Poster #: 1974

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A phase 1 clinical trial in older adults with a novel low-dose T cell enhanced self-amplifying mRNA vaccine candidate (GRT-R910) demonstrates strong and broad boost in cellular and humoral immune responses following primary series with ChAdOx1-S SARS-CoV-2 vaccine (GO-009; CORAL-BOOST)

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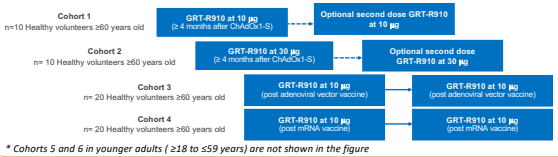
BACKGROUND:

The SARS-CoV-2 pandemic continues, and with each new variant, the possibility of vaccine-evasion increases. Authorized vaccines have provided protection against severe disease, but lack of long-lasting immunogenicity is still a matter of great concern, especially in older adults who are at risk due to immunosenescence. Protection provided by authorized vaccines wanes over time. GRT-R910, a T cell enhanced SARS-CoV-2 vaccine candidate, has a potential to improve and broaden the cell-mediated immune response and induce immunity against more conserved genes. This may be key to long-term, durable protection and may prove to be a useful approach against novel Coronaviruses.

METHODS:

GO-009 (CORAL-BOOST) is an open-label study, conducted in the UK, of a self-amplifying mRNA (samRNA) vaccine candidate encoding for wild type (WT) Spike (S) and highly conserved non-S CD8+ T cell epitopes (GRT-R910). GRT-R910 is administered as 1 or 2 boost vaccinations after prior vaccination with an authorized adenovirus or mRNA SARS-CoV-2 vaccine. The first two cohorts assessed 10µg and 30µg doses of GRT-R910 in older (≥60 years of age) adults who had received the primary ChAdOx1-S series. Subsequent cohorts assess two boost doses of 10µg in older and younger adults who have received an adenovirus or mRNA vaccine. PBMC samples were collected for immunological assessment at different visits from day 1 up to day 365. The primary objectives are safety and reactogenicity and secondary objectives include cellular and humoral immunogenicity post-GRT-R910 vaccination(s). Preliminary safety and reactogenicity from cohorts 1-4 (older adults) and initial immunogenicity data post the first boost data from cohorts 1-2 are presented, no second boost data presented.

Figure 1: GO-009 Study Design*



** Cohorts 5 and 6 in younger adults (≥18 to ≤59 years) are not shown in the figure*

ENROLLMENT STATUS:

- A total of 33 subjects were enrolled between September 16, 2021 and August 23, 2022; cohort 1 (n=10), cohort 2 (n=7), cohort 3 (n=9) and cohort 4 (n=7).
- Enrollment in cohort 2 was closed in December 2021 with a total of 7 participants in response to the inability to recruit previously unvaccinated individuals due to the successful national vaccination campaign.
- In cohorts 1 and 2, seven subjects did not receive a second booster dose due to the following: 1) adverse events (prolonged grade 1 and 2 local site reaction, grade 3 adverse reaction), 2) delayed consent for the booster, 3) ineligibility due to SARS-CoV-2 infection, and/or 4) International travel.
- Cohorts 1, 2, and 3 received a primary series of two doses of ChAdOx1-S vaccine. Cohort 3 also received a booster dose of BNT162b2, while cohort 4 received a primary series of BNT162b2 as well as a booster dose of BNT162b2 prior to enrollment. None of the subjects received Ad26.COV2-S or mRNA-1273 vaccine.

DEMOGRAPHICS:

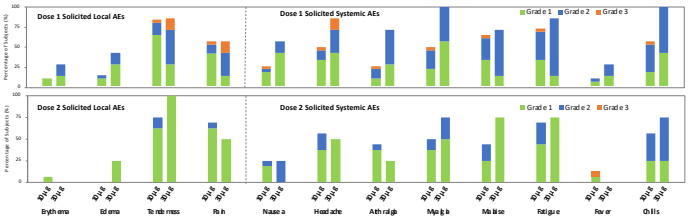
Table 1: Demographics of study cohorts 1, 2, 3, and 4 consisting of older population. For cohorts 1 and 2 administration of second dose of GRT-R910 was optional.

