CT. gov NCT #: 05435027

Poster #:BES0404

Durable immune response induced by self-amplifying mRNA (samRNA) SARS-CoV-2 vaccine candidates in HIV negative and people living with HIV (PLWH) populations in South Africa

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BACKGROUND:

The protection provided by currently approved vaccines against symptomatic SARS-CoV-2 infection wanes over time, diminishing in 6 months to below levels expected to provide protection. An ideal next-generation SARS-CoV-2 vaccine should provide more durable antibody responses and greater breadth of protection (humoral & cellular). Our next-generation SARS-CoV-2 vaccine program, CORAL, aims to deliver this. CORAL-CEPI (NCT05435027) is an ongoing Phase I study in South Africa evaluating three self-amplifying mRNA (samRNA)-based SARS-CoV-2 vaccine candidates. 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, SARS-CoV-2 serostatus or prior vaccination status.

METHODS:

Vaccine candidates GRT-R914, GRT-R912, and GRT-R918 encode full-length Spike (Beta or Omicron$_{BA.1}$), Nucleocapsid (full-length or selected T cell epitopes [TCEs]), and non-Spike TCEs from conserved viral proteins (Fig.1). GRT-R914 and GRT-R912 were evaluated in HIV negative and PLWH populations who were SARS-CoV-2 anti-Spike and anti-Nucleocapsid seronegative or seropositive at baseline (Parts A/B/C). In Part D, GRT-R918 was evaluated in adults who were either previously vaccinated against SARS-CoV-2 or vaccine naïve (Fig.2) and HIV negative or people living with HIV (PLWH). The primary objective is safety (reactogenicity and all adverse events [AEs]). Secondary objectives assess ancestral Spike-specific binding IgG (bAb) and neutralizing antibodies (nAbs) to SARS-CoV-2 variants as well as T cell responses against Spike and TCEs.

Fig. 1: Vaccine candidates GRT-R914, GRT-R912, and GRT-R918 delivers Spike and selected conserved sequences from viral genes

GRT-R914 (TCE9 cassette): *full-length Spike$_{Beta}$ and epitopes derived from Nucleocapsid, ORF3a, Membrane, and Non-structural Proteins (NSP) as TCE9.*

GRT-R912 (TCE11+N cassette): *full-length Spike$_{Beta}$ and full-length Nucleocapsid, with epitopes derived from Membrane and NSP as TCE11*

GRT-R918 (TCE11 + N cassette + omicron BA.1 spike): *full-length Spike$_{Omicron\ BA.1}$ and full length Nucleocapsid, with epitopes derived from Membrane and NSP as TCE11*

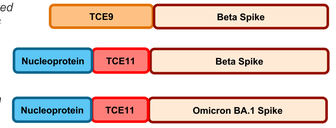
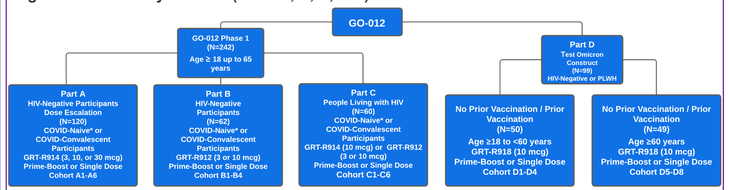


Fig. 2: GO-012 Study Schema (Parts A, B, C, & D)



