CLINICAL STUDY REPORT

A randomized, double-blind, placebo controlled, clinical study to measure the effect of natural phytochemical formulation on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in delayed onset muscle soreness (DOMS), and related inflammation and stress in healthy untrained subjects.

Investigational Drug Name: Rephyll® Capsule

Protocol No., Version, Date	ECTS/22/002
Report Version	00
Date of report	30 JUN 2023
Supersedes Version No.	None
Date of Superseded Version No.	Not Applicable

Sponsor	**CRO**
Aurea Biolabs Private Limited, XI/304A, Kadayiruppu, Kolenchery, Cochin, Kerala-682311	**Ethicare Clinical Trial Services** 410 to 412, G-Block, Titanium City Centre, 100 Feet Road, Nr. Sachin Tower, Satellite, Ahmedabad – 380015, Gujarat, India

CONFIDENTIAL

1.0 TITLE PAGE

STUDY TITLE:
A randomized, double-blind, placebo controlled, clinical study to measure the effect of natural phytochemical formulation on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in delayed onset muscle soreness (DOMS), and related inflammation and stress in healthy untrained subjects.

NAME OF INVESTIGATIONAL PRODUCT: Rephyll® Capsule

INDICATION: Muscle fatigue, endurance energy supply, recovery and neuro muscular activation and related inflammation and stress in delayed onset muscle soreness (DOMS)

DESIGN: A randomized, double-blind, placebo controlled, clinical study.

NAME OF THE SPONSOR:
Dr. Manish Grover
CEO, Aurea Biolabs Pvt. Ltd

PROTOCOL IDENTIFICATION NUMBER: ECTS/22/002

STUDY DATES:
Date of first subject enrolment: 04 JUL 2022
Date of last subject completed: 12 OCT 2022
Interim report submitted: 15 OCT 2022
Date of Data base lock: 18 JAN 2023

INVESTIGATOR AND SITE NAME:

Site No.	Name of Investigator	Site Address
01	Dr. Akhil Mukim	Parikh Hospital, Near police station, Sardar Patel Ring Rd, opp. Nikol, Nikol, Ahmedabad, Gujarat 382350
02	Dr. Vaishal Sheth	Navneet Memorial Hospital "Sushrusha", near Sardar Patel Samaj CG Road Opp. Navranpura telephone exchange, Navrangpura, Ahmedabad-380009, India.

SPONSOR REPRESENTATIVE:

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GCP STATEMENT:

This study was performed in compliance with ICH Good Clinical Practise (GCP) including the archiving of essential documents. Also comply with all requirements regarding the obligations of the Sponsor and all other pertinent requirements of the New Drugs and Clinical Trials Rules, 2019.

DATE OF REPORT: 30 JUN 2023

2.0 SYNOPSIS

NAME OF SPONSOR**:** Aurea Biolabs Private Limited.	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER VOLUME**:** PAGE**:**NA	FOR NATIONAL AUTHORITY USE ONLY
NAME OF FINISHED PRODUCT**:** Rephyll®-(Natural Phytochemical Formulation)		NA
NAME OF ACTIVE INGREDIENT**:** Phytocannabinoid β-caryophyllene		

Title of the Study:

A randomized, double-blind, placebo controlled, clinical study to measure the effect of natural phytochemical formulation on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in delayed onset muscle soreness (DOMS), and related inflammation and stress in healthy untrained subjects.

Investigators, Study Centers:

Site No.	Name of Investigator	Site Address
01	Dr. Akhil Mukim	Parikh Hospital, Near police station, Sardar Patel Ring Rd, opp. Nikol, Nikol, Ahmedabad, Gujarat 382350
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Contract Research Organization, Medical Writing, Data Management & Statistical Analysis:	**Ethicare Clinical Trial Services** 410 to 412, G-Block, Titanium City Centre, 100 Feet Road, Nr. Sachin Tower, Satellite, Ahmedabad – 380015, Gujarat, India Tel: +91-7940069486, Mobile: +91 9825585119

Study period: Date of first subject enrolment: 04 JUL 2022 Date of last subject completed: 12 OCT 2022	**Phase of Development:** Phase III

Objectives:

Primary objective

- To study the effects of a supplement on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in DOMS and related inflammation and stress compared to placebo.

Secondary objective

- To evaluate the safety and tolerability of study supplement.

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Methodology:

This was a randomized, double-blind, placebo controlled, clinical study to measure the effect of natural phytochemical formulation on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in delayed onset muscle soreness (DOMS) and related inflammation and stress in healthy untrained subjects.

The study was conducted on 110 (105 completed) healthy untrained subjects in India.

The study consists of 5 visits as described below.
Visit 1: Screening and randomization visit: Day -5 to 1
Visit 2: Follow up visit: Day 4 (after 72 hrs. of exercise)
Visit 3: Follow up visit: Day 15 ± 1 day
Visit 4: End of study visit: Day 30 ± 3 days
Visit 5: Telephonic Follow-up (Post Study Visit): Day 60 ± 5 days

After the informed consent process and completion of all screening assessments, and once all the inclusion/exclusion criteria were met, the eligible healthy untrained subjects were enrolled in the study. Untrained subjects were chosen based on the subject with tendency to do exercise less than 4 hours a week. All the laboratory investigations were done in local laboratory at the time of screening visit (Visit 1) which were required for confirming the subject's eligibility at the time of randomisation visit. At the randomization visit, subjects meeting all inclusion criteria and none of the exclusion criteria underwent for randomization.

Subjects were randomized in the study based on the randomization schedule in 1:1. Screening and randomization can be either done on the same day or on different days.

On the day of randomization, all subjects were either given test product or placebo. Subjects had to consume 02 oral capsules of 250 mg each (total 500 mg) daily morning for 30 days after breakfast. The subject started the treatment from visit 1 (randomization) onwards.

During the randomization visit, subjects performed specifically designed eccentric exercises that focuses on lower body muscles like calf, hamstring, adductors and quadriceps muscle. These exercises produced DOMS to the muscles of the healthy untrained subjects. Efficacy parameters were measured either during exercise and/or before or after exercise. Those parameters were for

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evaluation of muscle fatigue, endurance energy supply and recovery, neuromuscular activation, stress and anti-inflammatory biomarkers, subjective pain score etc.

After randomization visit, all subjects were instructed to visit the site as per the scheduled visit. Visit 2 (Day 4), Visit 3 (Day 15 ± 1 day) were follow-up visits, Visit 4 (V4) Day 30 ± 3 days was end of treatment visit and Visit 5 (V5) Day 60 ± 5 was Telephonic Follow-up (Post Study Visit). The IP accountability was cross checked at the time of visit and recorded in CRF.

Physical examination and vital signs were measured during each visit of study. At each visit, subjects were carefully monitored for all adverse events. During the treatment period, the data pertaining to primary and secondary endpoints like muscle fatigue, endurance energy supply and recovery, neuro muscular activation, stress and anti-inflammatory biomarkers, subjective pain score and type and incidence of adverse events were collected. Laboratory samples were collected at baseline, all follow-up and end of study visits.

Statistical comparisons were made between the test and placebo (to compare clinical effectiveness).

A total of 110 subjects were randomised out of 144 subjects screened. 34 subjects were screened failure. Randomized subjects were equally divided between the test and placebo group. There were 05 subjects who discontinued from the study and so 105 subjects completed the study. The study was conducted at 02 sites in India, both sites were comparable in facility and strictly followed the same study protocol. The recruitment period was lasted approximately 1.5-2 months; the treatment duration was of maximum of a 30 days and safety follow up was 30 days after treatment completion. The below table highlights the disposition of the subjects in the study.

Number of Subjects:

	Test (N=55) n	**Placebo (N=55) n**	**Overall (N=110) n**
Number of Subjects Randomised in the Study	55	55	110
Number of Subjects who Completed the Study	54	51	105
Number of Subjects Analysed for PP Population	54	51	105
Number of Subjects Analysed for mITT Population	55	55	110
Number of Subjects who Discontinued from the Study	01	04	05

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Abbreviations: N = Number of subjects in the specified treatment; n = Number of subjects in specified category;

Main Criteria for Inclusion:

Following are the criteria based on which each subject was considered for inclusion in the study.

1. Subject had provided written, signed and dated informed consent to participate in the study.
2. Subject willing and able to comply with the protocol.
3. Male or female subjects between 19-50 years of age (both inclusive).
4. Untrained subjects as defined by, less active that is regular exercise for less than 4 h per week.
5. Subject was in good health as determined by a health history and as per investigators discretions.
6. Subject was untrained in resistance/power exercise.

Investigational product, dose and mode of administration, batch number;

Test Product (T):

Name	:	Rephyll®
Manufacturer	:	Aurea Biolabs Private Limited
Batch No.	:	2205100036
Manufacturing Date	:	11-05-2022
Expiry Date	:	10-11-2023
Dose	:	02 oral capsules of 250 mg each (total will be 500 mg) daily morning for 30 days after breakfast.
Mode of Administration	:	Oral

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NAME OF ACTIVE INGREDIENT: Phytocannabinoid β-caryophyllene		

Placebo:

Name	:	Placebo
Manufacturer	:	Aurea Biolabs Private Limited
Batch No.	:	2205100037
Manufacturing Date	:	13-05-2022
Expiry Date	:	12-11-2023
Dose	:	02 oral capsules of 250 mg each (total will be 500 mg) daily morning for 30 days after breakfast.
Mode of Administration	:	Oral

Dosage Administration and Duration of Treatment:

The subjects were randomised to receive the test products; Rephyll® or placebo 02 oral capsules of 250 mg each (total will be 500 mg only) orally, daily morning for 30 days after breakfast.

Criteria for evaluation:

Primary endpoints:

1. Change in muscle fatigue
2. Change in endurance energy supply and recovery
3. Change in neuro muscular activation
4. Change in stress and anti-inflammatory biomarkers
5. Change in BP and pulse
6. Change in CBC and blood lipids
7. Subjective pain score

Secondary endpoints:

1. Type and incidence of adverse events

Statistical analysis:

Primary efficacy analysis:

Mean change in efficacy parameters from baseline to end of study were analyzed using unpaired "t" test or Mann Whitney test depending upon the distribution of data (For between group comparison). For Within group comparison, mean change in efficacy parameters from baseline to end of study were analyzed using paired "t" test or Wilcoxon test depending upon the

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distribution of data. Normality test (Shapiro-Wilks test) was used to check the distribution of data. All tests were 2 sided. P values of less than 0.05 was considered as statistically significant difference between treatment groups. The data presented as mean (±Standard deviation) with 95 % confidence interval of treatment difference.

Secondary efficacy analysis:

Secondary end points were analyzed using descriptive statistics. All treatment emergent serious and non-serious adverse events (reported and/or observed) were summarized. Safety was analyzed by descriptive methods in all subjects who have received at least a single dose of the drug.

SUMMARY OF RESULTS:

Efficacy Results:

1. **Change in Muscle Fatigue**

Change in parameters to evaluate muscle fatigue showed significant improvement after 30 days of treatment with test product. Statistically significant improvement was seen in Fatigue Index and rating of perceived exertion. Clinical improvement was seen in creatine kinase, myoglobin in blood, lactic acid in blood, where the % of subjects showing clinical improvement were more as compared to placebo after 30 days of treatment.

Change in muscle fatigue conclude that as the muscle involvement increases in subjects taking test product. The higher the score of Fatigue Index, the better subject's ability to maintain eccentric performance. Similarly rating of perceived exertion (RPE), score of level of exertion decreased after 30 days of test product treatment. The subjects taking test product showed light or no exertion during exercise after 30 days of treatment. Table 2.1 provides the summary of analysis of muscle fatigue.

Other parameters showing changes in muscle fatigue were creatine kinase, aspartate aminotransferase, alanine aminotransferase, myoglobin in blood, lactic acid in blood, blood urea nitrogen and electrolytes like glucose, Na^+, K^+.

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Table 2.1 Change in muscle fatigue

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
FATIGUE INDEX			
PP population	N=54	N=51	
Baseline (Visit 1)	166.08 (101.02)	152.39 (73.11)	13.6900 (-20.6115 to 47.9915) **P=0.4304**
End of Study visit (EOS)	222.13 (143.24)*	159.54 (74.81)	62.5900 (17.9729 to 107.2071), **P=0.0064**
Change from baseline at EOS	56.04 (143.47)	7.16 (79.54)	48.8800 (3.6150 to 94.1450), P=0.0346
RPE SCORE			
PP population	N=54	N=51	
Enrollment Visit 1 (Day 1) after exercise	12.26 (1.73)	12.41 (1.81)	-0.1500 (-0.8352 to 0.5352) P= 0.6651
End of Study visit (EOS) Visit 4 after exercise (Day 30)	9.24 (2.01)*	11.04 (1.96)*	-1.8000 (-2.5690 to -1.0310), **P= 0.0001**
Change from Enrollment Visit 1 (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-3.02 (2.47)	-1.37 (2.42)	1.6500 (0.7028 to 2.5972), **P= 0.0008**

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population;
Test: Rephyll®-(Natural Phytochemical Formulation)

2. Change in endurance energy supply and recovery:

Endurance energy supply and recovery was evaluated with Respiratory exchange ratio (RER), maximum oxygen consumption (VO2max), heart rate and other laboratory parameters like creatine, phosphocreatine, Adenosine-5'-triphosphate (ATP) and Lactic acid threshold in blood.

RER is result of the volume of CO2 produced and the volume of O2 consumed during exercise. RER increases with exercise intensity. Results shows statistically significant response with Test product as compared to placebo after 30 days of treatment.

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Change in Adenosine-5-triphosphate (ATP) was statistically significant from baseline to Day 30 within test group and placebo group. This shows that the energy supply was increased in subjects after test product consumption.

Change in Lactic Acid Threshold measured during exercise at baseline and at day 30. Data shows that the concentration of lactic acid remain low after 30 days of treatment with test product as compared to placebo.

VO2max results showed that less O2 was consumed during exercise after 30 days of treatment as compared to exercise at 0 day (baseline). So, in rephyll treated group less oxygen is required to perform exercise.

Table 2.2 Change in endurance energy supply and recovery

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Respiratory exchange ratio			
PP population	N=54	N=51	
Enrollment Visit 1 (Day 1) after exercise	1.54 (0.72)	1.37 (0.74)	0.1700 (-0.1126 to 0.4526) P= 0.2356
End of Study visit (EOS) Visit 4 after exercise (Day 30)	1.36 (0.66)	1.39 (0.53)	-0.0300 (-0.2625 to 0.2025), P= 0.7985
Change from Enrollment Visit 1 (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-0.18 (0.49)	0.02 (0.54)	0.2000 (0.0006 to 0.3994), **P= 0.0493**
ATP (nmol/ml)			
PP population	N=54	N=51	
Enrollment Visit 1 (Day 1) before exercise	1.15 (0.45)	1.27 (0.60)	-0.1200 (-0.3245 to 0.0845) P=0.2473
Follow up Visit 3 (Day 15)	2.61 (1.63)*	2.55 (1.24)*	0.0600 (-0.5030 to 0.6230), P= 0.8330
End of Study visit (EOS) Visit 4 before exercise (Day 30)	2.65 (0.91) *	2.43 (1.00)*	0.2200 (-0.1497 to 0.5897), P= 0.2407

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Change from Enrollment Visit 1 (Day 1) before exercise at follow up visit 3 (Day 15)	1.47 (1.62)	1.25 (1.34)	-0.2200 (-0.7973 to 0.3573), P= 0.4515
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	1.46 (1.20)	1.00 (1.35)	-0.4600 (-0.9538 to 0.0338), P= 0.0675
VO2max_Max oxygen consumption (mL/kg/min)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	37.98 (3.48)	37.47 (3.32)	0.5100 (-0.8079 to 1.8279) P= 0.4446
End of Study visit (EOS) Visit 4 (Day 30)	36.63 (4.26)	37.91 (2.64)	-1.2800 (-2.6612 to 0.1012), P= 0.0690
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	-1.35 (3.19)	0.45 (2.82)	1.8000 (0.6320 to 2.9680), **P= 0.0029**
Time to threshold (mins)			
Baseline	23.23 (13.19)	22.45 (15.33)	0.7800 (-4.6252 to 6.1852), P=0.7754
EOS	25.52 (06.53)	22.48 (08.13)	3.0400 (0.2529 to 5.8271), **P=0.0328**

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population;
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Lactic Acid Threshold in blood											
	Test Enrollment Visit 1 (Day 1) (mmol/l)						**Test EOS Visit 4 (Day 30) (mmol/l)**				
Time points	**1**	**2**	**3**	**4**	**5**	**Time points**	**1**	**2**	**3**	**4**	**5**
Mean	5.71	6.03	6.57	7.16	7.71	Mean	5.27	5.87	6.68	6.98	7.18
SD	3.45	3.55	3.95	4.55	4.55	SD	4.01	3.73	4.13	4.19	3.72
Min	1	1.1	1.6	1.8	1.7	Min	1	1.4	1.9	2.3	2.3
Max	13.8	13.7	17.5	19.1	20.8	Max	17.8	15.3	17.6	19.7	20.3
	Placebo Enrollment Visit 1 (Day 1) (mmol/l)						**Placebo EOS Visit 4 (Day 30) (mmol/l)**				
Time points	**1**	**2**	**3**	**4**	**5**	**Time points**	**1**	**2**	**3**	**4**	**5**

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Mean	5.31	5.63	6.45	6.45	6.78	Mean	4.90	5.57	6.07	7.11	7.58
SD	3.51	3.27	3.62	3.34	3.77	SD	3.03	3.08	2.98	3.45	3.63
Min	1.1	0.9	1.3	1.5	1.9	Min	1.5	1.5	2.4	2.7	3.9
Max	13.7	14.8	16.1	18.7	20.5	Max	12.6	13.7	12.8	14.9	18.8

3. Change in Neuro Muscular Activation

Neuro muscular activation was measured by Electromyogram (of the four lower limb muscles Calf Muscles (Gastrocnemius), Hamstring muscles, Adductor muscles and Quadriceps muscle), time for standing with one leg and vestibular function test.

Electromyogram (EMG) was used to evaluate the neuro muscular activation at the time of eccentric exercise of lower limb muscles. The changes in neuro muscular activation evaluated at baseline and at day 30. As the muscle involved during exercise get activated, maximum amplitude of EMG was measured. In the analysis of neuromuscular efficiency there were no statistically significant differences between test product and placebo, but at clinical level large effect was observed for peak amplitude for all the four muscles. Effort in EMG for Gastrocnemius muscle showed statistically significant difference (P= 0.0354) between test and placebo at day 30, similarly for Adductor muscle, the effort in EMG showed statistically significant difference (P=0.0144) between test and placebo at day 30.

Parameter of time for standing on one leg, showed statistically no-significant difference. It was similar in both at baseline and at day 30. In Vestibular Function Test (VFT) it can be concluded that there was no imbalance reported in any of subject in any of groups. For VFT, score of the activities like subject's balance, spontaneous response, sensory response and visual vertical reports were recorded. After 30 days of the treatment there was no change or minor change reported in VFT which can be considered as normal functioning of the subjects; also, the changes were not statistically significant.

4. Change in Stress and Anti-inflammatory Biomarkers

Cortisol, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), IL-6 and TNF-α are the stress and anti-inflammatory biomarkers evaluated during study at baseline, mid of the study and day 30. On mid of the study either day 4 or day 15, the level of biomarkers was increased at non-significant level as compared to baseline but were within normal reference range only.

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The mean value was decreased at day 30. CRP was seen much lower in test group as compared to placebo. Similar trend was observed with IL-6 and TNF- Alpha levels. Reduction in level of stress and inflammatory biomarkers were variable in different parameters. After 30 days of treatment with test product, improvement was seen in 64% subjects for CRP, 44% subjects for ESR, 36% subjects for IL-6 levels; while in placebo group the same improvement was seen with 41%, 25% and 14% of subjects for CRP, ESR and IL-6 levels respectively.

5. Change in BP and Pulse

Blood pressure and pulse were reported within normal range only and no clinical significance was reported at any level of the vital signs of the subjects during entire study duration.

6. Change in CBC and Blood Lipids

There were no statistically significant differences observed in CBC and blood lipid levels. There were no clinically significant values observed during study period either at baseline or at 30 days or assessment.

7. Subjective Pain Score

Subjective pain score was inspected utilizing numerical pain intensity scale. On visual assessment score (VAS) scale ranged from 0 (no pain at all) to 10 (extremely intense pain), pain score was evaluated between test and placebo groups at baseline, day 4, day 15 and at day 30. Results showed that there was statistically significant improvement seen in the pain reduction between test and placebo on day 4, day 15 and after 30 days of treatment while performing exercises. Change in pain score was 2.13 in test group and 1.86 in placebo group from baseline to 30 days. Though the improvement was not statistically significant, the clinical results showed the efficacy of the test product for pain management.

Table 2.3 Subjective Pain Score

	Test	Placebo	P value (Between group comparison)
Pain score			
PP population	N=54	N=51	
Baseline	4.09 (1.17)	4.00 (0.89)	0.64
Follow up visit 02 (Day 4)	3.00* (1.27)	3.78 (1.12)	0.001
Follow up visit 03 (Day 15)	1.46* (1.24)	2.14* (1.02)	0.003

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End of Study visit (EOS)	2.44* (0.92)	3.80 (0.80)	<0.001
Change from Enrollment Visit 1 (Day 1) at follow up visit 2 (Day 4)	-1.08 (1.11)	-0.22 (0.94)	<0.001
Change from Enrollment Visit 1 (Day 1) at follow up visit 3 (Day 15)	-2.65 (1.15)	-1.86 (0.94)	<0.001
Change from Enrollment Visit 1 (Day 1) at EOS Visit 4 (Day 30)	-1.63 (0.92)	-0.20 (0.72)	<0.001

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population;
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Safety Results:

Extent of exposure:

Total number of usage was 5972 (3076 test and 2896 placebo) capsules in which 93% and 88% usage were by subjects of test and placebo group respectively.

Table 2.3 Summary of Exposure (safety population)

Parameter	Test n (%)	Placebo n (%)	Overall n (%)
Total number of usage as per protocol	3300	3300	6600
Total number of actual usage	3076 (93.21)	2896 (87.76)	5972 (90.48)

Adverse events:

Brief summary of TEAEs: No SAE was reported during the entire course of the study. A total of 02 AEs were reported in 02 subjects during the screening period and were not referred to as TEAE. No TEAE was reported after subject enrolment in the study till last visit.

Vital signs, physical examination and other observations related to safety: Value of each vital sign (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and temperature) was comparable in the both treatment groups. Haematological parameters were also in acceptable range and all the other values were within clinically acceptable limits.

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Based on an assessment of the extent of exposure, AEs, physical examination and vital sign measurements, safety profile of test product is safe and well tolerated for use in healthy subjects.

Conclusion:

Eccentric exercise is known to cause muscle damage, this study was made experimentally feasible to investigate the potential role of exercise-induced muscle micro damage as a stimulus for physiological and biochemical adaptation.

Rephyll®, natural phytochemical formulation was effective on muscle fatigue, endurance of energy supply, recovery and neuro muscular activation in delayed onset muscle soreness (DOMS) and related inflammation and stress in healthy untrained subjects.

Efficacy of β-caryophyllene (Rephyll®) was significantly proven in muscle fatigue and endurance of energy supply which provides potential effectiveness of Rephyll® for prevention of DOMS. Improvement in neuro muscular activation and overall inflammation and stress biomarkers in untrained subjects, confirms the helpfulness of product in trained person. Product was safe and well tolerated by the subjects during as well as after study duration.

Date of Report: 30 JUN 2023

3.0 TABLE OF CONTENTS

LIST OF FIGURES INCLUDED IN THE TEXT

LIST OF TABLES

4.0 LIST OF ABBREVIATIONS& DEFINITION OF TERMS

AE	Adverse Event
ANOVA	Analysis of variance
CDSCO	Central Drugs Standard Control Organization
CEO	Chief Executive Officer
CI	Confidence Interval
CRF	Case Report Form
CRO	Clinical Research Organisation
DCGI	Drugs Controller General of India
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Institutional Ethics Committee
IP	Investigational Product
ITT	Intent-to-treat Analysis
mITT	Modified Intent-to-treat Analysis
n	Number of Subjects
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IUPAC	International Union of Pure and Applied Chemistry
LAR	Legally Acceptable Representative
LOCF	Last Observation Carried Forward
PP	Per Protocol
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOP	Standard Operating Procedure
TEAE	Treatment-Emergent Adverse Event
VAS	Visual Analogue Score
WMA	World Medical Association

Note: The terminology “Patient” was considered as “Healthy Subject” wherever applicable in clinical study report.

