SELF-AMPLIFYING mRNA SARS-COV-2 VACCINES ELICIT ROBUST, CROSS-REACTIVE AND DURABLE NEUTRALIZING BOOSTER RESPONSES IN PREVIOUSLY mRNA VACCINATED ADULTS

JENNY GUEK-HONG LOW[1], SIMONE RICHARDSON[2,3], PENNY L MOORE[2,3], TERRI HOPKINS[4], IGOR SMOLENOV[4], PAD CHIVUKULA[4], BENJAMIN N GREENER[4]

[1]SINGHEALTH INVESTIGATIONAL MEDICINE UNIT & SINGAPORE GENERAL HOSPITAL, DEPARTMENT OF INFECTIOUS DISEASES, OUTRAM ROAD, CENTRAL, SG; [2]SA MRC ANTIBODY IMMUNITY RESEARCH UNIT, SCHOOL OF PATHOLOGY, UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG, GAUTENG, ZA; [3]NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES OF THE NATIONAL HEALTH LABORATORY SERVICES, JOHANNESBURG, GAUTENG, ZA; [4]ARCTURUS THERAPEUTICS, SAN DIEGO, CA, USA

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BACKGROUND

- Approved mRNA COVID-19 vaccines demonstrate lower immunogenicity against emergent SARS-CoV-2 variants and relatively rapid waning of antibodies.[1,2]
- We evaluated the immunogenicity and safety of three self-amplifying RNA (sa-mRNA) COVID-19 vaccines developed by Arcturus Therapeutics Inc (NCT05012943).
- The three vaccines are formulated with a proprietary lipid nanoparticle (LNP) technology (LUNAR®) and sa-mRNA encoding for replicase protein and a transgene region that encodes for the SARS-CoV-2 full length S glycoprotein.
- ARCT-021, ARCT-154, and ARCT-165 vaccines encode the SARS-CoV-2 full-length S glycoprotein of, respectively, the ancestral strain in native conformation, prefusion-stabilized B.1 variant including the D614G mutation, and prefusion-stabilized Beta variant.

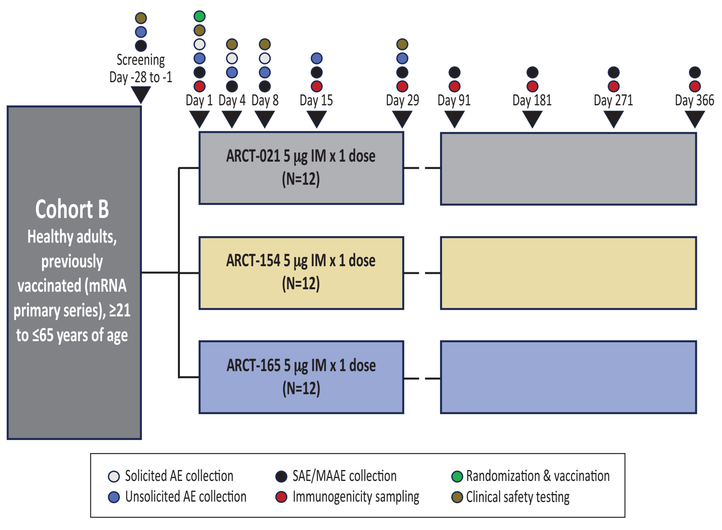
STUDY OBJECTIVES

- To describe the safety and reactogenicity of three investigational SARS-CoV-2 sa-mRNA vaccines.
- To describe the immunogenicity of three investigational SARS-CoV-2 sa-mRNA vaccines through neutralizing antibodies against the ancestral strain with D614G mutation and other SARS-CoV-2 variants including Beta (B.1.351), Delta (B.1.617.2), and Omicron (BA.1, BA.2, and BA.4/5).

METHODS

- In this phase 1/2 randomized, observer-blind study in the US and Singapore, we recruited 36 adults previously immunized with approved COVID-19 mRNA vaccines as a primary series at least 5 months prior to enrollment.
- Participants were healthy adults, ≥21 to ≤65 years of age, without known history of SARS-CoV-2 infection.
- Participants were randomized 1:1:1 to receive one booster dose on Day 1 of either ARCT-021, ARCT-154, or ARCT-165 vaccine. **Figure 1**.

