**Supplementary materials**

**Safety and compliance of Spermidine treatment**

No serious adverse reactions or serious adverse events were reported in the placebo and the spermidine groups. There were no adverse events that were considered by the investigator to be related to the study protocol or nutraceutical. Biochemical and haematological parameters in venous blood at 0 and 2 weeks were unchanged in both treatment groups (Table 3). Adverse events occurred in 2 participants in the placebo group (11%) and 2 participants in the spermidine recipients (10%) (Supplementary Materials). No adverse event led to study being paused or discontinued. Compliance with daily supplementation or placebo was very good with only 2 doses missed in 13 weeks of treatment.

**COVID-19 cases**

There were no severe cases of COVID-19 for the duration of the trial. For the first 5 weeks of the study there were no cases of COVID-19. For the remainder of the study the number of cases of COVID-19 were comparable between the placebo (5 participants) and the nutraceutical group (6 participants).

No participants reported SARS-CoV-2 infection at weeks 0 and 2.  However, 11 participants reported COVID-19 illness during the study: one at week 5, two at week 9, one at week 11, two at week 15, one at week 19, two at week 24 and two at week 31. All participants reported mild illness and there were no hospital admissions, or administration of antivirals or steroids. Five of these participants were in the placebo group, and six were in the spermidine group, with comparable COVID-19 incidence between groups

**Adverse events**

There were 4 adverse events during the study. One participant was diagnosed with abnormal liver function tests on day 1, and upon further investigation was diagnosed with liver disease. Unblinding confirmed this participant was in the placebo arm and their data were excluded from analysis. One participant was diagnosed with localised melanoma during the trial, again in the placebo arm. One participant in the spermidine arm experienced a small pulmonary embolus, which did not require hospitalisation, resulting from a confirmed COVID-19 infection at week 15. One participant in the spermidine group, with a 3-year history of gallstones, had an elective cholecystectomy at week 37.

**Concurrent medical conditions**

37 participants reported concurrent medical conditions for which they were taking medication at the point of recruitment and for the duration of the trial, which were comparable between placebo and nutraceutical groups. No participants took immunosuppressants or immune-modifying medications.

**Compliance and tolerability of the supplement**

At week 2, no participants reported missed doses. At week 13, nine participants reported some missed doses, 4 participants taking the placebo (22%) and 5 participants taking spermidine (25%). The maximum number of doses missed in the spermidine group was 2 doses in 13 weeks (0.73% of doses). Antibody levels, cellular immunity biomarkers, autophagy or cell senescence markers were comparable between participants who had missed doses and the per-protocol group.

**Biochemistry and haematology results**

Full blood count profiles were performed at weeks 0 and 2. Results of placebo and spermidine groups were comparable. There were no marked differences in haematological profiles (haemoglobin, MCHC, MCV, RBC, HCT, MCH, WCC, platelet count) or in biochemistry profiles (urea and electrolytes, eGFR, liver function tests, creatine kinase, bone profile, lipid profile and iron profile) between each timepoint in placebo and spermidine groups (Table 3).



**Table 3**: Biological and haematological parameters were measured at baseline (week 0) and at a follow-up appointment (week 2) in all participants. There were no statistically significant differences between placebo and treatment groups observed. MCV (mean cell volume); MCH (mean cell haemoglobin); MCHC (mean corpuscular haemoglobin concentration); eGFR (estimated glomerular filtration rate). fL (femtoliter); pg – (picograms); mmol (millimole); µmol (micromole); g (gram); U/L (units per litre). The Wilcoxon test was employed to analyse the differences between the baseline and two-week measurements for both the Placebo and Spermidine groups.