An Interim Report of the Safety, Reactogenicity, and Immunogenicity of a Self-amplifying mRNA (samRNA) COVID-19 Vaccine GRT-R910 as a Booster in Healthy Adults

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Introduction

- The self-amplifying mRNA (samRNA) platform (Gritstone bio, Inc) has been safe and immunogenic in cancer patients.[1]
- Next-generation COVID-19 vaccines that provide durable protection against COVID-19 across different variants among vulnerable populations are needed.
- GRT-R910 (Gritstone bio, Inc) utilizes a fully synthetic Venezuelan Equine Encephalitis Virus (VEEV)-based self-amplifying mRNA vector formulated into lipid nanoparticles.
  - Encodes full-length spike (S) prefusion modified from the ancestral strain with D614G mutation and highly conserved non-S SARS-CoV-2 T cell epitope (TCE) sequences predicted using EDGE™ , a previously published algorithm that allows for accurate prediction of HLA-peptide complexes[2] combined with selected validated epitopes.[3,4]
  - The TCE and design to elicit T cell responses makes this vaccine construct unique from authorized vaccines.

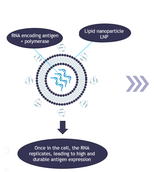


Figure from Gritstone bio, Inc

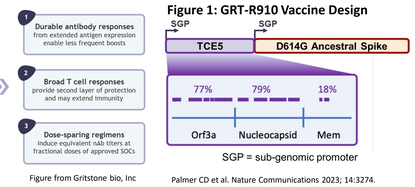


Figure 1: GRT-R910 Vaccine Design

Palmer CD et al. Nature Communications 2023; 14:3274.

- GRT-R910 was tested in a phase 1 study as a booster in healthy adults. We report the interim safety, including reactogenicity, and humoral immunogenicity data from this trial (NCT04776317). Cellular immunogenicity analyses are underway.

Methods

- This phase 1 open-label dose escalation study enrolled healthy adults who previously completed an approved mRNA COVID-19 vaccine series ≥ 112 days prior to enrollment. Groups of 10 adults aged 18-60 years were boosted with GRT-R910 at 3 or 6 mcg. Groups of 8-10 adults > 60 years were boosted with GRT-R910 at 3, 6, or 10 mcg.
- Solicited injection site and systemic reactogenicity events were collected for 7 days, unsolicited adverse events (AEs) for 28 days, and serious adverse events (SAEs) for 365 days post vaccination.
- ELISA IgG against SARS-CoV-2, pseudovirus neutralization, and live virus focus reduction neutralization assays were assessed at Days 1, 15, 29, 85, 181, and 366 against ancestral strain, B.1.1.539, and BA.4/5.
- Participants who self-reported COVID-19 during the study, developed a positive nucleocapsid (N)-antibody after Day 1, or reported receipt of non-study COVID-19 vaccine were censored in the immunogenicity analyses.

Results

Participants:

48 participants were enrolled and received GRT-R910 in this study between September 2021 and June 2022.

Table 1: Reasons participants were censored in the immunogenicity analyses by time point

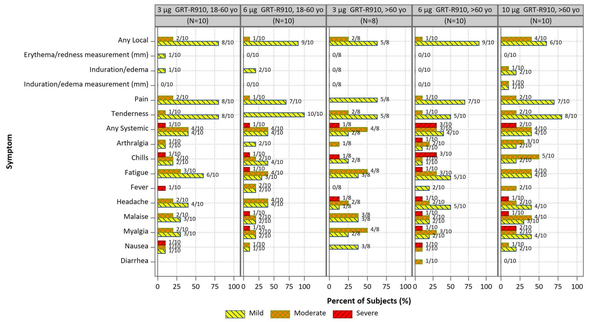
Time Point	Reason for Censoring	3 µg, 18-60 yo	6 µg, 18-60 yo	3 µg, >60 yo	6 µg,* >60 yo**	10 µg,* >60 yo**
Day 1	Remaining in analysis	10	10	8	10	10
Day 15	Remaining in analysis	10	10	8	10	10
Day 29	Remaining in analysis	10	10	8	10	10
Day 85	Remaining in analysis	10	10	6	9	10
	Covid-19 Infection	-	-	2	1	-
Day 181	Remaining in analysis	5	5	4	7	10
	Covid-19 Infection	3	4	4	3	-
	Out-of-study Booster	2	2	-	-	-
Day 366	Remaining in analysis	2	2	2	2	5
	Covid-19 Infection	5	7	5	5	1
	Out-of-study Booster	3	4	3	7	4

*participants in these groups also received an approved mRNA COVID-19 booster ≥ 112 days prior to enrollment
**2 of the 10 enrolled in these groups had COVID-19 prior to enrollment by N-antibody
Participants with visits excluded from the population for multiple reasons are counted once per row for each reason.

Reactogenicity:

No severe injection site reactogenicity events were observed. Overall, out of 48 participants enrolled across all groups, 8 reported at least 1 severe systemic reactogenicity event (Figure 2). Most severe systemic reactogenicity events were transient, with most severely graded AEs lasting for 1 day or less. No SAEs have been reported.

