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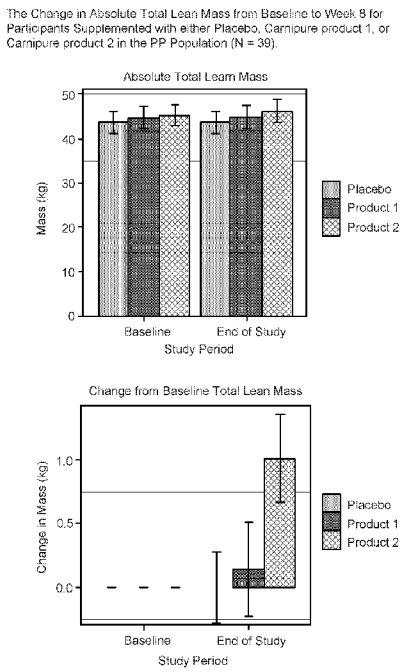

FIG. 1

(57) Abstract: A method and composition suitable for preserving muscle mass and function by increasing muscle protein synthesis and/or decreasing muscle protein degradation in mammals is disclosed. In one embodiment, the mammals are administered a protein building composition comprising at least two of an essential amino acid, an amino acid derivative, and a nitrogenous organic acid. In a particular embodiment, the protein building composition comprises leucine, L-carnitine, and creatine. The protein building composition can decrease TNF-a and increase mTOR expression in muscle. A pharmaceutical composition and its production method are also disclosed.

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METHOD AND COMPOSITION FOR INCREASING MUSCLE PROTEIN SYNTHESIS AND/OR FUNCTIONAL STRENGTH IN MAMMALS AS WELL AS METHOD OF PRODUCING A COMPOSITION

RELATED APPLICATIONS

[0001] The present application is based on and claims priority to U.S. Provisional Patent application Serial No. 62/273,880, filed on December 31, 2015, and U.S. Provisional Patent application Serial No. 62/269,573, filed on December 18, 2015, both of which are incorporated herein by reference.

BACKGROUND

[0002] Many mammals may experience functional deterioration as they enter mid to late adulthood. Functional deterioration relates to a decline in the ability to carry out basic functional activities such as eating and walking. Compromised motor function can, in turn, lead to loss of independence and a decreased quality of life.

[0003] A major contributor to functional deterioration in both sedentary and physically active mammals is sarcopenia, an age-related condition characterized by a gradual decline in muscle mass, strength, and function. In sarcopenia, the body experiences a global shift from muscle protein synthesis to muscle degradation.

[0004] Proteinogenic amino acid molecules can be categorized as essential and non-essential amino acids. Non-essential amino acids, which can be synthesized in the body, include alanine, asparagine, aspartic acid, glutamic acid, arginine, cysteine, glutamine, tyrosine, glycine, proline, and serine. Essential amino acids, such as histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine, cannot be biosynthesized and instead must be consumed via food or supplementation. In muscle protein synthesis, the availability of essential amino acids is rate-limiting. Therefore, supplementation of essential amino acids can potentiate protein synthesis. Muscle protein synthesis is activated by the mammalian target of rapamycin (mTOR) pathway. The mTOR pathway senses and responds to changes in amino acids and growth factors such as insulin-like growth factor (IGF-1). In particular, the mTOR complex phosphorylates ribosomal protein S6K, which in turn phosphorylates ribosomal protein S6 and substrates eIF4B and 4EBP1, consequently promoting mRNA translation

and protein synthesis. The proteins involved in the mTOR pathway can serve as biomarkers for protein synthesis.

[0005] The NFκβ (p65/p50) pro-inflammatory signaling pathway has also been implicated in regulating muscle functionality. NFκβ protein levels are strongly upregulated in muscle atrophy, while inhibition of the NFκβ (p65/p50) pathway can prevent muscle degradation.

[0006] The ubiquitin-proteasome system (UPS) can facilitate muscle degradation, breaking down muscle proteins into peptides and then free amino acids. In the UPS-pathway, target muscle proteins are tagged with a degradation signal and then degraded into peptides by the 26s proteasome. The UPS-pathway can be mediated by atrogin-1 and MuRF-1, two E3 ubiquitin-protein ligases, and by cytokines such as interleukin (IL)-6, IL-8, and tumor necrosis factor (TNF)-α, which produce pro-inflammatory signals. These factors can serve as biomarkers for muscle protein degradation. Protein degradation and functional deterioration may be amplified in mammals with sarcopenia and in older mammals with sedentary lifestyles. Muscle protein building requires both new protein synthesis and prevention of protein degradation. While physical activity, even in light or moderate amounts, can lead to muscle hypertrophy and increased functionality, muscle disuse results in a decrease in protein synthesis and an increase in muscle breakdown. In addition, mTOR activation can be delayed in older adults, leading to decreased protein synthesis. Furthermore, extended periods of inactivity can lead to a decreased protein synthetic response to amino acid supplementation. Sarcopenia-related functional deterioration can be a reinforcing loop, as muscle loss and decreased functionality can interfere with physical activity. In turn, decreased physical activity leads to further muscle loss and decreased functionality.

[0007] In the past, leucine and creatine have been administered to mammals in order to increase muscle mass and strength. In particular, many of the supplements administered to elderly mammals for increasing muscle protein synthesis comprise complicated and expensive mixtures of amino acids. For example, U.S. Patent No. 7,790,688, which is incorporated by reference herein, discloses compositions containing a complex blend of essential amino acids, creatine, and low-glycemic carbohydrates.

Further, it is well-known in the art that ingestion of 20 grams or more of essential amino acids is necessary for stimulation of muscle protein synthesis in the elderly. As protein intake increases, however, urea production can increase in some individuals.

[0008] Consequently, a need exists for a supplement that can increase muscle protein synthesis, lean mass, functional strength, and/or overall quality of life in mammals without having any substantial adverse effects on other body functions. A need also exists for a simpler and less expensive supplement that can improve muscle mass and/or functional strength leading to increase in physical activity in elderly mammals and mammals with sarcopenia.

SUMMARY

[0009] The present disclosure is generally directed to a method and composition for increasing protein synthesis and/or functional strength in mammals. The present disclosure is also directed to a method and composition for slowing down or delaying muscle wasting or sarcopenia in sedentary and physically active mammals.

[0010] In accordance with the present disclosure, the method comprises the step of administering to a mammal an effective amount of a protein building composition. Of particular advantage, the protein building composition can increase muscle protein synthesis, lean mass, functional strength, physical activity, and/or overall quality of life in mammals without having any substantial adverse effects on other body functions.

[0011] The protein building composition may comprise a supplement, a food product, or a beverage. For instance, the protein building composition can be incorporated into milkshake drinks, juices, cereal bars, vitamins including gummy vitamins, powders, foods or may be in the form of a supplement.

[0012] In one embodiment, the protein building composition may be administered to a mammal that has an age of more than 50% of its expected life span. In an alternate embodiment, the protein building composition may be administered to a mammal that has an age of less than 50% of its expected life span. The mammal may regularly participate in physical activity. In another embodiment, the mammal may participate mainly or exclusively in sedentary behavior. In a particular embodiment, the mammal is a human.

[0013] In one embodiment, the protein building composition may comprise at least two of any essential amino acid components, amino acid derivatives, and/or nitrogenous organic acids, such as creatine. The essential amino acid component may comprise leucine and derivatives and/or salts thereof. The amino acid derivative may comprise carnitine and derivatives and/or salts thereof. In one embodiment, the protein building composition comprises an amino acid derivative combined with an amino acid component. In an alternative embodiment, the protein building composition may comprise an amino acid derivative combined with a nitrogenous organic acid. In still another embodiment, the protein building composition may comprise a mixture of an amino acid derivative, an amino acid component, and a nitrogenous organic acid.

[0014] In one embodiment, the amino acid derivative comprises L-carnitine. In a particular embodiment, the amino acid derivative comprises L-carnitine L-tartrate. In a further embodiment, the protein building composition may contain a nitrogenous organic acid and derivatives and/or salts thereof. In one embodiment, the protein building composition may comprise creatine and derivatives and/or salts thereof.

[0015] In one embodiment, leucine and salts, metabolites, and/or derivatives thereof may be present in the amino acid component at a concentration greater than about 5% by mass. In one embodiment, a metabolite of leucine, such as β-Hydroxy β-methylbutyric acid (HMB), may be present in the amino acid component. In one embodiment, leucine is present in a concentration of about 10% to 90% by mass, such as about 20% to 80% by mass, such as about 30% to 70% by mass. In a preferred embodiment, leucine is present in a concentration of about 35 to 65% by mass.

[0016] In one embodiment, L-carnitine may be present in the amino acid component at a concentration greater than about 5% by mass. L-carnitine may be present in a substantially pure crystalline form or as salts, metabolites, and/or lipid and non-lipid derivatives of L-carnitine. In one embodiment, L-carnitine is present in a concentration of about 10% to 90% by mass, such as about 20% to 80% by mass, such as about 25% to 75% by mass, such as about 30% to 60% by mass. In a preferred embodiment, L-carnitine is present in a concentration of about 40% to 70% by mass.

[0017] In one embodiment, creatine and salts, metabolites, and/or derivatives thereof may be present in the supplement composition at a concentration of greater than about

0.5% by mass, such as greater than about 1% by mass, such as greater than about 5% by mass, such as greater than about 10% by mass, such as greater than about 20% by mass, such as greater than about 40% by mass, such as greater than about 60% by mass, such as greater than about 80% by mass, such as greater than about 90% by mass, such as greater than about 99% by mass. In a preferred embodiment, creatine is present in the composition at a concentration of about 30% to about 45% by mass. In one embodiment, creatine may comprise creatine monohydrate and chelated creatine, such as magnesium-chelated creatine and other metal-chelated creatine. The protein building composition can be administered to the mammal regularly or occasionally. For instance, the protein building composition can be administered to the mammal at least every one to three days, such as daily. In one embodiment, a daily portion may be taken in one or several servings. Each dose may be from about 5 milligrams to about 30,000 milligrams, such as from about 5 milligrams to about 20,000 milligrams, such as from about 50 milligrams to about 10,000 milligrams. Each dose may be from about 1 milligram per kilogram body weight per day to about 10,000 milligrams per kilogram per day, such as from about 5 milligrams per kilogram per day to about 5,000 milligrams per kilogram per day. The protein building composition can be administered orally and can be combined with a food composition.

[0018] In one embodiment, the pharmaceutical composition of the present disclosure is combined with various additives and ingredients in order to improve various properties. For instance, the protein building composition of the present disclosure may be combined with a stabilizer package for reducing the hydroscopic properties of the composition. The stabilizer package can also make the composition easier to handle and/or pour, especially when the composition comprises a granular composition.

[0019] In one embodiment, for instance, the present disclosure is directed to a pharmaceutical composition comprising a protein building composition combined with a polymer binder and a stabilizer package. The stabilizer package may comprise oxide particles, such as silica, combined with a salt of a carboxylic acid. The salt of a carboxylic acid may comprise a salt of a fatty acid, such as a fatty acid having a carbon chain length of from about 6 carbon atoms to about 40 carbon atoms, such as from about 12 carbon atoms to about 28 carbon atoms. In one embodiment, the salt of the

carboxylic acid comprises a stearate salt, such as calcium stearate, sodium stearate, magnesium stearate, mixtures thereof, and the like. The polymer binder, on the other hand, may comprise a polysaccharide and/or a film-forming polymer. The polymer binder, for instance, may comprise starch such as a modified starch, maltodextrin, gum arabic, arabinogalactan, a gelatin, or mixtures thereof.

[0020] In one embodiment, the pharmaceutical composition may further contain a coating material. The coating material may comprise a fat. The coating material may form a continuous or a discontinuous coating over the pharmaceutical composition. In one embodiment, the coating material comprises a hydrogenated palm oil combined with palm stearine. For instance, the hydrogenated palm oil and palm stearine may be combined at a weight ratio of from about 10:1 to about 1:1, such as from about 5:1 to about 3:1.

[0021] The present disclosure is also directed to a method of producing a pharmaceutical composition containing the protein building composition. The method includes the steps of combining the protein building composition with a polymer binder and a stabilizer package. In one embodiment, for instance, the protein building composition is first combined with the polymer binder via a spray dry process and then combined with the stabilizer package which may comprise a dry mix (i.e. a powder or granular material). The method may further include the step of optionally applying a coating material to the mixture containing the protein building composition, the polymer binder, and the stabilizer package. The coating material may comprise a fat, such as a hydrogenated oil.

[0022] In one embodiment, the pharmaceutical composition contains the oxide particles, such as the silica particles, in an amount from about 0.01% to about 1.5% by weight, the salt of the carboxylic acid in an amount from about 0.5% to about 5% by weight and the polymer binder in an amount from about 8% to about 40% by weight. When present, the coating material may be contained in the polymer composition in an amount from about 5% to about 35% by weight.

[0023] Other features and aspects of the present disclosure are discussed in greater detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] A full and enabling disclosure of the present disclosure is set forth more particularly in the remainder of the specification, including reference to the accompanying figures, in which:

[0025] The Figures are graphical representations of the results obtained in the example described below.

DEFINITIONS

[0026] The term "MET," or "metabolic equivalent," means the ratio of the rate of energy expended during an activity to the rate of energy expended at rest. A body at rest has a rate of energy expenditure of 1 MET. If a body performs a 2 MET activity, the body has expended 2 times the energy used by the body at rest. The term "physical activity" means bodily movement with an energy expenditure rate equal to or greater than 3 MET. Non-limiting examples of "physical activity" include bicycling, sexual activity, giving birth, jogging, walking at a speed of about 3 mph or greater, calisthenics, jumping rope, running, sprinting, or any combinations thereof.

[0027] In one embodiment, "physical activity" can mean a negative energy balance in the mammal, such as weight loss, diets, aging, gestation, and lactation.

[0028] The term "physically active" means regularly participating in body movements with an energy expenditure rate of greater than or equal to 3 MET.

[0029] In one embodiment, "physically active" can mean regularly meeting medically recommended standards for amount, intensity, and type of physical activity performed by a mammal.

[0030] The terms "sedentary" or "sedentary activity" mean participating mainly or exclusively in body movements with an energy expenditure rate of less than 3 MET. Non-limiting examples of "sedentary" activities include sleeping, resting, sitting or reclining, watching television, writing, working at a desk, using a computer, typing, walking at a speed of less than about 3 mph, or any combinations thereof.

[0031] In one embodiment, "sedentary" can mean a failure to regularly meet medically recommended standards for amount, intensity, and type of physical activity performed by a mammal.

[0032] The term "L-carnitine" may contain L-carnitine and derivatives and/or salts thereof. L-carnitine can include L-carnitine base or derivatives and/or salts thereof including substantially pure crystalline L-carnitine, any fatty acid derivatives thereof, acetyl L-carnitine, valeryl L-carnitine, isovaleryl L-carnitine, benzyl L-carnitine, L-leucyl L-carnitine, L-valyl L-carnitine, other L-amino acyl carnitines, salts of L-amino acyl L-carnitine, L-carnitine HCL, L-carnitine L-tartrate, L-carnitine fumarate, propionyl L-carnitine, L-carnitine phosphate, acetyl L-carnitine L-aspartate, acetyl L-carnitine citrate, acetyl L-carnitine maleate, acetyl L-carnitine phosphate, acetyl L-carnitine fumarate, propionyl L-carnitine orotate, acetyl L-carnitine orotate, butyryl L-carnitine orotate, propionyl L-carnitine fumarate, L-carnitine oxalate, L-carnitine sulfate, GPLC glycine propionyl L-carnitine, and the like.

[0033] The term "mammal" includes any mammal that may experience skeletal muscle degradation or synthesis and includes human, canine, equine, feline, bovine, ovine, or porcine mammals.

[0034] The phrase "effective amount" means an amount of a compound that promotes, improves, stimulates, or encourages a response to the particular condition or disorder or the particular symptom of the condition or disorder.

[0035] The term "supplement" means a product in addition to the normal diet of the mammal but may be combined with a mammal's normal food or drink composition. The supplement may be in any form but not limited to a solid, liquid, gel, capsule, or powder. A supplement may also be administered simultaneously with or as a component of a food composition which may comprise a food product, a beverage, a pet food, a snack, or a treat. In one embodiment, the beverage may be an activity drink.

[0036] The term "functional strength" means an individual's ability to competently and safely perform daily life activities. In one embodiment, functional strength may be associated with energy, muscle potency, agility, flexibility, balance, and injury resistance.

DETAILED DESCRIPTION

[0037] It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only, and is not intended as limiting the broader aspects of the present disclosure.

[0038] The present disclosure is directed to a method and composition for increasing muscle protein synthesis and/or functional strength in mammals. As will be explained below, the present disclosure is generally directed to a protein building composition that when administered to a mammal in an effective amount preserves or increases muscle mass and function by increasing muscle protein synthesis and/or functional strength and/or decreasing protein degradation. The present disclosure is further generally directed to administering to a mammal an effective amount of a protein building composition that increases muscle protein synthesis and/or functional strength.

[0039] In one embodiment, the protein building composition comprises an amino acid derivative combined with at least one other component. For instance, the amino acid derivative may be combined with an amino acid, an organic acid, or both an amino acid and an organic acid. The amino acid derivate may comprise a carnitine, such as L-carnitine. The amino acid may comprise an essential amino acid. In one embodiment, the amino acid may comprise leucine. The protein building composition may further comprise an organic acid, such as a nitrogenous organic acid. The organic acid may comprise creatine.

[0040] The inventors of the present disclosure unexpectedly discovered that the components of the protein building composition disclosed herein synergistically work together to increase muscle protein synthesis and/or functional strength. Surprisingly, it was discovered that administering a protein building composition containing L-carnitine, combined with leucine, creatine, or both leucine and creatine to a mammal can increase muscle protein synthesis and/or functional strength while also preventing muscle degradation, decreasing inflammation, and improving upper and lower body strength. In one embodiment, the protein building composition may also contain vitamin D3. Of particular advantage, the above results can be achieved without administering the high dosage of amino acids required in previous compositions. In addition, the protein building composition of the present disclosure produces no noticeable side effects. For instance, administering the protein building composition regularly can be done without showing any clinically significant change in kidney function.

[0041] The protein building composition of the present disclosure can be a nutritional supplement in the form of a pill, tablet or capsule. Alternatively, the protein building

composition may be incorporated into a food or beverage. For instance, the protein building composition may be incorporated in to a milkshake drink, a juice, a cereal bar, a vitamin such as a gummy vitamin, or a powder. The powder can be mix with any suitable liquid for ingestion.

[0042] The amino acid derivative may be any suitable carnitine, such as L-carnitine and any derivatives and/or salts thereof. L-carnitine is a quaternary amine that can be biosynthesized from lysine and methionine. L-carnitine is known to promote beta-oxidation of long-chain fatty acids by facilitating their transfer across the mitochondrial membrane. L-carnitine may be present in a substantially pure crystalline form or as salts, metabolites, and/or lipid and non-lipid derivatives of L-carnitine.

[0043] In one embodiment, L-carnitine may be present in the composition at a concentration greater than about 5% by mass, such as greater than about 10% by mass, such as greater than about 15% by mass, such as greater than about 20% by mass, such as greater than about 25% by mass, such as greater than about 30% by mass, such as greater than about 35% by mass, such as greater than about 40% by mass, such as greater than about 45% by mass, such as greater than about 50% by mass, such as greater than about 55% by mass, such as greater than about 60% by mass, such as greater than about 65% by mass, such as greater than about 70% by mass, such as greater than about 75% by mass. In general, L-carnitine may be present in the composition at a concentration less than about 75% by mass, such as less than about 70% by mass, such as less than about 65% by mass, such as less than about 60% by mass, such as less than about 55% by mass, such as less than about 50% by mass, such as less than about 45% by mass, such as less than about 40% by mass, such as less than about 35% by mass, such as less than about 30% by mass, such as less than about 25% by mass, such as less than about 20% by mass, such as less than about 15% by mass, such as less than about 10% by mass.

[0044] As stated above, the composition may comprises an amino acid in combination with the amino acid derivate. The amino acid may be leucine and any derivatives, metabolites, and/or salts thereof. Leucine is a branched-chain α-amino acid. Leucine is known to stimulate protein synthesis via association with eukaryotic

initiation factors in translation. In one embodiment, the amino acid may comprise a metabolite of leucine, such as HMB.

[0045] In one embodiment, leucine may be present in the amino acid component at a concentration greater than about 10% by mass, such as greater than about 15% by mass, such as greater than about 20% by mass, such as greater than about 25% by mass, such as greater than about 30% by mass, such as greater than about 35% by mass, such as greater than about 40% by mass, such as greater than about 45% by mass, such as greater than about 50% by mass, such as greater than about 55% by mass, such as greater than about 60% by mass, such as greater than about 65% by mass, such as greater than about 70% by mass, such as greater than about 75% by mass. In general, leucine may be present in the amino acid component at a concentration less than about 75% by mass, such as less than about 70% by mass, such as less than about 65% by mass, such as less than about 60% by mass, such as less than about 55% by mass, such as less than about 50% by mass, such as less than about 45% by mass, such as less than about 40% by mass, such as less than about 35% by mass, such as less than about 30% by mass, such as less than about 25% by mass, such as less than about 20% by mass, such as less than about 15% by mass.

[0046] As described above, the protein building composition may comprise the amino acid derivative in combination with either an amino acid or an organic acid or may comprise an amino acid derivative in combination with both an amino acid or an organic acid. The organic acid may be creatine and derivatives and/or salts thereof. Creatine is a nitrogenous organic acid that can be biosynthesized from glycine and arginine. Creatine increases the formation of ATP and in a phosphorylated form serves as an energy reserve in skeletal muscles. Creatine can improve the physiological response to high-intensity and resistance exercise.

[0047] In one embodiment, the composition may include creatine and derivatives and analogs and/or salts thereof. In one embodiment, the composition may include creatine phosphate; creatine monohydrate; creatine ethyl ester; magnesium creatine chelate; creatine HCL; creatine-MG-complex (acetate); phosphocreatine-Mg-complex (acetate); creatine sugar amides and salts thereof as described in U.S. Patent No.

8,546,369, incorporated by reference herein; (Boc)2-creatine and derivatives thereof as described in PCT Publication WO 2014/097335, incorporated by reference herein; other derivatives and salts of creatine; and any combinations thereof.

[0048] In one embodiment, creatine may be present in the amino acid component at a concentration greater than about 15% by mass, such as greater than about 20% by mass, such as greater than about 25% by mass, such as greater than about 30% by mass, such as greater than about 35% by mass, such as greater than about 40% by mass, such as greater than about 45% by mass, such as greater than about 50% by mass, such as greater than about 55% by mass, such as greater than about 60% by mass, such as greater than about 65% by mass, such as greater than about 70% by mass, such as greater than about 75% by mass, such as greater than about 80% by mass. In general, creatine may be present in the amino acid component at a concentration less than about 80% by mass, such as less than about 75% by mass, such as less than about 70% by mass, such as less than about 65% by mass, such as less than about 60% by mass, such as less than about 55% by mass, such as less than about 50% by mass, such as less than about 45% by mass, such as less than about 40% by mass, such as less than about 35% by mass, such as less than about 30% by mass, such as less than about 25% by mass, such as less than about 20% by mass, such as less than about 15% by mass, such as less than about 10% by mass.

[0049] In one embodiment, the composition may comprise one or more vitamins. In one particular embodiment, the composition may comprise vitamin D3. Vitamin D can regulate muscle contractility. Other vitamins may include but are not limited to vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B9, vitamin B12, vitamin C, vitamin E, vitamin K, riboflavin, niacin, folic acid, pyridoxine, thiamine, pantothenic acid, biotin, and any combinations thereof. The composition may further comprise other minerals, herbs, botanicals, and essential fatty acids. In one embodiment, the protein building composition may comprise magnesium and/or salts thereof.

[0050] In one embodiment, the one or more vitamins may be present in the composition in an amount of about 1 to about 5,000 IU per dose, such as about 10 to about 2,500 IU per dose, such as about 50 to about 1,500 IU per dose, such as about

100 IU to about 1,000 IU per dose, such as about 250 IU to about 750 IU per dose, such as about 300 IU to about 600 IU per dose.

[0051] In one embodiment, the amino acids, amino acid derivatives, and/or organic acids and derivatives and/or salts thereof may be included in the composition as free form organic compounds. Alternately, the components may be included in the composition as intact proteins and/or other macromolecules. In a further embodiment, the amino acids, amino acid derivatives, and/or organic acids and derivatives and/or salts thereof may be included in the composition as a combination of free form organic compounds and intact protein and/or other macromolecules.

[0052] The different components can be present in the protein building composition at various ratios depending upon the particular application and the desired result. The weight ratio between the amino acid derivative and the amino acid, for instance, can generally be from about 1:10 to about 10:1, such as from about 1:3 to about 3:1. In one embodiment, the weight ratio between the amino acid derivative and the amino acid may be from about 1:1 to about 1:2.

[0053] The weight ratio between the amino acid derivative and the organic acid, on the other hand, can generally be from about 1:10 to about 5:1, such as from about 1:1 to about 1:5, such as from about 1:1 to about 1:3. In one particular embodiment, the protein building composition contains the amino acid derivative combined with the amino acid and the organic acid. The weight ratio between the amino acid derivative and the amino acid can be about 3:4, while the weight ratio between the amino derivative and the organic acid can be about 1:2.

[0054] The present disclosure is also directed to methods of administering the protein building composition disclosed herein. L-carnitine in combination with leucine and creatine has been discovered to increase protein synthesis and/or functional strength in mammals. In order to increase muscle protein synthesis and/or functional strength, the present disclosure is directed to a method of administering to a mammal an effective amount of a protein building composition. The above advantages and benefits may be realized without any adverse consequences. In addition, in one embodiment, the mammal may experience no clinically substantial difference in kidney function.

[0055] In one embodiment, a mammal is administered an effective amount of an protein building composition containing an amino acid component. The amino acid component may comprise leucine. Leucine may be administered in a dosage from about 5 to 10,000 milligrams per day, such as from about 5 to about 5,000 milligrams per day, such as from about 50 milligrams to about 3,000 milligrams per day. The dosage, for instance, can be greater than about 100 milligrams per day, such as greater than about 250 milligrams per day, such as greater than about 500 milligrams per day, such as greater than about 750 milligrams per day. Based on body mass, the dosage can be from about 1 milligram per kilogram of body weight per day to about 1,000 milligrams per kilogram body weight per day. For example, the dosage may be from about 5 milligrams per kilogram body weight per day to about 750 milligrams per kilogram body weight per day. In one particular embodiment, the dosage can be from about 10 milligrams per kilogram body weight per day to about 500 milligrams per kilogram body weight per day. In another particular embodiment, the dosage can be greater than about 1 milligrams per kilogram body weight per day, greater than about 5 milligrams per kilogram body weight per day, greater than about 10 milligrams per kilogram body weight per day, greater than about 15 milligrams per kilogram body weight per day, greater than about 20 milligrams per kilogram body weight per day, greater than about 25 milligrams per kilogram body weight per day, greater than about 30 milligrams per kilogram body weight per day, or greater than about 35 milligrams per kilogram body weight per day.

[0056] The mammal can also be administered an effective amount of an amino acid derivative. The amino acid derivative may comprise L-carnitine. L-carnitine may be administered in a dosage from about 5 to 10,000 milligrams per day, such as from about 5 to about 5,000 milligrams per day, such as from about 50 milligrams to about 3,000 milligrams per day. The dosage, for instance, can be greater than about 100 milligrams per day, such as greater than about 250 milligrams per day, such as greater than about 500 milligrams per day, such as greater than about 750 milligrams per day. Based on body mass, the dosage can be from about 1 milligram per kilogram of body weight per day to about 1,000 milligrams per kilogram body weight per day. For example, the dosage may be from about 5 milligrams per kilogram body weight per day

to about 750 milligrams per kilogram body weight per day. In one particular embodiment, the dosage can be from about 10 milligrams per kilogram body weight per day to about 500 milligrams per kilogram body weight per day. In another particular embodiment, the dosage can be greater than about 1 milligrams per kilogram body weight per day, greater than about 5 milligrams per kilogram body weight per day, greater than about 10 milligrams per kilogram body weight per day, greater than about 15 milligrams per kilogram body weight per day, greater than about 20 milligrams per kilogram body weight per day, greater than about 24 milligrams per kilogram body weight per day, greater than about 28 milligrams per kilogram body weight per day, or greater than about 30 milligrams per kilogram body weight per day.

[0057] In one embodiment, a mammal is administered an effective amount of an protein building composition containing an organic acid and derivative and/or salt thereof. The organic acid may comprise creatine. Creatine may be administered in a dosage from about 5 to 15,000 milligrams per day, such as from about 5 to about 10,000 milligrams per day, such as from about 50 milligrams to about 5,000 milligrams per day. The dosage, for instance, can be greater than about 100 milligrams per day, such as greater than about 500 milligrams per day, such as greater than about 1,000 milligrams per day, such as greater than about 1,250 milligrams per day. Based on body mass, the dosage can be from about 1 milligram per kilogram of body weight per day to about 1,000 milligrams per kilogram body weight per day. For example, the dosage may be from about 5 milligrams per kilogram body weight per day to about 750 milligrams per kilogram body weight per day. In one particular embodiment, the dosage can be from about 10 milligrams per kilogram body weight per day to about 500 milligrams per kilogram body weight per day. In another particular embodiment, the dosage can be greater than about 1 milligrams per kilogram body weight per day, greater than about 5 milligrams per kilogram body weight per day, greater than about 10 milligrams per kilogram body weight per day, greater than about 15 milligrams per kilogram body weight per day, greater than about 20 milligrams per kilogram body weight per day, greater than about 30 milligrams per kilogram body weight per day, greater than about 40 milligrams per kilogram body weight per day, or greater than about 50 milligrams per kilogram body weight per day.