5.0 ETHICS

5.1 Independent Ethics Committee (IEC)

The clinical study protocol (Version no. 00, Dated 18 APR 2022), informed consent form (Version no. 01, dated 03 JUN 2022) (in English and in vernacular language like Gujarati and Hindi) and all other relevant study documentations were reviewed and approved by the responsible ethics committee. Ethics committee details along with approval letters are provided in **Appendix 16.1.3**. The protocol is provided in **Appendix 16.1.1**.

Table 5.1.1: Ethics committees

Sr. No.	Investigator Name	Ethics committee name	Chairperson	Ethics Committee registration/re-registration number	Date of approval
1.	Dr. Akhil Mukim	Riddhi Medical Nursing Home IEC	Dr. Kinal V Shah	ECR/886/Inst/GJ/2016/RR-19	22 MAY 2022
2.	Dr. Vaishal Sheth				

5.2 Ethical Conduct of the Study

The study commenced only after a written approval was obtained from the ethics committee of each site. The study was conducted in accordance with the protocol, pertinent requirements of CDSCO, International Council for Harmonisation (ICH) (Step 5) 'Guidance on Good Clinical Practice' (E6) and 'Declaration of Helsinki'. All associates assisting in the conduct of the study were informed regarding their obligations.

5.3 Subject Information and Consent

The Subject Information Sheet and Informed Consent Form (ICF) included all elements required by the ICH GCP, as well as applicable local regulatory requirements and adhered to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to undergoing any study procedures, subjects were fully informed about the nature, scope, and possible treatment risks and consequences of the study, and they were asked to read, sign, and date the ICF. The informed consent form was translated into their vernacular language for easy understanding. All the subjects and LAR/impartial witness (as applicable) signed and dated the informed consent form at screening visit. Each subject was given adequate time to provide informed consent of his or her own free will and subjects were given the opportunity to have their questions answered by the delegated staff member. All subjects had given copy of the signed informed consent for record prior to prior to the initiation of any study procedures and the original consent form was kept in the subject's records. Prospective participants were informed of their right to withdraw from the study at any time without prejudice. A sample subject Information Sheet and Informed Consent Form are provided in **Appendix 16.1.3**.

6.0 INVETIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Study Sponsor

Aurea Biolabs Private Limited,
XI/304A, Kadayiruppu, Kolenchery, Cochin, Kerala-682311
Phone: +91 484 284 4500, +91 484 276 0497
Fax: + 91 484 276 0689
e-mail-info@aureabiolabs.com
Website: https://aureabiolabs.com/

6.2 Investigators

Site Activities: Study management, on-site protocol activities, physical examination, and review of medical records, medical supervision, and efficacy and safety evaluation as per approved protocol requirements. Table 6.2.1 lists the names and addresses of all the investigators who participated in the study.

A summary of investigators (along with curriculum vitae) is available in **Appendix 16.1.4**.

Table 6.2.1: List of Investigator and Site Address

Site No.	Name of Investigator	Site Address
01	Dr. Akhil Mukim	Parikh Hospital ,Near police station, Sardar Patel Ring Rd, opp. Nikol, Nikol, Ahmedabad, Gujarat 382350
02	Dr. Vaishal Sheth	Navneet memorial Hospital “Sushrusha”, near Sardar Patel Samaj CG Road Opp. Navranpura telephone exchange, Navrangpura, Ahmedabad-380009, India.

6.3 Site of Manufacture

Test Product: Aurea Biolabs Private Limited, Kerala
Placebo: Aurea Biolabs Private Limited, Kerala

6.4 Monitoring, Data Management and Medical writing

Name of study Co-ordinator: Mr. Jay Punatar
Name of study monitors: Mr. Khushal Vyas, Ms. Deepika Tiwari
Name of Medical writer: Ms. Dhara Shah, Dr. Ishita Basera
Name of QA personnel: Mr. Sandeep Patel and Dr. Minal Khamar
Data Management: Ms. Heena Diwan

7.0 INTRODUCTION

Delayed onset muscle soreness (DOMS) is a combination of muscle pain and stiffness occurring several hours after unaccustomed exercise, particularly when eccentric muscle activity is involved, it can induce muscle damage. An inflammatory response and the reactive oxygen species (ROS) production is triggered by this mechanical stress.[1]

DOMS is linked to muscle soreness, decreased range of motion, muscle fibre disruption, changed joint kinematics, decreased strength, and acute tissue damage, all of which led to future athletic performance degradation and/or injury risk. The most severe occurrences of muscle damage are caused by activities that involve eccentric exercise.[2]

Therefore, recovery from DOMS and muscle damage is becoming increasingly important so that any sports person or athlete or any individual with interest in exercise may undergo training more frequently to increase long-term performance.

Cryotherapy, stretching, massage, compression, ultrasound, oral nonsteroidal anti-inflammatory medications (NSAIDS), and exercise are some of the therapeutic techniques for the management of DOMS-related symptoms. Several nutritional supplements (e.g., protein powders, vitamin C, fish oil, and chondroitin sulphate) have also been studied, with varying outcomes.[3]

Recently β-Caryophyllene has the distinction of being the first known “dietary cannabinoid,” a common component of food that has “Generally Recognized as Safe” (GRAS) status and is approved by the FDA for food use. β-Caryophyllene is the primary sesquiterpene contributing to the spiciness of black pepper; it is also a major constituent of cloves, hops, rosemary, copaiba, and cannabis.[4]

In recent years, modulatory and pharmacological effects of BCP have been demonstrated in numerous organs such as liver, kidney and brain. BCP has been reported to exert therapeutic effects as antioxidant, anti-inflammatory and anticancer.[5]

Rephyll® is unique natural pain management formulation incorporates the phytocannabinoid β-caryophyllene (derived from black pepper) using cutting-edge Zeal technology; formulated by nanofiber weaving (NFW) technology through well-organized nanofiber (NF) fabrication using homogenization with high pressure followed by a spray drying process that can expand the utilization outline of BCP, particularly in the pharmaceutical and nutraceutical industries.[6]

The important objectives of this study were to assess the effects of Rephyll® on DOMS compared to placebo on pain, neuromuscular activity, muscle fatigue and to evaluate the effects on blood parameters and the incidence of adverse events.

8.0 STUDY OBJECTIVES

Primary Objective:

- To study the effects of a supplement on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in DOMS and related inflammation and stress compared to placebo.

Secondary Objective:

- To evaluate the safety and tolerability of study supplement.

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan:

This was a randomized, double-blind, placebo controlled, clinical study to measure the effect of natural phytochemical formulation on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in delayed muscle soreness (DOMS) and related inflammation and stress in healthy untrained subjects.

The study was conducted in 110 (105 completed) subjects with delayed muscle soreness (DOMS) in India.

The study consists of 5 visits as described below

- Visit 1: Screening and randomization visit: Day -5 to 1
- Visit 2: Follow up visit: Day 4 (after 72 hrs of exercise)
- Visit 3: Follow up visit: Day 15 ± 1 day
- Visit 4: End of study visit: Day 30 ± 3 days
- Visit 5: Telephonic Follow-up (Post Study Visit): Day 60 ± 5 days

The study was conducted on 110 subjects at 02 sites in India. The treatment duration was of maximum of 30 days of actual study period per subject and overall study period including 30 days follow up after treatment is 60 days.

The study outline design is demonstrated in Figure 9.1.1 below.

The list of study procedures, assessments and schedule of events for all study visits are provided in Table 9.1.1.

On Visit 1 (Day -5 to 1), the screening period lasted for 5 days. During the screening visit, after signing the informed consent document, the subjects were evaluated with respect to inclusion and exclusion criteria. Healthy untrained subjects were considered to be qualified for inclusion in this study. Baseline determinations were taken into consideration while screening subjects (Demographic data, personal and medical history, assessment for solicited medical conditions and medication history, vital signs, physical examination, laboratory investigations).

Randomization visit (Day 1): Subjects meeting all inclusion criteria and none of exclusion criteria after completion of the screening period underwent baseline assessments during the randomization visit. During the randomization visit, measurement of endurance energy supply and recovery with RER, maximum oxygen consumption (VO2 max), measurement of neuromuscular activation activity test with the help of Electromyography. Prior to the electromyography eccentric exercise was done that focused on calf, hamstring, adductors and quadriceps muscles.

All subjects in the study were randomized in the study based on the randomization schedule in 1:1, all subjects were either given test product or placebo, 02 oral capsules of 250 mg each (total will be 500 mg) daily morning for 30 days after breakfast. Subject started the treatment from randomization visit onwards. All subjects were instructed to visit the site as per the scheduled visit. The IP accountability was cross checked at the time of visit and accounted for in CRF. Visit 2 (Day 4), 3 (Day 15 ± 1 day) were follow-up visits and Visit 4 Day 30 ± 3 days end of treatment visit, Visit 5 Telephonic Follow-up (Post Study Visit at Day 60 ± 5 days) was also performed.

Physical examination and vital signs were measured during each visit of study. At each visit subjects were carefully monitored for all adverse events. During the treatment period, the data pertaining to primary and secondary endpoints such as Change in muscle fatigue, Change in endurance energy supply and recovery, Change in neuro muscular activation, Change in stress and anti-inflammatory biomarkers, Change in BP and pulse, Change in CBC and blood lipids, Subjective pain score and type and incidence of adverse events were collected. Laboratory samples were collected at baseline, all follow-up and end of study visits. (Detail is provided in **Appendix 16.1.1**.)

During telephonic follow up visit, subjects were asked for their health, their concern related to study procedure, study medication, any adverse event occurred, usage of concomitant medication and overall satisfaction of the study.

Protocol for performing eccentric exercises is described as below. Eccentric exercises were conducted using same protocol at both sites, under direct supervision of trained personal, for same time period for each subject

Eccentric Exercise protocol:

1. Exercise one: Calf muscles eccentric loading- toe raise

In this exercise the subject was asked to stand on a step with their heels hanging over the side of the step. The subjects were asked to raise on their toes and then slowly lower their heel past the step to the count of 4 going down. The subjects then were performed a toe raise ready for the next repetition. The exercise was performed for four times. This exercise was designed to develop eccentric loading to the calf muscles, the gastrocnemius and the soleus.

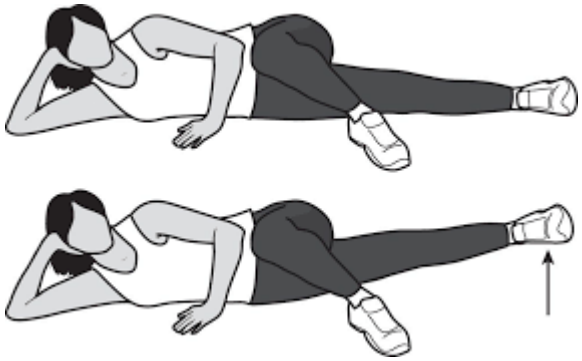
Post Exercise, Lactic acid Threshold will be measured by prick method.

2. Exercise two: Eccentric loading to the hamstrings-ball exercise

In this exercise the subjects were asked to lie on a mat on the floor. Their feet (heels) were on an exercise ball and their knees were extended. The exercise was performed by lifting their hips off the floor and bringing their knees to their chest. The subjects then slowly extended their legs holding their hips off the floor, to the count of 4. This process was repeated four times. Thus, performing an eccentric loading to the hamstrings.

3. Exercise three: eccentric load to the adductors of the hip- side lying lift

In this exercise the subjects were asked to side lie on a mat on the floor. Their top leg was resting on a platform that shall be 0.66 meter over the other foot. The subject was then asked to raise the bottom foot off the floor with their knee straight. After reaching the under surface of the platform, the subject was asked to slow lower the leg to the count of 4. Four repetitions were performed.



4. Exercise four: eccentric loading of the quadriceps muscle group-decline board.

In this exercise the subject was asked to stand on one leg, on a decline board with an angle of 30 degrees. The subjects were asked to slowly bend their knee, to the count of 4, until they could no longer see their toes. They instructed to extend their knee. After they performed four repetitions the subjects were going to switch their legs and were performing the same exercise on the opposite side.

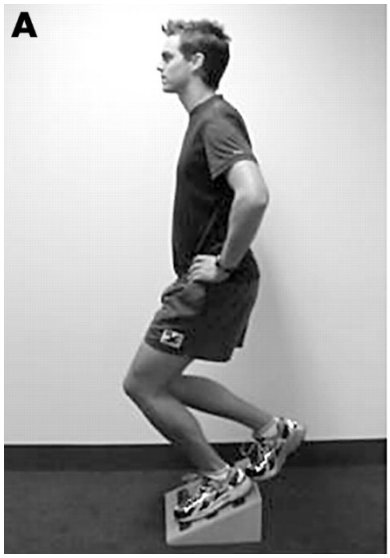
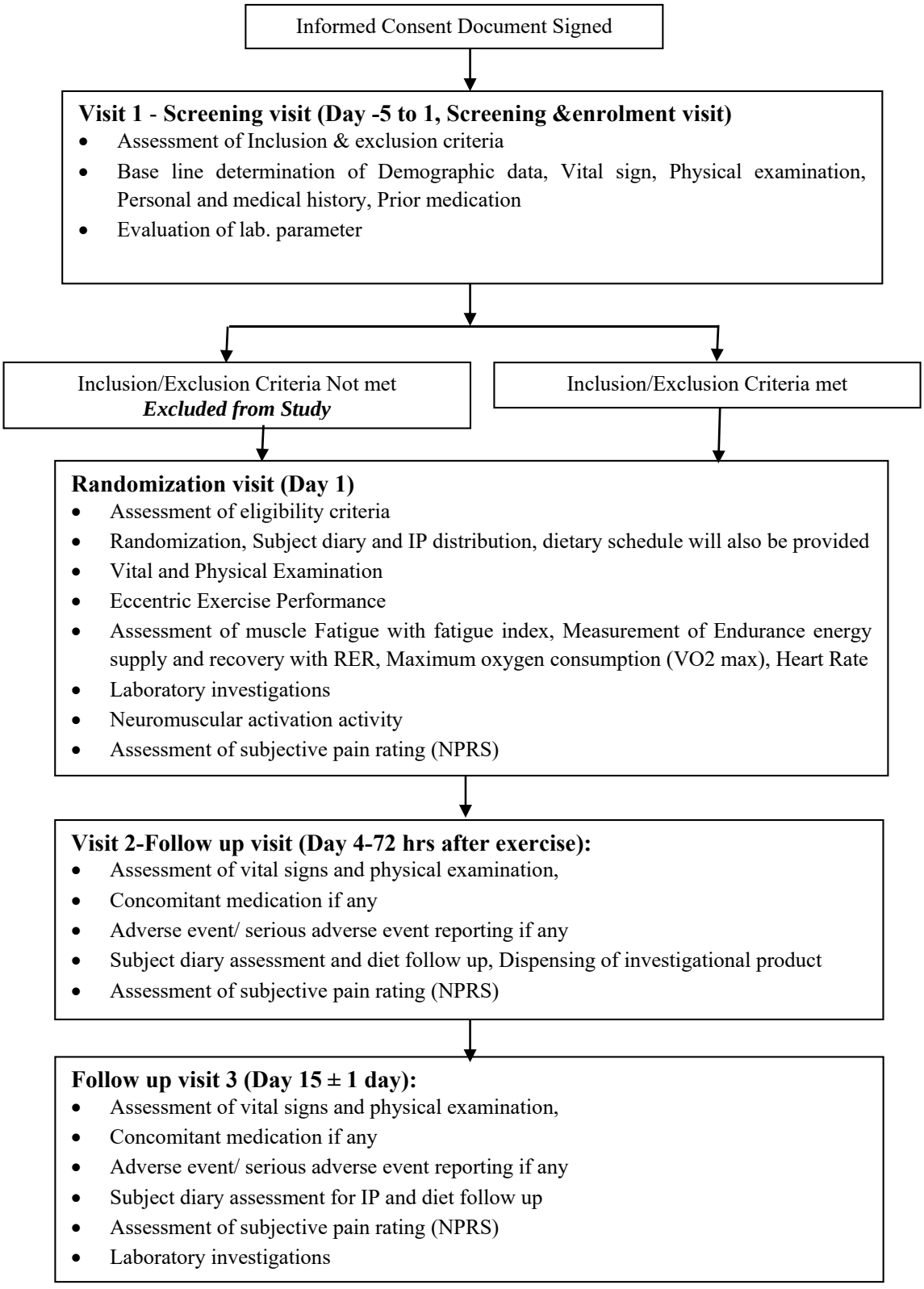


Table 9.1.1: Study procedure

Activity	Screening visit	Randomization visit	Follow up visit	Follow up visit	End of study visit	Telephonic Follow up visit
Visit Number	**Visit 1**		**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Days	**Day -5 to 1**	**Day 1**	**Day 4, 72hrs**	**15 ± 1 Day**	**Day 30 ± 3**	**Day 60 ± 5**
Informed Consent	X	-	-	-	-	-
Inclusion/ Exclusion Criteria	X	X	-	-	-	-
Medical history	X	X	-	-	-	-
Personal History	X	X	-	-	-	-
Demographic data	X	-	-	-	-	-
Physical examination including vital signs	X	X	X	X	X	-
Prior Medications	X	X	-	-	-	-
Concomitant Medications	-	-	X	X	X	X
Urine pregnancy test (For female subjects only)	X	-	-	-	-	-
Assessment of muscle fatigue with Fatigue index	-	X	-	-	X	-
Endurance energy supply and recovery with RER	-	X	-	-	X	-
VO2 max	-	X	-	-	X	
Neuromuscular activation Test	-	X	-	-	X	-
Subjective pain rating (NPRS)	-	X	X	X	X	-
Eccentric Exercise	-	X	-	-	X	-
Issuance of IP, Subject Diary and Diet Chart	-	X	-	-	-	-
Administration of study medication	-	-	X	X	X	-
Subject Diary Review & Diet Follow-up	-	X	X	X	X	-
Adverse event (after signing ICF)	X	X	X	X	X	X

Figure 9.1.1: Study Flow Chart



End of Study Visit 4 (Day 30 ± 3 days)

- Assessment of vital signs and physical examination,
- Concomitant medication if any
- Adverse event/ serious adverse event reporting,
- Subject diary assessment (for IP) & Follow-up
- Retrieval of investigational product and subject diary, diet follow up
- Performance of Eccentric Exercise
- Assessment of subjective pain rating (NPRS)
- Assessment of muscle fatigue with fatigue index, RPE,
- Endurance energy supply and recovery with RER, Maximum oxygen consumption (VO2 max), heart rate
- Neuro muscular activation,
- Laboratory investigations

Telephonic Follow-up Visit 5 – (Day 60 ± 5 days, Post Study Visit):

- Telephonic follow up for wellness of the subjects
- Concomitant medication if Any
- Adverse event/ serious adverse event reporting if any

9.2 Study Design

The study was a randomized, double-blind, placebo controlled, clinical study to measure the effect of natural phytochemical formulation on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in delayed muscle soreness (DOMS) and related inflammation and stress in healthy untrained subjects.

9.3 Selection of Study Population

Subject selection for the study was done based on the following inclusion and exclusion criteria. Subjects were eligible for enrolment into the study, if they met all of the inclusion criteria and none of the exclusion criteria.

9.3.1 Inclusion Criteria

1. Subject has provided written, signed and dated informed consent to participate in the study.
2. Subject was willing and able to comply with the protocol.
3. Male or female subjects between 19-50 years of age (both inclusive).
4. Subjects should be untrained as defined by, less active that is regular exercise for less than 4 h per week.
5. Subject is in good health as determined by a health history and as per Investigator discretion.
6. Subject is untrained in resistance/power exercise.

9.3.2 Exclusion Criteria

1. Subject is participating in another clinical trial or has received an investigational product within thirty days prior to enrolment.
2. Subject has a history of alcohol or other drug abuse in the past year.
3. Subject has a significant history or current presence of treated or untreated bleeding disorder, diabetes mellitus, high blood pressure (BP) [systolic BP> 140 and/or diastolic BP> 90], thyroid disease, tachyarrhythmia, heart disease, kidney disease, or liver disease.
4. Subject currently suffers from a sleep disorder and/or has a known history of (or is currently being treated for) clinical depression, eating disorder(s) or any other psychiatric condition(s), which in the opinion of the investigator, might put the subject at risk and/or confound the results of the study.
5. Subject has a known allergy or sensitivity to any ingredient in the test product.
6. Subject has any medical condition or uses any medication, nutritional product, dietary supplement or program, which in the opinion of the investigator, might interfere with the conduct of the study or place the subject at risk.
7. Subject has a history of difficulty swallowing large pills or tablets.
8. Subject has used creatine within 9 weeks prior to screening.

9. Subject has a history of orthopaedic injury or surgery within the last year.
10. Subject has any physical condition considered a contraindication to the type of exercise performed in the study.
11. Subject has had an abnormal resting ECG.
12. Investigator is uncertain about subject's capability or willingness to comply with the protocol requirements.

9.3.3 Removal of Subjects from the Study

Subjects were informed that they were free to withdraw from the study at any time for any reason or, if necessary. The Investigator might withdraw a subject from the study for any of the following reasons:

- If the subject withdrew his or her consent for any reason.
- If the subject's condition had worsened to the degree that the investigator feels, it is unsafe for the subject to continue in the study.
- If the subject discontinued early from the study due to lack of treatment effect.
- If the subject's drug code was unblinded.
- If an adverse event occurred for which the subject desired to discontinue treatment or the investigator determined that it was in the subject's best interest to be discontinued.
- If there was a significant protocol deviation (such as use of prohibited medication during the study conduct).
- If a concomitant therapy was reported or required which is liable to interfere with the results of the study.
- If the subject was lost to follow-up. (In such cases, all attempts made by the investigator to reach the subject by telephone to be documented in source documents before considering that subject as lost to follow-up.)
- If the female subject became pregnant.
- Administrative reasons.

9.4 Treatments

9.4.1 Dosage and Administration:

The subjects were randomized to receive either test or placebo in a 1:1 ratio. The details of both the products are listed below. All the subjects were instructed to take 02 oral capsules of 250 mg each (total will be 500 mg) daily morning for 30 days after breakfast.

Detailed instructions of IP administration procedure are provided in the study protocol, **Appendix 16.1.1.**

Test Product:

Name	Rephyll®
Manufacturer	Aurea Biolabs Private Limited
Batch No.	2205100036
Mfg. Date	11 May 2022
Exp. Date	10 Nov 2023
Dose	02 oral capsules of 250 mg each (total will be 500 mg only) to be ingested orally**,** daily morning for 30 days after breakfast".
Mode of Administration	Oral

Placebo:

Name	Placebo
Manufacturer	Aurea Biolabs Private Limited
Batch No.	2205100037
Mfg. Date	13 May 2022
Exp. Date	12 Nov 2023
Dose	02 oral capsules of 250 mg each (total will be 500 mg only), to be ingested orally**,** daily morning for 30 days after breakfast".
Mode of Administration	Oral

Study centres were instructed regarding study medication to be stored, prior to dispensing, at a controlled temperature in a locked and limited access area at the study centre and also instructed not to freeze the study medication. Subjects were instructed to store the medication below 30°C.

A Certificate of analysis for both the products is appended in **Appendix 16.1.6.**

9.4.2 Method of Assigning Subjects to Treatment Groups

Eligible subjects were randomized to receive either of the two products. Either the test or placebo, pre-labelled product was dispensed to subject in 1:1 ratio.

A copy of the randomization schedule is given in **Appendix 16.1.7**.

9.4.3 Selection of Doses in the Study

The dose of study drug was selected by sponsor based on previous pilot study.

9.4.4 Selection and Timing of Dose for Each Subject

Each subject was instructed to take 02 oral capsules of 250 mg each (total will be 500 mg) ingested with sufficient water/liquid, daily morning for 30 days after breakfast.

9.4.5 Blinding

As the present study was double blind, both study site staff and subjects were blinded to the random assignments of subject to the study treatment arms. Within the test and placebo arm, study products were supplied in identical packaging by Sponsor/IP supplier. At each site, Investigator received the double-blind study medication already randomized and labelled with a pre-printed consecutive treatment assignment (randomization) number. The treatment assignment number assigned as the subject determined to be eligible for randomization into the study, i.e., at randomization visit, and that number was recorded on a treatment assignment (randomization) CRF page. Investigational product was assigned using the next available treatment assignment number.

Randomization documentation and other pharmacy records were stored in a secure location in the site pharmacy (apart from the rest of the participant file). This information was not accessible to study staff members who complete other study procedures with subject. Blinding was maintained until all data were entered into the study database, all study endpoint data and other data included in the final analysis have been completed and verified, and the data has been locked for final analysis. This was explained to subject as part of the informed consent process. Only the pharmacist of CRO had full access to randomisation list and site personnel including the investigator were only had treatment assignment number.

