

Supplementary Table S1: Inclusion-exclusion criteria

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none">• Healthy and recreationally active males (Age: 40-70 years; BMI: 20-29 kg/m²) with serum Total testosterone \geq 300 ng/dL.• International index of erectile function (IIEF) score between 17 and 25. Sexual desire domain (Q.11 and Q.12) of IIEF score of $<$ 3 each.• Stable sexual relationship and sexually active.• Refrain from beginning any new energy-boosting, protein- or testosterone-boosting, or health-related therapies throughout the study and from taking vitamins, minerals, or herbal remedies for at least 15 days before the screening visit.• Agreed to maintain current diet and activity level and refrain from drinking coffee, caffeinated drinks, or beverages 24 hrs before the evaluation days.• Willing to follow an approved birth control measure if partner has childbearing potential.• Agreed to provide written informed consent.	<ul style="list-style-type: none">• Blood pressure $>$140/90 mmHg, fasting plasma glucose (FBG) $>$125 mg/dL and abnormal ECG.• Physical disability that may limit sexual function or erectile dysfunction.• Oligospermia or any other sexual problems• History of any major/genital surgeries, psychiatric, endocrine, and sleep-related disorders, dysfunctions related to the genito-urinary system, including benign prostate hyperplasia, muscular dystrophy & cardiovascular diseases,• Anabolic drugs, corticosteroids, PDE-5 inhibitors, and testosterone replacement therapy• Recreational drugs, alcohol ($>$ 3 standard drinks per week), and smokers ($>$ 3 cigarettes per day).• Participated in a clinical study within the last 30 days before recruitment or concurrently participating in another study.