[0058] The protein building composition can be administered regularly, such as at least two to four times a week. For instance, the protein building composition may be administered to the mammal at least every one to three days. Further, the protein building composition may be administered more than one time per day. For instance, the protein building composition may be administered to the mammal one to four times per day. In one particular embodiment, the protein building composition is administered daily. The dosage can be from about 5 to 30,000 milligrams per day, such as from about 5 to about 20,000 milligrams per day, such as from about 10 milligrams to about 10,000 milligrams per day, such as from about 20 milligrams to about 5,000 milligrams per day, such as from about 50 milligrams to about 2,500 milligrams per day. Based on body mass, the dosage can be from about 1 milligram per kilogram of body weight per day to about 10,000 milligrams per kilogram body weight per day. For example, the dosage may be from about 5 milligrams per kilogram body weight per day to about 7,500 milligrams per kilogram body weight per day, such as from about 10 milligrams per kilogram body weight per day to about 5,000 milligrams per kilogram body weight per day, such as from about 15 milligrams per kilogram body weight per day to about 2,500 milligrams per kilogram body weight per day, such as from about 20 milligrams per kilogram body weight per day to about 1,000 milligrams per kilogram body weight per day, such as from about 25 milligrams per kilogram body weight per day to about 750 milligrams per kilogram body weight per day, such as from about 30 milligrams per kilogram body weight per day to about 500 milligrams per kilogram body weight per day, such as from about 35 milligrams per kilogram body weight per day to about 250 milligrams per kilogram body weight per day.

[0059] The protein building composition can be administered to the mammal in any suitable form using any suitable administration route. For example, the composition can be administered orally alone, in combination with a food composition, or as part of a food composition. The composition may also be part of a dietary supplement or as a nutraceutical composition.

[0060] The protein building composition can be administered orally as a solid, liquid, suspension, or gas. The composition may be administered via buccal or sublingual administration. In one embodiment, the protein building composition may be

administered as a capsule, tablet, caplet, pill, troche, drop, lozenge, powder, granule, syrup, tea, drink, thin film, seed, paste, herb, botanical, and the like.

[0061] In addition to being administered orally, the supplement dose can also be administered using other routes including intranasal, intravenous, intramuscular, intragastric, and the like.

[0062] When the protein building composition is combined with a food or beverage composition, the food or beverage composition may comprise any suitable composition for consumption by the mammal. Such compositions include complete foods or beverages intended to supply the necessary dietary requirements for mammal or food supplements such as treats and snacks. The food composition may comprise pellets, a drink, a bar, a prepared food contained in a can, a milk shake drink, a juice, a dairy food product, or any other functional food composition. The food composition may also comprise any form of a supplement such as a pill, soft gel, gummy figurine, wafer, or the like.

[0063] A food composition ingested by the mammal in addition to the protein building composition may also be rich in L-carnitine, leucine, and/or creatine. The protein building composition of the present disclosure, for instance, is intended to provide additional L-carnitine, leucine, and/or creatine in addition to the normal amounts contained in a standard diet and/or the amounts produced by the body.

[0064] The mammal treated in accordance with the present disclosure can comprise any suitable mammal. For instance, the mammal may be human or canine. The protein building composition can be fed to a mammal of any age such as from parturition through the adult life in the mammal. In various embodiments the mammal may be a human, dog, a cat, a horse, a pig, a sheep, or a cow. In many embodiments, the mammal can be in early to late adulthood. For instance, the active mammal may have an age that is at least 10%, such as least 15%, such as least 20%, such as least 25%, such as least 30%, such as least 35%, such as least 40%, such as least 45%, such as least 50%, such as least 55%, such as least 60%, such as least 65%, such as least 70%, such as least 75%, such as least 85%, such as least 90%, such as least 95% of its expected life span. The mammal may have an age such that it is less than about 95%, such as less than about 90%, such as less than about 85%, such as less

than about 80%, such as less than about 75%, such as less than about 70%, such as less than about 65%, such as less than about 60%, such as less than about 55%, such as less than about 50%, such as less than about 45%, such as less than about 40%, such as less than about 35%, such as less than about 30%, such as less than about 25%, such as less than about 20%, such as less than about 15%, such as less than about 10% of its expected life span. A determination of life span may be based on actuarial tables, calculations, or the like.

[0065] The protein building composition may be administered to the mammal according to the present disclosure regardless of the frequency, intensity, or type of physical activity performed by the mammal. The mammal may participate in physical activities with various MET values. In one embodiment, the mammal may regularly participate in light to intense physical activity. Light physical activity may have a MET of from about 3 MET to about 6 MET. Moderate physical activity may have a MET of from about 6 MET to about 10 MET. Intense physical activity may have a MET of about 10 MET or greater. In another embodiment, the mammal may infrequently participate in physical activity. In yet another embodiment, the mammal may lead a sedentary lifestyle, wherein the mammal may rarely or never participate in physical activity. In a sedentary lifestyle, a mammal may participate mainly or exclusively in sedentary activities.

[0066] The protein building composition may be administered to the mammal before, during, or after a period of physical activity. Alternately, the composition may be administered to the mammal before, during, or after a period of sedentary activity. For instance, the composition may be administered to the mammal during an extended period of bed rest or other extended period of inactivity.

[0067] The protein building composition is administered in an amount sufficient to increase muscle protein synthesis, increase functional strength, or increase both muscle protein synthesis and functional strength without requiring the mammal to participate in physical activity.

[0068] Muscle protein synthesis, in one embodiment, can be determined by monitoring the biomarkers, mTOR expression and phosphorylation and its related upstream and downstream proteins in the pathway, in skeletal muscle. Specifically,

mTOR expression can be determined and recorded before and after a period of activity. For a mammal treated in accordance with the present disclosure, mTOR expression before and after a period of time may vary by more than 10%, such as by more than 20%, such as by more than 40%, such as by more than 60%, such as by more than 80%, such as by more than 100%, such as by more than 150%, such as by more than 200%.

[0069] In one embodiment, the mammals treated in accordance with the present disclosure may have total mTOR values after a period of activity that are at least 10%, such as at least 20%, such as at least 30%, such as at least 40%, such as at least 50%, such as at least 60%, such as at least 100% greater than the same mammal that is not administered the protein building composition.

[0070] Protein synthesis can be monitored by androgens, androgen receptors, insulin, IGF-1, IGF-1 receptors and any known stimulator of protein synthesis.

[0071] In addition to increased muscle protein synthesis, the protein building composition can also increase functional strength. In particular, the protein building composition can increase lean muscle mass and upper and lower body strength. Functional strength can be measured by a composite endpoint of strength and muscle measures. The composite endpoint may be the product of the values for muscle mass (kg), upper extremity strength by dynamometer (kg), lower extremity strength by dynamometer (kg), and 6-minute walk test (meters). Comparative measurements can be taken prior to and after a period of activity.

[0072] In one embodiment, mammals treated in accordance with the present disclosure may have composite endpoints after a certain period of time that are at least 10%, such as at least 25%, such as at least 50%, such as at least 75%, such as at least 100% more than the same mammal that is not administered the L-carnitine supplement.

[0073] The protein building composition of the present disclosure may also reduce inflammation. Inflammation, in one embodiment, can be determined by monitoring the biomarker, TNF-α, in skeletal muscle. TNF-α is an inflammatory marker involved in protein degradation. Reduction in TNF-α values may indicate a reduction in protein degradation and muscle wasting. TNF-α values can be determined and recorded before and after a period of activity. For a mammal treated in accordance with the present

disclosure, TNF-α values before and after a period of time may vary by more than 0.5%, such as by more than 1%, such as by more than 5%, such as by more than 10%, such as by more than 20%, such as by more than 40%, such as by more than 60%, such as by more than 80%, such as by more than 100%, such as by more than 150%, such as by more than 200%.

[0074] In one embodiment, the mammals treated in accordance with the present disclosure may have total TNF-α values after a period of activity that are at least 0.5%, such as at least 1%, such as at least 5%, such as at least 10%, such as at least 20%, such as at least 30%, such as at least 40%, such as at least 50%, such as at least 60%, such as at least 100% less than the same mammal that is not administered the protein building composition.

[0075] Reduced inflammation can lead to decreased protein degradation.

[0076] In one embodiment, the compositions of the present disclosure may contain other amino acids, including but not limited to alanine, arginine, asparagine, aspartate, cysteine, glutamic acid, glutamine, glycine, proline, serine, tyrosine, histidine, isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, and any combinations thereof.

[0077] The protein building composition of the present disclosure may further comprise one or more excipients. Exemplary but non-limiting excipients include antiadherents, such as magnesium stearate; binders, such as saccharides, sugar alcohols, gelatin, and synthetic polymers; coatings, such as cellulose ether hydroxypropyl methylcellulose (HPMC), shellac, corn protein zein, gelatin, fatty acids, and waxes; coloring agents, such as titanium oxide and azo dyes; disintegrants, such as modified starch sodium starch glycolate and crosslinked polymers including polyvinylpyrrolidone and sodium carboxymethyl cellulose; fillers, such as maltodextrin; flavoring agents, such as mint, liquorice, anise, vanilla, and fruit flavors including peach, banana, grape, strawberry, blueberry, raspberry, and mixed berry; glidants, such as fumed silica, talc, and magnesium carbonate; lubricants, such as talc, silica, and fats including vegetable stearin, magnesium stearate, and stearic acid; preservatives, such as antioxidants, vitamins, retinyl palmitate, selenium, the amino acids cysteine and

methionine, citric acid, sodium citrate, and parabens; sorbents; sweeteners, such as sucrose and sucralose; and vehicles, such as petrolatum and mineral oil.

[0078] In one embodiment, the protein building composition of the present disclosure may be combined with various additives and components that can improve one or more properties of the composition. For example, in one embodiment, the additive composition may be combined with a stabilizer package that may serve to stabilize at least one property of the composition. In one particular embodiment, for instance, a stabilizer package may be added to the composition in an amount sufficient to reduce the hydroscopic properties of the composition and/or prevent the composition from absorbing moisture. A stabilizer package may also be combined with the protein building composition in order to improve the handling properties of the composition. For instance, the stabilizer package may allow the composition to have better flow properties, especially when in granular form.

[0079] In one embodiment, the protein building composition may be combined with a polymer binder in conjunction with a stabilizer package. In addition, a coating material may also be applied to the composition after the composition has been combined with the polymer binder and the stabilizer package. The coating material, for instance, may contain at least one fat. In accordance with the present disclosure, the above components can be added to any suitable pharmaceutical composition in addition to the protein building composition of the present disclosure. For instance, the above components may be added to any pharmaceutical composition containing a carnitine or an amino acid.

[0080] The polymer binder and the stabilizer package may be combined with the protein building composition in a manner that homogeneously incorporates the stabilizer package into the product. In one embodiment, for instance, the protein building composition of the present disclosure is first combined with a polymer binder, such as through a spray dry process, and then combined with the stabilizer package. The polymer binder may comprise any suitable pharmaceutically acceptable polymer, such as film-forming polymers and/or polysaccharides. Particular examples of polymer binders that may be used in accordance with the present disclosure include starch, maltodextrin, gum arabic, arabinogalactan, gelatin, and mixtures thereof. In one

embodiment, the polymer binder is added to the pharmaceutical composition in an amount of at least about 5% by weight, such as at least about 8% by weight, such as at least about 10% by weight, such as at least about 15% by weight. One or more polymer binders are present in the composition in an amount less than about 50% by weight, such as in an amount less than about 45% by weight, such as in an amount less than about 40% by weight, such as in an amount less than about 35% by weight, such as in an amount less than about 30% by weight.

[0081] In one embodiment, the polymer binder may comprise a starch, such as a modified starch. The starch, for instance, may be derived from corn or waxy maize. In one embodiment, the starch may comprise HI-CAP100 starch sold by National Starch and Chemical Company.

[0082] In an alternative embodiment, the polymer binder may comprise arabinogalactan. Arabinogalactan is a soluble polysaccharide that not only can serve as a polymer binder but may also provide other benefits. For instance, arabinogalactan may enhance the adaptive immune response in some circumstances. Arabinogalactan is described, for instance, in U.S. Patent No. 8,784,844, which is incorporated herein by reference.

[0083] In one embodiment, larch arabinogalactan may be used as the polymer binder. Larch arabinogalactan is a highly branched polysaccharide that is composed of galactose units and arabinose units in the approximate ratio of 6:1. Larch arabinogalactan is extracted from large trees. The polysaccharide has a galactan backbone with side chains of galactose and arabinose. Arabinogalactan is commercially available from Lonza Ltd.

[0084] Once the polymer binder is combined with the protein building composition such as through a spray dry process, the resulting mixture can then be combined with a stabilizer package. In one embodiment, the stabilizer package comprises oxide particles in combination with a salt of a carboxylic acid. In one particular embodiment, the stabilizer package may comprise a dry product, such as a powder or granular product that is combined with the protein building composition and polymer binder. The combination of oxide particles and a salt of a carboxylic acid have been found to provide numerous advantages and benefits when combined with the protein building

composition. For instance, the stabilizer package has been found to stabilize the protein building composition and make the composition less hydroscopic. The composition is also easier to handle and, when in granular form, produces a free-flowing product.

[0085] The oxide particles that may be added to the pharmaceutical composition may comprise silica. For instance, the oxide particles may comprise precipitated silica particles. The silica particles may have a particle size (d50, laser defraction following ISO Test 13320) of less than about 55 microns, such as less than about 40 microns, such as less than about 30 microns, such as less than about 25 microns, such as less than about 20 microns, such as less than about 15 microns, such as less than about 12 microns, such as less than about 10 microns, such as less than about 8 microns, such as less than about 6 microns, such as less than about 4 microns, such as less than about 2 microns, such as less than about 1 micron. The particle size is typically greater than about 0.5 microns, such as greater than about 1 micron. The particles may have a specific surface area (ISO Test 9277) of greater than about 120 m^2/g, such as greater than about 130 m^2/g, such as greater than about 150 m^2/g, such as greater than about 170 m^2/g, such as greater than about 200 m^2/g, such as greater than about 220 m^2/g. The specific surface area is generally less than about 500 m^2/g. The oxide particles, such as the silica particles, can be present in the pharmaceutical composition in an amount greater than about 0.01% by weight, such as in an amount greater than about 0.05% by weight, such as in an amount greater than about 0.1% by weight. The oxide particles are generally present in an amount less than 5% by weight, such as in an amount less than about 2% by weight, such as in an amount less than about 1.5% by weight, such as in an amount less than 0.5% by weight.

[0086] In addition to the oxide particles, the stabilizer package may also include a salt of a carboxylic acid. The salt of a carboxylic acid may comprise a salt of a fatty acid. The fatty acid, for instance, may have a carbon chain length of from about 6 carbon atoms to about 40 carbon atoms, such as from about 12 carbon atoms to about 28 carbon atoms. In one embodiment, the salt of the carboxylic acid may comprise a stearate salt. The stearate salts that may be used include calcium stearate, sodium stearate, magnesium stearate, mixtures thereof, and the like. In one embodiment, the

salts of the carboxylic acid may include both hydrophilic groups and hydrophobic groups. The salt of the carboxylic acid may be present in the pharmaceutical composition in an amount greater than about 0.5% by weight, such as in an amount greater than about 1% by weight, such as in an amount greater than about 1.5% by weight. The salt of the carboxylic acid is generally present in an amount less than about 5% by weight, such as in an amount less than about 4% by weight, such as in an amount less than about 3% by weight.

[0087] In addition to the polymer binder and the stabilizer package, the composition may include various other components and ingredients. In one embodiment, for instance, the composition may contain a citric acid ester, such as a citric acid ester of a mono and/or diglyceride of a fatty acid. The composition may also contain a lecithin, such as a lecithin obtained from rapeseed, sunflower, and the like. The above components can be present in the composition in relatively minor amounts, such as less than about 2% by weight, such as less than about 1.5% by weight, such as less than about 1% by weight. The above components are generally present in an amount greater than about 0.05% by weight, such as in an amount greater than about 0.1% by weight.

[0088] Once the above components are combined together to form the pharmaceutical composition, the composition can optionally be combined with a coating material. In one embodiment, for instance, the pharmaceutical composition may comprise a granular composition to which a coating material is applied that contains a fat. The coating material, for instance, may comprise a hydrogenated oil, such as hydrogenated palm oil. In one particular embodiment, the coating material may comprise hydrogenated palm oil combined with palm stearine. In one embodiment, the hydrogenated oil may be present in the pharmaceutical composition in an amount from about 5% to about 35% by weight. The palm stearine, on the other hand, may be present in the pharmaceutical composition in an amount from about 2% to about 10% by weight. When present together, the weight ratio between the hydrogenated palm oil and the palm stearine may be from about 10:1 to about 1:1, such as from about 6:1 to about 2:1. In one embodiment, the hydrogenated palm oil and the palm stearine are present at a weight ratio of about 4:1.

[0089] The present disclosure may be better understood with reference to the following examples.

Example No. 1

[0090] A randomized, double-blind, placebo-controlled study was conducted to evaluate the effects of two protein building compositions formulated according to the present disclosure on muscle protein synthesis, functional strength, lean body mass, and overall quality of life in healthy older adults.

[0091] The study was conducted with a sample size of 42 healthy older adults, with 14 subjects randomized to each study arm in a double-blind manner at a ratio of 1:1:1. Each subject was selected for compliance with the inclusion and exclusion criteria shown in Tables 1 and 2.

Table 1. Inclusion Criteria For Test Subjects

Healthy male or female adults, aged 55 to 70 years
BMI of 21 kg/m^2 to 33 kg/m^2
Subjects in good physical condition such that they can perform exercise testing safely, as determined by the Qualified Investigator based on medical history, physical examination, electrocardiogram and laboratory results
Subjects who are sedentary and not currently engaging in any regular exercise.
Subjects who agree to maintain their current level of activity and current dietary habits throughout the trial period.
Subjects who have given voluntary, written, informed consent to participate in the study.

Table 2. Exclusion Criteria For Test Subjects

Subjects who are smokers or have been a smoker within the past 1 year from screening.
Subjects who are pregnant or breastfeeding
Subjects who have experienced weight loss or gain of greater than 4.5 kg (approximately 10 lbs) within 3 months of randomization
Subjects diagnosed with active heart disease
Subjects with uncontrolled hypertension (≥ 140 mmHg)
Subjects with renal or hepatic impairment or disease
Subjects with any major diseases of the gastrointestinal, pulmonary or endocrine systems
Subjects with a history of seizures
Subjects with Type I and Type II Diabetes
Subjects with active cancer (excluding basal cell carcinoma)
Subjects with neurological or significant psychiatric illnesses, including Parkinson's disease and bi-polar disorder
Subjects with unstable thyroid disease
Subjects who are immuno-compromised (HIV positive, on anti-rejection medication, rheumatoid arthritis)
Subjects with metal fixation plates or screws from a previous surgery
Subjects who are taking oral anticoagulants (blood thinners) such as warfarin (Coumadin) or Dabigatran (Pradaxa) or antiplatelet agents such as Clopidogrel (Plavix)
Subjects who are regularly taking NSAID medications such as aspirin, must stop at least one

week prior to the micro-needle muscle biopsy procedures.
Subjects with a known allergy to anesthetic
Subjects who currently experience any medical condition that interferes with the ability to undergo physical strength testing during the study
Subjects currently taking NHPs must have been using their current dosing regimen for at least one month prior to baseline and must maintain their current dosing regimen throughout the trial and must not begin taking any new NHPs throughout the trial. If the subject wishes to stop taking the NHP prior to beginning the trial, they must do so at least 1 week prior to randomization.
Subjects who use illicit drugs or have a history of alcohol or drug abuse within the past 6 months
Subjects who currently consume greater than 2 standard alcoholic drinks per day.
Subjects who have participated in a clinical research trial within 30 days prior to randomization.
Subjects with an allergy or sensitivity to the investigational product ingredient.
Subjects who are cognitively impaired and/or who are unable to give informed consent
Subjects who have abnormal laboratory results or any other medical or psychological condition which, in the opinion of the Qualified Investigator, may adversely affect the subject's ability to complete the study or its measures or which may pose significant risk to the subject.

[0092] The compositions of the three nutritional supplements are shown in Table 3. Subjects received one of the three supplements based on whether they were in the Sample 1, Sample 2, or the placebo group. The Sample 1 group received 4 grams of the designated composition per day. The Sample 2 group received 8 grams of the designated composition per day. The placebo group received 3 grams of the designated composition per day. Subjects were instructed to empty the contents of the sachet of the designated composition into one bottle of orange juice and shake vigorously for 1 min, then drink the entire bottle. Each sachet for Sample 1 and Sample 2 contained 2.2 g of L-carnitine tartrate. Subjects were instructed to start taking the product the day after randomization (Day 1). The subjects continued to take the product for an 8 week period.

[0093] Subjects were asked to maintain their current physical activity levels and dietary habits throughout the trial.

Table 3. L-Carnitine and Placebo Supplement Compositions

	Active Ingredients	**Other Ingredients**
Sample 1	L-carnitine (1500 mg)	Maltodextrin
		Sucrose
		Colloidal Silicon Dioxide
		Mixed Berry Flavor
		Sucralose

	Active Ingredients	Other Ingredients
Sample 2	L-carnitine (1500 mg)	Sucrose
	L-Leucine (2000 mg)	Colloidal Silicon Dioxide
	Creatine monohydrate (3000 mg)	Mixed Berry Flavor
	Vitamin D3 (400IU)	Sucralose
Placebo		Tartaric Acid
		Maltodextrin
		Sucrose
		Colloidal Silicon Dioxide
		Mixed Berry Flavor
		Sucralose

[0094] Assessments were conducted at Day 0, Day 29±3, and Day 57±3 of the study. On Day 29, subjects were contacted via phone to monitor adverse events and changes in concomitant medications as well as to foster compliance with the study dosing regimen.

[0095] Data was analyzed for the per protocol population, which consisted of all participants who consumed at least 80% of treatment or placebo doses, did not have any major protocol violations and completed all study visits and procedures connected with measurement of the primary variable. The per-protocol population contained 39 subjects, as 3 subjects were excluded from the original 42 subject population for protocol violations. For statistical analysis, within-group changes over 8 weeks of supplementation, and pre-to-post-strength testing changes, were tested for significance by the paired Student t test or the non-parametric Wilcoxon Signed-ranks test. Between-group differences in 8-week changes were tested for significance by the unpaired Student t test or the non-parametric Mann-Whitney U test. In the following tables, treatment groups with differing letter superscripts are significantly different. Probability values $P \leq 0.05$ are statistically significant.

[0096] Total lean mass was measured for each participant on Day 0 and Day 57±3 via dual-energy X-ray absorptiometry (DXA). As shown in Fig. 1 and Table 4, total lean mass was significantly increased (+1.01 kg, P = 0.013) in the Sample 2 group, but not in Sample 1 (-0.03 kg, P = 0.915) or the placebo (0.0 kg, P = 0.986) groups.

[0097] As revealed in Fig. 2, arm lean mass significantly differed between Sample 1 and 2 (P = 0.012) by the end of 8 weeks, with Sample 1 showing a slight reduction (-

0.137 kg) in arm mass and Sample 2 demonstrating a minor increase (+0.135 kg) in arm mass.

[0098] Fig. 3 demonstrated that participants supplemented with Sample 2 also had enhanced leg muscle mass (+0.35 kg, P = 0.005), which was not reflected in the placebo group (-0.03 kg, P = 0.811). Subjects on Sample 1 did exhibit a small, but non-significant increase in leg lean mass (+0.17 kg, P = 0.256) as well.

[0099] Illustrated in Fig. 4, total non-trunk lean mass increased significantly in the Sample 2 group by the end of the study (+0.48 kg, P = 0.006). This change was significantly greater than the placebo group (P<0.05), which tended to lose total non-trunk lean mass (-0.10 kg, P = 0.560). Sample 1 group maintained their total non-trunk lean mass for the duration of the study (+0.03 kg, P = 837).

Table 4: DXA Lean Masses at Baseline and at End of the Study for All Participants in the PP Population (N = 39).

	Placebo	Sample 1	Sample 2	Between Group P Values			
	Mean ±SD (n) Median (Min – Max) Within Group P Value‡	Mean ±SD (n) Median (Min – Max) Within Group P Value‡	Mean ±SD (n) Median (Min – Max) Within Group P Value‡	Overall Δ	Placebo vs Sample 1δ	Placebo vs Sample 2δ	Sample 1 vs Sample 2 δ
Total Lean Mass (kg)							
Baseline (Week 0)	43.7 ± 9.1 (14) 40.8 (30.4 – 60.1)	44.8 ± 8.8 (11) 40.5 (33 – 60.1)	45.2 ± 8.6 (14) 42.2 (34.9 – 65.2)	-	-	-	-
Visit 3 (Week 8)	43.7 ± 9.2 (14) 40.8 (29.7 – 60.6)	45.0 ± 8.9 (11) 40.9 (33.5 – 61.6)	46.2 ± 9.7 (14) 43 (35 – 68.6)	-	-	-	-
Change from Baseline to Week 8	-0.00 ± 1.04 (14) 0.23 (-2.11 – 1.36) p = 0.986	0.14 ± 1.22 (11) 0.48 (-1.61 – 1.6) p = 0.716	1.01 ± 1.30 (14) 0.98 (-1.37 – 3.41) **p = 0.013**	0.074	0.978	0.088	**0.169**
Arm Lean Mass (kg)							
Baseline (Week 0)	4.91 ± 1.47 (14) 4.8 (3.29 – 7.69)	5.11 ± 1.72 (11) 4.11 (3.21 – 7.42)	4.93 ± 1.43 (14) 4.4 (3.5 – 7.9)	-	-	-	-
Visit 3 (Week 8)	4.84 ± 1.40 (14) 4.37 (3.06 – 7.22)	4.99 ± 1.68 (11) 4.09 (3.12 – 7.3)	5.07 ± 1.52 (14) 4.66 (3.39 – 7.98)	-	-	-	-
Change from Baseline to Week 8	-0.071 ± 0.276 (14) 0.015 (-0.55 – 0.42) p = 0.351	-0.123 ± 0.088 (11) -0.12 (-0.3 – -0.02) **p < 0.001**	0.135 ± 0.252 (14) 0.15 (-0.45 – 0.48) p = 0.067	**0.019**	0.863	0.061	**0.026**
Leg Lean Mass (kg)							
Baseline (Week 0)	14.59 ± 3.13 (14) 13.98 (10.92 – 20.34)	14.30 ± 2.88 (11) 13.07 (10.91 – 19.02)	14.41 ± 3.06 (14) 13.87 (11.29 – 20.98)	-	-	-	-
Visit 3 (Week 8)	14.6 ± 3.2 (14) 13.6 (10.2 – 20.1)	14.6 ± 3.0 (11) 13.1 (11.7 – 20.1)	14.8 ± 3.2 (14) 14.1 (11.1 – 21.6)	-	-	-	-

Change from Baseline to Week 8	-0.03 ± 0.46 (14) -0.05 (-0.73 – 0.7) p = 0.811	0.29 ± 0.50 (11) 0.16 (-0.49 – 1.05) p = 0.086	0.35 ± 0.39 (14) 0.38 (-0.35 – 0.99) p = 0.005	0.069	0.185	0.076	0.947
Total Non-Trunk Lean Mass (kg)							
Baseline (Week 0)	19.5 ± 4.5 (14) 18.4 (14.2 – 27.7)	19.4 ± 4.5 (11) 16.8 (14.2 – 26.4)	19.3 ± 4.4 (14) 17.9 (14.8 – 28.9)	-	-	-	-
Visit 3 (Week 8)	19.4 ± 4.6 (14) 17.9 (13.3 – 27)	19.6 ± 4.6 (11) 16.8 (14.8 – 27.4)	19.8 ± 4.7 (14) 18.4 (14.5 – 29.5)	-	-	-	-
Change from Baseline to Week 8	-0.10 ± 0.64 (14) 0.02 (-1.2 – 1.12) p = 0.560	0.16 ± 0.51 (11) 0.14 (-0.67 – 0.93) p = 0.315	0.48 ± 0.56 (14) 0.54 (-0.48 – 1.22) **p = 0.006**	**0.037**	0.499	**0.029**	0.360
Trunk Lean Mass (kg)							
Baseline (Week 0)	23.2 ± 10.8 (14) 20.1 (13.9 – 58)	23.9 ± 6.4 (11) 23.2 (16.4 – 39.3)	27.6 ± 11.0 (14) 23.6 (17.5 – 57.4)	-	-	-	-
Visit 3 (Week 8)	22.4 ± 6.2 (14) 20.2 (14 – 37.9)	22.1 ± 4.0 (11) 22.2 (16.1 – 29.9)	23.0 ± 4.1 (14) 22.5 (17.7 – 31.9)	-	-	-	-
Change from Baseline to Week 8	-0.8 ± 10.1 (14) 0.1 (-30.9 – 19.3) p = 0.973*	-1.7 ± 5.1 (11) -0.4 (-17.1 – 0.6) p = 0.271*	-4.6 ± 9.9 (14) -0.2 (-28.4 – 1.7) p = 0.101*	0.943*	0.969*	0.942*	0.997*

N, number; SD, standard deviation; Min, minimum; Max, maximum; kg, kilogram
Δ Between-group comparisons were made using ANCOVA. δ Pairwise between-group comparisons were made using the Tukey procedure. Within-group comparisons were made using the paired Student t-test. * Logarithmic transformation was required to achieve normality. Treatment groups with differing letter superscripts are significantly different. Probability values P≤0.05 are statistically significant.

