choline	25
L Valine	40
L Ornithine	25
GTF Chromium	0.1
Excipients:	
HPMC E19 (Methyl cellulose), Silicon dioxide, Magnesium stearate, Stearic acid, Elcema (cellulose).	

Table 3: Each 2ml of GenF20Plus liquid contains**:**

Alpha GPC - 350 mg Growth Factor Proprietary Blend: 2000 ng (equal blend per ingredient) GABA (Gamma Amino Butyric Acid), Mucuna Pruriens (seed), Moomiyo Extract Stimulator Factor Proprietary Blend: 1000 ng (equal blend per ingredient) Ornithine Alpha Ketoglutarate, L-Glutamine, L-Arginine, L-Lysine, L-Valine, L-Isoleucine, L-Tyrosine and Glycine
Other Ingredients: Filtered water, glycerine, citric acid, stevia, berry flavor, sodium benzoate, and potassium sorbate.

7.3.3 Method of Assigning Patients to Treatment Groups

A total of 70 subjects were assigned to either active arm or placebo arm in a ratio1:1, according to a computerized randomization schedule. Block randomization was done by using blocks of four in this study with the help of Stats direct software version 2.7.8. The randomization codes were secured in tamper- evident sealed envelopes at the respective sites. Each envelope mentioned the Subject ID & the treatment allocated. The Master Randomization Chart were sealed in an envelope and maintained in the Trial Master File (TMF).

7.3.4 Selection of Doses in the Study

The product is already marketed with recommended daily dosage of 2 tablets (approximately 4 gm/day) and 4 ml/day for liquid for a total period of 12 weeks. Thus the same dosage was used to collect evidence in the present study.

7.3.5 Selection and Timing of Dose for each Patient

Each group received 2 tablets and 2 ml of liquid each in the morning and in the evening for a total period of 12 weeks. The tablets were given one hour before meals and liquid was administered sublingually with the help of a dropper, kept for 30 sec and then swallowed.

7.3.6 Blinding

Subjects, investigators, monitors and data analysts were blinded to the treatment assignment. Independent personnel not involved in the execution and analysis of the trial, performed blinding procedures at the IP manufacturing unit. Placebo and active treatments were made indistinguishable and packed in identical containers with identical labels. The Placebo tablets were masked with respect to parameters of size, colour, weight and thickness. GenF20 Plus liquid and Placebo liquid was packaged in identical amber colored plastic bottles. Berry flavor

with sodium saccharin and sucralose was added to the placebo liquid in order to simulate a taste similar to that of the active ingredient.

The blinding codes were secured in tamper - evident sealed envelopes at the respective study sites. Each envelope mentioned the Subject ID & the treatment allocation (active or placebo). Each subject received study medications in carton (containing a bottle of 124 tablets and 3 bottles of liquid) at each visit which was identical for both active and placebo group.

7.3.7 Prior and Concomitant Therapy

During the course of the study, the subjects were not allowed to take any other medication used for any of the study indications. Subjects who required taking medicines for any other complaints during the course of the study were allowed to do so only after consultation with the investigator. If this was not possible, subjects were required to inform the investigator at the earliest. In such cases, the investigator decided whether or not the subject can continue in the trial, considering any possibility of effect of the medication consumed on the efficacy or safety outcomes of the study. The investigator maintained the record of concomitant medication in the CRF. (Table 20 in appendix I)

***Concomitant Medications Permitted*:**

All medicines which are not mentioned in the list of prohibited medications were allowed to be used by the patient but only after consulting the investigator.

***Concomitant Medications Prohibited*:**

Anticholinergics like Dicycloverine, Atropine, Scopolamine, Ipratropium bromide, Oxitropium bromide, Tiotropium, Glycopyrolate. Other herbal supplements/ medicines for increasing growth hormone levels, decreasing body weight / fat, increasing libido and energy levels, and improving quality of sleep and memory, Anti-depressants, Oral contraceptives, estrogen supplements and corticosteroids

7.3.8 Treatment Compliance

For monitoring treatment compliance, proper instructions about obligations and responsibilities were given to the subjects regarding the trial procedures and IP dosage and administration. The subjects were asked to return the unused tablets and liquid at each follow up visit. A record of dispensed and returned medication was maintained in the CRF and IP accountability log at the site in order to ensure that the subject is taking the medication properly throughout the treatment duration. Any subject consuming less than 85% of the required dose during the treatment period was withdrawn from the study. A record of any concomitant medication taken by the subject was maintained in the CRF.

7.4 Efficacy and Safety Variables

7.4.1 Efficacy and Safety Measurements Assessed and Flow Chart

Safety variables

Following parameters were checked to assess safety. Subjects who developed abnormality in any of the following parameters were withdrawn from study depending on the severity and seriousness of the condition.

- **Vital Parameters:** Pulse rate**,** Systolic and diastolic blood pressure
- **Systemic Examination:** CVS, RS & Musculoskeletal system.
- **Laboratory Tests:** Complete blood count, Urine routine, SGPT, S.Creatinine, ECG
- **Monitoring of Adverse/Serious Adverse Events:** All subjects were monitored for any adverse reaction or adverse events or serious adverse events at each follow up visit.

Efficacy Variables

1) QoL questionnaire: QoL questionnaire was administered to each subject at every visit to rate their feelings or responses during the 4 weeks. The parameters to be rated were– Energy levels, Memory, Libido, and Quality of sleep on grade scale of 1 to 5 [1-poor, 2-fair, 3-good, 4-very good, 5-excellent].

2) Serum IGF-1 Level: On day 0 and day 84, IGF-1 levels were measured after an overnight fast (10-12 hrs).

3) BMI: BMI was calculated at each visit.

4) Waist Circumference: Waist circumference was calculated by locating the upper hip bone and placing a measuring tape around the abdomen (ensuring that the tape measure is horizontal).

5) Body Fat and Lean Body Mass: Bioelectrical impedance analysis was used to measure body fat percentage via an Omron body fat analyzer HBF-200. Lean body mass was calculated using formula: Lean Body Mass (Kg) = Total Body Weight (Kg) – Body Fat (Kg)

6) Global Assessment of efficacy by subject: On the last day of the treatment, the Subject's global assessment for efficacy was recorded based on their perception about the improvement in the overall health as follows:

- **Good**: if the subject felt that there has been a large improvement in overall health.
- **Fair**: if there has been a moderate level of improvement in overall health.
- **Poor**: If the subject felt that there is no change in the overall health or if it has worsened as compared to baseline

