January 25, 2022

VIA ELECTRONIC SUBMISSION
http://www.regulations.gov

Douglas Stern
U.S. Food and Drug Administration
Deputy Director for Regulatory Affairs
Center for Food Safety and Applied Nutrition
5001 Campus Drive
College Park, MD 20740

Re: Docket No. FDA-2021-P-0938
Request for information on the use of N-acetyl cysteine (NAC) in products marketed as dietary supplements

Pure Encapsulations, LLC ("Pure Encapsulations®") is pleased to have this opportunity to provide the following comments in response to the Food and Drug Administration's ("FDA") request for information on the use of N-acetyl cysteine (NAC) in products marketed as dietary supplements. Specifically, FDA requested data and information on the historical use and safety of NAC as a dietary supplement. Pure Encapsulations is a recognized innovative leader in the development, manufacturing, and commercialization of vitamins, minerals, and supplements free from unnecessary additives and many common allergens, offering science-based nutritional solutions through health care professionals. Pure Encapsulations is a part of Nestlé Health Science with its portfolio of brands and complementary business model providing science-based nutritional solutions for consumers, patients, doctors, nurses, and other partners in health care. Pure Encapsulations has been marketing NAC as a dietary supplement for 30 years and, as such, is well positioned to provide information in response to FDA's request. Indeed, we feel an obligation to do so. Health care professionals, their patients, and consumers have come to rely on these products and have collectively expressed concern over FDA's recent actions to limit access to these safe and effective dietary supplements.

Introduction

In July 2020, FDA issued a series of warning letters focused on dietary supplement products positioned as hangover remedies.[1] In those same warning letters, FDA asserted that NAC, an ingredient common to a number of those products being addressed, cannot be marketed in dietary supplements under 201(ff)(3)(B)(i) of the Food, Drug & Cosmetic Act (FDCA), which prohibits manufacturers from marketing dietary supplements if they contain an article that was approved as a drug prior to its use in dietary supplements or food, commonly referred to as "drug preclusion". This assertion by FDA was seen by the

[1] Pure Encapsulations was not a recipient of such a warning letter, nor does Pure Encapsulations position its NAC-containing products for hangovers.

dietary supplement industry as a shift in longstanding policy, and rightly so, as NAC-containing dietary supplement products are widely available and have been safely consumed for decades. Already an established dietary supplement prior to 1994, NAC is clearly identified on industry lists developed at that time, firmly establishing NAC as what is commonly referred to as a "grandfathered" dietary ingredient. Further, the safety of NAC as a dietary supplement has not been challenged. The recent decision by FDA to object to NAC as a dietary supplement was, therefore, not based on safety concerns, but on a retroactive application of the drug preclusion clause.

As an active member of the Council for Responsible Nutrition ("CRN"), we would first like to express support for the comments submitted by CRN. Briefly, we request FDA to review CRN's petition and comments in earnest, especially regarding a) industry's position that drug preclusion was not intended to be applied retroactively, b) that FDA should not consider an inhaled drug as the same "article" as an oral dietary supplement, and c) that FDA espousing a change in policy via warning letter without adequate explanation creates confusion in the marketplace. We have seen significant business interruptions as health care professionals, online retailers, and payment platforms have prohibited the sale of NAC-containing dietary supplements in response to FDA's position, despite the matter remaining under consideration, as evidenced by FDA's request for additional information. These and other items addressed by CRN on behalf of the dietary supplement industry are important points that we feel must be urgently addressed by FDA, and we intend our comments, discussed below, to complement those put forth by CRN.

As requested, we hereby provide the following additional information on the historical use of NAC as a dietary supplement, including adverse events, as well as safety data obtained from recent clinical studies.

Historical Data

Pure Encapsulations was founded in 1991, providing dietary supplement products for sale through licensed health care professionals. No pharmaceutical products were, or have ever been, sold by the company. A retained physical copy of the *Physician's Product List* from August 1992 confirms that NAC (N-acetylcysteine, 500 mg) was available as a dietary supplement for purchase at that time **[See Attachment A]**. This adds to the already existing evidence that NAC was clearly available as a dietary supplement in the U.S. prior to October 15, 1994, the date delineating "old" and "new" dietary ingredients, as per the Dietary Supplement Health and Education Act of 1994 (DSHEA).

Available sales records for NAC-containing dietary supplement products sold by Pure Encapsulations and its associated professional brands were obtained from 2013 to the present. All product complaints, including adverse event reports, were then assessed for these products for the corresponding 9-year period. In total, 2,808,867 individual product units were sold by the company during this time. Each of these products contained NAC, alone or in combination with other dietary ingredients, at doses ranging from 50 mg NAC

to 1.8 g NAC per daily serving size. A total of 54 adverse events were identified, corresponding to an adverse event per unit sold rate of 0.002%.

Focusing on those products containing NAC alone, without additional dietary ingredients, a total of 1,027,803 units were sold during this period, with doses ranging from 500 mg NAC to 900 mg NAC per serving and recommend use up to 3 servings/d and 2 servings/d, respectively, for a maximum daily dose of 1.8 g. Each product unit provided between 1-3 months' supply. A total of 18 adverse events were identified for these products during this period, again corresponding to an overall adverse event rate per unit sold of approximately 0.002%. Upon further assessment, the majority of these events, 12 in total, were related to gastrointestinal effects, e.g., diarrhea, upset stomach, nausea, vomiting, and heartburn. Other events reported included headache, shortness of breath, eczema, and back pain. No meaningful or actionable associations or trends were identified. Overall, adverse events were extremely rare, mild, non-serious, and resolved on their own. No serious adverse event reports (sAERs) were identified for these products during this period. A record of one sAER was obtained from 2012, prior to the available sales data, related to choking on the capsule.

Clinical Studies

The safety of NAC was recently assessed in a randomized, double-blind, placebo-controlled clinical trial of 117 healthy older adults, aged 60-85 years. The study was designed by the Nestlé Institute of Health Sciences, Nestlé Research, and sponsored by Nestlé Health Science. The clinical trial was conducted at Profil Institute for Metabolic Health in Neuss, Germany, which carried out recruitment and executed the study under monitoring of auditors from the local authorities. A statistical analysis protocol was defined in collaboration with Profil Institute, which led the primary data analysis. Health monitoring was performed by medical staff and the principal investigator from Profil Institute. The complete manuscript has been submitted for publication and is currently under peer review. To accommodate FDA's request for information, a comprehensive Safety Report was prepared in advance, which includes a summary of all available safety data from the trial **[See Attachment B]**. In brief, subjects received placebo or one of three different daily doses of NAC, in combination with the amino acid glycine, for a period of two weeks. The groups were supplemented at 2.4 g/d (1.2 g NAC + 1.2 g glycine), 4.8 g/d (2.4 g NAC + 2.4 g glycine) or 7.2 g/d (3.6 g NAC + 3.6 g glycine). A full panel of blood, biochemical, and other relevant safety markers was quantified for each subject before and after the intervention. No differences were observed for any of the markers except for a statistically significant increase in the liver enzyme alkaline phosphatase (ALP), which was observed only at the combined 4.8g/d and 7.2g/d doses. Even at these higher doses, the values for ALP remained within the normal range and the change was not considered clinically relevant. Overall, this multi-dose study of rigorous design provides clear evidence that two weeks of daily supplementation with NAC, in combination with glycine, is safe and well-tolerated in healthy older adults.