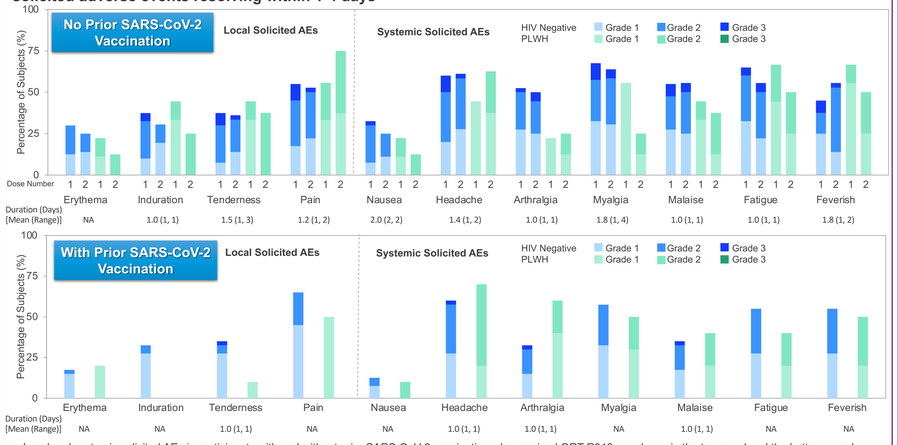
** SARS-CoV-2 Naïve participants defined as SARS-CoV-2 anti-Nucleocapsid (anti-N) IgG seronegative at baseline. N represents participants who received at least one dose of the study vaccine.*

RESULTS:

Safety: A total of 341 participants received at least one dose of the study vaccine. One hundred forty participants received GRT-R914. 102 and 99 participants have received GRT-R912 and GRT-R918, respectively. Among vaccinated participants, most reactogenicity was grade 1 or 2 and transient in nature (Fig. 3). Eight out of 140 (5.7%) participants who received GRT-R914, 8 out of 102 (7.8%) participants who received GRT-R914, and 9 out of 99 (9.1%) participants who received GRT-R918 reported grade 3 solicited AEs which mostly resolved within 1-4 days. A slight increase in reactogenicity was observed in PLWH compared to HIV-negative participants. A slight increase in reactogenicity was observed in the younger population compared to the elder population after GRT-R918 administration. No vaccine-related SAEs or severe COVID-19 cases were reported in participants who received study vaccine.

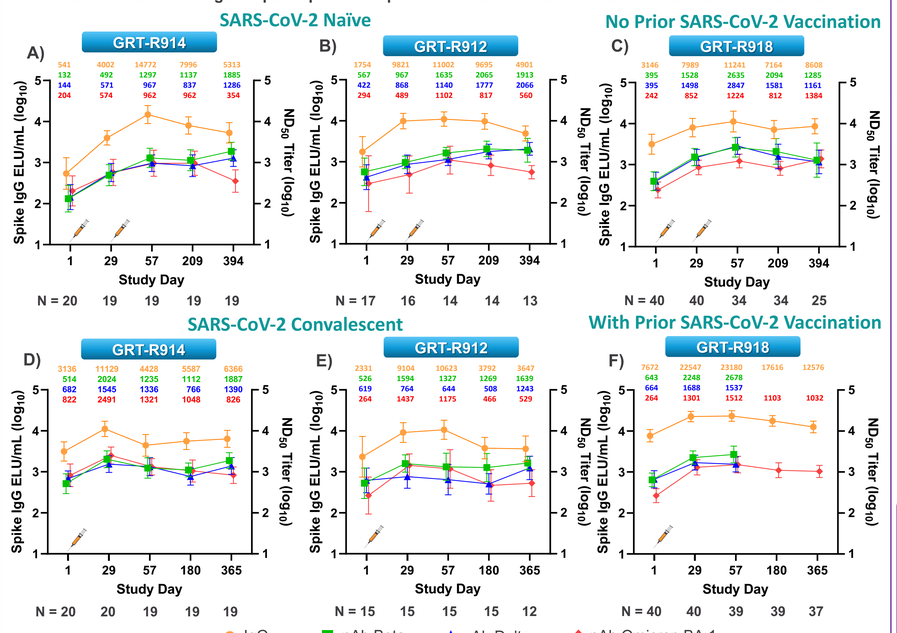
Immunogenicity: Immunogenicity is presented for participants who received at least one 10µg dose of GRT-R914, GRT-R912, or GRT-R918. In HIV-negative individuals with either SARS-CoV-2 serostatus, vaccination with GRT-R914 and GRT-R912 resulted in an increase of bAb levels to ancestral Spike (Spike$_{WT}$) and nAb titers against Beta and Delta variants that were maintained through 12 months (Fig. 4). Neutralizing antibodies against Omicron BA.1 remained durable through 6- or 12-months. GRT-R918 elicited bAbs and vaccine-specific nAbs against Omicron BA.1 that were durable through 12 months. Beta and Delta nAb titers increased in participants irrespective of vaccination status at baseline; titers remained durable through 12-months in participants who had not previously received a SARS-CoV-2 vaccination (Beta/Delta 6/12-month data pending in previously vaccinated groups). In the PLWH population, GRT-R912 and GRT-R918 vaccine candidates increased levels of bAbs and nAbs against Beta, Delta, and Omicron BA.1 through 12 months (Fig. 5). Administration of GRT-R914 increased nAb titers against Beta and Delta (Omicron BA.1 nAb data analysis pending) through 12 months; durability was also observed with binding antibodies. T cell responses to vaccine antigens were increased and/or maintained after administration of any vaccine candidate in the majority of HIV-negative or PLWH participants tested to date (Fig. 6) .