Flow Chart of Efficacy and Safety Measurements

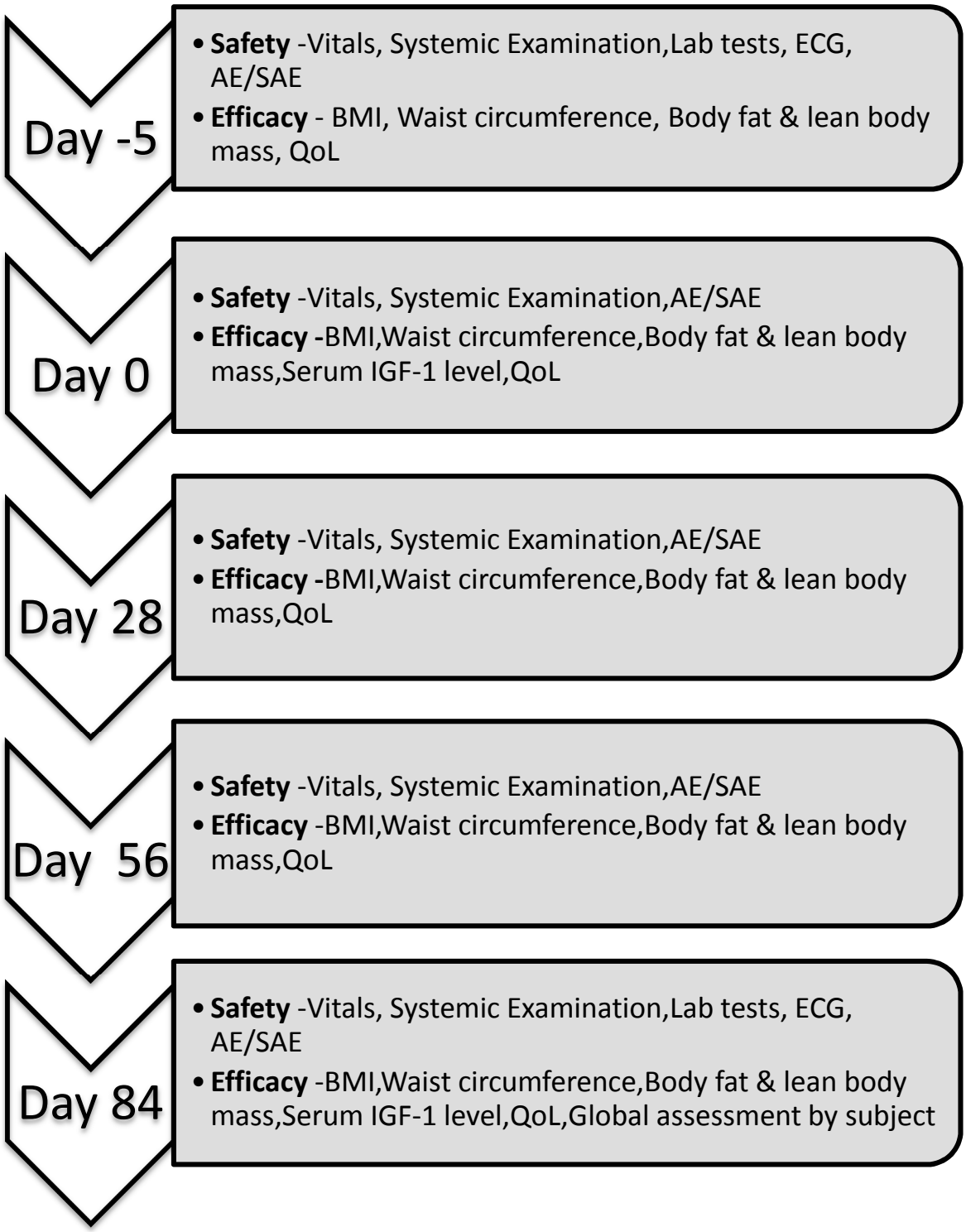

Figure 2. Flow chart of efficacy and safety measurements assessed in the study

7.4.2 Appropriateness of Measurements

GenF20 Plus is composed of ingredients that are known in traditional medicine to stimulate the pituitary to secrete growth hormone.

IGF 1 levels: Release of HGH in the blood circulation stimulates the liver to produce IGF-1 and mediate the action of HGH. Thus decreasing levels of HGH in blood circulation gets translated as decreasing levels of IGF-1. GenF20 Plus was postulated to stimulate anterior pituitary to secrete HGH and thereby increase serum IGF-1 levels. Thus measuring levels of serum IGF-1 levels was included as one of the efficacy variables.

The study design allowed incorporating sample population with at least few of the symptoms presented by relative HGH deficient population. Aging cause's progressive decline in the secretion of HGH and obesity is associated with suppressed levels of circulating HGH[6]. The inclusion criteria of age between 35 to 65 years and BMI between 18.5 to 29.9 kg/m^2 was chosen to have study population with subclinical HGH levels associated with increased weight and age.

Weight Reduction: HGH stimulates lipolysis by stimulating triglyceride breakdown and oxidation in adipocytes, providing FFAs and glycerol as substrates for energy metabolism. A study by Rudman *et al* [7] has shown beneficial effects of HGH administration in a group of elderly healthy men with low plasma IGF-1 values, but no underlying pituitary pathology. Low doses of HGH increased lean body mass and bone mineral density, decreased body fat and lowered LDL cholesterol. Thus GenF20plus is postulated to restore the levels of HGH and thereby stimulate lipolysis causing reduction weight. To assess the efficacy of GenF20 plus in weight reduction; BMI, WC, body fat and lean body mass change from baseline to EoT was included as efficacy variables.

Also presence of any 2 of the following conditions: poor quality of sleep, decreased memory, decreased libido and low energy levels was chosen as inclusion criteria to capture the effect of GenF20 Plus on the symptoms associated with HGH decline. IGF 1 is known to improve cognitive function, improve sleep quality, enhance libido and increase energy levels.

Sleep: Approximately 70% of the daily HGH output occurs during early sleep throughout adulthood. Chronic insomnia of a lower degree can disturb HGH secretion. Vgontzas and colleagues[8] measured urinary HGH in 15 young adults (age <40 years) who had chronic insomnia. Twenty-four-hour urinary HGH excretion was detectable in only three insomniacs, two of whom had low indices of sleep disturbance. GenF20plus is hypothesized to restore the levels of HGH and thereby stimulate better sleep.

Decreased memory / forgetfulness: There is a gradual reduction of memory with age termed as age-associated memory impairment (AAMI)[9]. Research suggests that with continued intellectual engagement may ameliorate progression of AAMI[10].

HGH and IGF-I receptors are expressed in brain (hippocampus, pituitary and hypothalamus). HGH and IGF-I can pass the blood-brain barrier. An improvement in cognitive functioning in HGH-deficient patients by HGH substitution has been shown[11].

One study found an age-related reduction in the expression of HGH receptor mRNA in different regions of the brain, especially in the areas that affect mood, cognition, memory and learning. Thus low levels of HGH associated with ageing may be a factor in the impaired cognitive function. An improvement in cognitive functioning in HGH-deficient patients by HGH substitution has been shown[12]. GenF20plus is proposed to be able to improve HGH deficient memory impairment.

Decreased libido: The age-related decrease in libido is attributed to a decline in sex hormones level. A decline in sexual interest and desire is frequently reported to be more severe in aging women than aging men. Thus GenF20plus is assumed to restore levels of sex hormones and improve libido.

Decreased energy levels: Ageing is one of the causative factors identified for chronic fatigue in many people. Clark *et al.* demonstrated that the risk for persistent (> 2.5 years) chronic fatigue is associated with age greater than 38 years[13].

Quality of life questionnaire was used as an efficacy variable to assess change in sleep quality, improvement in memory, libido and energy levels. Also subject's global assessment for efficacy was recorded based on their perception about the improvement in the overall health to get a better understanding.

7.5 Data Quality Assurance

The following steps were taken to ensure collection of accurate, consistent, complete and reliable data:

- Before initiation of the study, an investigators' meeting was held in order to facilitate the discussion and resolution of various scientific, operational and other issues that were foreseen for the study. During the meet, the study personnel were trained on the CRF filling rules and administration of the QoL questionnaire to ensure appropriate and standardized capture of data. All personnel were also trained on the correct usage of the Omron Body fat analyzer to ensure recording of error free data.
- BMI, body fat percentage and lean body mass was recorded using standardized and calibrated Omron body fat analyzer HBF-200 across all the sites.
- A central laboratory approved by the National Accreditation board for testing & Calibration Laboratories (NABL) in accordance with ISO15189:2003, was employed in the study for evaluation of laboratory biochemical tests including serum IGF 1 levels.
- Monitoring visits were made by the CRO personnel every two months to ensure that the data collected was accurate, complete, in compliance with the protocol requirements and consistent with the source documents. A co monitoring visit was also conducted by project manager at each site.
- An internal audit was performed by the quality assurance department to verify the trial documents in accordance with the protocol and GCP

7.6 Statistical Methods Planned In the Protocol And Determination Of Sample Size

7.6.1 Statistical Analysis Plans

Study populations

Two types of study population were defined for statistical analyses:

1. The intention-to-treat (ITT) population consisted of all subjects who were randomized, received the study drug and reported at least one post-baseline assessment. The Last Observation Carried Forward (LOCF) imputation method was used to handle missing data.
2. The per-protocol (PP) population comprised of subjects who reported for all protocol stipulated study visits and did not have any major protocol deviations related to the evaluation of efficacy.

Statistical and Analytical methods

1. The final analysis was done at the end of the study using Epi Info, True Epistat and MS Excel XP.
2. All statistical tests were applied at 95% confidence interval
3. Baseline characteristics of the two groups were first compared using ANOVA (Analysis of Variance)
4. Mean changes in vital parameters, laboratory hematological tests from baseline to end-of-treatment were compared across the groups by ANOVA
5. Changes in IGF-1 values, BMI, body fat percentage, lean body mass, waist circumference and QoL parameters from baseline to end of treatment was compared across the two groups using ANOVA.
6. For global assessment, good and fair was clubbed together as satisfactory and poor was denoted as unsatisfactory and chi square test was used for analysis across the 2 groups. Continuous variables are summarized using descriptive statistics (n, mean, standard error of mean, median, minimum and maximum) and categorical variables are summarized as the number (and percentage) of patients in each category.
7. No interim analysis was conducted during the study
8. Withdrawal and protocol deviation cases are reported and described

Hypotheses:

The null hypothesis (H_0) is that there is no difference in the IGF-1 levels between the 2 groups (on the study medication and the placebo). The alternative hypothesis (H_A) is that there is difference between the groups

Efficacy analysis:

The efficacy analyses were conducted on the ITT population.

