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First study of a Self-amplifying mRNA (samRNA) Vaccine, GRT-R910, as a Booster against COVID-19 in Healthy Volunteers ≥60 Years of Age - Preliminary Evidence of Durable Immunity

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Background: First-generation of COVID-19 vaccines played a critical role in addressing the pandemic but have shown limited duration and breadth of protection because vaccine-elicited humoral immunity is transient (thus requiring boosters). Self-amplifying mRNA (samRNA), a next-generation platform technology, has demonstrated the potential to drive broad and durable cellular and humoral immunity against SARS-CoV-2. CORAL-BOOST (NCT05148962) is evaluating the safety and immunogenicity of a samRNA SARS-CoV-2 vaccine candidate (GRT-R910) in healthy adults.

Methods: This phase I, open-label, multi-centre study was conducted in the UK. GRT-R910 encodes for Wild-type Spike (S) and highly conserved non-S T cell epitopes from ORF3a, Nucleocapsid, and Membrane (Fig. 1). Healthy adults ≥60 years were enrolled into cohorts 1 and 2 and received 1 dose of GRT-R910 after a primary series of Vaxzevria, with a subset receiving an optional second dose. Cohorts 3 and 4 assessed 2 doses of GRT-R910 after adenoviral or mRNA primary series, respectively (Fig. 2). The primary endpoint was to evaluate adverse events (AEs) and secondary objectives included magnitude and breadth of T cell response and SARS-CoV-2 specific IgG binding and neutralizing antibody (nAb) responses.