An ongoing academic program on the safety and efficacy of NAC supplementation is also being conducted at Baylor College of Medicine, and data were made available to us with permission to submit in response to FDA's request. This work is not sponsored by Pure Encapsulations or Nestlé Health Science. In a recent randomized, double-blind, placebo-controlled trial, young and healthy older adults were supplemented with high-dose NAC (dosing was based on weight at 0.81 mmol/kg/d; on average approximately 7 g/d), again in combination with a similar dose of glycine. Young adult subjects were supplemented for 2 weeks, and older adults for 16 weeks. Blood levels of alanine transaminase (ALT), aspartate transaminase (AST), and creatinine were measured at baseline and 2, 4, 8, 12, and 16 weeks post-supplementation. All subjects exhibited normal levels of these markers and no changes were observed throughout the course of the intervention, as shown **[See Attachment C, Table 1]**. No adverse effects were observed. Individual values are not provided, as the manuscript is currently under review. Full safety data will be available upon publication.

In a published open-label clinical trial of otherwise similar design, the same investigators assessed the impact of approximately 7 g/d NAC supplementation in 8 healthy older adults for 24 weeks, with an additional 12-week follow up after discontinuing the supplement.[2] Again, transaminases and creatinine were measured at baseline and 4, 8, 12, 16, 20, and 24 weeks post-supplementation. No adverse effects were observed, and no changes were observed at any time point **[See Attachment C, Table 2]**. Similar results were demonstrated in an open-label trial of 8 HIV-positive but otherwise healthy adults supplemented with NAC (0.83 mmol/kg/d) and glycine for 12 weeks.[3] No changes in safety parameters or adverse effects were observed during the course of the study **[See Attachment C, Table 3]**.

Conclusion

Taken together, these data clearly establish that NAC has a long history of use as a dietary supplement and that NAC supplementation is safe and well tolerated. Nine years of complaints data were reviewed for NAC products, alone or in combination with other ingredients, at recommended total daily intake levels of NAC up to 1.8 g/d. The incidence of adverse effects associated with the use of these NAC-containing dietary supplement products is very low. The clinical study evidence we obtained further supports the safety of NAC supplementation at a variety of doses, including higher doses than typically found in commercially available dietary supplement products.

These data only add to what is already known and well established. Supplements containing NAC are widely available and have been safely used for decades. If FDA maintains its current position, those who have come to rely on these products will no longer be able to access them, all with no evidence of a safety concern. It is, therefore, essential that FDA revisit its recent actions against NAC-containing dietary supplements.

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[2] Kumar, et. al. Clin Transl Med. 2021;11:e372.

[3] Kumar, et. al. Biomedicines. 2020;8(10):390.

We appreciate the opportunity to participate in this process and thank FDA for considering this and other submissions to the docket. We further ask that FDA move swiftly to a clear and definitive resolution, as consumer access to NAC-containing products remains impacted while FDA continues to evaluate this matter.

Respectfully submitted,

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pure encapsulations, inc.

The Millworks · 156 River Road Willington, CT 06279 · 800-753-CAPS · 203-429-2900

Physician's Product List

(Effective August 1992)

NAC

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
N-acetylcysteine 500 mg.

[redacted]

Pancreatic Enzyme Formula

bottle size: 60's, 180's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
pure pancreatin (lactose free) 500 mg., provides: lipase 17,500 USP units, protease 110,000 USP units, amylase 120,000 USP units
1-2 capsules with each meal

Quercetin

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
quercetin 250 mg.
2-4 capsules per day, in divided doses, with meals

Taurine

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
taurine 500 mg.
2-4 capsules per day, in divided doses, with meals

About Our Company:

Founded by Physicians

Pure Encapsulations, Inc. was founded by physicians who use nutritional supplements in their practice.

Hypo-allergenic Formulas

Pure Encapsulations products are free of common allergens, such as dairy, yeast, corn, sugar, starch, soy, preservatives and hydrogenated oils.

How to Order

To order, please contact:

Pure Encapsulations, Inc.
The Millworks, 156 River Road
Willington, Connecticut 06279
800-753-CAPS · 203-429-2900
203-487-4508 (fax)

Orders are accepted on open account (15 day terms), with MasterCard, VISA or by C.O.D. to qualified accounts.

Orders are processed the day they are received. Second day delivery service is free for orders over $100. *Include a $7.50 handling fee for orders under $100.*

Quantity Discounts

48 bottles - 5%, 96 bottles - 8%, 144 bottles - 10% (bottles can be mixed to reach discount levels)

Returns

Returns are accepted within 30 days of shipment for merchandise credit only.

Pure Encapsulations products are sold only through licensed physicians.

Minerals

Boron

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
boron (glycinate) 2 mg., magnesium (aspartate) 18 mg.
1-3 capsules per day, in divided doses, with meals

Calcium (Citrate)

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
calcium (citrate) 150 mg.
2-3 capsules per day, in divided doses, with meals

Calcium (Microcrystalline Hydroxyapatite)

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
calcium (microcrystalline hydroxyapatite) 150 mg.
1-3 capsules per day, in divided doses, with meals

Calcium Magnesium

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
calcium (citrate) 80 mg., magnesium (citrate) 80 mg.
2-4 capsules per day, in divided doses, with meals

Copper

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
copper (glycinate) 2 mg., magnesium (aspartate) 19 mg.
1-2 capsules per day, in divided doses, with meals

Iron-C

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
iron (glycinate) 7.5 mg., iron (aspartate) 7.5 mg., pure ascorbic acid 175 mg.
1-2 capsules per day, in divided doses, with meals

Magnesium (Citrate)

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
magnesium (citrate) 150 mg.
1-4 capsules per day, in divided doses, with meals

Manganese

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
manganese (aspartate) 5 mg., manganese (citrate) 5 mg., magnesium (aspartate) 17 mg.
1-3 capsules per day, in divided doses, with meals

Mineral 650

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

six capsules contain:
calcium (citrate) 300 mg., magnesium (citrate) 250 mg., manganese (aspartate) 20 mg., zinc (picolinate) 25 mg., potassium (aspartate) 99 mg., copper (glycinate) 2 mg., iron (glycinate) 10 mg., selenium (selenomethionine) 200 mcg., chromium (NiChrom) 200 mcg., vanadium (aspartate) 100 mcg., molybdenum (aspartate) 100 mcg., iodine (potassium iodide) 100 mcg., boron (glycinate) 2 mg.
3-6 capsules per day, in divided doses, with meals

Mineral 650 without copper and iron

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

six capsules contain:
(same as above formula without copper and iron)
3-6 capsules per day, in divided doses, with meals

NiChrom

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
NiChrom (chromium, nicotinic acid, glutathione) 200 mcg., magnesium (aspartate) 21 mg.
2 capsules per day, in divided doses, with meals

Potassium (Aspartate)

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
potassium (aspartate) 99 mg.
2 capsules per day, in divided doses, with meals

Potassium Magnesium

bottle size: 90's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
potassium (aspartate) 99 mg., magnesium (aspartate) 70 mg.
4 capsules per day, in divided doses, with meals

Selenium

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

each capsule contains:
selenium (selenomethionine) 200 mcg., magnesium (aspartate) 18 mg
1 capsule per day, with meal

Zinc 15

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

zinc (picolinate) 15 mg., magnesium (aspartate) 15 mg.
1-4 capsules per day, in divided doses, with meals

Zinc 30

bottle size: 60's | suggested retail: [redacted] | physician price: [redacted]

zinc (picolinate) 30 mg., magnesium (aspartate) 9 mg.
1-2 capsules per day, in divided doses, with meals

ATTACHMENT B

Randomized, Controlled Trial of NAC Supplementation in Healthy Older Adults: Safety Report

Report prepared by Abby Klosterbuer, PhD, RDN – Medical Affairs Manager, Nestlé Health Science
based on manuscript by Lizzo et al:
Lizzo G et al. A randomized controlled trial in healthy older adults to determine efficacy of glycine and n-acetylcysteine supplementation on glutathione redox status & oxidative damage.
Manuscript submitted, 2022.