Supplementary Table S2: Assessment of General health survey (GHS) scores

	Evaluation	Mean ± SD	P value (vs. baseline)	P value (vs. placebo)	95% CI (vs. Baseline)	95% CI (vs. placebo)	P value, change from baseline (vs. placebo)
<i>Libido</i>							
Placebo	Baseline	3.92 ± 1.039	-	-	-	-	-
	Day 14	3.85 ± 0.847	0.5922	-	-0.28, 0.42	-	-
	Day 42	3.95 ± 0.797	0.6717	-	-0.31, 0.37	-	-
	Day 84	3.92 ± 0.896	0.9611	-	-0.35, 0.35	-	-
LN18178	Baseline	3.74 ± 0.856		0.3158	-	-0.17, 0.53	-
	Day 14	4.33 ± 1.139	< 0.0001	< 0.0001	0.22, 0.96	0.11, 0.85	< 0.0001
	Day 42	4.98 ± 1.142	< 0.0001	< 0.0001	0.87, 1.61	0.67, 1.39	< 0.0001
	Day 84	5.53 ± 1.571	< 0.0001	< 0.0001	1.32, 2.26	1.14, 2.08	< 0.0001
<i>Muscle mass</i>							
Placebo	Baseline	3.85 ± 0.943	-	-	-	-	-
	Day 14	3.80 ± 0.886	0.6326	-	-0.28, 0.38	-	-
	Day 42	3.95 ± 0.818	0.3618	-	-0.22, 0.42	-	-
	Day 84	4.03 ± 0.850	0.1706	-	-0.15, 0.51	-	-
LN18178	Baseline	3.61 ± 0.901		0.1760	-	-0.10, 0.58	-
	Day 14	4.16 ± 0.841	< 0.0001	< 0.0001	0.23, 0.87	0.04, 0.68	< 0.0001
	Day 42	4.81 ± 1.109	< 0.0001	< 0.0001	0.83, 1.58	0.50, 1.22	< 0.0001
	Day 84	5.39 ± 1.532	< 0.0001	< 0.0001	1.31, 2.25	0.91, 1.81	< 0.0001
<i>Muscle strength</i>							
Placebo	Baseline	3.76 ± 1.023	-	-	-	-	-
	Day 14	3.83 ± 0.769	0.4765	-	-0.26, 0.40	-	-
	Day 42	3.90 ± 0.712	0.4090	-	-0.18, 0.46	-	-
	Day 84	4.05 ± 0.918	0.0221	-	-0.06, 0.64	-	-
LN18178	Baseline	3.77 ± 0.866		0.9584	-	0.31, 1.05	-
	Day 14	4.44 ± 1.000	< 0.0001	< 0.0001	0.32, 1.02	0.28, 0.94	< 0.0001
	Day 42	5.02 ± 1.142	< 0.0001	< 0.0001	0.87, 1.63	0.77, 1.47	< 0.0001
	Day 84	5.72 ± 1.612	< 0.0001	< 0.0001	1.47, 2.43	1.19, 2.15	< 0.0001
<i>Energy</i>							
Placebo	Baseline	4.20 ± 0.924	-	-	-	-	-
	Day 14	4.22 ± 0.832	0.9528	-	-0.30, 0.34	-	-
	Day 42	4.07 ± 0.848	0.3603	-	-0.19, 0.45	-	-
	Day 84	4.27 ± 0.887	0.7083	-	-0.26, 0.40	-	-
LN18178	Baseline	3.74 ± 0.791		0.0043	-	0.14, 0.78	-
	Day 14	4.39 ± 0.774	< 0.0001	0.0018	0.36, 0.94	-0.13, 0.47	< 0.0001
	Day 42	4.95 ± 1.109	< 0.0001	< 0.0001	0.85, 1.57	0.52, 1.24	< 0.0001
	Day 84	5.77 ± 1.402	< 0.0001	< 0.0001	1.61, 2.45	1.07, 1.93	< 0.0001
<i>Stamina</i>							
Placebo	Baseline	3.75 ± 1.044	-	-	-	-	-
	Day 14	3.81 ± 0.819	0.4765	-	-0.28, 0.40	-	-
	Day 42	3.88 ± 0.697	0.3263	-	-0.19, 0.45	-	-
	Day 84	4.14 ± 0.918	0.0066	-	0.03, 0.75	-	-
LN18178	Baseline	3.54 ± 0.803		0.2466	-	-0.13, 0.55	-
	Day 14	4.11 ± 0.838	< 0.0001	0.0004	0.27, 0.87	-0.005, 0.60	0.0004
	Day 42	4.93 ± 1.067	< 0.0001	< 0.0001	1.04, 1.74	0.72, 1.38	< 0.0001
	Day 84	5.51 ± 1.594	< 0.0001	< 0.0001	1.50, 2.44	0.89, 1.85	< 0.0001
<i>Sleep</i>							
Placebo	Baseline	3.69 ± 0.987	-	-	-	-	-

	Day 14	4.02 ± 0.881	0.0042	-	-0.01, 0.67	-	-
	Day 42	4.32 ± 0.973	0.0004	-	0.27, 0.99	-	-
	Day 84	4.53 ± 1.056	< 0.0001	-	0.47, 1.21	-	-
LN18178	Baseline	3.70 ± 0.823		0.9678	-	-0.32, 0.34	-
	Day 14	4.54 ± 0.908	< 0.0001	0.0005	0.52, 1.16	0.19, 0.85	0.0011
	Day 42	5.37 ± 0.938	< 0.0001	< 0.0001	1.34, 2.00	0.70, 1.40	< 0.0001
	Day 84	6.30 ± 1.133	< 0.0001	< 0.0001	2.23, 2.97	1.37, 2.17	< 0.0001
<i>Total GHS score</i>							
Placebo	Baseline	23.17 ± 3.649	-	-	-	-	-
	Day 14	23.53 ± 2.812	0.2248	-	-0.83, 1.55	-	-
	Day 42	24.07 ± 3.090	0.1220	-	-0.33, 2.13	-	-
	Day 84	24.93 ± 3.908	0.0005	-	0.38, 3.14	-	-
LN18178	Baseline	22.11 ± 2.920		0.9678	-	-0.16, 2.28	-
	Day 14	25.96 ± 3.756	< 0.0001	< 0.0001	2.60, 5.10	1.21, 3.65	< 0.0001
	Day 42	30.05 ± 4.454	< 0.0001	< 0.0001	6.54, 9.34	4.57, 7.39	< 0.0001
	Day 84	34.21 ± 7.837	< 0.0001	< 0.0001	9.91, 14.29	7.01, 11.55	< 0.0001

