9. Efficacy Evaluation

9.1. Data Sets Analysed

The analysis population for pharmacodynamics was defined as all subjects who were validated (randomised), received the study treatment, and have at least one post-baseline assessment of the parameter being analyzed. Note that all validated subjects completed the study.

9.2. Demographics and other Baseline Characteristics

9.2.1. Demographics

A total of 24 male subjects were enrolled in the study. Their mean (SD) age was 28.5 (8.5) years, range 19-45 years, mean (SD) height was 180.5 (5.3) cm, range 169.2-191.7 cm, weight was 75.0 (11.0) kg, range 58.15-95.9 kg, mean (SD) BMI was 23.0 (3.2) kg/m^2, range 18.3-30.0 kg/m^2.

Demographic and baseline data are listed in the Safety Report.

9.3. Measurements of Treatment Compliance

Treatments were administered to the subjects under supervision at the clinical research unit, therefore there was full treatment compliance.

9.4. Analysis of Efficacy

The efficacy and pharmacodynamic analyses were conducted after completion of the study.

9.4.1. Pharmacodynamic/Efficacy results

In this efficacy section, the following codes are used to indicate treatment arms:

Table 9 – Treatment arms and codes

Treatment code	Treatment received
AAA	Active – Active – Active
APA	Active – Placebo – Active
AAP	Active – Active – Placebo
APP	Active – Placebo – Placebo
PPP	Placebo – Placebo – Placebo

Note that for all figures of data collected between 4-28 the first 4 weeks are considered the zero-point, and for figures between 28-68 weeks, week 24 is considered the zero-point.

9.4.1.1. Anti-pneumococcal IgM

The anti-pneumococcal IgM titer was increased between subjects who received Prevenar-13 compared to placebo, with an estimated difference of 13128.5 RLU/100ms (P=0.0020) for the first 4 weeks as displayed in figure 2.

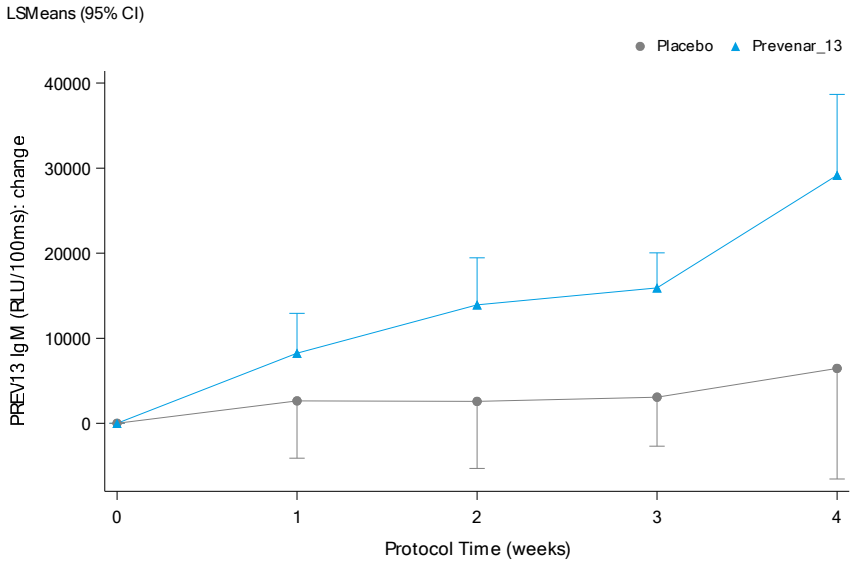

Figure 2 – Anti-pneumococcal IgM during weeks 0-4

There was also a significantly different anti-pneumococcal IgM titer between subjects who received active treatment compared to only placebo: estimated difference: 9272.0 RLU/100ms (P=0.0005) and 5480.2 RLU/100ms (P=0.0158) for weeks 0-24 as displayed in figure 3.