The safety and efficacy of n-acetylcysteine (NAC) supplementation, in combination with glycine, was recently assessed in a randomized, double-blind, placebo-controlled trial of healthy older adults. This study evaluated markers of glutathione status and oxidative stress and monitored safety and tolerability over 2 weeks of supplementation with up to 3.6 g/d NAC and 3.6 g/d glycine, known glutathione precursors. The trial was sponsored by Nestlé and was registered at clinicaltrials.gov: NCT05041179. The purpose of this report is to summarize the study design and safety outcomes.

Participants:
The clinical trial enrolled 117 older adults aged 60 to 85 years, who were recruited to represent healthy aging in the absence of disabling chronic medical conditions. Eligible participants had BMI 25-35 kg/m^2, HbA1c <6.5%, and engaged in <1 hour of strenuous exercise per week. Individuals were excluded if they had hypertension, diabetes, other major chronic medical conditions (e.g., dementia, frailty, malignancies). Heavy smokers (>5 cigarettes/d) and those with history of alcoholism or drug abuse were also excluded. Participants were asked to refrain from smoking, use of medications (except stable therapy with thyroid hormones, anti-hypertensive medications, hormonal contraception, or menopausal hormone replacement therapy), high protein supplements, and consumption of antioxidants, vitamins, and herbal supplements prior to and during the study. See **Appendix A** for a full list of exclusion criteria.

In addition, a non-interventional group of young, healthy volunteers (n=20) was recruited to assess age-related differences in oxidative stress and glutathione status. Eligible participants for this cohort were aged 20-40 years with BMI of 18.5-30 kg/m^2 and HbA1c <5.7%.

Design:
The study utilized a single-center, randomized, double-blind, placebo-controlled, 4-arm design. Following the screening visit, participants in the older cohort were randomized in a 1:1:1:1 ratio to four different arms: placebo, 2.4 g actives, 4.8 g actives, or 7.2 g actives (described in the “Nutrition Intervention” section below). A medical examination (body measurements, vital signs, physical exam) and blood sampling were completed at each study visit. Results are reported on days 1 and 15 of the supplementation period.

The primary outcome was level of total glutathione (GSH-T) in whole blood compared to placebo at the end of the study (2 weeks). Secondary outcomes included the ratio of free reduced to oxidized glutathione (GSH-F:GSSG) and markers of oxidative stress, including malondialdehyde (MDA) and total cysteine. Safety and tolerability were monitored throughout the course of the study.

Nutrition Intervention:
Participants were randomized to receive placebo (isomaltulose) or three different daily doses of NAC + glycine (referred to as GlyNAC) for two weeks. GlyNAC was provided as a 1:1 ratio of glycine and NAC and was supplemented at 2.4 g/d (1.2 g NAC + 1.2 g glycine), 4.8 g/d (2.4 g NAC + 2.4 g glycine) and 7.2 g/d (3.6 g NAC + 3.6 g glycine). Each daily dose of the study products was divided into two servings consumed in the morning and evening as a powder dissolved in water (**Table 1**).

Table 1. Composition of daily supplements per study arm

		Active (g)			Placebo (g)
		Arm A (7.2 g/d GlyNAC)	Arm B (4.8 g/d GlyNAC)	Arm C (2.4 g/d GlyNAC)	Arm D (isomaltulose)
	Ingredients				
Morning Dose (3 sachets)	NAC	1.8	1.2	0.6	-
	Glycine	1.8	1.2	0.6	-
	Isomaltulose	-	1.2	2.4	3.6
Evening Dose (3 sachets)	NAC	1.8	1.2	0.6	-
	Glycine	1.8	1.2	0.6	-
	Isomaltulose	-	1.2	2.4	3.6
Total Daily Dose	NAC	3.6	2.4	1.2	-
	Glycine	3.6	2.4	1.2	-
	Isomaltulose	-	2.4	4.8	7.2
Total Weight		7.2	7.2	7.2	7.2

Safety Measurements:
Safety was assessed via monitoring of adverse events and blood biochemistry analysis performed by MLM Medical Labs (Moenchengladbach, Germany). Basal blood hematology and biochemistry were performed at the screening visit, Day 1 of supplementation, and at the end of the study (Day 15). Blood was collected 60 minutes before and 120 minutes after product intake for assessment of any acute changes in hematological and biochemical markers. Participants received a mixed meal (breakfast) after product intake during these study visits.

Safety parameters assessed included: hematocrit, hemoglobin, erythrocytes, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCH concentration, platelets, leukocytes, sodium, potassium, creatinine, glucose, insulin, total cholesterol, triglycerides, aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyltransferase (ɣ-GT). An exhaustive list of all parameters evaluated can be found in **Appendix B**.

Results:
Participants
A total of 117 older adults (64 female / 53 male; mean age 65.5 years; mean BMI 28.9) were enrolled and randomized, with 114 completing 2 weeks of supplementation. No severe adverse effects were reported and none of the study participants discontinued GlyNAC due to adverse effects. Two of the three participants opted not to participate in the final visit due to COVID-19 travel restrictions, and one participant discontinued due to high blood pressure. The non-interventional control group included 20 young adults (9 female / 11 male; mean age 31.7 years; mean BMI 23.8). Baseline characteristics of study participants can be found in **Table 2**.

Glutathione Status / Oxidative Stress
Compared to younger adults, older adults had significantly higher oxidative stress ($p<0.0001$ for both MDA and total cysteine) and lower glycine ($p=0.01$). Older adults also had significantly increased oxidized glutathione (GSSG), leading to a significantly lower GSH:GSSG ratio ($p=0.002$).

Supplementation with GlyNAC led to dose-dependent increases in circulating glycine and total oxidized cysteine, indicating efficient absorption within one hour at all doses tested.

Safety
A comprehensive safety panel of relevant blood markers was quantified for each study subject at the beginning of the study and after two weeks of supplementation. No differences were observed between placebo and GlyNAC groups for any markers, except for a statistically significant, but not clinically meaningful difference in alkaline phosphatase (ALP). See **Table 3** for key safety outcomes. All other values for hematological and biochemical measures remained within normal range throughout the duration of the study (**See Appendix C**).

Conclusions:
Glutathione is a key intracellular antioxidant, and its synthesis is thought to be regulated such that cells maintain sufficient antioxidant capacity while preventing overproduction of antioxidants that could interfere with reactive oxygen species (ROS) signalling. Both NAC and glycine are glutathione precursors. This randomized, placebo-controlled study provides evidence that even among a cohort representing healthy aging, several markers of oxidative damage are elevated, indicating that older age is associated with a shift towards a pro-oxidative redox balance. This study also provides evidence that daily supplementation with 1.2-3.6 g NAC, in combination with glycine, is safe and well-tolerated in older adults.

