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Durable Immune Response Induced by Self-amplifying mRNA (samRNA) SARS-CoV-2 Vaccine Candidates in Vaccine-naïve HIV Negative and People Living with HIV (PLWH) Populations

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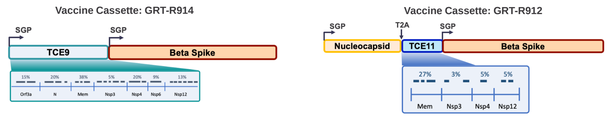
BACKGROUND:

An ideal next-generation SARS-CoV-2 vaccine should provide more durable antibody responses and greater breadth of protection (humoral & cellular) than those observed with first generation SARS-CoV-2 vaccines. Gritstone's vaccines utilize a potent samRNA platform and, in addition to Spike (S), targets conserved SARS-CoV-2 antigens. CORAL-CEPI (NCT05435027) is an ongoing Phase I study evaluating three samRNA-based SARS-CoV-2 vaccine candidates in both HIV negative and PLWH vaccine-naïve South African populations. Preliminary study results show favorable safety with durable total IgG and neutralizing antibody (nAb) as well as broad T cell responses induced by samRNA vaccine candidates regardless of HIV or SARS-CoV-2 serostatus.

METHODS:

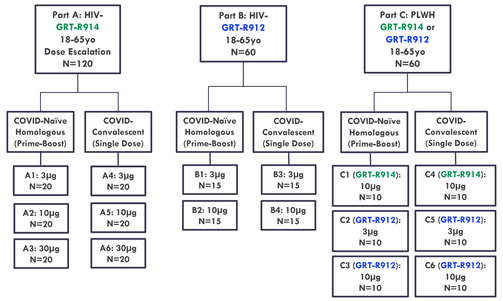
Three samRNA SARS-CoV-2 vaccine candidates, GRT-R912, GRT-R914 and GRT-R918 (GRT-R918 not reported), are being evaluated in the CORAL-CEPI study. GRT-R914 and GRT-R912 encode a full length $Spike_{Beta\ (501Y.V2)}$ protein and T cell epitope sequences (TCEs) from conserved viral proteins. GRT-R912 also expresses a full length nucleocapsid (N) protein (Fig.1). The samRNA vaccines were administered either as 1 dose to SARS-CoV-2 anti-N IgG seropositive individuals or as a 2-dose regimen to seronegative adults at baseline, regardless of HIV serostatus (Fig.2). Primary objectives include local and systemic reactogenicity up to 7 days post vaccination, unsolicited adverse events (AEs) up to 28 days, and serious AEs and adverse events of special interest (AESI) up to 12 months after the last vaccination. Secondary objectives assess ancestral (WT) S-specific binding IgG (bAb) and nAbs to SARS-CoV-2 variants (Beta & Delta) as well as T cell responses against S and additional TCEs.

Fig. 1. Vaccine Cassette Design of GRT-R914 and GRT-R912



GRT-R914 encodes full-length $Spike_{Beta}$ and Nucleocapsid, ORF3a, Membrane, and Non-structural Proteins (NSP) as TCEs. GRT-R912 encodes full-length $Spike_{Beta}$ and a full length Nucleocapsid protein, with Membrane and NSP epitopes to provide TCEs beyond Spike.

Fig. 2. GO-012 Study Schema (Part A, B, and C)



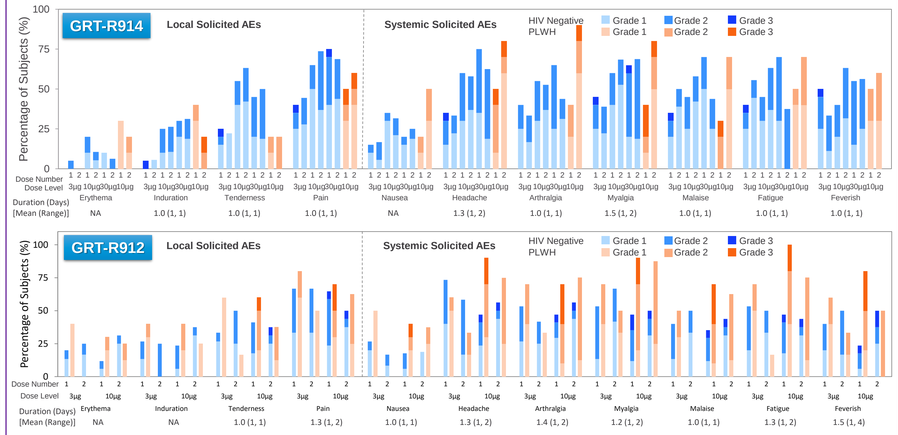
** SARS-CoV-2 Naïve participants defined as SARS-CoV-2 anti-N IgG seronegative at baseline. N is the planned number of participants.*

RESULTS:

Safety: A total of 140 participants received GRT-R914, and an additional 102 received GRT-R912. Most reactogenicity was grade 1 or 2 and transient amongst all participants (Fig.3). Eight out of 140 (5.7%) and 8 out of 102 (7.8%) participants who received GRT-R914 or GRT-R912 reported grade 3 solicited AEs which resolved within 1-2 days. There was no significant difference between reactogenicity in participants based on their SARS-CoV-2 anti-N IgG serostatus at baseline. A slight increase in reactogenicity was observed in PLWH compared to HIV-negative participants. Reactogenicity increased slightly at 30µg compared to the lower doses after GRT-R914 administration. No vaccine-related SAEs or severe COVID-19 cases were reported in participants who received either vaccine.