Changes in IGF-1 values, BMI, body fat percentage, lean body mass, and waist circumference from baseline to Day 84 was compared across the two groups using ANOVA.

Changes in IGF-1 values from baseline to Day 84 were compared across the two groups using ANCOVA with baseline values as the covariate.

Data on QoL parameters was compared across the two groups using ANOVA.

Responses to global efficacy question by subject, graded as good, fair and poor was summarized as follows: good and fair was clubbed as satisfactory responses while poor was denoted as an unsatisfactory response. An analysis of satisfactory and unsatisfactory responses across the 2 study groups was analyzed by the chi-square test.

Safety Analysis:

All adverse events were listed patient wise, classified according to body system; frequency and relationship to the study drug. Vital parameters was analyzed in the ITT population and laboratory parameters was analyzed in a subset of subjects in whom complete laboratory data was available. Vital parameters and laboratory parameters were analyzed across the group by ANOVA.

7.6.2 Determination of Sample Size

Since this was the first exploratory clinical study, no statistical method was used for sample size calculation. An arbitrarily chosen sample size of 60, with 30 in each group, was planned in the study to detect a statistical difference between IP and placebo.

8. Study Patients

8.1 Disposition of Patients

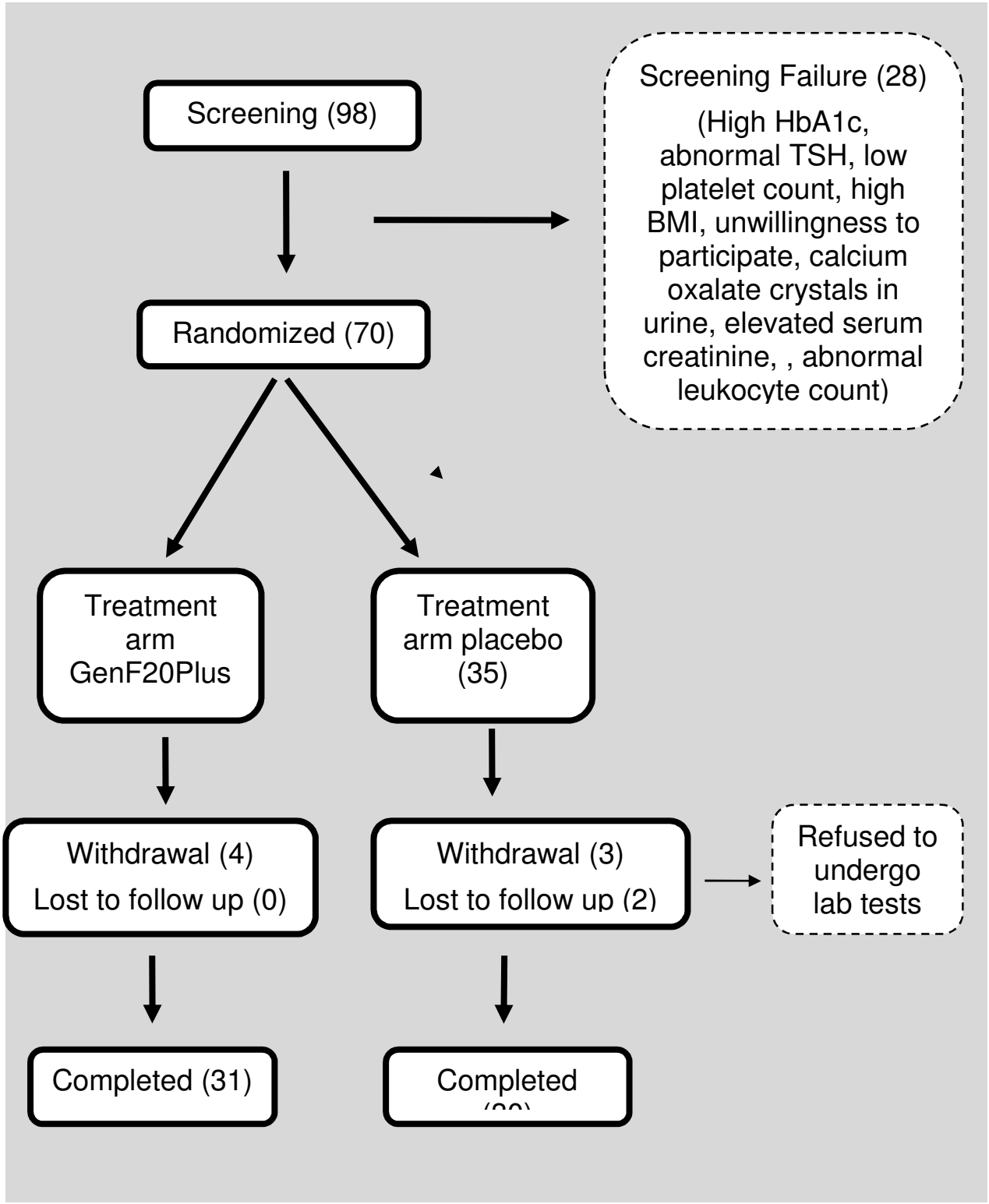

Figure 3: Flowchart showing disposition of patients

A total of 98 subjects were screened for the study; out of which 28 subjects were screening failures. The remaining 70 subjects were randomized and allocated to either treatment arm A (GenF20Plus) (n=35) or treatment arm B (Placebo) (n=35). The major reasons for screening failures included high HbA1c levels (n=7), abnormal TSH levels (n=6), low platelet count (n=2) and high BMI (n=2). 8 subjects were unwilling to participate in the study. Other reasons for screening failure were presence of calcium oxalate crystals in urine (n=1), elevated serum creatinine (n=1) and abnormal leukocyte count (n=1).

Out of the randomized 70 subjects, 7 subjects were withdrawn from the study because they were unwilling to undergo laboratory tests and 2 subjects were lost to follow up. The total number of completed subjects is 61 (31 in arm A and 30 in arm B).

The IDs of subjects who were withdrawn and lost to follow up from this study are as follows:

Lost to follow up (2): GFP37, GFP41

Withdrawn (5): GFP01, GFP03, GFP08, GFP09, GFP10, GFP11 and GFP17

8.2 Protocol Deviations

There were total 14 protocol deviations observed in the study. Fifty percent of them (n=7) happened as safety assessments were not done on day 84. Two subjects came late for their day 84 visit and one subject came late for day 0 visit. Two subjects were recruited late in the study. One subject had less than 85 % compliance. One subjects ECG assessment was not done on day 84. There was no major impact on the study.

Table 4: List of all protocol deviations

Center ID	Subject ID	Deviation	Reason for Deviation
VLDM01	GFP03	subject was recruited late in the study	as the collected blood (Hemogram) was degenerated repeated sample was asked for
	GFP05	subject was recruited late into study	as the hemogram sample was degenerated repeat specimen was asked for
	GFP05	safety assessment (ECG) was not done at day 84 visit	subject forgot to do ECG and doesn't report to the site after that
VLDM02	GFP25	safety assessment (blood investigations) not done, only IGF was collected	missed by coordinator
	GFP26	safety assessment (blood investigations) not done, only IGF was collected	missed by coordinator
	GFP27	safety assessment (blood investigations) not done, only IGF was collected	missed by coordinator
	GFP28	safety assessment (blood investigations) not done, only IGF was collected	missed by coordinator
	GFP29	safety assessment (blood investigations) not done, only IGF was collected	missed by coordinator
	GFP30	safety assessment (blood investigations) not done, only IGF was collected	missed by coordinator
	GFP36	safety assessment (blood investigations) not done, only IGF was collected	missed by coordinator
	GFP32	subject had come 5 days late for day 84 visit	subject was out of station
	GFP32	Subject compliance less than 85% (actual compliance 81.57%)	subject was out of station
VLDM03	GFP13	subject had come 2 day late for baseline visit	subject was out of station
	GFP13	Subject had come 5 day late for day 84 blood investigations. subject came within window period	subject was out of station

9. Efficacy Evaluation

9.1 Data Sets Analyzed

Efficacy analysis was conducted on the per-protocol population consisting of 61 subjects who completed the study. There were 31 subjects in active group and 30 in placebo group.

