

Anthonet Koen¹, Essack Mitha², Jon Jusif Allagappen³, Mrinmayee Dhar⁴, Atul Nagare⁵, Christine D. Palmer⁶, Harshni Venkatraman⁶, Jason R Jaroslavsky⁶, Jenchun Kuan⁶, Lauren D Kraemer⁵, Lindsey Arcebucho⁶, Lorenzo Hernandez⁶, Martina Marrali⁶, Meghan G. Hart⁶, Sonia Kounlavouth⁶, Pedro Garbes⁶, Andrew Allen⁵, Karin Jooss⁵, Shabir Madhi¹

Affiliations: ¹Wits Vaccines & Infectious Diseases Analytics (VIDA) Research Unit, South Africa – Johannesburg (South Africa), ²Newtown clinical research centre, South Africa – Newtown (South Africa), ³Setshaba Research Centre – Pretoria (South Africa), ⁴Shandukani Research – Johannesburg (South Africa), ⁵Gritstone bio, Inc. – Emeryville (United States), ⁶Gritstone bio, Inc. – Cambridge (United States)

Background: CORAL-CEPI (NCT05435027) is the first study evaluating multiple self-amplifying mRNA (samRNA) constructs in vaccine-naïve and SARS-CoV-2 convalescent subjects, and people living with HIV in South Africa. Here, we are providing interim results from part A (Figs. 1 & 2). First-generation vaccines against SARS-CoV-2 played a critical role in reducing morbidity and mortality of SARS-CoV-2 infections but have shown limited duration and breadth of protection due to waning antibody levels, thus requiring boosts. samRNA, a next-generation vaccine platform technology, has demonstrated the potential to drive broad and durable cellular and humoral immunity against SARS-CoV-2.

Methods: CORAL-CEPI is a phase I, open-label, parallel-group, dose-escalation study of samRNA vaccine candidates (GRT-R914, GRT-R912, and GRT-R918) in healthy adults (vaccine-naïve, SARS-CoV-2 convalescent) and People Living with HIV. GRT-R914, which includes sequences for full-length Beta Spike and selected sequences of Nucleocapsid, ORF3a, Membrane, and Non-structural Proteins (NSP) genes (Fig. 1), was administered in Part A as two doses [SARS-CoV-2 anti-N IgG seronegative (“naïve”)] or as one dose [SARS-CoV-2 anti-N IgG seropositive (convalescent)] in HIV-negative adults (18-65yo). Doses of 3µg, 10µg, and 30µg of GRT-R914 were tested (Fig. 2). The primary endpoints include signs and symptoms of local and systemic reactogenicity up to seven days, unsolicited adverse events up to 28 days, and serious adverse events up to 12 months after the last vaccination. Secondary endpoints include assessment of SARS-CoV-2 specific binding and neutralizing antibodies as well as induction of T cell responses.

Fig. 1. GRT-R914 vaccine delivers Spike and selected conserved sequences from seven additional viral genes