[00100] Lower leg strength was assessed by average leg dynamometry for each participant on Day 0 and Day 57±3. As shown in Fig. 5 and Table 5, lower leg strength was significantly increased in the Sample 2 group (+1.0 kg, P = 0.029). This increase in leg dynamometry corresponds with the rise in leg muscle mass (DXA scan) and was significantly different from the placebo group (P = 0.012), which exhibited reduced average leg strength (-2.8 kg, P = 0.061) by the end of study. Sample 1 significantly differed from the placebo group (P = 0,023) and maintained their average leg strength throughout the study duration (-0.4 kg, P = 0.764). Upper body strength markers, including average left and right hand, as well as average arm strength did not significantly change for any treatment group.

Table 5: Dynamometry Results at Baseline and at End of the Study for All Participants in the PP Population (N = 39).

	Placebo	Sample 1	Sample 2	Between Group P Values

	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Overall [Δ]	Placebo vs Sample 1 [δ]	Placebo vs Sample 2 [δ]	Sample 1 Vs Sample 2 [δ]
Average Right Hand (kg)							
Baseline (Week 0)	28.3 ± 10.3 (14) 27.5 (4.5 – 45.6)	26.5 ± 10.3 (11) 26.3 (11.2 – 45.9)	24.0 ± 9.9 (14) 26 (7.6 – 40.8)	-	-	-	-
Visit 3 (Week 8)	28.6 ± 11.6 (14) 25.2 (3.9 – 49.8)	24.9 ± 10.7 (11) 23.3 (10.3 – 42.3)	25.6 ± 9.4 (14) 25.7 (10 – 41.1)	-	-	-	-
Change from Baseline to Week 8	0.3 ± 4.9 (14) -0.7 (-4.8 – 14.2) p = 0.819	-1.5 ± 4.2 (11) 0.3 (-11.6 – 4.2) p = 0.257	1.7 ± 6.3 (14) 0.3 (-6.8 – 19.5) p = 0.345	0.383	0.619	0.884	0.358
Average Left Hand (kg)							
Baseline (Week 0)	27.1 ± 11.2 (14) 26.8 (4.7 – 48.2)	26.2 ± 12.1 (11) 24.8 (9.4 – 52.1)	23.8 ± 10.6 (14) 25.3 (8.3 – 41.5)	-	-	-	-
Visit 3 (Week 8)	27.3 ± 10.2 (14) 26.2 (5.1 – 42)	25.8 ± 12.1 (11) 26.1 (9.8 – 50.9)	26.2 ± 9.6 (14) 25.3 (10.1 – 40.8)	-	-	-	-
Change from Baseline to Week 8	0.2 ± 4.3 (14) 1.1 (-7.6 – 7.7) p = 0.869	-0.3 ± 4.1 (11) -0.6 (-10.6 – 4.1) p = 0.791	2.3 ± 4.9 (14) 1.9 (-3.3 – 16.2) p = 0.095	0.363	0.921	0.552	0.366
Average Arm (kg)							
Baseline (Week 0)	27.7 ± 10.7 (14) 27.1 (4.6 – 46.9)	26.3 ± 11.2 (11) 25.7 (10.3 – 49)	23.9 ± 10.1 (14) 26.1 (7.9 – 41.1)	-	-	-	-
Visit 3 (Week 8)	27.9 ± 10.8 (14) 25.3 (4.5 – 45.9)	25.4 ± 11.3 (11) 24.1 (10 – 46.6)	25.9 ± 9.3 (14) 25.6 (10 – 39.9)	-	-	-	-
Change from Baseline to Week 8	0.2 ± 4.2 (14) 0 (-5.5 – 10) p = 0.828	-0.9 ± 4.0 (11) -0.1 (-11.1 – 4.2) p = 0.455	2.0 ± 5.3 (14) 0.9 (-3.8 – 17.8) p = 0.186	0.354	0.744	0.725	0.322
Average Leg (kg)							
Baseline (Week 0)	13.5 ± 6.4 (14) 12.4 (4.5 – 24.5)	15.7 ± 5.1 (11) 16.8 (6.9 – 23.6)	12.3 ± 7.2 (14) 10.5 (4.5 – 24.6)	-	-	-	-
Visit 3 (Week 8)	10.7 ± 3.6 (14) 9.9 (6.5 – 19.3)	15.7 ± 5.1 (11) 15.1 (9.4 – 26.6)	13.4 ± 6.2 (14) 13.1 (6 – 23.3)	-	-	-	-
Change from Baseline to Week 8	-2.8 ± 4.8 (14)[a] -2 (-14.8 – 2.4) p = 0.061[†]	0.0 ± 4.5 (11)[b] 1.1 (-8.6 – 5.2) p = 0.952[†]	1.0 ± 2.0 (14)[b] 1.2 (-3.8 – 4.5) **p = 0.029**[†]	**0.006**[†]	**0.016**[†]	**0.014**[†]	0.988[†]

N, number; SD, standard deviation; Min, minimum; Max, maximum; kg, kilogram
Δ Between-group comparisons were made using ANCOVA. δ Pairwise between-group comparisons were made using the Tukey procedure. Within-group comparisons were made using the paired Student t-test. †Square root transformation required to achieve normality. Treatment groups with differing letter superscripts are significantly different. Probability values P≤0.05 are statistically significant.

[00101] The participants completed the six minute walk test on Day 0 and Day 57±3. Table 6 shows that participants taking placebo had a significant reduction in their out of breath score after walking at the end of study relative to baseline (-0.43, P<0.05). There

were no notable changes in the total meters walked, out of breath score before walking, and fatigue score before/after walking in all treatment groups.

Table 6: Six Minute Walk Test at Baseline and at End of the Study for All Participants in the PP Population (N = 39).

	Placebo	Sample 1	Sample 2	Between Group P Values			
	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Overall $^{\Delta}$	Placebo vs Sample 1 $^{\delta}$	Placebo vs Sample 2 $^{\delta}$	Sample 1 Vs Sample 2 $^{\delta}$
Meters Walked in Six Minutes (m)							
Baseline (Week 0)	526 ± 80 (14) 542 (336 – 633)	458 ± 127 (11) 442 (239 – 695)	432 ± 109 (14) 460 (220 – 540)	-	-	-	-
Visit 3 (Week 8)	530 ± 100 (14) 560 (220 – 627)	444 ± 119 (11) 497 (220 – 560)	462 ± 113 (14) 490 (238 – 600)	-	-	-	-
Change from Baseline to Week 8	3 ± 69 (14) -3 (-116 – 140) p = 0.704†	-14 ± 107 (11) -8 (-222 – 135) p = 0.617†	30 ± 70 (14) 27 (-120 – 138) p = 0.126†	0.310†	0.326†	0.961†	0.449†
Out of Breath Score Before Walking							
Baseline (Week 0)	0.00 ± 0.00 (14) 0 (0 – 0)	0.09 ± 0.30 (11) 0 (0 – 1)	0.21 ± 0.80 (14) 0 (0 – 3)	-	-	-	-
Visit 3 (Week 8)	0.000 ± 0.000 (14) 0 (0 – 0)	0.045 ± 0.151 (11) 0 (0 – 0.5)	0.036 ± 0.134 (14) 0 (0 – 0.5)	-	-	-	-
Change from Baseline to Week 8	0.00 ± 0.00 (14) 0 (0 – 0) p = 1.000‡	-0.05 ± 0.15 (11) 0 (-0.5 – 0) p = 1.000‡	-0.18 ± 0.67 (14) 0 (-2.5 – 0) p = 1.000‡	0.555$^{¤}$	0.93$^{¤}$	0.94$^{¤}$	1.00$^{¤}$
Out of Breath Score After Walking							
Baseline (Week 0)	1.04 ± 0.91 (14) 1 (0 – 3)	0.55 ± 0.79 (11) 0 (0 – 2)	1.07 ± 2.16 (14) 0 (0 – 7)	-	-	-	-
Visit 3 (Week 8)	0.61 ± 0.56 (14) 0.5 (0 – 2)	0.41 ± 0.58 (11) 0.5 (0 – 2)	1.00 ± 1.79 (14) 0 (0 – 5)	-	-	-	-
Change from Baseline to Week 8	-0.43 ± 0.70 (14) -0.5 (-2 – 0.5) **p = 0.044**‡	-0.14 ± 0.64 (11) 0 (-1.5 – 0.5) p = 0.590‡	-0.07 ± 0.87 (14) 0 (-2 – 2) p = 0.730‡	0.347$^{¤}$	0.45$^{¤}$	0.46$^{¤}$	1.00$^{¤}$
Change in Out of Breath Score After Walking							
Baseline (Week 0)	1.04 ± 0.91 (14) 1 (0 – 3)	0.45 ± 0.65 (11) 0 (0 – 2)	0.86 ± 1.60 (14) 0 (0 – 5)	-	-	-	-
Visit 3 (Week 8)	0.61 ± 0.56 (14) 0.5 (0 – 2)	0.36 ± 0.45 (11) 0.5 (0 – 1.5)	0.96 ± 1.70 (14) 0 (0 – 5)	-	-	-	-
Change from Baseline to Week 8	-0.43 ± 0.70 (14) -0.5 (-2 – 0.5) **p = 0.044**‡	-0.09 ± 0.66 (11) 0 (-1.5 – 0.5) p = 0.792‡	0.11 ± 0.68 (14) 0 (-1 – 2) p = 0.792‡	0.155$^{¤}$	0.33$^{¤}$	0.20$^{¤}$	0.98$^{¤}$

Fatigue Score Before Walking							
Baseline (Week 0)	0.54 ± 0.93 (14) 0 (0 – 3)	0.50 ± 1.02 (11) 0 (0 – 3)	0.21 ± 0.54 (14) 0 (0 – 2)	-	-	-	-
Visit 3 (Week 8)	0.39 ± 0.92 (14) 0 (0 – 3)	0.18 ± 0.60 (11) 0 (0 – 2)	0.25 ± 0.80 (14) 0 (0 – 3)	-	-	-	-
Change from Baseline to Week 8	-0.14 ± 0.57 (14) 0 (-1 – 1) p = 0.387‡	-0.32 ± 1.27 (11) 0 (-3 – 2) p = 0.461‡	0.04 ± 0.95 (14) 0 (-1.5 – 3) p = 0.854‡	0.929¤	0.98¤	0.99¤	0.94¤
Fatigue Score After Walking							
Baseline (Week 0)	0.82 ± 0.91 (14) 0.5 (0 – 3)	0.82 ± 1.03 (11) 0.5 (0 – 3)	0.64 ± 1.36 (14) 0 (0 – 5)	-	-	-	-
Visit 3 (Week 8)	0.61 ± 0.86 (14) 0.5 (0 – 3)	0.45 ± 0.88 (11) 0 (0 – 3)	0.93 ± 1.25 (14) 0.25 (0 – 3)	-	-	-	-
Change from Baseline to Week 8	-0.21 ± 0.64 (14) -0.25 (-1.5 – 1) p = 0.266‡	-0.36 ± 1.38 (11) 0 (-3 – 2.5) p = 0.348‡	0.29 ± 1.17 (14) 0 (-2 – 3) p = 0.394‡	0.254¤	0.98¤	0.38¤	0.33¤
Change in Fatigue Score After Walking							
Baseline (Week 0)	0.29 ± 0.64 (14) 0.25 (-1 – 2)	0.32 ± 0.64 (11) 0 (-0.5 – 2)	0.43 ± 1.33 (14) 0 (0 – 5)	-	-	-	-
Visit 3 (Week 8)	0.21 ± 0.26 (14) 0 (0 – 0.5)	0.27 ± 0.34 (11) 0 (0 – 1)	0.68 ± 1.05 (14) 0 (0 – 3)	-	-	-	-
Change from Baseline to Week 8	-0.07 ± 0.68 (14) 0 (-1.5 – 1.5) p = 0.660‡	-0.05 ± 0.65 (11) 0 (-1.5 – 1) p = 1.000‡	0.25 ± 1.03 (14) 0 (-2 – 2.5) p = 0.341‡	0.437¤	0.92¤	0.47¤	0.75¤

N, number; SD, standard deviation; Min, minimum; Max, maximum
Δ Between-group comparisons were made using ANCOVA. δ Pairwise between-group comparisons were made using the Tukey procedure. Within-group comparisons were made using the paired Student t-test. †Square root transformation required to achieve normality. ¤Between-group comparisons were made using the Kruskal Wallis test. ‡Within-group comparisons were made using the signed-rank test. Probability values P≤0.05 are statistically significant.

[00102] Quality of life was determined by the participants' responses to the RAND SF-36 questionnaire on Day 0 and Day 57±3 shown in Table 7. The SF-36 questionnaire was developed at RAND as part of the Medical Outcomes Study. The Sample 1 group showed a trend towards increasing their energy/fatigue ratio (+6.1, P = 0.073) by the end of the study relative to baseline. All other quality of life measures, including physical functioning, role functioning (physical or emotional), emotional well-being, social functioning, pain, and general health were not significantly changed by any intervention.

Table 7: SF-36 Questionnaire Results at Baseline and at End of the Study for All Participants in the PP Population (N = 39).

	Placebo	Sample 1	Sample 2	P Value¤

	Mean ±SD (n) Median (Min – Max) Within Group P Value[‡]	Mean ±SD (n) Median (Min – Max) Within Group P Value[‡]	Mean ±SD (n) Median (Min – Max) Within Group P Value[‡]	Overall [¤]	Placebo vs Sample 1[δ]	Placebo vs Sample 2[δ]	Sample 1 Vs Sample 2[δ]
Physical Functioning							
Baseline (Week 0)	88.6 ± 16.2 (14) 97.5 (50 – 100)	86.4 ± 15.2 (11) 95 (60 – 100)	81.1 ± 19.0 (14) 90 (35 – 100)	-	-	-	-
Visit 3 (Week 8)	88.6 ± 14.6 (14) 97.5 (65 – 100)	85.9 ± 12.0 (11) 85 (60 – 100)	80.7 ± 13.4 (14) 82.5 (50 – 100)	-	-	-	-
Change from Baseline to Week 8	0.0 ± 8.3 (14) 0 (-15 – 20) p = 1.000	-0.5 ± 7.2 (11) 0 (-15 – 15) p = 0.890	-0.4 ± 14.9 (14) -2.5 (-25 – 35) p = 0.720	0.713	0.78	0.21	0.63
Role Functioning/Physical							
Baseline (Week 0)	90.2 ± 19.7 (14) 100 (50 – 100)	97.7 ± 5.1 (11) 100 (87.5 – 100)	90.2 ± 17.1 (14) 100 (50 – 100)	-	-	-	-
Visit 3 (Week 8)	93.8 ± 12.7 (14) 100 (62.5 – 100)	95.5 ± 11.6 (11) 100 (62.5 – 100)	92.9 ± 16.0 (14) 100 (50 – 100)	-	-	-	-
Change from Baseline to Week 8	3.6 ± 19.9 (14) 0 (-25 – 50) p = 0.588	-2.3 ± 7.5 (11) 0 (-25 – 0) p = 1.000	2.7 ± 25.6 (14) 0 (-50 – 50) p = 0.833	0.596	0.99	1.00	0.98
Role Functioning/Emotional							
Baseline (Week 0)	96.4 ± 13.4 (14) 100 (50 – 100)	100.0 ± 0.0 (11) 100 (100 – 100)	97.6 ± 6.1 (14) 100 (83.3 – 100)	-	-	-	-
Visit 3 (Week 8)	100.0 ± 0.0 (14) 100 (100 – 100)	93.9 ± 13.5 (11) 100 (66.7 – 100)	95.2 ± 12.1 (14) 100 (66.7 – 100)	-	-	-	-
Change from Baseline to Week 8	3.6 ± 13.4 (14) 0 (0 – 50) p = 1.000	-6.1 ± 13.5 (11) 0 (-33.3 – 0) p = 0.346	-2.4 ± 14.4 (14) 0 (-33.3 – 16.7) p = 0.577	0.319	0.72	0.79	0.99
Energy/Fatigue							
Baseline (Week 0)	68.9 ± 21.0 (14) 72.5 (25 – 90)	68.2 ± 17.4 (11) 70 (35 – 90)	58.2 ± 20.1 (14) 60 (10 – 80)	-	-	-	-
Visit 3 (Week 8)	68.6 ± 16.5 (14) 65 (35 – 100)	77.3 ± 11.7 (11) 80 (60 – 100)	57.5 ± 19.3 (14) 60 (20 – 85)	-	-	-	-
Change from Baseline to Week 8	-0.4 ± 19.6 (14)[a,b] 0 (-40 – 45) p = 0.780	9.1 ± 10.0 (11)[b] 10 (-5 – 25) **p = 0.025**	-0.7 ± 15.8 (14)[a] 0 (-45 – 15) p = 0.691	0.135	0.419	0.341	**0.027**
Emotional Well-Being							
Baseline (Week 0)	84.9 ± 15.2 (14) 88 (40 – 100)	86.5 ± 7.4 (11) 88 (76 – 100)	76.3 ± 14.2 (14) 82 (48 – 96)	-	-	-	-
Visit 3 (Week 8)	84.3 ± 12.8 (14) 86 (52 – 100)	87.3 ± 12.2 (11) 92 (60 – 100)	81.1 ± 10.2 (14) 84 (60 – 92)	-	-	-	-
Change from Baseline to Week 8	-0.6 ± 13.8 (14) 0 (-32 – 36) p = 0.670	0.7 ± 10.1 (11) 4 (-24 – 12) p = 0.509	4.9 ± 12.8 (14) 4 (-12 – 28) p = 0.261	0.432	0.70	0.54	0.17
Social Functioning							
Baseline (Week 0)	51.8 ± 4.5 (14) 50 (50 – 62.5)	50.0 ± 5.6 (11) 50 (37.5 – 62.5)	48.2 ± 8.3 (14) 50 (25 – 62.5)	-	-	-	-
Visit 3 (Week 8)	50.0 ± 0.0 (14) 50 (50 – 50)	52.3 ± 9.4 (11) 50 (37.5 – 75)	56.2 ± 19.5 (14) 50 (25 – 100)	-	-	-	-
Change from Baseline to Week 8	-1.8 ± 4.5 (14) 0 (-12.5 – 0) p = 0.346	2.3 ± 10.9 (11) 0 (-12.5 – 25) p = 0.572	8.0 ± 20.0 (14) 0 (-12.5 – 50) p = 0.202	0.368	0.93	0.78	0.96
Pain							

Baseline (Week 0)	84.1 ± 18.3 (14) 90 (45 – 100)	83.4 ± 12.3 (11) 80 (57.5 – 100)	77.7 ± 15.1 (14) 78.8 (42.5 – 100)	-	-	-	-
Visit 3 (Week 8)	84.8 ± 14.6 (14) 90 (67.5 – 100)	83.0 ± 15.4 (11) 90 (57.5 – 100)	78.0 ± 20.6 (14) 85 (35 – 100)	-	-	-	-
Change from Baseline to Week 8	0.7 ± 11.0 (14) 0 (-12.5 – 22.5) p = 1.000	-0.5 ± 13.0 (11) 0 (-22.5 – 12.5) p = 1.000	0.4 ± 23.3 (14) -5 (-32.5 – 57.5) p = 0.944	0.900	0.90	0.66	0.92
General Health							
Baseline (Week 0)	85.4 ± 14.3 (14) 90 (55 – 100)	85.9 ± 14.3 (11) 90 (50 – 100)	75.7 ± 16.9 (14) 82.5 (40 – 95)	-	-	-	-
Visit 3 (Week 8)	83.2 ± 12.3 (14) 80 (60 – 100)	86.0 ± 8.2 (11) 85 (70 – 100)	77.5 ± 13.7 (14) 80 (55 – 100)	-	-	-	-
Change from Baseline to Week 8	-2.1 ± 11.4 (14) 0 (-30 – 10) p = 0.892	0.1 ± 12.2 (11) 0 (-15 – 31.2) p = 0.733	1.8 ± 11.9 (14) -2.5 (-15 – 30) p = 0.662	0.930	0.78	0.59	0.25

N, number; SD, standard deviation; Min, minimum; Max, maximum
¤ Between-group comparisons were made using the Kruskal Wallis test. δ Pairwise between-group comparisons were made using the Tukey procedure. ‡Within-group comparisons were made using the paired Student t-test. Probability values P≤0.05 are statistically significant.

[00103] For mRNA analysis, muscle biopsies were taken from participants (n=38) at Day 0 and at Day 57±3 to evaluate the effect of Sample 1 and 2 or placebo on mRNA expression levels within the Ubiquitin-proteasome pathway, growth factor/protein signaling, and pro-inflammatory signaling pathways. mRNA was isolated from muscle tissue collected at baseline and end-of-study. From the mRNA, cDNA was synthesis and analyzed using RT-PCR techniques. Anabolic/protein synthesis signaling genes (androgen receptor, insulin receptor, IGF-1 & IGF-1 receptor), catabolic/protein degradation signaling genes (atrogin-1 & MuFR1) and cytokines/cytokine receptors (IL-6, IL-6 receptor, TNFα, TNFrSF1A, TNFrSF1B) genes were assayed along with GAPDH as the endogenous control. The mRNA expression for the muscle biopsies collected suggests that the Samples affect both the anabolic and catabolic pathways.

[00104] For the growth factor/protein signaling genes, Table 8 reveals that there were no significant between group differences observed; however, there was a trend for both Carnitine groups to have greater transcription of these genes compared to placebo.

[00105] The subject number (N = 38) for Table 8 is reflected by the processing and isolation of mRNA from subjects' muscle biopsies taken on Day 0 and Day 57±3. Baseline and end of study muscle samples were required for this analysis (to see relative changes in the requested markers) and some of the subjects did not have enough skeletal muscle to yield the amount of mRNA required to run the molecular analysis.

Table 8: Relative Changes in Quantity of Gene Transcription (mRNA) from Baseline to End of the Study for All Participants in the PP Population (N = 38).

	Placebo	Sample 1	Sample 2	P Value[¤]			
	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Overall [¤]	Placebo vs Sample 1[δ]	Placebo vs Sample 2[δ]	Sample 1 Vs Sample 2[δ]
Androgen Receptor							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	0.93 ± 0.43 (14) 0.82 (0.47 – 1.67) p = 0.192*	0.94 ± 0.37 (11) 1.01 (0.24 – 1.41) p = 0.335*	1.10 ± 0.42 (13) 1.08 (0.61 – 2.26) p = 0.703*	0.421*	0.529*	0.999*	0.459*
Atrogin-1							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	0.98 ± 0.44 (14) 0.94 (0.38 – 1.68) p = 0.375*	1.51 ± 0.61 (11) 1.25 (0.97 – 2.68) **p = 0.013***	1.25 ± 0.46 (13) 1.1 (0.57 – 2.17) p = 0.142*	**0.030***	0.545*	**0.025***	0.205*
Insulin-like Growth Factor-1							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	0.52 ± 0.28 (14) 0.52 (0.14 – 1.23) **p < 0.001***	0.74 ± 0.53 (11) 0.62 (0.04 – 1.52) p = 0.070*	1.04 ± 0.72 (13) 0.86 (0.19 – 2.82) p = 0.404*	0.122*	0.223*	0.990*	0.143*
Insulin-like Growth Factor-1 Receptor							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	1.05 ± 0.65 (14) 0.99 (0.29 – 2.99) p = 0.515*	1.37 ± 1.21 (11) 1.21 (0.11 – 4.51) p = 0.817*	1.41 ± 0.86 (13) 1.13 (0.3 – 3.03) p = 0.422*	0.647*	0.745*	0.996*	0.663*
IL-6							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	0.56 ± 0.37 (14) 0.57 (0.05 – 1.3) **p = 0.005***	1.64 ± 2.09 (11) 0.77 (0.03 – 7.08) p = 0.460*	1.06 ± 0.69 (13) 0.8 (0.22 – 2.47) p = 0.473*	0.194*	0.870*	0.453*	0.183*
IL-6 Receptor							

Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	1.06 ± 1.07 (14) 0.74 (0.27 – 4.28) p = 0.249*	1.29 ± 0.88 (11) 1.17 (0.31 – 3.3) p = 0.885*	1.28 ± 0.68 (13) 1.2 (0.39 – 2.84) p = 0.455*	0.371*	0.949*	0.584*	0.368*
Insulin Receptor							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	0.97 ± 0.58 (14) 1.02 (0.1 – 2.29) p = 0.235*	1.26 ± 1.36 (11) 0.91 (0.22 – 4.96) p = 0.556*	1.18 ± 0.83 (13) 0.92 (0.09 – 3.49) p = 0.744*	0.813*	0.966*	0.933*	0.799*
MuRF1							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	1.23 ± 0.76 (14) 1.02 (0.48 – 3.24) p = 0.679*	2.00 ± 1.27 (11) 1.8 (0.9 – 5.44) **p = 0.005***	1.40 ± 1.10 (13) 1.2 (0.37 – 4.68) p = 0.503*	0.092*	0.178*	0.100*	0.957*
TNF-α							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	0.43 ± 0.37 (14) 0.32 (0.02 – 1.28) **p = 0.001***	0.76 ± 1.13 (11) 0.48 (0.02 – 3.99) **p = 0.033***	1.13 ± 1.17 (13) 0.57 (0.28 – 4.44) p = 0.320*	0.054*	0.188*	0.873*	0.053*
TNF Receptor Superfamily 1A							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	0.61 ± 0.31 (14) 0.57 (0.17 – 1.15) **p = 0.001***	0.83 ± 0.54 (11) 0.74 (0.18 – 1.91) p = 0.097*	1.00 ± 0.61 (13) 0.86 (0.35 – 2.67) p = 0.385*	0.145*	0.501*	0.722*	0.124*
TNF Receptor Superfamily 1B							
Relative Quantity change in Gene Transcription (normalized to GAPDH) Baseline compared to End of Study	0.67 ± 0.38 (14) 0.58 (0.18 – 1.44) **p = 0.004***	0.75 ± 0.58 (11) 0.58 (0.09 – 1.92) p = 0.056*	1.04 ± 0.70 (13) 0.93 (0.21 – 3.1) p = 0.432*	0.217*	0.237*	0.936*	0.353*

N, number; SD, standard deviation; Min, minimum; Max, maximum

Δ Between-group comparisons were made using ANCOVA. δ Pairwise between-group comparisons were made using the Tukey procedure. Within-group comparisons were made using the paired Student t-test. Within-group comparisons were made using the paired Student t-test. Probability values P≤0.05 are statistically significant.

[00106] The muscle biopsies taken on Day 0 and Day 57±3 from participants (n=33) were used to evaluate the effect of Sample 1 and 2 or placebo on protein expression/activity of the mTOR/S6K/4EBP1 protein synthesis and NFκβ (p65/p50) pro-inflammatory signaling pathways. Protein was isolated from muscle tissue collected at baseline and end-of-study, when pre- and post-exercise biopsies were collected. Post-exercise muscle biopsies were obtained approximately 1h following the pre-exercise biopsies. Western blotting was done with equal concentrations (40µg) of protein separated on 8-12% SDS-PAGE gels, which were then transferred onto nitrocellulose membranes, and immune-labeled with antibodies specific to each protein of interest. Detection of these antibodies was done using enhanced chemiluminescence (ECL).

[00107] As shown in Table 9, there were notable changes in the muscle protein levels of participants taking Sample 1 and Sample 2 from week 0 (baseline) to week 8 (end of study) pre-exercise. In Table 9, in order to minimize variability between runs, the areas under of the curve were standardized relative to the micrograms of protein.

[00108] Figures 6-9 illustrate changes in mTOR expression from baseline to week 8 in each treatment group. As seen in Table 9 and Fig. 9, within group, participants on Sample 2 showed a significant 81% increase in total mTOR expression (p=0.017) at week 8 – pre-exercise relative to baseline mTOR levels.

[00109] Figures 14-17 illustrate changes in Phospho-4EBP1 and Total-4EBP1 from baseline to week 8 in each treatment group. As shown in Table 9 and Fig. 15, Sample 2 had a trend towards a 24% reduction in the phosphorylation of 4EBP-1 protein (p=0.057) at week 8 – pre-exercise compared to week 0.

[00110] Figures 18-21 illustrate changes in Phospho-P65 and Total-P65 from baseline to week 8 in each treatment group. As seen in Table 9 and Fig. 22, the Sample 1 group showed a significant within group decrease of 38% for p65 phosphorylation of the NF-κβ complex (p=0.021) when comparing week 0 to week 8 – pre-exercise. As shown in Fig. 21, there was a trend towards the Sample 1 group having a significantly reduced amount of total p65 expression compared to the placebo group when comparing week 0 to week 8 – pre-exercise (p = 0.087).

