9.4.2 Identity of Investigational Product(s)

The investigational drug Livitol supplied for this study is a combination of three bioactive molecules formulated in a mixture of Polymolecular compounds with a defined mechanism of action (Boeravinone B –insulin resistance, Phyllanthin – hepatic steatosis, Picroside-I – anti-inflammatory). Refer Table 1 for the composition of Livitol tablet.

Patients were instructed to store the bottle in a dry place at room temperature not exceeding 30°C and not to be frozen.

Table 1: Composition of Livitol Tablet

Each 880 mg Tablet Contains:			
Sl. No.	**Ingredients**	**Quantity (mg)**	**Quantity. For 10000 tablets (in kg)**
1.	Bhuiamla powder (*Phyllanthus* niruri)	275.500	2.755
2.	Punarnava powder (*B. diffusa*)	166.000	1.660
3.	Kutki powder (Picrorhiza kurroa)	99.600	0.996
4.	Blend of Bhuiamla, Punarnava, and Kutki extracts	83.700	0.837
5.	Maltodextrin	44.300	0.443
6.	Cellulose powder	120.00	1.200
7.	Dicalcium phosphate dehydrate	30.000	0.300
8.	Crosscarmellose sodium	20.000	0.200
9.	Magnesium stearate	6.000	0.060
10.	Colloidal silicon dioxide	5.000	0.050
Total weight of core tablet		**850.00**	**8.500**
Coating material			
11.	Opadry-White-Ready-mix	15.000	0.150
12.	Opadry-Maroon-Ready-mix	15.000	0.150
13.	Isopropyl alcohol	Qs	1.900
14.	Purified water	Qs	0.800
Total weight of coated tablet		**880.00**	**8.800**

Comparator drug was a matching placebo and was identical in the appearance with Livitol.

Details on Lot number of Livitol and placebo are provided in Table 2

Table 2: Study Drugs and Lot Numbers

Study Drug	**Dosage Form**	**Lot Number**	**Manufacturing Date**	**Expiration Date**
Livitol Active (Test Product)	Tablet	CF22001	Feb 2022	Jan 2024
Livitol Placebo (Reference Product)	Tablet	CE22001	Jan 2022	Dec 2023

9.4.3 Method of Assigning Subjects to Treatment Groups

After confirming the eligibility of the patients based on the inclusion/exclusion criteria, randomization of patients were carried out using statistical analysis system (SAS®)

Table 3: Study Flow Chart

Visits	V1	V2	V3	V4	V5	
	Screening	Randomization	Week 4	Week 12	Week 24	Unscheduled Visit**
	D (-14) to (-1)	D0	Day 28 ± 3 days	Day 84 ± 7 days	Day 168± 7 days	
Informed Consent	X					
Demographics	X					
Height, weight, waist circumference	X				X	
Diagnosis and Baseline Disease Characteristics	X					
Medical History	X					
Prior Disease-Specific Therapies/Medications	X					
Physical Examination	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X
12-Lead ECG	X				X	X
Laboratory Tests – Hematology[$]	X			X	X	X
Laboratory Tests – Chemistry (Liver and Renal Function Tests)[a]	X			X	X	X
Serology[b]	X					
Urinalysis	X				X	
Inclusion and Exclusion Criteria (I/E)	X					
Randomization		X				
Fasting blood glucose, Fasting insulin. HOMA-IR	X			X	X	X
HbA1c	X			X	X	X
Lipid profile	X			X	X	X
Urine pregnancy test[#]	X	X	X	X	X	X
Ultrasound[*]	X			X	X	
MRI-PDFF Assessments	X				X	
FIB-4 Score	X			X	X	
Dispense study drug		X	X	X		X
Study Drug Accountability and Compliance			X	X	X	X
Concomitant Medication	X	X	X	X	X	X
Adverse Events (AE)	X	X	X	X	X	X

Abbreviations: ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CBC=complete blood count, d=day, ECG=electrocardiogram, FIB-4=fibrosis-4, GGT=gamma-glutamyl

9.8 Changes in the Conduct of the Study or Planned Analyses

9.8.1 Changes in Study Conduct

There were no amendments prepared for this study. However, a few protocol clarification letters and a guidance document were generated during the conduct of the study. The major changes in each protocol clarification letter and guidance document are summarized in the Table 4.