Characteristic	C1 (N = 10)	C2 (N = 07)	C3 (N = 09)	C4 (N = 07)
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)	65 (61 – 71)	74 (67 – 86)
Female (%)	40	71	44	43
BMI (kg/m^2, mean(range))	26 (21 - 35)	28 (22 - 35)	25 (21 – 30)	25 (21 – 32)
Received a 2nd dose (%)	6 (60%)	4 (57%)	6 (67%)	4 (57%)

SAFETY AND REACTOGENICITY:

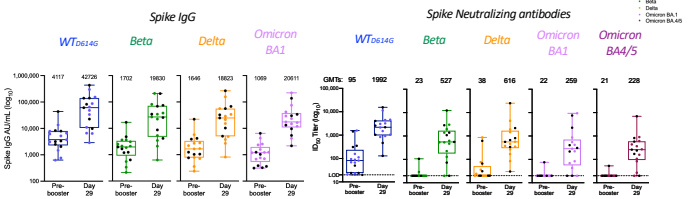
- Solicited adverse events in the 10µg and 30µg dose cohorts in the dose escalation portion (Cohorts 1 & 2) and 10µg expansion cohorts (Cohorts 3 & 4) were mostly Grade 1 or 2 and transient in nature
  - Grade 3 events occurred in a single subject in cohort 2 at the 30µg dose cohort and in a single subject in cohort 3 at the 10µg dose cohort
- 11 unsolicited, treatment related Grade 1 to 2 adverse events were reported all of which had recovered or resolved by the data cutoff date, i.e., August 23, 2022
  - Events included transient laboratory abnormalities, frequent bowel movements, palpitations, anxiety disorder, and acute pancreatitis (subject had a history of recurrent episodes of acute pancreatitis)
- 2 unrelated serious adverse events were reported
  - Grade 2 bacterial pneumonia and Grade 3 coronary artery disease
- Subjects who received a primary series of either ChAdOx1-S or BNT162b2 vaccine have shown no difference in reactogenicity

Figure 2: Solicited adverse events for cohorts 1-4 at a dose of 10µg and 30µg during the initial 8 days after vaccination



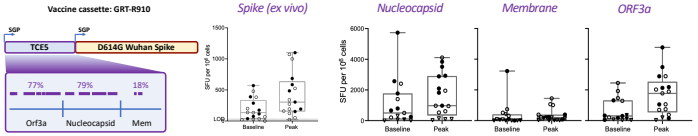
HUMORAL AND T CELL RESPONSES 4 WEEKS AFTER A SINGLE GRT-R910 10µg OR 30µg DOSE:

Figure 3: Single boost with GRT-R910 samRNA increases binding and neutralizing antibodies against WT$_{D614G}$ Spike and Variants of Concern Beta, Delta, and Omicron 4 weeks after a single 10µg or 30µg dose



AU/mL = Arbitrary units per mL; ID$_{50}$ titer = Median infective dose; Geometric mean of AU/mL or ID$_{50}$ titer values notated. Treatment day = day 1 single dose (10µg or 30µg) of GRT-R910 samRNA was administered. Boxes and horizontal bars denote interquartile range (IQR) and median values, respectively. Whisker endpoints are equal to the maximum and minimum values. 17 shown, 10 subjects from cohort 1 (10µg) and 7 subjects from cohort 2 (30µg, denoted by black circles).

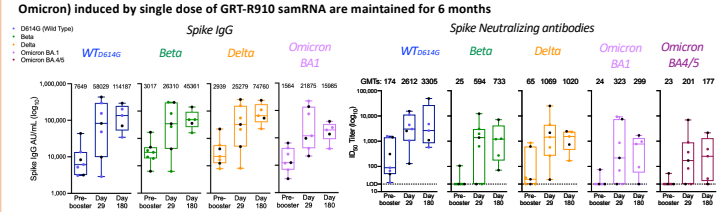
Figure 4: Single boost with GRT-R910 samRNA increases T cell responses against Spike and non-Spike T cell epitope (TCE) regions included in the vaccine 1-4 weeks after a single 10µg or 30µg dose



SFU = Spot forming units per 10^6 cells; Treatment day = day 1 single dose (10µg or 30µg) of GRT-R910 samRNA was administered. Peak = maximum T cell response at either day RT-R910 dose. Boxes and horizontal bars denote interquartile range (IQR) and median values, respectively. Whisker endpoints are equal to the maximum and minimum values. 17 subjects day 8 or day 29 after shown, 10 subjects from cohort 1 (10µg) and 7 subjects from cohort 2 (30µg, denoted by black circles). Ex vivo = overnight ELISpot (Spike only). Responses to Nucleocapsid, Membrane and ORF3a are after in vitro expansion. Circles denote positive responses, triangles denote responses <LOD/<2x DMSO control.