[00111] As shown in Table 9 and Fig. 6, there were also significant within group changes in muscle protein levels of participants taking Sample 1 and Sample 2 from

week 0 (baseline) to week 8 (end of study) post-exercise. As illustrated in Figures 6-9, phosphorylation of mTOR was significantly increased by 41% (p=0.015) in the Sample 1 group and reduced by 35% (p=0.051) in the Sample 2 group. However, as Fig. 9 shows, total mTOR expression was increased by 56% (p=0.058) in the Sample 2 group, which was borderline significant and may compensate for the decrease in its phosphorylation for this group at week 8 – post-exercise relative to baseline. As seen in Fig.7, between groups, there was a significant difference between the Sample 1 and Sample 2 groups when comparing the changes from week 0 to week 8 – post-exercise of phospho-mTOR (p = 0.016).

[00112] Figures 10-13 illustrate changes in Phospho-S6K and Total-S6K from baseline to week 8 in each treatment group. As seen in Fig 11, S6K phosphorylation was significantly decreased by 36% (p=0.019) in the Sample 1 group when comparing week 0 to week 8 – post-exercise. On the other hand, as shown in Fig. 13, total S6K protein expression was significantly increased by 101% (p=0.038) in the Sample 1 group when comparing week 0 to week 8 – post-exercise, and trended towards a significant increase of 47% in the Sample 2 group (p=0.098) as well.

[00113] As illustrated in Fig. 14 and 15, the phosphorylation of 4EBP-1 was significantly decreased by 56% (p=0.04) and 38% (p=0.019), respectively in Sample 1 and Sample 2 groups when comparing within group changes at week 0 to week 8 – post-exercise.

[00114] As shown in Fig. 19, phosphorylation of the p65 subunit of NF-κβ was significantly reduced by 56% (p=0.017) in the Sample 1 group at week 8 – post-exercise relative to baseline.

[00115] Figures 22 and 23 illustrate changes in Total-P50 from baseline to week 8 in each treatment group. As seen in Fig. 25 and 26, there were no significant changes in total p50 expression from baseline to week 8 in any of the treatment groups.

[00116] In Figure 24, a representative immuno-blot for each indicated protein is shown for each treatment group (at baseline vs. end of study, 8 weeks). GAPDH was used as an internal loading control. In Fig. 14, T = total and P = phospho antibodies.

[00117] The subject number (N = 33) for Table 9 is reflected by the processing and isolation of protein from subjects muscle biopsies. Baseline and end of study muscle

samples were required for this analysis (to see relative changes in the requested markers) and some of the subjects did not have enough skeletal muscle to yield the amount of protein required to run the molecular analysis.

Table 9: Quantity of Proteins at Week 0 and Pre and Post Exercise at Week 8 for All Participants in the PP Population (N = 33).

	Placebo	Carnipure Product 1	Carnipure Product 2	P Value[¤]			
	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Overall [Δ]	Placebo vs Carnipure Product 1[δ]	Placebo vs Carnipure Product 2[δ]	Carnipure Product 1 Vs Carnipure Product 2 [δ]
AUC of Phospho-mTOR per Microgram Protein (x10[5])							
Week 0 Baseline Pre-Exercise	8.5 ± 4.4 (10) 6.8 (2.4 – 15.9)	6.8 ± 4.5 (11) 4.5 (2.3 – 17)	7.6 ± 3.4 (12) 6.9 (2.4 – 15)	-	-	-	-
Week 8 Pre-Exercise	8.5 ± 3.9 (10) 8 (2.8 – 13.3)	7.9 ± 5.4 (11) 5.9 (2.6 – 19)	8.7 ± 4.2 (12) 9.5 (2.7 – 14.7)	-	-	-	-
Week 8 Post-Exercise	7.0 ± 4.8 (10) 5.8 (1.5 – 15.7)	9.6 ± 4.6 (11) 9.7 (2.4 – 16)	5.1 ± 2.1 (11) 4.4 (2 – 8.8)	-	-	-	-
Change from Week 0 to Week 8 Pre-Exercise	0.0 ± 5.5 (10) 0.7 (-10.5 – 7) p = 0.938*	1.1 ± 5.7 (11) 1.5 (-13 – 9.6) p = 0.442*	1.1 ± 4.7 (12) 0.4 (-8.3 – 8.8) p = 0.556*	0.978*	1.000*	0.985*	0.980*
Change from Week 0 to Week 8 Post-Exercise	-1.5 ± 3.4 (10) -0.9 (-9.5 – 3.1) p = 0.255*	2.8 ± 3.3 (11) 2.3 (-2.5 – 7.2) p = 0.015*	-2.7 ± 3.5 (11) -2 (-8.5 – 2.1) p = 0.051*	0.016*	0.078*	0.800*	0.016*
Change from Pre-Exercise to Post-Exercise Week 8	-1.5 ± 5.6 (10) -2.8 (-9.8 – 9.8) p = 0.245*	1.7 ± 5.5 (11) 2.8 (-11.1 – 10.5) p = 0.237*	-3.4 ± 5.3 (11) -1.2 (-11.8 – 3.9) p = 0.105*	0.067*	0.246*	0.776*	0.061*
AUC of Total mTOR per Microgram Protein (x10[5])							
Week 0 Baseline Pre-Exercise	5.6 ± 4.7 (10) 5.1 (0.2 – 13.5)	6.0 ± 5.3 (11) 5.9 (0.5 – 17.9)	4.3 ± 4.7 (12) 2.8 (0.7 – 17.7)	-	-	-	-
Week 8 Pre-Exercise	5.0 ± 5.2 (10) 3.3 (0.1 – 15.9)	7.5 ± 7.0 (11) 6 (0.3 – 18.5)	7.8 ± 7.2 (12) 4.7 (1.4 – 26.1)	-	-	-	-
Week 8 Post-Exercise	6.7 ± 4.4 (10) 5.7 (1.4 – 15.7)	7.4 ± 6.4 (11) 5.6 (1 – 18.7)	7.0 ± 5.5 (11) 4.2 (1.1 – 18.3)	-	-	-	-
Change from Week 0 to Week 8 Pre-Exercise	-0.7 ± 4.7 (10) -0.3 (-10.7 – 6.7) p = 0.590*	1.5 ± 5.5 (11) 0.5 (-8.5 – 9.8) p = 0.795*	3.5 ± 4.3 (12) 2.7 (-0.8 – 10.9) p = 0.017*	0.122*	0.758*	0.112*	0.364*
Change from Week 0 to Week 8 Post-Exercise	1.0 ± 3.6 (10) 0.8 (-6.6 – 6.5) p = 0.121*	1.5 ± 5.8 (11) 0.8 (-6.7 – 13.7) p = 0.487*	2.4 ± 5.6 (11) 2.1 (-9 – 10.6) p = 0.058*	0.858*	0.864*	0.994*	0.905*
Change	1.7 ± 4.2 (10)	-0.0 ± 7.0 (11)	-1.3 ± 7.5 (11)	0.591*	0.721*	0.587*	0.967*

from Pre-Exercise to Post-Exercise Week 8	1.3 (-7.5 – 7.1) p = 0.057*	1.1 (-16.5 – 10) p = 0.650*	-0.3 (-17.3 – 8) p = 0.637*				
AUC of Phospho-S6K per Microgram Protein ($x10^1$)							
Week 0 Baseline Pre-Exercise	8.3 ± 4.1 (10) 8 (1.7 – 14.3)	10.8 ± 3.4 (11) 9.7 (8.1 – 18)	8.4 ± 4.3 (12) 8 (1.6 – 17.4)	-	-	-	-
Week 8 Pre-Exercise	8.2 ± 4.5 (10) 8.2 (2.8 – 15.9)	11.4 ± 3.6 (11) 11.7 (4.8 – 15.2)	11.2 ± 8.9 (12) 8.4 (3.9 – 35.2)	-	-	-	-
Week 8 Post-Exercise	9.4 ± 9.4 (10) 7.1 (1.1 – 34.3)	6.9 ± 1.8 (11) 7.2 (4.9 – 10.6)	7.3 ± 4.6 (11) 6 (2 – 17.8)	-	-	-	-
Change from Week 0 to Week 8 Pre-Exercise	-0.1 ± 4.0 (10) 1.4 (-6.2 – 5.3) p = 0.959*	0.5 ± 4.5 (11) 0.2 (-9 – 6.5) p = 0.816*	2.7 ± 7.5 (12) 1.8 (-5.3 – 24.6) p = 0.159*	0.449*	0.546*	0.482*	0.999*
Change from Week 0 to Week 8 Post-Exercise	1.1 ± 11.1 (10) -0.3 (-8 – 30.8) p = 0.774*	-3.9 ± 4.0 (11) -2.4 (-13 – -0.9) p = 0.005*	-0.8 ± 3.4 (11) 0.4 (-9.4 – 4) p = 0.384*	0.864*	0.852*	0.972*	0.943*
Change from Pre-Exercise to Post-Exercise Week 8	1.1 ± 10.5 (10) -2.8 (-7.9 – 28.9) p = 0.812*	-4.4 ± 4.8 (11) -3.8 (-9.9 – 5.8) p = 0.019*	-4.0 ± 7.8 (11) -3.1 (-25.6 – 3.4) p = 0.046*	0.870*	0.946*	0.858*	0.977*
AUC of Total S6K per Microgram Protein ($x10^1$)							
Week 0 Baseline Pre-Exercise	18.6 ± 14.0 (10) 16.1 (4.7 – 44)	17.7 ± 12.5 (11) 17.3 (0.4 – 41.9)	19.2 ± 9.0 (12) 18.9 (7.5 – 31.7)	-	-	-	-
Week 8 Pre-Exercise	26.6 ± 14.7 (10) 24.1 (1.3 – 57.6)	20.3 ± 12.2 (11) 23 (2 – 43)	19.5 ± 7.3 (12) 20.4 (8.1 – 29.8)	-	-	-	-
Week 8 Post-Exercise	28.3 ± 28.0 (10) 20.3 (6.4 – 102.4)	35.6 ± 37.1 (11) 18.2 (6.1 – 122.5)	28.3 ± 17.5 (11) 28.2 (6.8 – 57)	-	-	-	-
Change from Week 0 to Week 8 Pre-Exercise	8.0 ± 13.8 (10) 10.8 (-17.8 – 26.9) p = 0.373*	2.6 ± 13.9 (11) 1.6 (-25.4 – 20.5) p = 0.310*	0.2 ± 13.0 (12) -0.1 (-23.5 – 20.1) p = 0.833*	0.825*	0.841*	0.861*	0.998*
Change from Week 0 to Week 8 Post-Exercise	9.8 ± 29.5 (10) 1.3 (-24.1 – 83.4) p = 0.180*	17.9 ± 34.5 (11) 7 (-11.3 – 104.8) p = 0.038*	9.1 ± 13.3 (11) 4.3 (-11.7 – 31.5) p = 0.098*	0.665*	0.692*	0.996*	0.739*
Change from Pre-Exercise to Post-Exercise Week 8	2 ± 37 (10) -11 (-27 – 101) p = 0.965*	15 ± 37 (11) 4 (-30 – 99) p = 0.162*	10 ± 16 (11) 1 (-12 – 35) p = 0.218*	0.919*	0.920*	0.946*	0.997*
AUC of Phospho-4EBP1 per Microgram Protein ($x10^1$)							
Week 0 Baseline Pre-Exercise	23.1 ± 14.6 (10) 21.8 (2 – 41.2)	27.5 ± 20.6 (11) 28.4 (4.3 – 64)	22.9 ± 12.6 (12) 23.3 (6.8 – 52.4)	-	-	-	-
Week 8	14.6 ± 11.1	21.0 ± 21.8	17.5 ± 14.6	-	-	-	-

Pre-Exercise	(10) 12.5 (3.9 – 34)	(11) 12.8 (0.4 – 62)	(12) 13.2 (2 – 46)				
Week 8 Post-Exercise	16.2 ± 10.5 (10) 17.3 (3.4 – 31.1)	12.2 ± 6.5 (11) 9.7 (4.8 – 22.9)	13.9 ± 11.9 (11) 10.9 (1.8 – 33.9)	-	-	-	-
Change from Week 0 to Week 8 Pre-Exercise	-8.5 ± 15.4 (10) -1.3 (-34.8 – 6) p = 0.276*	-6.5 ± 12.7 (11) -2 (-29.8 – 14.3) p = 0.153*	-5.5 ± 16.6 (12) -4.8 (-39 – 21.5) p = 0.057*	0.924*	0.918*	0.985*	0.968*
Change from Week 0 to Week 8 Post-Exercise	-6.9 ± 14.2 (10) -8 (-35.2 – 11.7) p = 0.316*	-15.3 ± 19.8 (11) -5.5 (-56.1 – 4.3) p = 0.040*	-8.8 ± 11.1 (11) -4.9 (-25 – 4.2) p = 0.019*	0.583*	0.802*	0.556*	0.908*
Change from Pre-Exercise to Post-Exercise Week 8	1.6 ± 15.0 (10) 2.5 (-28 – 24.7) p = 0.816*	-8.8 ± 23.6 (11) -0.7 (-54.1 – 17.9) p = 0.898*	-0.9 ± 15.9 (11) -0.1 (-26.2 – 25.2) p = 0.865*	0.765*	0.915*	0.745*	0.938*
AUC of Total 4EBP1 per Microgram Protein ($x10^1$)							
Week 0 Baseline Pre-Exercise	10.1 ± 5.2 (10) 8.3 (4.8 – 19.9)	20.0 ± 10.6 (11) 18.2 (3.5 – 38.8)	20.8 ± 11.4 (12) 18.7 (3.9 – 47.1)	-	-	-	-
Week 8 Pre-Exercise	21.1 ± 32.3 (10) 10.3 (1.8 – 110.6)	16.4 ± 13.5 (11) 12.4 (5.7 – 42.9)	13.8 ± 7.0 (12) 14.7 (0.8 – 28.2)	-	-	-	-
Week 8 Post-Exercise	14.6 ± 11.0 (10) 11.7 (1.1 – 34.3)	17.8 ± 7.3 (11) 17.9 (3.8 – 27.9)	16.1 ± 13.6 (11) 12.8 (3.3 – 51.4)	-	-	-	-
Change from Week 0 to Week 8 Pre-Exercise	11.0 ± 33.1 (10) 1.9 (-4.8 – 104.7) p = 0.619*	-3.6 ± 10.9 (11) -4.3 (-19.7 – 17.6) p = 0.170*	-7.0 ± 14.3 (12) -2.6 (-38.8 – 10.2) p = 0.151*	0.827*	0.967*	0.821*	0.916*
Change from Week 0 to Week 8 Post-Exercise	4.5 ± 8.9 (10) 2.6 (-7.4 – 21.3) p = 0.819*	-2.2 ± 12.6 (11) -3 (-23.6 – 17.3) p = 0.817*	-5.0 ± 11.4 (11) -3.2 (-27.1 – 15.7) p = 0.114*	0.713*	0.873*	0.972*	0.698*
Change from Pre-Exercise to Post-Exercise Week 8	-6.5 ± 31.4 (10) 3.6 (-92.7 – 19.6) p = 0.725*	1.4 ± 16.5 (11) 5 (-30 – 20.5) p = 0.497*	3.6 ± 15.5 (11) 0.5 (-10.9 – 43.1) p = 0.607*	0.461*	0.428*	0.773*	0.828*
AUC of Phospho-p65 per Microgram Protein ($x10^1$)							
Week 0 Baseline Pre-Exercise	9.0 ± 10.1 (10) 5.4 (2.1 – 30.9)	19.4 ± 15.2 (11) 16.1 (4.3 – 54.4)	10.9 ± 10.2 (12) 10.3 (2 – 40.3)	-	-	-	-
Week 8 Pre-Exercise	10.0 ± 8.9 (10) 5.3 (1 – 23.8)	12.1 ± 8.2 (11) 9.3 (4.6 – 26.5)	11.1 ± 10.2 (12) 7.9 (1.6 – 32.2)	-	-	-	-
Week 8 Post-Exercise	7.4 ± 7.0 (10) 8.1 (0.4 –	8.6 ± 4.3 (11) 9.5 (1.2 – 18.6)	7.4 ± 4.1 (11) 6.6 (1.2 – 15.4)	-	-	-	-

	20.6)						
Change from Week 0 to Week 8 Pre-Exercise	1.0 ± 6.8 (10) -0.5 (-10.6 – 15) p = 0.837*	-7.4 ± 12.0 (11) -4 (-37 – 9.8) p = 0.021*	0.2 ± 6.6 (12) -0.6 (-8.1 – 16.8) p = 0.705*	0.488*	0.508*	0.973*	0.574*
Change from Week 0 to Week 8 Post-Exercise	-1.7 ± 10.5 (10) -1.6 (-22.8 – 18.5) p = 0.272*	-10.8 ± 15.2 (11) -6.6 (-48.9 – 5.3) p = 0.017*	-3.3 ± 10.9 (11) 0.5 (-33.7 – 6.2) p = 0.444*	0.522*	0.737*	0.497*	0.946*
Change from Pre-Exercise to Post-Exercise Week 8	-2.6 ± 9.5 (10) -4.8 (-12.3 – 19.3) p = 0.303*	-3.5 ± 9.0 (11) 1.5 (-19.8 – 5.4) p = 0.275*	-3.2 ± 11.3 (11) -0.1 (-25.6 – 8.1) p = 0.701*	0.302*	0.330*	0.407*	0.982*
AUC of Total p65 per Microgram Protein (x10^3)							
Week 0 Baseline Pre-Exercise	13.8 ± 11.8 (10) 9.2 (1.7 – 31)	6.8 ± 5.6 (11) 3.5 (1.4 – 18.2)	11.4 ± 8.2 (12) 10.3 (1 – 26.1)	-	-	-	-
Week 8 Pre-Exercise	14.2 ± 9.2 (10) 13.2 (2.6 – 26.5)	6.0 ± 4.6 (11) 5 (1.5 – 16.7)	9.0 ± 5.4 (12) 7.7 (1.5 – 21.1)	-	-	-	-
Week 8 Post-Exercise	11.1 ± 8.1 (10) 8.3 (3.1 – 27.5)	8.6 ± 7.1 (11) 6 (1.3 – 21.1)	8.8 ± 6.8 (11) 5.8 (2.9 – 26.6)	-	-	-	-
Change from Week 0 to Week 8 Pre-Exercise	0.4 ± 9.1 (10) 1.5 (-14.7 – 17.6) p = 0.245*	-0.8 ± 5.9 (11) 0.1 (-11.4 – 9.1) p = 0.775*	-2.4 ± 8.4 (12) -0.5 (-19.7 – 6) p = 0.787*	0.103*	0.087*	0.372*	0.617*
Change from Week 0 to Week 8 Post-Exercise	-2.7 ± 13.5 (10) -1.9 (-25.2 – 19.3) p = 0.952*	1.8 ± 7.1 (11) 2.7 (-6 – 19.7) p = 0.565*	-3.5 ± 9.1 (11) -2.2 (-20.9 – 10.4) p = 0.367*	0.671*	0.667*	0.796*	0.969*
Change from Pre-Exercise to Post-Exercise Week 8	-3.1 ± 9.4 (10) -3.3 (-18.7 – 9.5) p = 0.323	2.6 ± 9.4 (11) 1 (-9.6 – 19.6) p = 0.379	-0.9 ± 10.5 (11) -2.6 (-15.3 – 23.3) p = 0.787	0.509*	0.478*	0.773*	0.821*
AUC of Total-p50 per Microgram Protein (x10^3)							
Week 0 Baseline Pre-Exercise	15.7 ± 6.0 (10) 16.8 (7.7 – 21.9)	13.9 ± 9.2 (11) 9.5 (5.7 – 33.6)	11.6 ± 6.3 (12) 8.5 (3.3 – 21.6)	-	-	-	-
Week 8 Pre-Exercise	18.2 ± 6.5 (10) 19.1 (7.8 – 27.7)	13.8 ± 8.0 (11) 14.3 (6 – 34.7)	12.8 ± 5.3 (12) 11.7 (4.4 – 21.6)	-	-	-	-
Week 8 Post-Exercise	21.6 ± 14.1 (10) 21.6 (3.2 – 48.4)	10.6 ± 6.7 (11) 9.1 (3.2 – 21.6)	17.4 ± 12.6 (11) 15.5 (4.5 – 41.1)	-	-	-	-
Change from Week 0 to Week 8 Pre-Exercise	2.5 ± 6.0 (10) 1.8 (-9 – 12) p = 0.237*	-0.0 ± 4.4 (11) 0.5 (-7.1 – 9.6) p = 0.599*	1.2 ± 5.1 (12) 0.4 (-7.6 – 9.6) p = 0.352*	0.380*	0.397*	0.487*	0.986*
Change from	5.8 ± 15.2 (10) 1.7 (-12.9 –	-3.2 ± 10.3 (11) -0.3 (-27.7 –	5.4 ± 11.7 (11) 1.2 (-10 – 33)	0.209*	0.243*	0.967*	0.331*

Week 0 to Week 8	37.7) p = 0.683*	6.7) p = 0.294*	p = 0.248*				
Post-Exercise Change from Pre-Exercise to Post-Exercise Week 8	3.3 ± 15.6 (10) 2.1 (-14.5 – 37) p = 0.912*	-3.2 ± 11.2 (11) 0.9 (-28.8 – 7.1) p = 0.240*	4.2 ± 13.4 (11) 4.6 (-11.5 – 33.3) p = 0.727*	0.174*	0.165*	0.778*	0.419*

N, number; SD, standard deviation; Min, minimum; Max, maximum; AUC, area under the curve
Δ Between-group comparisons were made using ANCOVA. δ Pairwise between-group comparisons were made using the Tukey procedure. Within-group comparisons were made using the paired Student t-test. *Logarithmic transformation required to achieve normality. Probability values P≤0.05 are statistically significant.

[00118] Anthropometrics and vital signs were taken for each participant prior to Day 0 and on Day 57±3. As seen in Table 10, there were no significant between-group differences for both systolic and diastolic blood pressure as well as heart rate, weight, and BMI for all post randomization time points. Within groups, there was a significant change in diastolic blood pressure for the Sample 1 group, as well as mean heart rate in the Sample 2 group relative to baseline. All blood pressure and heart rate values were within acceptable clinical range.

Table 10: Vital Signs for All Participants Enrolled in the Study at Baseline and Week 8 (N=42).

	Placebo Mean ±SD (n) Median (Min – Max) Within Group P Value	Sample 1 Mean ±SD (n) Median (Min – Max) Within Group P Value	Sample 2 Mean ±SD (n) Median (Min – Max) Within Group P Value	P Value Δ
Mean Systolic Blood Pressure (mmHg)				
Baseline (Week 0)	112.2 ± 9.5 (14) 112.7 (97.3 – 131.3)	119.1 ± 10.3 (14) 117.5 (104.7 – 141.7)	115.7 ± 12.9 (14) 115.7 (96 – 138.3)	-
Visit 3 (Week 8)	112.0 ± 11.1 (13) 112.7 (94 – 134.3)	121.2 ± 11.1 (14) 121.3 (101.3 – 140)	118.3 ± 12.9 (14) 118.7 (94 – 142)	-
Change from Baseline to Week 8	0.4 ± 11.0 (13) 0.3 (-18.7 – 20) p = 0.902	2.1 ± 8.5 (14) 2.7 (-14 – 21) p = 0.373	2.6 ± 12.3 (14) 1.7 (-18 – 20) p = 0.435	0.447
Mean Diastolic Blood Pressure (mmHg)				
Baseline (Week 0)	69.2 ± 6.9 (14) 70.2 (54.7 – 78.7)	70.0 ± 7.0 (14) 70.8 (60.7 – 84.7)	71.9 ± 9.1 (14) 73.3 (52.3 – 85.7)	-
Visit 3 (Week 8)	69.3 ± 6.1 (13) 69.3 (60 – 80)	74.1 ± 6.3 (14) 73.5 (62.7 – 88)	74.9 ± 11.9 (14) 75.5 (55.3 – 96.7)	-
Change from Baseline to Week 8	0.1 ± 7.4 (13) -0.3 (-10.7 – 19.3) p = 0.952	4.1 ± 6.0 (14) 5.8 (-11.3 – 11.3) **p = 0.024**	3.0 ± 7.6 (14) 3.5 (-9.7 – 16.7) p = 0.162	0.223
Mean Heart Rate (BPM)				
Baseline (Week 0)	73.6 ± 12.6 (14) 69.8 (52 – 103.3)	71.6 ± 7.3 (14) 72 (56.3 – 83.3)	71.7 ± 6.9 (14) 72.5 (54.7 – 81.3)	-
Visit 3 (Week 8)	68.1 ± 7.2 (13) 69.3 (53.3 – 81.3)	69.9 ± 7.1 (14) 69.2 (56 – 85)	66.6 ± 5.2 (14) 66.7 (58.7 – 74.7)	-
Change from Baseline to Week 8	-3.2 ± 10.6 (13) -3.3 (-20.7 – 13.3) p = 0.297	-1.7 ± 8.4 (14) -1.3 (-16 – 13.3) p = 0.464	-5.1 ± 7.6 (14) -4.7 (-22.7 – 8) **p = 0.024**	0.391
Weight (kg)				

Baseline (Week 0)	72.1 ± 8.3 (14) 71.2 (60.5 – 86.2)	74.8 ± 13.4 (14) 75.3 (55.8 – 98.2)	76.5 ± 14.2 (14) 72.8 (56 – 102)	-
Visit 3 (Week 8)	73.1 ± 8.0 (13) 73 (61.5 – 88)	75.3 ± 13.4 (14) 75 (57 – 97.9)	77.0 ± 14.1 (14) 74.5 (56.5 – 102.3)	-
Change from Baseline to Week 8	0.23 ± 0.82 (13) 0.2 (-1.5 – 1.8) p = 0.294‡	0.46 ± 1.89 (14) 0.65 (-3.2 – 4.6) p = 0.330‡	0.48 ± 1.23 (14) 0.5 (-2.2 – 3) p = 0.116‡	0.678¤
BMI (kg/m^2)				
Baseline (Week 0)	26.00 ± 1.83 (14) 25.16 (23.49 – 30.18)	26.54 ± 3.03 (14) 26.78 (21.8 – 31.56)	27.60 ± 3.05 (14) 27.31 (22.58 – 32.48)	-
Visit 3 (Week 8)	26.22 ± 2.00 (13) 25.6 (23.67 – 30.81)	26.70 ± 2.96 (14) 26.89 (22.27 – 31.46)	27.77 ± 2.89 (14) 27.69 (22.66 – 32.58)	-
Change from Baseline to Week 8	0.10 ± 0.28 (13) 0.07 (-0.45 – 0.63) p = 0.239	0.16 ± 0.66 (14) 0.24 (-1.17 – 1.51) p = 0.372	0.17 ± 0.47 (14) 0.18 (-0.88 – 1.13) p = 0.195	0.820

N, number; SD, standard deviation; Min, minimum; Max, maximum; mmHg, millimeters of mercury; BPM, beats per minute. Δ Between-group comparisons were made using ANCOVA. ¤ Between group were made using the Kruskal Wallis test. Within-group comparisons were made using the paired Student t-test. ‡ Within group were made using the Sign Rank test. Probability values P≤0.05 are statistically significant.

[00119] Blood samples were taken for each participant taken prior to Day 0 and on Day 57±3 to measure hematology and clinical chemistry parameters. Table 11 demonstrates that there were no significant between group changes in hematology and clinical chemistry parameters for participants, with the exception of creatinine (P = 0.027), estimated globular filtration rate (P = 0.029), and aspartate transaminase (P = 0.034) concentrations. However, these markers remained within their established clinical reference ranges.

[00120] There were five safety parameters that showed significant within group change from screening to the end of study (week 8). White blood cell count (P = 0.021), lymphocyte count (P = 0.022), and aspartate transaminase levels (P = 0.033) increased for subjects on Sample 1, while chloride levels decreased significantly (P = 0.013) for this group. The creatinine concentration (P = 0.05) was significantly increased for the Sample 2 group. Estimated globular filtration rate (P=0.069) was not significantly changed for subjects within the Sample 2 group. Overall, all hematological and clinical parameters were within acceptable clinical range for this population.

Table 11: Haematology and Clinical Chemistry Parameters for All Enrolled Participants at Screening and Week 8 (N=42).