Table 4: Changes in the Conduct of the Study

Protocol Clarification Letter 1, Dated 13 Jun 2022 (Regarding MRI-PDFF and FFA Estimation) • It was clarified that MRI-PDFF was to be performed as per the approved protocol in the MRI machine available at the clinical trial site facility. Further, the MRI-PDFF reports depicting the hepatic fat content were certified by radiologist. So, no separate radiology manual was prepared in the study. • The FFA estimation was not readily available at the selected central laboratory. Additionally, FFA analysis was requiring serum samples to be stored, transported, and analyzed under frozen conditions (-20°C). Thus, due to several logistical challenges, it was clarified that FFA would not be analyzed during the study.
Protocol Clarification Letter 2, Dated 14 Nov 2022 (Regarding AV Recording and Breaking of Blinding in IWRS) • It was clarified that AV recording was not applicable for this study. • It was clarified that for breaking of blinding IWRS would be used.

Abbreviations: AV=audio/video, FFA=free-fatty acid, IWRS= Interactive Web Response Systems, MRI-PDFF= magnetic resonance imaging proton-density-fat-fraction,

9.8.2 Changes to the Planned Statistical Analyses

In primary efficacy analysis, the mean change in hepatic fat measured by MRI-PDFF was similar in both test and reference groups. Being a phase 2 exploratory study, additional post-hoc analysis was performed to check the change in hepatic fat among patients with different extents of hepatic fat at baseline. For this, the study population was stratified into those with <20% hepatic fat at baseline and those with ≥20% at baseline. These analyses are presented in Table 14 and Table 15, respectively.

In addition to tables presenting absolute change in values of hepatic fat from baseline, tables presenting percentage change in values from baseline were also generated, to give a better understanding of impact of the interventions, relative to baseline hepatic fat content.

For the primary endpoint analysis, the mITT population was considered, which was defined as those who were randomized and had baseline and week 24 MRI-PDFF assessment performed. However, this definition did not consider the possibility of ultrasonography (USG) assessment being performed (at Weeks 12 and 24) in the absence of MRI-PDFF. To incorporate this data in the analysis, a post-hoc analysis of USG grading of fatty liver, was performed in the ITT population (defined in SAP) and a responder analysis was performed

10. STUDY SUBJECTS AND TREATMENT

10.1 Disposition of Subjects

A total of 188 patients were screened at 09 study sites across India, of which 112 patients were screen failures and the remaining 76 patients were randomized (n=38 in livitol group and n=38 in placebo group) (Listing 16.2.1.1).

All patients received at least 1 dose of study drug during the 24-week treatment period (n=38 in livitol group and n=38 in placebo group) and were included in safety population.

Of the total 76 patients who received at least 1 dose of study drug during the study, 71 patients (93.42%) completed the study, out of which 36 patients [94.74%] were from livitol group and 35 patients [92.11%] from placebo group and 5 patients (6.58%) early terminated from the study (2 patients [5.26%] from the livitol group and 3 patients [7.89%] from the placebo group). The reasons for early termination were withdrawal of consent (4 patients [5.26%]) and lost to follow–up (1 patient [1.32%]) (Table 5).

Table 5 Patient Disposition – Enrolled Population

	Statistics	Livitol (N = 38)	Placebo (N = 38)	Total (N = 76)
Number of Subjects Screened[1]	n			188
Number of Screen Failures	n			112
Number of Subjects Randomized but not dosed	n	0	0	0
Number of Subjects Randomized (ITT)	n(%)	38 (100)	38 (100)	76 (100)
Number of Subjects in Safety Population	n(%)	38 (100)	38 (100)	76 (100)
Number of Subjects in modified Intent To Treat (mITT) Population	n(%)	34 (89.47)	34 (89.47)	68 (89.47)
Number of Subjects in Per-Protocol (PP) Population	n(%)	31 (81.58)	30 (78.95)	61 (80.26)
Number of Subjects who completed the Study	n(%)	36 (94.74)	35 (92.11)	71 (93.42)
Number of Subjects who Early terminated the study	n(%)	2 (5.26)	3 (7.89)	5 (6.58)
Reason for Early termination	n(%)			
Consent withdrawn		1 (2.63)	3 (7.89)	4 (5.26)
Lost to Follow-up		1 (2.63)	0	1 (1.32)

Note 1: Percentages were calculated based on number of subjects in respective treatment groups
Note 2: [1] = Subject who provided informed consent
Reference: Table 14.1.1.1 and Listings 16.2.1.1, 16.2.1.2, 16.2.1.3, and 16.2.1.4.