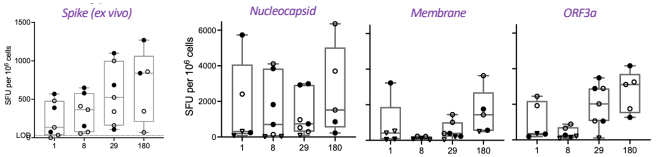
HUMORAL AND T CELL RESPONSES INDUCED BY SINGLE GRT-R910 DOSE MAINTAINED FOR 6 MONTHS:

Figure 5: Binding and neutralizing antibody responses against WT$_{D614G}$ Spike and Variants of Concern (Beta, Delta, and Omicron) induced by single dose of GRT-R910 samRNA are maintained for 6 months



AU/mL = Arbitrary units per mL; ID$_{50}$ titer = Median infective dose; Geometric mean of AU/mL or ID$_{50}$ titer values notated. Treatment day = day 1 single dose (10µg or 30µg) of GRT-R910 samRNA was administered. Boxes and horizontal bars denote interquartile range (IQR) and median values, respectively. Whisker endpoints are equal to the maximum and minimum values. 7 subjects from cohorts 1 (10µg) and 2 (30µg, subjects denoted by black circles). Two subject timepoints were excluded at D180 due to positive COVID19 diagnosis (D108 & D110) and BNT162b2 vaccination (D137 & 135) prior to D180 timepoint.

Figure 6: T cell responses against Spike and non-spike T cell epitopes induced by single dose of GRT-R910 are maintained for 6 months



SFU = Spot forming units per 10^6 cells; Treatment day = day 1 single dose (10µg or 30µg) of GRT-R910 samRNA was administered. Boxes and horizontal bars denote interquartile range (IQR) and median values, respectively. Whisker endpoints are equal to the maximum and minimum values. 7 subjects shown, 4 subjects s from cohort 1 (10µg) and 3 subjects from cohort 2 (30µg, denoted by black circles). Ex vivo = overnight ELISpot (Spike only). Responses to Nucleocapsid, Membrane and ORF3a are after in vitro expansion. Circles denote positive responses, triangles denote responses <LOD/<2x DMSO control. Two subject timepoints were excluded at D180 due to positive COVID19 diagnosis (D108 & D110) and BNT162b2 vaccination (D137 & 135) prior to D180 timepoint.

KEY OUTCOMES:

- This is the first clinical trial that addresses the safety and immunogenicity of a T cell enhanced samRNA SARS-CoV-2 vaccine candidate in healthy adults ≥60 years of age
- Both 10µg and 30µg of GRT-R910 cohorts showed favorable safety profile and were well-tolerated in this study population regardless of primary vaccine (ChAdOx1-S or BNT162b2 primary series)
  - Solicited adverse events were mostly Grade 1 or 2 and transient in nature
  - There was a trend for increased reactogenicity in the 30µg group
  - There was no trend of increased reactogenicity after the second dose of GRT-R910 (no worse than after the first dose)
- IgG binding and neutralizing antibodies demonstrated a boost of anti-S antibodies after one dose of GRT-R910; geometric mean ID$_{50}$ titers from 92 to 2370 and 99 to 1553 for 10 and 30µg, respectively
  - Antibody responses were durable through at least day 180 and were broadly cross-reactive against the most significant variants of concern (including Beta, Delta, Omicron, and Omicron BA.4/5)
  - Neutralizing potency against variants of concern was modestly lower versus vaccine variant (wild type)
- ELISpot analyses of T cell data demonstrated that GRT-R910 boosted and broadened T cell responses to Spike-specific, and induced T cell responses to non-Spike T cell epitopes

CONCLUSIONS:

- GRT-R910 was well tolerated when administered after a primary series of adenovirus (ChAdOx1-S) or mRNA (BNT162b2) SARS-CoV-2 vaccine in healthy older adults
- GRT-R910 as a boost dose after a primary series of ChAdOx1-S induced:
  - Durable, broadly cross-reactive anti-Spike antibody titers
  - Durable T cells targeting both Spike and non-Spike epitopes
- Additional GO-009 study data, including younger and post-mRNA subjects from remaining cohorts and immune data of second dose GRT-R910 will be presented at a later date
- GRT-R910 is also being evaluated in the Phase 1 DMID20-0034 Study (NCT04776317)
- GRT-R912 (Beta Spike), GRT-R914 (Beta Spike), and GRT-R918 (Omicron Spike) samRNA SARS-CoV-2 vaccines are currently being evaluated in the Phase 1 GO-012 Study (NCT05435027)

Gritstone bio Website

Acknowledgment: Special thanks to Dan Koralek, Senior Director Gritstone bio, Inc.