	Placebo	Sample 1	Sample 2	P Value Δ
	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	
Hemoglobin Concentration (g/L)				
Screening	138.4 ± 7.9 (14) 137.5 (128 – 156)	144.0 ± 10.0 (14) 143.5 (131 – 159)	140.3 ± 12.6 (14) 136 (124 – 167)	-

Visit 3 (Week 8)	138.6 ± 6.5 (14) 138 (128 – 151)	141.6 ± 9.3 (13) 140 (124 – 154)	137.9 ± 12.2 (14) 138 (116 – 159)	-
Change from Screening to Week 8	0.3 ± 7.6 (14) 1.5 (-15 – 11) p = 0.834‡	-1.2 ± 6.5 (13) 1 (-14 – 12) p = 0.505‡	-2.4 ± 7.1 (14) 0 (-18 – 7) p = 0.307‡	0.559¤
Hematocrit (L/L)				
Screening	0.4021 ± 0.0236 (14) 0.4 (0.37 – 0.45)	0.4229 ± 0.0246 (14) 0.43 (0.39 – 0.46)	0.4093 ± 0.0300 (14) 0.4 (0.37 – 0.47)	-
Visit 3 (Week 8)	0.4064 ± 0.0178 (14) 0.41 (0.38 – 0.44)	0.4162 ± 0.0260 (13) 0.41 (0.37 – 0.46)	0.4036 ± 0.0310 (14) 0.405 (0.34 – 0.45)	-
Change from Screening to Week 8	0.0043 ± 0.0217 (14) 0.005 (-0.04 – 0.04) p = 0.420‡	-0.0046 ± 0.0176 (13) -0.01 (-0.04 – 0.03) p = 0.337‡	-0.0057 ± 0.0187 (14) 0 (-0.05 – 0.02) p = 0.262‡	0.374¤
White Blood Cell Count (x E9/L)				
Screening	5.91 ± 1.16 (14) 5.65 (4.6 – 7.9)	5.88 ± 1.88 (14) 5.3 (3.8 – 9.3)	6.25 ± 1.86 (14) 6 (3.8 – 10.8)	-
Visit 3 (Week 8)	5.64 ± 1.32 (14) 5.6 (3.7 – 8.7)	6.59 ± 1.75 (13) 6.4 (4.3 – 10.5)	6.17 ± 1.91 (14) 6.15 (3.9 – 11)	-
Change from Screening to Week 8	-0.28 ± 1.10 (14) -0.3 (-2.2 – 1.3) p = 0.441‡	0.68 ± 0.83 (13) 0.5 (-0.4 – 2.3) **p = 0.021**‡	-0.08 ± 0.87 (14) 0 (-1.4 – 1.2) p = 0.753‡	0.054¤
Red Blood Cell Count (x E12/L)				
Screening	4.48 ± 0.26 (14) 4.47 (3.94 – 5.04)	4.72 ± 0.40 (14) 4.7 (4.01 – 5.34)	4.55 ± 0.35 (14) 4.49 (4.08 – 5.12)	-
Visit 3 (Week 8)	4.58 ± 0.22 (14) 4.56 (4.23 – 4.95)	4.66 ± 0.44 (13) 4.61 (3.96 – 5.4)	4.44 ± 0.34 (14) 4.42 (3.87 – 5.01)	-
Change from Screening to Week 8	0.09 ± 0.35 (14) 0.03 (-0.41 – 0.93) p = 0.329*	-0.07 ± 0.21 (13) -0.05 (-0.48 – 0.31) p = 0.244*	-0.11 ± 0.30 (14) -0.07 (-0.97 – 0.21) p = 0.212*	0.222*
Mean Corpuscular Volume (fL)				
Screening	89.9 ± 3.0 (14) 89 (85.1 – 96.3)	89.7 ± 4.6 (14) 88.2 (83.3 – 100.2)	89.9 ± 3.5 (14) 90.8 (81.2 – 93.6)	-
Visit 3 (Week 8)	88.6 ± 3.7 (14) 89 (80.5 – 96.3)	89.2 ± 3.0 (13) 89 (84.6 – 93.8)	90.8 ± 3.0 (14) 91.2 (84.4 – 95.3)	-
Change from Screening to Week 8	-1.28 ± 3.55 (14) -0.15 (-12.6 – 1.4) p = 0.221‡	0.40 ± 1.16 (13) 0.8 (-3 – 1.5) p = 0.077‡	0.86 ± 2.21 (14) 0.4 (-1.9 – 7.2) p = 0.116‡	0.091¤
Mean Corpuscular Hemoglobin (pg)				
Screening	30.89 ± 1.08 (14) 30.9 (28.9 – 33)	30.61 ± 1.75 (14) 30.15 (28.3 – 35.2)	30.86 ± 1.40 (14) 31.15 (27.7 – 33.3)	-
Visit 3 (Week 8)	30.32 ± 1.40 (14) 30.35 (27.3 – 33.2)	30.45 ± 1.10 (13) 30.4 (28.5 – 32.1)	31.04 ± 1.25 (14) 31.35 (28.7 – 33.6)	-
Change from Screening to Week 8	-0.56 ± 1.42 (14) -0.15 (-5.2 – 0.4) p = 0.162*	0.19 ± 0.36 (13) 0.2 (-0.6 – 0.8) p = 0.070*	0.19 ± 0.74 (14) 0.1 (-0.5 – 2.3) p = 0.371*	0.093*
Mean Corpuscular Hemoglobin Concentration (g/L)				
Screening	343.6 ± 5.6 (14) 342.5 (336 – 356)	341.1 ± 5.6 (14) 340 (331 – 351)	342.9 ± 6.7 (14) 342.5 (333 – 356)	-
Visit 3 (Week 8)	342.2 ± 5.5 (14) 341 (333 – 353)	341.2 ± 5.4 (13) 341 (331 – 349)	342.1 ± 6.0 (14) 340 (335 – 353)	-
Change from Screening to Week 8	-1.4 ± 6.2 (14) -3 (-11 – 11) p = 0.362‡	0.9 ± 3.9 (13) 1 (-7 – 9) p = 0.331‡	-0.9 ± 5.1 (14) -1.5 (-9 – 6) p = 0.599‡	0.449¤
Red Cell Distribution Width (%)				
Screening	13.61 ± 0.40 (14) 13.45 (13.1 – 14.4)	13.91 ± 0.47 (14) 13.9 (12.8 – 14.5)	13.58 ± 0.51 (14) 13.55 (12.8 – 14.4)	-

Visit 3 (Week 8)	13.56 ± 0.34 (14) 13.6 (13 – 14.3)	13.83 ± 0.48 (13) 13.7 (13.1 – 14.7)	13.61 ± 0.56 (14) 13.75 (12.3 – 14.4)	-
Change from Screening to Week 8	-0.06 ± 0.30 (14) -0.05 (-0.9 – 0.4) p = 0.778*	-0.10 ± 0.43 (13) 0 (-1.2 – 0.6) p = 0.123*	0.03 ± 0.41 (14) 0.15 (-0.9 – 0.6) p = 0.685*	0.838
Platelet Count (x E9/L)				
Screening	239 ± 34 (14) 246 (186 – 305)	265 ± 63 (14) 254 (190 – 424)	271 ± 65 (14) 268 (145 – 371)	-
Visit 3 (Week 8)	235 ± 29 (14) 238 (190 – 273)	275 ± 68 (13) 266 (171 – 430)	258 ± 63 (14) 262 (140 – 362)	-
Change from Screening to Week 8	-4.6 ± 20.9 (14) 3 (-36 – 42) p = 0.615‡	5.4 ± 15.4 (13) 5 (-19 – 33) p = 0.289‡	-13.0 ± 28.3 (14) -5 (-67 – 41) p = 0.090‡	0.118¤
Neutrophil Count (x E9/L)				
Screening	3.41 ± 0.64 (14) 3.3 (2.4 – 4.5)	3.17 ± 1.36 (14) 2.95 (1.6 – 6.4)	3.59 ± 1.21 (14) 3.25 (2 – 6.4)	-
Visit 3 (Week 8)	3.15 ± 0.77 (14) 3.15 (1.6 – 4.8)	3.63 ± 1.32 (13) 3.7 (1.5 – 6)	3.34 ± 1.35 (14) 3.15 (1.6 – 6.8)	-
Change from Screening to Week 8	-0.26 ± 0.72 (14) -0.55 (-1.1 – 1.1) p = 0.184‡	0.44 ± 0.89 (13) 0.2 (-0.8 – 1.9) p = 0.146‡	-0.25 ± 0.89 (14) -0.2 (-2.4 – 1) p = 0.421‡	0.104¤
Lymphocyte Count (x E9/L)				
Screening	1.84 ± 0.58 (14) 1.95 (0.8 – 2.9)	1.91 ± 0.59 (14) 1.7 (1.3 – 3)	1.96 ± 0.76 (14) 2 (0.6 – 3.5)	-
Visit 3 (Week 8)	1.84 ± 0.56 (14) 1.75 (0.9 – 3)	2.13 ± 0.65 (13) 2 (1.2 – 3.3)	2.03 ± 0.97 (14) 1.8 (0.6 – 4.1)	-
Change from Screening to Week 8	-0.00 ± 0.53 (14) 0.05 (-1.1 – 0.9) p = 0.944‡	0.18 ± 0.23 (13) 0.2 (-0.3 – 0.5) **p = 0.022**‡	0.07 ± 0.95 (14) -0.05 (-0.8 – 3.1) p = 0.555‡	0.208¤
Monocyte Count (x E9/L)				
Screening	0.457 ± 0.165 (14) 0.4 (0.3 – 0.9)	0.564 ± 0.165 (14) 0.55 (0.3 – 0.9)	0.514 ± 0.141 (14) 0.5 (0.3 – 0.7)	-
Visit 3 (Week 8)	0.450 ± 0.170 (14) 0.4 (0.3 – 0.8)	0.600 ± 0.153 (13) 0.6 (0.4 – 1)	0.564 ± 0.128 (14) 0.55 (0.3 – 0.7)	-
Change from Screening to Week 8	-0.007 ± 0.138 (14) 0 (-0.3 – 0.2) p = 0.928‡	0.031 ± 0.111 (13) 0 (-0.1 – 0.3) p = 0.518‡	0.050 ± 0.151 (14) 0 (-0.2 – 0.4) p = 0.276‡	0.732¤
Eosinophil Count (x E9/L)				
Screening	0.164 ± 0.101 (14) 0.15 (0 – 0.4)	0.186 ± 0.196 (14) 0.1 (0.1 – 0.8)	0.171 ± 0.114 (14) 0.1 (0.1 – 0.5)	-
Visit 3 (Week 8)	0.164 ± 0.108 (14) 0.1 (0 – 0.4)	0.169 ± 0.063 (13) 0.2 (0.1 – 0.3)	0.186 ± 0.146 (14) 0.15 (0 – 0.6)	-
Change from Screening to Week 8	-0.000 ± 0.068 (14) 0 (-0.1 – 0.1) p = 0.824‡	-0.000 ± 0.191 (13) 0 (-0.6 – 0.2) p = 0.388‡	0.014 ± 0.077 (14) 0 (-0.1 – 0.1) p = 0.774‡	0.405¤
Basophil Count (x E9/L)				
Screening	0.007 ± 0.027 (14) 0 (0 – 0.1)	0.036 ± 0.050 (14) 0 (0 – 0.1)	0.036 ± 0.050 (14) 0 (0 – 0.1)	-
Visit 3 (Week 8)	0.007 ± 0.027 (14) 0 (0 – 0.1)	0.038 ± 0.051 (13) 0 (0 – 0.1)	0.036 ± 0.063 (14) 0 (0 – 0.2)	-
Change from Screening to Week 8	0.000 ± 0.000 (14) 0 (0 – 0) p = 1.000‡	0.008 ± 0.028 (13) 0 (0 – 0.1) p = 1.000‡	0.000 ± 0.078 (14) 0 (-0.1 – 0.2) p = 1.000‡	0.626¤
Fasting Glucose Concentration (mmol/L)				
Screening	5.50 ± 0.33 (14) 5.45 (5 – 6.1)	5.20 ± 0.44 (14) 5.15 (4.6 – 6)	5.33 ± 0.53 (14) 5.2 (4.6 – 6.2)	-

Visit 3 (Week 8)	5.37 ± 0.56 (14) 5.3 (4.6 – 6.9)	5.28 ± 0.70 (14) 5.1 (4.3 – 7.1)	5.06 ± 0.76 (14) 5.05 (2.7 – 5.8)	-
Change from Screening to Week 8	-0.13 ± 0.47 (14) -0.1 (-1.2 – 0.8) p = 0.344‡	0.08 ± 0.68 (14) 0 (-0.8 – 1.9) p = 0.969‡	-0.27 ± 0.79 (14) -0.15 (-2.5 – 0.6) p = 0.209‡	0.762¤
Creatinine Concentration (µmol/L)				
Screening	71.7 ± 13.8 (14) 74 (49 – 90)	72.3 ± 11.1 (14) 73 (53 – 88)	63.8 ± 7.8 (14) 64.5 (49 – 77)	-
Visit 3 (Week 8)	73.1 ± 13.1 (14) 72.5 (53 – 92)	71.6 ± 11.4 (14) 69 (53 – 95)	70.7 ± 17.8 (14) 70.5 (33 – 105)	-
Change from Screening to Week 8	1.4 ± 7.7 (14)[a,b] 1.5 (-21 – 12) p = 0.161‡	-0.7 ± 7.4 (14)[a] -0.5 (-17 – 15) p = 0.623‡	6.9 ± 15.5 (14)[b] 5 (-34 – 34) **p = 0.050**‡	**0.027**¤
Estimated Globular Filtration Rate (mL/min/1.73m^2)				
Screening	84.1 ± 17.9 (14) 81 (59 – 113)	81.0 ± 10.4 (14) 80.5 (64 – 103)	91.5 ± 15.8 (14) 87.5 (69 – 119)	-
Visit 3 (Week 8)	81.4 ± 15.4 (14) 84.5 (54 – 102)	83.6 ± 11.1 (14) 78.5 (67 – 105)	83.8 ± 15.7 (14) 81 (62 – 121)	-
Change from Screening to Week 8	-2.8 ± 15.0 (14)[a,b] -3 (-30 – 34) p = 0.345‡	2.6 ± 11.0 (14)[b] 4 (-26 – 24) p = 0.147‡	-7.7 ± 18.9 (14)[a] -9.5 (-38 – 43) p = 0.069‡	**0.029**¤
Sodium Concentration (mmol/L)				
Screening	144.36 ± 2.37 (14) 144 (141 – 148)	144.57 ± 2.50 (14) 145 (141 – 150)	142.79 ± 2.49 (14) 143.5 (138 – 146)	-
Visit 3 (Week 8)	145.36 ± 2.17 (14) 145 (142 – 150)	144.64 ± 3.18 (14) 145 (140 – 152)	142.86 ± 2.28 (14) 143 (140 – 148)	-
Change from Screening to Week 8	1.00 ± 2.60 (14) 1.5 (-2 – 5) p = 0.163‡	0.07 ± 3.00 (14) -1 (-3 – 7) p = 0.944‡	0.07 ± 3.38 (14) 0 (-5 – 9) p = 0.918‡	0.549¤
Potassium Concentration (mmol/L)				
Screening	5.10 ± 0.47 (14) 5.15 (4 – 5.7)	5.11 ± 0.29 (14) 5.1 (4.8 – 5.6)	4.85 ± 0.46 (14) 4.9 (3.8 – 5.7)	-
Visit 3 (Week 8)	5.04 ± 0.59 (14) 5 (4 – 6.4)	5.04 ± 0.38 (14) 5 (4.5 – 5.6)	4.75 ± 0.57 (13) 4.8 (3.6 – 5.9)	-
Change from Screening to Week 8	-0.06 ± 0.67 (14) -0.05 (-1.3 – 1) p = 0.861‡	-0.08 ± 0.46 (14) -0.1 (-1 – 0.6) p = 0.637‡	-0.08 ± 0.49 (13) -0.1 (-1.1 – 0.6) p = 0.806‡	0.599
Chloride Concentration (mmol/L)				
Screening	107.64 ± 1.86 (14) 107 (105 – 112)	108.29 ± 1.77 (14) 109 (105 – 111)	105.50 ± 1.91 (14) 105.5 (103 – 108)	-
Visit 3 (Week 8)	106.86 ± 2.35 (14) 106 (103 – 110)	106.50 ± 2.59 (14) 106 (101 – 110)	105.00 ± 2.04 (14) 106 (102 – 108)	-
Change from Screening to Week 8	-0.79 ± 1.85 (14) -1 (-3 – 3) p = 0.152‡	-1.79 ± 2.04 (14) -2 (-5 – 2) **p = 0.013**‡	-0.50 ± 2.24 (14) -1 (-5 – 4) p = 0.393‡	0.241¤
Total Bilirubin (µmol/L)				
Screening	9.4 ± 2.7 (14) 9 (6 – 15)	10.2 ± 3.0 (14) 9.5 (7 – 19)	10.9 ± 3.5 (14) 11 (6 – 18)	-
Visit 3 (Week 8)	10.4 ± 4.3 (14) 9 (5 – 23)	8.8 ± 2.4 (14) 8 (7 – 15)	11.4 ± 3.3 (14) 11.5 (7 – 18)	-
Change from Screening to Week 8	1.0 ± 4.1 (14) 0.5 (-3 – 14) p = 0.671‡	-1.4 ± 3.8 (14) -0.5 (-12 – 4) p = 0.219‡	0.5 ± 3.2 (14) 1 (-3 – 7) p = 0.776‡	0.315¤
Aspartate Transaminase (U/L)				
Screening	24.3 ± 4.5 (14) 24 (16 – 34)	23.0 ± 3.6 (14) 22 (18 – 29)	26.1 ± 5.5 (14) 27 (17 – 33)	-

Visit 3 (Week 8)	24.3 ± 3.8 (14) 24 (18 – 31)	27.1 ± 7.4 (14) 25 (20 – 48)	26.5 ± 10.1 (13) 24 (17 – 57)	-
Change from Screening to Week 8	0.0 ± 4.1 (14)[a] 0.5 (-11 – 6) p = 0.506‡	4.1 ± 6.7 (14)[b] 2.5 (-4 – 23) **p = 0.033‡**	0.9 ± 11.2 (13)[a] -1 (-9 – 36) p = 0.503‡	**0.034¤**
Alanine Transaminase (U/L)				
Screening	24.9 ± 9.8 (14) 22.5 (12 – 47)	23.1 ± 5.9 (14) 22 (15 – 35)	25.5 ± 7.7 (14) 26 (13 – 38)	-
Visit 3 (Week 8)	24.3 ± 5.6 (14) 25 (15 – 35)	25.9 ± 7.3 (14) 24.5 (14 – 41)	25.0 ± 12.2 (14) 22 (14 – 63)	-
Change from Screening to Week 8	-0.6 ± 7.0 (14) 1 (-17 – 6) p = 0.753‡	2.9 ± 6.2 (14) 4 (-7 – 15) p = 0.150‡	-0.5 ± 14.0 (14) -1.5 (-17 – 43) p = 0.223‡	0.566*
Gamma-Glutamyltransferase (U/L)				
Screening	24.3 ± 12.9 (14) 19.5 (10 – 48)	19.2 ± 10.2 (14) 16 (9 – 50)	23.5 ± 14.0 (14) 19 (9 – 61)	-
Visit 3 (Week 8)	23.6 ± 10.0 (14) 20.5 (9 – 44)	20.8 ± 15.9 (14) 14 (10 – 69)	21.7 ± 14.5 (14) 18 (9 – 58)	-
Change from Screening to Week 8	-0.7 ± 12.9 (14) -2 (-38 – 16) p = 0.801‡	1.6 ± 6.4 (14) 0.5 (-5 – 19) p = 0.779‡	-1.8 ± 4.6 (14) -2.5 (-7 – 11) p = 0.074‡	0.281¤

N, number; SD, standard deviation; Min, minimum; Max, maximum; g, gram; L, liter; fL, femtoliter; pg, picogram; mmol, millimoles; µmol, micromoles; mL, milliliter; min, minutes; m, meters; U, units; µg, microgram; nmol, nanomoles.
Δ Between-group comparisons were made using ANCOVA. Within-group comparisons were made using the paired Student t-test. * Logarithmic transformation was required to achieve normality. ¤Between-group comparisons were made using the Kruskal Wallis test. ‡Within group were made using the Wilcoxon signed-rank test. Treatment groups with differing letter superscripts are significantly different. Probability values P≤0.05 are statistically significant.

[00121] A model was run on creatinine concentration with compliance, treatment group and their interaction as covariates. Table 12 reveals that compliance was not related to creatinine concentration.

Table 12: Clinical Creatinine Parameters as a Function of Compliance for PP Participants at Screening and Week 8 (N=39).

Creatinine Concentration (µmol/L)				
Screening	71.7 ± 13.8 (14) 74 (49 – 90)	69.5 ± 10.3 (11) 70 (53 – 84)	63.8 ± 7.8 (14) 64.5 (49 – 77)	-
Visit 3 (Week 8)	73.1 ± 13.1 (14) 72.5 (53 – 92)	69.5 ± 7.6 (11) 68 (53 – 81)	70.7 ± 17.8 (14) 70.5 (33 – 105)	-
Change from Screening to Week 8	1.4 ± 7.7 (14)[a,b] 1.5 (-21 – 12) p = 0.161‡	0.0 ± 6.1 (11)[a] 0 (-7 – 15) p = 0.572‡	6.9 ± 15.5 (14)[b] 5 (-34 – 34) **p = 0.050‡**	**0.030¤**

[00122] The primary endpoint was a composite endpoint of the changes in Lean Body Mass (as assessed by DXA scan) and functional muscle strength (as assessed by 6 Minute Walk Test, Lower Body Dynamometry and Upper Body Dynamometry) of subjects administered Sample 2 compared to those administered placebo from baseline to week 8. The composite endpoint was calculated by multiplying the results of each

component score (kg lean muscle mass x meters walked x kg resistance lower body x kg resistance upper body) to derive a composite score (expressed in arbitrary units). The percent change in composite score between baseline and week 8 was derived for comparison between Sample 2 and Placebo.

Table 13: Absolute and Percentage Change in the Composite Endpoint at Baseline and at End of the Study for All Participants in the PP Population (N = 39).

	Placebo	Sample 1	Sample 2	Between Group P Values			
	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Mean ±SD (n) Median (Min – Max) Within Group P Value	Overall Δ	Placebo vs Sample 1 δ	Placebo vs Sample 2 δ	Sample 1 vs Sample 2 δ
Composite Endpoint ($x10^3$)							
Baseline (Week 0)	11,032 ± 11,501 (14) 7,870 (559 – 39,977)	10,921 ± 11,142 (11) 5,997 (1,269 – 37,560)	6,313 ± 5,485 (14) 4,466 (677 – 19,276)	-	-	-	-
Visit 3 (Week 8)	7,611 ± 4,893 (14) 6,334 (360 – 16,803)	10,620 ± 11,893 (11) 6,734 (1,404 – 42,706)	8,367 ± 7,025 (14) 6,475 (1,135 – 26,858)	-	-	-	-
Change from Baseline to Week 8	-3,421 ± 8,073 (14)[a] -1,231 (-26,672 – 4,814) p = 0.232*	-301 ± 3,467 (11)[a,b] -374 (-8,681 – 5,146) p = 0.534*	2,054 ± 2,359 (14)[b] 858 (-406 – 7,582) **p = 0.008***	**0.022***	0.826*	**0.021***	0.113*

N, number; SD, standard deviation; Min, minimum; Max, maximum; BMI, body mass index; kg, kilogram; m, meter; cm, centimeter Δ Between-group comparisons were made using ANCOVA. δ Pairwise between-group comparisons were made using the Tukey procedure. Within-group comparisons were made using the paired Student t-test. * Logarithmic transformation was required to achieve normality. ¤Between-group comparisons were made using the Kruskal Wallis test. ‡Within-group comparisons were made using the signed-rank test. Treatment groups with differing letter superscripts are significantly different. Probability values P≤0.05 are statistically significant.

[00123] As revealed in Fig. 25 and Table 11, there was a significant absolute change (P = 0.008) in the primary composite endpoint [MM (kg) x US (kg) x LS (kg) x 6W (m)] for participants taking Sample 2 (n=42, ITT population). This absolute change was significant compared to the placebo group (P = 0.016) and approached significance when compared to the Sample 1 group (P = 0.077). Notably, when expressed as a percentage, the absolute change in composite endpoints for the Sample 2 group translated into a 63.5 percentage point increase over placebo.

Example No. 2

[00124] As described above, in one embodiment, the protein building composition of the present disclosure may be combined with a stabilizer package for improving one or

more properties of the composition. The following example provides exemplary formulations, but is not intended to limit the invention. In fact, the stabilizer package and the process for incorporating the stabilizer package into the composition may be used in any suitable pharmaceutical composition and may not be limited solely to the protein building composition of the present disclosure.

[00125] In one embodiment, the following components may be first mixed together. The components include a protein building composition in accordance with the present disclosure combined with a polymer binder. In Sample No. 1, the polymer binder is modified starch. In Sample No. 2, the polymer binder is larch arabinogalactan. The below components can be spray dried into a granule to form a granular product. For instance, the spray pressure can be about 2 bar while the spray rate can be from about 10 to about 20 grams per minute.

	Sample No. 1				Sample No. 2			
			(dry)	(incl. moisture)			(dry)	(incl. moisture)
	Quant.	**Assay**	**Product**	**Product**	**Quant.**	**Assay**	**Product**	**Product**
	g	**%**	**g**	**%**	**g**	**%**	**g**	**%**
Water	1900	0.0%	5	0.50%	1700	0.0%	5	0.50%
L-Carnitine	185	99.9%	185	18.46%	185	99.9%	185	18.46%
Creatine monohydrate	420	87.9%	369	36.92%	420	87.9%	369	36.92%
L-Leucine	246	100.0%	246	24.62%	246	100.0%	246	24.62%
vitamin D3	0.10	100.0%	0	0.01%	0.10	100.0%	0	0.01%
Sodium stearate/citric acid esters/rapeseed lecithin	10	100.0%	10	1.00%	20	100.0%	20	2.00%
Modified Starch	195	95.0%	185	18.50%	0	95.0%	0	0.00%
Larch arabinogalactan	0	94.7%	0	0.00%	195	94.7%	185	18.50%
	0	100.0%	0	0.00%	0	100.0%	0	0.00%
Isolated product [g]	560.00	1'400.00	800		2'000.00			
Properties (granulate, agglom.)	granulate	granulate	granulate		granulate			
Particlesize d10 [µm]	204.59	235.73	136.86		235.96			
Particlesize d50 [µm]	300.39	331.22	226.10		262.65			
Particlesize d90 [µm]	450.04	472.33	411.51		363.10			
Bulk density [kg/L]	0.56	0.52	0.58		0.68			
Moisture [%] (100°C/25min)	2.30	2.18	4.28		3.90			
Moisture [%] (KFT)	0.93	0.86	1.88		2.55			

[00126] After the above granular product is produced, the product can be mixed with a stabilizer package. The stabilizer package may comprise a dry mix of calcium stearate and silica. The calcium stearate can be added in an amount of about 2.5% by weight, while the silica may be added in an amount of about 0.2% by weight. Because the stabilizer package is a dry mix, a pharmaceutical composition is produced that comprises a granular mixture. The stearate and silica serve to stabilize the granular particles.

[00127] To the granular mixture, a fat coating material can be applied. The fat coating material may comprise a combination of hydrogenated palm oil and palm stearine. In one embodiment, hydrogenated palm oil is added in an amount of 16% by weight, while palm stearine is added in an amount of 4% by weight of the resulting pharmaceutical composition. In an alternative embodiment, the hydrogenated palm oil is added in an amount of 24% by weight, while the palm stearine is added in an amount of 6% by weight of the pharmaceutical composition.

[00128] These and other modifications and variations to the present invention may be practiced by those of ordinary skill in the art, without departing from the spirit and scope of the present invention, which is more particularly set forth in the appended claims. In addition, it should be understood that aspects of the various embodiments may be interchanged both in whole or in part. Furthermore, those of ordinary skill in the art will appreciate that the foregoing description is by way of example only, and is not intended to limit the invention so further described in such appended claims.

What Is Claimed:

1. A method for preserving muscle mass and function by increasing muscle protein synthesis and/or decreasing muscle protein degradation in mammals, the method comprising administering to the mammal an effective amount of a protein building composition, said protein building composition comprising an amino acid derivative combined with an amino acid component, a nitrogenous organic acid or derivative thereof or both an amino acid component and a nitrogenous organic acid or derivative thereof, wherein the amino acid derivative comprises a carnitine or a derivative thereof.

2. A method as defined in claim 1, wherein the protein building composition contains the amino acid component which comprises an essential amino acid.

3. A method as defined in claim 2, wherein the amino acid component comprises leucine.

4. A method as defined in claim 1, wherein the amino acid derivative comprises L-carnitine.

5. A method as defined in any of the preceding claims, wherein the protein building composition contains the nitrogenous organic acid which comprises creatine.

6. A method as defined in claim 5, wherein the nitrogenous organic acid comprises magnesium chelated creatine.

7 A method as defined in claim 1, wherein the protein building composition further comprises magnesium or salts thereof.

8. A method as defined in claim 1, wherein the protein building composition further comprises vitamin D.

9. A method as defined in claim 1, wherein the protein building composition is contained in a food product or beverage.

10. A method as defined in claim 1, wherein the protein building composition is administered at least every one to three days or is administered for at least 50 consecutive days or is administered one to four times a day.

11. A method as defined in claim 4, wherein L-carnitine is administered to the mammal in an amount from 50 milligrams to 5,000 milligrams per dose.

12. A method as defined in claim 3, wherein leucine is administered to the mammal in an amount from 50 milligrams to 5,000 milligrams per dose.

13. A method as defined in claim 1, wherein the mammal is a human or wherein the mammal is sedentary or wherein the mammal is physically active.

14. A method as defined in claim 4, wherein L-carnitine is administered to the mammal in an amount from 100 milligrams to 3,000 milligrams per dose.

15. A method as defined in claim 3, wherein leucine is administered to the mammal in an amount from 100 milligrams to 4,000 milligrams per dose.

16. A method as defined in claim 5, wherein creatine is administered to the mammal in an amount from 0 milligrams to 20,000 milligrams per dose.

17. A method as defined in claim 1, wherein the protein building composition is administered to the mammal in an amount sufficient to increase lean muscle mass in the mammal or wherein the protein building composition is administered to the mammal in an amount sufficient to treat or prevent sarcopenia.

18. A method as defined in claim 1, wherein the protein building composition is administered to the mammal in an amount sufficient to decrease the amount of TNF-α in the muscles.