Fig. 3: Solicited AEs of GRT-R918 10µg dose(s) were mostly grade 1 or 2 and transient in nature, with reported grade 3 solicited adverse events resolving within 1-4 days



Local and systemic solicited AEs in participants with and without prior SARS-CoV-2 vaccination who received GRT-R918 are shown in the top panel and the bottom panel, respectively. Data are reported for HIV negative (blue) and PLWH (orange) populations. Data from participants who received GRT-R912 and GRT-R914 were previously reported in ECCMID 2023 and IDWeek 2023. Duration is for grade 3 solicited AEs.

Fig. 4: Spike$_{WT}$ IgG bAbs and nAbs against Beta, Delta, or Omicron BA.1 variants are induced and maintained through at least 12-months in HIV-negative participants irrespective of SARS-CoV-2 serostatus or vaccination status at baseline



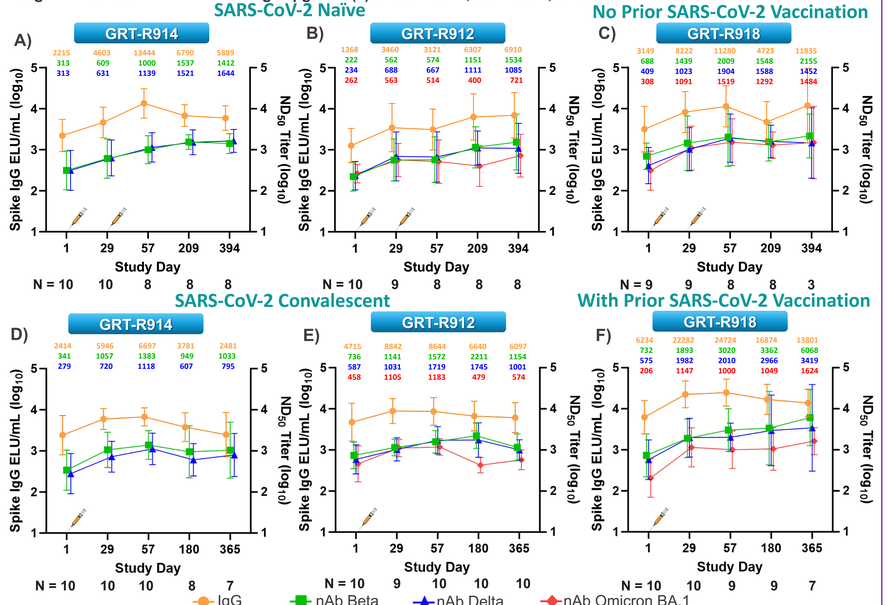
IgG bAb levels to Spike$_{WT}$ (ELU/mL) and nAb titers against Beta, Delta, and Omicron BA.1 variants (ND$_{50}$ titer) are shown (where available) for participants who received 1 or 2 doses of 10µg GRT-R914 (A and D), GRT-R912 (B and E), or GRT-R918 (C and F). Geometric means with 95% CIs are shown. Lower limit of quantitation (LLOQ): 62 ND$_{50}$ Titer (nAb), 50.3 ELU/mL (IgG)

