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Durable Immune Response Induced by a Self-amplifying mRNA (samRNA) SARS-CoV-2 Vaccine Candidate in Adults Previously Vaccinated with mRNA or Adenovirus Primary Series

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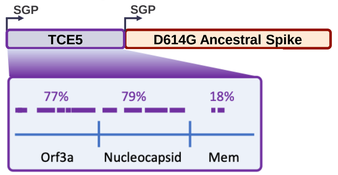
BACKGROUND

Neutralizing antibodies (nAbs) induced by authorized SARS-CoV-2 vaccines wane within months, requiring frequent boosters. Ideally, next-generation vaccines should generate broad and durable cell-mediated and humoral immune responses to protect against infection and severe disease. GRT-R910, a samRNA-based SARS-CoV-2 vaccine candidate targeting Spike (S) and conserved viral epitopes, was administered as a booster following adenoviral or mRNA primary series in older (≥ 60 years) adults (CORAL-BOOST, NCT05148962). Study results indicate GRT-R910 has a favorable safety profile and can induce strong, durable IgG and nAb responses to vaccine-encoded Spike and additional variants of concern (VOCs) along with broad T cell responses to S and non-S epitopes.

METHODS

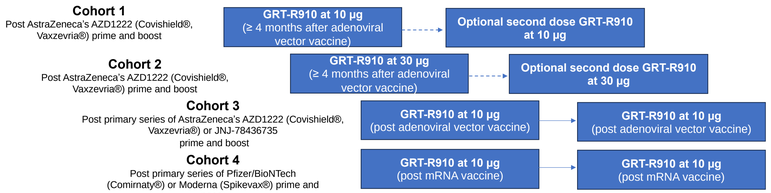
- GRT-R910, encoding ancestral $Spike_{D614G}$ and highly conserved non-S T cell epitopes (TCE) (Fig. 1), was tested in this open-label, phase I study conducted in the UK.
- Booster doses of 10 or 30µg of GRT-R910 were assessed in older adults who received $Spike_{WT}$ adenoviral (Cohorts 1, 2, and 3) or mRNA vaccines (Cohort 4) as primary series (Fig. 2).
- GRT-R910 was administered to Cohorts 1 and 2 as either 1 or 2 doses. In individuals receiving 2 doses, the optional second dose was administered approximately 4 months after the first GRT-R910 vaccination.
- Two doses of GRT-R910 were administered to Cohorts 3 and 4 at a 4-week interval.
- The primary objective was safety (solicited adverse events [AEs] up to 7 days post vaccination, unsolicited AEs, serious AEs [SAEs]), and secondary objectives included measurement of induction and durability of S-specific IgG antibodies and nAbs post GRT-R910 boost as well as T cell responses to S and non-S epitopes.

Figure 1: GRT-R910 Vaccine Design



GRT-R910 vaccine cassette design encoding full length $Spike_{D614G}$ and TCE5 epitopes. SGP: sub-genomic promoter. % of full-length proteins included in TCE cassettes are shown.

Figure 2: CORAL-BOOST Study Design



Nine participants in Cohort 3 received a mRNA booster prior to enrollment in addition to the adenoviral primary series.

Table 1: Demographics

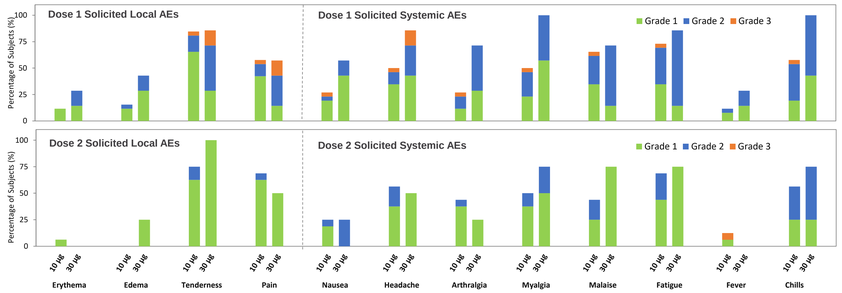
Characteristic	C1 (N = 10)	C2 (N = 7)	C3 (N = 10)	C4 (N = 10)
Dose	10µg day 1 and 113	30µg day 1 and 113	10µg day 1 and 29	10µg day 1 and 29
Age (years, mean (range))	69 (63 - 81)	67 (61 - 74)	66 (61 – 73)	74 (67 – 86)
Female (%)	40	71	40	40
BMI (kg/m^2, mean (range))	26 (21 - 35)	28 (22 - 35)	26 (21 – 31)	25 (21 – 32)
Received a 2nd dose (%)	6 (60%)	4 (57%)	8 (80%)	7 (70%)