19. A method as defined in claim 1, wherein the protein building composition is administered to the mammal in an amount sufficient to increase mTOR expression in the muscles.

20. A method as defined in claim 1, wherein mTOR expression is increased by greater than 40% after activity in comparison to the same mammal that has not received the protein building composition.

21. A composition for increasing muscle protein synthesis and/or functional strength, comprising a protein building composition, said protein building composition comprising an amino acid component, an amino acid derivative, and a nitrogenous organic acid comprising creatine, wherein the amino acid component comprises leucine and the amino acid derivative comprises L-carnitine.

22. A composition as defined in claim 21, wherein L-carnitine is present in the protein building composition in an amount from 30 milligrams to 5,000 milligrams per dose, wherein leucine is present in the protein building composition in an amount from

30 milligrams to 5,000 milligrams per dose, and wherein creatine is present in the protein building composition in an amount from 50 milligrams to 20,000 milligrams per dose.

23. A composition for increasing muscle protein synthesis and/or functional strength, comprising a protein building composition, said protein building composition comprising an organic acid comprising creatine and an amino acid constituent comprising:

(A) leucine, wherein leucine is present in an amount greater than 40% by mass of the amino acid constituent; and

(B) L-carnitine, wherein L-carnitine is present in an amount greater than 15% by mass of the amino acid constituent.

24. A pharmaceutical composition comprising:

a protein building composition combined with a polymer binder and a stabilizer package, the stabilizer package comprising oxide particles and a salt of a carboxylic acid.

25. A pharmaceutical composition as defined in claim 24, wherein the oxide particles comprise silica and the salt of a carboxylic acid comprises a salt of a fatty acid.

26. A pharmaceutical composition as defined in claim 25, wherein the salt of the fatty acid comprises calcium stearate, sodium stearate, magnesium stearate, or mixtures thereof and wherein the polymer binder comprises a starch, gum arabic, maltodextrin, arabinogalactan, gelatin, a polysaccharide or mixtures thereof.

27. A pharmaceutical composition as defined in claim 24, wherein the salt of a carboxylic acid comprises a salt of a fatty acid, the fatty acid having a carbon chain length of from about 6 carbon atoms to about 40 carbon atoms, such as from about 12 carbon atoms to about 28 carbon atoms.

28. A pharmaceutical composition as defined in claim 24, wherein the protein building composition comprises a carnitine, an amino acid, and an organic acid.

29. A pharmaceutical composition as defined in claim 24, further comprising a coating material comprising a fat; and wherein the coating material comprises a hydrogenated palm oil and wherein the coating material further comprises palm stearine.

30. A pharmaceutical composition as defined in claim 24, wherein the polymer binder comprises a starch, gum arabic, maltodextrin, arabinogalactan, gelatin, or mixtures thereof, and wherein the oxide particles comprise silica and the salt of a carboxylic acid comprises a stearate salt, and wherein the pharmaceutical composition further contains a coating material comprising a fat, the silica being present in the composition in an amount from about 0.1% to about 1.5%, the stearate salt being present in the composition in an amount from about 0.5% to about 5% by weight, the coating material being present in the composition in an amount from about 5% to about 40% by weight, the protein building composition comprising a carnitine.

31. A method of producing a pharmaceutical composition comprising:

combining a protein building composition with a polymer binder in a spray dry process;

combining the polymer building composition and the polymer binder with a stabilizer package, the stabilizer package comprising oxide particles and a salt of a carboxylic acid, the stabilizer package comprising a dry mix; and

optionally applying a coating material after the protein building composition, the polymer binder, and the stabilizer package have been combined.

32. A method as defined in claim 31, wherein the protein building composition comprises a carnitine.

33. A method as defined in claim 32, wherein the protein building composition further comprises an amino acid, such as leucine.

34. A method as defined in claim 33, wherein the protein building composition further comprises creatine.

35. A method as defined in claim 31, wherein the pharmaceutical composition comprises a granular product.

36. A method as defined in claim 31, further comprising the step of forming the pharmaceutical composition into tablets.

The Change in Absolute Total Lean Mass from Baseline to Week 8 for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 39).

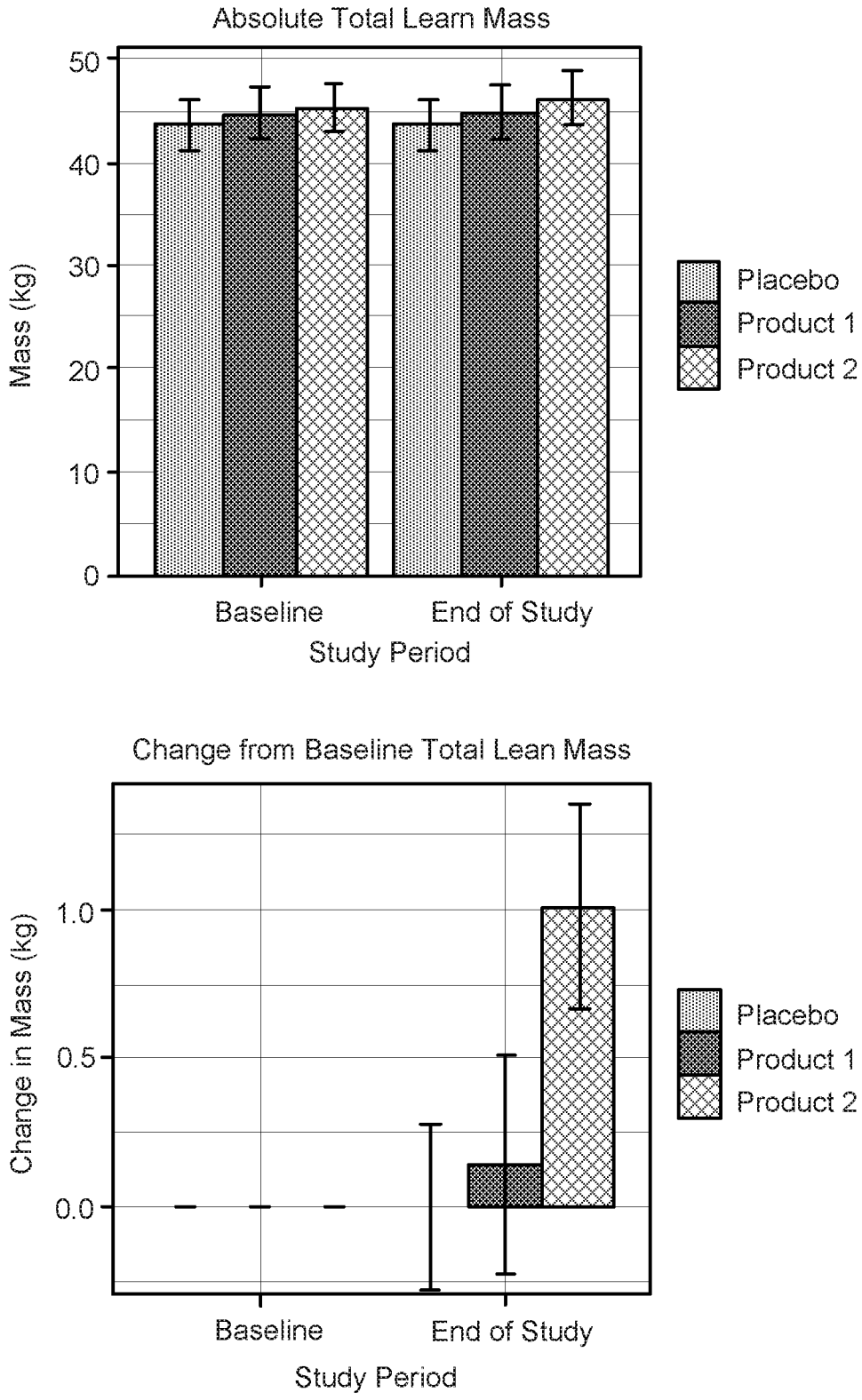


FIG. 1

The Change in Arm Lean Mass from Baseline to Week 8 for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 39).

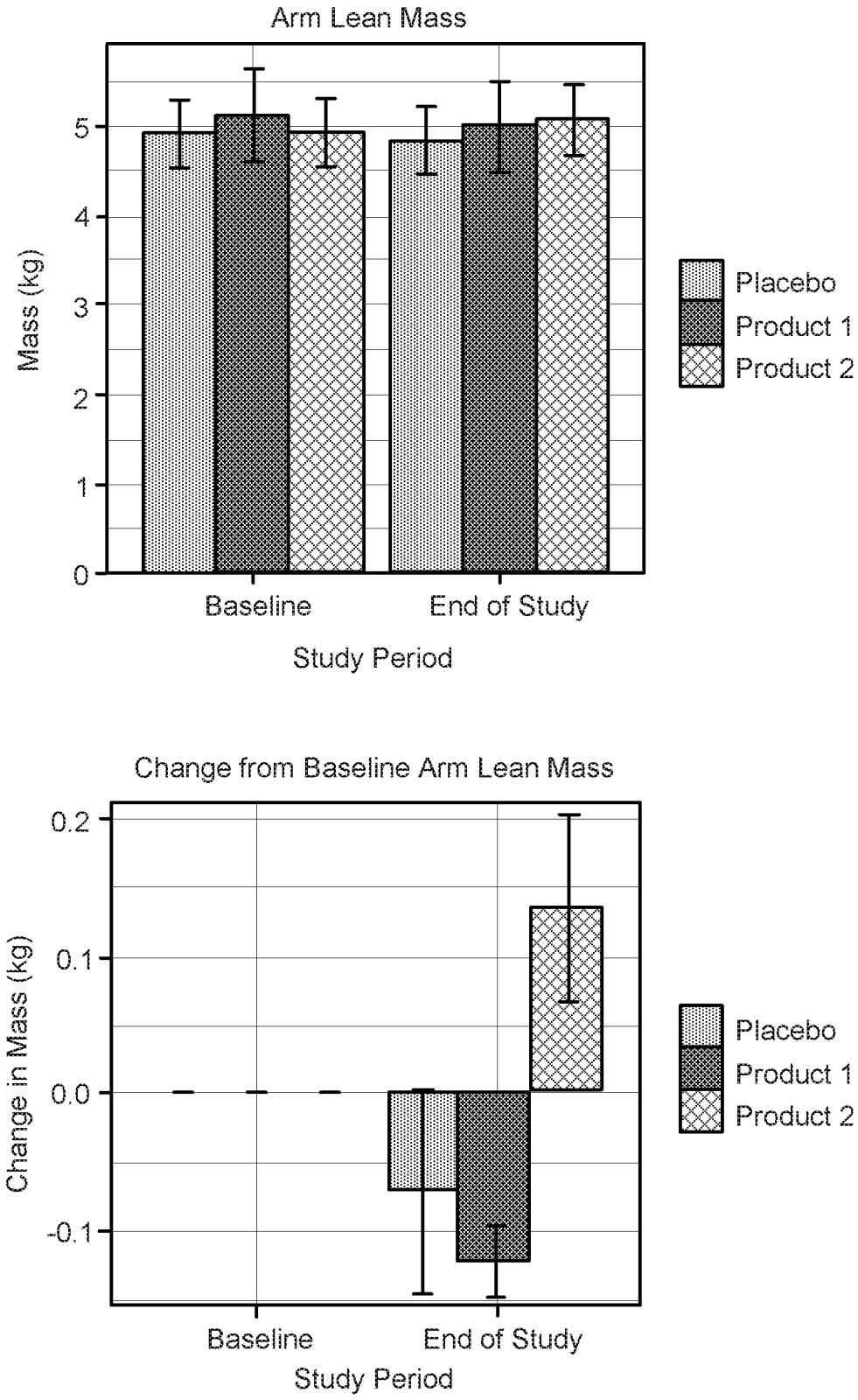


FIG. 2

The Change in Leg Lean Mass from Baseline to Week 8 for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 39).

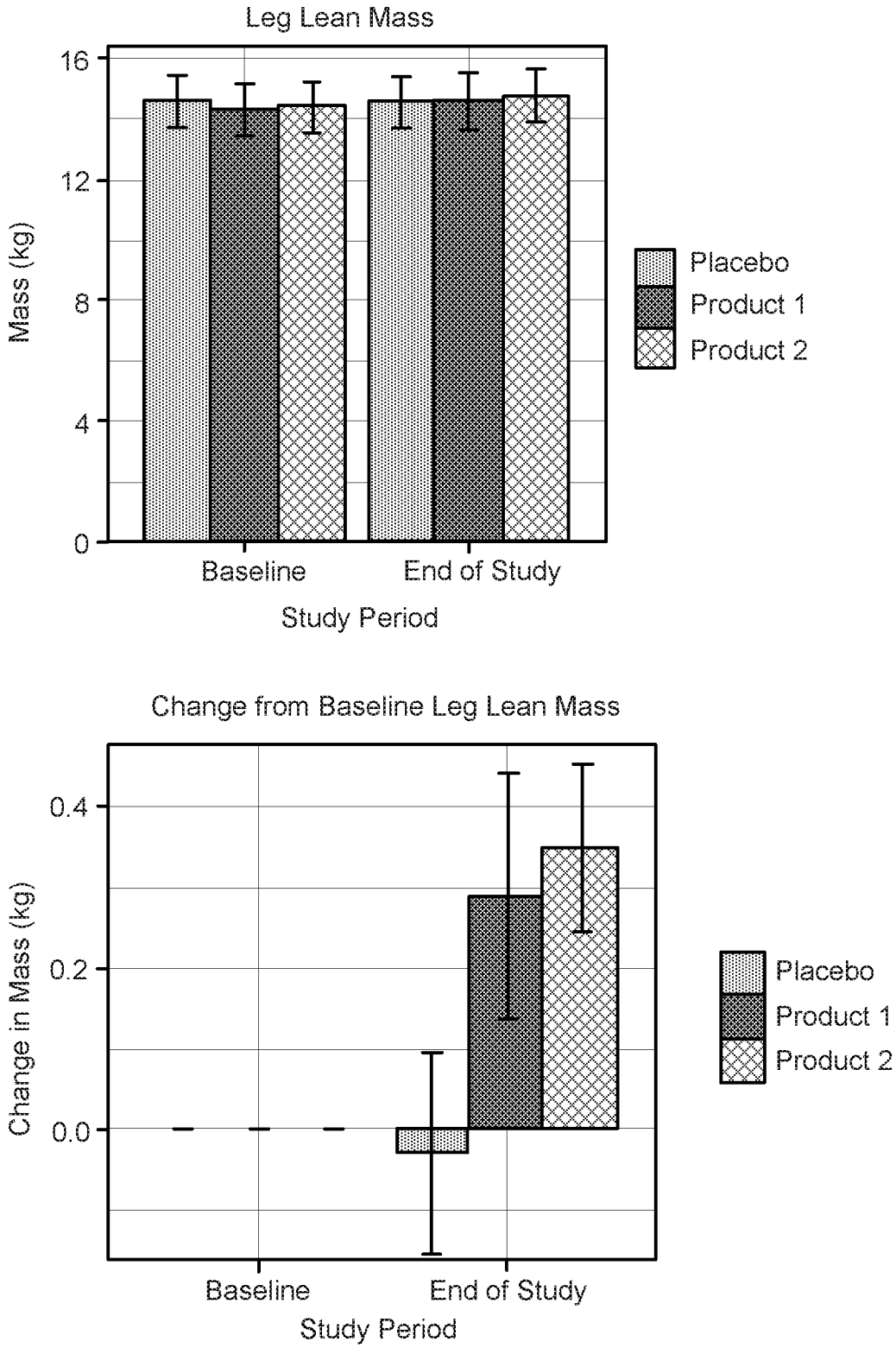


FIG. 3

The Change in Total Non-Trunk Lean Mass from Baseline to Week 8 for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 39).

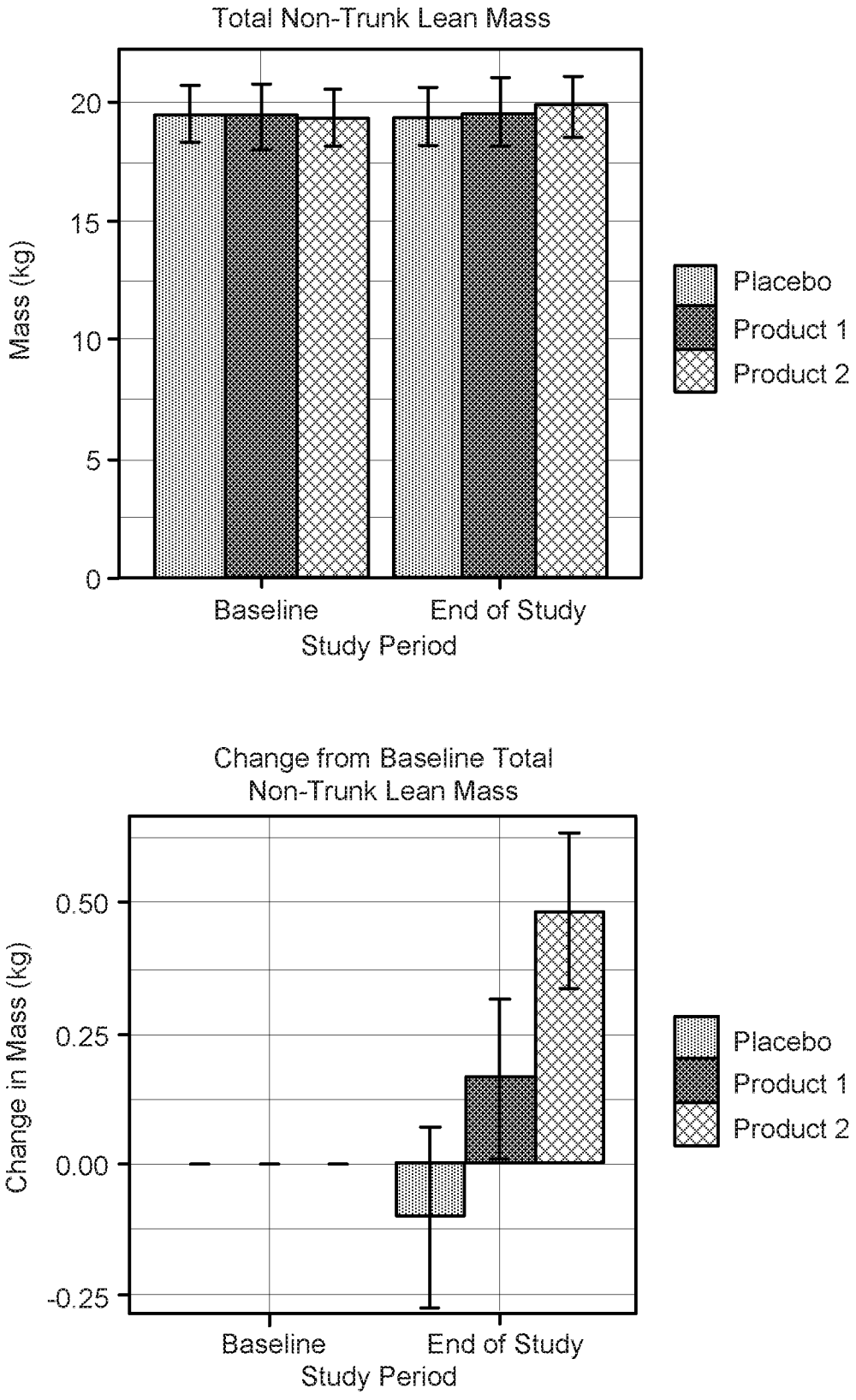


FIG. 4

The Change in Absolute Average Leg Strength from Baseline to Week 8 for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 39).

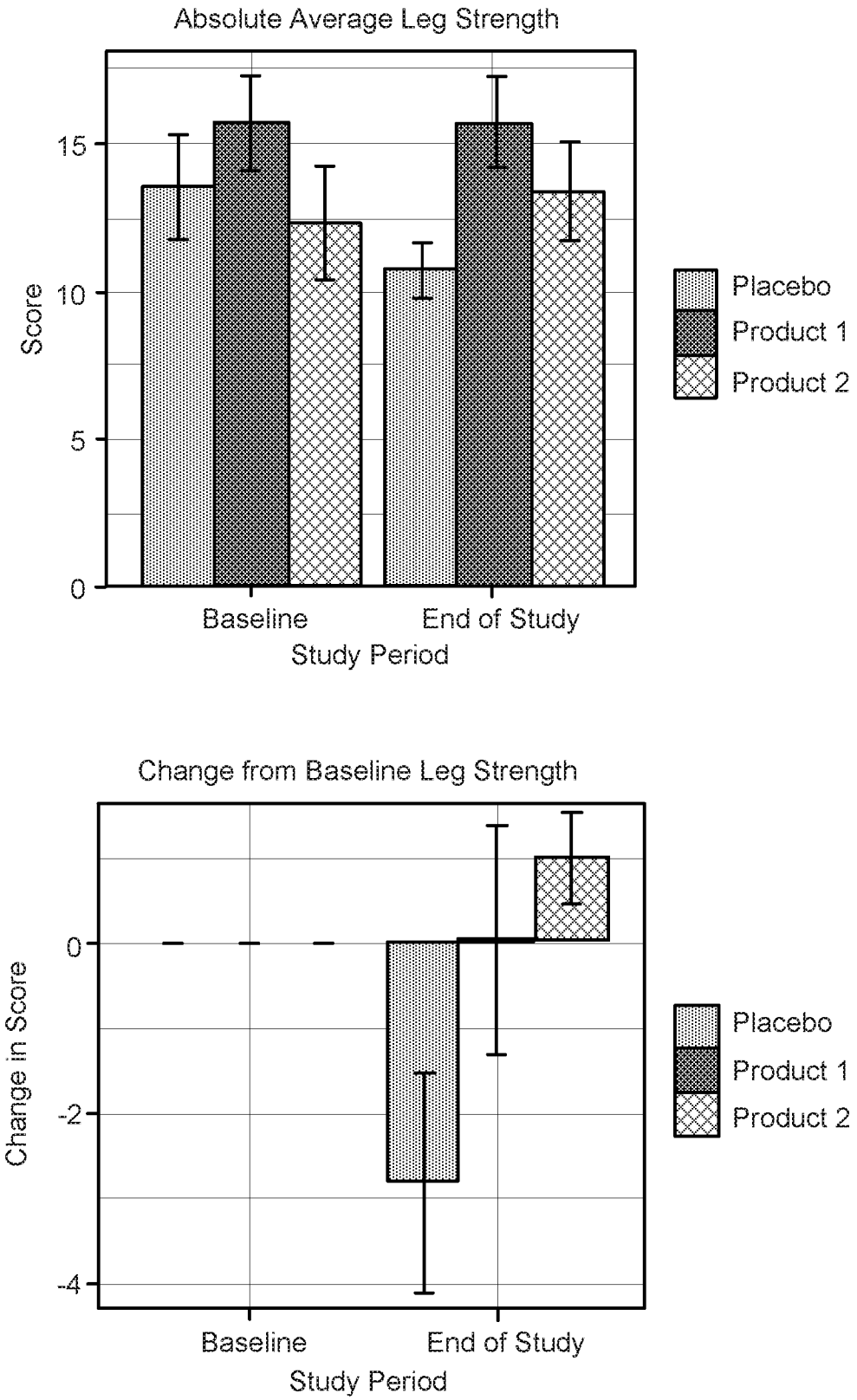
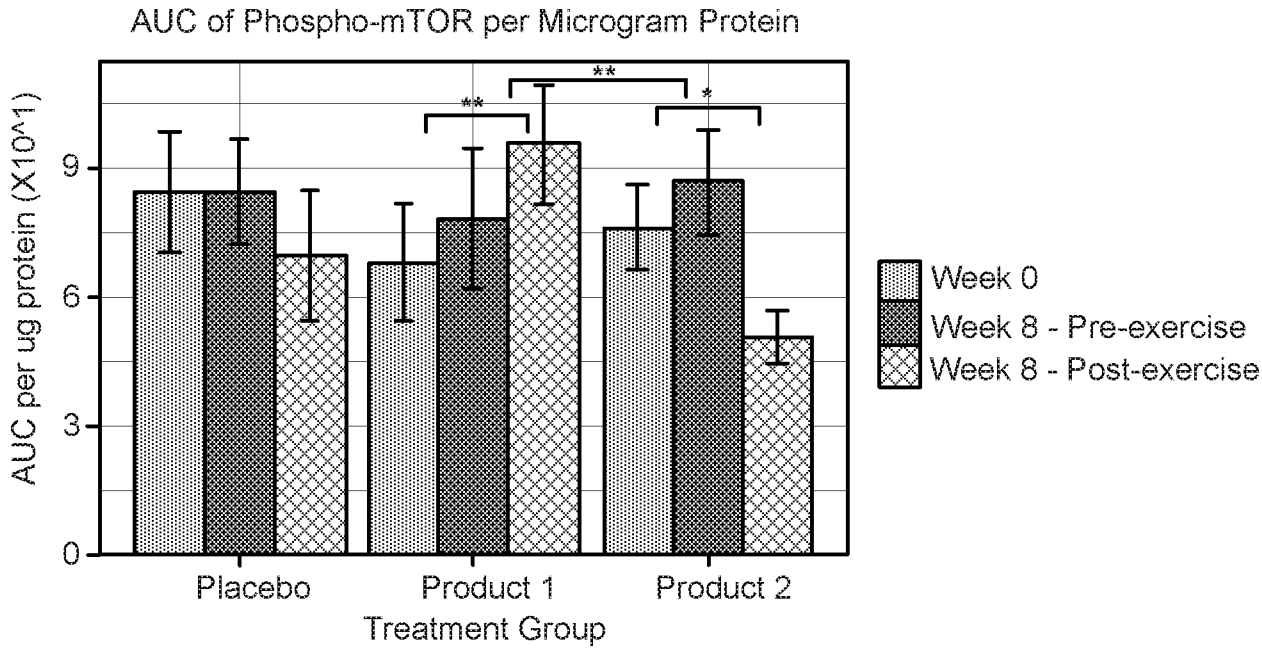


FIG. 5

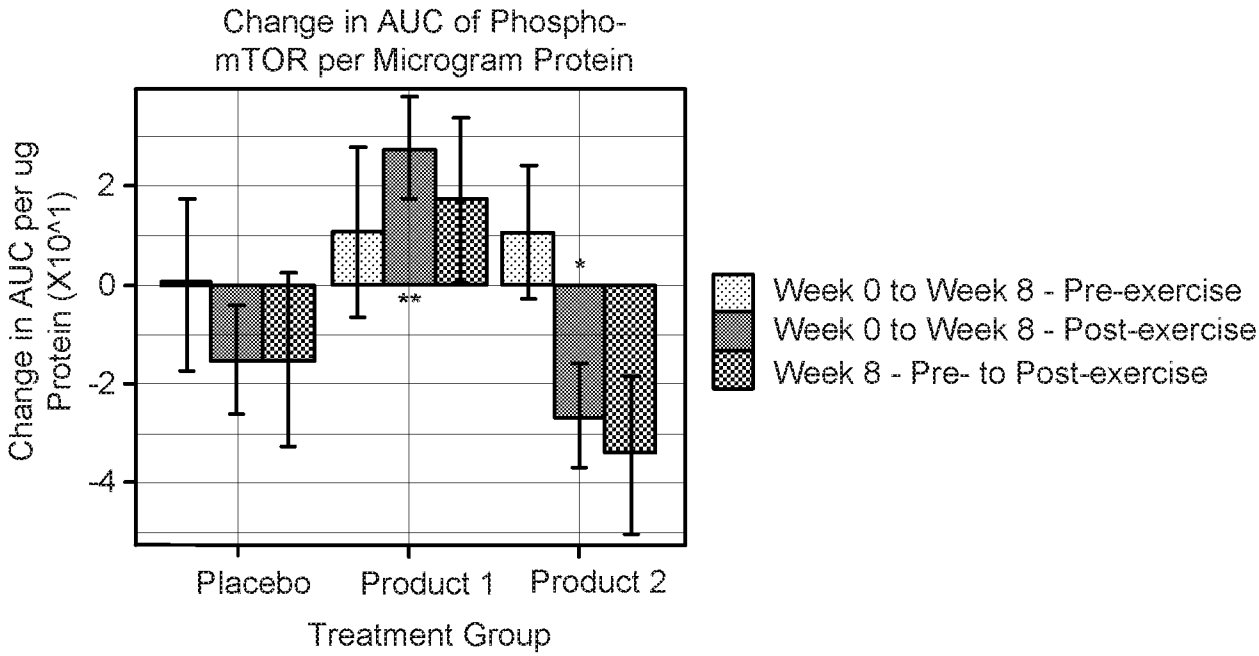
The AUC per µg of protein for Phospho-mTOR from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