9.2 Demographic and Other Baseline Characteristics

No significant differences were observed in the demographic and baseline characteristics of subjects between the two groups.

Table 5 showing baseline parameters in both the groups

Baseline Characteristics	GenF 20 (n=35)	Placebo (n=35)	P value
Age			
• Mean (SD)	40.57 (6.01)	42.00 (7.21)	0.3710
• Max - Min	64-35	58-35	
Sex			
• Male (n)	18	13	0.33
• Female (n)	17	22	
Pre existing conditions (n)	6	4	
Concomitant medication (n)	5	4	
Alcoholics (n)	2	0	
Cigarette Smokers (n)	0	0	
Low Energy (n)	35	31	
Decreased Memory (n)	18	13	
Decreased Libido (n)	9	10	
Poor Sleep (n)	27	32	
Serum IGF1 levels (ng/ml) Mean (SD)	134.52 (44.17)	123.47 (44.59)	0.34
BMI (kg/m^2)			
• Mean (SD)	24.59 (3.15)	25.47(2.94)	0.82
• Min – Max	18.52 – 29.60	19.52 -30.10	
BMI category			
• Normal (n)	19	13	
• Obese (n)	0	1	0.25
• Overweight (n)	16	21	
Duration of complaints in days	89.57 (39.16)	83.51 (37.22)	

9.3 *Measurements of Treatment Compliance*

Subjects in both groups showed good adherence to study medication (Table 6). There was no significant difference in the treatment compliance between groups. One subject from the placebo group showed low compliance of 81.57% (recorded as protocol deviation) at only one visit and was allowed to continue in the study.

Table 6 Percent compliance across different timelines

Percent Compliance	Time points	GenF 20 (n=31)	Placebo (n=30)	P value
IP (Tablets)	Day0 – Day 28	97.39 (3.42)	94.27 (18.31)	0.35
	Day 28 – Day 56	96.00 (4.52)	97.03 (4.45)	0.37
	Day 56 – Day 84	97.45 (3.39)	96.00 (6.30)	0.26
IP (Liquid)	Day0 – Day 28	95.32 (18.91)	92.64 (25.51)	0.64
	Day 28 – Day 56	97.74 (6.06)	99.04 (7.85)	0.47
	Day 56 – Day 84	99.78 (7.02)	99.04 (6.49)	0.67
Values are expressed as Mean (SD), p computed using ANOVA				

9.4 Efficacy Results

9.4.1 Analysis of BMI, Waist circumference, Body fat and Lean body mass

At the end of 12 weeks of treatment, the BMI, waist circumference and body fat did not show a significant decrease and lean body mass did not show a significant increase from baseline to end-of-treatment in both, GenF20 and placebo groups. Even though the change from baseline to end of treatment occurred slightly more in the active group than in the placebo group, it was neither statistically nor clinically significant.

Table 7: Efficacy in PP Population

Parameters	Time	GenF 20 (N=31)	Placebo (N=30)	p
BMI ($kg/m^{2)}$	Baseline	25.78 (8.27)	25.43 (2.88)	0.82
	EoT	25.67 (8.23)	25.23 (2.95)	0.78
	Change Baseline - EOT	-0.11 (0.63)	-0.20 (0.79)	0.62
	P value baseline - EoT	0.96	0.79	
Waist circumference	Baseline	36.26 (5.04)	36.12 (5.19)	0.91
	EoT	35.96 (4.85)	35.87 (5.01)	0.94
	Change Baseline - EOT	-0.30 (0.81)	-0.25 (0.76)	0.79
	P value baseline - EoT	0.81	0.85	
Body fat	Baseline	26.55 (10.97)	28.16 (7.06)	0.50
	EoT	25.66 (11.65)	27.75 (7.35)	0.41
	Change Baseline - EOT	-0.89 (1.85)	-0.41 (1.34)	0.2487
	P value baseline - EoT	0.76	0.83	
Lean body mass	Baseline	47.31 (6.92)	47.41 (7.59)	0.96
	EoT	47.59 (6.99)	47.53 (7.79)	0.98
	Change Baseline - EOT	0.27 (0.88)	0.12 (0.99)	0.52
	P value baseline - EoT	0.88	0.95	
Values are expressed as Mean (SD), p computed using ANOVA				

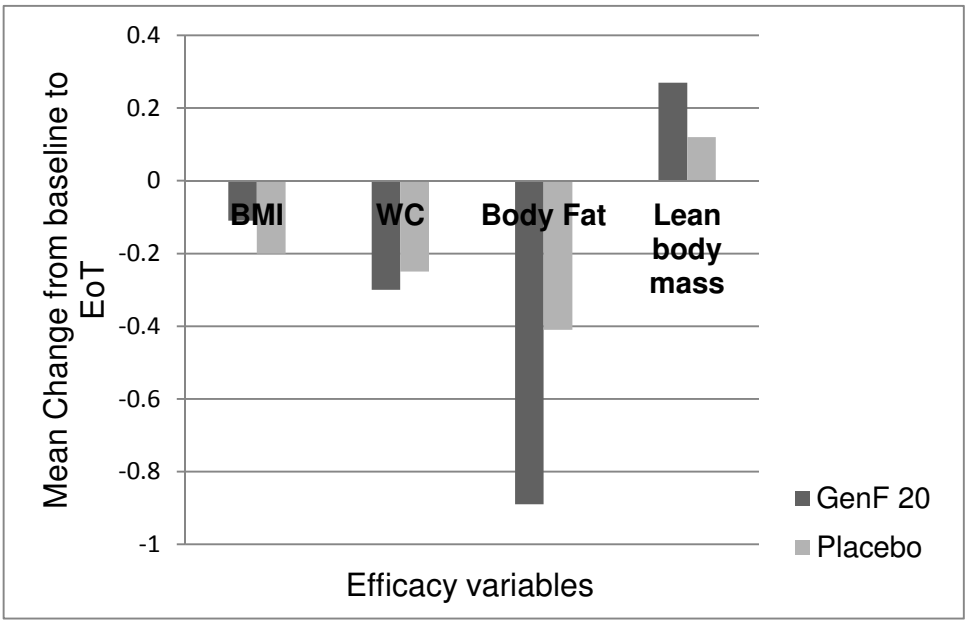

Figure 4 showing mean change from baseline to end of treatment for BMI, waist circumference, body fat and lean body mass

9.4.2 Serum IGF 1 Levels

GenF20 Plus was postulated to stimulate anterior pituitary gland to secrete HGH and thereby increase serum IGF-1 levels. Thus measuring levels of serum IGF-1 was included as one of the efficacy variables to indirectly assess HGH levels.

The levels of serum IGF-1 decreases as age increases. Thus to get better understanding in the change in serum IGF-1 levels, sub group analysis by ANOVA was done by making two sub groups based on subjects' age; group1 with subjects aged ≥ 40 years (Table 8) and group 2 with subjects aged <40 years (Table 9). One-Way ANCOVA was then performed to adjust the baseline variations for both the subgroups.