9.4.6 Prior and Concomitant Therapy

At each study visit, the investigator had to question the screened/enrolled subjects about any medication(s) taken by the subject or given to the subject. All treatments and/or medications were recorded with the generic name of the medication (trade names were allowed for combination drugs, i.e. multi-component drugs), medical indication, total daily dose, route of administration, start and end dates of treatment. Medication prescribed for any other disease during the trial period was clearly documented in the concomitant medication form. Also the prohibited medication was stopped prior to enrolment in the study and the same has been documented.

9.4.7 Treatment Compliance

Investigational products were dispensed to enrolled subject by the authorized personnel at the site. All the subjects were instructed to bring back all empty wrapper of the product and subject's diary on the day of the end of the treatment. The site person recorded the total amount of investigational product used by subject in the CRF based on the pill count of dispensed verses consumed.

The designated study person maintained accurate records of the dates and amounts of drug received, to whom it was dispensed and accounted on a drug accountability form.

The used/ unused study medications were kept at the study site. Drug administration details were noted on the individual subject's CRF and are available in Appendix 16.2.5.

9.5 Efficacy and Safety Variables

The work instructions for evaluation of efficacy and safety variables were written based on the literature, principles and requirements of GCP as defined by regulatory agencies' standards and in accordance with the principles enunciated in the Declaration of Helsinki (Seoul, 2008).

9.5.1 Primary evaluation criteria:

Change in Muscle Fatigue

For measurement of Muscle Fatigue, lab parameters were evaluated as per protocol that include: Creatine kinase CK, Aspartate aminotransferase AST, Alanine aminotransferase ALT, Myoglobin in blood, Lactic acid in blood, Blood urea nitrogen BUN and electrolytes like Glucose, Na+, K. Fatigue index was evaluated by evaluating the effort made by each of four muscles and the same was measured by instrument 'electromyogram (EMG)'. Rating of perceived exertion RPE was measured by Borg Rating Scale. Borg rating scale was Score Level of exertion. The level was evaluated from 'No exertion at all' to 'Maximal exertion'.

Change in endurance energy supply and recovery

This endpoint involves measurement of Respiratory exchange ratio, RER which was calculated by dividing the volume of CO2 produced by the volume of O2. Other parameters evaluated was maximum oxygen consumption VO2max and heart rate. Laboratory parameter measurement includes creatinine, phosphocreatinine, Adenosine-5'-triphosphate (ATP) and Lactic acid threshold.

Lactic acid threshold in blood was measured via instrument 'Lacto Spark' that measures blood lactate with 0.5 µl of capillary blood and returns results in 5 seconds.

Change in neuro muscular activation

It was determined by the electromyography of lower limbs, time for standing with one leg and vestibular function tests.

Surface EMG measured the nerve conduction in the study during exercise. It involves placing small sensors called surface electrodes on the skin to assess the ability of the motor neurons to send electrical signals. Several electrodes were applied to the surface of skin. Electrodes were attached to lower limb muscles (gastrocnemius, hamstring, quadricep and adductor). A computer translated these signals into graphs or numerical values that is interpreted by investigator. These electrodes had evaluated motor neurons communicated with muscles. Once the test was completed, the electrodes were removed from the skin.

Time for standing with one leg was measured by surface electrode. The electrode was attached to one of the limb muscles and subjects were asked to stand with one leg. Time in seconds was noted once the muscle activation was detected.
For measurement of Vestibular function tests (vestibule-ocular reflex etc.) subjects were asked to lie down on flat surface then subject's head was tilt on left and right. Eye movement was checked for present or suppressed and same was recorded.
Vestibular function tests:

- Eye movement was completely recorded during the procedure. It was clinical bedside tests include 8 parts.

1. Spontaneous nystagmus – steady head position, record for 30 secs
2. Saccades – two fingers left right (5 times); up down (5 times),
3. Smooth pursuits – left to right hand movements,
4. Gaze evoked nystagmus – 5 seconds in each direction
5. Head impulse test – each side twice
6. Subjective visual vertical
7. Vestibulospinal Stepping test – close eyes, hands forward not touching the body, 100 steps to be taken at same spot. After 100 steps, measure length from starting point and angle of deviation from starting point.

<98 cms length from starting point	Normal
<45 degrees angle deviation from starting point	Normal

8. Modified Clinical Test of Sensory Interaction in Balance (CTSIB-M)

Change in stress and anti-inflammatory biomarkers
Laboratory parameters like cortisol, C-reactive protein CRP, Erythrocyte sedimentation rate ESR, IL-6 and TNF-α were evaluated by measuring their concentrations in blood plasma samples.

Change in BP and pulse
Blood pressure and pulse were recorded by investigator as per respective timepoints.

Change in CBC and blood lipids
Blood parameters like CBC and blood lipids like cholesterol, triglyceride, LDL and HDL were evaluated by laboratory tests at baseline and at day 30.

Subjective Pain Score
It was inspected utilizing numerical pain intensity scale. The visual assessment score (VAS) scale ranged from 0 (no pain at all) to 10 (extremely intense pain).

9.5.2 Safety Assessment

- Treatment emergent serious and non-serious adverse events
- Alteration in clinical laboratory parameters from baseline to end of the treatment.

9.5.3 Appropriateness of Measurements

All parameters and measurements conducted in the study were reliable and accurate to accomplish study endpoints. Safety assessments conducted were commonly accepted measures of safety outcomes in this phase of clinical effectiveness with clinical endpoint study. AEs and concomitant medications were captured on study CRFs from AE forms and concomitant medication from.

9.5.4 Drug Concentration Measurement

Not applicable; no drug concentration measurements were conducted in this study.

9.6 Data Quality Assurance

The investigator at each site attested that the clinical portion of this study was performed in compliance with the site's standard operating procedures (SOPs) and study work instructions. The SOPs and study work instructions were written based on the principles and requirements of GCP as defined by regulatory agencies' standards and in accordance with the principles enunciated in the Declaration of Helsinki (Seoul, 2008). Collection of data was performed according to SOPs and study work instructions, which were written based on the principles of GCP.

A site initiation visit was conducted prior to the start of the study. The PI, study coordinators, and research staff were trained on the protocol, study procedures and assessments, study drug administration, and GCP. Monitoring of the study conducted by monitor through onsite or offsite visits and performed regular verifications of the source document with CRF with sufficient frequency to ensure compliance with the protocol, adherence to local regulatory requirements and ICH/GCP principles, correct supply and storage of study products, accurate reporting of AEs, proper CRF and source documentation completion, maintenance and retention of study records, and accurate study product accountability. At each monitoring visit, source documents were reviewed for compliance with the study protocol and GCPs. All subject data entered in CRFs, were reviewed and verified against source documents.

The CRF was designed to capture and record all the protocol-required information for each study subject. Data validation procedures were programmed during the CRF designing to identify any data discrepancies. Both univariate and multivariate checks were performed such as missing values, valid range checks for data fields and numerical values.

Data were entered into the CRF from the subjects' records and source documents by the site personnel. The designated study monitor reviewed 100% CRFs for accuracy and completeness during on-site monitoring visits and/or remote monitoring against the source data at the site. Data queries were resolved with the Investigator as needed.

Data Management team reviewed the subject data 100% and generated queries as needed. Any inconsistencies noted in the process were queried and sent to the study site for resolution as per the standard operating procedures for data cleaning. Queries were reviewed and the changes were incorporated in the database and the database was updated.

The site-specific PI Signed off the site CRF's for all the subjects enrolled in the study prior to database lock.

A final database quality assessment was then conducted to ensure data completeness, all discrepancies resolved and all AEs had been reconciled in the clinical database and clinical database of the study met the specified error-free criteria.

Study specific QA audit was conducted to verify the site data and cross check any discrepancies in data. Internal data audits were conducted and study documents were reviewed by Ethicare Quality Assurance (QA). Audit certificate is provided in **Appendix 16.1.8**.

9.7 Statistical Methods Planned in the Protocol Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Efficacy Analysis:

Primary efficacy analysis: Mean change in efficacy parameters from baseline to end of study were analyzed using unpaired "t" test or Mann Whitney test depending upon the distribution of data (For between group comparison). For Within group comparison, mean change in efficacy parameters from baseline to end of study were analysed using paired "t" test or Wilcoxon test depending upon the distribution of data. Normality test (Shapiro-Wilks test) was used to check the distribution of data. All tests were 2 sided. P values of less than 0.05 was considered as statistically significant difference between treatment groups. The data presented as mean (Standard deviation) with 95 % confidence interval of treatment difference.

Modified Intention to Treat (mITT): It included all randomized subjects who met all inclusion/exclusion criteria, applied at least one dose of assigned treatment, and provided at least one post-baseline evaluation available for the primary endpoint.

Per Protocol (PP): It included all randomized subjects who complete the study as per the protocol without any major protocol deviation/protocol violation.

Safety Analysis:

Adverse Events

All AEs were recorded. All treatment-emergent adverse events (TEAE) were recorded according to body systems. The number and percentage of subjects experiencing TEAE in each treatment group were summarized descriptively Subjects experiencing TEAE were summarized in each treatment group.

The detailed statistical analysis plan (SAP) is appended in **Appendix 16.1.9**.

9.7.2 Determination of Sample Size

To achieve a total of approximately 100 evaluable subjects, 110 subjects enrolled (Group A: 55, Group B: 55).

9.8 Changes to Study Conduct or Planned Analyses

Regarding IP administration dose:

In the protocol, IP administration dose has been mentioned as “Single oral 500 mg dosage in capsule form, daily morning for 30 days after breakfast”. In actual the dose is “02 capsules of 250 mg, daily morning for 30 days after breakfast.”

Regarding Neuro muscular activation test:

In the protocol it has been mentioned that for neuro muscular activation test “walking time, reaction time and number of side step movement will be performed”. In actual the same was not performed, in healthy subjects there was no practical use to get such data, as in the study other more intricate parameters like EMG, standing on one leg and vestibular function test were being performed to get the result for neuro muscular activation.

Fatigue index via repeated Sprint ability testing:

In the protocol it has been mentioned that “muscle fatigue index will be evaluated by repeated sprint ability testing”. In actual the same was evaluated by using an EMG machine considering the welfare of the subject as for sprint ability testing, the subject has to sprint on a treadmill which conflicted with eccentric exercise. Hence, muscle fatigue index was evaluated from the data generated by the EMG machine during eccentric exercise.

10 STUDY SUBJECTS

10.1 Disposition of Study Subjects

A consort style flow diagram for subject disposition is presented in Figure 10.1.1. The diagram shows the number of subjects who entered into this study, were randomized and were available for analysis. A total of 144 subjects were screened and total 110 subjects were randomised into the study.

Total five subjects (05) were considered as discontinued from the study. Hence, a total of 110 subjects completed the study.

Subject disposition is summarised for the all-screened subjects in Table 10.1.1. Listing for subjects' disposition is presented in **Appendix 16.2.1**.

	Test (N=55) n	**Placebo (N=55) n**	**Overall (N=110) n**
Number of Subjects Screened	NA	NA	144
Number of screened failure subjects	NA	NA	34
Number of Subjects Randomised in the Study	55	55	110
Number of Subjects who Completed the Study	54	51	105
Number of Subjects Analysed for mITT Population	55	55	110
Number of Subjects who Discontinued from the Study	01	04	05
Primary Reason for discontinuation:			
Adverse event	00	00	00
Lost to follow-up	00	01	01
Study terminated by sponsor	00	00	00
Withdrawal by subject	01	03	04
Physician decision	00	00	00
Pregnancy	00	00	00
Protocol violation (wrong randomized)	00	00	00
Drug code un-blinded	00	00	00
Protocol non-compliance	00	00	00
Re-infection	00	00	00
Death	00	00	00
Other	00	00	00
Abbreviations: mITT = modified intent to treat; N = number of subjects in the specified treatment; n = number of subjects in specified category.			

Study site wise subject disposition is presented in Table 10.1.2.

Table 10.1.2: Accounting of Trial Subjects

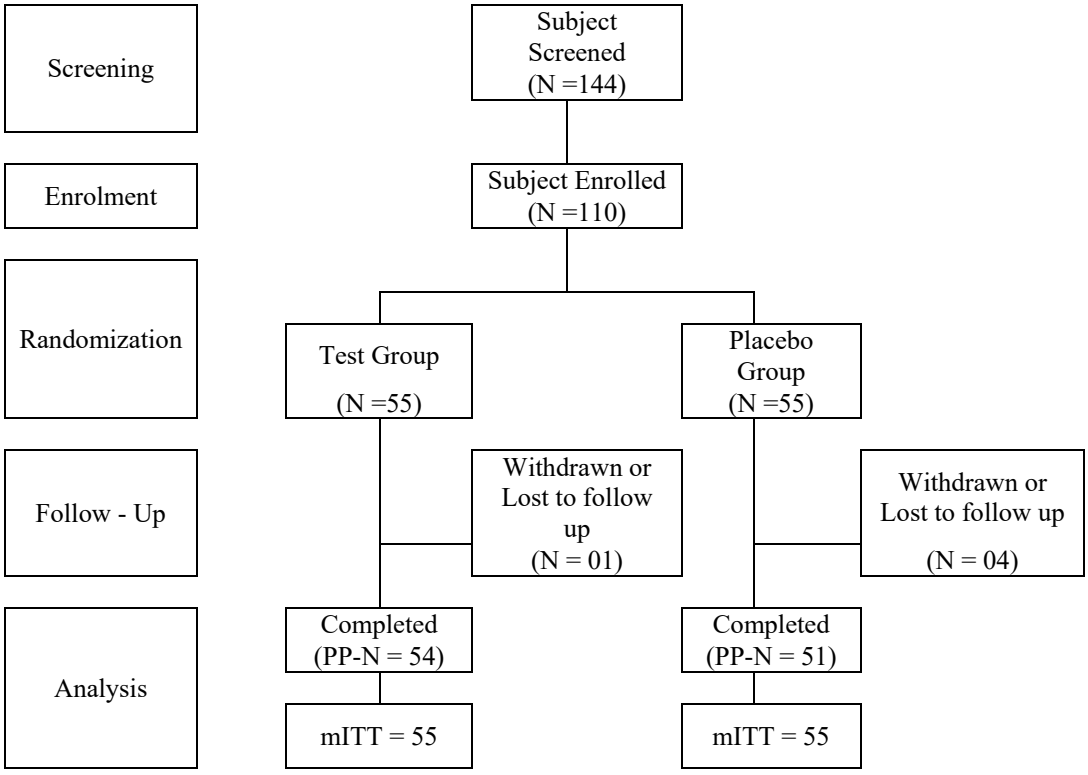
Site No.	Investigators Name	Screened	Randomized	Withdrawal	Completed
01	Dr. Akhil Mukim	99	70	04	66
02	Dr. Vaishal Sheth	45	40	01	39
Total		**144**	**110**	**05**	**105**

Table 10.1.3: Summary of subject disposition - Site wise

Site No.	Investigator Name	Total Enrolled Subjects	
		Test (A)	Placebo (B)
01	Dr. Akhil Mukim	35	35
02	Dr. Vaishal Sheth	20	20
Total		**55**	**55**

Diagrammatic representation of subject disposition is presented in Figure 10.1.1.

Figure 10.1.1: Diagram of disposition of the subject



10.2 Protocol Deviations

There was no major protocol deviation observed during the study conduct. All minor protocol deviations for the all randomised subjects are summarised and presented by-subject in **Appendix 16.2.2**.

10.2.1 Deviation in failure to comply with eligibility criteria

None of the subjects considered as wrong randomised or failed to comply with eligibility criteria.

10.2.2 Deviations in the per protocol

Mainly protocol deviations were related to visit schedule deviation by subjects.

However, those with visit schedule out of window were included in the analysis because the deviations were considered minor as they were still close to scheduled time point.

There were no protocol violations which led to withdrawal of subjects from the study. Protocol deviations were related to the visit schedule, as subjects were not able to present at scheduled visit date.

Table 10.2.1: Summary of Protocol Deviation – All Randomised Subjects

Type of Deviation	Overall (N=105) n
Visit Schedule	17

None of the subjects with major protocol deviation were identified and none excluded from analysis which impact on study results.

All deviations were minor and did not impact the study results.

11 EFFICACY EVALUAITON

11.1 Data Sets Analysed

Sufficient subjects were enrolled for this study to ensure the 110 evaluable subjects. 105 subjects completed the clinical portion of the study in its entirety.

105 subjects were considered for the statistical analysis for primary end point for mITT population.

All subjects who were eligible, randomized and completed study have been included in the analysis.

Table 11.1.1 Summary of analysis data sets by centre and treatment

	Test (N=55) n	**Placebo (N=55) n**	**Overall (N=110) n**
Number of Subjects Screened	NA	NA	144
Number of screened failure subjects	NA	NA	34
Number of Subjects Randomised in the Study	55	55	110
Number of Subjects who Completed the Study	54	51	105
Number of Subjects Analysed for PP Population	54	51	105
Number of Subjects Analysed for mITT Population	55	55	110
Number of Subjects who Discontinued from the Study	01	04	05
Abbreviations: N = Number of subjects in the specified treatment; n = Number of subjects in specified category; mITT = Modified Intent-to-Treat.			

11.2 Demographic and Other Baseline Characteristics

Subjects' demographic characteristics age, gender and weight have been summarized for each treatment group in Table 11.2.1. The binary and categorical variables have been presented as numbers (with percentages). The means (along with standard deviation) have been presented for continuous normally distributed data.

Total 110 male and female subjects were enrolled in the study, out of those 85 subjects were male and 25 subjects were female. The sex distribution is almost similar across the groups. Out of 110 subjects, test and placebo groups distribution is similar in both groups i.e. 55 subjects in each group.

All mean values are expressed as mean (SD). Age was found to be in a range of 22 to 50 years. In all subjects of Test group, age with a mean of 37.64 (7.57) years and mean weight was 64.33 (10.85) kg. For all subjects of Placebo Group, age with a mean of 37.31 (6.55) years and mean weight at 64.65 (11.04) kg. In general, all the

baseline characteristics were well balanced across the groups. Lost to follow-up or withdrew consent subjects were not replaced at any time point.

Listing of all screened subjects for demographic characteristic, medical history, prior and concomitant medications are presented in **Appendix 16.2.4.**

Table 11.2.1: Summary of Demographic Information

	Age (Years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Overall Data (110 Subjects)				
Minimum	22	140	39.9	14.1
Maximum	50	178	91	36.8
Mean (SD)	37.47 (7.05)	162.47 (8.32)	64.49 (10.90)	24.48 (4.07)
Overall Data - Test (55 Subjects)				
Minimum	24	140	39.9	17
Maximum	50	178	91	36.8
Mean (SD)	37.64 (7.57)	163.25 (8.67)	64.33 (10.85)	24.18 (3.96)
Test Male (46 Subject)				
Minimum	24	147	39.9	17
Maximum	50	178	91	32.1
Mean (SD)	36.91 (7.66)	165.44 (6.94)	64.81 (11.25)	23.63 (3.62)
Test Female (09 Subject)				
Minimum	30	140	50	21.2
Maximum	50	165	79	36.8
Mean (SD)	41.33 (6.16)	152 (8.14)	61.88 (8.66)	26.97 (4.67)
Overall Data - Placebo (55 Subjects)				
Minimum	22	145	40.8	14.1
Maximum	49	176	90	35.5
Mean (SD)	37.31 (6.55)	161.69 (7.95)	64.65 (11.04)	24.79 (4.18)
P value (Between test and placebo)	**0.8073**	**0.3276**	**0.8784**	**0.4338**
Placebo Male (39 Subject)				
Minimum	23	151	40.8	14.1
Maximum	49	176	90	30.1
Mean (SD)	37.13 (6.56)	164.72 (5.88)	64.66 (11.65)	23.82 (3.90)
Placebo Female (16 Subject)				
Minimum	22	145	48.6	21.3
Maximum	46	169	84.3	35.5
Mean (SD)	37.75 (6.71)	154.31 (7.61)	64.61 (9.76)	27.17 (3.99)
Data of Female (25 Females)				
Minimum	22	140	48.6	21.2
Maximum	50	169	84.3	36.8

	Age (Years)	**Height (cm)**	**Weight (kg)**	**BMI (kg/m^2)**
Mean (SD)	39.04 (6.62)	153.48 (7.72)	63.62 (9.29)	27.09 (4.15)
Data of Male (85 Males)				
Minimum	23	147	39.9	14.1
Maximum	50	178	91	32.1
Mean (SD)	37.01 (7.14)	165.11 (6.45)	64.74 (11.37)	23.71 (3.73)
P values (Between female And male)	**0.207**	**0.0001**	**0.6537**	**0.0002**
Average values are presented as mean (SD).				

11.3 Measurements of Treatment Compliance

The subjects were administered the study drugs. One arm received the test product Rephyll® which is natural phytochemical formulation and other arm received placebo product once daily for 30 days. IP dispensed and IP consumed by subjects were recorded in CRF.

11.4 Pharmacodynamics Results and Tabulations of Individual Subject Data

11.4.1 Efficacy Analysis

11.4.1.1. CHANGE IN MUSCLE FATIGUE:

Creatine kinase, CK

Change in Creatinine Kinase, CK was compared from Visit 1 (Enrollment visit (Day 1)) after exercise to visit 2 (day 4, 72 hrs.), Visit 3 (15 days) and Visit 4 after exercise (Day 30).

The high serum levels of CK depend on sarcomeric damage arising either from strenuous exercise or from muscular pathology. Strenuous exercise that damages skeletal muscle cell structure results in an increase in total CK. Resting CK levels are higher in athletes, but the significant increases of CK occurred after exercise are usually lower in trained subjects when compared with untrained subjects. Increased CK levels after eccentric exercise are associated with muscle injury, with a pronounced increase between 2 and 7 days after exercise.

From result it can be seen that on day 4 (72hr) of exercise there was increase in the CK level in both test and placebo groups. But in placebo group the level of CK increase was higher than test group on day 4 and day 15 after exercise. This shows muscle injury was higher in placebo group as compared to the test group, though there was no statistically significant difference. CK levels do not decrease between days 4 and 10, probably without an adaptation to training. Non-significant data is the result of variability amongst subjects.

As per figure 11.4.1.1, % of subjects showing improvement in creatine kinase is specified. 50% subjects of test group showed improvement in the creatine kinase level at end of study visit and 18% subjects from placebo group showed improvement at the end of study visit.

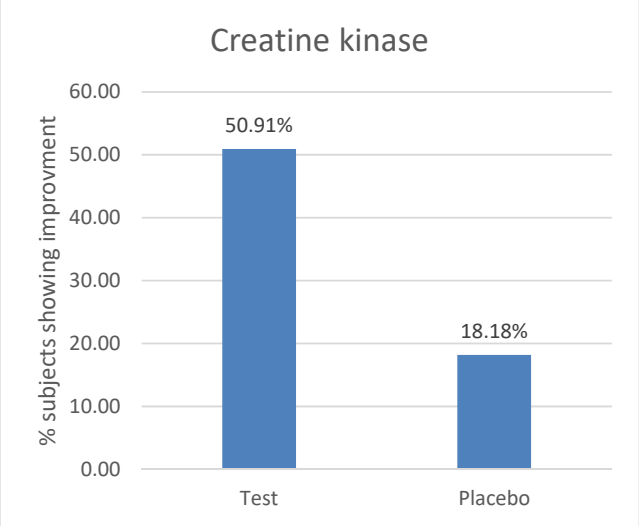
Table: 11.4.1.1 Change in Creatine kinase

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Creatine kinase, CK (U/L)			
PP population	N=54	N=51	
Enrollment visit (Day 1) after exercise	97.41 (51.22)	114.92 (53.00)	-17.5100 (-37.2097 to 2.1897) P= 0.0809
Follow up visit # 2 (day 4, 72 hrs.)	106.54 (70.10)	120.04 (48.01)	-13.5000 (-36.8878 to 9.8878), P= 0.2550
Follow up visit # 3 (15 days)	111.70 (66.79)	120.80 (66.56)	-9.1000 (-34.9213 to 16.7213), P= 0.4862
End of Study visit (EOS) after exercise (Day 30).	107.28 (66.69)	122.69 (58.15)	-15.4100 (-39.6867 to 8.8667), P= 0.2109

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Change from Enrollment visit at follow up visit # 2	7.89 (54.65)	7.56 (50.88)	-0.3300 (-20.7976 to 20.1376), P= 0.9746
Change from Enrollment at follow up visit # 3	14.30 (44.82)	8.18 (65.27)	-6.1200 (-27.6872 to 15.4472), P= 0.5748
Change from Enrollment at EOS	10.21 (52.43)	7.42 (45.12)	-2.7900 (-21.7722 to 16.1922), P= 0.7713
mITT population	N=55	N=55	
Enrollment visit (Day 1) after exercise	97.47 (50.75)	111.27 (54.32)	-13.8000 (-33.6689 to 6.0689) P= 0.1714
Follow up visit # 2 (day 4, 72 hrs.)	106.54 (70.10)	118.98 (48.13)	-12.4400 (-35.1671 to 10.2871), P= 0.2804
Follow up visit # 3 (15 days)	111.70 (66.79)	120.12 (66.07)	-8.4200 (-33.5300 to 16.6900), P= 0.5077
End of Study visit (EOS) after exercise (Day 30)	107.28 (66.69)	122.63 (57.55)	-15.3500 (-38.8939 to 8.1939), P= 0.1990
Change from Enrollment at follow up visit # 2 (day 4, 72 hrs.)	7.89 (54.65)	6.33 (51.12)	-1.5600 (-21.5609 to 18.4409), P= 0.8774
Change from baseline at follow up visit # 3 (15 days)	14.30 (44.82)	8.63 (64.69)	-5.6700 (-26.7045 to 15.3645), P= 0.5942
Change from baseline at EOS after exercise (Day 30)	8.15 (54.09)	5.53 (45.86)	-2.6200 (-21.5738 to 16.3338), P= 0.7846

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population;
Test: Rephyll®-(Natural Phytochemical Formulation)

Figure 11.4.1.1 % subjects showing improvement in Creatine kinase



Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT)

Change in Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) was compared between Screening Visit (Day 1) and Visit 4 after exercise (Day 30).