Abstract/Poster number: 02893/BES0404 Funding support: CEPI

Acknowledgments: Special thanks to Pedro Garbes, Daniel O. Koralek, Christine D. Palmer, and J.J. Allagappen. Study sponsor, Gritstone bio, Inc., also acknowledges the laboratory services of VisMederi srl for this study.

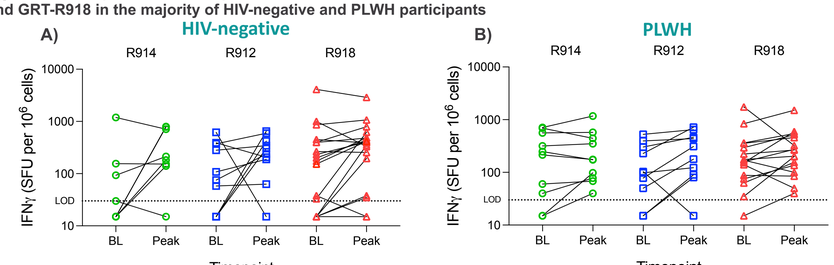
Gritstone bio website

Fig. 5: IgG levels to Spike$_{WT}$ and nAb titers to Beta, Delta, or Omicron BA.1 variants are increased and remain durable through 12 months in PLWH following 10µg dose(s) of GRT-R914, GRT-R912, or GRT-R918



IgG bAb levels to Spike$_{WT}$ (ELU/mL) and nAb titers against Beta, Delta, and Omicron BA.1variants (ND$_{50}$ titer) are shown (where available) for PLWH participants receiving 1 or 2 doses of 10µg GRT-R914 (A and D), GRT-R912 (B and E), or GRT-R918 (C and F). Geomeans with 95% confidence intervals are shown. LLOQ: 62 ND$_{50}$ Titer (nAb), 50.3 ELU/mL (IgG)

Fig.6: Vaccine-specific T cell responses are increased and/or maintained after administration of GRT-R914, GRT-R912, and GRT-R918 in the majority of HIV-negative and PLWH participants



T cell responses to vaccine antigens as assessed by ex-vivo ELISpot in HIV negative (A) and PLWH (B) participants. Baseline (BL) and peak response after vaccination (1 or 2 doses of 10µg) with GRT-R914, GRT-R912, or GRT-R918 are shown. Data for each vaccine candidate are inclusive of SARS-CoV-2 serostatus and prior vaccination status. Mean of replicate wells and sum of positive Spike and non-Spike 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:

- NCT05435027 is the first study assessing 3 samRNA-based SARS-CoV-2 vaccine candidates in HIV-negative and PLWH populations in South Africa
- All doses of GRT-R914, GRT-R912, and GRT-R918 were well tolerated in both HIV-negative and PLWH participants irrespective of age, SARS-CoV-2 serostatus, or prior SARS-CoV-2 vaccination status at baseline
- GRT-R914, GRT-R912, and GRT-R918 increased and maintained IgG levels and nAb titers against VOCs for at least 12 months when administered at a 10µg dose in HIV-negative and PLWH participants irrespective of prior SARS-CoV-2 vaccination status or serostatus (additional Beta, Delta, and Omicron BA.1 data pending)
- Antigen-specific T cell responses were increased in the majority of participants tested to date after administration of any of the 3 samRNA vaccine candidates
- Gritstone's samRNA platform is well tolerated and has shown to drive robust and durable binding (igG) and neutralizing antibodies (nAb) across SARS-CoV-2 variants in addition to broad T cell responses to both Spike and non-Spike epitopes