Table 2. Baseline Characteristics of Study Participants
Anthropometric and metabolic characteristics of young (non-interventional cohort) and older (interventional cohort) study participants and differences in oxidative stress-related markers

	Young Adults		Older Adults		P (young vs. older)
n	Count (F/M) 20 (9/11)		Count (F/M) 117 (64/53)		-
	Mean	SD	Mean	SD	
Age (yr)	31.7	5.71	65.5	4.49	-
Body weight (kg)	71.26	11.83	83.5	10.45	<0.0001
BMI (kg/m2)	23.81	3.06	28.89	2.79	<0.0001
HbA1c (%)	5.2	0.25	5.66	0.28	<0.0001
Fasting plasma glucose (mmol/l)	n.d.		5.61	0.49	-
Fasting plasma insulin (pmol/l)	n.d.		9.27	5.72	-
HOMA-IR	n.d.		2.34	0.14	-
ISI (composite)	n.d.		118.2	6.16	-
Triglycerides (mmol/l)	0.868	0.406	1.284	0.544	0.002
HDL cholesterol (mmol/l)	1.375	0.275	1.508	0.365	0.151
LDL cholesterol (mmol/l)	3.116	0.814	3.759	0.92	0.002
Glycine in plasma (uM)	271.6	92.3	229.4	61.67	0.01
Cysteine-T in plasma (uM)	276	26.86	314.8	33.54	<0.0001
GSH-T normalized to hematocrit (mg/L)	938.1	146.51	921.5	205.34	0.73
GSH-F:GSSG normalized to hematocrit	15.26	3.24	11.78	4.69	0.002
MDA (umol/l)	0.136	0.018	0.158	0.019	<0.0001
	Median [IQR]		Median [IQR]		
C-reactive protein (mg/l)	0.4 [0.725]		1.6 [1.9]		<0.0001

Means are compared using parametric t statistics and median using nonparametric Wilcoxon/Mann–Whitney tests. Cysteine-T, total cysteine disulfides; GSH-T; total glutathione; GSH-F; free reduced glutathione; ISI, insulin sensitivity index; MDA, malondialdehyde.

Table 3a. Safety Outcomes Assessed Before and After Treatment
See Appendix C for a list of additional safety outcomes

		Screening	Baseline		End of Study	
	Dose		Pre-Dose	P^a	Pre-dose	P^c
Systolic Blood Pressure (mmHg)	Placebo	133.3 ± 7.25	134.1 ± 11.71	0.988	130.7 ± 7.49	0.528
	2.4 g	131.9 ± 6.31	128.3 ± 13.39	0.641	126.8 ± 13.67	0.952
	4.8 g	131.5 ± 7.10	131.3 ± 8.84	0.100	126.9 ± 10.24	0.278
	7.2 g	131.7 ± 7.66	130.3 ± 11.05	0.960	130.6 ± 11.69	0.999
Diastolic Blood Pressure (mmHg)	Placebo	82.9 ± 5.52	80.2 ± 6.57	0.380	78.8 ± 6.24	0.838
	2.4 g	83.1 ± 6.17	79.4 ± 6.55	0.231	77.4 ± 9.24	0.702
	4.8 g	83.2 ± 5.63	80.4 ± 6.43	0.297	77.6 ± 6.59	0.343
	7.2 g	84.7 ± 4.28	83.5 ± 6.62	0.769	79 ± 8.10	0.258

Values are expressed as LS-Means with 95% Confidence Interval. Statistics performed using a linear mixed model.
P^a=adjusted p-value pre-dose vs screening
P^c= p-value for change from baseline to end of study at pre-dose

Table 3b. Safety Outcomes Assessed Before and After Treatment
See Appendix C for a list of additional safety outcomes

		Baseline		End of Study			
	Dose	Pre-Dose	Post-dose (120 min)	Pre-dose	Post-dose (120 min)	P^c	P^e
Creatinine (umol/L) Normal Range: 65.4-119.3 umol/L (M) 52.2-91.9 umol/L (F)	Placebo	66.19 (61.42, 71.34)	64.01 (59.39, 68.98)	66.19 (61.42, 71.34)	64.33 (59.69, 69.33)	0.998	-
	2.4 g	64.08 (59.54, 68.98)	60.89 (56.57, 65.54)	64.94 (60.32, 69.91)	61.93 (57.52, 66.67)	0.453	0.545
	4.8 g	71.30 (66.33, 76.65)	69.01 (64.20, 74.19)	71.87 (66.84, 77.28)	69.37 (64.52, 74.59)	0.645	0.161
	7.2 g	65.52 (60.95, 70.44)	63.22 (58.81, 67.96)	65.09 (60.55, 69.98)	61.79 (57.47, 66.44)	0.700	0.848
Glucose (mmol/L) Normal Range: <5.6 mmol/L (fasting) <7.8 mmol/L (non-fasting)	Placebo	5.617 (5.37,5.88)	6.143 (5.87,6.43)	5.532 (5.29,5.79)	5.99 (5.73,6.27)	0.504	-
	2.4 g	5.397 (5.16,5.64)	6.138 (5.87,6.42)	5.408 (5.17,5.66)	6.226 (5.92,6.51)	0.925	0.483
	4.8 g	5.718 (5.47,5.97)	6.450 (6.18,6.74)	5.674 (5.43,5.93)	6.305 (6.03,6.59)	0.730	0.429
	7.2 g	5.614 (5.37,5.86)	6.275 (6.01,6.55)	5.509 (5.27,5.75)	6.419 (6.14,6.71)	0.394	0.897
Insulin (mIU/L) Normal Range: <25 mIU/L (fasting) 16-166 mIU/L (2hr post)	Placebo	8.18 (6.61,10.12)	34.95 (28.25,43.24)	7.74 (6.26,9.58)	34.79 (28.12,43.04)	0.523	-
	2.4 g	6.65 (5.4,8.2)	28.93 (23.47,35.66)	6.68 (5.41,8.24)	33 (26.73,40.74)	0.966	0.331
	4.8 g	9.07 (7.38,11.14)	40.59 (33.05,49.86)	9.76 (7.93,12)	37.83 (30.75,46.53)	0.390	0.127
	7.2 g	8.74 (7.12,10.74)	33.51 (27.28,41.16)	8.35 (6.8,10.25)	34.82 (28.31,42.84)	0.582	0.618

Triglycerides (mmol/L) Normal Range: <1.7 mmol/L	Placebo	1.351 (1.16,1.58)	1.581 (1.35,1.85)	1.214 (1.04,1.41)	1.422 (1.22,1.66)	**0.029**	-
	2.4 g	1.087 (0.93,1.27)	1.242 (1.07,1.45)	0.989 (0.85,1.15)	1.207 (1.04,1.41)	0.052	0.066
	4.8 g	1.227 (1.06,1.43)	1.4 (1.21,1.63)	1.204 (1.04,1.4)	1.436 (1.23,1.67)	0.698	0.940
	7.2 g	1.198 (1.03,1.39)	1.360 (1.17,1.58)	1.208 (1.04,1.4)	1.369 (1.17,1.59)	0.859	0.963
ALP (IU/L) Normal Range: 44-147 IU/L	Placebo	61.60 (56.73, 66.89)	61.95 (57.05, 67.27)	60.67 (55.87, 65.88)	61.14 (56.3, 66.38)	0.262	-
	2.4 g	63.97 (58.99, 69.37)	64.01 (59.03, 69.41)	65.26 (60.18, 70.77)	65.06 (59.99, 70.55)	0.143	0.216
	4.8 g	68.70 (63.44, 74.39)	68.80 (63.54, 74.50)	70.66 (65.25, 76.52)	70.93 (65.49, 76.81)	**0.035**	**0.009**
	7.2 g	67.72 (62.54, 73.34)	67.60 (62.42, 73.19)	70.52 (65.12, 76.36)	70.13 (64.76, 75.95)	**0.002**	**0.010**
AST (IU/L) Normal Range: 10-40 IU/L	Placebo	20.10 (18.33, 22.03)	20.07 (18.31, 22.01)	19.06 (17.38, 20.89)	18.69 (17.05, 20.49)	0.115	-
	2.4 g	18.75 (17.13, 20.52)	18.80 (17.18, 20.58)	18.96 (17.32, 20.77)	18.83 (17.19, 20.62)	0.737	0.942
	4.8 g	21.20 (19.40, 23.17)	21.72 (19.88, 23.74)	21.54 (19.7, 23.55)	21.22 (19.41, 23.20)	0.635	0.061
	7.2 g	20.49 (18.75, 22.39)	20.41 (18.68, 22.31)	20.90 (19.13, 22.84)	20.46 (18.71, 22.37)	0.539	0.156