Fig. 1. GRT-R910 Vaccine Design

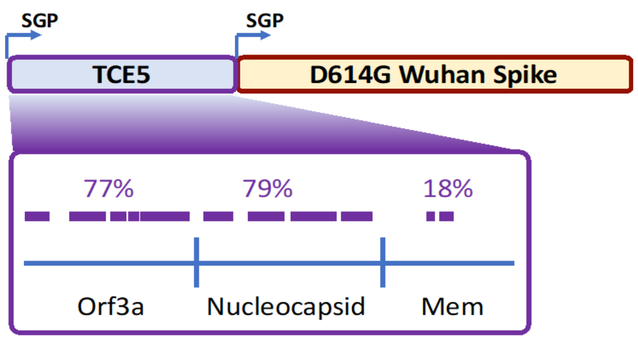


Fig. 2. CORAL-BOOST (NCT05148962) Study Design

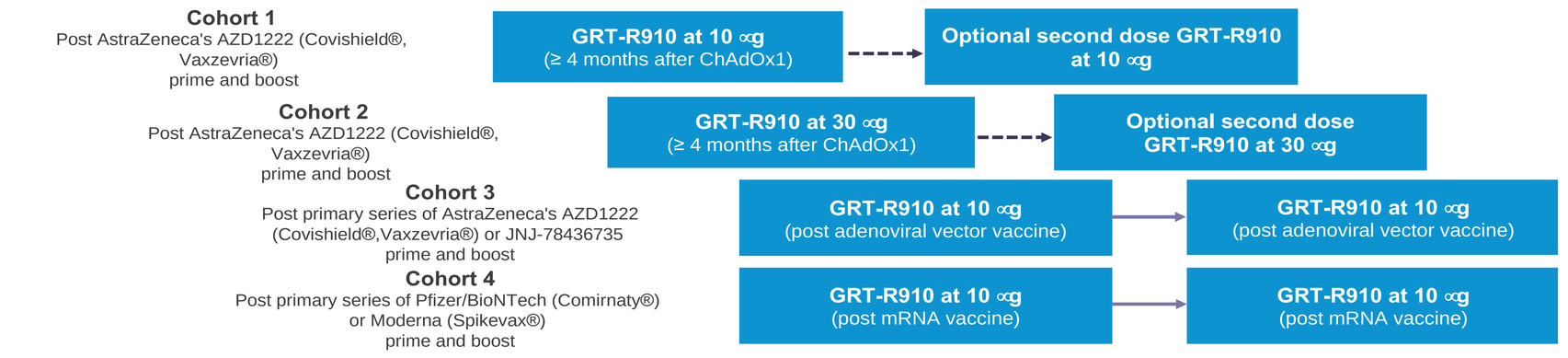
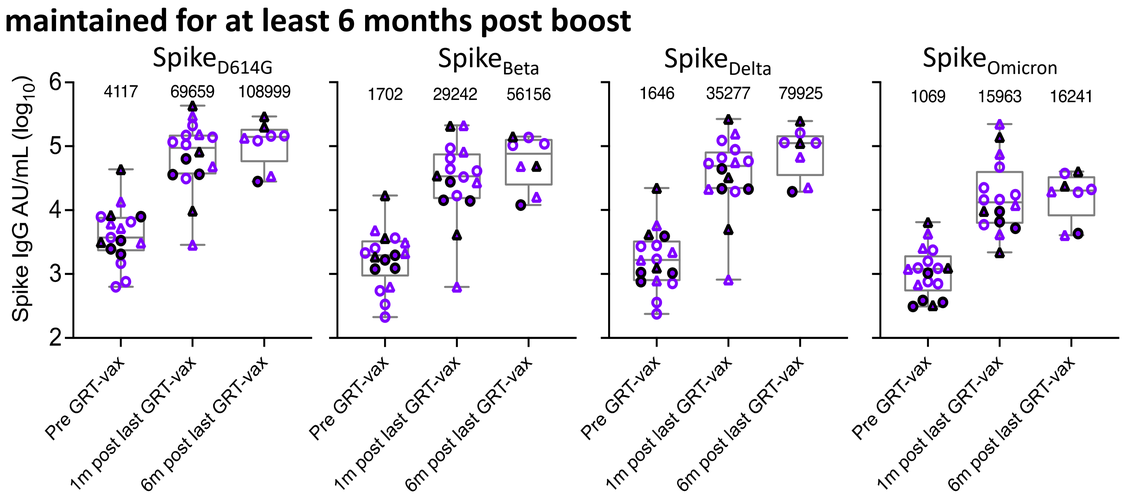
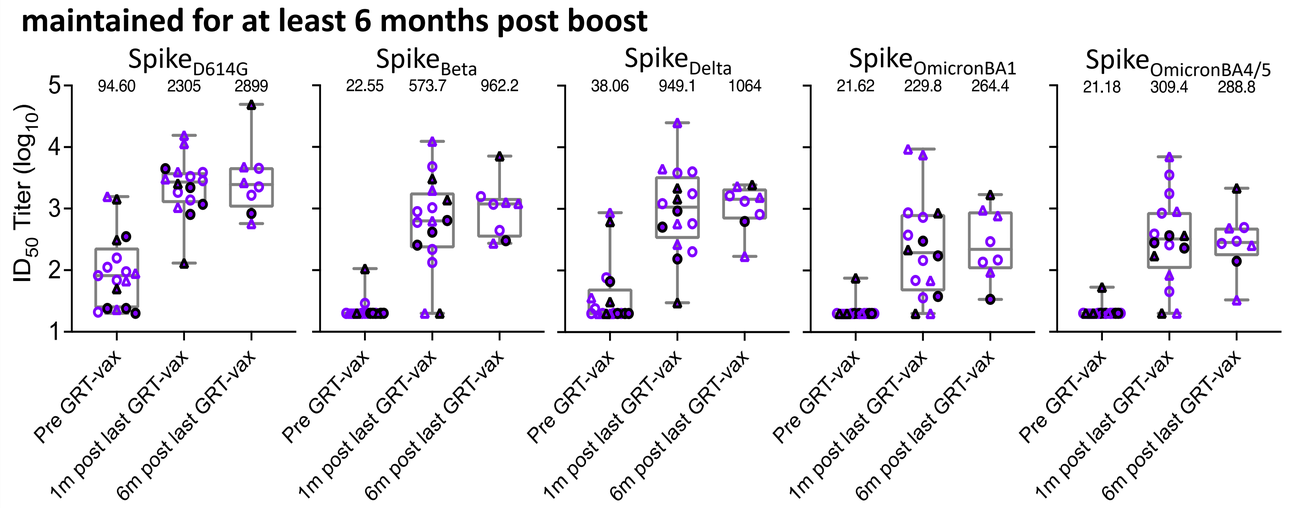