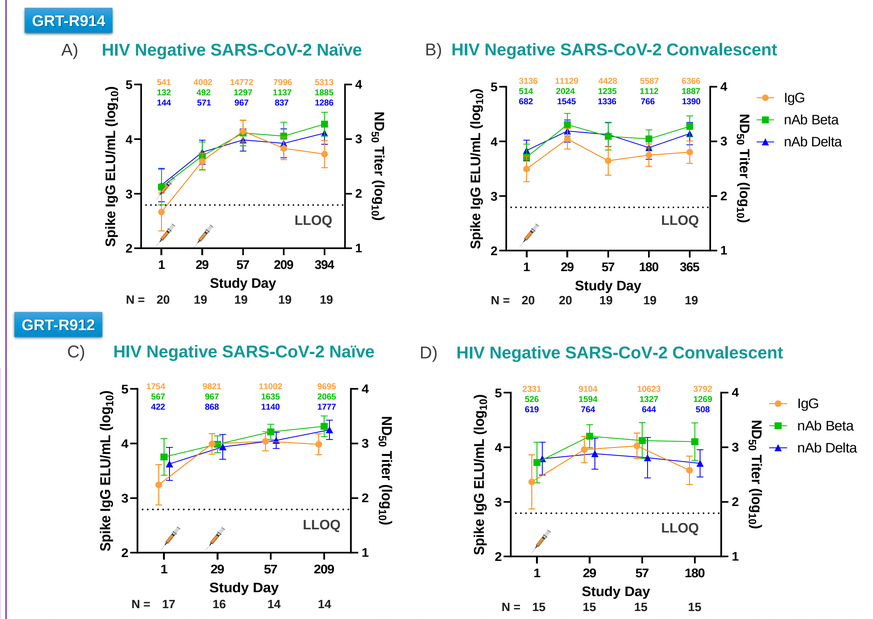
Immunogenicity: Immunogenicity is presented for participants receiving 10µg of either GRT-R914 or GRT-R912. IgG bAb levels to ancestral Spike ($Spike_{WT}$) and nAb titers against Beta & Delta viruses increased after GRT-R914 administration in HIV negative participants who were both SARS-CoV-2 naïve and convalescent (Fig.4). Durable antibody levels were observed through 12 months. Administration of GRT-R912 also resulted in an increase in IgG bAb and nAb levels that were maintained for at least 6 months in both SARS-CoV-2 naïve and convalescent participants (Fig.4). In PLWH, both vaccine candidates increased levels of bAbs and nAbs against Beta and Delta that persisted for at least 6 months (Fig.5). T-cell responses to Spike and non-Spike epitopes were increased and/or maintained through 6 months post vaccination with either vaccine (Fig. 6).

Fig. 3: Solicited AEs of GRT-R914 and GRT-R912 in both SARS-CoV-2 naïve HIV negative and PLWH participants were mostly grade 1 or 2 and transient in nature, with reported grade 3 solicited adverse events resolving within 1-2 days.



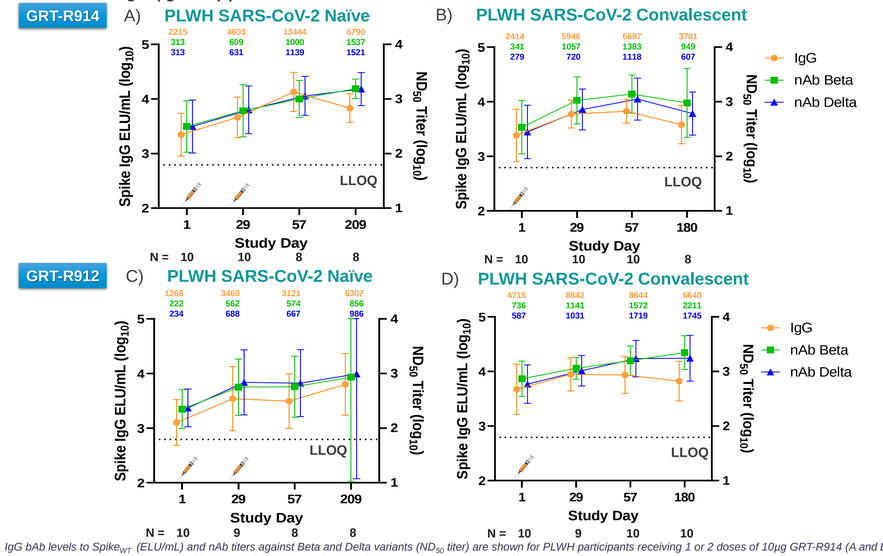
Local and systemic solicited AEs in SARS-CoV-2 naïve participants after 1 or 2 doses of either GRT-R914 (top panel) or GRT-R912 (bottom panel). Data reported for HIV negative (blue) and PLWH (red) populations. Duration is for grade 3 solicited AEs.