A patient-wise data on disposition is provided in Listing 16.2.1.1, Listing 16.2.1.2, Listing 16.2.1.3, and Listing 16.2.1.4.

10.2 Protocol Deviations

Of the 76 patients enrolled in the study, there were 60 patients (78.9%) with at least 1 protocol deviation (Table 6). Overall, 10 of 76 patients (13.2%; 5 patients in each group) had at least 1 major protocol deviation during the study.

The major protocol deviations included assessment window deviation (4 patients [5.3%]), assessments deviation (3 patients [3.9%]), visit window deviation (2 patients [2.6%]), and eligibility deviation (1 patient [1.3%]).

A detailed summary of protocol deviations for each patient is provided in Listing 16.2.2.1.

Table 6 Protocol Deviations – Safety Analysis Set

Protocol Deviation Type	Livitol (N=38) n (%)	Placebo (N=38) n (%)	Total (N=76) n (%)
Subjects having atleast one protocol deviation[1]	29 (76.3)	31 (81.6)	60 (78.9)
Subjects with atleast one major protocol deviation[1]	5 (13.2)	5 (13.2)	10 (13.2)
Category of major protocol deviation[2]			
Assessment deviation	2 (5.3)	1 (2.6)	3 (3.9)
Assessment window deviation	2 (5.3)	2 (5.3)	4 (5.3)
Eligibility deviation	0	1 (2.6)	1 (1.3)
Visit window deviation	1 (2.6)	1 (2.6)	2 (2.6)

Note 1[1]: Percentages for the patients with at least one protocol deviation was based on the number of subjects in respec tive treatment group in safety population
Note 2: [2] = Percentages for category of major protocol deviation was based on number of patients with at least one major protocol deviation in respective treatment group in safety population.
Note 3: Same subjects can be counted multiple times under different categories but once within category.
Reference: Table 14.1.1.2 and Listing 16.2.2.1

11. EFFICACY EVALUATION

11.1 Data Sets Analyzed

The data sets planned for analysis in this study are defined in Section 9.7.1.2.

A total of 76 patients were randomized. All patients received at least 1 dose of study drug and were included in the safety population. All 76 patients (100.0%) were included in the ITT population; 68 patients (89.47%) were included in the mITT population, and 61 patients (80.26%) were included in the PP population (Table 7).

The details of individual patients excluded from efficacy analysis are presented in Listing 16.2.1.3.

Table 7 Data Sets Analyzed

	Statistics	Livitol (N = 38)	Placebo (N = 38)	Total (N = 76)
Number of Subjects Randomized (ITT)	n(%[1])	38 (100)	38 (100)	76 (100)
Number of Subjects in Safety Population	n(%[1])	38 (100)	38 (100)	76 (100)
Number of Subjects in modified Intent To Treat (mITT) Population	n(%[1])	34 (89.47)	34 (89.47)	68 (89.47)
Number of Subjects in Per-Protocol (PP) Population	n(%[1])	31 (81.58)	30 (78.95)	61 (80.26)

[1] = Percentages are based on number of total patients enrolled.
Reference: Table 14.1.1.1 and Listing 16.2.1.3.

11.2 Demography and Baseline Characteristics

A summary of demographic and baseline characteristics is presented in Table 8. The demographic and baseline characteristics of the patients were in line with the study inclusion and exclusion criteria and generally similar in both the groups.

Of the 76 patients who received at least 1 dose of study drug 58 patients (76.32%) were male and 18 patients (23.68%) were female. All the patients were Asians. The median age of patients was 44.5 years (Range: 20 to 62 years), which was similar in both the treatment groups. At baseline, in majority (47 patients [61.87%]) of the patients NAFLD symptoms were present.

The patient-wise data on demographic characteristics is provided in Listing 16.2.4.1.