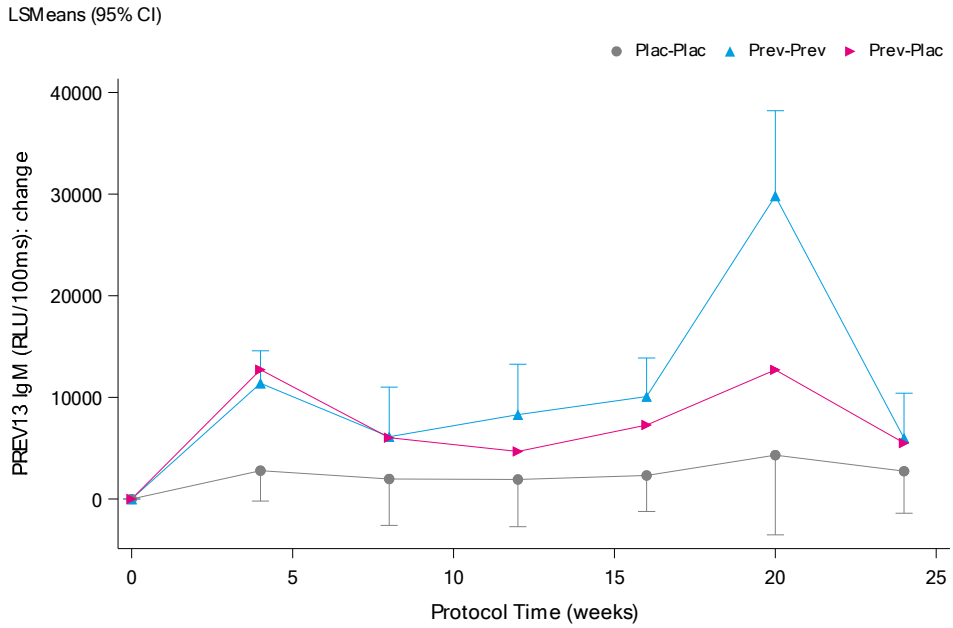

Figure 3 - Anti-pneumococcal IgM during weeks 0-24

Between weeks 0 and 40, only subjects in treatment arms AAA and AAP displayed a significantly higher anti-pneumococcal IgM response compared to PPP (estimated difference 8189.1 RLU/100ms, P=0.0209 and 10320.1 RLU/100ms, P=0.0505). In addition, subjects who received APA displayed a significantly lower anti-pneumococcal IgM titer compared to AAA (estimated difference -9333.1 RLU/100ms, P=0.0413). There were no significantly different IgM titers between other groups. These results are displayed in figure 4.

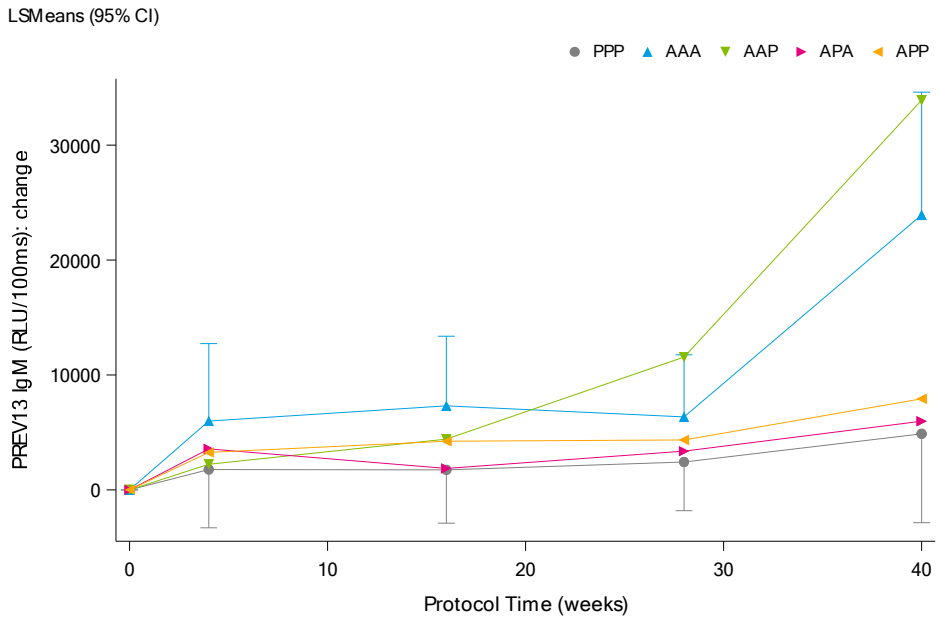

Figure 4 - Anti-pneumococcal IgM during weeks 0-40

9.4.1.2. Anti-pneumococcal IgG

The anti-pneumococcal IgG titer was increased between subjects who received Prevenar-13 compared to placebo, with an estimated difference of 19187.8 RLU/100ms (P<0.0001) for the first 4 weeks as displayed in figure 5.

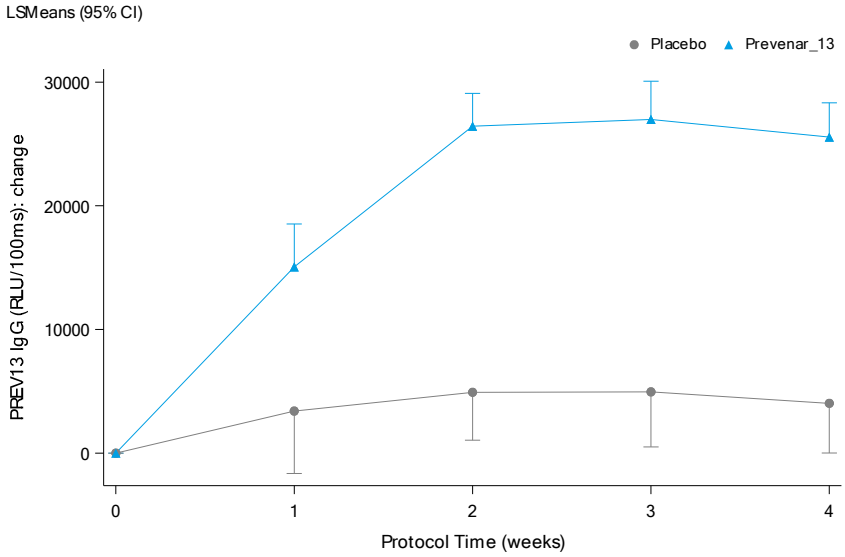

Figure 5 – Anti-pneumococcal IgG during weeks 0-4

There was also a significantly different anti-pneumococcal IgG titer between subjects who received active treatment compared to only placebo: estimated difference: 17155.5 RLU/100ms (P<0.0001) and 16656.9 RLU/100ms (P<0.0001) for weeks 0-24 as displayed in figure 6.