Table 8: Subgroup analysis (age≥40yrs)

ANOVA [Values are expressed as Mean (SD), p computed using ANOVA]				
Variables	**Time**	**GenF 20 (N=12)**	**Placebo (N=13)**	**p**
Serum IGF (ng/ml)	Baseline	130.61 (47.08)	96.67 (29.54)	0.04
	EoT	145.20 (36.55)	99.84 (27.30)	0.001
	Change Baseline - EOT	14.59 (40.08)	3.17 (16.09)	0.35
	P value baseline - EoT	0.41	0.78	
	Percentage change	19.14 (34.34)	8.16 (31.3)	0.41
ANCOVA				
Variables	**Time**	**GenF 20(N=12)**	**Placebo(N=13)**	**p**
Serum IGF (ng/ml)	Observed Mean	14.59	3.17	
	Adjusted Mean	22.69	-4.31	0.02
	Observed %age change	19.14	8.16	
	Adjusted %age change	28.57	-0.55	0.017

In the subgroup age≥40, there was increase in the serum IGF-1 levels at the end of 12 weeks in GenF20Plus group as compared to the placebo group (Table 8). The change was not statistically significant between the 2 groups. After ANCOVA the mean increase in IGF-1 values was statistically significant (p = 0.02) in GenF20 Plus group as compared to the placebo group. The percentage increase of the same subgroup was also statistically significant (p=0.017)

Table 9: Subgroup analysis (age<40yrs)

ANOVA [Values are expressed as Mean (SD), p computed using ANOVA]				
Variables	**Time**	**GenF 20 (N=18)**	**Placebo (N=17)**	**p**
Serum IGF (ng/ml)	Baseline	138.13 (42.31)	143.96 (43.82)	0.019
	EoT	149.84 (51.09)	152.73 (55.48)	0.002
	Change Baseline - EOT	12.71 (34.41)	8.78 (47.05)	0.78
	P value baseline - EoT	0.45	0.61	
	Percentage change	11.03 (27.09)	9.32 (31.13)	0.88
ANCOVA				
Variables	**Time**	**GenF 20(N=18)**	**Placebo(N=17)**	**p**
Serum IGF (ng/ml)	Observed Mean	12.71	8.78	
	Adjusted Mean	12.71	9.46	0.84
	Observed %age change	11.03	9.32	
	Adjusted %age change	10.38	10.01	1.00

In the subgroup age<40, the observed change after ANOVA was not clinically nor statistically significant. Even after ANCOVA there was no improvement either in clinical values or percentage change.

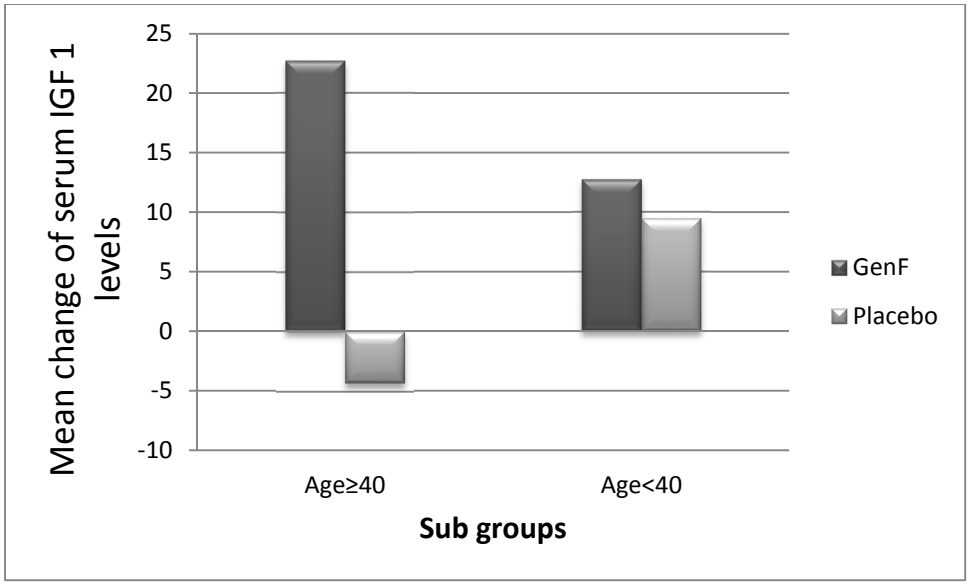

Figure 5: Mean change of serum IGF I levels from baseline to EoT by ANCOVA in subgroup age≥40 yrs and subgroup age<40 yrs

Table 10: Serum IGF1 levels of the whole group

Variables	Time	GenF 20 (N=30)	Placebo (N=30)	p
	Baseline	134.52 (44.17)	123.47 (44.59)	0.34
Serum IGF 1	EoT	147.98 (45.19)	129.81 (52.13)	0.15
(ng/ml)	Change Baseline - EOT	13.46 (36.12)	6.35 (36.56)	0.45
	P value baseline - EoT	0.25	0.61	
Values are expressed as Mean (SD), p computed using ANOVA				

The serum IGF-1 levels of the whole group increased from baseline to end-of-treatment in both the groups. The mean (SD) change occurred more in the GenF20 plus group than in the placebo group However it failed to reach statistical significance (p=0.45).

The significant increase in the serum IGF-1 levels in the subgroup age ≥ 40 in the GenF20 plus group as compared to the placebo group is attributable to the consumption of GenF20 plus. In the sub group age<40, sustained inherent mechanism of the body of secreting normal levels of serum IGF-1 levels might be the reason of not showing considerable increase.

9.4.3 Quality Of Life Questionnaire

Quality of life questionnaire was analyzed using ANOVA to assess the change in memory, libido, energy levels and quality of sleep from baseline to end of treatment; measured on a Likert scale. There was no significant difference in the baseline and end of treatment values between the GenF20 Plus and placebo group for all the four variables. There was improvement in all the variables from baseline to end of treatment in both active and placebo group. The change was statistically significant for variable memory, energy level and sleep quality in both active and placebo group. But the change was not statistically significant between the two groups. The GenF20 Plus group failed to show significant improvement as compared to placebo group (Table 11). Improvement in all of the above parameters is difficult to attain in short duration of 12 weeks. The longer the duration of these impairments, longer will be the time required to observe substantial improvement.

Table 11: Assessment of Quality of Life Questionnaire variables

Variables	Time	GenF 20 N=22	Placebo N=19	p
QoL (Memory) N=41	Baseline	2.04 (0.90)	2.10 (0.81)	0.82
	EoT	2.76 (1.16)	2.77 (1.15)	0.97
	Change Baseline - EOT	0.41 (0.80)	0.31 (0.48)	0.66
	P value baseline - EoT	0.0243	0.04	
Variables	**Time**	**GenF 20 N=18**	**Placebo N=15**	**p**
QoL (Libido) N=33	Baseline	2.50 (0.78)	2.47 (0.99)	0.91
	EoT	3.00 (1.14)	3.05 (1.35)	0.89
	Change Baseline - EOT	0.17 (0.71)	0.20 (0.41)	0.87
	P value baseline - EoT	0.12	0.17	
Variables	**Time**	**GenF 20 N=31**	**Placebo N=28**	**p**
QoL (Energy levels) N=59	Baseline	1.16 (0.37)	1.21 (0.50)	0.64
	EoT	2.39 (0.80)	2.14 (0.93)	0.28
	Change Baseline - EOT	1.22 (0.80)	0.93 (0.86)	0.17
	P value baseline - EoT	0.00	0.00	
Variables	**Time**	**GenF 20 N=27**	**Placebo N=29**	**p**
QoL (Quality of Sleep) N=56	Baseline	1.52 (0.70)	1.24 (0.63)	0.13
	EoT	2.55 (0.93)	2.10 (1.08)	0.10
	Change Baseline - EOT	1.04 (0.85)	0.86 (1.02)	0.49
	P value baseline - EoT	0.00	0.0005	
Values are expressed as Mean (SD), p computed using ANOVA				

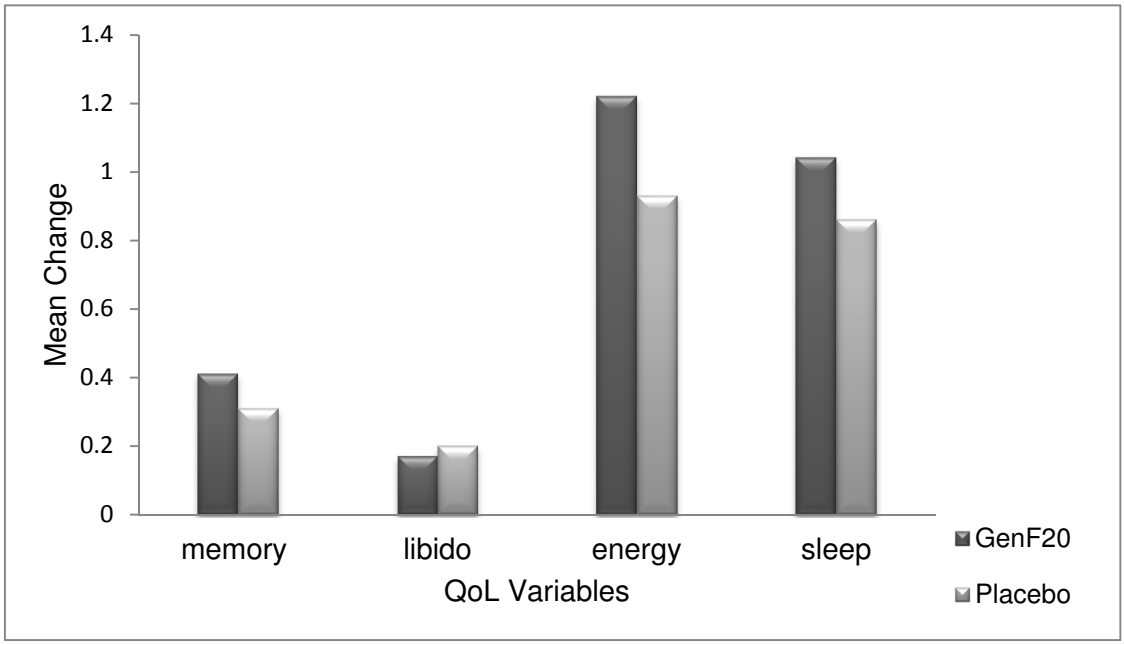

Figure 6 Mean change from baseline to end of treatment for QoL variables of active and placebo group