Table 8 Demographic and Baseline Characteristics – Randomized Population

Characteristic (Unit)	Statistics	Livitol (N=38)	Placebo (N=38)	Total (N=76)
Age (Years)	n	38	38	76
	Mean (SD)	45.3 (10.21)	45.8 (10.19)	45.6 (10.13)
	Median	44.5	45.5	44.5
	Min, Max	20, 62	29, 62	20, 62

Characteristic (Unit)	Statistics	Livitol (N=38)	Placebo (N=38)	Total (N=76)
Gender	n (%)			
Male		33 (86.84)	25 (65.79)	58 (76.32)
Female		5 (13.16)	13 (34.21)	18 (23.68)
Race	n (%)			
Asian		38 (100)	38 (100)	76 (100)
Diagnosis And Baseline Disease Characteristics	n (%)			
NAFLD Symptoms present		21 (55.26)	26 (68.42)	47 (61.84)

Note 1: Percentages were calculated based on number of subjects in respective treatment groups in safety population.
Reference: Table 14.1.2.1 and Listings 16.2.4.1 and 16.2.4.3

The summary of anthropometric parameters (height, weight, waist circumference, and BMI at all visits) is provided in Table 14.3.9.1. The patient-wise data on anthropometric parameters is provided in Listing 16.2.11.1.

11.2.1 Medical History

A total of 63 patients (82.89%) had at least one known significant medical history. The most common (≥10%) medical history as per SOC were metabolism and nutrition disorders (73.68%), followed by vascular disorders (17.11%), gastrointestinal disorders (15.79%), social circumstances (15.79%).

The most common (≥10%) medical history as per PT were obesity (40.79%), type-2 diabetes mellitus (26.32%), hypertension (17.11%), post menopause (15.79%), nausea (14.47%), decreased appetite (13.16%), and dyslipidemia (13.16%).

The Summary of medical history by SOC and PT is provided in Table 14.1.3.1. A patient-wise data on medical history is provided in Listing 16.2.4.2.

11.2.2 Prior and Concomitant Medications

A summary of patients with prior and concomitant medication is presented in Table 14.1.4.1 and Table 14.1.5.1, respectively for the safety analysis population.

A total of 2 patients (2.6%) received at least one prior medication, both were from placebo group. Overall, the most common prior medications received by the patients by ATC level 1 were, antidiarrheal, intestinal anti-inflammatory/anti-infective agents, drugs for acid related disorders, drugs for functional gastrointestinal disorders, antibacterial for systemic use (2 patients [2.6%], each).

A total of 47 patients (61.8%) received at least 1 concomitant medication. The most common concomitant medications received by the patients by ATC level 1 were, drugs used in diabetes (23 patients [30.3%]), drugs for acid related disorders (19 patients [25.0%]), bile and liver therapy (13 patients [17.1%]), and agents acting on the renin-angiotensin system (10 patients [13.2%]).

A patient-wise data on who received at least 1 prior and concomitant medication are provided in Listing 16.2.4.4 and Listing 16.2.4.5, respectively.

11.3 Measurement of Treatment Compliance

Compliance was monitored at all visits during the study after randomization visit. The mean (SD) study drug compliance was 96.6% (4.07). All patients had ≥80% compliance (Table 9).

A patient-wise data on study drug administration is presented in Listing 16.2.5.1.

Table 9 Study Drug Compliance – Safety Population

Characteristics	Statistics	Livitol (N =38)	Placebo (N =38)	Total (N =76)
Compliance (%)	n	38	38	76
	Mean (SD)	96.9 (4.46)	96.3 (3.66)	96.6 (4.07)
	Median	98.8	97.0	98.3
	Min, Max	82, 100	88, 100	82, 100
Compliance (%) is < 80%	n (%)	0	0	0
>= 80%		38 (100)	38 (100)	76 (100)

Note 1: Percentages were calculated based on number of subjects in respective treatments groups in safety population.
Note 2: Compliance = (Tablets taken / Tablets supposed to be taken) x 100%.
Reference: Table 14.1.6.1 and Listing 16.2.5.1

11.4 Efficacy Results

The efficacy analysis was performed on mITT and PP sets.

11.4.1 Analysis of Efficacy

11.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint included change in hepatic fat content from baseline to Week 24, assessed by MRI-PDFF.

The summary of mean and mean change in hepatic fat content from baseline to Week 24 is presented in Table 10 and Table 11 for mITT and PP population, respectively. The mean change in hepatic fat content from baseline to Week 24 for the mITT and PP population is presented in In mITT population, the LS mean (SD) change in hepatic fat content after 24-