There was no difference observed between test and placebo group in change level of AST or ALT. Within group comparison shows that there is no statistically significant change at end of study visit compared to baseline. This indicates that in this study, there was no major muscle damage in the subject due to eccentric exercise. Eccentric exercises in this study are not expected to result into major muscle damage.

Table: 11.4.1.2 Change in Aspartate aminotransferase

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
AST (U/L)			
PP population	N=54	N=51	
Screening Visit (Day 1)	29.70 (23.98)	26.12 (19.70)	3.5800 (-4.9421 to 12.1021) P= 0.4067
End of Study visit (EOS) Visit 4 after exercise (Day 30)	34.02 (43.98)	26.35 (18.71)	7.6700 (-5.5490 to 20.8890), P= 0.2525
Change from Screening Visit (Day 1) at EOS Visit 4 after exercise (Day 30)	4.31 (35.01)	0.24 (18.35)	-4.0700 (-14.9831 to 6.8431), P= 0.4612
mITT population	N=55	N=55	
Screening Visit (Day 1	29.53 (23.79)	26.16 (19.27)	3.3700 (-5.0386 to 11.7786) P= 0.4285
End of Study visit (EOS) Visit 4 after exercise (Day 30)	34.02 (43.98)	26.35 (18.71)	7.6700 (-5.1043 to 20.4443), P= 0.2366
Change from Screening Visit (Day 1) at EOS Visit 4 after exercise (Day 30)	3.87 (34.83)	1.73 (19.33)	-5.6000 (-16.2468 to 5.0468), P= 0.2995
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®-(Natural Phytochemical Formulation)			

Table: 11.4.1.3 Change in Alanine aminotransferase

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
ALT (U/L)			
PP population	N=54	N=51	
Screening Visit (Day 1)	26.78 (20.66)	25.65 (15.86)	1.1300 (-6.0288 to 8.2888) P= 0.7549
End of Study visit (EOS) Visit 4 after exercise (Day 30)	27.15 (20.83)	23.65 (19.21)	3.5000 (-4.2682 to 11.2682), P= 0.3736
Change from Screening Visit (Day 1) at EOS Visit 4 after exercise (Day 30)	0.37 (19.74)	-2.00 (17.13)	-2.3700 (-9.5415 to 4.8015), P= 0.5137
mITT population	N=55	N=55	
Screening Visit (Day 1)	26.56 (20.53)	25.93 (16.05)	0.6300 (-6.3350 to 7.5950) P= 0.8580
End of Study visit (EOS) Visit 4 after exercise (Day 30)	27.15 (20.83)	23.65 (19.21)	3.5000 (-4.0735 to 11.0735), P= 0.3617
Change from Screening Visit (Day 1) at EOS Visit 4 after exercise (Day 30)	0.09 (19.66)	-4.00 (18.63)	-4.0900 (-11.3292 to 3.1492), P= 0.2652
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®-(Natural Phytochemical Formulation)			

Myoglobin in blood

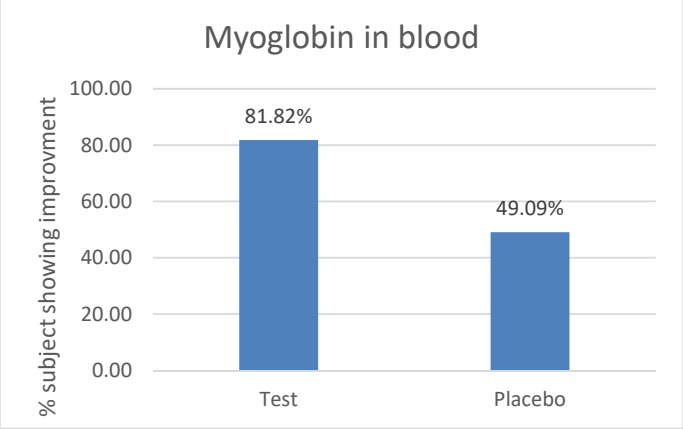
Change in Myoglobin was compared between Visit 1 (Day 1) after exercise and Visit 4 after exercise (Day 30).

There was clinical improvement seen in test group as compared to placebo group. As observed in figure 11.4.1.2, there was more variation reported in subjects so there was no statistically significant difference. In test group, 81.8% subject showed improvement in myoglobin level whereas in placebo group the improvement was seen in 49% subject.

Table: 11.4.1.4 Change in Myoglobin in blood

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Myoglobin (ng/mL)			
PP population	N=54	N=51	
Enrollment Visit, (Day 1) after exercise	58.42 (49.34)	78.83 (122.70)	-20.4100 (-56.2409 to 15.4209) P= 0.2612
End of Study visit (EOS) Visit 4 after exercise (Day 30)	40.67 (16.22)	62.17 (78.95)	-21.5000 (-43.2729 to 0.2729), P= 0.0529
Change from Enrollment Visit (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-17.75 (45.36)	-15.11 (114.90)	2.6400 (-30.8242 to 36.1042), P= 0.8760
mITT population	N=55	N=55	
Enrollment Visit (Day 1) after exercise	57.90 (49.04)	75.55 (118.67)	-17.6500 (-52.4460 to 17.1460) P= 0.3168
End of Study visit (EOS) Visit 4 after exercise (Day 30)	40.67 (16.22)	62.17 (78.95)	-21.5000 (-43.0422 to 0.0422), P= 0.0504
Change from Enrollment Visit (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-17.97 (44.96)	-16.52 (110.81)	1.4500 (-30.5119 to 33.4119), P= 0.9285
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®-(Natural Phytochemical Formulation)			

Figure 11.4.1.2 % subjects showing improvement in Myoglobin in blood



Lactic acid in blood

Change in lactic acid was compared from Visit 1 (Day 1) after exercise to Visit 2 (Day 4) and Visit 4 after exercise (Day 30). There was no statistically significant change seen between test and placebo groups.

Change reported from baseline to end of study visit was 0.86 in test group and 0.25 in placebo group. In test group, concentration of lactic acid in blood was reported to be reduced at 14% from baseline to end of study visit while in placebo group there was 2% reduction observed. Test group having lesser concentration as compared to baseline after 30 days of treatment showed that there was lesser muscle fatigue as compared to baseline after 30 days of treatment with test product. There was more % reduction reported with subjects in test group as compared to placebo group.

Table: 11.4.1.5 Change in Lactic acid in blood

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Lactic Acid in blood (mmol/L)			
PP population	N=54	N=51	
Enrollment Visit 1 (Day 1) after exercise	5.97 (3.51)	5.27 (3.28)	0.7000 (-0.6346 to 2.0346) P= 0.3006
Follow up visit 2 (Day 4)	6.93 (3.22)	6.22 (2.38)	0.7100 (-0.4024 to 1.8224) P= 0.2083
End of Study visit (EOS) Visit 4 after exercise (Day 30)	5.11 (3.76)	5.12 (3.29)	-0.0100 (-1.3980 to 1.3780), P= 0.9886
Change from Enrollment Visit (Day 1) after exercise at follow up visit	0.96 (1.71)	0.95 (2.18)	-0.0100 (-0.7797 to 0.7597) P= 0.9795
Change from Enrollment Visit (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-0.86 (2.14)	-0.25 (2.24)	0.6100 (-0.2506 to 1.4706), P= 0.1628
mITT population	N=55	N=55	
Enrollment Visit 1 (Day 1) after exercise	5.89 (3.53)	5.17 (3.27)	0.7200 (-0.5661 to 2.0061) P= 0.2696
Follow up Visit 2 (Day 4)	6.93 (3.22)	6.22 (2.38)	0.7100 (-0.3602 to 1.7802) P= 0.1913
End of Study visit (EOS) Visit 4 after exercise (Day 30)	5.11 (3.76)	5.12 (3.29)	-0.0100 (-1.3454 to 1.3254) P= 0.9882
Change from Enrollment Visit 1 (Day 1) after exercise at follow up Visit 2 (Day 4)	0.96 (1.71)	0.95 (2.18)	-0.0100 (-0.7505 to 0.7305), P= 0.9787
Change from Enrollment Visit 1 (Day 1) after exercise at EOS	-0.86 (2.14)	-0.25 (2.24)	0.6100 (-0.2180 to 1.4380), P= 0.1471

Visit 4 after exercise (Day 30)			
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®-(Natural Phytochemical Formulation)			

Blood urea nitrogen, BUN

Change in BUN was compared between Visit 1 (Day 1) before exercise and Visit 4 before exercise (Day 30). There was no major change in level of BUN. Subject doing heavy exercise, their BUN level reported to be high. In this study, the level reported to be not much change. In current study, the exercise was eccentric and that is not affecting the blood BUN level.

Table: 11.4.1.6 Change in Blood urea nitrogen

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
BUN (mg/dL)			
PP population	N=54	N=51	
Enrollment Visit 1 (Day 1) before exercise	8.25 (2.62)	8.66 (3.14)	-0.4100 (-1.5269 to 0.7069) P= 0.4682
End of Study visit (EOS) Visit 4 before exercise (Day 30)	8.63 (2.93)	8.78 (2.98)	-0.1500 (-1.2941 to 0.9941), P= 0.7954
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	0.39 (2.47)	0.12 (2.27)	-0.2700 (-1.1897 to 0.6497), P= 0.5617
mITT population	N=55	N=55	
Enrollment Visit 1 (Day 1) before exercise	8.28 (2.60)	8.58 (3.12)	-0.3000 (-1.3855 to 0.7855) P= 0.5849
End of Study visit (EOS) Visit 4 before exercise (Day 30)	8.63 (2.93)	8.78 (2.98)	-0.1500 (-1.2670 to 0.9670), P= 0.7906
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	0.20 (2.81)	0.44 (3.06)	-0.6400 (-1.7504 to 0.4704), P= 0.2558
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®-(Natural Phytochemical Formulation)			

Fatigue index

Fatigue index was evaluated of the 4 lower limb muscles during Eccentric Exercise Performance.

- Calf Muscles (Gastrocnemius)
- Hamstring muscles
- Adductor muscles
- Quadriceps muscle

Fatigue index was calculated using muscular activity of the above specified muscles. Muscular activity was evaluated through EMG. The average muscular activity of 4 muscles was calculated during eccentric exercise. Difference in the muscular activity was calculated further as the Fatigue Index. The difference was compared at Day 1 and Day 30 after exercise. More the fatigue index lesser the fatigue suffered by subject and need of greater volume eccentric exercise was needed to cause exhaustion.

Result showed that the fatigue index was high in the test group as compared to placebo. Reported fatigue index at 30 days was statistically significant in test group (222.13) as compared to placebo (159.54). Change from baseline to 30 days found in test group is 56.04 and while in placebo group it found to be 7.16 and same was statistically significant between test and placebo group.

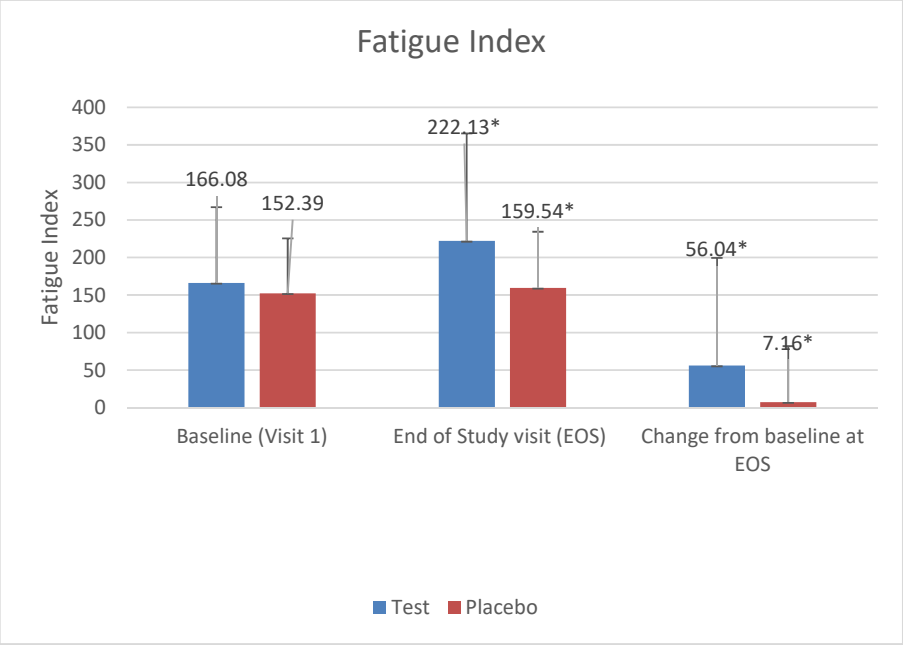
Also in test group, within group comparison shows statistically significant difference at end of study visit as compared to baseline. This confirms that there was significantly lesser muscle fatigue in subjects after 30 days of treatment with test product.

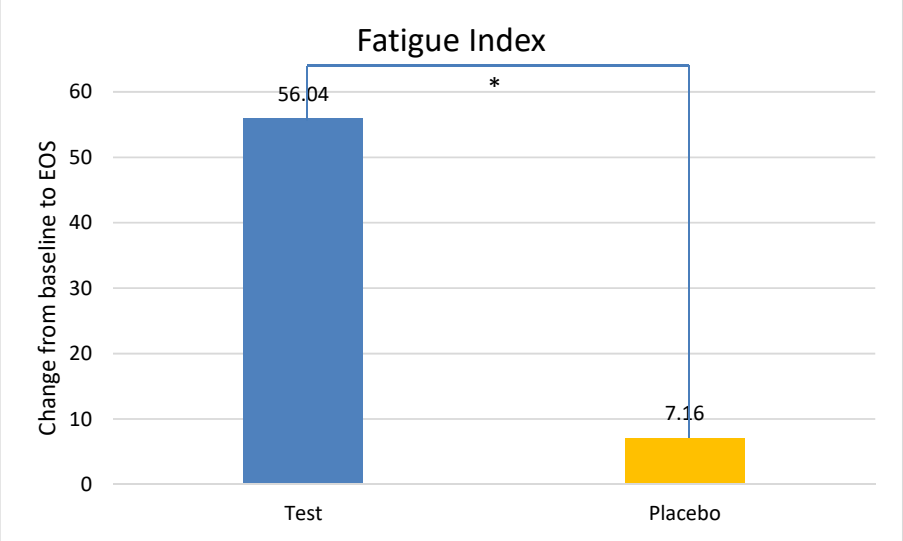
Table: 11.4.1.7 Change in Fatigue Index

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Fatigue index			
PP population	N=54	N=51	
Baseline (Visit 1)	166.08 (101.02)	152.39 (73.11)	13.6900 (-20.6115 to 47.9915) P=0.4304
End of Study visit (EOS)	222.13 (143.24)*	159.54 (74.81)	62.5900 (17.9729 to 107.2071), **P=0.0064**
Change from baseline at EOS	56.04 (143.47)	7.16 (79.54)	48.8800 (3.6150 to 94.1450), **P=0.0346**
mITT population	N=55	N=55	
Baseline (Visit 1)	165.70 (100.12)	153.38 (75.03)	12.3200 (-21.1200 to 45.7600) P=0.4668
End of Study visit	222.13 (143.24)*	159.54 (74.81)	62.5900 (19.3984 to 105.7816) **P=0.0049**
Change from baseline at EOS	52.38 (144.70)	5.44 (92.66)	57.8200 (11.8951 to 103.7449), **P=0.0141**

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N=number of subjects; PP=per protocol; mITT: modified intent-to treat population;
Test: Rephyll®

Figure 11.4.1.4: Summary of Fatigue Index





Rating of perceived exertion, RPE: (measured by Borg rating Scale.)

RPE was evaluated using Borg Rating Scale. Score Level of increased exertion showed more exertion by the subject during exercise.

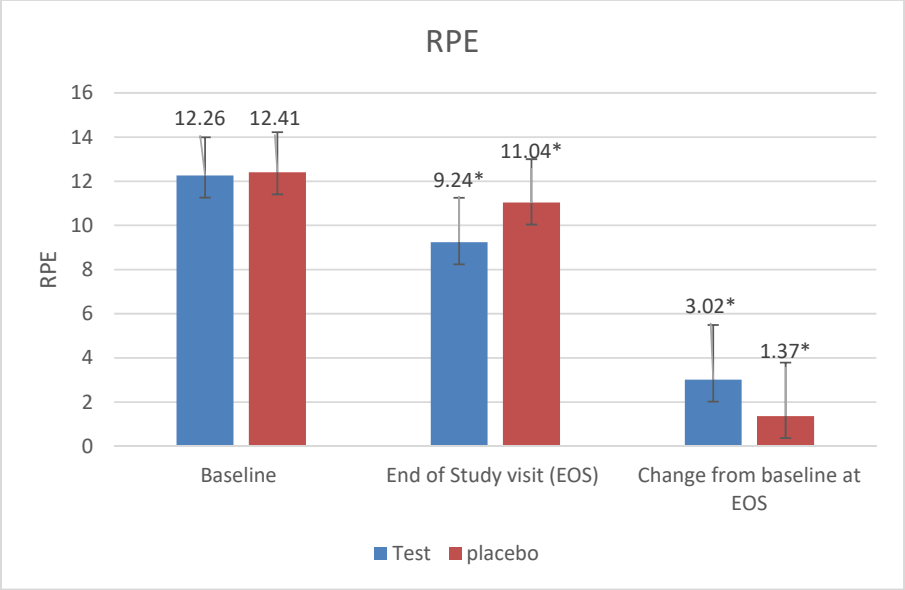
Result showed that the exertion during exercise at day 1 was similar between both groups. But after 30 days of treatment, subjects in test group reported less exertion as compared to subjects in placebo group. The difference between test and placebo group in RPE was statistically significant at day 30. That shows that test group had less exertion during exercise as compared to placebo group. Borg rating scale was from 6 to 20. 6 denoted as 'No exertion at all' and 20 denoted as 'Maximal exertion'. At baseline, the RPE was reported as somewhat hard (12-13). At end of the study, RPE reported as 9 which denoted as very light in test group while 11 which denoted as light. Between group this comparison is statistically significant ($p<0.05$). Also change from baseline is statistically significant ($p<0.05$).

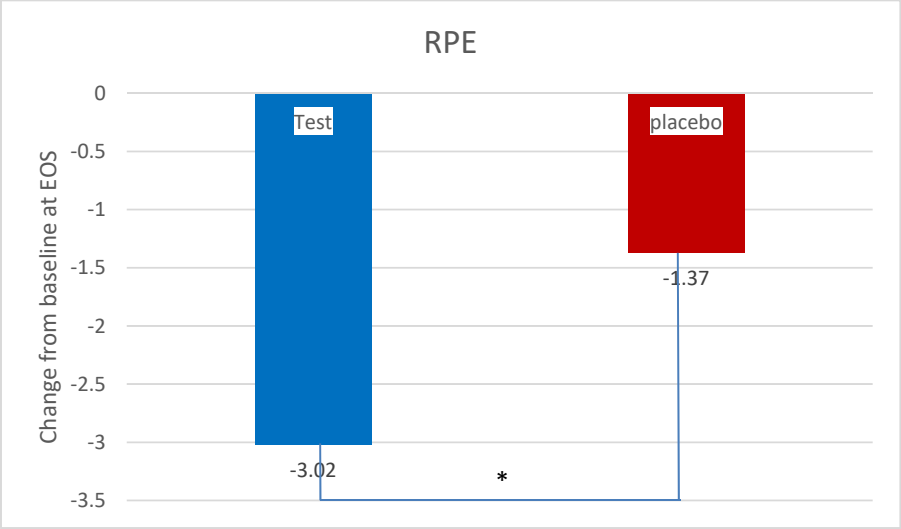
Table: 11.4.1.8 Change in Rating of perceived exertion, RPE

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
RPE score			
PP population	N=54	N=51	
Enrollment Visit 1 (Day 1) after exercise	12.26 (1.73)	12.41 (1.81)	-0.1500 (-0.8352 to 0.5352) P= 0.6651
End of Study visit (EOS) Visit 4 after exercise (Day 30)	9.24 (2.01)*	11.04 (1.96)*	-1.8000 (-2.5690 to -1.0310), P= 0.0001
Change from Enrollment Visit 1 (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-3.02 (2.47)	-1.37 (2.42)	1.6500 (0.7028 to 2.5972), P= 0.0008
mITT population	N=55	N=55	
Enrollment Visit 1 (Day 1) after exercise	12.24 (1.72)	12.38 (1.81)	-0.1400 (-0.8074 to 0.5274) P= 0.6784
End of Study visit (EOS) Visit 4 after exercise (Day 30)	9.24 (2.01)*	11.04 (1.96)*	-1.8000 (-2.5504 to -1.0496), P= 0.0001
Change from Enrollment Visit 1 (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-3.16 (2.68)	-2.15 (3.66)	1.0100 (-0.2024 to 2.2224), P= 0.1016

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®

Figure 11.4.1.5: Summary of Rating of perceived exertion, RPE





Glucose, Na^+ ,K^+

Glucose was measured before and immediately after exercise at day 1 and day 30. Na^+ and K^+ was measured before and immediately after exercise and 30 mins after exercise.

There was no change in data of electrolytes reported in the study. This shows that there was no much impact of eccentric exercise on the electrolyte which make changes in level after exercise.