Fig. 4: IgG levels to $Spike_{WT}$ and nAb levels to Beta and Delta variants are increased and maintained for 6 or 12 months in HIV negative, SARS-CoV-2 naïve and convalescent participants following 10µg dose(s) of GRT-R914 and GRT-R912



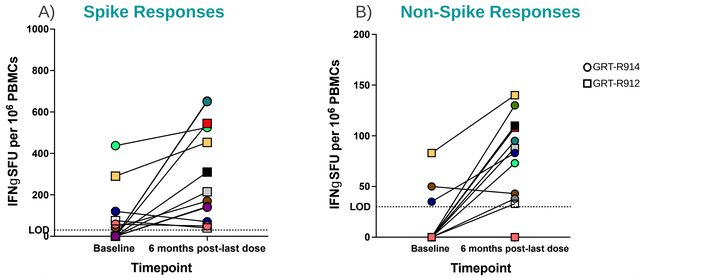
IgG bAb levels to $Spike_{WT}$ (ELU/mL) and nAb titers against Beta and Delta variants (ND_{50} titer) are shown for participants receiving 1 or 2 doses of 10µg GRT-R914 (A and B) or GRT-R912 (C and D). Geometric means with 95% confidence intervals are shown. Lower limit of quantitation (LLOQ): 62 ND_{50} Titer (nAb), 50.3 ELU/mL (IgG)

Fig. 5: IgG levels to $Spike_{WT}$ and nAb levels to Beta and Delta variants are increased and maintained for 6 months in PLWH following 10µg dose(s) of GRT-R914 and GRT-R912



IgG bAb levels to $Spike_{WT}$ (ELU/mL) and nAb titers against Beta and Delta variants (ND_{50} titer) are shown for PLWH participants receiving 1 or 2 doses of 10µg GRT-R914 (A and B) or GRT-R912 (C and D). Geomeans with 95% confidence intervals are shown. LLOQ: 62 ND_{50} Titer (nAb), 50.3 ELU/mL (IgG)

Fig.6: Spike and/or non-Spike T cell responses are increased and/or maintained through 6 months in the majority of participants assessed at the 10µg dose level



Spike (A) and non-Spike (B) (TCE & Nucleocapsid) responses assessed by ex-vivo ELISpot in a subset of individuals dosed with 10µg of GRT-R912 (10 subjects tested) or GRT-R914 (9 subjects tested). Responses were measured in both naïve and convalescent participants at baseline and 6 months after last dose. Colors represent individual participants with an increase or maintenance of response (GRT-R912: n=6; GRT-R914: n=7). Mean of replicate wells and sum of positive peptide pool responses are shown. Limit of detection (LOD) = 30 interferon gamma (IFNγ) spot forming units (SFU) per 10^6 peripheral blood mononuclear cells (PBMCs).

CONCLUSIONS:

- CORAL-CEPI (NCT05435027) is the first study assessing a samRNA-based vaccine in the PLWH population in South Africa.
- All doses of GRT-R914 and GRT-R912 were well tolerated in both HIV-negative participants and PLWH irrespective of SARS-CoV-2 serostatus at baseline.
- GRT-R914 and GRT-R912 increased and maintained IgG levels for at least 12 months at the 10µg dose against $Spike_{WT}$ 7.7-fold and 5.9-fold, respectively, in HIV negative, anti-N IgG seronegative participants.
- For PLWH who were anti-N IgG seronegative at baseline, IgG levels were increased and maintained for at least 6 months (as of data cut-off date) against $Spike_{WT}$ 2.4-fold (GRT-R914) and 5.6-fold (GRT-R912) at the 10µg dose. Twelve-month data are pending.
- Neutralizing antibody levels were increased and sustained for at least 12 months after GRT-R914 and at least 6 months after GRT-R912 vaccination at the 10µg dose level. Twelve-month data for GRT-R912 including nAbs against Omicron are pending.
- Spike and non-Spike T cell responses were increased and/or maintained in majority of individuals receiving either GRT-R914 or GRT-R912 vaccine candidates. T cell data from PLWH are pending.
- Overall, Gritstone's samRNA platform is well tolerated in both HIV negative and PLWH populations and is able to induce robust and durable binding and neutralizing antibodies along with broad cellular immune responses.

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Gritstone bio website