2 Synopsis

Name of Sponsor/Company:	UMC Utrecht
Name of Finished Product:	Comirnaty
Name of Active Ingredient:	BNT162b2
Title of Study:	A Phase 2, Comparative Randomised Trial to Evaluate the impact of reduced COVID-19 mRNA vaccination regimen on immunological responses and reactogenicity in paediatric subjects with prior SARS-CoV-2 immunity
Investigators:	Dr. Bruijning-Verhagen Dr. Vaessen Dr. Oberthür Dr. Tøndel Dr. Knudsen Dr. Bruun Mikalsen Dr. Døllner Dr. Woxenius Dr. Silverdahl Dr. Papaevangelou Dr. Tsolia Dr. Roilides
Study centre(s):	UMC Utrecht Amphia Hospital UKK Uniklinik Köln Haukeland University Hospital Oslo University Hospital Stavanger University Hospital St Olavs University Hospital Queen Silvia Children's Hospital Umeå University Hospital University General Hospital Attikon "P. & A. Kyriakou" Children's Hospital Hipokration Hospital
Publication (reference):	N/A
Studied period (years): Date of first subject enrolled Date of last subject completed	1,5 years 24-Aug-2022 06-May-2024
Phase of development:	Phase II

Objectives:	**Primary objective:** To determine if the humoral immune response of a single compared to a two dose COVID-19 vaccination regimen is non-inferior in paediatric subjects who are immunologically primed by natural infection. **Secondary Objectives:** 1. To assess the safety and reactogenicity profile of a single dose COVID-19 vaccine regimen against SARS-CoV-2 in paediatric subjects with a history of prior SARS-CoV-2 infection, compared to the two dose regimen. 2. To assess the medium (6 months) and long term (12 month) humoral immune response of the single COVID-19 vaccine dosing regimen against wild-type SARS-CoV-2 in paediatric subjects with a history of prior SARS-CoV-2 infection. 3. To assess the short (28 days), medium and long term humoral immune response of the single dose COVID-19 vaccine regimen against SARS-CoV-2 variants of concern (VoCs) in paediatric subjects with a history of prior SARS-CoV-2 infection.
Methodology:	A two arm randomized controlled trial. Subjects were randomised to receive either: 1) a Comirnaty 10 µg or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg first dose followed by a second Comirnaty 10 µg or Comirnaty Original/Omicron BA.4-5 5/5 µg dose or Comirnaty Omicron XBB.1.5 10 µg (the second dose was the same vaccine as the first dose), or 2) a single Comirnaty 10 µg dose or Comirnaty Original/Omicron BA.4-5 5/5 µg or Comirnaty Omicron XBB.1.5 10 µg of vaccine. Assessment of immunogenicity endpoints by study of neutralizing antibodies at 28 days, 6 months, and 12 months. Assessment of safety by eDiary to record solicited adverse events for 7 days after each dose and unsolicited adverse events during the total follow up.
Number of subjects (planned and analysed):	200 subjects planned – 31 subjects enrolled and analysed
Diagnosis and main criteria for inclusion:	Healthy paediatric subjects with a prior SARS-CoV-2 infection
Test product, dose and mode of administration, batch number:	Test product and dose: BNT162b2 • Comirnaty 10 microgram • Comirnaty Original/Omicron BA.4-5 5/5 microgram • Comirnaty Omicron XBB.1.5 10 microgram Mode of administration: intramuscular Batch numbers: See Appendix 16.1.2
Duration of treatment:	One or two vaccine doses, with a ~3-12 week interval

Reference therapy, dose and mode of administration, batch number:	N/A
Statistical methods	**Primary Analysis**: The primary analyses of this study will be non-inferiority comparisons of the primary endpoint between the control and intervention arm in the per protocol (PP) population. A linear model with the log10 transformed SARS-CoV-2 neutralizing titers as dependent variable and with independent variables treatment group, log10 transformed baseline titers and sex. Based on the linear model estimates for the factor treatment group, the null hypothesis that the intervention group is inferior to the standard two dose BNT162b2 vaccination regimen is tested. Non-inferiority is defined as a 1.5-fold difference for GMTs or 0.176 on the log scale (base 10). Based on the linear model 2-sided 95% confidence intervals for the fold difference in GMT will be computed. **Safety Analysis:** For the binary reactogenicity outcome 'any solicited systemic adverse event grade 2 or higher in 7 days' the null hypothesis of no difference in the proportions will be tested on an unadjusted two-sided significance level of 5%. The hypothesis tests will be performed by logistic regression with independent variables treatment group and sex. **Other:** Secondary immunogenicity outcomes are analysed as the primary endpoint.
Operational management:	Ecraid
Results	Between 31-May-2022 and 9-Jan-2024, 31 subjects were enrolled with a mean age of 8.6 years in the two-dose arm and 8.5 in the single dose arm. Fifteen subjects received the two-dose vaccination regimen, and 16 subjects received a single dose. The GMT of neutralizing antibodies against wild-type SARS-CoV-2 at day 28 after completion of the primary series was 1801.1 (95%CI:1357.9-2388.9) in the two-dose arm versus 1715.5 (95%CI:1064.2-2765.4) in single dose arm (model based GMT-ratio estimate: 0.942 (95% -Ci:0.554-1.601), p=0.042). At month 6 and 12 post-vaccination the median neutralizing antibody titers stayed above 100 IU/ml in both arms, with 6-months GMTs of 417.7 (95%CI: 192.7-905.3) and 233.6 (95%CI: 105,7-516.1, in the two-dose and single dose arm, respectively (model based GMT-ratio estimate: 1.766 (95%-CI:0.627-4.978), p=0.627), and 12-months GMTs of 359 (95%CI: 222.6-579) and 100.7 (95%CI: 25.6-396.4)(model based GMT-ratio estimate: 2.957 (95%-CI: 0.751 ; 11.65),p=0.842). Similarly, both arms demonstrated robust increases in the anti-RBD titers against SARS-CoV-2 wild type following vaccination with GMFR from before vaccination to day 28 of 68.1(95%-CI: 26.9 ; 172.8) and 40.2 (95%-CI: 13.1 ; 123.2) in the single dose and two dose vaccine regimens, respectively. The anti-RBD IgG responses declined at 6- and 12-months post-vaccination; however, they remained higher

	than pre-vaccination levels, with observed GMFR > 10 in both vaccination regimens at the 12-month mark. Results for neutralizing antibodies against VOC BA.5 and JN.1, showed similar trends in vaccine responses but overall lower observed titers compared to titers for SARS-CoV-2 wild-type. A total of 8 subjects (53,33%) in the two dose arm versus 5 (31,25%) in the single dose arm reported at least one solicited systemic adverse event (AE) grade ⩾ 2 in the 7 days after each and any vaccine dose. A total of 3 subjects (20%) in the two dose arm versus 0 (0%) in the one dose arm reported at least one SAE grade ⩾ 3 on the CTCAE or one Adverse Event of Special Interest (AESI) in the 12 months post-vaccination. In the two dose arm, 2 subjects reported a SAE Grade 3 or higher after any vaccine dose and 1 subject reported an AESI. No noteworthy differences were observed in the two dose arm between first and second dose.
Conclusion:	Both single and two dose regimens induced robust and long-lasting (up to 12 months) neutralizing and anti-RBD immune responses, but non-inferiority of the single dose regimen could not be demonstrated. Both regimens also induced long-lasting neutralizing responses to different VOCs, but titers were generally lower compared to SARS-CoV-2 wild-type. No new safety concerns were identified based on the safety analysis.