Table: 11.4.1.9 Change in Glucose

	Before Exercise			Immediately After exercise		
	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**	**Test**	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Glucose (mg/dL)						
PP population	N=54	N=51		N=54	N=51	
Enrollment Visit 1 (Day 1) after exercise	94.16 (25.97)	93.11 (23.96)	1.0500 (-8.6369 to 10.7369) P= 0.8302	88.89 (21.09)	88.18 (22.58)	0.7100 (-7.5481 to 8.9681) P= 0.8650
End of Study visit (EOS) Visit 4 after exercise (Day 30)	89.70 (22.75)	96.80 (35.27)	-7.1000 (-18.5235 to 4.3235), P= 0.2205	95.42 (21.82)	94.96 (41.68)	0.4600 (-12.1143 to 13.0343), P= 0.9423
Change from baseline at EOS	-4.87 (28.00)	5.29 (24.37)	10.1600 (-0.0249 to 20.3449), P= 0.0506	6.32 (24.67)	6.69 (31.09)	0.3700 (-10.4619 to 11.2019), P= 0.9461
mITT population	N=55	N=55		N=55	N=55	
Enrollment Visit 1 (Day 1) after exercise	94.16 (25.97)	93.11 (23.96)	1.0500 (-8.6369 to 10.7369) P= 0.8302	88.89 (21.09)	88.18 (22.58)	0.7100 (-7.5481 to 8.9681) P= 0.8650
End of Study visit (EOS) Visit 4 after exercise (Day 30)	89.70 (22.75)	96.80 (35.27)	-7.1000 (-18.5235 to 4.3235), P= 0.2205	95.42 (21.82)	94.96 (41.68)	0.4600 (-12.1143 to 13.0343), P= 0.9423
Change from baseline at EOS	-4.87 (28.00)	3.35 (39.66)	1.5200 (-11.4557 to 14.4957), P= 0.8168	3.05 (29.57)	6.69 (31.09)	3.6400 (-7.8279 to 15.1079), P= 0.5306

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population;
Test: Rephyll®-(Natural Phytochemical Formulation)

Table: 11.4.1.10 Change in Na^+

	Before Exercise			Immediately After exercise			30 min after exercise		
	Test	**Placebo**	**Effect Size****	**Test**	**Placebo**	**Effect Size****	**Test**	**Placebo**	**Effect Size****
Na+ (mmol/L)									
PP population	N=54	N=51		N=54	N=51		N=54	N=51	
Baseline	140.25 (2.51)	139.62 (2.55)	0.6300 (-0.3496 to 1.6096) P= 0.2050	139.56 (2.22)	139.33 (2.01)	0.2300 (-0.5912 to 1.0512) P= 0.5798	139.56 (2.61)	139.45 (2.22)	0.1100 (-0.8304 to 1.0504) P= 0.817
End of Study visit (EOS)	136.62 (18.58)	139.53 (2.55)	-2.9100 (-8.1169 to 2.2969), P= 0.2703	138.62 (3.18)	139.29 (2.30)	-0.6700 (-1.7496 to 0.4096), P= 0.2212	138.34 (2.92)	138.90 (2.39)	-0.5600 (-1.5962 to 0.4762), P= 0.2863
Change from baseline at EOS	-3.64 (18.37)	-0.20 (2.88)	3.4400 (-1.7218 to 8.6018), P= 0.1892	-0.98 (2.89)	-0.2 (2.22)	0.7800 (-0.2216 to 1.7816), P= 0.1256	-1.25 (2.95)	-0.55 (2.56)	0.7000 (-0.3717 to 1.7717), P= 0.1981
mITT population	N=55	N=55		N=55	N=55		N=55	N=55	
Baseline	140.25 (2.51)	139.62 (2.55)	0.6300 (-0.3263 to 1.5863) P= 0.1944	139.56 (2.22)	139.33 (2.01)	0.2300 (-0.5704 to 1.0304) P= 0.5702	139.56 (2.61)	139.45 (2.22)	0.1100 (-0.8058 to 1.0258) P= 0.8123
End of Study visit (EOS)	136.62 (18.58)	139.53 (2.55)	-2.9100 (-7.9225 to 2.1025), P= 0.2524	138.62 (3.18)	139.29 (2.30)	-0.6700 (-1.7189 to 0.3789), P=0.2082	138.34 (2.92)	138.90 (2.39)	-0.5600 (-1.5685 to 0.4485), P= 0.2735
Change from baseline at EOS	-3.64 (18.37)	-0.20 (2.88)	0.4400 (-1.5298 to 8.4098), P= 0.1729	-0.98 (2.89)	-0.2 (2.22)	0.7800 (-0.1940 to 1.7540), P= 0.1154	-1.25 (2.95)	-0.45 (2.22)	0.8000 (-0.1868 to 1.7868), P= 0.1110

**95% CI of treatment difference and P value (Between group comparison)
*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population;
Test: Rephyll®

Table: 11.4.1.11 Change in K^+

	Before Exercise			Immediately After exercise			30 min after exercise		
	Test	**Placebo**	**Effect Size****	**Test**	**Placebo**	**Effect Size****	**Test**	**Placebo**	**Effect Size****
K+ (mmol/L)									
PP population	N=54	N=51		N=54	N=51		N=54	N=51	
Baseline	4.51 (0.77)	4.50 (0.63)	0.0100 (-0.2632 to 0.2832) P= 0.9423	4.47 (0.66)	4.53 (0.63)	-0.0600 (-0.3100 to 0.1900) P= 0.6351	4.45 (0.67)	4.53 (0.70)	-0.0800 (-0.3452 to 0.1852) P= 0.5509
End of Study visit (EOS)	6.86 (17.79)	4.44 (0.59)	2.4200 (-2.5244 to 7.3644), P= 0.3340	4.33 (0.78)	4.42 (0.70)	-0.0900 (-0.3774 to 0.1974) P= 0.5360	4.33 (0.84)	4.33 (0.59)	0.0000 (-0.2825 to 0.2825), P= 1.0000
Change from baseline at EOS	2.33 (17.80)	-0.38 (1.19)	-2.7100 (-7.6650 to 2.2450), P= 0.2806	-0.22 (0.97)	-0.44 (1.19)	-0.2200 (-0.6303 to 0.1903), P= 0.2903	-0.20 (1.03)	-0.51 (1.20)	-0.3100 (-0.7421 to 0.1221), P= 0.1578
mITT population	N=55	N=55		N=55	N=55		N=55	N=55	
Baseline	4.51 (0.77)	4.50 (0.63)	0.0100 (-0.2559 to 0.2759) P= 0.9407	4.47 (0.66)	4.53 (0.63)	-0.0600 (-0.3100 to 0.1900) P= 0.6351	4.45 (0.67)	4.53 (0.70)	-0.0800 (-0.3390 to 0.1790) P= 0.5416
End of Study visit (EOS)	6.86 (17.79)	4.44 (0.59)	2.4200 (-2.3375 to 7.1775), P= 0.3156	4.33 (0.78)	4.42 (0.70)	-0.0900 (-0.3701 to 0.1901), P= 0.5256	4.33 (0.84)	4.33 (0.59)	0.0000 (-0.2744 to 0.2744), P= 1.0000
Change from baseline at EOS	2.22 (17.66)	-0.38 (1.19)	-2.6000 (-7.3308 to 2.1308), P= 0.2784	-0.30 (1.12)	-0.44 (1.19)	-0.1400 (-0.5768 to 0.2968), P= 0.5265	-0.28 (1.18)	-0.51 (1.20)	-0.2300 (-0.6798 to 0.2198), P= 0.3131

**95% CI of treatment difference and P value (Between group comparison)
*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population;
Test: Rephyll®

11.4.1.2. CHANGE IN ENDURANCE ENERGY SUPPLY AND RECOVERY

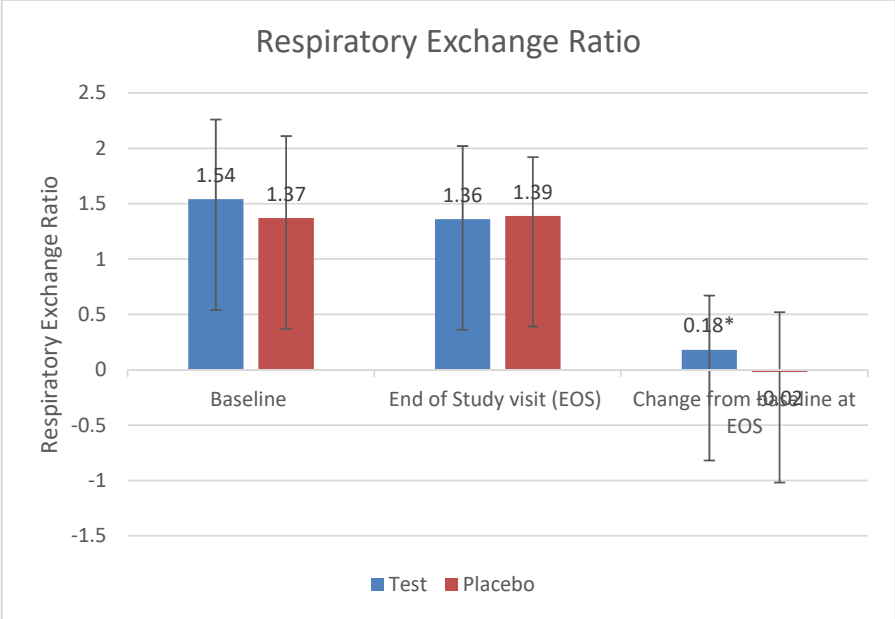
Respiratory exchange ratio, RER:

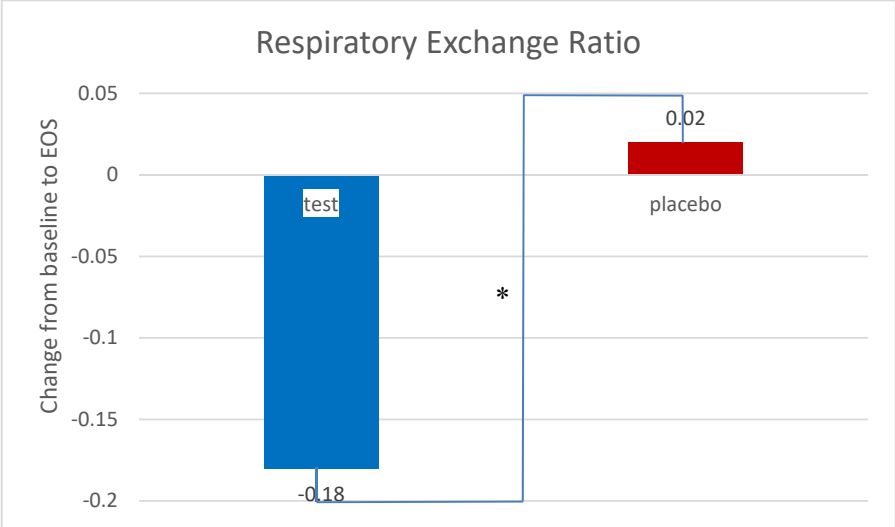
RER was calculated by dividing the volume of CO2 produced by the volume of O2 consumed. RER increases with exercise intensity. Results showed positive response of Test product after 30 days. There was statistically significant difference found between test and placebo subjects for RER after 30 days of treatment.
The RER commonly exceeds 1.0 during strenuous exercise. During non–steady-state, strenuous exercise, the volume of CO2 production rises as a result of hyperventilation and the increased buffering of blood lactic acid derived from skeletal muscles. As the subjects were untrained or less active for regular exercise, RER exceeded during exercise.

Table: 11.4.1.2.1 Change in Respiratory exchange ratio, RER

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Respiratory exchange ratio			
PP population	N=54	N=51	
Enrollment Visit 1 (Day 1) after exercise	1.54 (0.72)	1.37 (0.74)	0.1700 (-0.1126 to 0.4526) P= 0.2356
End of Study visit (EOS) Visit 4 after exercise (Day 30)	1.36 (0.66)	1.39 (0.53)	-0.0300 (-0.2625 to 0.2025), P= 0.7985
Change from Enrollment Visit 1 (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-0.18 (0.49)	0.02 (0.54)	0.2000 (0.0006 to 0.3994), **P= 0.0493**
mITT population	N=55	N=55	
Enrollment Visit 1 (Day 1) after exercise	1.55 (0.73)	1.36 (0.74)	0.1900 (-0.0878 to 0.4678) P= 0.1781
End of Study visit (EOS) Visit 4 after exercise (Day 30)	1.36 (0.66)	1.39 (0.53)	-0.0300 (-0.2562 to 0.1962), P= 0.7932
Change from Enrollment Visit 1 (Day 1) after exercise at EOS Visit 4 after exercise (Day 30)	-0.22 (0.57)	0.02 (0.54)	0.2400 (0.0301 to 0.4499), **P= 0.0254**
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Figure 11.4.1.2.1: Summary of Respiratory exchange ratio, RER





Creatine:

Change in Creatine was compared between Enrollment Visit 1 (Day 1) before exercise and Visit 4 before exercise (Day 30). Creatine level decreased after 30 days of the treatment in test group as compared to placebo group. The reduction was 12% in test group while in placebo group there was 6% increase in level of Creatine. There was no significant change between test and placebo group.

Table: 11.4.1.2.2 Change in Creatine

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Creatine (mg/dL)			
PP population	**N=54**	**N=51**	
Enrollment Visit 1 (Day 1) before exercise	0.95 (0.99)	0.83 (0.15)	0.1200 (-0.1580 to 0.3980) P= 0.3939
End of Study visit (EOS) Visit 4 before exercise (Day 30)	0.83 (0.18)	0.88 (0.19)	-0.0500 (-0.1216 to 0.0216), P= 0.1691
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	-0.12 (0.93)	0.05 (0.14)	0.1700 (-0.0911 to 0.4311), P= 0.1995
mITT population	**N=55**	**N=55**	
Enrollment Visit 1 (Day 1) before exercise	0.96 (0.98)	0.83 (0.16)	0.1300 (-0.1456 to 0.4056) P= 0.3518
End of Study visit (EOS) Visit 4 before exercise (Day 30)	0.83 (0.18)	0.88 (0.19)	-0.0500 (-0.1216 to 0.0216), P= 0.1691
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	-0.14 (0.94)	0.05 (0.14)	0.1900 (-0.0640 to 0.4440), P= 0.1411
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Phosphocreatine

Change in Phosphocreatine was compared from Enrollment Visit 1 (Day 1) before exercise and Visit 4 before exercise (Day 30). There was no significant change in level of phosphocreatine after 30 days of treatment between both groups.

Table: 11.4.1.2.3 Change in Phosphocreatine

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Phosphocreatine (U/L)			
PP population	**N=54**	**N=51**	
Enrollment Visit 1 (Day 1) before exercise	95.56 (48.55)	115.64 (56.47)	-20.0800 (-40.4277 to 0.2677) P= 0.0530
End of Study visit (EOS) Visit 4 before exercise (Day 30)	107.38 (64.60)	120.59 (53.13)	-13.2100 (-36.1778 to 9.7578), P= 0.2566
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	10.17 (48.17)	5.02 (46.16)	-5.1500 (-23.4302 to 13.1302), P= 0.5776
mITT population	**N=55**	**N=55**	
Enrollment Visit 1 (Day 1) before exercise	95.64 (48.10)	112.41 (56.69)	-16.7700 (-36.6410 to 3.1010) P= 0.0973
End of Study visit (EOS) Visit 4 before exercise (Day 30)	107.38 (64.60)	120.59 (53.13)	-13.2100 (-35.5655 to 9.1455), P= 0.2441
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	8.13 (50.01)	2.98 (52.30)	-11.1100 (-30.4507 to 8.2307), P= 0.2574

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®

Adenosine-5'-triphosphate (ATP)

Change in Adenosine-5-triphosphate (ATP) was compared from Enrollment Visit 1 (Day 1) before exercise to Visit 3 (Day 15) and Visit 4 before exercise (Day 30). Comparing the change from baseline to 30 days, statistically significant difference in ATP was seen from baseline to Visit 4 (i.e. Day 30) between test group and placebo group in mITT population.

Within group comparison shows that the there is significant difference seen at 15 days and 30 days in both test and placebo group.

Improvement in ATP level was seen 130% in test product and 91% in placebo at the end of study visit. Level wise the difference was seen as 1.46 and 1.00 nmol/ml in test product and placebo respectively in PP population. In mITT population the same difference was seen as 1.42 and 0.86 nmol/ml in test product and placebo respectively. Comparison between the changes from baseline to end of study visit in mITT population is statistically significant between test and placebo.

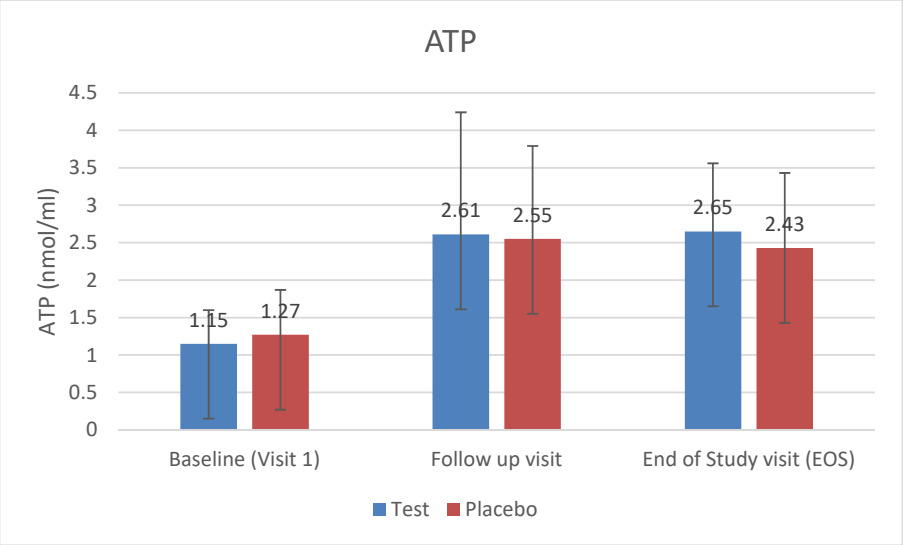
Table: 11.4.1.2.4 Change in Adenosine-5'-triphosphate (ATP)

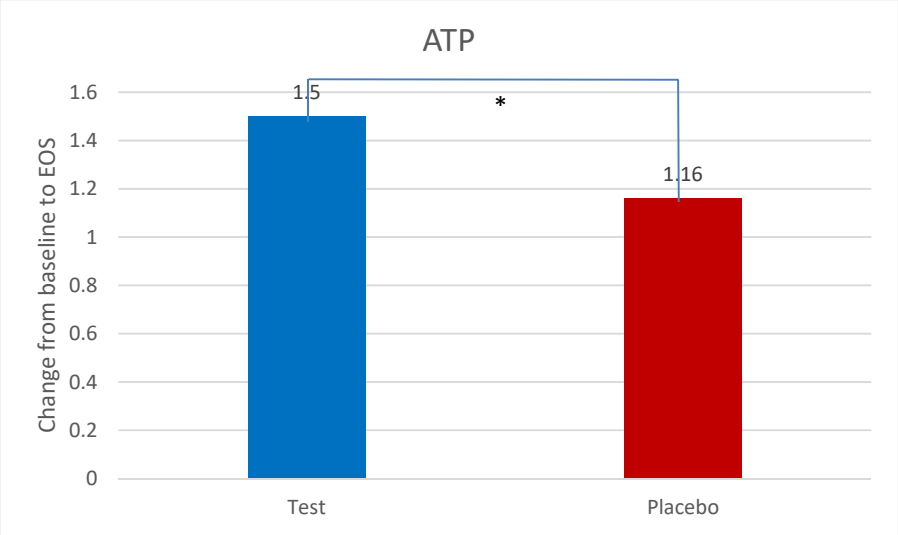
	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
ATP (nmol/ml)			
PP population	**N=54**	**N=51**	
Enrollment Visit 1 (Day 1) before exercise	1.15 (0.45)	1.27 (0.60)	-0.1200 (-0.3245 to 0.0845) P=0.2473
Follow up Visit 3 (Day 15)	2.61 (1.63)*	2.55 (1.24)*	0.0600 (-0.5030 to 0.6230), P= 0.8330
End of Study visit (EOS) Visit 4 before exercise (Day 30)	2.65 (0.91) *	2.43 (1.00)*	0.2200 (-0.1497 to 0.5897), P= 0.2407
Change from Enrollment Visit 1 (Day 1) before exercise at follow up visit 3 (Day 15)	1.47 (1.62)	1.25 (1.34)	-0.2200 (-0.7973 to 0.3573), P= 0.4515
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	1.46 (1.20)	1.00 (1.35)	-0.4600 (-0.9538 to 0.0338), P= 0.0675
mITT population	**N=55**	**N=55**	
Enrollment Visit 1 (Day 1) before exercise	1.15 (0.44)	1.24 (0.59)	-0.0900 (-0.2867 to 0.1067) P=0.3665
Follow up Visit 3 (Day 15)	2.61 (1.63)*	2.52 (1.24)*	0.0900 (-0.4574 to 0.6374) P=0.7451
End of Study visit (EOS) Visit 4 before exercise (Day 30)	2.65 (0.91)*	2.43 (1.00)*	0.2200 (-0.1414 to 0.5814) P=0.2302
Change from Enrollment Visit 1 (Day 1) before exercise at follow up visit 3 (Day 15)	1.43 (1.63)	1.11 (1.39)	-0.3200 (-0.8926 to 0.2526) P=0.2704

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Change from Enrollment Visit 1 (Day 1) before exercise at EOS Visit 4 before exercise (Day 30)	1.42 (1.22)	0.86 (1.39)	-0.5600 (-1.0543 to -0.0657), P= 0.0268

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N=number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®

Figure 11.4.1.2.2: Summary of Adenosine-5'-triphosphate (ATP)





Lactic acid threshold in blood

Lactic acid Threshold was measured at Visit 1 (Day 1) and Visit 4 (Day 30) during exercise. Total 5 times blood sample was collected to evaluate that lactic acid threshold had been achieved. The mean data of individual time point of lactic acid concentration has been presented in below table and the comparison graph plot between group and within group comparison made also presented after table. The lactate threshold is the point at which, during incremental exercise, lactate builds up in the blood stream at a level that is higher than resting values. It is also a point during exhaustive, all-out exercise at which lactate builds up in the bloodstream faster than the body can remove it. Higher time to achieve lactic acid threshold means more capacity to perform exercise. Table 11.4.1.2.5 showed the time to achieve the lactic acid threshold. At baseline, time for lactic acid threshold was almost similar in both groups (23.23 mins in test and 22.45 mins in placebo group). In End of study visit, the time was similar as baseline in placebo group but in test group the time increases at the end of study visit (25.52 mins in test group and 22.48 mins in placebo group). Subjects in test group took more time to reach threshold than placebo. This leads to conclusion that the point of exhaustion is achieved late in test group, compared to that for placebo group.

Table 11.4.1.2.6 showed the concentration of lactic acid at each 5 times blood sample collected during exercise. The concentration is increases at each time point. In 5th time point the concentration is lower in test group compared to placebo. This shows that the subject exhaustion time is delayed in test group compared to placebo. Data showed that the concentration of lactic acid remained low after 30 days of treatment with test product as compared to placebo.