Values present mean ± SD. placebo (n=59) and LN18178 (n=57). CI: Confidence interval; P < 0.05 was considered as statistically significant for 'within the group' and 'between the groups' comparison analysis using paired t-test and ANCOVA, respectively, as described in materials and methods

Supplementary Table S3: Adverse events

Group	Adverse events	Severity
Placebo (n=59)	Bloating (1)	Mild
	Abdominal pain (1)	Mild
LN18178 (n=57)	Vomiting (1)	Mild
	Nausea (1)	Mild
	Headache (1)	Mild

Supplementary Table S4: Safety parameters

Parameters	Group	n	Mean ± SD	Change from baseline (Mean ± SD)	P value (vs. baseline)	P value (vs. placebo)
Hematology						
<i>Hemoglobin (g/dL)</i>						
Baseline	Placebo	60	14.66 ± 0.94	-		
	LN18178	60	14.38 ± 0.87	-		0.0955
Day 84	Placebo	59	14.55 ± 0.69	-0.09 ± 1.06	0.5112	
	LN18178	57	14.46 ± 0.67	0.06 ± 1.07	0.6937	0.4626
<i>Platelet count (10⁵/μL)</i>						
Baseline	Placebo	60	253.05 ± 56.99	-		
	LN18178	60	255.05 ± 66.20	-		0.8595
Day 84	Placebo	59	248.81 ± 52.51	-2.42 ± 73.17	0.8001	
	LN18178	57	254.67 ± 40.26	0.26 ± 70.48	0.9776	0.5029
<i>Red blood cells (10⁶/mm³)</i>						
Baseline	Placebo	60	4.97 ± 0.30	-		
	LN18178	60	4.90 ± 0.30	-		0.2505
Day 84	Placebo	59	4.99 ± 0.23	0.02 ± 0.32	0.5733	
	LN18178	57	5.06 ± 0.30	0.15 ± 0.34	0.0013	0.113
<i>Erythrocyte sedimentation rate (mm/hr)</i>						
Baseline	Placebo	60	6.08 ± 2.08	-		
	LN18178	60	6.10 ± 2.16	-		0.9657
Day 84	Placebo	59	6.51 ± 1.82	0.39 ± 2.41	0.2198	
	LN18178	57	6.10 ± 2.16	0.19 ± 2.79	0.6032	0.7354
<i>Hematocrit (%)</i>						
Baseline	Placebo	60	44.92 ± 2.89			
	LN18178	60	45.07 ± 2.40			0.76
Day 84	Placebo	59	45.08 ± 2.58	0.22 ± 3.47	0.6326	
	LN18178	57	45.58 ± 2.61	0.55 ± 2.88	0.1538	0.3032
<i>Total white blood cells count (10³/μL)</i>						
Baseline	Placebo	60	7.08 ± 1.43	-		
	LN18178	60	7.27 ± 1.51	-		0.4797
Day 84	Placebo	59	7.81 ± 1.21	0.70 ± 1.48	0.0006	
	LN18178	57	8.08 ± 1.17	0.82 ± 1.65	0.0004	0.2297
<i>Neutrophils (%)</i>						
Baseline	Placebo	60	60.33 ± 6.01	-		
	LN18178	60	61.97 ± 6.18	-		0.1447
Day 84	Placebo	59	63.61 ± 6.02	3.22 ± 6.82	0.0006	
	LN18178	57	64.11 ± 5.74	1.89 ± 6.58	0.034	0.6515
<i>Lymphocytes (%)</i>						
Baseline	Placebo	60	30.18 ± 4.82	-		
	LN18178	60	29.25 ± 4.91	-		0.2958
Day 84	Placebo	59	28.14 ± 5.12	-2.08 ± 6.02	0.0100	
	LN18178	57	27.74 ± 5.03	-1.33 ± 5.72	0.0841	0.6731
<i>Eosinophils (%)</i>						
Baseline	Placebo	60	2.90 ± 1.31	-		
	LN18178	60	2.40 ± 1.06	-		0.0234
Day 84	Placebo	59	2.78 ± 1.04	-0.07 ± 1.65	0.7533	
	LN18178	57	2.61 ± 1.13	0.28 ± 1.53	0.1722	0.4119
<i>Monocytes (%)</i>						
Baseline	Placebo	60	6.58 ± 1.88	-		0.4912