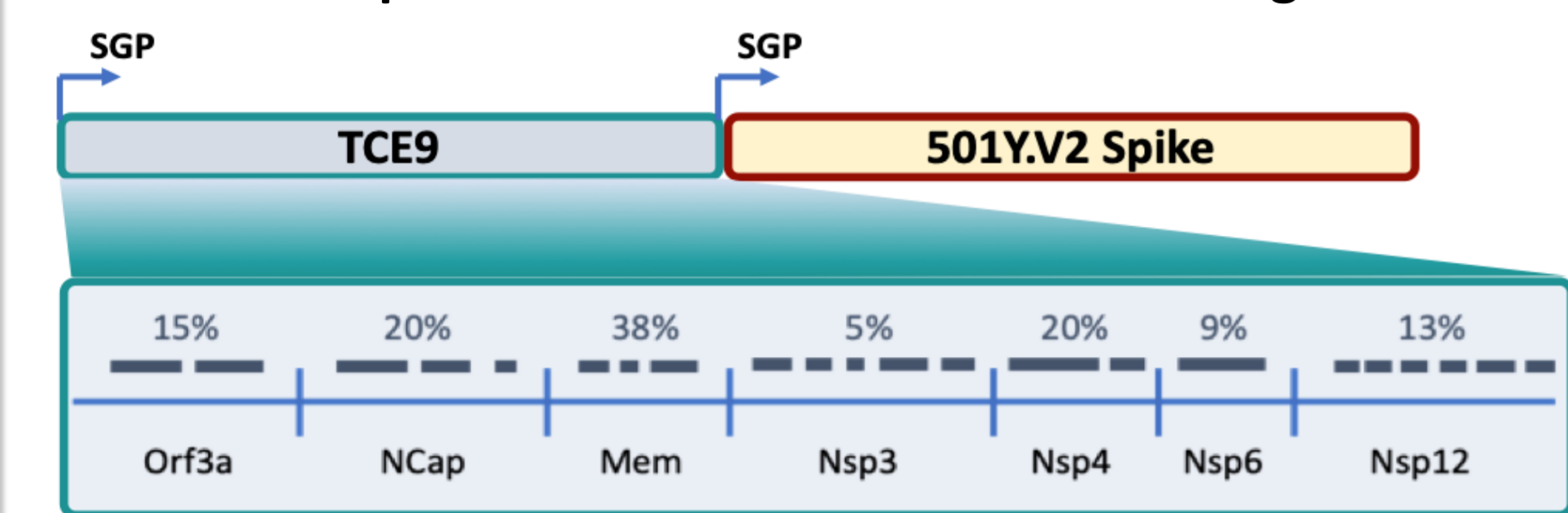
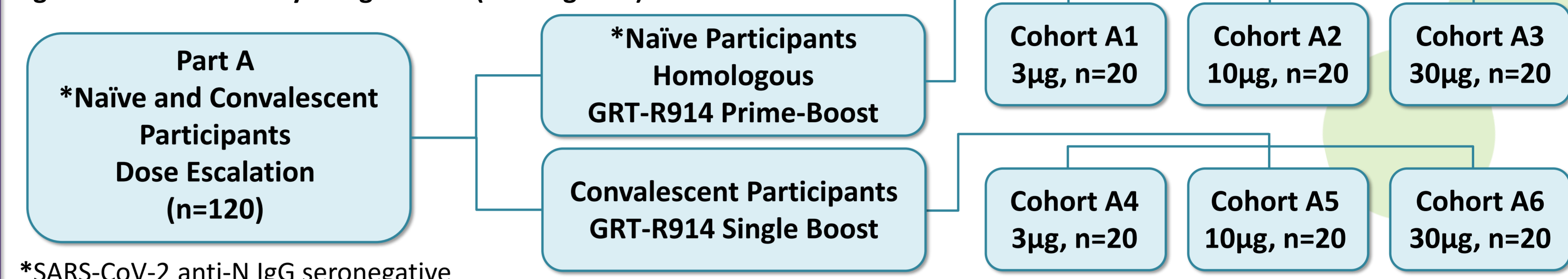


Fig. 2. CORAL-CEPI study design Part A (HIV negative)



Results: Safety: Most reactogenicity events were grade 1 or 2 and transient in nature. Five participants reported grade 3 solicited adverse events, which resolved within 1-4 days. Reactogenicity increased slightly at 30µg compared to the lower doses and there was no significant difference between reactogenicity in cohorts that were SARS-CoV-2 anti-N IgG seropositive versus seronegative (Fig. 3). **Immunogenicity:** Spike-specific antibody levels against WT (IgG) were increased following GRT-R914 administration in naïve (2 doses) and convalescent (1 dose) individuals and maintained for at least 6 months at the 3µg and 10µg dose levels (Fig. 4). Neutralizing antibody (nAb) levels against vaccine-specific strain Beta (Fig. 1) and VOC Delta (not included in vaccine) are increased in both naïve and convalescent individuals after GRT-R914 administration and maintained for 6 months at the selected (10µg) dose (Fig. 5 and 6). Preliminary data from cohorts A3 and A6 (30µg for naïve and convalescent, respectively) show the same durability of IgG and Beta nAb antibody levels through 6 months following vaccination (data not shown). The majority of T cell responses post GRT-R914 administration were focused on NSP and Nucleocapsid, irrespective of previous SARS-CoV-2 exposure (Fig. 7).