RESULTS

SAFETY: Solicited AEs were predominantly mild to moderate and transient. Nine grade 3 solicited AEs were observed in three subjects who received 10µg and one subject who received 30µg. Most Grade 3 solicited AEs reported were local pain, tenderness, and headache that were transient in nature. A slight increase in reactogenicity was observed at 30µg compared to 10µg. No vaccine-related SAEs or severe COVID-19 cases were reported in participants who received GRT-R910 (Fig 3).

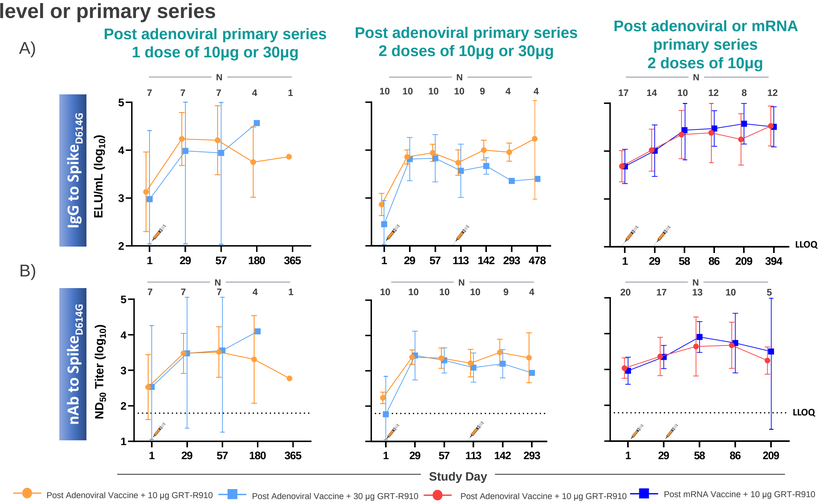
IMMUNOGENICITY: IgG binding antibodies and nAbs against $Spike_{D614G}$ were increased and maintained through 6-or 12-months post-vaccination in individuals receiving either 10 or 30µg GRT-R910 irrespective of vaccination interval or SARS-CoV-2 primary series (Fig.4). Durability was observed for nAbs against VOCs in Cohort 1 and 2 participants (Fig. 5). This assessment is pending for Cohorts 3 and 4. T cell responses against Spike or TCE were increased after vaccination across all cohorts and an increase in breadth of response to Spike and TCE was observed (Fig. 6).

Figure 3: GRT-R910 is well tolerated in adults ≥60 years of age



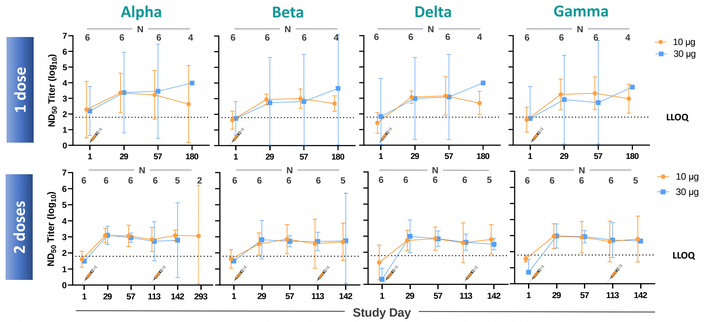
Solicited adverse events during the 7 days after vaccination for Cohorts 1-4 who received 1 or 2 doses of 10µg (Cohorts 1, 3, and 4) or 30µg (Cohort 2) of GRT-R910

Figure 4: IgG binding antibodies and nAbs against $Spike_{D614G}$ are boosted and maintained through 6 or 12 months after 1 or 2 doses of GRT-R910 regardless of dose level or primary series