Values are expressed as LS-Means with 95% Confidence Interval. Statistics performed using a linear mixed model
P^c = p-value for change from baseline to end of study at pre-dose
P^e = p-value end of study at pre-dose comparing placebo vs active dose group

Appendix A. Exclusion Criteria

Subject Exclusion Criteria	Non-interventional Cohort	1. Receipt of any medicinal product or nutritional product in clinical development within 30 days before enrolment in this trial. 2. Any history or presence of clinically relevant comorbidity, as judged by the Investigator. 3. Signs of acute illness as judged by the Investigator. 4. Any serious systemic infectious disease during four weeks prior enrolment in this trial 5. Clinically significant abnormal screening laboratory tests, as judged by the Investigator. 6. AST and/or ALT > 2 times the upper limit of normal. 7. Elevated serum creatinine values above the upper limit of normal. 8. Systolic blood pressure < 90 mmHg or >139 mmHg and/or diastolic blood pressure < 50 mmHg or >89 mmHg (excluding white-coat hypertension; therefore, a repeat test showing results within range will be acceptable). 9. Heart rate at rest outside the range of 50-90 beats per minute. 10. Clinically significant abnormal standard 12-lead electrocardiogram (ECG) after 5 minutes resting in supine position at screening, as judged by the Investigator. 11. Significant history of alcoholism or drug abuse as judged by the Investigator; consuming >24 grams alcohol/day (for males), 12 grams alcohol/day (for females) on average. 12. Smoking or use of nicotine substitute products. 13. Any medication (prescription & non-prescription drugs) within 14 days before screening. 14. Blood donation or blood loss of >500 mL within the last 3 months prior to screening. 15. Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation. 16. If female, pregnant or breast-feeding. 17. Consumption of high protein supplements within 60 days of screening & during the study. 18. Consumption of any antioxidant, vitamins, and herbal supplements within 2 weeks prior to screening and during the study.
	Interventional Cohort	1. Known or suspected hypersensitivity to any component of the trial products. 2. Receipt of any medicinal product or nutritional product in clinical development within 30 days before randomisation in this trial. 3. History of multiple and/or severe allergies to drugs or foods or a history of severe anaphylactic reaction. 4. Any history or presence of clinically relevant comorbidity, as judged by the investigator. 5. Signs of acute illness as judged by the Investigator. 6. Any serious systemic infectious disease during four weeks prior to first intake of the trial product, as judged by the Investigator. 7. Clinically significant abnormal screening laboratory tests, as judged by the Investigator. 8. AST and/or ALT > 2 times the upper limit of normal. 9. Elevated serum creatinine values above the upper limit of normal. 10. Systolic blood pressure < 90 mmHg or >139 mmHg and/or diastolic blood pressure < 50 mmHg or >89 mmHg (excluding white-coat hypertension; therefore, a repeat test showing results within range will be acceptable). 11. Heart rate at rest outside the range of 50-90 beats per minute. 12. Clinically significant abnormal standard 12-lead electrocardiogram (ECG) after 5 minutes resting in supine position at screening, as judged by the Investigator. 13. Significant history of alcoholism or drug abuse as judged by the Investigator; consuming >24 grams alcohol/day (for males), 12 grams alcohol/day (for females) on average. 14. Smoking more than 5 cigarettes or the equivalent per day. 15. Inability or unwillingness to refrain from smoking and use of nicotine substitute products 3 days prior and during the intervention. 16. Tested positive for Hepatitis Bs antigen. 17. Tested positive for hepatitis C antibodies. 18. Positive result to the test for HIV-1/2 antibodies or HIV-1 antigen. 19. Any medication (prescription and non-prescription drugs) within 14 days before test product intake with the exception of stable therapy with thyroid hormones, anti-hypertensive medication (except beta blockers) and if female with the exception of hormonal contraception or menopausal hormone replacement therapy. 20. Blood donation or blood loss of >500 mL within the last 3 months prior to screening 21. Mental incapacity, unwillingness or language barriers precluding adequate understanding or co-operation. 22. Consumption of high protein supplements within 60 days of screening & during the study.

		23. Consumption of any antioxidants, vitamins and herbal supplements within 2 weeks prior to randomization and during the study.
Test Day Exclusion Criteria	Screening	1. Fasting (except intake of water) for less than 8 hours. 2. Strenuous exercise within the last 24 hours as judged by the investigator. 3. Any medical condition or AE that could interfere with the procedures of the study, as judged by the Investigator.
	Day 1 and Day 15 of supple-mentation	1. Fasting for less than 10 hours (up to 200 mL of water are allowed) 2. Strenuous exercise within the last 48 hours as judged by the investigator 3. Protein-rich meal in the evening before as judged by the investigator 4. Consumption of alcohol, caffeine- and/or methylxanthine-containing products in the last 24 hours before the measurement (i.e., coffee, coke, black/green tea, chocolate, cacao, energy drinks)

Appendix B. Safety Panel Parameters

Safety Panel 1	
Hematology	
Hematocrit	Leukocytes
Hemoglobin	Neutrophile granulocytes (total count and relative)
Erythrocytes	Lymphocytes (total count and relative)
Mean corpuscular volume (MCV)	Monocytes (total count and relative)
Mean corpuscular hemoglobin (MCH)	Eosinophil granulocytes (total count and relative)
MCH concentration (MCHC)	Basophile granulocytes (total count and relative)
Thrombocytes (platelets)	
Biochemistry	Uric acid
Sodium	Total protein
Potassium	Albumin
Calcium	Total bilirubin
Chloride	Creatine kinase
Phosphate	Alkaline phosphatase
Creatinine	Gamma glutamyltransferase (y-GT)
Urea	Lactic dehydrogenase (LDH)
AST (aspartate aminotransferase)	C-reactive protein
ALT (alanine aminotransferase)	High-density lipoprotein (HDL) cholesterol
Total cholesterol	Triglycerides
Low-density lipoprotein (LDL) cholesterol	
Coagulation (screening only)	
International normalized ratio (INR)	Activated partial thromboplastin time (APTT)
Infectious Serology (screening only)	
Hepatitis B surface antigen	HIV-1/2 combi
Hepatitis C antibodies	
Other (screening only)	
HbA1c	B-HCG (females only; young control group only)
Safety Panel 2	
Hematology	
Hematocrit	MCH concentration (MCHC)
Hemoglobin	Thrombocytes (platelets)
Erythrocytes	Leukocytes
Mean corpuscular volume (MCV)	
Mean corpuscular hemoglobin (MCH)	
Biochemistry	
Sodium	AST (aspartate aminotransferase)
Potassium	Alkaline phosphatase
Creatinine	Gamma glutamyltransferase (y-GT)
Glucose	Insulin
Total cholesterol	Triglycerides