	LN18178	60	6.35 ± 1.82	-		
Day 84	Placebo	59	5.47 ± 1.51	-1.07 ± 2.10	0.0002	
	LN18178	57	5.54 ± 1.64	-0.81 ± 2.08	0.0050	0.8132
<i>Basophils (%)</i>						
Baseline	Placebo	60	0.00 ± 0.00	-		1.000
	LN18178	60	0.00 ± 0.00	-		
Day 84	Placebo	59	0.00 ± 0.00	0.00 ± 0.00	1.000	1.000
	LN18178	57	0.00 ± 0.00	0.00 ± 0.00	1.000	
Blood biochemistry						
<i>Fasting Blood Glucose (mg/dL)</i>						
Baseline	Placebo	60	87.65 ± 6.16	-		0.9672
	LN18178	60	87.60 ± 7.08	-		
Day 84	Placebo	59	89.71 ± 5.49	1.90 ± 7.96	0.0722	0.3156
	LN18178	57	88.75 ± 4.69	1.07 ± 7.36	0.2770	
<i>Creatinine (mg/dL)</i>						
Baseline	Placebo	60	0.92 ± 0.12	-		0.7239
	LN18178	60	0.92 ± 0.13	-		
Day 84	Placebo	59	0.90 ± 0.11	-0.01 ± 0.16	0.5294	0.5290
	LN18178	57	0.92 ± 0.16	0.00 ± 0.20	0.9217	
<i>Blood urea nitrogen (mg/dL)</i>						
Baseline	Placebo	60	15.51 ± 3.29	-		0.6600
	LN18178	60	15.75 ± 2.63	-		
Day 84	Placebo	59	16.32 ± 2.10	0.80 ± 3.37	0.0724	0.2580
	LN18178	57	15.84 ± 2.49	0.19 ± 2.99	0.6283	
<i>Uric Acid (mg/dL)</i>						
Baseline	Placebo	60	5.72 ± 0.82	-		0.3248
	LN18178	60	5.57 ± 0.81	-		
Day 84	Placebo	59	5.69 ± 0.79	0.00 ± 0.97	0.9787	0.0416
	LN18178	57	5.98 ± 0.70	0.44 ± 1.03	0.0023	
<i>Sodium (mmol/L)</i>						
Baseline	Placebo	60	139.87 ± 2.30	-		0.8761
	LN18178	60	139.93 ± 2.38	-		
Day 84	Placebo	59	140.07 ± 2.26	0.19 ± 3.23	0.6596	0.3129
	LN18178	57	140.47 ± 2.05	0.58 ± 3.15	0.1708	
<i>Potassium (mmol/L)</i>						
Baseline	Placebo	60	4.66 ± 0.32	-		0.4258
	LN18178	60	4.70 ± 0.34	-		
Day 84	Placebo	59	4.51 ± 0.43	-0.14 ± 0.43	0.0138	0.9413
	LN18178	57	4.52 ± 0.39	-0.20 ± 0.43	0.0012	
<i>Alkaline Phosphate (IU/L)</i>						
Baseline	Placebo	60	90.57 ± 21.79	-		0.9898
	LN18178	60	90.62 ± 21.08	-		
Day 84	Placebo	59	92.53 ± 20.38	1.20 ± 16.10	0.5681	0.8260
	LN18178	57	93.37 ± 20.82	2.51 ± 10.83	0.0858	
<i>Aspartate transaminase (U/L)</i>						
Baseline	Placebo	60	22.87 ± 5.52	-		0.5675
	LN18178	60	22.28 ± 5.62	-		
Day 84	Placebo	59	23.95 ± 4.68	1.00 ± 6.21	0.2214	0.5145
	LN18178	57	24.51 ± 4.53	2.19 ± 6.85	0.0190	
<i>Alanine aminotransferase (U/L)</i>						
Baseline	Placebo	60	30.78 ± 8.23	-		0.1682