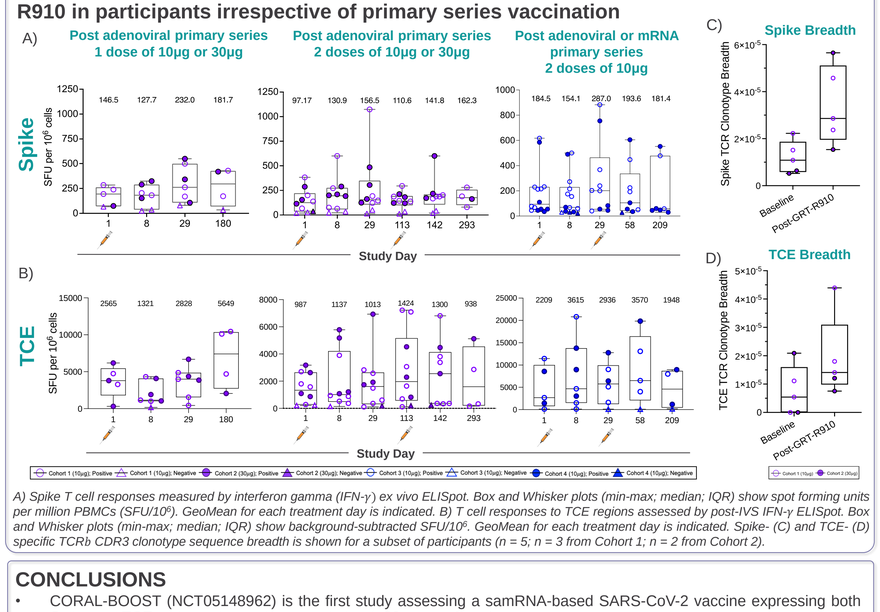
Binding antibodies (IgG) (A) and nAbs (B) against $Spike_{D614G}$ measured in participants after receiving boost dose(s) of 10µg or 30µg of GRT-R910 post adenoviral and 30µg mRNA vaccine primary series. Geometric means with 95% confidence intervals are shown. Lower limit of quantitation (LLOQ): 50.3 ELU/mL; 62 ND_{50} Titer

Figure 5: nAbs against VOCs are increased and maintained through at least 6 months after either 1 or 2 doses of GRT-R910 post adenoviral primary series



nAbs against VOCs Alpha, Beta, Delta, and Gamma measured in participants after receiving boost dose(s) of 10µg or 30µg GRT-R910. Geometric means with 95% confidence intervals are shown. LLOQ: 62 ND_{50} Titer

Figure 6: Increase in magnitude and breadth of T cells after administration of GRT-R910 in participants irrespective of primary series vaccination



A) Spike T cell responses measured by interferon gamma (IFN-γ) ex vivo ELISpot. Box and Whisker plots (min-max; median; IQR) show spot forming units per million PBMCs (SFU/10^6). GeoMean for each treatment day is indicated. B) T cell responses to TCE regions assessed by post-IVS IFN-γ ELISpot. Box and Whisker plots (min-max; median; IQR) show background-subtracted SFU/10^6. GeoMean for each treatment day is indicated. Spike- (C) and TCE- (D) specific TCRb CDR3 clonotype sequence breadth is shown for a subset of participants (n = 5; n = 3 from Cohort 1; n = 2 from Cohort 2).

CONCLUSIONS

- CORAL-BOOST (NCT05148962) is the first study assessing a samRNA-based SARS-CoV-2 vaccine expressing both Spike and TCE antigens in an older population (≥60 years of age).
- GRT-R910 was well tolerated as a booster in participants who received adenoviral or mRNA primary vaccination series.
- High and sustainable IgG binding antibody responses were observed up to 12 months against $Spike_{D614G}$ across different dosing groups.
- Durable neutralizing antibody responses were observed for at least 6 months against $Spike_{D614G}$ and VOCs.
- GRT-R910 increased breadth of T cell responses against Spike and non-Spike T cell epitopes included in the vaccine.
- Overall, GRT-R910 was well tolerated as a booster in older adults regardless of primary SARS-CoV-2 vaccination series and induced robust, durable binding and neutralizing antibodies along with broad T-cell responses.

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