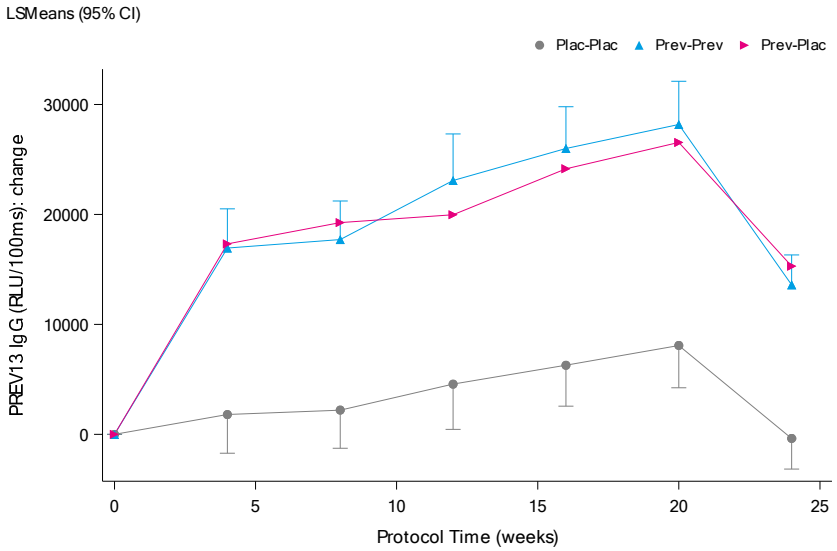

Figure 6 - Anti-pneumococcal IgG during weeks 0-24

Between weeks 0-40, subjects who received any active treatment displayed a significantly (P<0.0001 for all) higher anti-pneumococcal IgG titer, estimated means were 22733.6 RLU/100ms for AAA, 18439.7 RLU/100ms for AAP, 25805.3 for APA and 17116.7 RLU/100ms for APP. In addition, a significant difference was found between APA and AAP treatment (estimated difference 7365.6, P=0.0393) and APP and APA treatment (estimated difference -8688.6, P=0.0080). These results are displayed in figure 7.

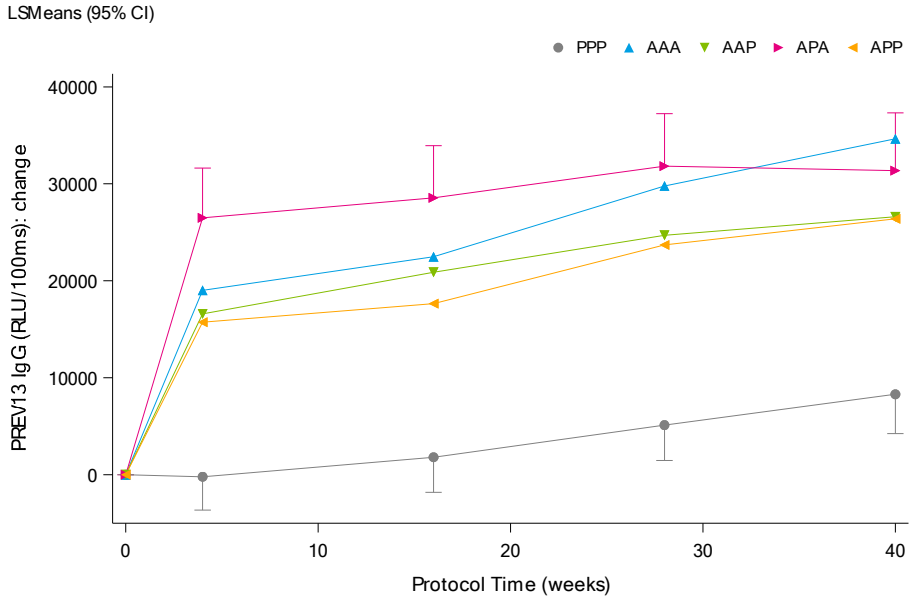

Figure 7 - Anti-pneumococcal IgG during weeks 0-40

9.4.1.3. Anti-oxLDL IgM

Anti-oxLDL IgM antibody titers were not significantly different between treatment groups during weeks 0-4 and 0-24. These results are displayed in figure 8 and 9 below. Note the difference between the absolute numbers in these figures (~10,000-20,000 RLU/100ms range) compared to the preclinical model (~150,000-200,000 RLU/100ms range)