9.4.4 Global Assessment by Subjects

Global assessment by subjects was recorded on day 84 to get a better understanding of the overall effect of the treatment. The responses were recorded as good, fair or poor. As per the statistical analysis plan, the good and fair category was clubbed together and then analysis was done using Pearson's Chi square test (Table 12). The difference was not statistically significant (p=0.53) but the number of subjects in good and fair category together is more in active group than placebo.

Table 12: Analysis of global assessment of Efficacy

Variables	Category	GenF 20 (N=31)	Placebo (N=30)	p
Global assessment by subject	Good & Fair (n)	21 (67.74%)	18 (60%)	0.53
	Poor (n)	10 (32.26%)	12 (40%)	
p computed using Pearson's chi square test				

9.5 Statistical/analytical issues

9.5.1 Adjustments for covariates

An adjustment of covariates was done for the sub group analysis of serum IGF 1 levels. The groups differed significantly in the baseline mean IGF 1 values. The normal serum IGF 1 physiological range is quite wide to accommodate these differences. But to ascertain the efficacy, in terms of change from baseline to end of treatment, ANCOVA was used to adjust the baseline differences. (Table 10)

9.5.2 Use of an "Efficacy Subset" of patients

Efficacy subset of population was used for the analysis of serum IGF 1 levels based on age. The normal physiological serum IGF 1 levels decreases as age increases. Thus the change observed in serum IGF 1 levels in the total population was diluted by the wide deviation in the values. Two sub groups were made; group 1 with age ≥40 years and subgroup 2 with age < 40 years to carry out ANOVA. (Table 9)

10. Safety Evaluation

10.1 Adverse Events (AE)

10.1.1 Brief summary of adverse events

There were a total of 12 adverse events (7 in active and 5 in placebo group) reported during the study procedure. Ten adverse events were of gastrointestinal system (8 were acidity cases and 2 were pain in abdomen). One case reported of headache and other case reported of skin eruptions just below eyes. Most of the adverse events were mild in severity and not related to the study drugs. There was not a single event with definite relation to any of the study drug. All adverse events were successfully resolved.

Table 13: System wise classification of adverse events

System	GenF 20 (N=35)		Placebo (N=35)	
	Probable	Not related	Probable	Not related
Gastrointestinal (n)	2	5	-	3
Head (n)	-	-	-	1
Skin (n)	-	-	-	1

Table14: Severity wise classification of adverse events

Severity	GenF 20 (N=35)	Placebo (N=35)
Mild (n)	5	5
Moderate (n)	2	0
Severe (n)	0	0
Total (n)	7	5

10.1.2 Display of adverse events

Table 15: Individual adverse events

Sub ID	AE Description	Intensity	Onset Date	Resolution Date	System	Relationship to study drug	Outcome	Treatment Given
GFP01	pain in abdomen, history of heavy diet in his village	Moderate	10/16/2011	10/22/2011	GI	Not Related	Resolved	Dicyclomine 10mg BD
GFP01	pain in abdomen, history of heavy diet in his village	Moderate	10/16/2011	10/22/2011	GI	Not Related	Resolved	Rabeprazole 20 mg OD
GFP18	eruption on face below eyes	Mild	10/12/2011	10/20/2011	Skin	Not Related	Resolved	Fluconazole 150mg OD
GFP47	Acidity	Mild	8/7/2011	8/8/2011	GI	Probable	Resolved	-
GFP48	Acidity	Mild	8/8/2011	8/9/2011	GI	Probable	Resolved	-
GFP61	Acidity	Mild	9/7/2011	9/9/2011	GI	Probable	Resolved	-
GFP63	Acidity	Mild	9/16/2011	9/17/2011	GI	Probable	Resolved	-
GFP68	Acidity	Mild	11/16/2011	11/17/2011	GI	Probable	Resolved	-
GFP46	Acidity	Mild	8/7/2011	8/8/2011	GI	Probable	Resolved	-
GFP45	Headache	Mild	7/31/2011	8/1/2011	Head	Probable	Resolved	-
GFP45	Acidity	Mild	7/31/2011	8/1/2011	GI	Probable	Resolved	-
GFP39	Acidity	Mild	9/7/2011	9/8/2011	GI	Probable	Resolved	-

10.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There was no incidence of a serious adverse event or death during the course of the study.

10.3 Clinical Laboratory Evaluation

Changes in laboratory measurements were analyzed in a subset of 52 subjects from PP population in whom complete laboratory data was available. When compared for changes from baseline to end-of-treatment, no statistically significant changes were observed in the hematology and biochemical laboratory variables within each group and between the two groups except for neutrophil count and serum creatinine level. This change was not clinically significant.

No significant changes were observed in any of the parameters of urine routine test.

Table 16 Safety Assessment in PP population subset (N=52)

Variables	Time	A (n=25)	B (n=27)	p
WBC (per c.mm)	Baseline	7056.00 (1578.52)	7318.52 (1767.01)	0.57
	EOT	7716.00 (2241.78)	8044.44 (2176.86)	0.59
	Change Baseline - EOT	660.00 (2188.03)	725.92 (1919.25)	0.91
	P value baseline - EOT	0.23	0.18	
RBC (mill/c.mm)	Baseline	4.70 (0.64)	4.74 (0.51)	0.78
	EOT	4.72 (0.69)	5.11 (2.23)	0.41
	Change Baseline - EOT	0.03 (0.45)	0.37 (2.16)	0.44
	P value baseline - EOT	0.89	0.40	
Hb (mg/dl)	Baseline	12.95 (2.19)	13.72 (1.39)	0.13
	EOT	13.34 (2.57)	13.72 (1.37)	0.50
	Change Baseline - EOT	0.39 (1.33)	0.00 (0.68)	0.18
	P value baseline - EOT	0.57	-	
Platelet (thou/µL)	Baseline	279.60 (55.78)	273.55 (60.73)	0.71
	EOT	265.24 (79.15)	265.44 (50.71)	0.99
	Change Baseline - EOT	-14.36 (56.99)	-8.11 (59.99)	0.70
	P value baseline - EOT	0.46	0.60	
Neutrophil (%)	Baseline	57.56 (7.47)	53.69 (7.41)	0.07
	EOT	62.04 (6.69)	57.89 (9.41)	0.07
	Change Baseline - EOT	4.48 (8.74)	4.92 (9.46)	0.86
	P value baseline - EOT	0.03	0.08	
Lymphocyte (%)	Baseline	31.60 (5.96)	34.69 (6.37)	0.08
	EOT	28.64 (4.90)	31.81 (6.78)	0.06
	Change Baseline - EOT	-2.96 (6.74)	-2.81 (7.43)	0.94
	P value baseline - EOT	0.06	0.12	