Note: laboratory tests included in safety panel 2 performed in conjunction with mixed meal for safety and compliance check (check of fasting state)

Appendix C. Additional Hematological and Biochemical Measures

Lizzo et al Safety Data.xlsx

	UNIT	VISIT	DOSE	TIME	MEAN	SD	MEDIAN	QUANTILE 25%	QUANTILE 75%
Cholesterol Desirable: <5.18 mmol/L Borderline high: 5.18-6.18 mmol/L High: >6.18 mmol/L All means and medians within desirable or borderline range	mmol/L	SCREENING	0		5.44	0.72	5.49	4.97	5.90
		SCREENING	2.4		5.47	0.83	5.59	5.00	6.03
		SCREENING	4.8		5.22	1.13	5.07	4.59	5.67
		SCREENING	7.2		5.68	1.01	5.54	4.98	6.47
		DAY 1	0	-60	5.03	0.73	5.04	4.68	5.53
		DAY 1	0	120	5.01	0.74	5.05	4.63	5.46
		DAY 1	2.4	-60	4.99	0.73	5.00	4.43	5.65
		DAY 1	2.4	120	4.96	0.68	4.97	4.30	5.49
		DAY 1	4.8	-60	4.72	1.06	4.68	3.97	5.37
		DAY 1	4.8	120	4.73	1.07	4.65	3.91	5.25
		DAY 1	7.2	-60	5.26	0.82	5.27	4.78	5.83
		DAY 1	7.2	120	5.24	0.81	5.40	4.75	5.74
		DAY 15	0	-60	4.98	0.70	4.99	4.61	5.33
		DAY 15	0	120	4.94	0.70	4.95	4.53	5.20
		DAY 15	2.4	-60	4.99	0.75	5.12	4.52	5.50
		DAY 15	2.4	120	4.96	0.70	5.15	4.56	5.45
		DAY 15	4.8	-60	4.84	1.00	4.66	4.33	5.49
		DAY 15	4.8	120	4.84	1.00	4.71	4.25	5.49
		DAY 15	7.2	-60	5.22	0.79	5.30	4.66	5.75
		DAY 15	7.2	120	5.20	0.76	5.26	4.61	5.62
Mean Corpuscular Hemoglobin (MCH) Normal Range: 1.71-2.05 fmol (27.5-33 pg) All means and medians within normal range	fmol	SCREENING	0		1.89	0.07	1.89	1.82	1.95
		SCREENING	2.4		1.89	0.14	1.92	1.84	1.97
		SCREENING	4.8		1.90	0.08	1.91	1.86	1.94
		SCREENING	7.2		1.91	0.08	1.92	1.84	1.95
		DAY 1	0	-60	1.89	0.08	1.89	1.84	1.95
		DAY 1	0	120	1.89	0.08	1.89	1.82	1.93
		DAY 1	2.4	-60	1.89	0.13	1.92	1.84	1.98
		DAY 1	2.4	120	1.89	0.13	1.92	1.82	1.97
		DAY 1	4.8	-60	1.89	0.08	1.92	1.87	1.95
		DAY 1	4.8	120	1.89	0.08	1.91	1.87	1.94
		DAY 1	7.2	-60	1.91	0.09	1.92	1.85	1.98
		DAY 1	7.2	120	1.90	0.08	1.92	1.84	1.95
		DAY 15	0	-60	1.88	0.08	1.89	1.82	1.96
		DAY 15	0	120	1.88	0.08	1.89	1.83	1.94
		DAY 15	2.4	-60	1.90	0.11	1.93	1.82	1.96
		DAY 15	2.4	120	1.91	0.10	1.94	1.84	1.98
		DAY 15	4.8	-60	1.91	0.08	1.93	1.88	1.95
		DAY 15	4.8	120	1.91	0.07	1.92	1.87	1.96
		DAY 15	7.2	-60	1.90	0.09	1.91	1.85	1.95
		DAY 15	7.2	120	1.90	0.08	1.92	1.85	1.96
Mean Corpuscular Hemoglobin Concentration (MCHC) Normal Range: 19.59-22.20 mmol/L All means and medians within normal range	mmol/L	SCREENING	0		21.16	0.62	21.05	20.75	21.53
		SCREENING	2.4		20.98	0.57	21.10	20.60	21.40
		SCREENING	4.8		21.05	0.40	21.00	20.80	21.20
		SCREENING	7.2		20.99	0.50	21.00	20.60	21.30
		DAY 1	0	-60	21.08	0.54	21.10	20.88	21.40
		DAY 1	0	120	21.21	0.54	21.30	21.08	21.53
		DAY 1	2.4	-60	20.90	0.60	20.90	20.60	21.30
		DAY 1	2.4	120	21.08	0.61	21.20	20.80	21.50
		DAY 1	4.8	-60	20.94	0.66	20.95	20.70	21.40
		DAY 1	4.8	120	21.12	0.57	21.10	20.80	21.60
		DAY 1	7.2	-60	21.00	0.50	21.00	20.60	21.30
		DAY 1	7.2	120	21.07	0.47	21.10	20.63	21.45
		DAY 15	0	-60	20.99	0.46	21.00	20.78	21.23
		DAY 15	0	120	21.13	0.50	21.05	20.80	21.50
		DAY 15	2.4	-60	20.98	0.52	20.95	20.60	21.33
		DAY 15	2.4	120	21.21	0.52	21.20	20.98	21.53
		DAY 15	4.8	-60	21.18	0.62	21.00	20.90	21.60
		DAY 15	4.8	120	21.28	0.51	21.30	21.00	21.60
		DAY 15	7.2	-60	21.05	0.48	20.95	20.73	21.48
		DAY 15	7.2	120	21.13	0.46	21.10	20.90	21.40
Mean Corpuscular Volume (MCV) Normal Range: 80-95 fL All means and medians within normal range	fL	SCREENING	0		89.2	3.0	88.7	87.1	92.0
		SCREENING	2.4		90.2	5.0	91.0	88.0	92.8
		SCREENING	4.8		90.0	3.2	90.1	88.5	92.6
		SCREENING	7.2		90.7	2.9	90.7	89.5	92.0
		DAY 1	0	-60	89.6	3.1	89.4	87.4	91.8
		DAY 1	0	120	89.1	3.2	88.7	86.6	91.1
		DAY 1	2.4	-60	90.4	5.5	90.7	87.7	93.5
		DAY 1	2.4	120	89.8	5.3	90.3	87.3	92.7
		DAY 1	4.8	-60	90.4	2.8	90.4	88.7	92.7
		DAY 1	4.8	120	89.6	3.0	89.6	86.5	92.1
		DAY 1	7.2	-60	90.8	3.0	91.1	89.4	92.3
		DAY 1	7.2	120	90.3	2.9	90.2	88.9	91.7
		DAY 15	0	-60	89.8	3.3	89.5	86.7	92.0
		DAY 15	0	120	89.2	3.1	89.1	86.6	91.9
		DAY 15	2.4	-60	90.7	4.0	90.3	87.9	93.7
		DAY 15	2.4	120	90.1	3.9	89.7	87.4	93.4
		DAY 15	4.8	-60	90.2	3.2	90.4	88.4	92.5
		DAY 15	4.8	120	89.8	3.2	89.4	88.0	92.3
		DAY 15	7.2	-60	90.4	3.1	90.4	88.3	91.7
		DAY 15	7.2	120	90.2	3.2	89.8	88.1	91.6
Erythrocytes Normal range (male): 4.35-5.65 Normal range (female): 3.92-5.13	/pl	SCREENING	0		4.70	0.33	4.60	4.50	4.93
		SCREENING	2.4		4.62	0.32	4.70	4.40	4.80
		SCREENING	4.8		4.78	0.45	4.90	4.63	5.00
		SCREENING	7.2		4.61	0.34	4.60	4.40	4.88
		DAY 1	0	-60	4.41	0.33	4.40	4.20	4.60
		DAY 1	0	120	4.41	0.30	4.40	4.20	4.50
		DAY 1	2.4	-60	4.29	0.34	4.30	4.10	4.50
		DAY 1	2.4	120	4.26	0.32	4.20	4.00	4.40
		DAY 1	4.8	-60	4.48	0.41	4.50	4.30	4.68
		DAY 1	4.8	120	4.46	0.40	4.50	4.30	4.60