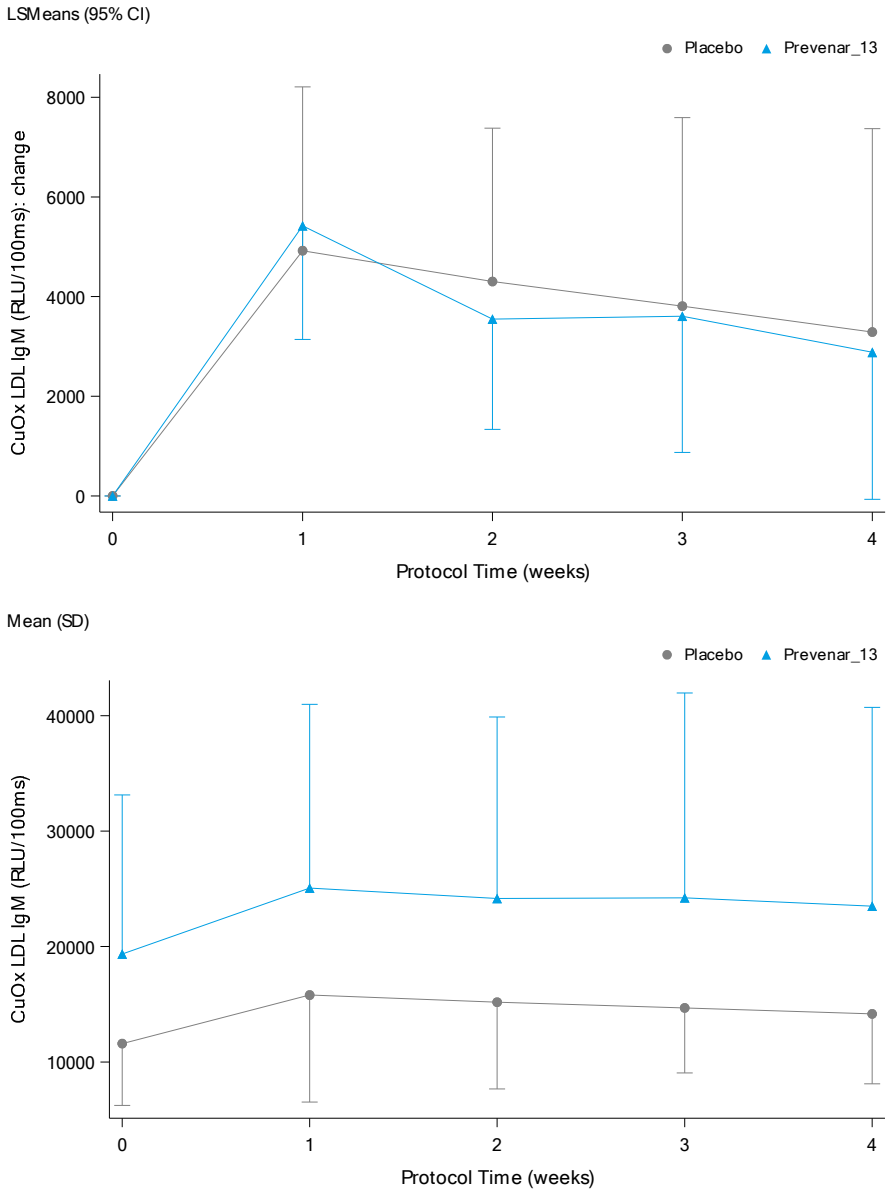

Figure 8A and 8B – Anti-oxLDL IgM during weeks 0-4, change from baseline (top panel) and absolute numbers (bottom panel)

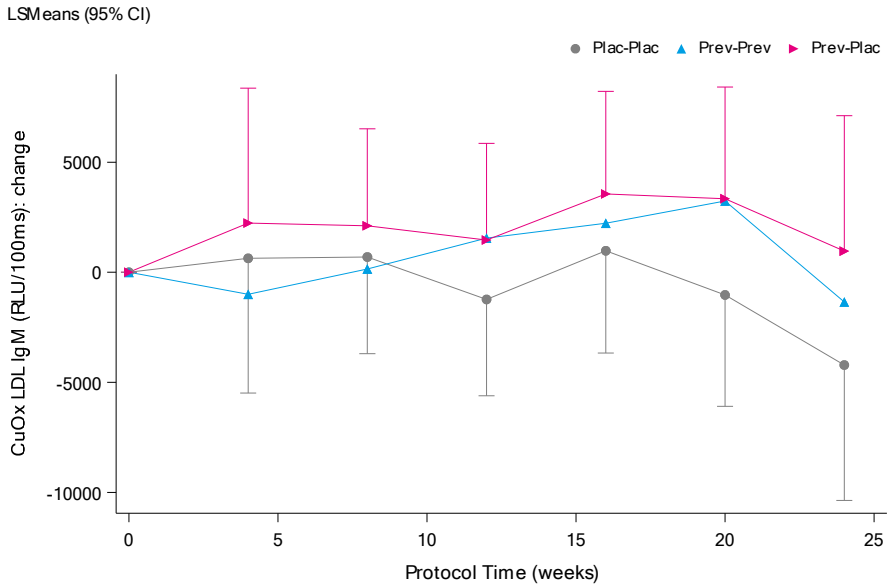

Figure 9 – Anti-oxLDL IgM during weeks 0-24

Anti-oxLDL IgM titers were significantly higher in subjects who were in the APA treatment group compared to placebo (estimated difference 12234.8 RU/100ms, P=0.0050), but the other treatment arms that received at least 1 active dose were not significantly different compared to placebo. In addition, the APP treatment arm displayed a significantly lower anti-oxLDL IgM titer compared to the APA treatment arm (estimated difference -14161.3, P=0.0024). Although not reaching statistical significance (P=0.0632), the estimated difference in anti-oxLDL IgM titer between the APP and AAA treatment groups was -7273.2. These results are displayed in figure 10 below.