PCV (%)	Baseline	39.90 (6.31)	42.25 (4.71)	0.13
	EOT	40.28 (7.18)	41.09 (4.06)	0.62
	Change baseline - EOT	0.37 (4.39)	-1.17 (2.62)	0.13
	P value Baseline- EOT	0.85	0.33	
Serum Creatinine (mg/dL)	Baseline	0.80 (0.19)	0.86 (0.19)	0.25
	EOT	0.73 (0.26)	0.77 (0.15)	0.57
	Change baseline - EOT	-0.07 (0.21)	-0.09 (0.19)	0.62
	P value Baseline- EOT	0.30	0.04	
SGPT (U/L)	Baseline	35.16 (11.52)	38.12 (12.67)	0.38
	EOT	38.68 (10.72)	40.81 (8.12)	0.42
	Change baseline - EOT	3.52 (9.42)	2.70 (9.82)	0.76
	P value Baseline- EOT	0.27	0.36	
Eosinophil (%)	Baseline	3.92 (3.89)	5.23 (5.21)	0.31
	EOT	3.64 (3.79)	4.96 (4.71)	0.27
	Change baseline - EOT	0.36 (3.41)	-0.77 (4.68)	0.33
	P value Baseline- EOT	0.80	0.84	
Basophils (%)	Baseline	0.00	0.00	-
	EOT	0.00	0.00	-
	Change baseline - EOT	0.00	0.00	-
	P value Baseline- EOT	-	-	
Monocyte (%)	Baseline	6.92 (2.25)	6.38 (2.25)	0.40
	EOT	5.68 (2.51)	5.30 (2.18)	0.56
	Change baseline - EOT	-1.24 (2.28)	-1.23 (2.45)	0.99
	P value Baseline- EOT	0.07	0.08	
Values are expressed as Mean (SD), p computed using ANOVA				

10.4 Vital signs, physical findings and other observations related to safety

Measurements of vital signs were analyzed in the ITT population of 70 subjects. The LOCF method was used to impute missing data on vital parameters. There were no significant alterations in any of the vital parameters when analyzed for changes from baseline to end of treatment within each group and between the groups.

Table 17: Assessment of vital parameters

Variables	Time	GenF 20 (n=35)	Placebo n=35)	p
Pulse (per min)	Baseline	75.68 (6.05)	76.31 (4.34)	0.62
	EOT	77.23 (5.36)	77.57 (3.91)	0.76
	Change Baseline - EOT	1.54 (5.38)	1.26 (3.49)	0.79
	P value baseline - EOT	0.26	0.21	

Systolic BP (mm Hg)	Baseline	122.00 (5.76)	123.66 (6.73)	0.27
	EOT	123.31 (8.00)	123.88 (5.24)	0.72
	Change Baseline - EOT	1.31 (6.91)	0.23 (7.30)	0.52
	P value baseline - EOT	0.43	0.87	
Diastolic BP (mm Hg)	Baseline	77.91 (5.75)	77.86 (6.74)	0.97
	EOT	77.88 (7.13)	78.40 (7.11)	0.76
	Change Baseline - EOT	-0.03 (6.15)	0.54 (8.81)	0.75
	P value baseline - EOT	0.98	0.74	
Respiratory rate (per min)	Baseline	17.11 (1.37)	17.48 (1.79)	0.33
	EOT	17.48 (1.42)	17.63 (1.48)	0.68
	Change Baseline - EOT	0.37 (1.16)	0.14 (1.54)	0.48
	P value baseline - EOT	0.27	0.72	
Values are expressed as Mean (SD), p computed using ANOVA				

11. Discussion and overall conclusions

The present study was undertaken with postulated role of GenF20 Plus in stimulating anterior pituitary gland to secrete HGH, which when released into the blood stream stimulates the liver to produce IGF-1, the primary mediator of the effects of HGH. Thus the study was undertaken to evaluate efficacy and safety of GenF20 Plus in improving serum IGF-1 levels and thereby improve quality of life by improving memory, libido, energy levels, sleep and body weight. The outcome variables were BMI, waist circumference, body fat and lean body mass to assess effect on body weight. The variables memory, libido, energy levels and quality of sleep were assessed through Quality of Life questionnaire. Also global assessment by subjects was used to get overall understanding.

The serum IGF-1 levels from baseline to end-of-treatment did increase more in the active group than in the placebo group. But the increase in levels was neither clinically nor statistically significant. The serum IGF-1 levels are known to decrease with increasing age. Hence to avoid dilution of data, subgroups were made with cut off as 40 years. ANCOVA was performed to adjust the baseline variations for both the sub groups. In the subgroup age≥40 years, a statistically significant increase was seen in serum IGF-1 levels in the GenF20 Plus group [22.69 (28.57%)] as compared to placebo [-4.31 (-0.55%)] (p= 0.02). The significant increase in the serum IGF 1 levels in the subgroup age ≥ 40 in the active group is attributable to consumption of GenF20 plus. Prolonged usage of GenF20 plus may be able to show a clinically significant increase in serum IGF-1 levels. In the subgroup age<40 years, there was no marked change in either of the treatment groups. This could be attributed to sustained inherent mechanism of the body to be able to secrete normal levels of serum IGF-1 levels below 40 years of age. This analysis enables to postulate that GenF20Plus is able to stimulate secretion of HGH and IGF 1 and this change is noticeably observed in population above 40 years of age. A long term study should be carried out to assess the safety and efficacy of GenF20 plus in increasing serum IGF 1 levels in subjects with age≥40

At the end of 12 weeks of treatment, the BMI, waist circumference, body fat and lean body mass did not show a significant increase from baseline to end-of-treatment in both, the GenF20 Plus and placebo group. There was statistically significant improvement in QoL variables of memory, energy level, and sleep from baseline to end of treatment in both the groups, but it failed to achieve statistical significance when compared between the two groups. Pearson's Chi square test on global assessment by subjects did not show a significant difference (p=0.80) between the active and placebo group.

GenF20 plus was well tolerated by all the subjects. There were a total of 12 adverse events reported (7 in active and 5 in placebo group) during the study. They were mild, not related to

the study drugs and were successfully resolved. No serious adverse event occurred in the study. No significant changes were observed in the hematology variables or vitals or routine urine test.

Replenishing depleting serum IGF 1 and HGH levels are postulated to attain benefits of younger age and relieve signs and symptoms of growth hormone decline. GenF20 Plus contains essential amino acids and other ingredients which are known to stimulate the production and secretion of HGH from the anterior pituitary gland. It is a natural product with no known serious side effects. It is postulated to combat ageing and boost up bodily functions. GenF20 plus is not intended for the consumption in subjects with known growth hormone deficiency. Instead its consumption is postulated to increase the declining levels of growth hormone in aging subjects by stimulating the pituitary gland. There are very few options available to effectively and safely improve the growth hormone levels. Thus GenF20 plus was intended to provide solution to improve HGH levels without any adverse events. HGH and IGF 1 are also used as a performance enhancing agents, to increase muscle mass and exercise endurance[14]. Given its potentially adverse effects, ranging from disruption of the insulin system to cancer, administration of the exogenous HGH and IGF-I is not a safe method. The growing abuse of HGH for muscle building by athletes and body builders and its related medico-legal issues also necessitates finding safe and acceptable alternative.

A preclinical study[15] has shown that HGH stimulates lipolysis in obese mice and thereby reduces body weight through decrease in total body fat. Also a large number of porcine studies have shown that HGH causes loss of fat mass through inhibition of adipocyte lipogenesis by reducing insulin sensitivity and fatty acid synthase. Treating growing pigs with pig HGH showed reduction in adipose tissue by as much as 60±80% while concurrently stimulating muscle growth by 40±60%[16]. A clinical study by Rudman *et al* has shown beneficial effects of HGH administration in a group of elderly healthy men with low plasma IGF-I values, but no underlying pituitary pathology. These studies support the hypothesis that increased levels of IGF I and HGH will stimulate lipolysis and cause reduction in body fat.

Approximately 70% of the daily HGH output occurs during early sleep throughout adulthood. Studies have shown decreased HGH levels in insomniacs[7]. There is also age related reduction in cognitive function associated with decrease in HGH levels[8]. Studies have shown improvement in cognitive functioning in HGH-deficient patients by HGH substitution[10]. Decrease in HGH levels cause low secretion levels of sex hormones; thereby decreasing libido. Ageing is also attributed to cause diminished energy levels[12]. Thus restoring HGH levels may stimulate sound sleep, improve memory, increase libido and restore energy levels.