	LN18178	60	28.80 ± 7.42	-		
Day 84	Placebo	59	34.19 ± 7.79	3.34 ± 9.32	0.0079	0.8501
	LN18178	57	33.88 ± 9.72	33.88 ± 9.72	0.0001	
<i>Bilirubin (mg/dL)</i>						
Baseline	Placebo	60	0.63 ± 0.21	-		0.6104
	LN18178	60	0.61 ± 0.19	-		
Day 84	Placebo	59	0.68 ± 0.20	0.05 ± 0.31	0.2552	0.6602
	LN18178	57	0.66 ± 0.21	0.04 ± 0.29	0.3246	
<i>Albumin (gm/dL)</i>						
Baseline	Placebo	60	4.39 ± 0.31	-		0.3020
	LN18178	60	4.33 ± 0.31	-		
Day 84	Placebo	59	4.33 ± 0.36	-0.06 ± 0.51	0.4066	0.2805
	LN18178	57	4.33 ± 0.31	-0.07 ± 0.48	0.2641	
<i>Low-density lipoprotein (mg/dL)</i>						
Baseline	Placebo	60	75.22 ± 17.62	-		0.1514
	LN18178	60	79.57 ± 15.25	-		
Day 84	Placebo	59	83.48 ± 10.80	7.93 ± 19.10	0.0023	0.6105
	LN18178	57	84.49 ± 10.59	5.28 ± 17.22	0.0244	
<i>High-density lipoprotein (mg/dL)</i>						
Baseline	Placebo	60	46.45 ± 5.41	-		0.0683
	LN18178	60	48.41 ± 6.21	-		
Day 84	Placebo	59	48.33 ± 6.14	1.77 ± 7.01	0.0566	0.2507
	LN18178	57	49.67 ± 6.37	1.80 ± 8.57	0.1182	
<i>Very-low-density lipoprotein (mg/dL)</i>						
Baseline	Placebo	60	22.66 ± 5.84	-		0.8283
	LN18178	60	22.43 ± 5.59	-		
Day 84	Placebo	59	24.40 ± 3.45	1.83 ± 6.53	0.0351	0.8762
	LN18178	57	24.29 ± 3.92	1.96 ± 5.98	0.0163	
<i>Triglycerides (mg/dL)</i>						
Baseline	Placebo	60	120.66 ± 19.09	-		0.3658
	LN18178	60	123.76 ± 18.31	-		
Day 84	Placebo	59	129.01 ± 14.77	8.64 ± 18.81	0.0008	0.3890
	LN18178	57	131.25 ± 13.10	8.30 ± 16.92	0.0005	
<i>Total cholesterol (mg/dL)</i>						
Baseline	Placebo	60	144.33 ± 18.62	-		0.0743
	LN18178	60	150.41 ± 18.33	-		
Day 84	Placebo	59	156.22 ± 13.62	11.55 ± 23.17	0.0003	0.3624
	LN18178	57	158.46 ± 12.76	9.04 ± 20.99	0.002	
<i>Creatine Kinase (U/L)</i>						
Baseline	Placebo	60	81.60 ± 11.44	-	-	0.8981
	LN18178	60	81.33 ± 11.31	-	-	
Day 84	Placebo	59	82.19 ± 9.97	-0.59 ± 1.47	0.5499	< 0.0001
	LN18178	57	74.07 ± 9.07	7.26 ± 2.24	< 0.0001	

Values present mean ± SD. P < 0.05 was considered as statistically significant for 'within the group' and 'between the groups' comparison analysis using paired t-test and ANCOVA, respectively.