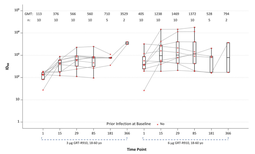
Figure 2: Solicited systemic and local reactogenicity within 7 days after receipt of GRT-R910



Humoral Immunogenicity Results:

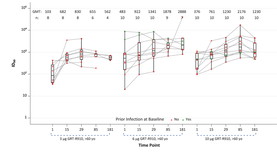
Pseudovirus neutralization

Figure 3: Pseudovirus (ID_{50}) neutralization antibody against SARS-CoV-2 D614G, Age 18-60 years



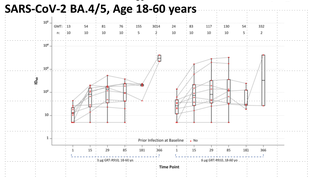
Boxes and horizontal bars denote interquartile range and median respectively
GMT = geometric mean titer

Figure 4: Pseudovirus (ID_{50}) neutralization antibody against SARS-CoV-2 D614G, Age > 60 years



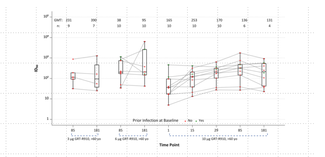
Boxes and horizontal bars denote interquartile range and median respectively
GMT = geometric mean titer

Figure 5: Pseudovirus (ID_{50}) neutralization antibody against SARS-CoV-2 BA.4/5, Age 18-60 years



Boxes and horizontal bars denote interquartile range and median respectively
GMT = geometric mean titer

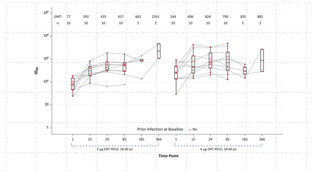
Figure 6: Distribution of pseudovirus (ID_{50}) neutralization antibody against SARS-CoV-2 BA.4/5, Age > 60 years



Boxes and horizontal bars denote interquartile range and median respectively
GMT = geometric mean titer
Data are not available for 3 and 6 mcg groups at Days 1, 15, and 29.

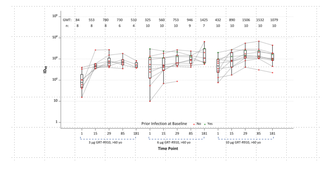
Focus Reduction Neutralization

Figure 7: Focus reduction neutralization test (ID_{50}) against SARS-CoV-2 D614G, Age 18-60 years



Boxes and horizontal bars denote interquartile range and median respectively
GMT = geometric mean titer

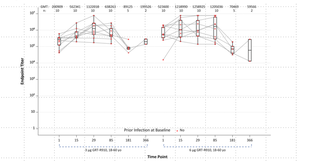
Figure 8: Focus reduction neutralization test (ID_{50}) against SARS-CoV-2 D614G, Age > 60 years



Boxes and horizontal bars denote interquartile range and median respectively
GMT = geometric mean titer

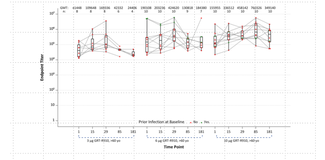
ELISA

Figure 9: ELISA IgG antibody against SARS-CoV-2 S-2P, Age 18-60 years



Boxes and horizontal bars denote interquartile range and median respectively
GMT = geometric mean titer

Figure 10: ELISA IgG antibody against SARS-CoV-2 S-2P, Age > 60 years



Boxes and horizontal bars denote interquartile range and median respectively
GMT = geometric mean titer

Note: N-antibody data (indicative of SARS-CoV-2 infection) are available for the following time points: 18-60 year old groups; >60 years dosed with 3mcg: Days 1, 85, and 181; >60 years, 6 and 10 mcg doses: Days 1, 85.

Discussion

- While transient systemic reactogenicity with GRT-R910 as a booster was observed, no safety signals were identified.
  - These results are consistent with the results of a separate trial of GRT-R910 in the UK among adults > 60 years who had previously completed the AstraZeneca ChAdOx1 AZD1222 series (GO-009 - NCT05148962).[5]
- Pseudovirus neutralization antibody, ELISA IgG antibody, and live virus focus reduction neutralization assays against SARS-CoV-2 D614G and variants of concern (VOC) demonstrate durable boosting of humoral immune responses to ancestral and VOC Spike (not all data shown) and durable neutralizing antibody responses up to 6 months for GRT-R910 vaccine groups.
  - This is in contrast to the waning of humoral immunity within 6 months that has been observed with the approved COVID-19 mRNA vaccines.[6]
- Our results are consistent with results from other phase 1 trials of GRT-R910 and similar vaccines (GRT-R912 and GRT-R914).
  - Robust and durable neutralizing antibody responses to ancestral Spike and variants of concern were observed through at least 6 months in the GO-009 trial in the UK among adults > 60 years who received GRT-R910.[5]
  - Robust and durable neutralizing antibody responses in unvaccinated (virus-naïve or convalescent) healthy volunteers, including people with HIV have been observed with similar Gritstone samRNA COVID-19 vaccines (GRT-R912 and GRT-R914) in South Africa (GO-012 – NCT05435027; IDWeek2023 Abstract 1538194/Poster 2372).
- Of the 48 participants enrolled in the study, 23 developed COVID-19 during the study. These infections were mild and did not require hospitalization.
- Cellular immunogenicity analyses are underway for our study.
  - The GO-09 trial demonstrated increased and/or broadened functional Spike-specific T cell responses and primed functional T cell responses to conserved non-Spike epitopes.[5]
- The safety, reactogenicity, and serological response data from our study, in conjunction with other published phase 1 trial data for GRT-R910, support this vaccine's continued development as a potential next generation vaccine.

References

[1]Palmer CD et al. Nature Medicine 2022; 28(8):1619-1629.
[2]Bulik-Sullivan B et al. Nature Biotechnology 2019; 37: 55-63.
[3]Grifoni A et al. Cell 2020; 181: 1489-1502.
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