	/pL	DAY 1	7.2	-60	4.34	0.33	4.30	4.20	4.60
All means and medians within normal, considering male and female ranges		DAY 1	7.2	120	4.31	0.32	4.30	4.10	4.50
		DAY 15	0	-60	4.37	0.35	4.35	4.10	4.60
		DAY 15	0	120	4.35	0.33	4.30	4.10	4.50
		DAY 15	2.4	-60	4.27	0.35	4.20	4.08	4.50
		DAY 15	2.4	120	4.23	0.34	4.20	4.08	4.40
		DAY 15	4.8	-60	4.41	0.40	4.40	4.20	4.60
		DAY 15	4.8	120	4.40	0.40	4.50	4.20	4.60
		DAY 15	7.2	-60	4.27	0.34	4.25	4.03	4.48
		DAY 15	7.2	120	4.23	0.33	4.20	4.00	4.40
		SCREENING	0		21.3	12.6	16	12	27.5
		SCREENING	2.4		27.7	35.4	17	14	23
		SCREENING	4.8		26.0	16.0	22	17	30
		SCREENING	7.2		27.2	15.2	23	18	32.5
		DAY 1	0	-60	19.8	11.7	16	10	28.5
		DAY 1	0	120	19.5	11.9	15	10	27.5
		DAY 1	2.4	-60	23.9	28.1	15	12	21
		DAY 1	2.4	120	23.2	27.5	14	12	20
Gamma Glutamyl Transferase (GGT)		DAY 1	4.8	-60	23.0	13.6	20	16	26.8
Normal Range: <30 IU/L	IU/L	DAY 1	4.8	120	22.7	13.1	20	15	26
		DAY 1	7.2	-60	23.7	13.1	20.5	16	29.8
All means and medians within normal range		DAY 1	7.2	120	23.3	12.7	20.5	15.5	30
		DAY 15	0	-60	19.2	10.3	14.5	10.8	30.5
		DAY 15	0	120	18.8	9.9	15	10	29.5
		DAY 15	2.4	-60	22.6	24.9	14.5	12	21
		DAY 15	2.4	120	22.1	24.1	14	12	20.3
		DAY 15	4.8	-60	22.4	14.4	20	16	27
		DAY 15	4.8	120	22.1	14.2	20	15	29
		DAY 15	7.2	-60	24.9	14.9	21	15	29
		DAY 15	7.2	120	24.4	15.0	21	15	29
		SCREENING	0		8.8	0.6	8.9	8.5	9.2
		SCREENING	2.4		8.7	0.6	8.9	8.3	9.2
		SCREENING	4.8		9.0	0.8	9.2	8.6	9.6
		SCREENING	7.2		8.8	0.7	8.7	8.1	9.1
		DAY 1	0	-60	8.3	0.6	8.5	8.0	8.7
		DAY 1	0	120	8.3	0.6	8.4	8.1	8.7
		DAY 1	2.4	-60	8.1	0.7	8.1	7.6	8.6
Hemoglobin		DAY 1	2.4	120	8.0	0.6	8.0	7.7	8.6
Normal Range (male): 8.7-11.2		DAY 1	4.8	-60	8.5	0.7	8.6	8.1	8.9
Normal Range (female): 7.4-9.9	mmol/L	DAY 1	4.8	120	8.4	0.7	8.6	8.0	8.9
		DAY 1	7.2	-60	8.2	0.7	8.3	7.8	8.7
All means and medians within normal, considering male and female ranges		DAY 1	7.2	120	8.2	0.7	8.3	7.7	8.6
		DAY 15	0	-60	8.2	0.7	8.3	7.9	8.5
		DAY 15	0	120	8.2	0.6	8.1	7.8	8.6
		DAY 15	2.4	-60	8.1	0.7	8.2	7.7	8.5
		DAY 15	2.4	120	8.1	0.6	8.2	7.6	8.4
		DAY 15	4.8	-60	8.4	0.7	8.5	7.9	8.9
		DAY 15	4.8	120	8.4	0.8	8.5	7.9	8.9
		DAY 15	7.2	-60	8.1	0.7	8.1	7.7	8.6
		DAY 15	7.2	120	8.0	0.6	8.0	7.6	8.4
		SCREENING	0		5.9	1.6	5.5	4.8	7.3
		SCREENING	2.4		6.0	1.6	5.6	5.1	6.6
		SCREENING	4.8		6.4	1.4	5.9	5.4	7.3
		SCREENING	7.2		6.1	1.4	6.1	5.4	6.7
		DAY 1	0	-60	5.3	1.2	5.3	4.4	6.1
		DAY 1	0	120	5.8	1.5	5.7	4.8	6.8
		DAY 1	2.4	-60	5.6	1.8	5.3	4.6	5.8
		DAY 1	2.4	120	5.9	1.8	5.5	4.9	5.9
Leukocytes		DAY 1	4.8	-60	5.8	1.4	5.4	4.8	6.6
Normal Range: 4.5-11.0	/nL	DAY 1	4.8	120	6.0	1.5	5.7	4.9	6.6
		DAY 1	7.2	-60	5.5	1.4	5.5	4.7	6.3
All means and medians within normal range		DAY 1	7.2	120	5.7	1.4	5.6	4.7	6.4
		DAY 15	0	-60	5.4	1.3	5.1	4.7	6.5
		DAY 15	0	120	5.8	1.4	5.8	5.0	6.6
		DAY 15	2.4	-60	5.7	1.7	5.2	4.5	6.2
		DAY 15	2.4	120	5.9	1.7	5.6	5.1	6.1
		DAY 15	4.8	-60	5.9	1.3	5.7	5.0	7.2
		DAY 15	4.8	120	6.0	1.2	5.7	5.3	6.5
		DAY 15	7.2	-60	5.5	1.1	5.5	5.0	6.1
		DAY 15	7.2	120	5.7	1.2	5.6	5.0	6.4
		SCREENING	0		248.2	52.9	252	215	287
		SCREENING	2.4		254.3	112.7	231	220	271
		SCREENING	4.8		252.6	55.3	241	226.3	294.8
		SCREENING	7.2		266.8	61.8	246	222.3	312
		DAY 1	0	-60	233.4	54.9	237	188.8	267.5
		DAY 1	0	120	232.7	56.5	229	192.5	277.3
		DAY 1	2.4	-60	238.9	96.4	223	202	247
		DAY 1	2.4	120	235.4	97.4	227	204	252
Platelets		DAY 1	4.8	-60	227.8	49.8	228.5	204.8	246
Normal Range: 150-400 / nL	/nL	DAY 1	4.8	120	231.8	50.1	230	203	251
		DAY 1	7.2	-60	244.0	56.6	233.5	204.5	277.8
All means and medians within normal range		DAY 1	7.2	120	241.5	60.7	220.5	202.3	283.5
		DAY 15	0	-60	233.9	55.6	228	195.3	263.3
		DAY 15	0	120	235.5	56.4	233	193.5	258.8
		DAY 15	2.4	-60	231.7	88.7	213	196	246
		DAY 15	2.4	120	233.2	88.9	215	202	256
		DAY 15	4.8	-60	230.5	42.8	234	208	253
		DAY 15	4.8	120	234.1	42.3	238	208.8	261.3
		DAY 15	7.2	-60	241.0	56.1	232	196.3	282.3
		DAY 15	7.2	120	243.8	59.3	232	197	295
		SCREENING	0		4.6	0.4	4.6	4.3	4.8