Table: 11.4.1.2.5 Summary of Time to achieve Lactic Acid Threshold (mins)

	Test N=55	Placebo N=55	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Baseline	23.23 (13.19)	22.45 (15.33)	0.7800 (-4.6252 to 6.1852), P=0.7754
EOS	25.52 (06.53)	22.48 (08.13)	3.0400 (0.2529 to 5.8271), P=0.0328

Figure 11.4.1.2.3: Time of Lactic Acid Threshold

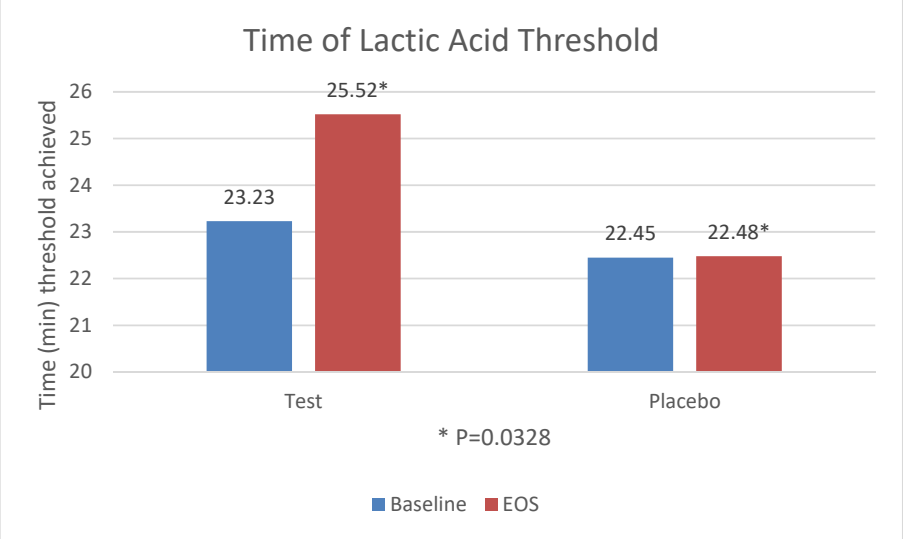
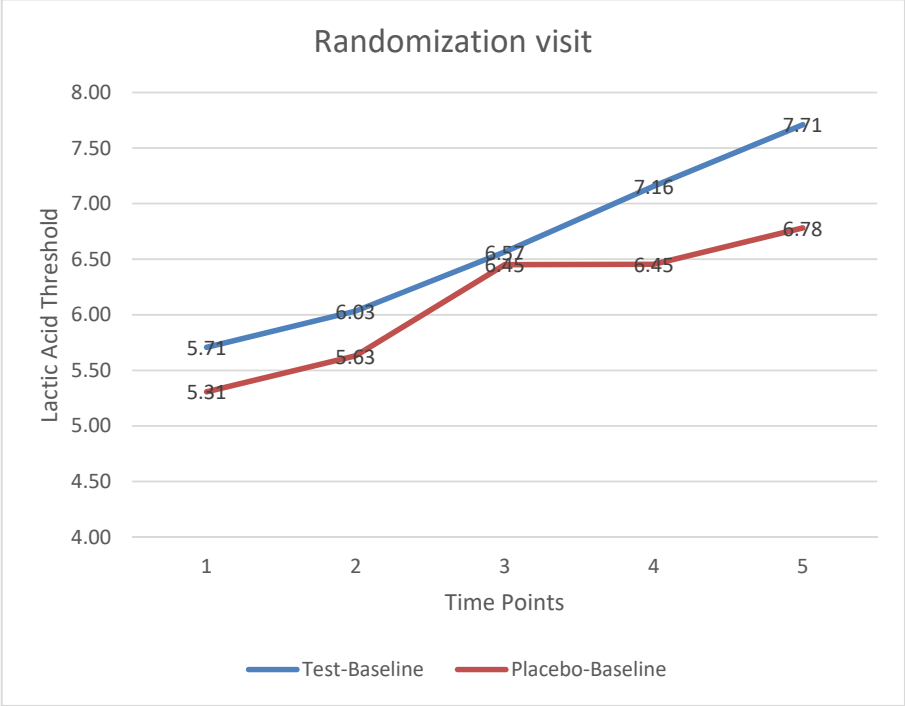


Table: 11.4.1.2.6 Change in Lactic acid threshold in blood

	Test Baseline (mmol/l)						Test EOS (mmol/l)				
Time points	**1**	**2**	**3**	**4**	**5**	**Time points**	**1**	**2**	**3**	**4**	**5**
Mean	5.71	6.03	6.57	7.16	7.71	**Mean**	5.27	5.87	6.68	6.98	7.18
SD	3.45	3.55	3.95	4.55	4.55	**SD**	4.01	3.73	4.13	4.19	3.72
Min	1	1.1	1.6	1.8	1.7	**Min**	1	1.4	1.9	2.3	2.3
Max	13.8	13.7	17.5	19.1	20.8	**Max**	17.8	15.3	17.6	19.7	20.3
	Placebo Baseline (mmol/l)						**Placebo EOS (mmol/l)**				
Time points	1	2	3	4	5	**Time points**	1	2	3	4	5
Mean	5.31	5.63	6.45	6.45	6.78	**Mean**	4.90	5.57	6.07	7.11	7.58
SD	3.51	3.27	3.62	3.34	3.77	**SD**	3.03	3.08	2.98	3.45	3.63
Min	1.1	0.9	1.3	1.5	1.9	**Min**	1.5	1.5	2.4	2.7	3.9
Max	13.7	14.8	16.1	18.7	20.5	**Max**	12.6	13.7	12.8	14.9	18.8

Figure 11.4.1.2.4: Summary of Between Group Comparison on Lactic Acid Threshold



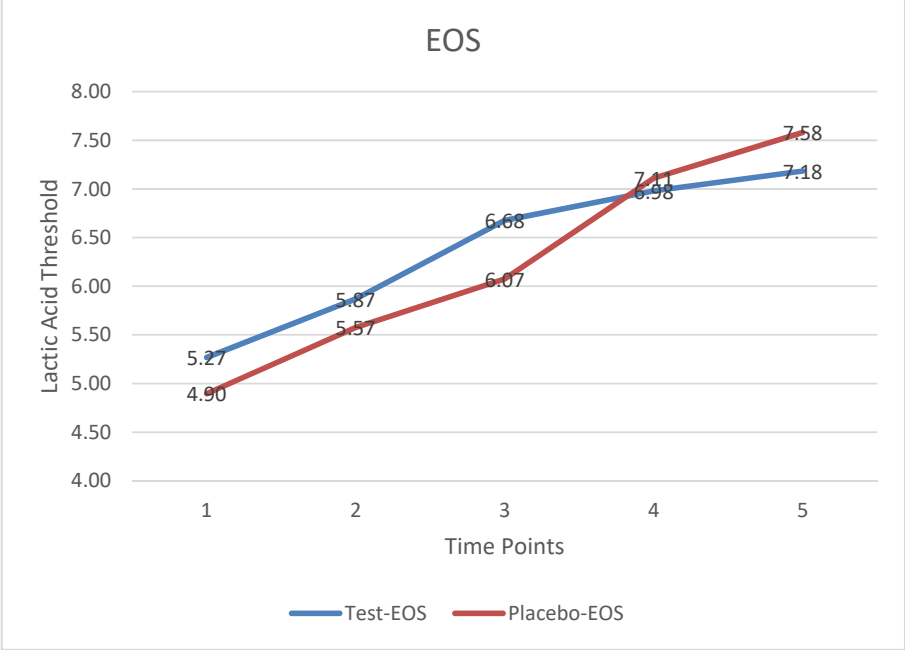
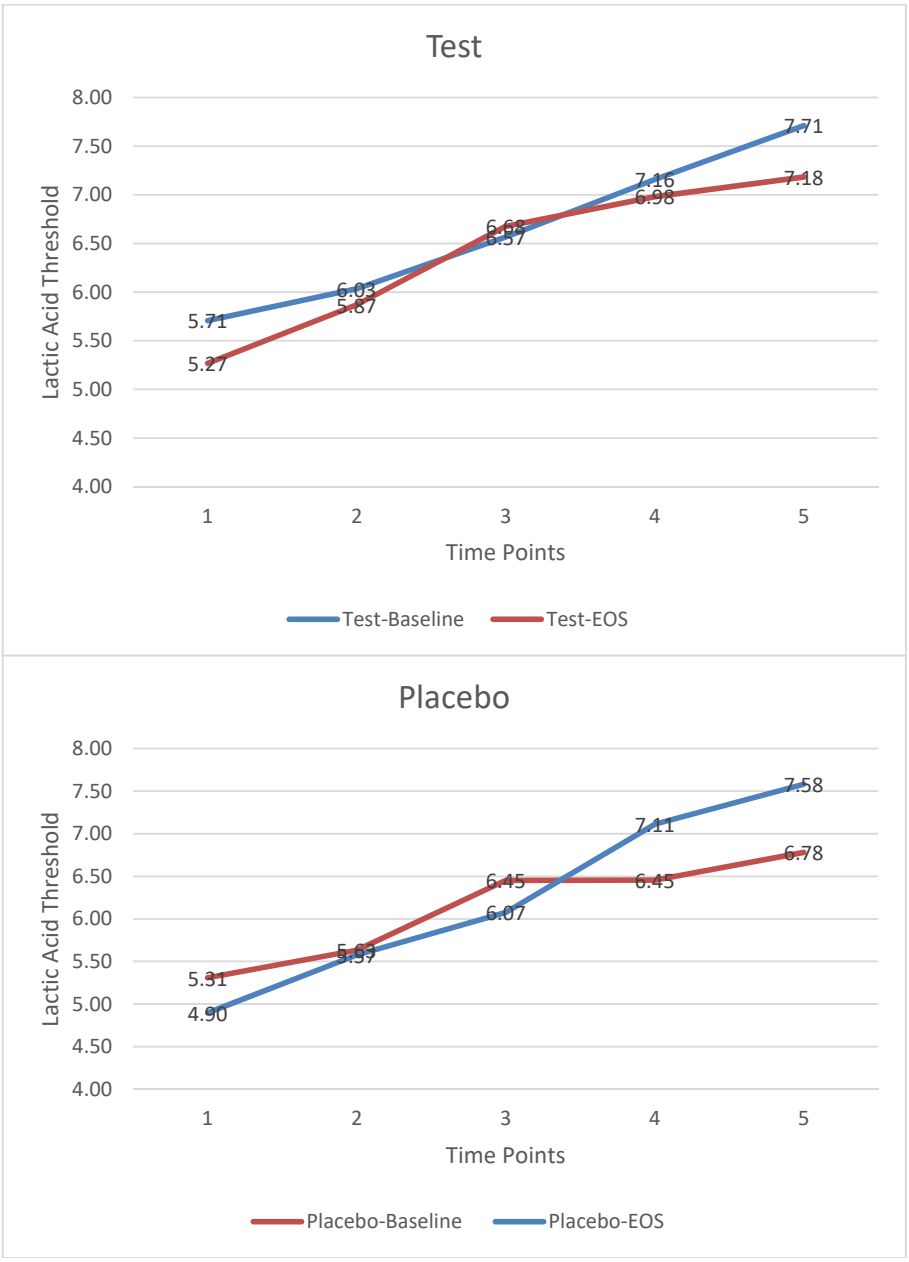


Figure 11.4.1.2.5: Summary of Within Group Comparison of lactic acid threshold



Maximum oxygen consumption, VO2max

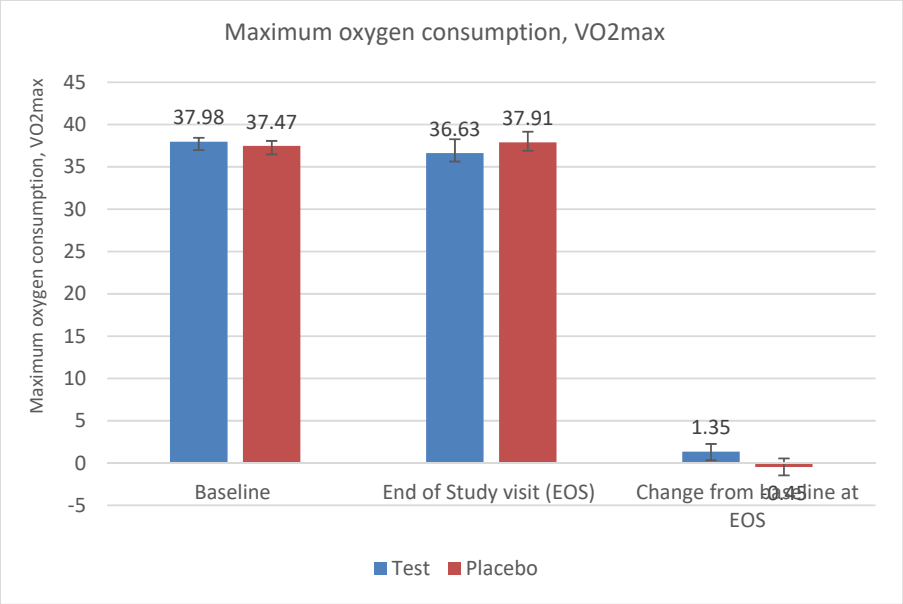
After 30 days of treatment as compared to baseline, less O2 was consumed after exercise. Hence, in treatment group less oxygen is consumed to conduct exercise, when compared to the oxygen consumed in treatment group.

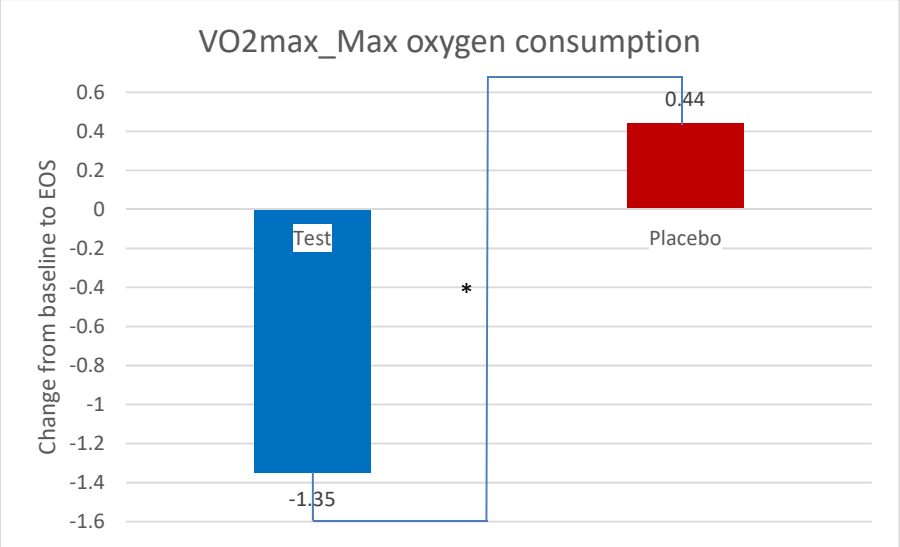
Table: 11.4.1.2.7 Summary of Maximum oxygen consumption, VO2max

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
VO2max_Max oxygen consumption (mL/kg/min)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	37.98 (3.48)	37.47 (3.32)	0.5100 (-0.8079 to 1.8279) P= 0.4446
End of Study visit (EOS) Visit 4 (Day 30)	36.63 (4.26)	37.91 (2.64)	-1.2800 (-2.6612 to 0.1012), P= 0.0690
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	-1.35 (3.19)	0.45 (2.82)	1.8000 (0.6320 to 2.9680), P= 0.0029
mITT population	N=55	N=55	
Enrollment Visit (Day 1)	38.07 (3.52)	37.42 (3.28)	0.6500 (-0.6360 to 1.9360) P= 0.3186
End of Study visit (EOS) Visit 4 (Day 30)	36.63 (4.26)	37.91 (2.64)	-1.2800 (-2.6195 to 0.0595), P= 0.0609
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	-2.11 (6.47)	0.45 (2.82)	2.5600 (0.6736 to 4.4464), P= 0.0083

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®

Figure 11.4.1.2.6: Summary of Maximum oxygen consumption, VO2max





Heart rate

Heart rate of the subject was measured at each visit of the study. There was no change in heart rate of the subject in both groups at each visit.

Table 11.4.1.2.8 Change in Heart rate

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
HR			
PP population	**N=54**	**N=51**	
Baseline	73.27 (4.75)	74.31 (5.70)	-1.0400 (-3.0664 to 0.9864) P= 0.3111
Follow up visit # 1	73.93 (4.73)	74.17 (4.08)	-0.2400 (-1.9541 to 1.4741) P= 0.7818
Follow up visit # 2	74.48 (6.02)	73.75 (5.15)	0.7300 (-1.4442 to 2.9042) P= 0.5070
End of Study visit (EOS)	74.28 (5.55)	73.57 (4.19)	0.7100 (-1.2018 to 2.6218), P= 0.4631
Change from baseline at follow up visit # 1	0.69 (4.97)	-0.16 (4.73)	-0.8500 (-2.7301 to 1.0301) P= 0.3720
Change from baseline at follow up visit # 2	1.24 (4.88)	-0.59 (5.44)	-1.8300 (-3.8280 to 0.1680) P= 0.0722
Change from baseline at EOS	1.04 (4.77)	-0.80 (4.86)	-1.8400 (-3.7042 to 0.0242), P= 0.0530
mITT population	**N=55**	**N=55**	
Baseline	73.27 (4.75)	74.31 (5.70)	-1.0400 (-3.0231 to 0.9431) P= 0.3009
Follow up visit # 1	73.93 (4.73)	74.17 (4.08)	-0.2400 (-1.9096 to 1.4296) P= 0.7762
Follow up visit # 2	74.48 (6.02)	73.75 (5.15)	0.7300 (-1.3874 to 2.8474), P= 0.4958
End of Study visit (EOS)	74.28 (5.55)	73.57 (4.19)	0.7100 (-1.1486 to 2.5686) P= 0.4506
Change from baseline at follow up visit # 1	0.69 (4.97)	-0.16 (4.73)	-0.8500 (-2.6838 to 0.9838), P= 0.3603
Change from baseline at follow up visit # 2	1.24 (4.88)	-0.59 (5.44)	-1.8300 (-3.7833 to 0.1233), P= 0.0660
Change from baseline at EOS	1.04 (4.77)	-0.80 (4.86)	-1.8400 (-3.6601 to -0.0199), P= 0.0476

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®

11.4.1.3. CHANGE IN NEURO MUSCULAR ACTIVATION

Electromyography (EMG)

Neuro muscular activation was evaluated with Electromyography (EMG). From results it can be seen that there was no not statistically significant change were detected in EMG (at Visit 4), between Test and placebo groups. Although there was clinical improvement seen in muscle response.

QUADRICEPS, GASTROCNEMIUS, HAMSTRING and ADDUCTOR muscles response before exercise and after exercise conducted at baseline and end of study visit have been presented in below tables. Gastrocnemius muscle only shows statistically significant response in effort. Other muscles do not shows statistically significant response but the clinically the response was improved after exercise on end of study visit with test product.

Table: 11.4.1.3.1 Summary of QUADRICEPS - Baseline Amplitude

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
QUADRICEPS - Baseline Amplitude (µV)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	357.20 (213.58)	338.29 (182.48)	18.9100 (-58.1882 to 96.0082) P= 0.6277
End of Study visit (EOS) Visit 4 (Day 30)	329.93 (188.29)	333.39 (185.08)	-3.4600 (-75.7748 to 68.8548), P= 0.9246
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	-27.28 (234.65)	-4.90 (126.69)	22.3800 (-51.2219 to 95.9819), P= 0.5478
QUADRICEPS - After exercise Peak Amplitude (µV)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	509.98 (302.34)	474.90 (233.10)	35.0800 (-69.8448 to 140.0048) P= 0.5088
End of Study visit (EOS) Visit 4 (Day 30)	532.91 (312.11)	488.20 (254.40)	44.7100 (-65.8720 to 155.2920), P= 0.4245
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	22.93 (323.95)	13.29 (219.31)	-9.6400 (-117.3406 to 98.0606), P= 0.8595
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®-(Natural Phytochemical Formulation)			

Table: 11.4.1.3.2 Summary of QUADRICEPS - EFFORT

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
QUADRICEPS - EFFORT			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	152.78 (169.21)	136.61 (103.39)	16.1700 (-38.4888 to 70.8288) P= 0.5587
End of Study visit (EOS) Visit 4 (Day 30)	202.98 (187.87)	154.80 (140.12)	48.1800 (-16.2627 to 112.6227), P= 0.1412
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	50.20 (221.47)	18.20 (168.82)	-32.0000 (-108.5484 to 44.5484), P= 0.4090
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table: 11.4.1.3.3 Summary of GASTROCNEMIUS- Baseline Amplitude

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
GASTROCNEMIUS - Baseline Amplitude (µV)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	450.31 (252.86)	379.71 (172.58)	70.6000 (-13.6737 to 154.8737) P= 0.0997
End of Study visit (EOS) Visit 4 (Day 30)	385.83 (155.37)	427.51 (185.40)	-41.6800 (-107.7487 to 24.3887), P= 0.2137
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	-64.48 (252.96)	47.80 (211.52)	112.280 (21.7550 to 202.80501), **P= 0.0156**
GASTROCNEMIUS - After exercise Peak Amplitude (µV)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	618.57 (283.75)	547.35 (214.40)	71.2200 (-26.5515 to 168.9915) P= 0.1516
End of Study visit (EOS) Visit 4 (Day 30)	665.37 (307.54)	622.33 (217.80)	43.0400 (-60.6505 to 146.7305), P= 0.4123
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	46.80 (349.57)	74.98 (253.54)	28.1800 (-90.6023 to 146.9623), P= 0.6390
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table: 11.4.1.3.4 Summary of GASTROCNEMIUS- EFFORT

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
GASTROCNEMIUS – EFFORT			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	168.26 (165.07)	167.65 (167.63)	0.9851 (-63.7968 to 65.0168) P= 0.9851
End of Study visit (EOS) Visit 4 (Day 30)	279.37 (248.12)	194.82 (140.43)	84.5500 (5.8975 to 163.2025), **P= 0.0354**
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	111.11 (282.86)	27.18 (194.37)	-83.9300 (-178.3986 to 10.5386), P= 0.0810
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table: 11.4.1.3.6 Summary of HAMSTRING - Baseline Amplitude

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
HAMSTRING - Baseline Amplitude (µV)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	414.17 (214.40)	370.92 (184.28)	43.2500 (-34.3339 to 120.8339) P= 0.2715
End of Study visit (EOS) Visit 4 (Day 30)	406.69 (201.80)	364.18 (182.01)	42.5100 (-32.0156 to 117.0356), P= 0.2606
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	-7.48 (281.75)	-6.75 (189.97)	0.7300 (-92.8266 to 94.2866), P= 0.9877
HAMSTRING - After exercise Peak Amplitude (µV)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	603.48 (241.19)	551.04 (266.11)	52.4400 (-45.7644 to 150.6444) P= 0.2921
End of Study visit (EOS) Visit 4 (Day 30)	608.67 (333.04)	535.33 (228.97)	73.3400 (-37.9052 to 184.5852), P= 0.1940
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	5.19 (385.83)	-15.71 (261.04)	-20.9000 (-149.1493 to 107.3493), P= 0.7472
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table: 11.4.1.3.7 Summary of HAMSTRING - EFFORT

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
HAMSTRING - EFFORT			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	189.31 (157.55)	180.12 (138.92)	9.1900 (-48.4322 to 66.8122) P= 0.7524
End of Study visit (EOS) Visit 4 (Day 30)	201.98 (183.22)	171.16 (122.06)	30.8200 (-29.8019 to 91.4419), P= 0.3157
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	12.67 (239.69)	-8.96 (152.24)	-21.6300 (-99.8637 to 56.6037), P= 0.5847
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table: 11.4.1.3.8 Summary of ADDUCTOR - Baseline Amplitude

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
ADDUCTOR - Baseline Amplitude (µV)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	381.17 (267.16)	342.45 (215.27)	38.7200 (-55.5202 to 132.9602) P= 0.4170
End of Study visit (EOS) Visit 4 (Day 30)	350.04 (216.75)	320.51 (197.24)	29.5300 (-50.8279 to 109.8879), P= 0.4678
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	-31.13 (287.57)	-21.94 (202.06)	9.1900 (-87.5238 to 105.9038), P= 0.8509
ADDUCTOR - After exercise Peak Amplitude (µV)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	535.15 (362.62)	467.63 (255.41)	67.5200 (-54.5280 to 189.5680) P= 0.2751
End of Study visit (EOS) Visit 4 (Day 30)	554.30 (375.71)	437.90 (243.27)	116.4000 (-6.8915 to 239.6915), P= 0.0640
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	19.15 (451.23)	-29.73 (223.52)	-48.8800 (-187.9796 to 90.2196), P= 0.4874
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table: 11.4.1.3.9 Summary of ADDUCTOR - EFFORT

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
ADDUCTOR - EFFORT			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	153.98 (191.91)	125.18 (116.09)	28.8000 (-51.6925 to 109.2925) P= 0.4796
End of Study visit (EOS) Visit 4 (Day 30)	204.26 (213.27)	117.39 (132.61)	86.8700 (17.6602 to 156.0798), **P= 0.0144**
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	50.28 (249.20)	-7.78 (173.79)	-58.0600 (-141.6708 to 25.5508), P= 0.1714
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Time for standing with one leg

There was not much difference found in the parameter of evaluating the time for standing on one leg. Data were almost similar in both groups and change from baseline was also similar in both groups. There was no statistically significant difference between test and placebo group subjects for parameter of time for standing one leg.

Table: 11.4.1.3.10 Summary of Time for standing with one leg

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Standing on one leg (sec)			
PP population	N=54	N=51	
Enrollment Visit (Day 1)	15.78 (4.66)	14.98 (4.75)	0.8000 (-1.0216 to 2.6216) P=0.3858
End of Study visit (EOS) Visit 4 (Day 30)	16.72 (5.14)	17.14 (4.57)*	-0.4200 (-2.3065 to 1.4665), P= 0.6598
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	0.94 (6.83)	2.16 (6.27)	1.2200 (-1.3220 to 3.7620), P= 0.3434
mITT population	N=55	N=55	
Enrollment Visit (Day 1)	15.69 (4.67)	15.27 (4.82)	0.4200 (-1.3738 to 2.2138) P=0.6435
End of Study visit (EOS) Visit 4 (Day 30)	16.72 (5.14)	17.14 (4.57)*	-0.4200 (-2.2583 to 1.4183) P=0.6515
Change from Enrollment Visit (Day 1) at EOS Visit 4 (Day 30)	0.73 (6.95)	0.62 (8.27)	-0.1100 (-2.9973 to 2.7773), P= 0.9399
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Vestibular function tests (VFT)

VFT, was evaluated with different parameters. Mostly the normal or balanced functions were observed after exercise. It was concluded that the vestibular functions of the subjects were normal.

None of the subject showed imbalance during performing the vestibular function activities. Score of the activities like subject's balance, spontaneous response, sensory response and visual vertical reports were recorded. After 30 days of the study there was no change or minor change reported in VFT which is considered to be normal functioning of the subjects also the changes are statistically non-significant.