Fig. 3. Binding antibodies (IgG) to $Spike_{D614G}$ and VOC Beta, Delta, and Omicron BA1 are boosted 5-20-fold (approx. Five-to-twenty fold) by GRT-R910 and maintained for at least 6 months post boost



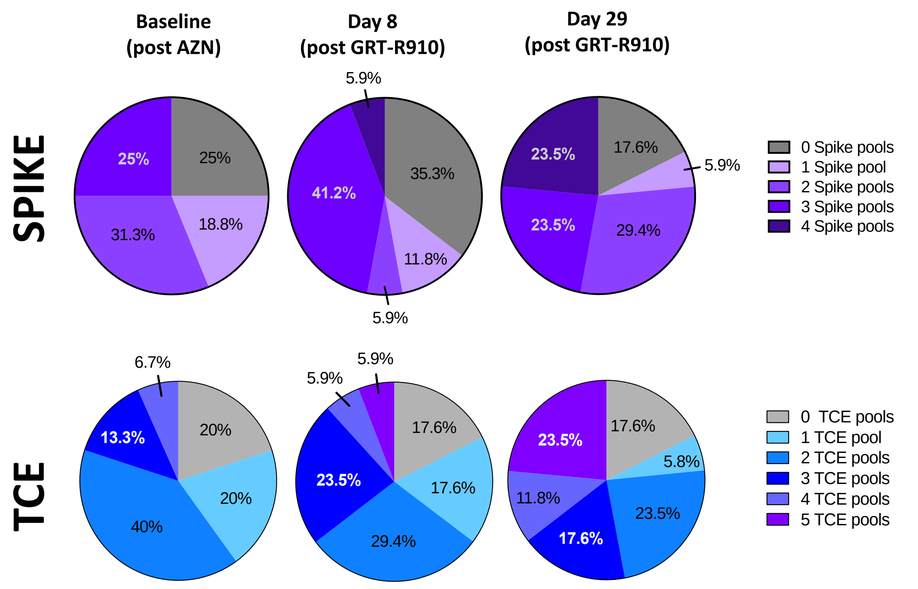
Cohort 1 (open symbols) and cohort 2 (closed symbols) with 6-month data following a single GRT-R910 dose at D1 (triangles) or two GRT-R910 doses at D1 and D113 (circles) available. Data from treatment days D1 baseline, 1-month post most recent GRT-R910 dose, and 6-months post most recent GRT-R910 dose. Geomeans as indicated.

Fig. 4. Neutralizing antibodies (nAb) to $Spike_{D614G}$ and VOC Beta, Delta, and Omicron BA1 & BA4/5 are boosted 10-25-fold (approx. Ten-to-twenty-five fold) by GRT-R910 and maintained for at least 6 months post boost