Fig. 3. Solicited adverse events for naïve cohorts (A1–A3) were mostly grade 1 or 2 and transient in nature, with reported grade 3 solicited adverse events resolving within 1-4 days

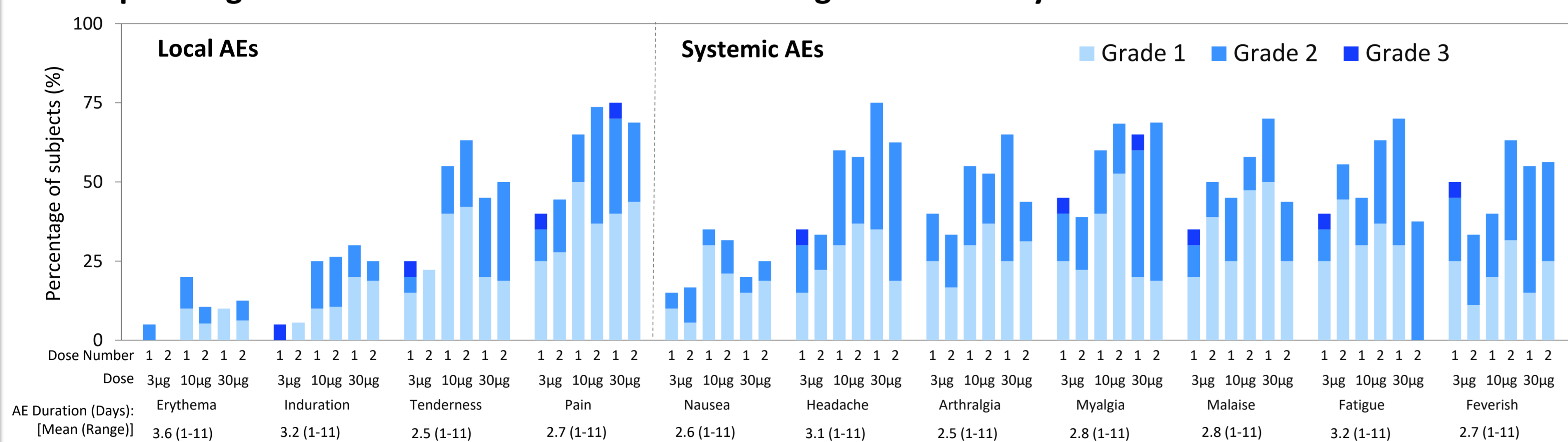


Fig. 4. IgG levels to Spike_{WT} are increased and maintained for 6 months in naïve and convalescent subjects following 10µg dose