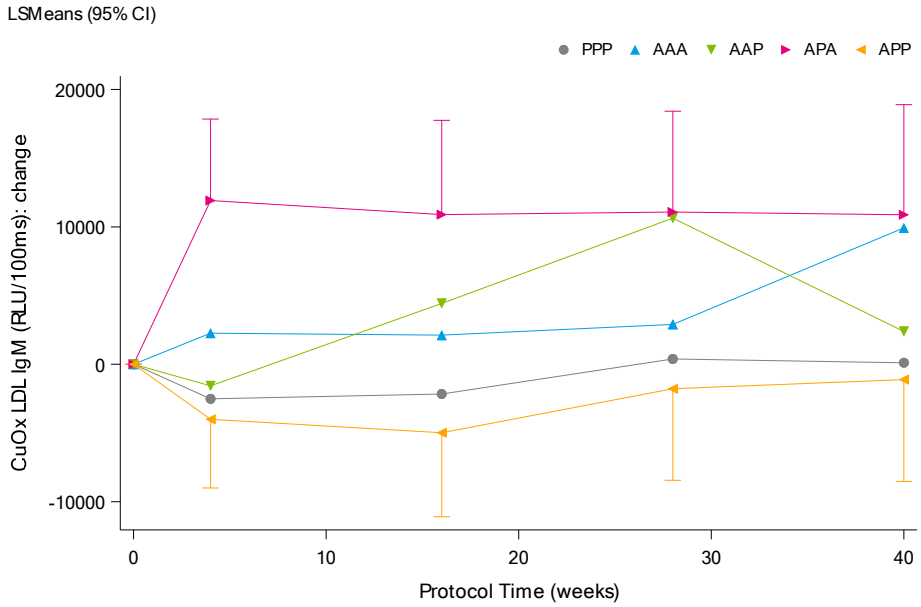

Figure 10 – Anti-oxLDL IgM during weeks 0-40

9.4.1.4. Anti-oxLDL IgG

Anti-oxLDL IgG antibody titers were not significantly different between treatment groups during weeks 0-4 and 0-24. These results are displayed in figure 11 and 12 below.