Potassium Normal Range: 3.6-5.2 mmol/L All means and medians within normal range	mmol/L	SCREENING	2.4		4.6	0.4	4.6	4.3	4.7
		SCREENING	4.8		4.7	0.4	4.6	4.4	4.9
		SCREENING	7.2		4.6	0.3	4.5	4.4	4.7
		DAY 1	0	-60	4.2	0.2	4.1	4.1	4.3
		DAY 1	0	120	4.1	0.2	4.1	4.0	4.2
		DAY 1	2.4	-60	4.1	0.1	4.1	4	4.2
		DAY 1	2.4	120	4.1	0.2	4.1	4	4.2
		DAY 1	4.8	-60	4.1	0.3	4	3.9	4.2
		DAY 1	4.8	120	4.1	0.2	4.1	4	4.2
		DAY 1	7.2	-60	4.2	0.3	4.1	4	4.3
		DAY 1	7.2	120	4.2	0.2	4.2	4	4.3
		DAY 15	0	-60	4.2	0.3	4.1	4	4.2
		DAY 15	0	120	4.1	0.2	4.1	4.0	4.2
		DAY 15	2.4	-60	4.2	0.2	4.2	4.1	4.3
		DAY 15	2.4	120	4.1	0.2	4.2	4	4.3
		DAY 15	4.8	-60	4.1	0.3	4.1	4	4.3
		DAY 15	4.8	120	4.1	0.3	4.1	4	4.3
		DAY 15	7.2	-60	4.2	0.3	4.2	3.9	4.3
		DAY 15	7.2	120	4.1	0.3	4.1	4	4.3
Sodium Normal Range: 135-145 mmol/L All means and medians within normal range	mmol/L	SCREENING	0		140.6	2.2	141	140	142
		SCREENING	2.4		140.5	2.1	141	140	141
		SCREENING	4.8		140.4	2.0	140	139	141
		SCREENING	7.2		140.8	2.2	141	139	142
		DAY 1	0	-60	140.5	2.3	141	139.8	142
		DAY 1	0	120	140.4	2.5	141	139	142
		DAY 1	2.4	-60	140.6	1.5	141	140	142
		DAY 1	2.4	120	140.5	1.5	141	140	141
		DAY 1	4.8	-60	139.8	1.9	140	139	141
		DAY 1	4.8	120	139.8	1.9	140	139	141
		DAY 1	7.2	-60	140.5	1.3	141	140	141
		DAY 1	7.2	120	140.3	1.7	140	139	141
		DAY 15	0	-60	140.4	2.1	141	138.8	142
		DAY 15	0	120	140.6	2.6	140.5	139	142.3
		DAY 15	2.4	-60	140.0	1.5	140	139	141
		DAY 15	2.4	120	140.0	1.6	140	139	141
		DAY 15	4.8	-60	140.0	1.9	140	139	141
		DAY 15	4.8	120	140.0	1.6	140	139	141
		DAY 15	7.2	-60	140.3	1.6	140	139	141.8
		DAY 15	7.2	120	140.0	1.7	140	139	141

ATTACHMENT C

Provided by Baylor College of Medicine

Table 1: Results from a completed randomized clinical trial (unpublished) supplementing N-acetylcysteine (NAC) and glycine in young (21-40 years) and healthy older (61-80 years) adults. Dose of NAC was 0.81 mmol/kg/d. Exclusion criteria were known diabetes, hypercortsolemia, untreated hypo/hyperthyroidism, untreated heart disease, active malignancy, ALT/AST >2x upper limit of normal, serum creatinine >1.5 mg/dL, and fasting triglycerides >500 mg/dL. Blood levels of liver transaminases and creatinine were monitored (a) in young humans before and after 2-weeks of supplementation with N-acetylcysteine and glycine, and (b) in older humans before and 2-weeks, 4-weeks, 8-weeks, 12-weeks, and 16-weeks after receiving N-acetylcysteine and glycine. No adverse events were observed throughout the trial.

	0w	**2w**	**4w**	**8w**	**12w**	**16w**
Alanine transaminase (ALT; U/L)						
Young adults (N=11)	Normal level	Normal level	-	-	-	-
Older adults (N=12 for 0w and 2w; N=11 for 4w, 8w, 12w, and 16w)	Normal level	Normal level	Normal level	Normal level	Normal level	Normal level
Aspartate transaminase (AST; U/L)						
Young adults (N=11)	Normal level	Normal level	-	-	-	-
Older adults (N=12 for 0w and 2w; N=11 for 4w, 8w, 12w, and 16w)	Normal level	Normal level	Normal level	Normal level	Normal level	Normal level
Creatinine (mg/dl)						
Young adults (N=11)	Normal level	Normal level	-	-	-	-
Older adults (N=12 for 0w and 2w; N=11 for 4w, 8w, 12w, and 16w)	Normal level	Normal level	Normal level	Normal level	Normal level	Normal level

Table 2: Safety data from a published open-label clinical trial in 8 older humans (71-80 years) before and after receiving N-acetylcysteine (0.81 mmol/kg/d) and glycine for 24-weeks. Data shown as Mean ± SD. Publication reference: doi: 10.1002/ctm2.372.

	0w	4w	8w	12w	16w	20w	24w
Alanine transaminase (U/L)	17.6 ± 2.9	18.6 ± 6.5	18.3 ± 4.7	15.6 ± 4.3	17.3 ± 4.5	18.4 ± 5.8	16.9 ± 4.7
Aspartate transaminase (U/L)	21.0 ± 4.1	18.3 ± 2.8	19.8 ± 3.7	17.1 ± 2.4	19.5 ± 7.1	21.5 ± 12.0	21.3 ± 4.9
Creatinine (mg/dl)	0.9 ± 0.3	0.9 ± 0.4	0.8 ± 0.3	0.8 ± 0.3	0.9 ± 0.4	0.8 ± 0.3	0.8 ± 0.3

Table 3: Safety data from a published open-label clinical trial in 8 HIV-patients (45-65 years) before and after receiving N-acetylcysteine (0.83 mmol/kg/d) and glycine for 12-weeks. Subjects were on stable antiretroviral regimens with suppressed viral loads and were otherwise healthy as per exclusion criteria. Data shown as Mean ± SD. Publication reference: doi: 10.3390/biomedicines8100390.

	0w	4w	8w	12w
Alanine transaminase (U/L)	27.5 ± 11.1	25.4 ± 11.2	24.3 ± 7.1	19.9 ± 5.5
Aspartate transaminase (U/L)	24.3 ± 3.5	25.3 ± 4.9	22.4 ± 3.1	21.1 ± 2.4
Creatinine (mg/dl)	0.8 ± 0.1	0.9 ± 0.3	0.9 ± 0.2	0.8 ± 0.2