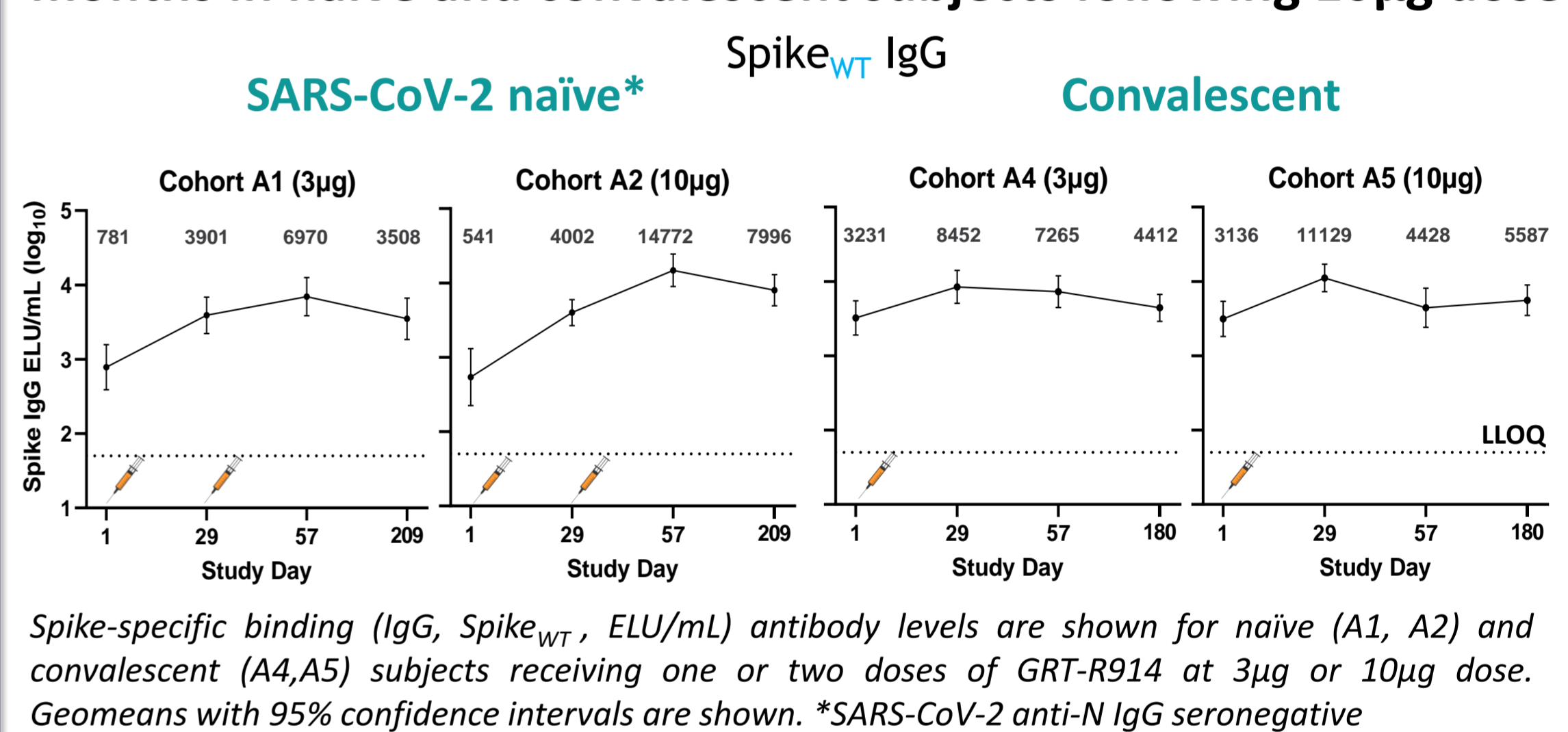


Fig. 5. nAb levels to Spike Beta and Delta are increased and maintained for 6 months following 10µg dose