* p-value ≤ 0.05; ** p-value ≤ 0.02

FIG. 6

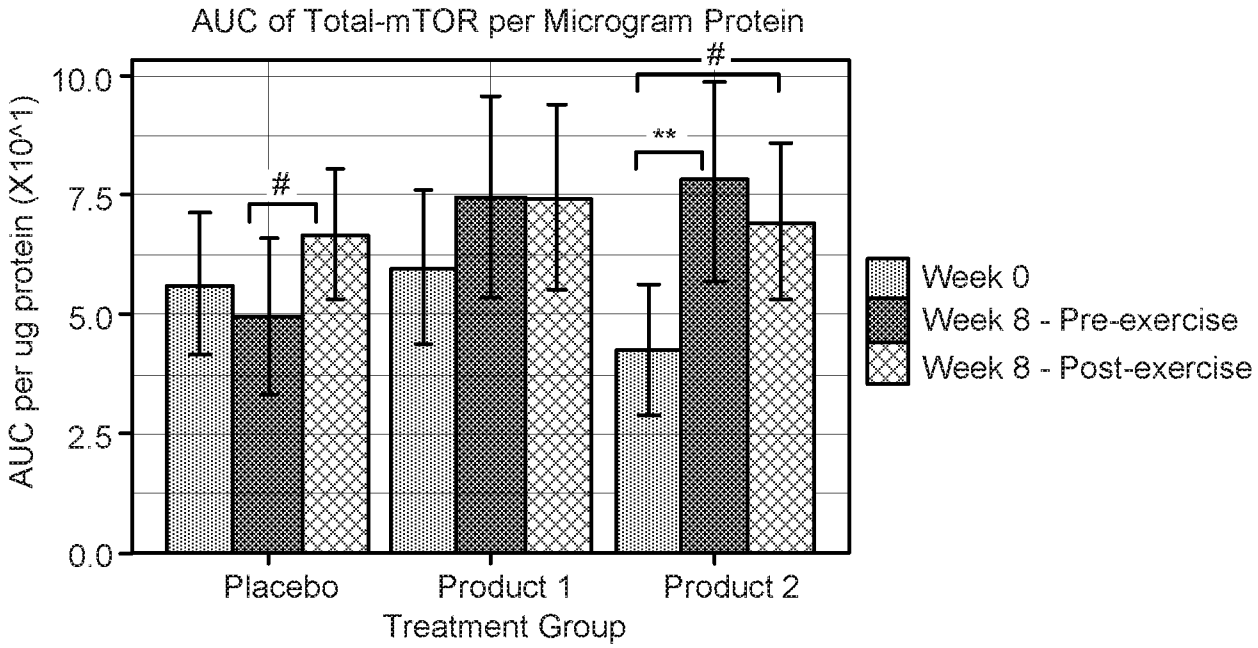
The Change in Phospho-mTOR from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



* p-value ≤ 0.05; ** p-value ≤ 0.02

FIG. 7

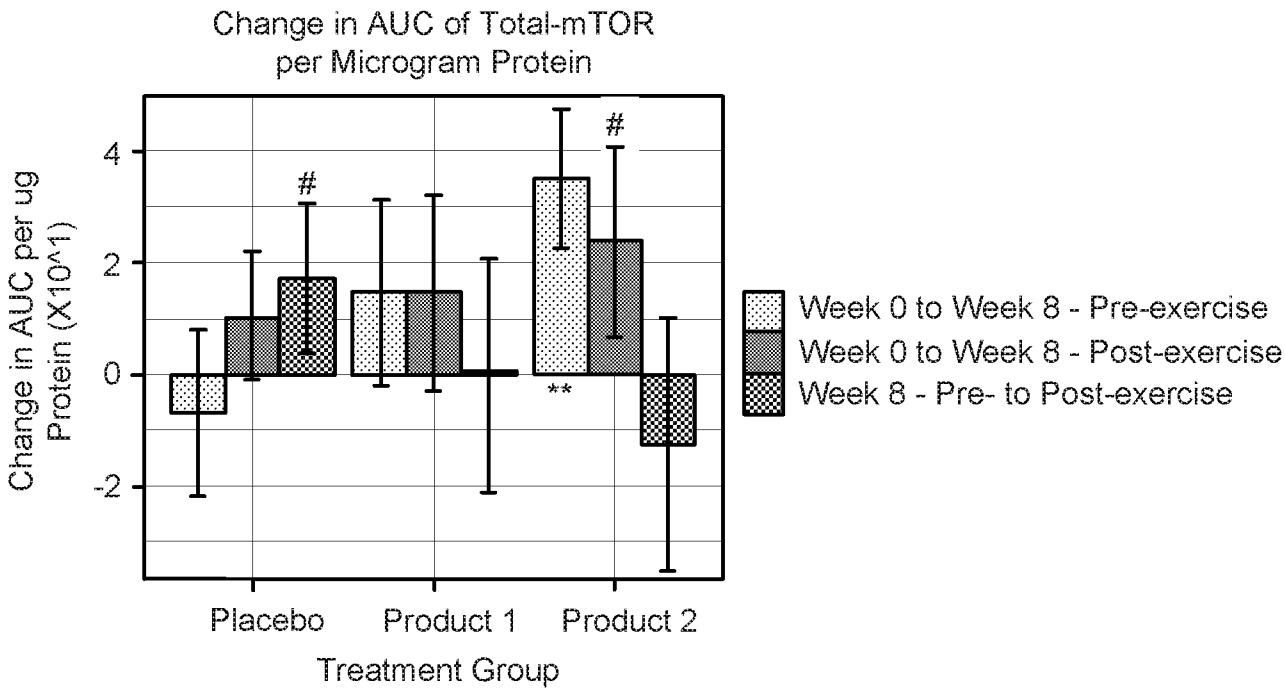
The AUC per µg of protein for Total-mTOR from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



p-value ≤ 0.10; * p-value ≤ 0.05; ** p-value ≤ 0.02

FIG. 8

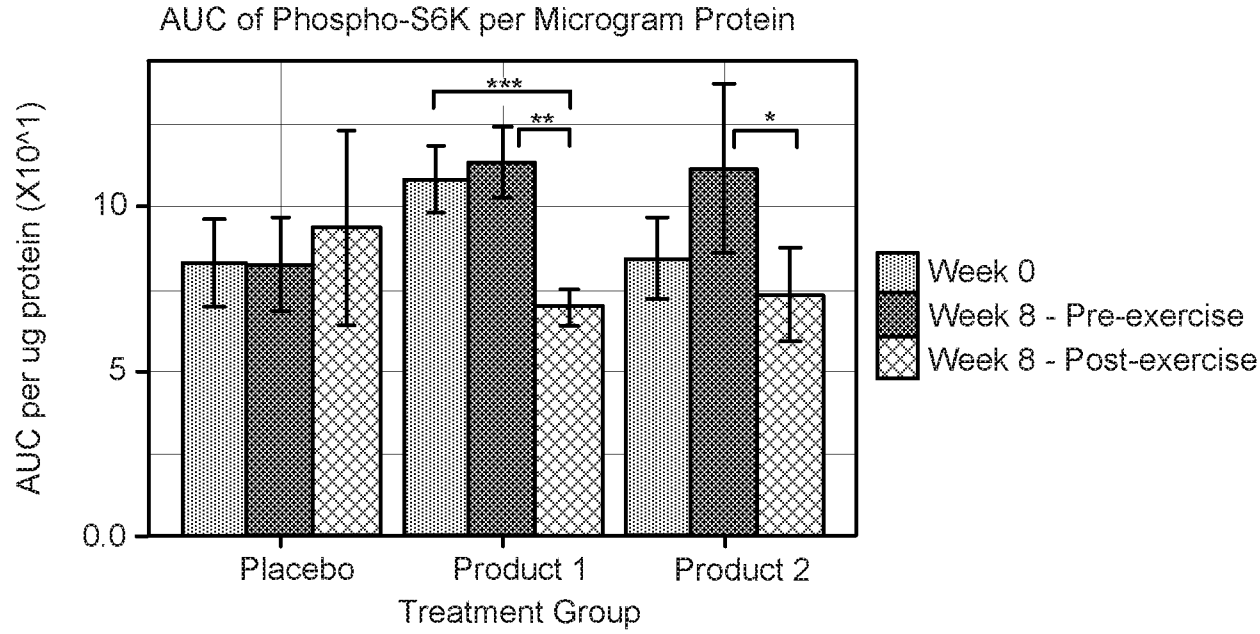
The Change in Total-mTOR from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



p-value ≤ 0.10; * p-value ≤ 0.05; ** p-value ≤ 0.02

FIG. 9

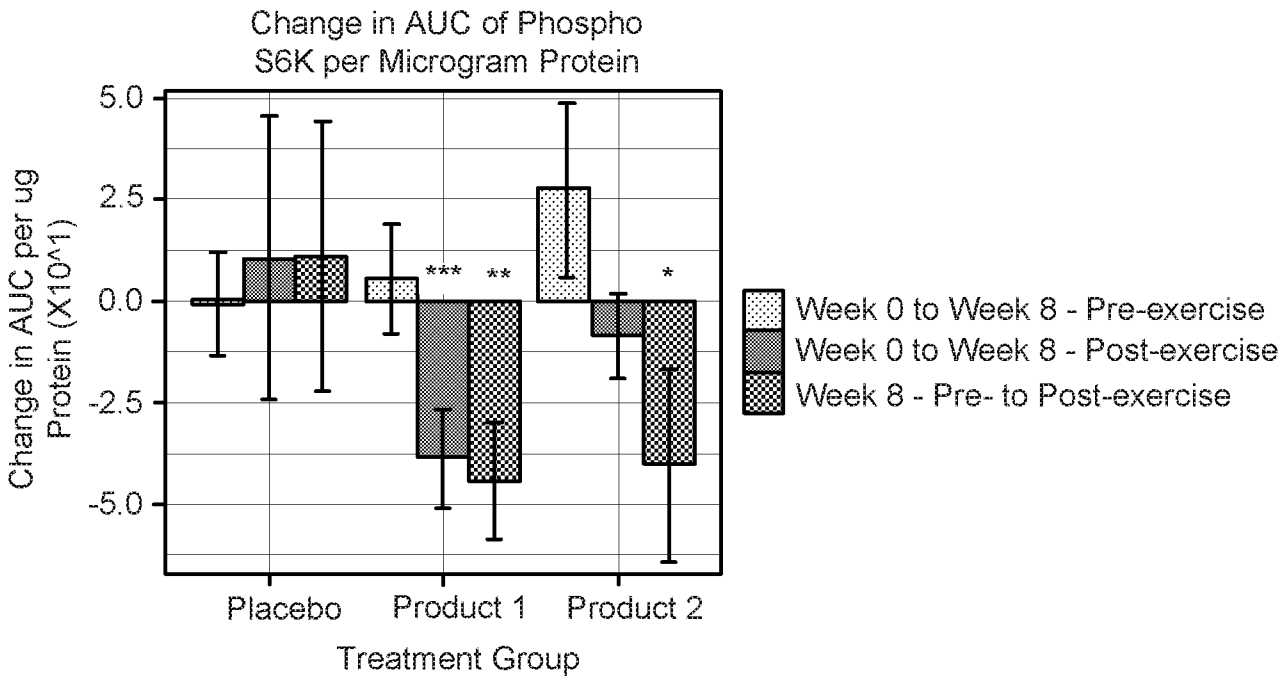
The AUC per µg of protein for Phospho-S6K from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



* p-value ≤ 0.05; ** p-value ≤ 0.02; *** p-value ≤ 0.01

FIG. 10

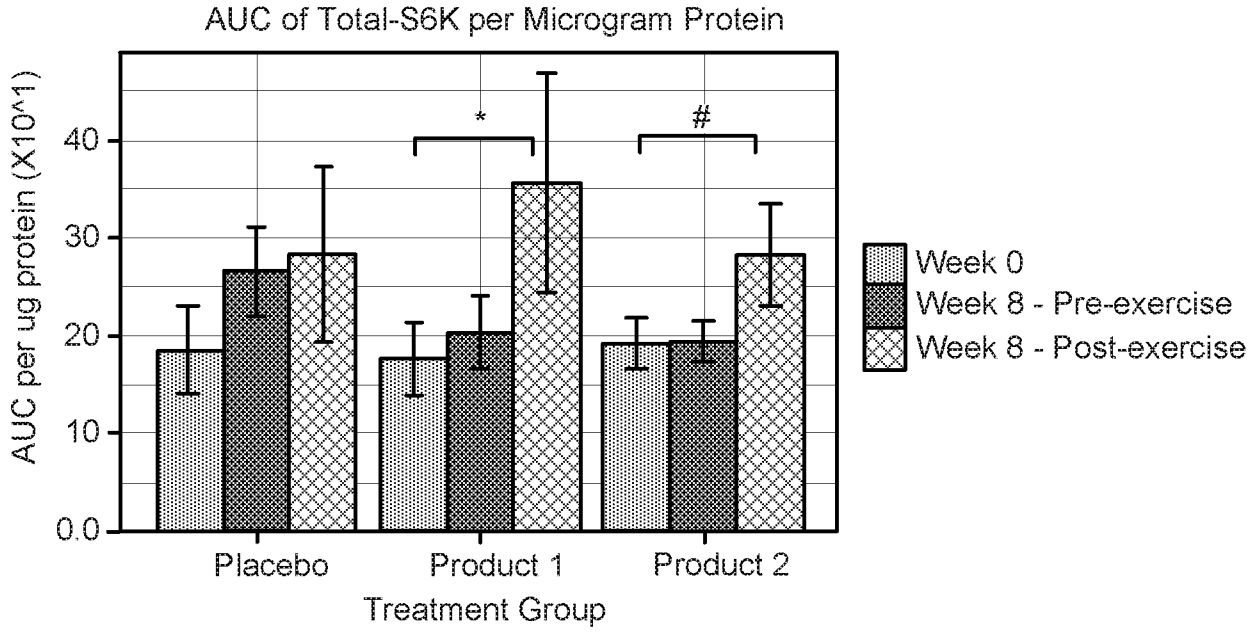
The Change in Phospho-S6K from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



* p-value ≤ 0.05; ** p-value ≤ 0.02; *** p-value ≤ 0.01

FIG. 11

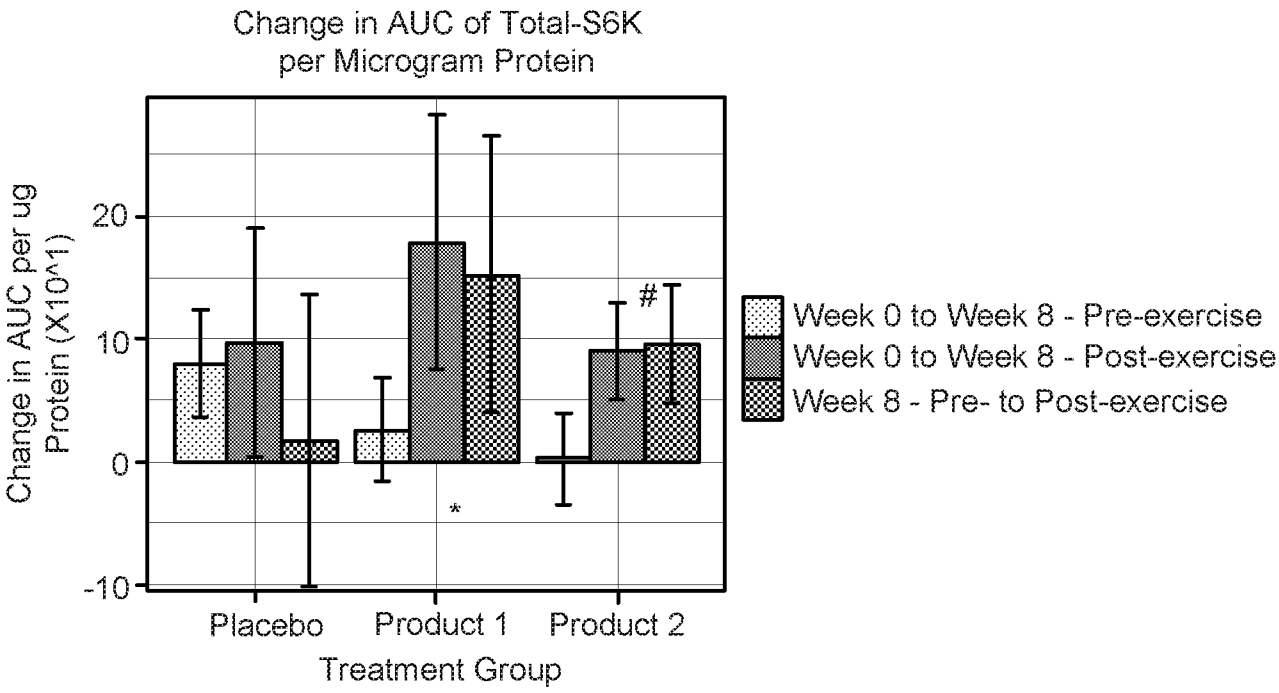
The AUC per µg of protein for Total-S6K from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



p-value ≤ 0.10; * p-value ≤ 0.05

FIG. 12

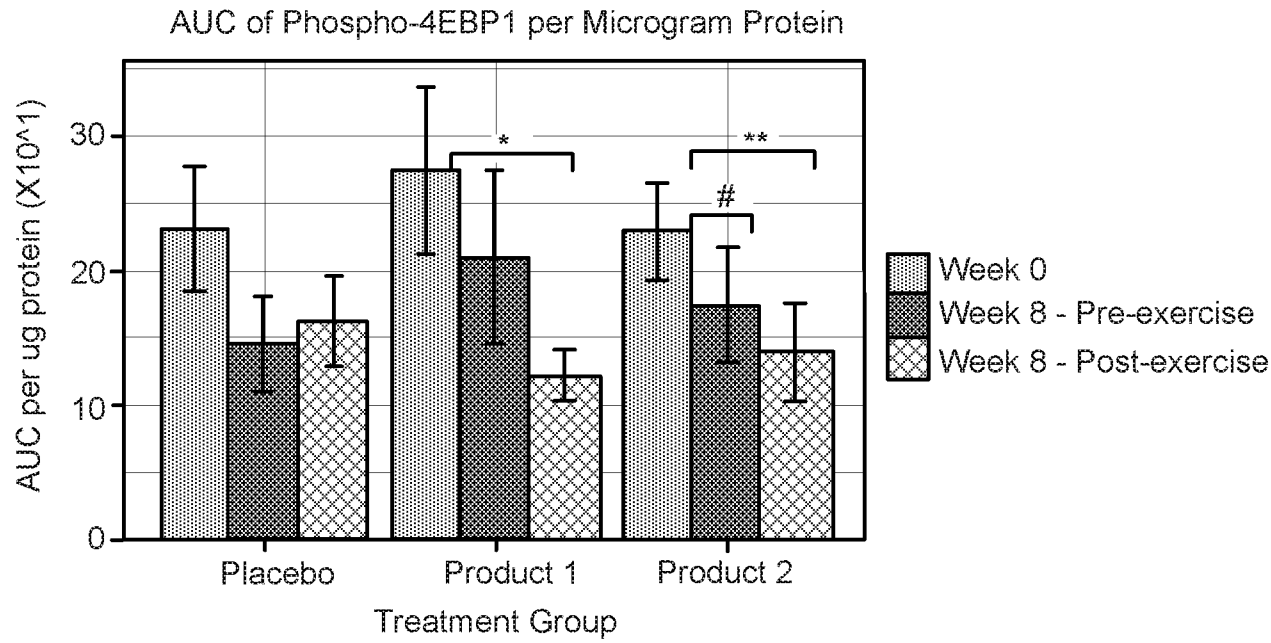
The Change in Total-S6K from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



p-value ≤ 0.10; * p-value ≤ 0.05

FIG. 13

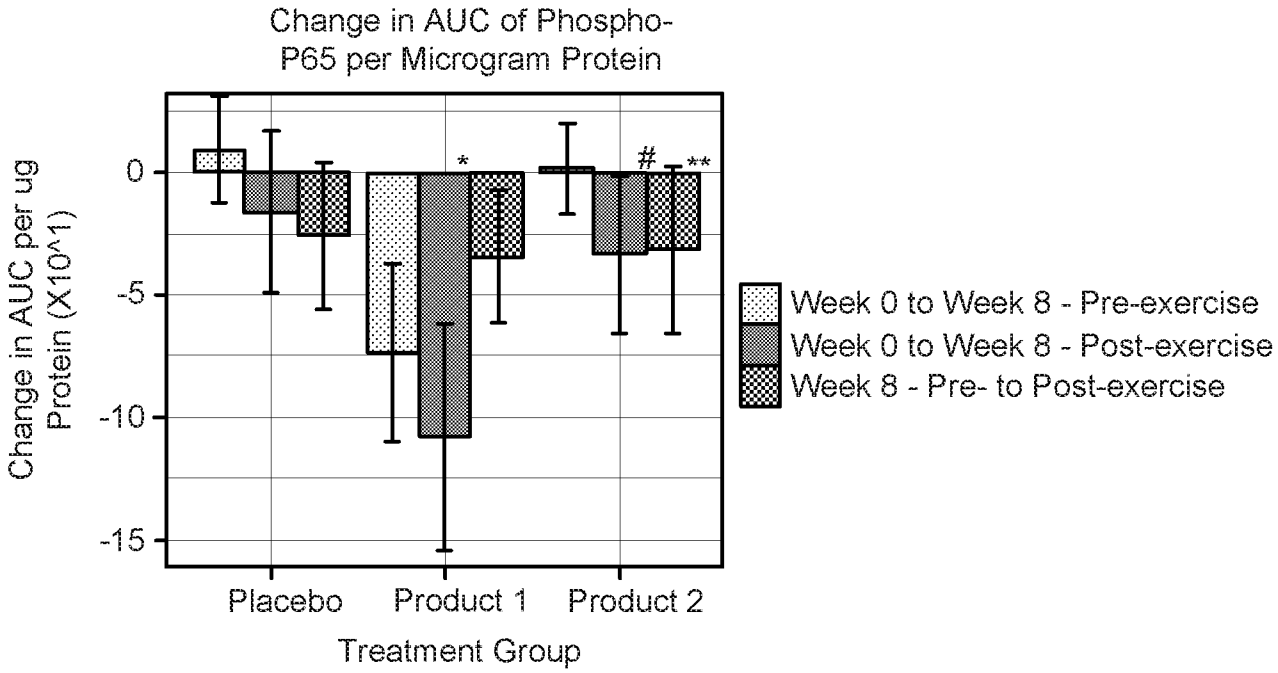
The AUC per µg of protein for Phospho-4EBP1 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



p-value ≤ 0.10; * p-value ≤ 0.05; ** p-value ≤ 0.02

FIG. 14

The Change in Phospho-4EBP1 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).



p-value ≤ 0.10; * p-value ≤ 0.05; ** p-value ≤ 0.02

FIG. 15

The AUC per µg of protein for Total-4EBP1 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

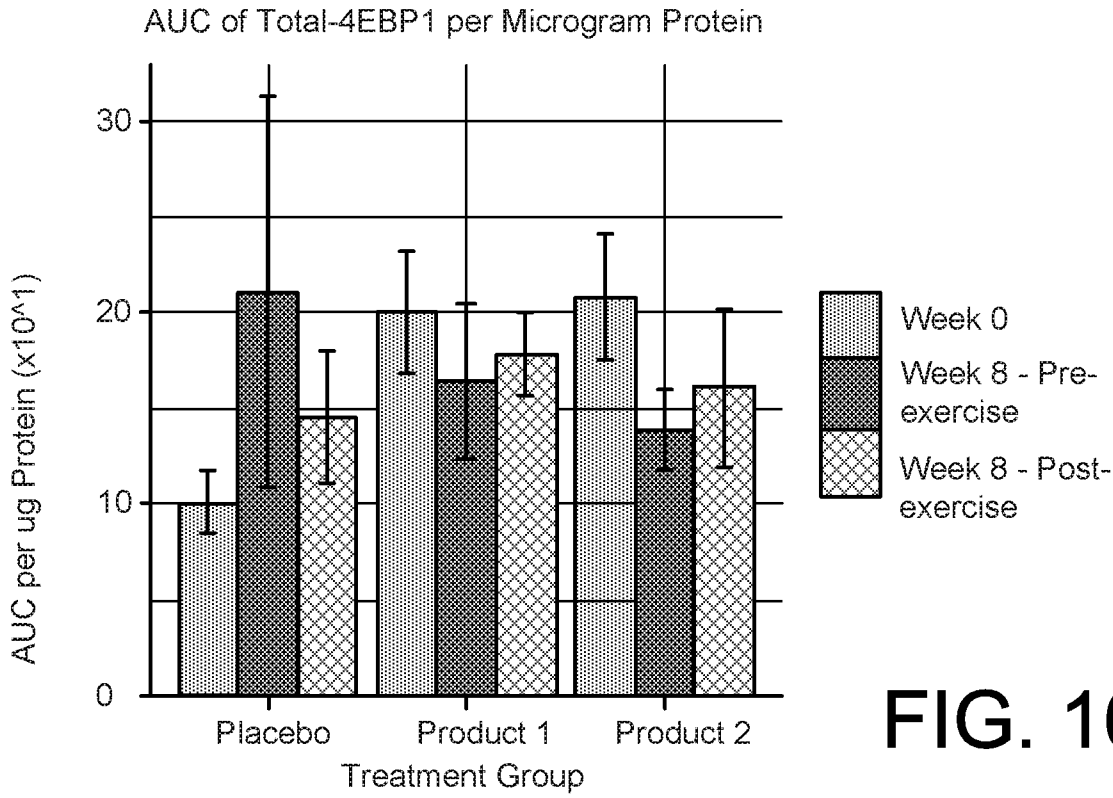


FIG. 16

The Change in Total-4EBP1 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

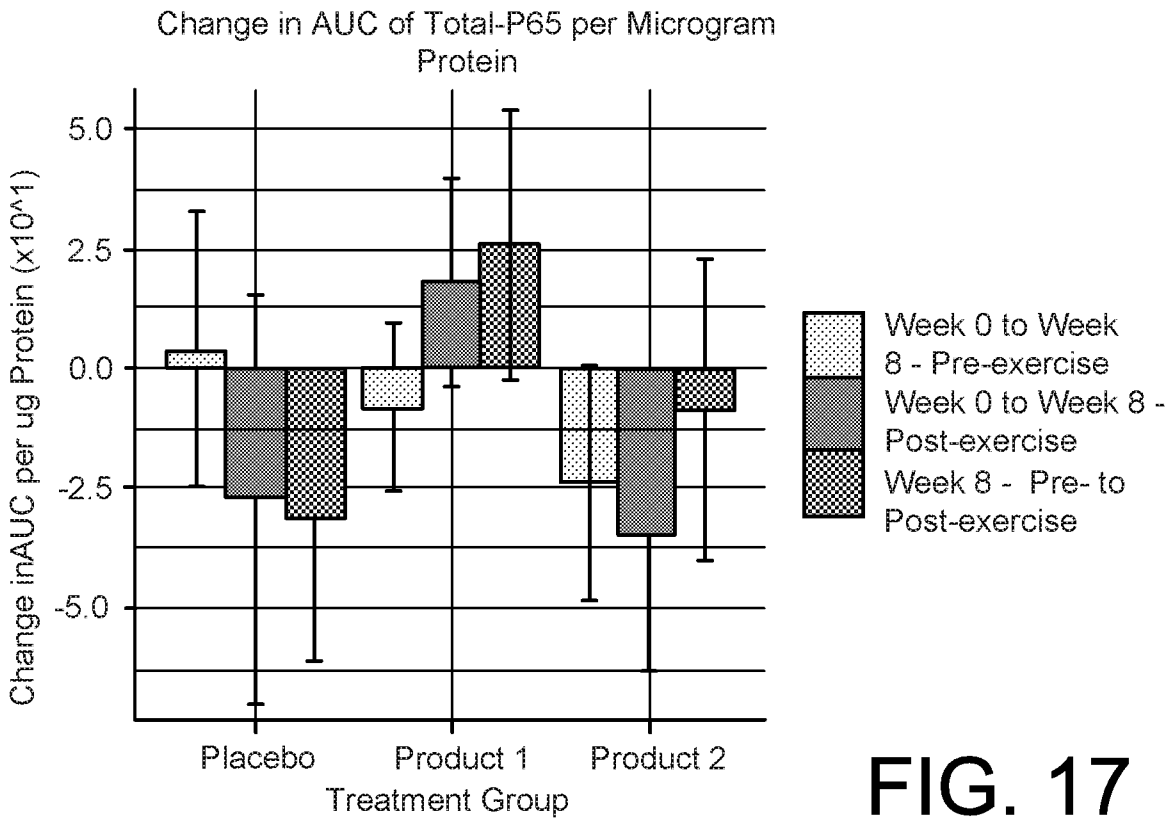


FIG. 17

The AUC per µg of protein for Phospho-P65 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