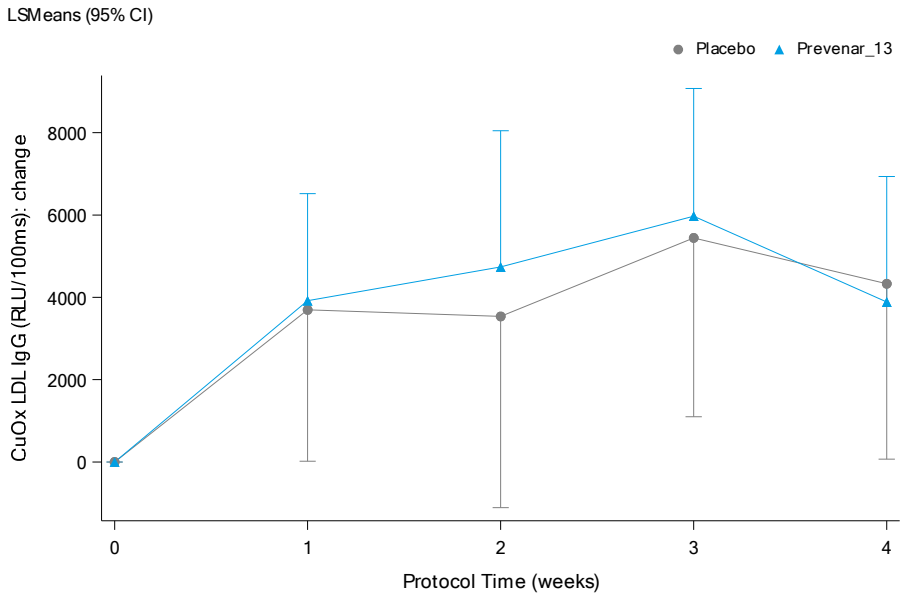

Figure 11 - Anti-oxLDL IgG during weeks 0-4

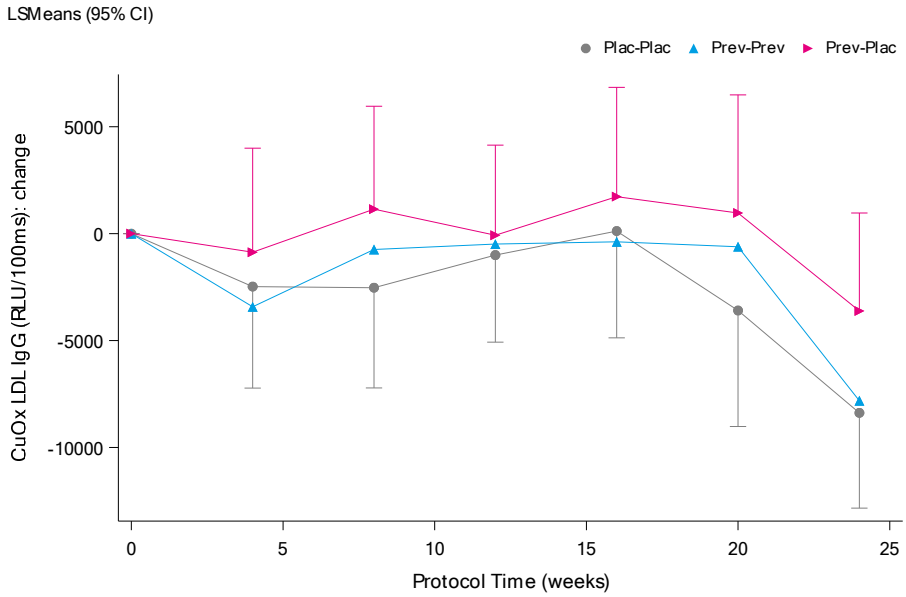

Figure 12 – Anti-oxLDL IgG during weeks 0-24

Anti-oxLDL IgG titers were significantly higher in subjects who were in the APA treatment group compared to placebo (estimated difference 9913.3 RU/100ms, P=0.0066), but the other treatment arms that received at least 1 active dose were not significantly different compared to placebo. In addition, the APP treatment arm displayed a significantly lower anti-oxLDL IgM titer compared to the APA treatment arm (estimated difference -14994.5, P=0.0010). The estimated difference in anti-oxLDL IgM titer between the APA and AAP treatment groups was 8813.7 (P=0.0420). These results are displayed in figure 13 below.

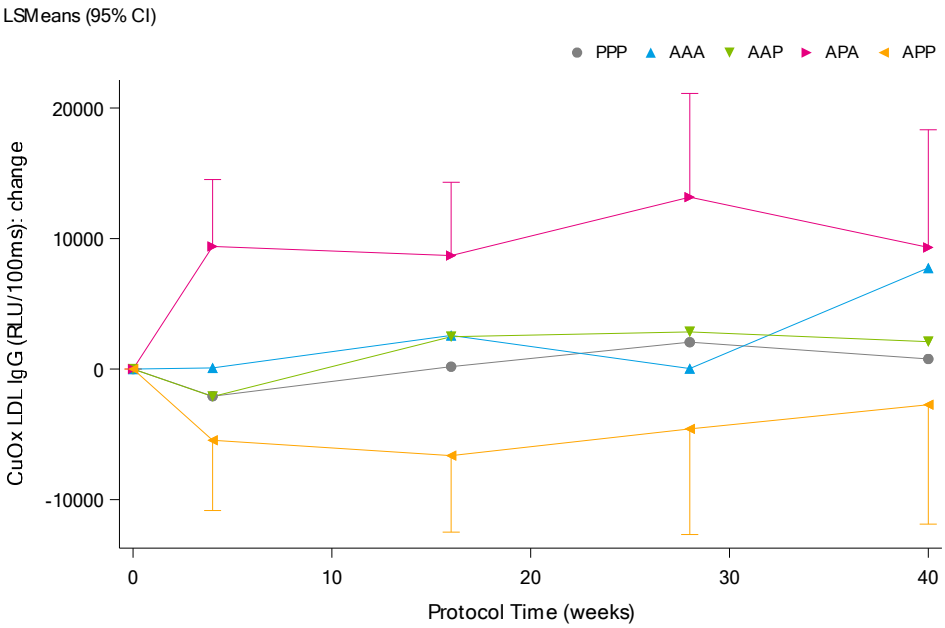

Figure 13 - Anti-oxLDL IgG during weeks 0-40

9.4.1.5. Cholesterol levels

For all cholesterol assessments (total cholesterol, LDL, HDL and triglycerides), there was no clear effect that was related to active treatment. In figures 14, 15, 16 and 17, the results for weeks 0-40 are displayed for all cholesterol assessments.