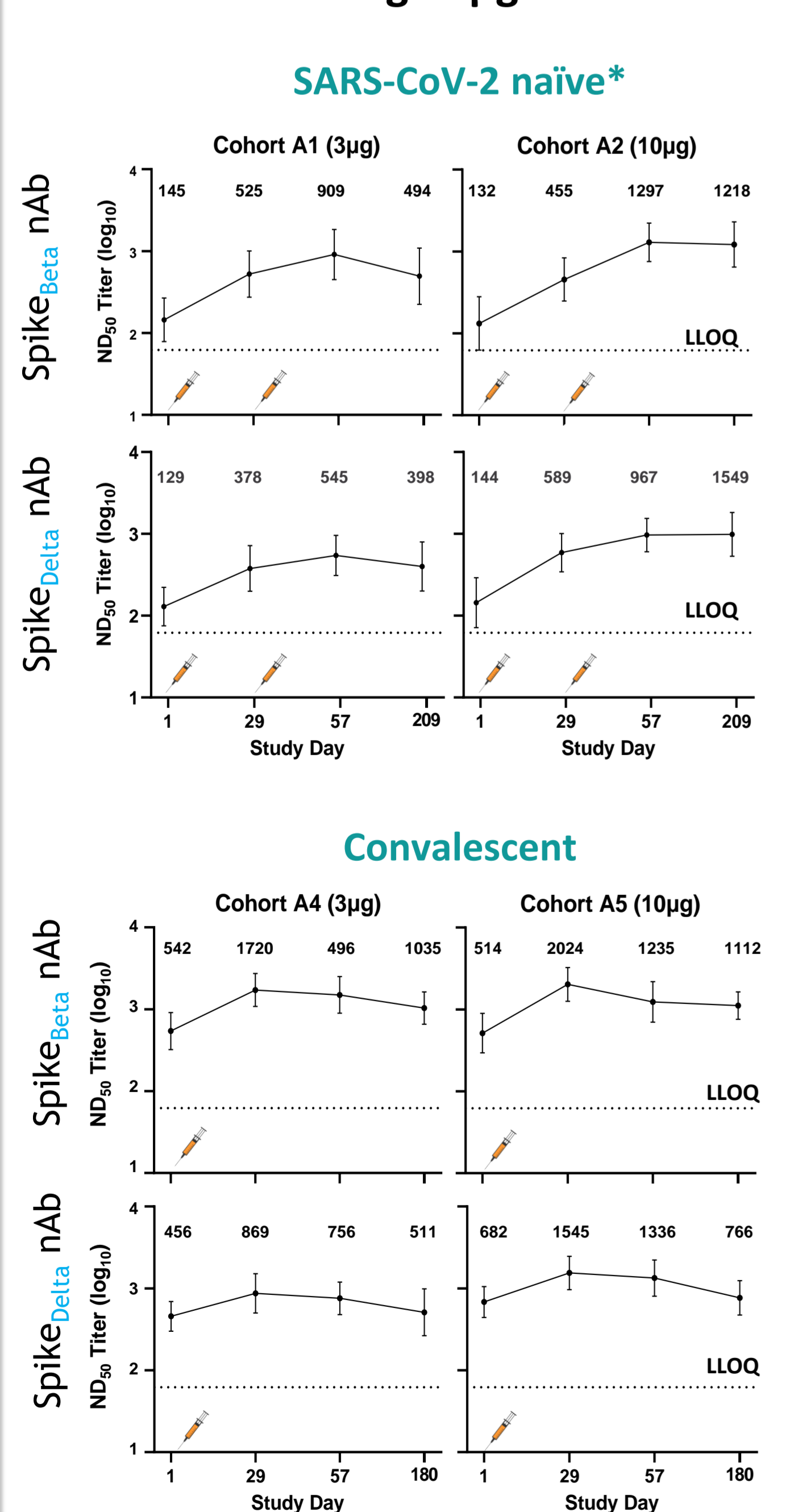


Fig. 6. Durable nAb responses against Beta and Delta VOCs elicited by GRT-R914 (samRNA) is maintained for 6 months