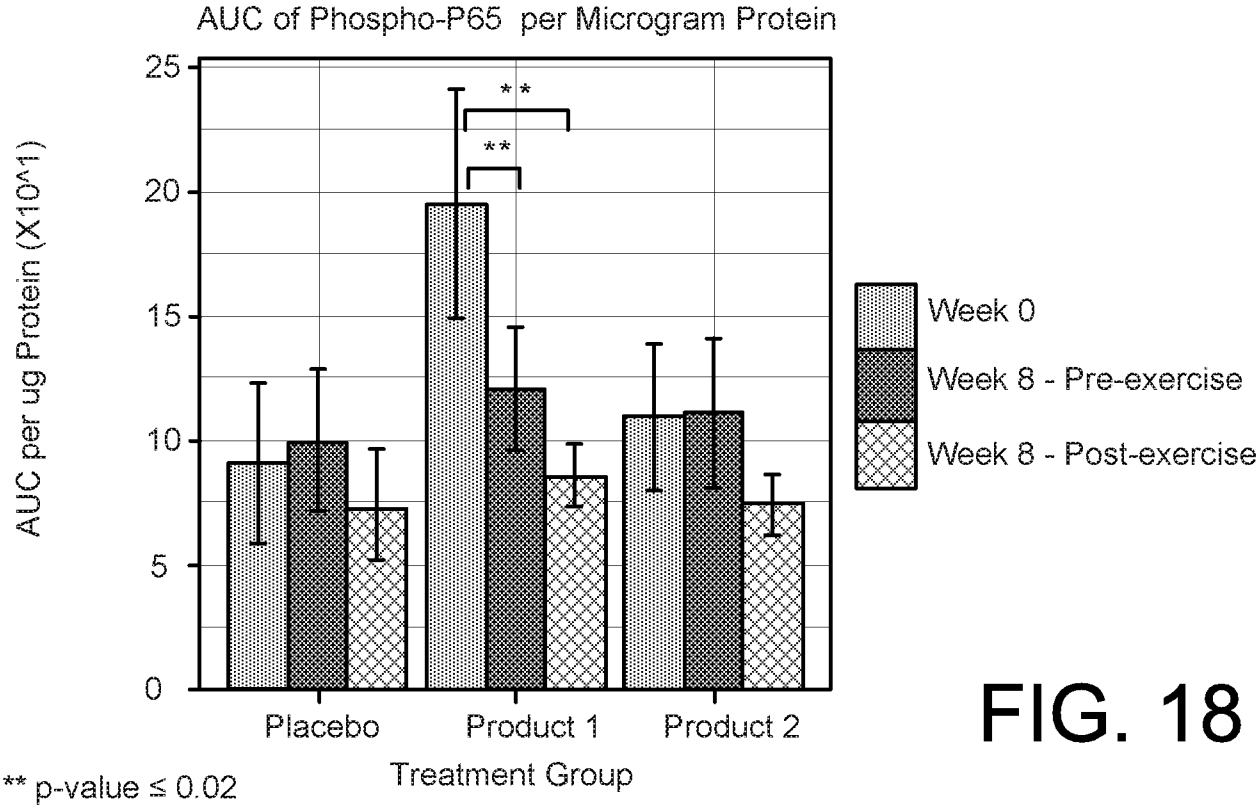


FIG. 18

** p-value ≤ 0.02

The Change in Phospho-P65 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

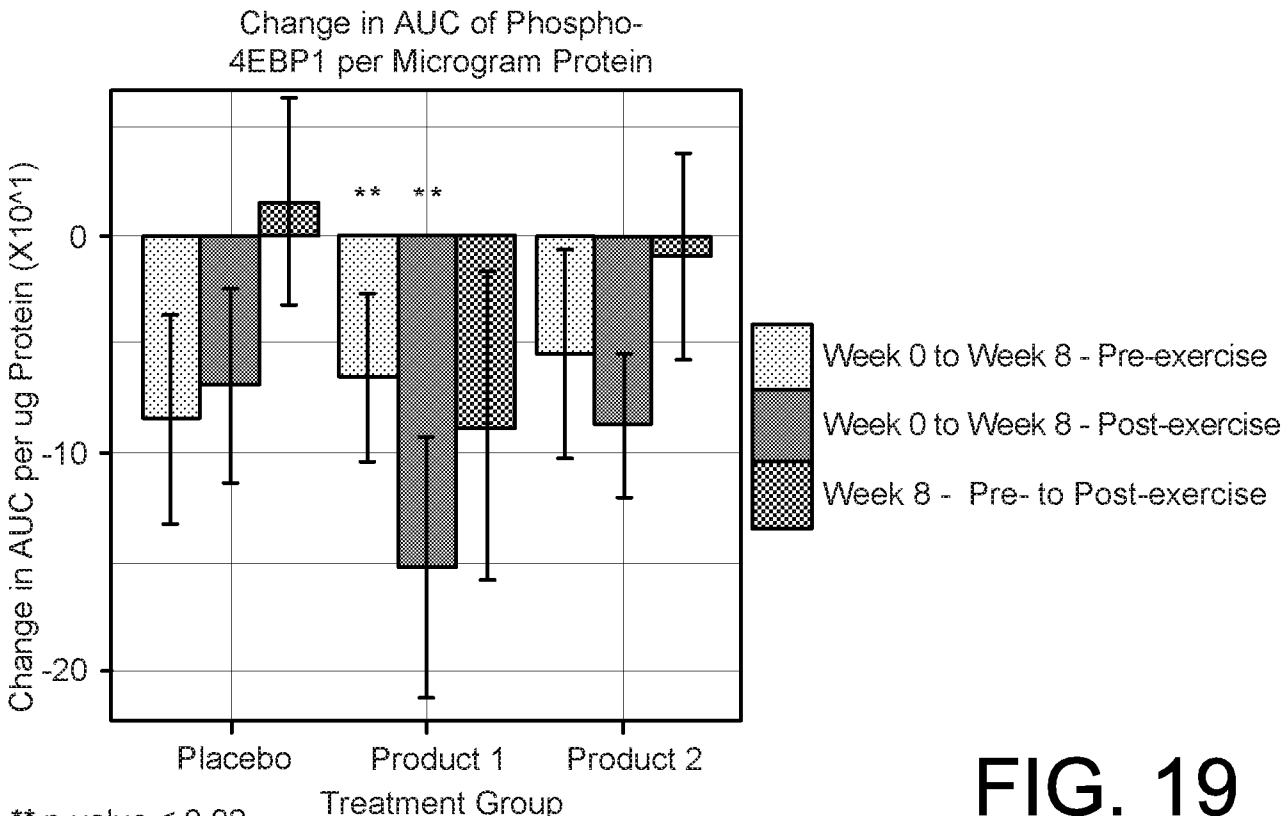


FIG. 19

** p-value ≤ 0.02

The AUC per µg of protein for Total-P65 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

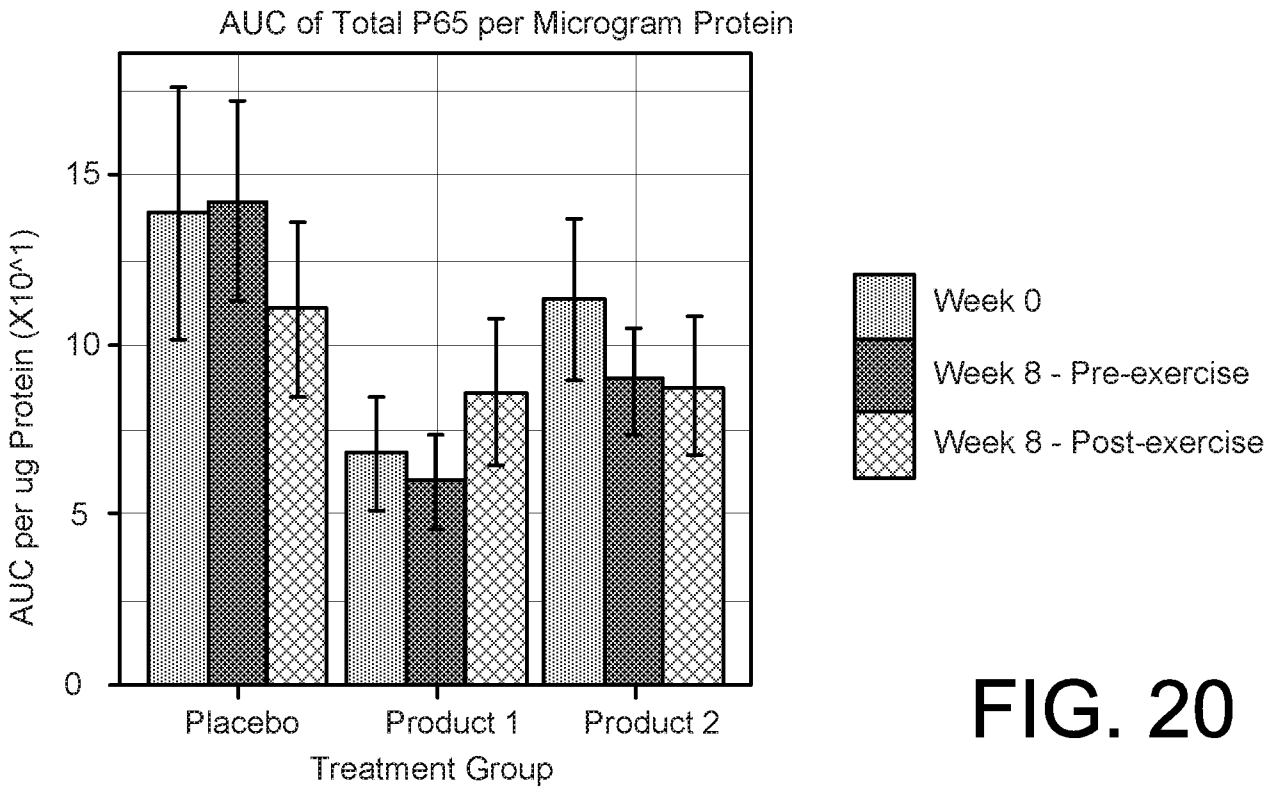


FIG. 20

The Change in Total-P65 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

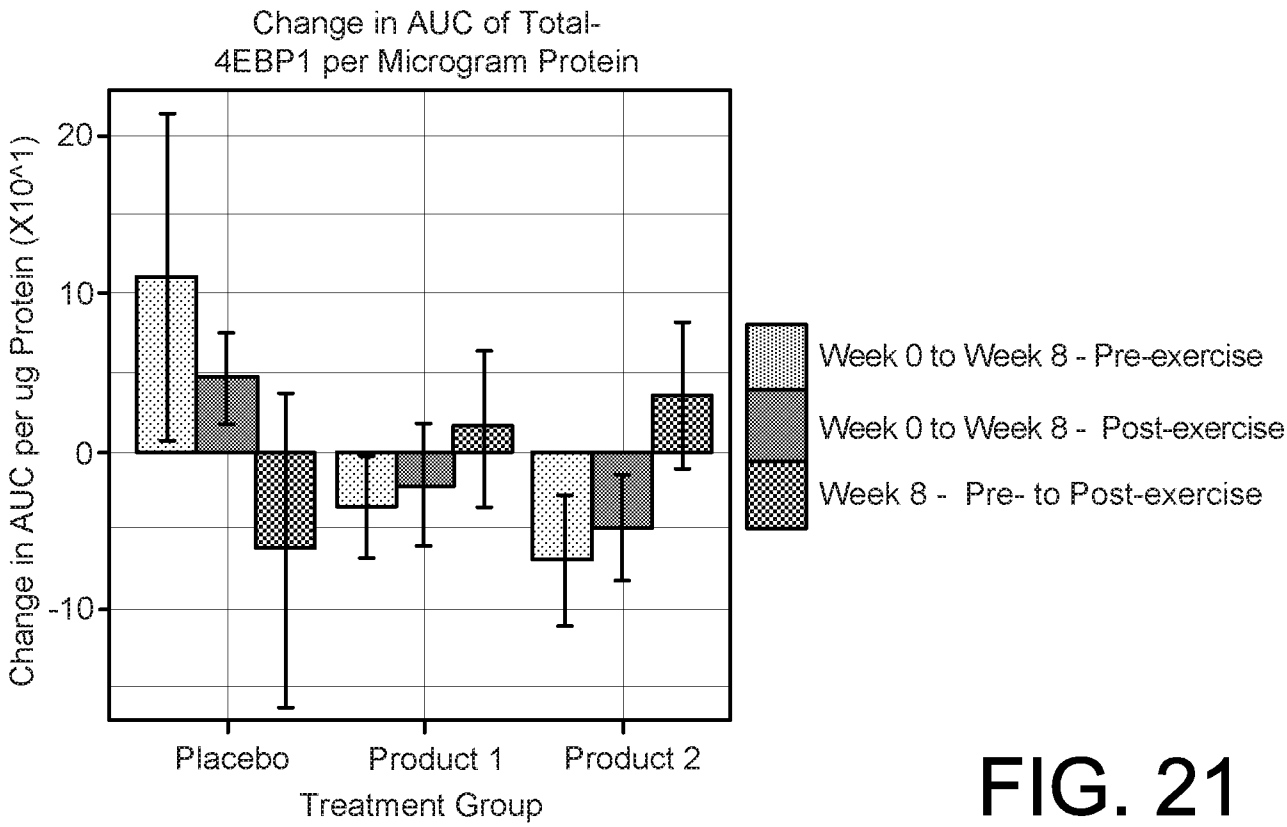


FIG. 21

The AUC per µg of protein for Total-P50 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

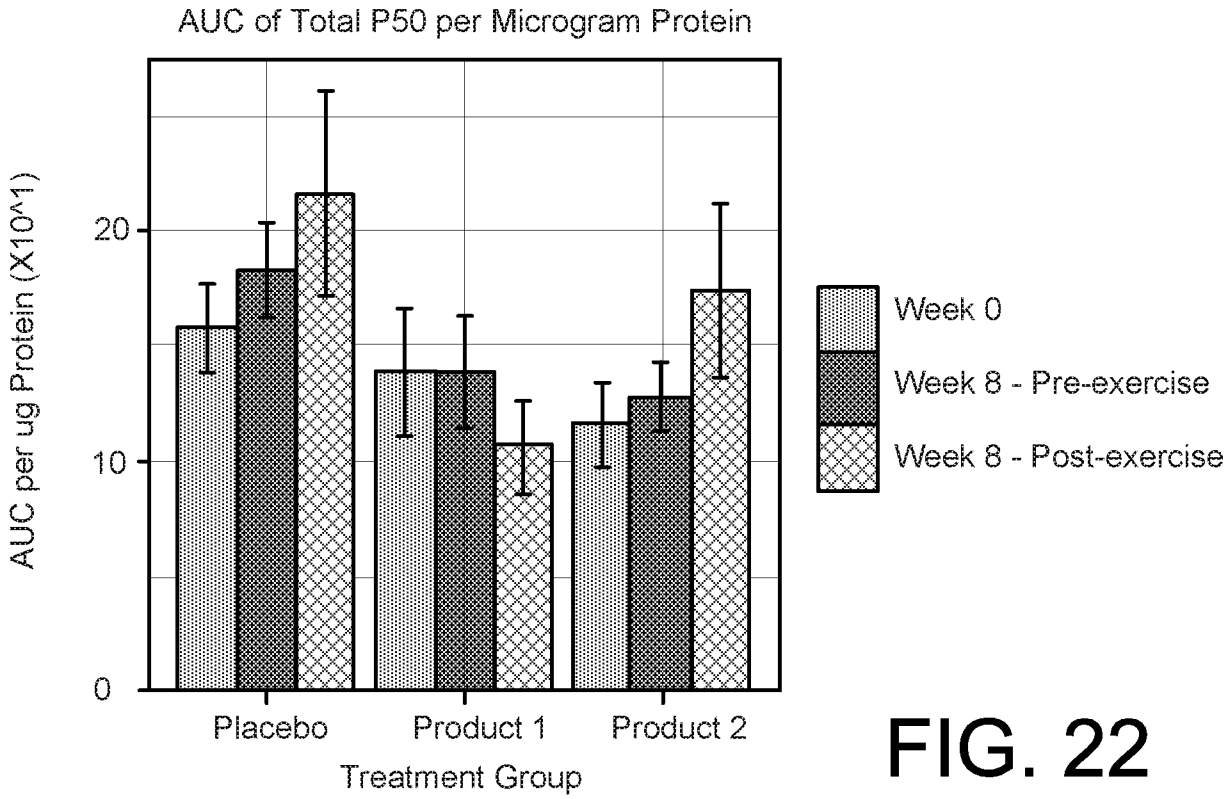


FIG. 22

The Change in Total-P50 from Baseline to Week 8 Pre and Post Exercise for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

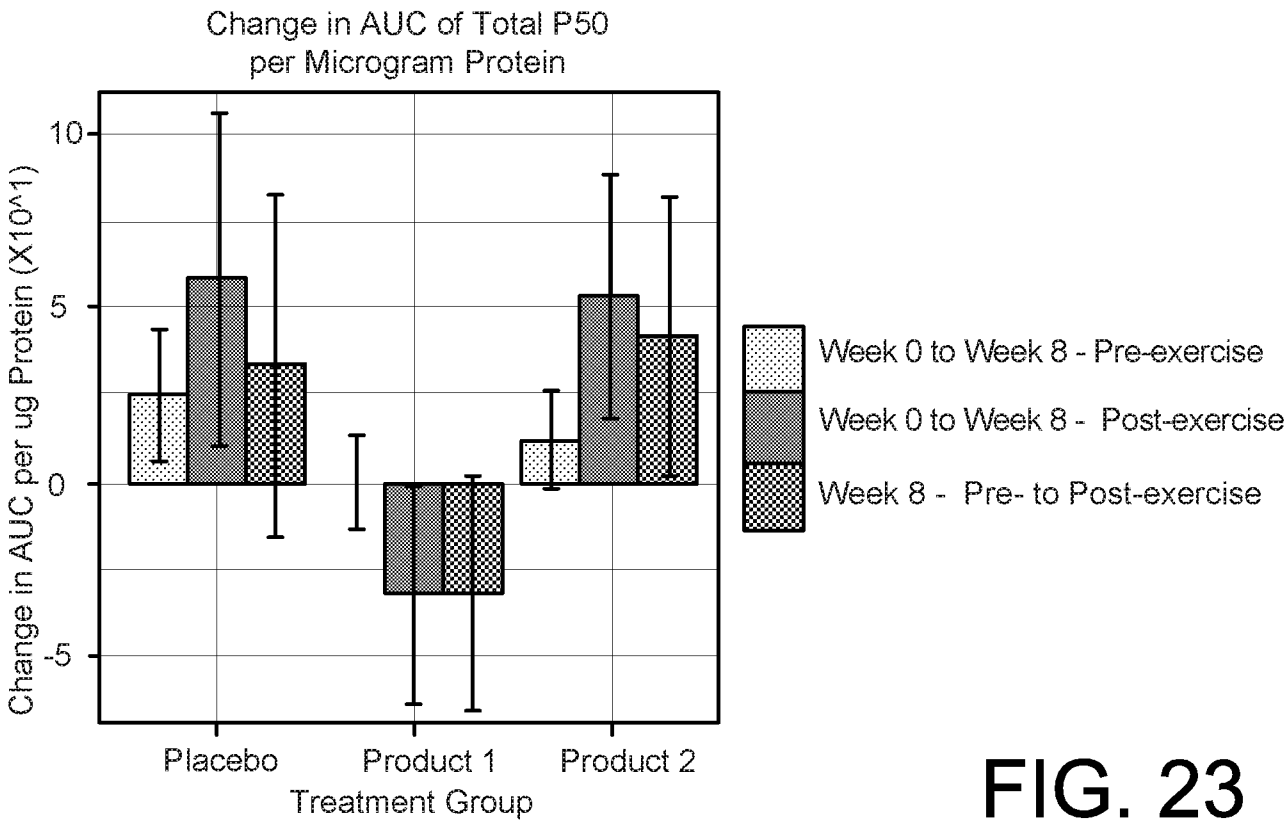


FIG. 23

A Representative Immuno-blot is Shown from Baseline to Week 8 for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 33).

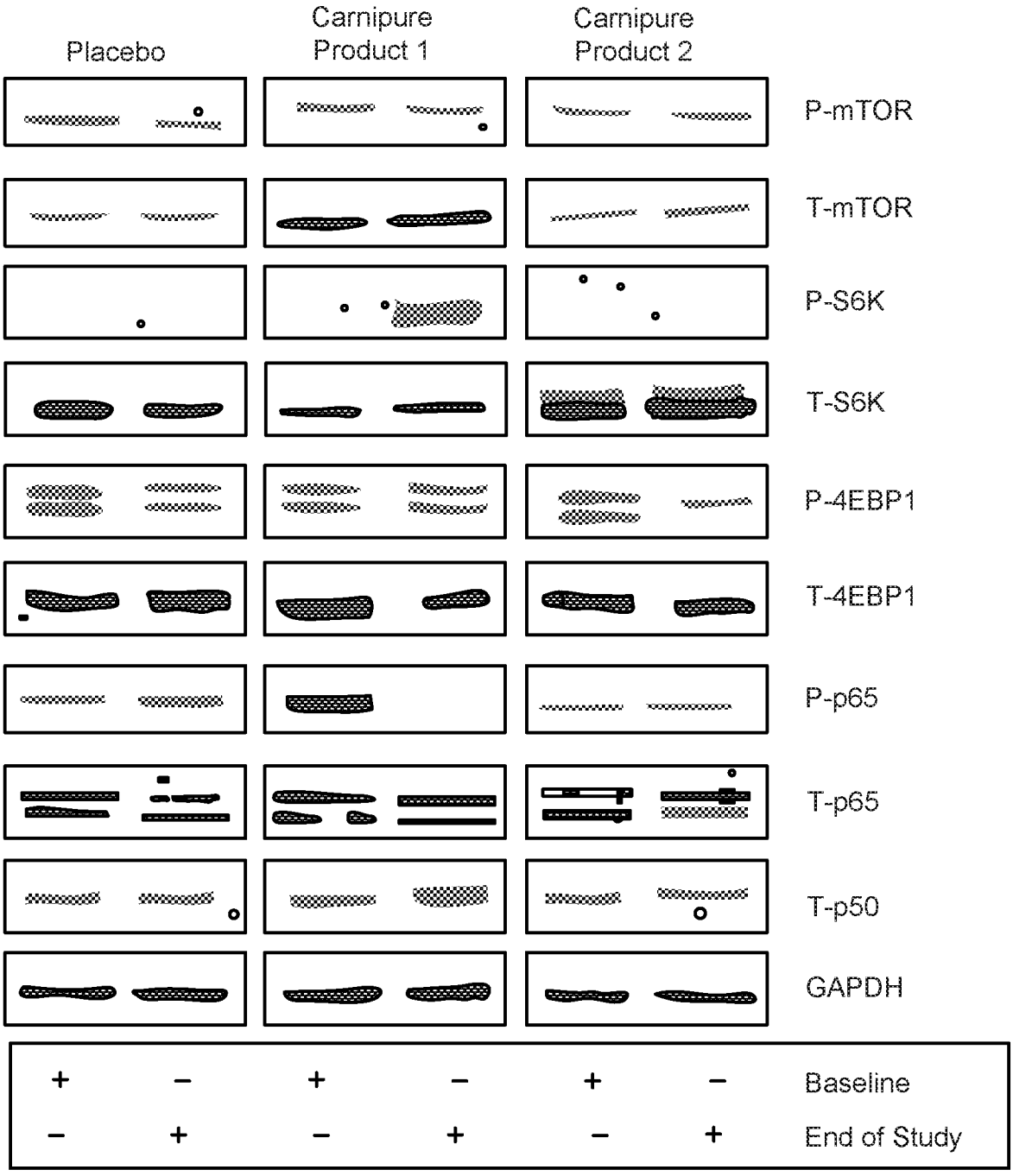


FIG. 24

The Change in Absolute Composite Score from Baseline to Week 8 for Participants Supplemented with either Placebo, Carnipure product 1, or Carnipure product 2 in the PP Population (N = 39).

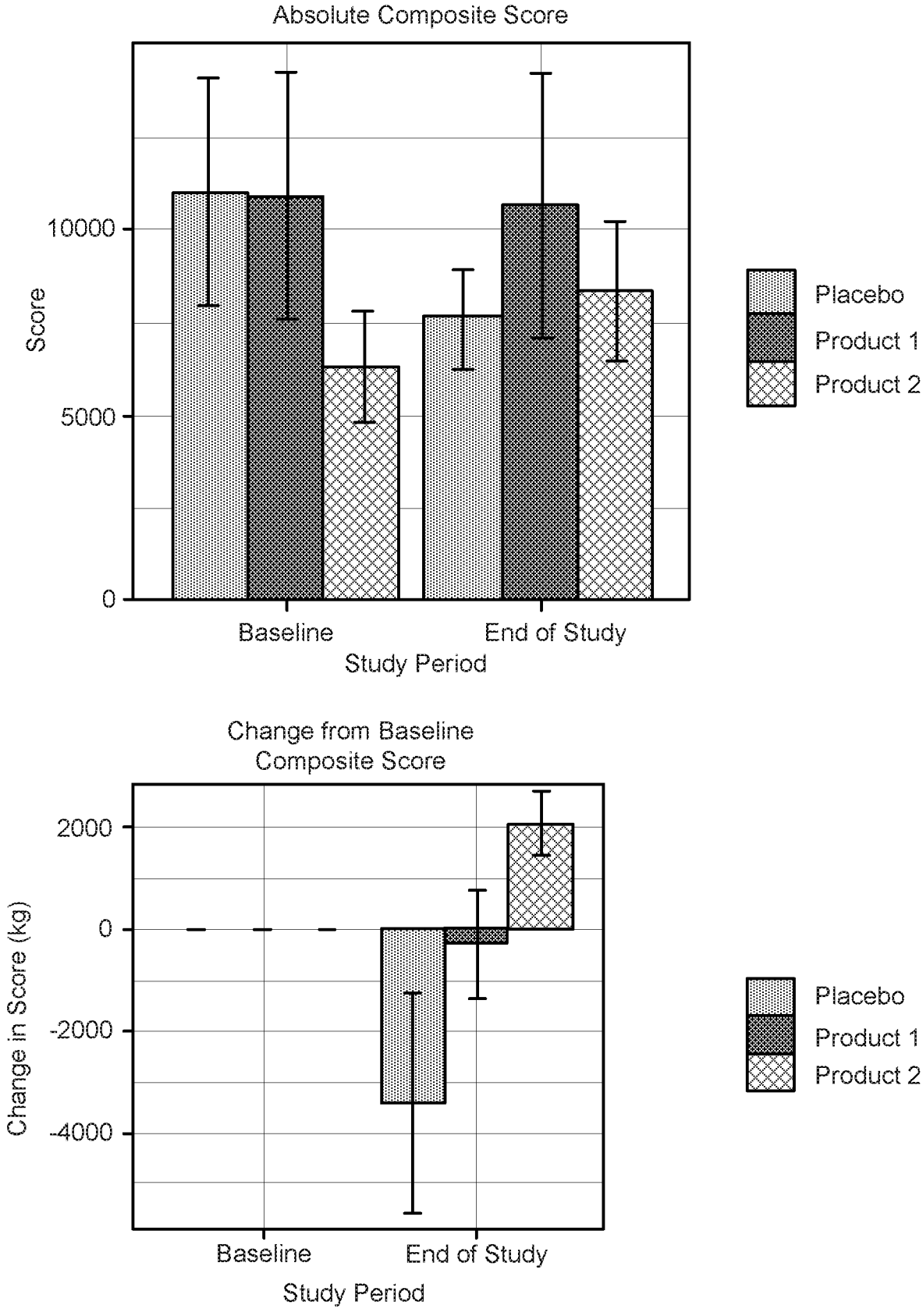


FIG. 25

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/067238

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23C9/152 A23K20/142 A23K20/174 A23L33/17
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A23C A23K A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2009/181903 A1 (WOLFE ROBERT [US] ET AL) 16 July 2009 (2009-07-16) paragraph [0002] paragraph [0010] - paragraph [0011] paragraph [0048] -----	21-23
X	WO 2008/115563 A1 (UNIV FLORIDA [US]; WHITE LESLEY JOAN [US]; PETTY HOLLY TASHA [US]; MCC) 25 September 2008 (2008-09-25) page 3, paragraph 2 - paragraph 4 page 6, paragraph 2 page 8, paragraph 2 - paragraph 5; claims 1-21 ----- -/--	21-23

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2017	17/03/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Oenhausen, Claudia

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/094772 A1 (ABBOTT LAB [US]) 25 June 2015 (2015-06-25) paragraph [0003] paragraph [0060] - paragraph [0061] paragraph [0067] - paragraph [0068] pharma; paragraph [0066] paragraph [0047]	21-36

X	US 2008/085343 A1 (PETTY HOLLY T [US] ET AL) 10 April 2008 (2008-04-10) paragraph [0036] - paragraph [0038]	21-23

T	CRUZ-JENTOFT ALFONSO J ET AL: "Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People", AGE AND AGEING, BAILLIERE TINDALL, LONDON, US, vol. 39, no. 4, 1 July 2010 (2010-07-01), pages 412-423, XP009167538, ISSN: 0002-0729, DOI: 10.1093/AGEING/AFQ034 [retrieved on 2010-04-13] abstract	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/067238

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009181903 A1	16-07-2009	AU 2008346842 A1	16-07-2009
		CA 2711809 A1	16-07-2009
		EP 2231141 A2	29-09-2010
		JP 2011509293 A	24-03-2011
		US 2009181903 A1	16-07-2009
		US 2010286023 A1	11-11-2010
		WO 2009088738 A2	16-07-2009
WO 2008115563 A1	25-09-2008	US 2008233245 A1	25-09-2008
		WO 2008115563 A1	25-09-2008
WO 2015094772 A1	25-06-2015	CN 106061291 A	26-10-2016
		EP 3091859 A1	16-11-2016
		US 2016361291 A1	15-12-2016
		WO 2015094772 A1	25-06-2015
US 2008085343 A1	10-04-2008	NONE	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/067238

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-20
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

Continuation of Box II.1

Claims Nos.: 1-20

Claims 1-20 on file were not searched as they include at least prophylactically treating sarcopenia by administering a composition for preserving muscle mass and function by increasing muscle protein and/or decreasing muscle protein degradation in mammals (cf claims 1 and 17 in combination). The description, cf paragraph [2]-[3] defines loss of health, independence and life quality due to sarcopenia, which has, as such, an established clinical definition. For claims 1-20 Rule 39.1(iv) PCT (method for treatment of the human or animal body by therapy) applies. Therefore these claims are not searched.