Main Analysis of the Primary Endpoint

Primary Objective

The primary objective of the study was to determine the need for, optimal timing of, and immune response following administration of an mRNA booster vaccination against SARS-CoV-2 in adults (≥18 years) previously vaccinated with mRNA SARS-CoV-2 vaccines. If the efficacy criterion was met, additional analyses were conducted to determine the optimal timing of a booster dose. This was assessed by modelling the schedule–response relationship using a logistic regression model where the timing of the booster dose was included as the predictor.

Primary Endpoint Hypothesis

The primary hypothesis tested whether, in at least one booster arm, the proportion of responders exceeded 50%. The primary endpoint was analysed using a one-sample, one-sided hypothesis test, with control of the family-wise error rate at 0.05 using the Bonferroni correction. As this analysis assessed the response rate within each booster arm against a predefined threshold (50%), no direct comparison between study arms was performed in the main analysis.

Statistical Hypothesis Testing and Estimation

Null Hypothesis (H_0): The proportion of responders at each booster timing group ≤ 50% ($p \leq 0.50$)
Alternative Hypothesis (H_1): The proportion of responders of at least one booster timing group> 50% ($p > 0.50$)

Booster Timing Group	n/N*	Proportion (95% CI)	P-value (>50%)
Booster BI (Baseline)	29/50	58.0% (44.2 to 70.6%)	0.16
Booster 2m (2 months)	35/47	74.5% (60.5 to 84.7%)	**<0.001***
Booster 4m (4 months)	23/48	47.9% (34.5 to 61.7%)	0.56
Booster 6m (6 months)	26/44	59.1% (44.4 to 72.3%)	0.15

Figure 22: *Number (n) and proportion of participants meeting the primary and titre-based secondary endpoints for each treatment arm using complete cases (N* indicates the number of non-missing observations). Proportions are shown as percentages with Wilson 95% confidence intervals (CIs). P-values are one-sided (whether proportions are larger than 50%) and calculated using a one-sample proportion test (based on a normal approximation). Values below the pre-defined threshold (0.0125) are indicated with an asterisk.*

Statistical Methods

For each booster timing arm, the proportion of responders was estimated with its 95% confidence interval (CI). A one-sample, one-sided test of proportion was used to evaluate whether the observed response rate exceeded the predefined threshold of 50%. To control the family-wise type I error rate at 0.05 across the four booster timing arms, Bonferroni correction was applied.

Conditional Analysis of Booster Timing and Presentation of Results

The 2-month booster group met this criterion (74.5%, 95% CI 60.5–84.7%; $p < 0.001$). As specified in the statistical analysis plan, meeting this efficacy criterion triggered an additional analysis to explore optimal booster timing. This analysis modelled the schedule-response relationship using a logistic regression with the best fitting fractional polynomials of grade 2 for the randomized booster timing group . The results reported therefore correspond to this prespecified schedule-response modelling analysis.