Table 11.4.1.3.11 Summary of vestibular function test - Length from Starting Point

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Length from Starting Point			
PP population	N=54	N=51	
Baseline (Visit 1)	52.70 (28.91)	56.57 (26.06)	-3.8700 (-14.5439 to 6.8039) P=0.4737
End of Study visit (EOS)	56.43 (49.07)	53.33 (25.90)	3.1000 (-12.2179 to 18.4179), P= 0.6890
Change from baseline at EOS	3.72 (41.41)	-3.24 (16.63)	-6.9600 (-19.3073 to 5.3873), P= 0.2662
mITT population	N=55	N=55	
Baseline (Visit 1)	52.58 (28.65)	55.51 (26.54)	-2.9300 (-13.3681 to 7.5081) P=0.5791
End of Study visit (EOS)	55.62 (48.98)	53.33 (25.90)	2.2900 (-12.5188 to 17.0988) P=0.7598
Change from baseline at EOS	3.04 (41.34)	-6.05 (20.49)	-9.0900 (-21.4219 to 3.2419), P= 0.1469
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of patients; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table 11.4.1.3.12 Summary of vestibular function test - Degrees angle deviation from starting point

	Test	**Placebo**	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Degrees angle deviation from starting point			
PP population	N=54	N=51	
Baseline (Visit 1)	23.06 (20.48)	25.65 (20.52)	-2.5900 (-10.5284 to 5.3484) P=0.5190

End of Study visit (EOS)	23.50 (23.95)	23.33 (22.91)	0.1700 (-8.9114 to 9.2514), P= 0.9705
Change from baseline at EOS	0.44 (18.16)	-2.31 (22.40)	-2.7500 (-10.6224 to 5.1224), P= 0.4900
mITT population	N=55	N=55	
Baseline (Visit 1)	23.18 (20.31)	25.15 (19.93)	-1.9700 (-9.5754 to 5.6354) P=0.6087
End of Study visit (EOS)	23.25 (23.80)	23.33 (22.91)	-0.0800 (-8.9095 to 8.7495) P= 0.9857
Change from baseline at EOS	0.07 (18.20)	-3.51 (22.07)	-3.5800 (-11.2258 to 4.0658), P= 0.3554
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of patients; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table 11.4.1.3.13 Summary of vestibular function test - Static (Without Background) Horizontal

	Test	**Placebo**	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Static (Without Background) Horizontal			
PP population	N=54	N=51	
Baseline (Visit 1)	258.30 (158.51)	286.59 (140.38)	-28.2900 (-86.3712 to 29.7912) P=0.3363
End of Study visit (EOS)	271.87 (150.76)	252.59 (160.70)	19.2800 (-41.0013 to 79.5613), P= 0.5273
Change from baseline at EOS	13.57 (193.09)	-34.00 (161.02)	-47.5700 (-116.5953 to 21.4553), P= 0.1747
mITT population	N=55	N=55	
Baseline (Visit 1)	260.07 (157.59)	278.82 (146.01)	-18.7500 (-76.1700 to 38.6700) P=0.5188
End of Study visit (EOS)	273.47 (149.83)	252.59 (160.70)	20.8800 (-37.8439 to 79.6039) P=0.4825
Change from baseline at EOS	13.40 (191.30)	-44.60 (166.59)	-58.0000 (-125.7997 to 9.7997), P= 0.0928
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of patients; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table 11.4.1.3.14 Summary of vestibular function test - Dynamic (With Background) Horizontal

	Test	**Placebo**	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Dynamic (With Background) Horizontal			
PP population	N=54	N=51	
Baseline (Visit 1)	115.67 (165.66)	143.00 (173.30)	-27.3300 (-92.9350 to 38.2750) P=0.4106
End of Study visit (EOS)	128.80 (169.97)	101.20 (158.54)	27.6000 (-36.1109 to 91.3109), P= 0.3922
Change from baseline at EOS	13.13 (204.37)	-41.80 (194.30)	-54.9300 (-132.2042 to 22.3442), P= 0.1616
mITT population	N=55	N=55	
Baseline (Visit 1)	120.07 (167.34)	145.93 (173.73)	-25.8600 (-90.3311 to 38.6111) P=0.4283
End of Study visit (EOS)	132.89 (171.10)	101.20 (158.54)	31.6900 (-30.6548 to 94.0348) P=0.3159
Change from baseline at EOS	12.82 (202.48)	-52.09 (196.45)	-64.9100 (-140.3135 to 10.4935), P= 0.0908
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of patients; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Table 11.4.1.3.15 Summary of vestibular function test - Static (Without Background) Vertical

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Static (Without Background) Vertical			
PP population	N=54	N=51	
Baseline (Visit 1)	89.20 (4.35)	89.16 (4.25)	0.0400 (-1.6259 to 1.7059) P= 0.9621
End of Study visit (EOS)	88.83 (3.90)	88.65 (3.93)	0.180 (-1.3359 to 1.6959), P= 0.8143
Change from baseline at EOS	-0.37 (5.73)	-0.51 (5.67)	-0.1400 (-2.3477 to 2.0677), P= 0.9002
mITT population	N=55	N=55	
Baseline (Visit 1)	89.27 (4.34)	88.95 (4.36)	0.3200 (-1.3242 to 1.9642) P=0.7004
End of Study visit (EOS)	88.85 (3.87)	88.65 (3.93)	0.2000 (-1.2742 to 1.6742) P=0.7885
Change from baseline at EOS	-0.42 (5.69)	-6.75 (23.16)	-6.3300 (-12.7042 to 0.0442), P= 0.0516
*p<0.05 vs baseline (within group comparison) otherwise not specified.			

Values are expressed as mean (SD). Abbreviation: N= number of patients; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®

Table 11.4.1.3.16 Summary of vestibular function test - Dynamic (With Background)

	Test	**Placebo**	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Dynamic (With Background) Vertical			
PP population	N=54	N=51	
Baseline (Visit 1)	93.20 (3.53)	92.94 (3.96)	0.2600 (-1.1902 to 1.7102) P=0.7229
End of Study visit (EOS)	92.07 (3.61)	92.98 (3.81)	-0.9100 (-2.3461 to 0.5261), P= 0.2117
Change from baseline at EOS	-1.13 (4.93)	0.04 (5.50)	1.1700 (-0.8493 to 3.1893), P= 0.2532
mITT population	N=55	N=55	
Baseline (Visit 1)	93.22 (3.49)	92.78 (4.09)	0.4400 (-0.9970 to 1.8770) P=0.5452
End of Study visit (EOS)	92.09 (3.58)	92.98 (3.81)	-0.8900 (-2.2873 to 0.5073) P=0.2095
Change from baseline at EOS	-1.13 (4.88)	6.56 (24.42)	-5.4300 (-12.0859 to 1.2259), P= 0.1088
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of patients; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

11.4.1.4. CHANGE IN STRESS AND ANTI-INFLAMMATORY BIOMARKERS

Cortisol, C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), IL-6 and TNF-α

Change in different biomarkers was compared from Screening Visit to Visit 2 (Day 4) to Visit 3 (Day 15) and Visit 4 (Day 30). There was no statistically significant difference found in within group or between group comparisons.

Cortisol

Cortisol is a glucocorticoid hormone that adrenal glands produce and release. Cortisol is an essential hormone that suppressing inflammation and regulating body stress response.

In current study, there is no statistical change reported in the level of cortisol. Though cortisol showing 5% reduction in level after 30 days of treatment in test group while in

placebo group 0.2% increase in level of cortisol was observed. In healthy subjects, level of cortisol are expected to remain within reference range.

Table: 11.4.1.4.1 Summary of Cortisol

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Cortisol (µg/dL)			
PP population	N=54	N=51	
Screening Visit	7.61 (3.02)	7.77 (3.17)	-0.1600 (-1.3580 to 1.0380) P=0.7916
End of Study visit (EOS) Visit 4 (Day 30) before exercise	7.24 (3.36)	7.79 (2.38)	-0.5500 (-1.6829 to 0.5829), P= 0.3379
Change from Screening Visit at EOS Visit 4 (Day 30) before exercise	-0.37 (3.44)	0.02 (3.42)	0.3900 (-0.9384 to 1.7184), P= 0.5617
mITT population	N=55	N=55	
Screening Visit	7.56 (3.01)	7.90 (3.16)	-0.3400 (-1.5064 to 0.8264) P=0.5646
End of Study visit (EOS) Visit 4 (Day 30) before exercise	7.24 (3.36)	7.81 (2.36)	-0.5700 (-1.6674 to 0.5274), P= 0.3055
Change from Screening Visit at EOS Visit 4 (Day 30) before exercise	-0.45 (3.47)	-0.52 (4.07)	-0.0700 (-1.4995 to 1.3595), P= 0.9229
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

C-reactive protein (CRP)

C-reactive protein (CRP) is an inflammatory marker produced and released by the liver under stimulation of cytokines. CRP is a useful marker of the acute phase reaction as it responds quickly to the inflammatory process, whether it is an infection, autoimmune disease or tissue necrosis. After the inflammation has resolved, concentrations fall rapidly. Once inflammation and its cause have been identified and treatment is started, there is usually no need for further C-reactive protein measurements.

In the current study, there were no significant alterations in CRP levels over time or between treatments. From individual data, it can be summarized that total in 64% of test and 41% of placebo subjects reduction in level of CRP was observed. From below table, it can be concluded that though there was statistically non-significant alterations in level of CRP, more number of subjects had reduction in CRP in test group as compared to placebo group.

At baseline, there is difference in the level of CRP in test and placebo which is 1.92 and 3.19 respectively. In test group, the level increases due to eccentric exercise while in placebo group there is higher value at baseline showed inflammation in those subjects.

So difference from baseline is difficult to assess in current study. From Day 4, the level can be seen in similar flow between test and placebo. At the end of study it can be seen that there is higher value in CRP level in placebo compared to test.

Table: 11.4.1.4.2 Summary of C-reactive protein (CRP)

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
C-reactive protein (CRP)			
PP population	N=54	N=51	
Screening Visit	1.92 (2.99)	3.19 (4.79)	-1.2700 (-2.8063 to 0.2663) P= 0.1042
Follow up visit 02 (Day 4)	2.82 (7.03)	2.49 (3.30)	0.3300 (-1.8162 to 2.4762), P= 0.7610
Follow up visit 03 (15 Days)	2.15 (2.68)	2.22 (2.34)	-0.0700 (-1.0461 to 0.9061), P= 0.8872
End of Study visit (EOS) Visit 4 (Day 30) before exercise	2.13 (3.02)	3.03 (3.90)	-0.9000 (-2.2457 to 0.4457), P= 0.1877
Change from Screening Visit at Follow up visit 02 (Day 4)	2.82 (7.03)	-0.70 (3.64)	2.1200 (-0.0659 to 4.3059), P= 0.0572
Change from Screening Visit at Follow up visit 03 (15 Days)	0.23 (3.15)	-0.97 (4.55)	-1.2000 (-2.7076 to 0.3076), P= 0.1175
Change from Screening Visit at EOS Visit 4 (Day 30) before exercise	0.21 (4.28)	-0.22 (4.72)	-0.4300 (-2.1722 to 1.3122), P= 0.6255
mITT population	N=55	N=55	
Screening Visit	1.90 (2.97)	3.03 (4.65)	-1.1300 (-2.6047 to 0.3447) P=0.1317
Follow up visit 02 (Day 4)	2.82 (7.03)	2.47 (3.27)	0.3500 (-1.7223 to 2.4223) P=0.7384
Follow up visit 03 (15 Days)	2.15 (2.68)	2.18 (2.33)	-0.0300 (-0.9792 to 0.9192), P= 0.9502
End of Study visit (EOS) Visit 4 (Day 30) before exercise	2.13 (3.02)	2.98 (3.88)	-0.8500 (-2.1641 to 0.4641), P= 0.2026
Change from Screening Visit at Follow up visit 02 (Day 4)	2.77 (6.98)	-0.69 (3.51)	2.0800 (-0.0082 to 4.1682), P= 0.0509
Change from Screening Visit at Follow up visit 03 (15 Days)	0.21 (3.13)	-0.96 (4.38)	-1.1700 (-2.6089 to 0.2689), P= 0.1099
Change from Screening Visit at EOS Visit 4 (Day 30) before exercise	0.19 (4.24)	-0.26 (4.54)	-0.4500 (-2.1103 to 1.2103), P= 0.5922

*p<0.05 vs baseline (within group comparison) otherwise not specified.
Values are expressed as mean (SD).
Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®

Erythrocyte Sedimentation Rate (ESR)

Erythrocyte sedimentation rate (ESR) rate may increase during acute inflammatory processes, acute and chronic infections, tissue damage (necrosis), rheumatoid, collagen disease, malignancy and physiological stress conditions (e.g. pregnancy). During an inflammatory reaction, the sedimentation rate is affected by increasing concentrations of fibrinogen, the main clotting protein, and alpha globulins.

Study results reported that there was no statistically significant difference in ESR level at baseline, day 4, day 15 and end of study visit.

Regular physical exercise, particularly of a high level, is associated with lower ESR values, as compared to individuals with low physical activity. Current study is associated with eccentric exercise and subjects were untrained for any kind of extraneous exercise. However, a few subjects reported lower ESR level at the end of the study. Reduction of ESR level reported in 44% subjects and 25% subjects in test and placebo group respectively.

Table: 11.4.1.4.3 Summary of Erythrocyte Sedimentation Rate

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
ESR (mm/hr)			
PP population	N=54	N=51	
Screening Visit	16.07 (11.97)	18.59 (15.83)	-2.5200 (-7.9328 to 2.8928) P=0.3580
Follow up visit 02 (Day 4)	13.87 (12.46)	18.47 (13.72)	-4.6000 (-9.6679 to 0.4679), P= 0.0748
Follow up visit 03 (15 Days)	17.98 (16.54)	19.14 (15.94)	-1.1600 (-7.4534 to 5.1334), P= 0.7154
End of Study visit (EOS) Visit 4 (Day 30) before exercise	20.33 (18.89)	24.32 (16.89)	-3.9900 (-10.9400 to 2.9600), P= 0.2575
Change from Screening Visit at Follow up visit 02 (Day 4)	-2.20 (9.62)	-0.12 (10.78)	2.0800 (-1.8698 to 6.0298), P= 0.2987
Change from Screening Visit at Follow up visit 03 (15 Days)	1.91 (13.96)	0.55 (13.22)	-1.3600 (-6.6289 to 3.9089), P= 0.6098
Change from Screening Visit at EOS Visit 4 (Day 30) before exercise	4.26 (16.28)	5.25 (18.71)	0.9900 (-5.7876 to 7.7676), P= 0.7726
mITT population	N=55	N=55	
Screening Visit	15.82 (12.00)	18.15 (15.40)	-2.3300 (-7.5481 to 2.8881) P=0.3781
Follow up visit 02 (Day 4)	13.87 (12.46)	18.67 (13.67)	-4.8000 (-9.7437 to 0.1437) P= 0.0569
Follow up visit 03 (15 Days)	17.98 (16.54)	19.06 (15.79)	-1.0800 (-7.1918 to 5.0318), P= 0.7268
End of Study visit (EOS) Visit 4 (Day 30) before exercise	20.33 (18.89)	23.88 (17.01)	-3.5500 (-10.3441 to 3.2441), P= 0.3027

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
Change from Screening Visit at Follow up visit 02 (Day 4)	-2.20 (9.53)	0.49 (10.99)	1.7100 (-2.1779 to 5.5979), P= 0.3852
Change from Screening Visit at Follow up visit 03 (15 Days)	1.84 (13.84)	0.13 (13.11)	-1.9700 (-7.0652 to 3.1252), P= 0.4451
Change from Screening Visit at EOS Visit 4 (Day 30) before exercise	4.15 (16.15)	4.00 (18.63)	-0.1500 (-6.7399 to 6.4399), P= 0.9641
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

IL-6

Interleukin-6 (IL-6) plays an important role in mediating inflammation and is a central stimulus for the acute-phase response. IL-6 is produced substantially by monocytes and macrophages after antigen activation, even though other cells (such as fibroblasts, endothelial cells, and T-lymphocytes) may also synthesise it. IL-6 is principally responsible for activating the hepatic synthesis of CRP, which has been considered the inflammatory biomarker of choice in orthopaedic surgery.

In current study, the level of IL-6 should increase with respect to eccentric exercise. With help of test product, at end of study visit the level should be lower as compared to baseline. The result showed the same effect. In test product, the level of IL-6 is reduced at the end of study visit in test product compared to placebo.

In test group the change from baseline to end of study visit for the level of IL-6 was 4% reduction whereas there was 26% increase in placebo group. Though there was increase in level reported at day 15 in the test group, after 30 days of the treatment there was reduction in IL-6 level; whereas in placebo group increase in IL-6 level was observed. However, the reduction was not statistically significant.

From baseline to 15 days of treatment, 23% subjects in test and 16% subjects in placebo group showed improvement. From baseline to 30 days of treatment, 25% subjects in test and 12% subjects in placebo group showed improvement. While from day 15 to day 30, there are 36% subjects in test and 14% subjects in placebo group showed improvement in IL-6 level.

Table: 11.4.1.4.4 Summary of IL-6

	Test	**Placebo**	**Effect Size, 95% CI of treatment difference and P value (Between group comparison)**
IL-6 (pg/mL)			
PP population	N=54	N=51	
Enrollment Visit 1(Day 1)	4.20 (4.60)	4.49 (7.12)	-0.2900 (-2.5972 to 2.0172) P= 0.8036
Follow up visit 03 (15 days)	5.21 (5.57)	4.57 (5.52)	0.6400 (-1.5076 to 2.7876), P= 0.5558
End of Study visit (EOS) Visit 4 (Day 30) before exercise	4.00 (2.21)	6.12 (7.96)	-2.1200 (-4.3537 to 0.1137), P= 0.0626
Change from Enrollment Visit 1(Day 1) at Follow up visit 03 (15 days)	2.49 (6.22)	0.08 (5.09)	2.5700 (0.3629 to 4.7771), **P= 0.0229**
Change from Enrollment Visit 1(Day 1) at EOS Visit 4 (Day 30) before exercise	-0.28 (4.52)	1.63 (7.36)	1.9100 (-0.4395 to 4.2595), P= 0.1100
mITT population	N=55	N=55	

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
Enrollment Visit 1(Day 1)	4.17 (4.56)	4.46 (6.89)	-0.2900 (-2.5395 to 1.9595) P=0.7987
Follow up visit 03 (15 days)	5.21 (5.57)	4.59 (5.47)	0.6200 (-1.5183 to 2.7583), P= 0.5665
End of Study visit (EOS) Visit 4 (Day 30) before exercise	4.00 (2.21)	6.16 (7.89)	-2.1600 (-4.3500 to 0.0300), P= 0.0532
Change from Enrollment Visit 1(Day 1) at Follow up visit 03 (15 days)	2.54 (6.17)	0.12 (5.06)	2.4200 (0.2873 to 4.5527), **P= 0.0265**
Change from Enrollment Visit 1(Day 1) at EOS Visit 4 (Day 30) before exercise	-0.32 (4.48)	1.37 (7.27)	1.6900 (-0.5924 to 3.9724), P= 0.1451
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

TNF-alpha

Tumor necrosis factor-α (TNF-α) is one of the pro-inflammatory cytokines. This cytokine has been implicated in various autoimmune and inflammatory diseases. Among cytokines, TNF-*α* is the main mediator of acute inflammatory response whose physiological function is stimulation of leukocytes, signalling to sites of inflammation and activating them in order to eradicate microorganisms and reduce inflammation. TNF-α has been identified as a major regulator of inflammatory responses.

In test group change from baseline to 15 days of treatment showed reduction of 24% in level of TNF-alpha. The change was statistically significant within test group. While in placebo group there was 20% reduction. The change from baseline to end of study showed 14% reduction in test group while in placebo group there was 6% reduction.

Table: 11.4.1.4.5 Summary of TNF-alpha

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
TNF-Alpha (pg/mL)			
PP population	N=54	N=51	
Enrollment Visit 1(Day 1) before exercise	23.86 (18.62)	23.30 (18.96)	0.5600 (-6.7148 to 7.8348) P= 0.8790
Follow up visit 03 (15 days)	17.94 (9.56)*	18.46 (12.03)	-0.5200 (-4.7138 to 3.6738), P= 0.8062
End of Study visit (EOS) Visit 4 (Day 30) before exercise	20.40 (13.40)	21.79 (14.70)	-1.3900 (-6.8294 to 4.0494), P= 0.6134
Change from Enrollment Visit 1(Day	-3.41 (18.80)	-1.52 (13.56)	1.8900 (-4.4865 to 8.2665), P= 0.5579

	Test	Placebo	Effect Size, 95% CI of treatment difference and P value (Between group comparison)
1) before exercise at Follow up visit 03 (15 days)			
Change from Enrollment Visit 1(Day 1) before exercise at EOS Visit 4 (Day 30) before exercise	-6.55 (22.40)	-5.27 (25.74)	1.2800 (-8.0447 to 10.6047), P= 0.7860
mITT population	N=55	N=55	
Enrollment Visit 1(Day 1) before exercise	23.82 (18.38)	23.12 (18.75)	0.7000 (-6.3177 to 7.7177) P= 0.8436
Follow up visit 03 (15 days)	17.94 (9.56)*	18.28 (11.91)	-0.3400 (-4.4219 to 3.7419), P= 0.8692
End of Study visit (EOS) Visit 4 (Day 30) before exercise	20.97 (13.83)	21.79 (14.70)	-0.8200 (-6.2145 to 4.5745), P= 0.7638
Change from Enrollment Visit 1(Day 1) before exercise at Follow up visit 03 (15 days)	-4.02 (18.80)	-1.62 (13.31)	2.4000 (-3.7566 to 8.5566), P= 0.4414
Change from Enrollment Visit 1(Day 1) before exercise at EOS Visit 4 (Day 30) before exercise	-5.64 (22.70)	-5.56 (25.43)	0.0800 (-9.0308 to 9.1908), P= 0.9861
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

11.4.1.5. Change in BP and Pulse

There was no change reported in subjects' blood pressure and pulse in both test and placebo groups.

Table 11.4.1.5.1 Summary of Safety results (Safety population) - Pulse (Beats/min) Result

	Test N=55	Placebo N=55	P value*
Baseline Visit #1			
Within normal limit	55.00	55.00	1.0000
Clinically non-significant	0.00	0.00	
Visit # 1.2			
Follow up # 2			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 3			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
End of Study visit (EOS)			

Within normal limit	54.00	51.00	1.0000
Clinically non-significant	0.00	0.00	
*by Fisher's exact test Values are expressed as number of subjects Abbreviation: N= number of subjects Test: Rephyll®			

Table 11.4.1.5.2. Summary of Safety results (Safety population) - Systolic Blood Pressure (mmHg) Result

	Test N=55	Placebo N=55	P value*
Baseline			
Within normal limit	55.00	55.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 2			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 3			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
End of Study visit (EOS)			
Within normal limit	54.00	51.00	1.0000
Clinically non-significant	0.00	0.00	
*by Fisher's exact test Values are expressed as number of subjects Abbreviation: N= number of subjects Test: Rephyll®			

Table 11.4.1.5.3. Summary of Safety results (Safety population) - Diastolic Blood Pressure (mmHg) Result

	Test N=55	Placebo N=55	P value*
Baseline			
Within normal limit	55.00	55.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 2			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 3			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
End of Study visit (EOS)			
Within normal limit	54.00	51.00	1.0000
Clinically non-significant	0.00	0.00	
*by Fisher's exact test Values are expressed as number of subjects Abbreviation: N= number of subjects Test: Rephyll®			

Table 11.4.1.5.4. Summary of Safety results (Safety population) – body temperature

	Test N=55	Placebo N=55	P value*
Baseline			
Within normal limit	55.00	55.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 2			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 3			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
End of Study visit (EOS)			
Within normal limit	54.00	51.00	1.0000
Clinically non-significant	0.00	0.00	
*by Fisher's exact test Values are expressed as number of subjects Abbreviation: N= number of subjects Test: Rephyll®			

Table 11.4.1.5.5. Summary of Safety results (Safety population) – Respiratory Rate (/min)

	Test N=55	Placebo N=55	P value*
Baseline			
Within normal limit	55.00	55.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 2			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
Follow up # 3			
Within normal limit	54.00	52.00	1.0000
Clinically non-significant	0.00	0.00	
End of Study visit (EOS)			
Within normal limit	54.00	51.00	1.0000
Clinically non-significant	0.00	0.00	
*by Fisher's exact test Values are expressed as number of subjects Abbreviation: N= number of subjects Test: Rephyll®			

11.4.1.6. Change in CBC and Blood lipids

There were no changes reported in CBC and blood lipids at baseline and at end of study visit. This shows that the treatments are not affecting subjects' general health condition.