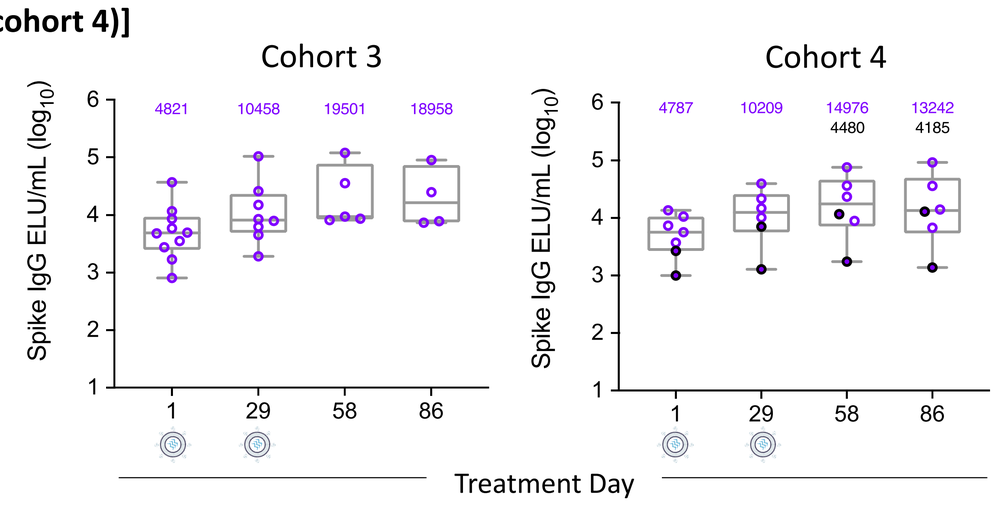
Cohort 1 (open symbols) and cohort 2 (closed symbols) with 6-month data following a single GRT-R910 dose at D1 (triangles) or two GRT-R910 doses at D1 and D113 (circles) available. Data from treatment days D1 baseline, 1-month post most recent GRT-R910 dose, and 6-months post most recent GRT-R910 dose. Geomeans as indicated.

Fig.5. GRT-R910 increases breadth of Spike and TCE-specific T cell responses in previously vaccinated older subjects (adenoviral primary series)



Pie charts depicting frequency (%) of participants (n=17) positive via ex vivo ELISpot for number of Spike OLP pools (0 = grey; 1 = lavender; 2 = light purple; 3 = medium purple; 4 = dark purple) and TCE pools (0 = grey; 1 = light blue; 2 = blue; 3 = navy blue; 4 = light purple; 5 = dark purple) at baseline and treatment days 8 and 29 after GRT-R910 dose. Percentages for each pie slice are indicated.

Fig.6 Booster with R910 (samRNA) increased $Spike_{WT}$-specific IgG levels regardless primary series of immunization [adenoviral (cohort 3) or mRNA (cohort 4)]



Cohort 3 and 4 with 3-month data following single GRT-R910 (closed circle) dose at D1 and two GRT-R910 (open circle) dose at D1 and D29 available. Geomeans as indicated. Note: Not all participants received a 2nd Dose

Result: ***Safety*****:** Solicited AEs were predominantly mild/moderate, and transient. Nine grade 3 solicited AEs were observed in 3 subjects at 10µg and one subject at 30µg had grade 3 solicited AEs (mainly local pain and tenderness, and headache which were transient in nature – Data not shown). ***Immunogenicity*****:** A single dose of GRT-R910 increased binding (IgG) and neutralizing (nAb) antibody levels to the vaccine-specific strain (WT) and VOCs (Cohorts 1 & 2; Fig. 3 & 4). Boosted antibody levels against WT and all VOC tested were maintained for at least 6 months after the GRT-R910 dose in subjects ≥60 years of age (Fig. 3 & 4). A single dose of GRT-R910 increased breadth and depth of T cell responses to S and non-S epitopes (Fig. 5). Administration of 2 doses of GRT-R910 increased $Spike_{WT}$-specific IgG responses irrespective of primary vaccination series (Cohorts 3 & 4; Fig. 6). Analyses assessing neutralization against WT and VOC and longitudinal responses in Cohorts 3 & 4 are ongoing.

Conclusions:

1. CORAL-BOOST (NCT05148962) is the first study assessing a samRNA-based SARS-CoV-2 vaccine in an older population (≥60 years of age)
2. GRT-R910 was well tolerated in this study population at all dose levels
3. Consistent longevity of neutralizing antibody response for at least 6 months was observed against different variants of concern not included in the vaccine construct
4. Administration of GRT-R910 increased breadth of T cell responses against Spike and non-Spike T cell epitopes included in the vaccine
5. This study is ongoing and final results will be communicated after the study has completed

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