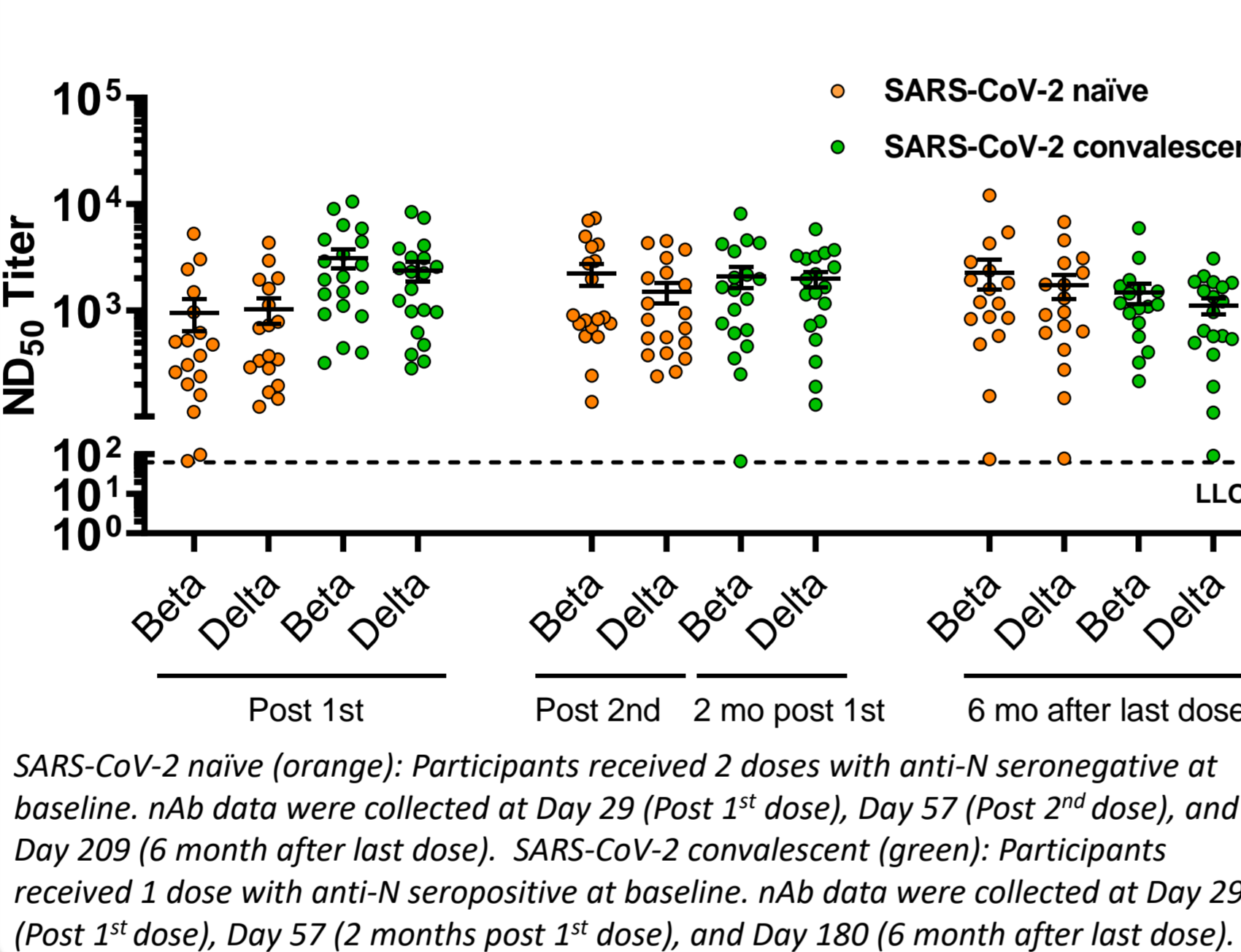


Fig. 8. The durability of the nAb response is influenced by