Table. 11.4.1.6.1 Baseline and end of study visit data of CBC and blood lipid

		Test N=55 Mean(SD)	**Placebo N=55 Mean(SD)**
TC (mg/dl)	110.00 – 200.00 mg/dL		
Baseline		164.05 (33.85)	170.65 (29.42)
EOS		170.11 (37.57)	179.38 (33.29)
TG (mg/dl)	40.00 – 200.00 mg/dL		
Baseline		145.57 (91.08)	129.54 (64.82)
EOS		134.80 (80.78)	141.10 (70.73)
LDL (mg/dl)	0.00 – 100.00 mg/dL		
Baseline		106.47 (35.18)	117.63 (29.66)
EOS		103.13 (33.92)	115.12 (32.69)
HDL (mg/dl)	40.00 – 60.00 mg/dL		
Baseline		45.54 (11.97)	45.90 (15.70)
EOS		49.04 (21.01)	46.40 (20.33)
Haemoglobin (G%)	13.0 – 17.0 G%		
Baseline		12.59 (2.18)	12.71 (1.68)
EOS		12.68 (2.34)	12.35 (1.70)
Total RBC (million/cumm)	4.50 – 5.50 million/cumm (for male), 3.80 – 4.80 million/cumm (for femal)		
Baseline		4.65 (0.73)	4.57 (0.54)
EOS		4.57 (0.75)	4.48 (0.55)
Total WBC (/µl)	4000.00-10000.00 / µl		
Baseline		7120.73 (1949.75)	7591.09 (1926.17)
EOS		6637.99 (2234.52)	7234.20 (1902.00)
Neutrophils (%)	40.00-70.00 %		
Baseline		59.54 (7.90)	59.07 (8.91)
EOS		59.66 (8.49)	58.17 (8.18)
Lymphocytes (%)	20.00-40.00 %		
Baseline		29.75 (7.29)	30.98 (8.12)
EOS		29.63 (7.95)	31.85 (7.68)
Eosinophils (%)	1.00-6.00 %		
Baseline		2.95 (2.22)	3.17 (2.17)
EOS		3.00 (2.40)	3.16 (2.16)

		Test N=55 Mean(SD)	**Placebo N=55 Mean(SD)**
Monocytes (%)	2.00-10.00 %		
Baseline		7.11 (2.05)	6.25 (1.67)
EOS		7.02 (2.30)	6.28 (1.55)
Basophiles (%)	0.00-2.00 %		
Baseline		0.63 (0.50)	0.52 (0.33)
EOS		0.68 (0.43)	0.53 (0.33)
Platelet Count (µl)	150000.00 – 410000.00 / µl		
Baseline		319672.73 (108024.18)	306509.09 (86920.75)
EOS		312462.96 (108804.43)	321280.00 (101905.53)
Haematocrit (%)	41% to 50% (For male) and 36% to 48% (for female)		
Baseline		38.32 (6.26)	38.88 (4.31)
EOS		37.88 (7.13)	37.70 (4.96)

11.4.1.7. Subjective pain score:

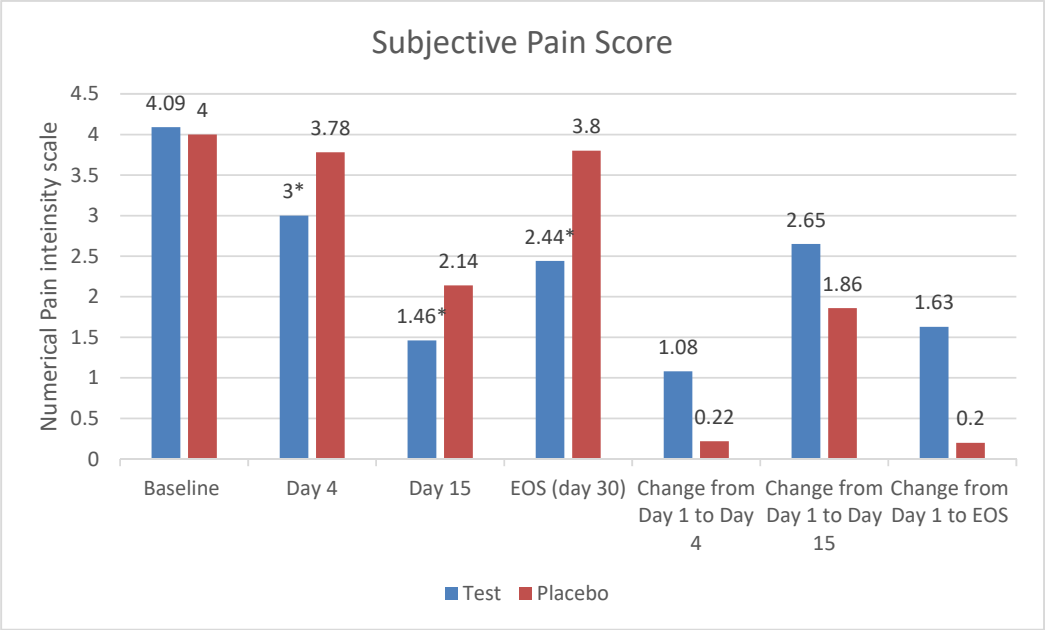
Subjective pain rating was inspected utilizing a numerical pain intensity scale. The visual assessment score (VAS) scale ranged from 0 (no pain at all) to 10 (extremely intense pain).

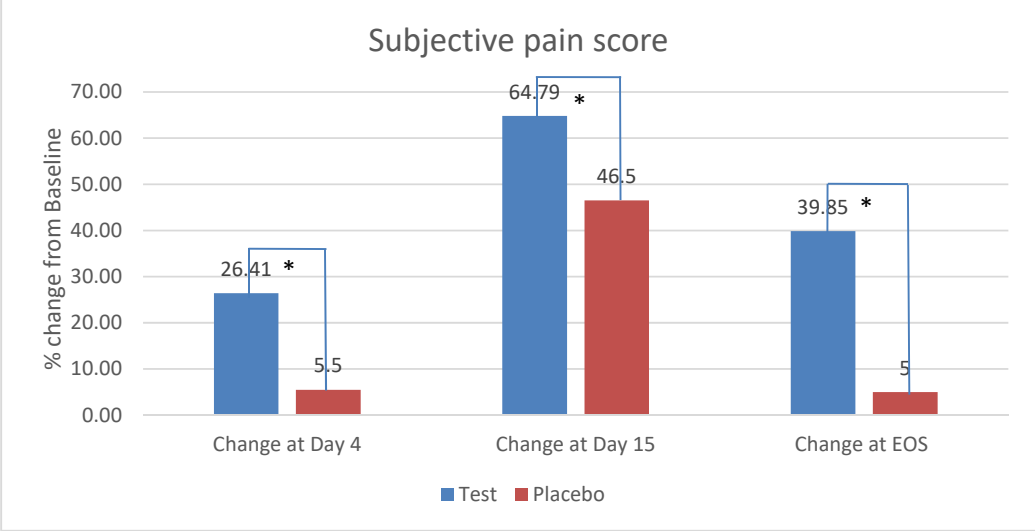
There was statistically significant improvement observed between test and placebo on day 4, day 15 and day 30. Moreover, within group analysis showed statistically significant reduction in pain score in subjects with test group, but such reduction cannot be spotted in placebo group.

Table: 11.4.1.7.1 Summary of Subjective Pain Score

	Test	**Placebo**	**P value (Between group comparison)**
Pain score			
PP population	N=54	N=51	
Baseline (Day 1) after exercise	4.09 (1.17)	4.00 (0.89)	0.64
Visit 1.2 (post exercise)			
Follow up visit 02 (Day 4)	3.00* (1.27)	3.78 (1.12)	0.001
Follow up visit 03 (Day 15)	1.46* (1.24)	2.14* (1.02)	0.003
End of Study visit (EOS) Day 30 after exercise	2.44* (0.92)	3.80 (0.80)	<0.001
Visit 4 (post exercise)			
Change from Enrolment Visit 1 (Day 1) at follow up visit 2 (Day 4)	-1.08 (1.11)	-0.22 (0.94)	<0.001
Change from Enrolment Visit 1 (Day 1) at follow up visit 3 (Day 15)	-2.65 (1.15)	-1.86 (0.94)	<0.001
Change from Enrolment Visit 1 (Day 1) at EOS Visit 4 (Day 30)	-1.63 (0.92)	-0.20 (0.72)	<0.001
*p<0.05 vs baseline (within group comparison) otherwise not specified. Values are expressed as mean (SD). Abbreviation: N= number of subjects; PP=per protocol; mITT: modified intent-to treat population; Test: Rephyll®			

Figure 11.4.1.7.1: Summary of Subjective Pain Score





11.4.2 Statistical /Analytical Issues

There was no Statistical Issue during the study.

11.4.2.1 Adjustments for Covariates

No adjustments were made.

11.4.2.2 Handling of Dropouts or Missing Data

There were no last-observation-carried-forward method (LOCF) for efficacy analysis planned in this study. Subjects not completed the study but had one post

baseline evaluation were included for mITT analysis. While subjects who completed all study visit and parameters were included in PP analysis.

11.4.2.3 Interim Analyses and Data Monitoring

Not applicable

11.4.2.4 Multicentre Studies

There were total of 2 sites in the study. Both sites were comparable. Exercise protocols were similar and all procedure conducted at both sites were similar. All laboratory investigations performed at the same laboratory facility and blinding was maintained throughout the study.

11.4.2.5 Multiple comparisons/Multiplicity

Not applicable

11.4.2.6 Use of an "Efficacy Subset" of Subjects

Not applicable

11.4.2.7 Active-Control studies intended to show Equivalence

Not applicable

11.4.2.8 Examination of Subgroups

Not applicable

11.4.3 Tabulation of Individual Response Data

Refer **Appendix 16.2.6** for the analysis data.

11.4.4. Drug Dose, Drug concentration and Relationships to Response

Not applicable

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable

11.4.6 by-Subject Listings

No formal by-subject displays were produced. However, each of the listings within the **Appendix 16.2** presents study information by subject.

11.4.7 Efficacy Conclusions

Efficacy of the study product was evaluated by many parameters in which change in muscle fatigue showed statistically significant improvement in evaluation of fatigue index and rating of perceived exertion (RPE), change in endurance of energy supply and recovery showed statistically significant improvement in evaluation of parameters such as respiratory exchange ratio (RER), Adenosine-5'-triphosphate (ATP), lactic acid threshold, Maximum oxygen consumption (VO2max). Subjective pain score showed statistically significant difference between group analysis for test and placebo groups and within group analysis in test group.

There was no any negative impact on subjects' CBC, blood lipids and blood pressure. All level were within normal limit or clinically non-significant level. For parameters, (found to be clinically effective in Rephyll® group as compared to placebo), though effects observed were not statistically significant, it can be correlated with subject to subject variability.

12 SAFETY EVALUATION

12.1 Extent of Exposure

Overall exposure of study treatment was same in both the groups. None of the subject required extra dose or reported overdose.

Summary of exposure duration are displayed in summary Table 12.1.1 below. The exposure detail i.e. IP dispensed and IP consumed, is presented in **Appendix 16.2.5**.

Table 12.1.1: Summary of Exposure– Safety Population

Parameter	Test (N=55) n (%)	Placebo (N=55) n (%)	Overall (N=110) n (%)
Number of IP consumption as per protocol	3300	3300	6600
Number of IP consumed	3076 (93.21)	2896 (87.76)	5972 (90.48)
Abbreviations: N = number of subjects in respective treatment; n = number of subjects in specified category. Note 1: Percentages are based on the number of subjects in the specified treatment.			

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

The safety analysis was performed on subjects allocated to receive Test group and Placebo group. Evaluation was performed for all groups who received at least a single dose of any of the treatment group. In current study, no AE was reported after receiving the treatment. At the time of screening, 2 AEs were reported and

both the subjects were not recruited in the study. After randomization, none of the subject reported any adverse event. The product was well tolerated by the subjects.

Overall summary of adverse event for safety population is presented in Table 12.2.1.1.

Table 12.2.1.1: Overall Summary of Adverse Events - Safety Population

Adverse event, n (%)	Test (N=55)	Placebo (N=55)	Overall (N=105)
Subjects who reported at least one AE	NA	NA	02
Subjects who reported at least one TEAE	00	00	00
Abbreviations: N = number of subjects in specified treatment; n = number of subjects having non-missing values at specified visit; TEAE = Treatment Emergent Adverse Event			

In this evaluation, there was no treatment attributable severe adverse event suggesting that treatments were safe in the both test as well as placebo group.

12.2.2 Display of Adverse Event

There were no TEAEs reported during the study duration.

12.2.3 Analysis of Adverse Events

Serious Adverse Events: No SAE was reported during the study.

Incidence of AE: No TEAE was reported during the study.

AEs with causality and severity:

Both of the adverse events reported at the time of screening were unlikely related to treatment. Both of reported AEs were mild in severity.

Subject withdrawn due to AE:

Both subjects were withdrawn and/or not recruited in the study.

12.2.4 Listing of Adverse Events by Subjects

All adverse events for each subject, including the events reported before enrolment are listed in **Appendix 16.2.7**.

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

12.3.1 Listing of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

None

12.3.1.2 Other Serious Adverse Events

None

12.3.1.3 Other Significant Adverse Events

None

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

No deaths or other serious adverse events occurred in this study.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

No deaths or other serious adverse events occurred in this study. Incidence of subjects discontinued due to AE was none.

12.4 Clinical Laboratory Evaluation

12.4.1 Listing of Individual Laboratory Measurements by Subject

Apart from efficacy laboratory parameters, urine pregnancy test for females was performed at screening visit. Results of pregnancy test performed are presented in **Appendix 16.2.8**.

12.4.2 Evaluation of Each Laboratory Parameter

No pregnancy case was reported during the study.

12.4.2.1 Laboratory Values over Time

Not applicable

12.4.2.2 Individual Subject Changes

Not applicable

12.4.2.3 Individual Clinically Significant Abnormalities

No clinically significant laboratory abnormalities observed during the study.

12.5 Vital Signs, Physical Findings and Other Observations Related to Safety

Physical examination and vital signs measurement were performed on each visit. All the values were evaluated for the clinical significance by Investigator or physician. Vital sign was evaluated as safety parameter. All the values were within clinically acceptable limits.

No clinically significant finding during the physical examination was observed during the study. Listing of physical examination assessment is presented in **Appendix 16.2.9**.

12.6 Safety Conclusion

Extent of exposure: Test product or placebo was consumed orally daily by all the subjects for 30 days. Overall compliance of study treatment was same in both the groups around 87-93%. None of the subject required extra dose or reported overdose.

Adverse events:

Brief summary of TEAEs: No SAE was reported during the study. A total of 02 AEs were reported in 02 subjects during screening. None of the AE was reported after randomization so none was referred as TEAE.

Physical examination and other observation related to safety: Based on an assessment of the extent of exposure, AEs, physical examination, safety profile of test product is comparable with that of placebo.

13 DISCUSSION AND OVERALL CONCLUSION

13.1 Discussion

In this study the effect of natural phytochemical formulation Rephyll® on muscle fatigue, endurance energy supply, recovery and neuro muscular activation in delayed onset muscle soreness (DOMS), and related inflammation and stress was measured in healthy untrained subjects.

DOMS is classified as a type I muscle strain injury and presents with tenderness or stiffness to palpation and/or movement. DOMS is usually associated with unfamiliar, high-force muscular work and is precipitated by eccentric actions. DOMS have induced muscle soreness using exercise protocols consisting of predominantly eccentric activity, i.e. downhill running, resisted cycling, ballistic stretching, isokinetic dynamometry, stepping and/or eccentric resistance exercise.[2] To generate DOMS in untrained healthy subject, the present study was designed with eccentric exercise for lower limb muscles.

In present study a total of 110 healthy untrained subjects of both genders were randomized; out of which 105 subjects completed the study. Healthy subjects with less active and performing regular exercise for less than 4 hours per week were considered as untrained subjects. Average age group was 22-50 years. All randomized subjects performed eccentric exercises.

In earlier human studies, supplementation of either vitamin E or C seems ineffective at influencing DOMS. NSAID supplementation attenuates soreness but does not accelerate recovery of strength. Ingestion of mixtures of tocopherols, docosahexaenoate, and flavanoids (quercetin and hesperetin) has been reported to attenuate systemic markers of inflammation (CRP, IL-6 etc other biomarkers). Furthermore, ingestion of a combination of ascorbic acid, tocopherol, and selenium reduced oxidative stress after eccentric exercise. However, muscle strength was not measured in either study. Connolly et al. reported that supplementation with polyphenols from tart cherry juice accelerated strength recovery, but muscle damage, inflammation, or oxidative stress was not measured. No single study in humans has yet shown that ingestion of nutritional supplements accelerates recovery of muscle function while simultaneously reducing inflammation or muscle damage.

For neuro muscular activity, the subjects' responses were positive after 30 days of treatment with Rephyll®. The change from baseline to end of study was statistically significant for muscles such as Gastrocnemius and Adductor in Rephyll® group. For neuromuscular response evaluation, though the results were not statistically significant, there was improvement in neuro muscular response after 30 days of Rephyll® treatment as compared to placebo. The sEMG reported greater muscle

activation after eccentric exercises after 30 days of treatment with Rephyll®, however the differences were not statistically significant.

For evaluation of other parameters of neuro muscular activation, none of the subjects reported imbalance after exercise as per vestibular function tests in both Rephyll® and placebo group. Furthermore, time for standing with one leg also reported to be similar.

In this study, parameters to evaluate muscle fatigue showed significant improvement after 30 days of treatment with Rephyll®. There was statistically significant improvement in Fatigue Index and rating of perceived exertion confirming improvement in fatigue level after 30 days treatment with Rephyll®.

In a study conducted by Amalraj A, *et al* there were no significant changes in myoglobin levels in the Rephyll® group and the myoglobin levels gradually increased in the placebo group until the end of the study; whereas in this study clinical improvement was seen in myoglobin levels, lactic acid in blood. In this study, more number of subjects showed clinical improvement in Rephyll® group as compared to placebo group after 30 days of treatment. The subjects taking Rephyll® showed light or very less exertion during exercise after 30 days of treatment.

In our study, parameters to measure change in endurance energy supply and recovery showed significant improvement with Rephyll®. There was statistically significant response in RER and increased energy supply. The concentration of lactic acid remained low and less O2 was consumed after exercise after 30 days of treatment with Rephyll®. Jordan *et al.* administered an oral ATP supplement to humans and reported no differences in whole blood concentrations of ATP following acute or chronic supplementation. As per present study results, rise in plasma ATP level was observed after 30 days of treatment suggesting the effect of Rephyll® in terms of availability of ATP in plasma which is source of energy.

The majority of the prior studies confirmed that the nutritional supplements improved severe indications linked with DOMS due to their anti-inflammatory properties.[12,13,14,15,16] In this study there were more reduction in inflammatory markers such as Cortisol, CRP, IL-6, ESR, TNF-α after 30 days in subject consuming Rephyll® as compared to placebo group.

In study by Amalraj *et. al.*, the VAS scale score was significantly decreased after day 2 in the Rephyll® group, which suggests that the consumption of Rephyll® can reduce the DOMS induced by maximal voluntary contraction exercise. the pain VAS score was significantly reduced from 3.55 to 2.50 in the Rephyll®-treated subjects from baseline to the end of the study; whereas, the pain VAS score increased marginally from 3.25 to 3.75 in the placebo group, which was not

statistically significant.[6] Study by Rattanaseth N[1], reported that persons who took curcumin supplement before exercise have pain score of about 1 score lower than those who took placebo in and post exercise at 1, 2, 3 and 4 days.

Current study also observed statistically significant improvement in pain score between Rephyll® and placebo on day 4, day 15 and day 30. Moreover, within group analysis showed statistically significant reduction in pain score in subjects with Rephyll® group, but such reduction cannot be spotted in placebo group. This might be due to the cannabimimetic anti-inflammatory activity of the Rephyll® which can be achieved by better reabsorption of interstitial fluid and cells to the bloodstream, leading to reduction in edema; reducing the development of prostaglandins and involvement of other eicosanoids in the inflammatory response to damage. These mechanisms of decrease in inflammation could further reduce the pain.[6]

Serum creatine kinase (CK) activity mirrors the mechanical-muscular strain of the training since CK leak into the plasma from skeletal muscle fibers when they are damaged, including membrane damage and myofibrillar disruptions characterized by myofilament disorganization and loss of integrity. Here, the elevated CK activity determined appears to support the explanation that damaged muscle fibers were partially responsible for the decline in performance. Similar to the present results, various studies with team sport athletes reported increased CK concentrations following intensified training or competition periods.

This study has several strengths. In agreement with studies regarding pain management there is significant reduction in subjective pain score similarly as per previous study. After 30 days consumption of Rephyll® there is indeed beneficial effect in the DOMS after eccentric exercise. Similarly as pervious study it confirms its effect on maintaining blood parameters, lipid profiles and vital signs same as baseline.

Looking in to the safety profile of both the groups; it was noted that there was no treatment emergent adverse event reported in subjects receiving either Rephyll® group or placebo group. Total of 02 AEs were reported in the study at the time of screening only.

No SAE was reported during the study.

During telephonic visit, 1 month after completion of the study treatment helped to evaluate the subjects' safety status, in which subjects were asked for their health and well-being, which were reported to be healthy and good in health by all aspects. None of the subject reported with any adverse event during 1 month after completion of study treatment also none of the subject reported to had taken any concomitant medication. Their satisfactory level of the study drug was good.

Mean value of each vital sign (blood pressure, pulse, respiratory rate and oral body temperature) was comparable in the two treatment groups. Based on an assessment of the extent of exposure, adverse events, physical examination and vital sign measurements, acceptability of Rephyll® is comparable with placebo.

Thus, Rephyll® has the potential for inhibiting DOMS, as recommended by its effects on muscle fatigue, endurance energy supply and recovery and neuro muscular activation without any adverse effects in DOMS in healthy untrained subjects. Rephyll® is recommended for muscle strengthening, energy endurance and recovery from inflammation due to DOMS.

13.2 Conclusion

Overall conclusion is Rephyll® shows beneficial effect after 30 days of treatment as compared to placebo. There are no safety issues reported during study treatment period and also after 30 days of study follow up period.

It can be concluded that Rephyll® is superior to placebo. Remarkably, during routine exercise of athletes or healthy subjects, the muscle fatigue will be decreased, there will be endurance in energy supply, subjective pain score will be low and in DOMS and related inflammation and stress will be reduced. As a result, subject's muscle activation and energy supply will be increased and no inflammation or stress will be observed.

Rephyll® was found to be well tolerated in subjects. Rephyll® was effective in reducing manifestations related to DOMS and improving recovery without any side effects.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data

Refer Table 11.2.1 and **Appendix 16.2.4**.

14.2 Efficacy Data

Refer **Appendix 16.2.6** for the all analysis data.

14.3 Safety Data

Refer **Appendix 16.2.9**.

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

No deaths or other serious adverse events occurred in this study.

14.3.3 Narratives of Deaths, Other serious and Certain Other Significant Adverse Events

No deaths or other serious adverse events occurred in this study.

14.3.4 Abnormal Laboratory Value Listing (each subject)

Not applicable

15 REFERENCE LIST

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16.0 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

16.1.2 Sample Case Report Form (include subject diary)

16.1.3 List of IECs or IRBs (plus the name of the committee chair), Ethics Committee Approval Letters, Sample Informed Consent Form and Sample Assent Form

16.1.4 List and description of Investigators and other important participant in the study, including brief CVs of the investigators.

16.1.5 Signatures of principal or coordinating investigator(s)

16.1.6 Listings of Subjects Receiving Test Drug(s) / Investigational Product(s) from Specific Batches where more than one batch was used

16.1.7 Randomisation Scheme (Subject identification and Treatment assigned)

16.1.8 Audit Certificates

16.1.9 Documentation of Statistical Methods

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used

16.1.11 Publications based on the study

16.1.12 Important Publications referenced in the report

16.2 Subject Data Listings

16.2.1 Subject Disposition

16.2.2 Protocol Deviations

16.2.3 Subjects Excluded from the Efficacy Analysis

16.2.4 Demographic Data and Baseline Characteristics

Listing Number	Listing Title	Population
16.2.4.1	Demographic data	All subjects
16.2.4.2	Medical History	All subjects
16.2.4.3	Concomitant Medication History	All subjects

16.2.5 Compliance and/or drug concentration data

16.2.6 Individual efficacy response data

16.2.7 Adverse event listings (each subject)

16.2.8 Listing of individual laboratory measurements by subjects

16.2.9 Other Safety Data

Listing Number	Listing Title	Population
16.2.9.1	List of Vital sign Measurement	All subjects
16.2.9.2	List of Physical Examination	All subjects