HGH and IGF-1 also have an important role in the promotion of vascular health and protect thrombotic and hemorrhagic strokes[17,18]. Low levels of IGF 1 have been associated with poor glycaemic control in type 2 diabetes and thereby increasing risk of cardiovascular diseases. Also it is known to suppress myocardial apoptosis and improve myocardial function[19]. Low serum IGF-I levels is also postulated to be associated with reduced T-cell mediated immunity in elderly[20]. Thus GenF20 plus by increasing serum IGF 1 levels may be able to provide health benefits to the aging population and prevent disease progression.

The present study has not shown improvement in all the parameters assessed in such short duration. The present study failed to show considerable reduction in BMI or waist circumference or body fat in both active and placebo groups. Parameter of sleep, memory, libido and energy levels also did not show substantial improvement. Improvement in all of the above parameters is difficult to attain in short duration of 12 weeks. The longer the duration of these impairments, longer will be the time required to attain normalcy or perceivable benefits by any agent. The fact that serum IGF 1 levels have increased with statistical significance in the sub group with age≥40 is an indication that prolonged usage of GenF20 Plus may show improvement in other parameters as well.

There is no single study in literature which has assessed improvement in all the above parameters together. Thus the duration of treatment for this pilot study was not chosen on a sound and validated rationale. Individual studies have shown efficacy of increased HGH levels to improve sleep quality, increase energy levels, and improve memory and libido. Thus prolonged consumption of GenF20 plus should increase HGH and IGF-1 levels and manifest improvement in the quality of life parameters. GenF20 plus may be required to be consumed for an extended period of time to show any considerable improvement in weight and body fat. In summary, GenF20 plus may not have delivered the projected efficacy results in this study, but is certainly worthy of further exploration as a potential agent to make quality of life better in overweight and aging population.

12. Appendices

Appendix I

Table 18: Concomitant medications

Subject ID	Medicine category	Indication	Dose	Frequency	Route	Start Date	End Date
Screening Failure	Thyroxin	Hypothyroidism	100mg	BD	oral	11/1/2011	
Screening Failure	Rabeprazole	Acidity	20mg	OD	oral	9/7/2011	9/8/2011
Screening Failure	Losartan	Hypertension	50mg	OD	oral	12/20/2008	
Screening Failure	Metformin	Diabetes Mellitus	500mg	BD	oral	1/1/2010	
Screening Failure	Atorvastatin	Hypertension	50mg	OD	oral	1/1/2010	
Screening Failure	Betahistine hydrochloride	Giddiness	16mg	BD	oral	7/26/2011	7/31/2011
Screening Failure	Esomeprazole	Acidity	40mg	OD	oral	7/26/2011	7/31/2011
GFP26	Oesmoprazole	Constipation	40mg	BD	oral	7/29/2011	8/2/2011
GFP26	Metronidazole	Constipation	100mg	BD	oral	7/29/2011	8/2/2011
GFP26	Paraffin powder	Constipation	2 TSF	OD	oral	7/29/2011	8/2/2011
GFP25	Voglibase+ Metformin	Diabetes	0.2+500 mg	OD	oral	1/1/2009	
GFP25	Glycomet	Diabetes	250mg	OD	oral	1/1/2009	
Screening Failure	Telmisartan4+ Amlodepin 2.5mg	Hypertension	5mg	OD	oral	4/20/2011	
Screening Failure	Multivitamin	General weakness	15mg	OD	oral	8/23/2011	

Screening Failure	Escilatopram	Insomnia	2.25mg	OD	oral	8/23/2011	
GFP11	Amlodepin+ Atenolol	Hypertension	5mg	OD	oral	1/1/2009	
Screening Failure	Alprazolam	Insomnia	0.5 mg	HS	oral	8/11/2011	
Screening Failure	Glimepiride	Diabetes Mellitus	1mg	OD	oral	1/1/2010	
Screening Failure	Metformin	Diabetes Mellitus	500mg	OD	oral	1/1/2010	
Screening Failure	Ramipril	Hypertension-stage-I	2.5mg	OD	oral	1/1/2011	
Screening Failure	Glimepiride	Diabetes Mellitus	1mg	OD	oral	5/1/2011	
Screening Failure	Metformin	Diabetes Mellitus	500mg	BD	oral	1/1/2011	
Screening Failure	Olmesartan	Hypertension	10mg	OD	oral	2/1/2011	
Screening Failure	Ecosprin	Diabetes Mellitus	75mg	OD	oral	2/1/2011	
Screening Failure	Metformin	Diabetes Mellitus	500mg	0.5 OD	oral	2/1/2011	
Screening Failure	Glimepiride	Diabetes Mellitus	1mg	OD	oral	3/1/2011	
Screening Failure	Metformin	Diabetes Mellitus	500mg	BD	oral	3/1/2011	
Screening Failure	Metaprolol	Hypertension	25mg	OD	oral	1/1/2011	
GFP02	Metformin	Diabetes Mellitus	10mg	TDS	oral	7/1/2011	
GFP02	Torsemide	Hypertension	10mg	twice a week	oral	7/1/2011	
GFP06	Amlodepine	Hypertension	2.5mg	OD	oral	1/1/2011	

GFP06	Atenolol	Hypertension	25mg	OD	oral	1/1/2011	
GFP01	Glimepiride	Diabetes Mellitus	1mg	OD	oral	1/15/2011	
GFP01	Metformin	Diabetes Mellitus	500mg	OD	oral	1/15/2011	
GFP01	Atorvastatin	Diabetes Mellitus	10mg	OD	oral	1/15/2011	
GFP01	Asprin	Diabetes Mellitus	75mg	OD	oral	1/15/2011	
GFP13	Nifedepine	Hypertension	10mg	OD	oral	1/1/2009	
GFP40	Balofloxacin	Urinary tract infection	100mg	BD	oral	7/22/2011	7/26/2011
GFP28	Telmisartan+ Amlodepin	hypertension	40mg+5 mg	OD	oral	1/1/2010	
GFP28	Sertatin	hypertension	25mg	once at night	oral	1/1/2010	
Screening Failure	Metformin	Diabetes Mellitus	250mg	OD	oral	1/1/2009	
Screening Failure	Telmisarten	Hypertension	20mg	OD	oral	1/1/2009	
Screening Failure	Rabeprazole	Acidity	20mg	once	oral	9/5/2011	9/7/2011

Appendix II

Table 19 showing pre existing conditions

Sub ID	Indication	Status	Start Date	End Date
Screening Failure	Thyroid	Ongoing	11/1/2010	
Screening Failure	Acidity	Ongoing	9/1/2011	
Screening Failure	Diabetes	Ongoing	1/1/2009	
GFP25	Diabetes	Ongoing	1/1/2009	
Screening Failure	Hypertension	Ongoing	1/1/2007	
Screening Failure	Diabetes	Ongoing	1/1/2010	
Screening Failure	Hypertension	Ongoing	1/1/2010	
Screening Failure	Giddiness	Resolved	7/26/2011	7/31/2011
GFP26	Constipation	Resolved	7/29/2011	8/2/2011
GFP26	Weakness	Resolved	7/29/2011	8/2/2011
GFP28	Hypertension	Ongoing	1/1/2010	
Screening Failure	Hypertension	Ongoing	4/20/2011	
Screening Failure	Weakness	Ongoing	8/23/2011	
Screening Failure	Insomnia	Ongoing	8/23/2011	
Screening Failure	Insomnia	Ongoing	8/11/2011	
Screening Failure	Type II Diabetes Mellitus	Ongoing	1/1/2003	
Screening Failure	Hypertension- Stage-1	Ongoing	1/1/2008	
Screening Failure	Diabetes Mellitus	Ongoing	1/1/2008	
Screening Failure	Diabetes Mellitus	Ongoing	1/1/2009	
Screening Failure	Hypertension	Ongoing	1/1/2001	
Screening Failure	Diabetes Mellitus	Ongoing	1/1/1992	

Screening Failure	Hypertension	Ongoing	1/1/2001	
GFP02	Hypertension	Ongoing	1/1/2010	
GFP02	Diabetes Mellitus	Ongoing	1/1/2010	
GFP06	Hypertension	Ongoing	1/1/2006	
GFP06	Hysterectomy done	Resolved	1/1/2000	1/1/2000
GFP01	Diabetes Mellitus	Ongoing	1/1/2005	
GFP13	Hypertension on regular treatment	Ongoing	1/1/2009	
GFP40	Urinary tract infection	Resolved		7/26/2011
GFP63	Thyroid	Ongoing	1/1/2008	
GFP31	Hypertension	Ongoing	1/1/2009	

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