mRNA vaccine type¹

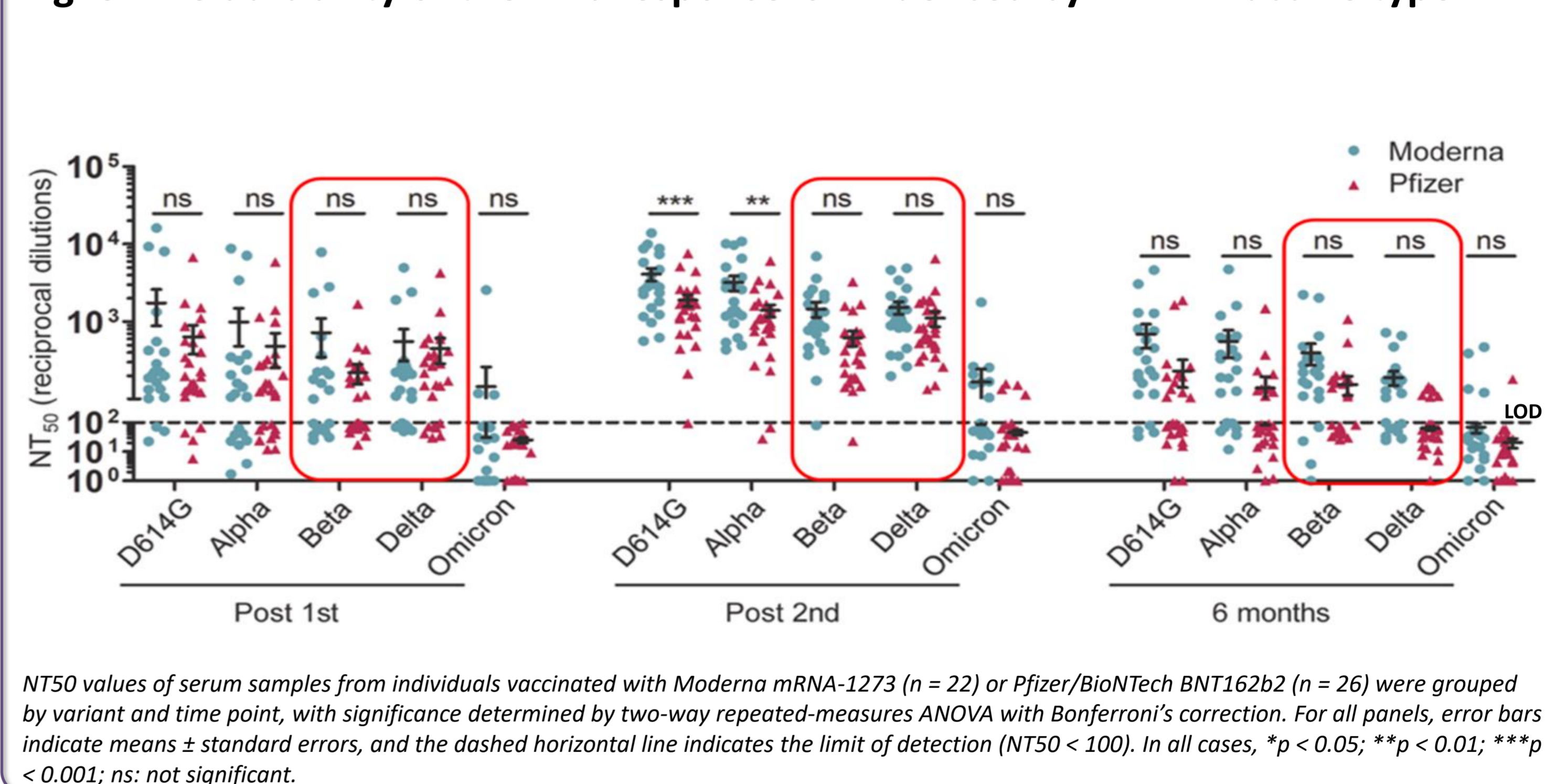
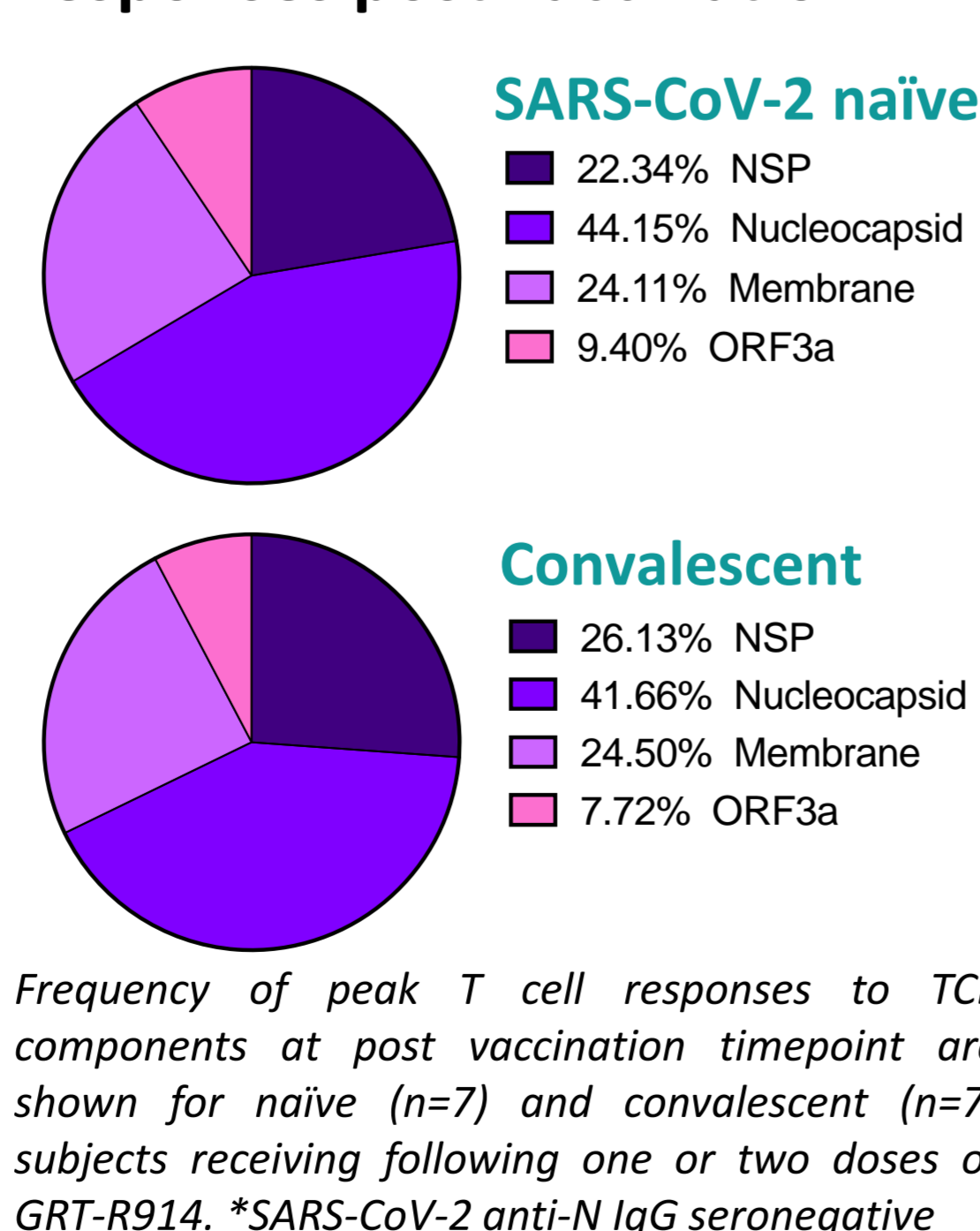