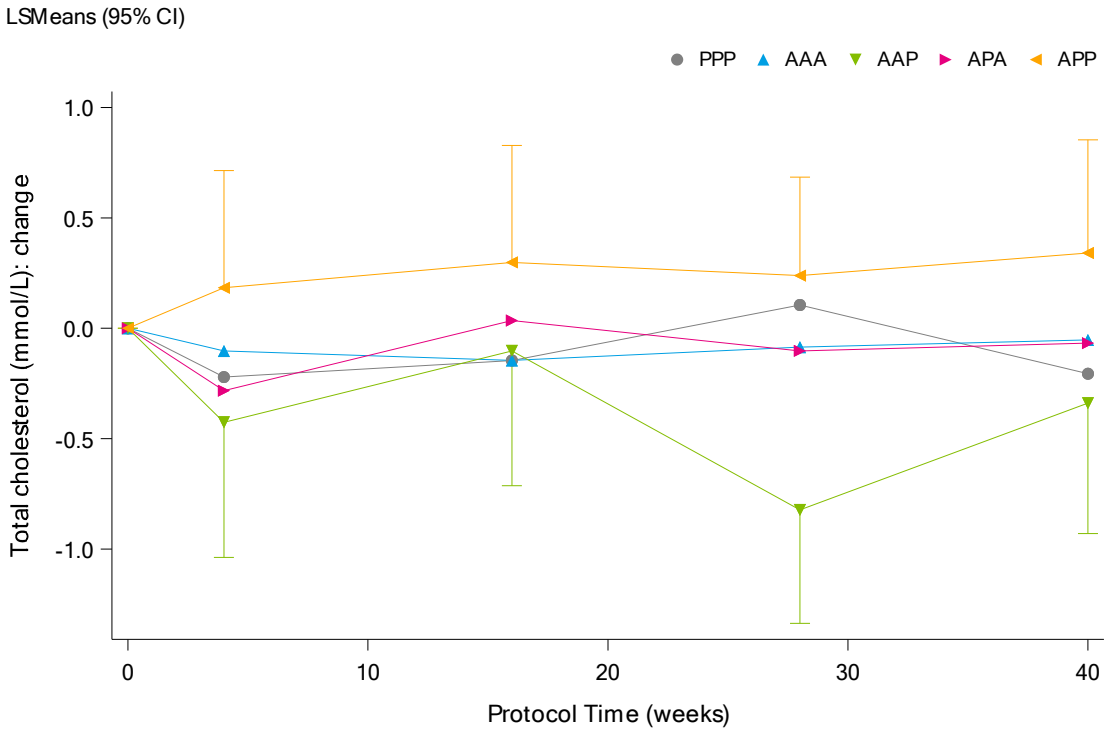

Figure 14 – Total cholesterol levels between treatment groups in weeks 0-40

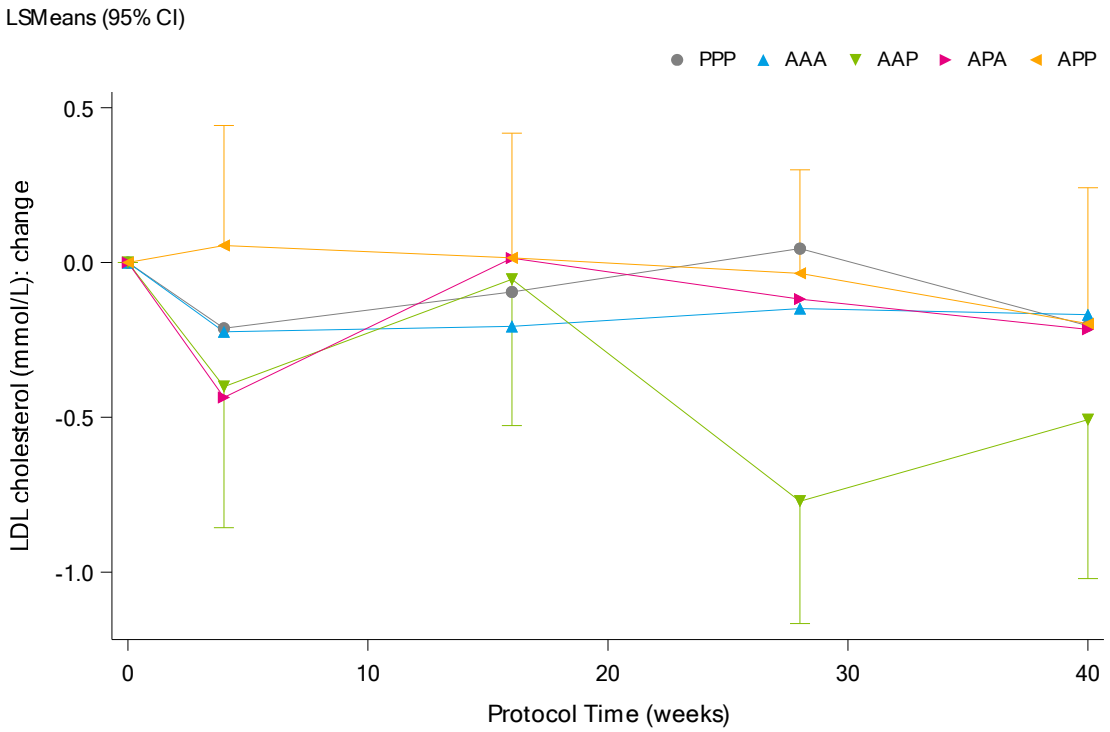

Figure 15– LDL cholesterol levels between treatment groups in weeks 0-40

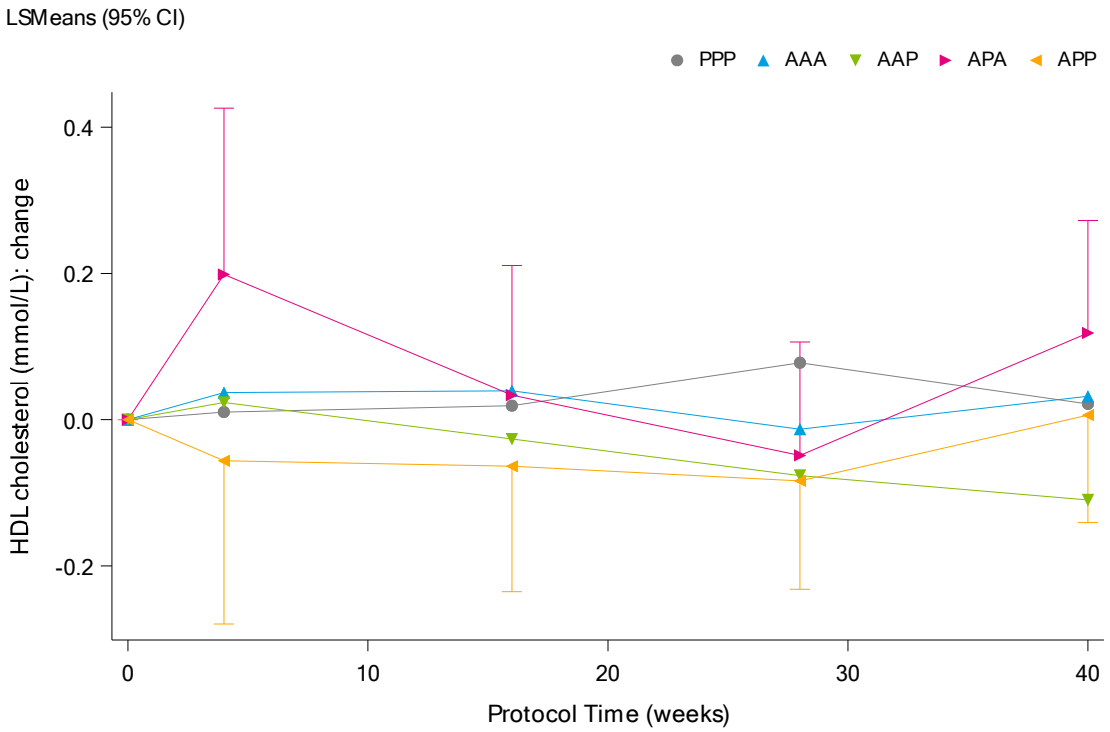

Figure 16– HDL levels between treatment groups in weeks 0-40

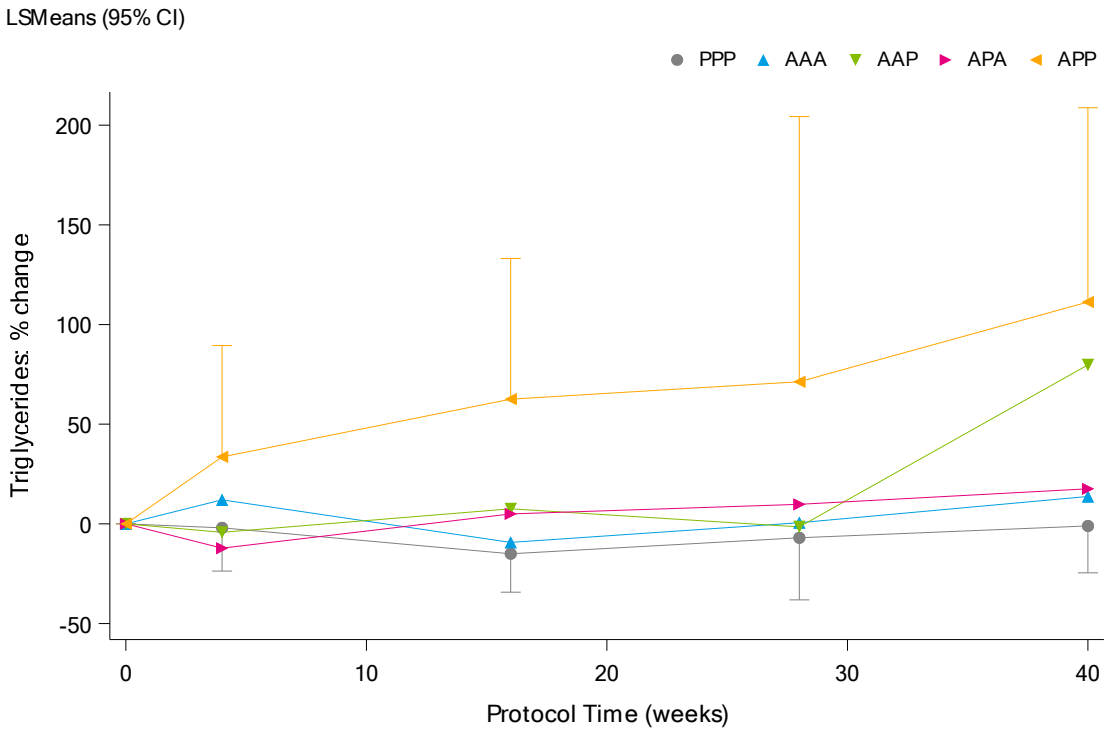

Figure 17 – Triglyceride levels between treatment groups in weeks 0-40

9.5. Summary of efficacy results

Prevenar-13 induced a significant increase in anti-pneumococcal IgM and IgG titers, which acts as a positive control in the present study. However, anti-oxLDL titers were not different between treatment groups at 24 weeks after the first administration. Overall, no relevant differences were observed in anti-oxLDL titers after 40 weeks between the different active and placebo groups. For none of the actively treated groups an effect on cholesterol levels was observed.