Fig. 7. Previous SARS-CoV-2 exposure dose not affect T cell responses post vaccination



Conclusions:

1. NCT05435027 is the first study assessing a samRNA-based vaccine in anti-N IgG seronegative at baseline and convalescent population in the South Africa
2. All doses of GRT-R914 (3µg, 10µg, and 30µg) were well tolerated in HIV negative, SARS-CoV-2 anti-N IgG seronegative and seropositive participants
3. GRT-R914 increased IgG titres against WT virus 27-fold and 3.5-fold at the 10µg dose in both anti-N IgG seronegative and seropositive cohorts, respectively
4. GRT-R914 (10µg) increased nAb titres against Beta and Delta VOC 8 to 10-fold in anti-N IgG seronegative, and 2 to 4-fold in anti-N IgG seropositive cohorts, respectively
5. IgG and nAb levels to Spike WT and VOC Beta and Delta boosted by GRT-R914 administration (10µg dose) did not significantly decrease for 6 months
6. Preliminary data in 30µg cohorts confirms longevity of IgG and nAb responses did not significantly decrease over a period of 6 months post vaccination, and complete datasets will be shown by Q4 2023.
7. Majority of post-vaccine T cell responses observed to TCE epitopes focused on NSP and Nucleocapsid, irrespective of prior SARS-CoV-2 exposure

The durability of antibodies induced by GRT-R914 (Fig.6) seems to be more sustained than the results reported by Evans et al¹. for mRNA vaccines (Fig.8). These vaccines were not studied head-to-head directly. There are limitations in this comparison, such as: a) study populations may not be entirely comparable; b) experience with circulating SARS-CoV-2 may be different; c) assays may not be entirely comparable; d) baseline values may be very different across studies

These results are consistent with our observations with a similar samRNA candidate tested as a boost in an older population in the UK (Abstract number: 03157/Poster number: EW0401 / E0797 ePoster)

Reference: ¹ Evans et al. *Sci Transl Med.* 2022
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