FIGURE 1. Study Schematic.



- Immunogenicity was assessed as neutralizing antibody titers against SARS-CoV-2 D614G strain and a panel of SARS-CoV-2 variants measured by pseudoviral microneutralization assay on Days 1, 15, 29, 91, 181, 271, and 366.
- Participants who received any other COVID-19 vaccines or had laboratory-confirmed SARS-CoV-2 infection during the follow-up period were excluded from immunogenicity analysis at subsequent timepoints.
- Solicited adverse events (AE) were assessed up to 7 days, unsolicited AEs up to 28 days, and serious AEs up to 366 days after vaccination.

RESULTS

- Demographics were well balanced across groups. **Table 1**.

TABLE 1. Demographics.

	ARCT-165 (N=12)	ARCT-154 (N=12)	ARCT-021 (N=12)	Total (N=36)
Age Years				
n	12	12	12	12
Mean (SD)	50 (13)	44 (13)	44 (16)	46 (14)
Median (Range)	54 (25-64)	45 (22-60)	43 (24-65)	46 (22-65)
Gender				
Male	6 (50%)	5 (42%)	3 (25%)	14 (39%)
Female	6 (50%)	7 (58%)	9 (25%)	22 (61%)
Ethnicity				
Hispanic or Latino	0	0	2 (17%)	2 (6%)
Not Hispanic or Latino	12 (100%)	12 (100%)	10 (83%)	30 (94%)
Race				
Asian	2 (17%)	2 (17%)	2 (17%)	6 (17%)
Black or African American	2 (17%)	0	1 (8%)	3 (8%)
White	8 (67%)	10 (83%)	9 (75%)	27 (75%)
Other	0	0	0	0
BMI (kg/m²)				
n	12	12	12	12
Mean (SD)	27 (4)	27 (4)	26 (4)	27 (4)
Median (Range)	28 (20-34)	27 (23-35)	27 (19-33)	27 (19-35)

- All three vaccines were well tolerated. Most solicited AEs were mild or moderate and resolved within 72 hours, and rates of related or severe AEs were low. **Figure 2**, **Table 2**. One unrelated SAE was reported in the group receiving ARCT-021.

FIGURE 2. Percentage of participants reporting solicited adverse events up to 7 days following administration of ARCT-165, ARCT-154, and ARCT-021. At each level of summarization, participants reporting more than one adverse event are counted only once using the highest toxicity grade.

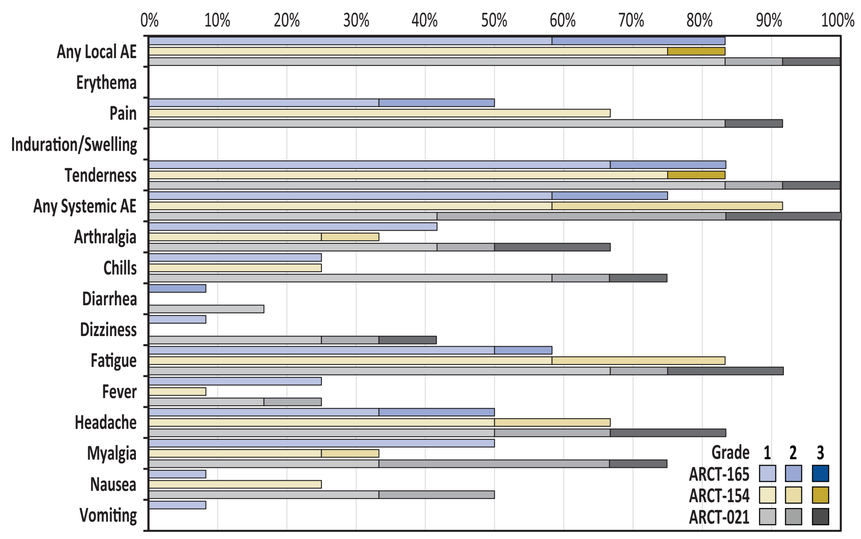


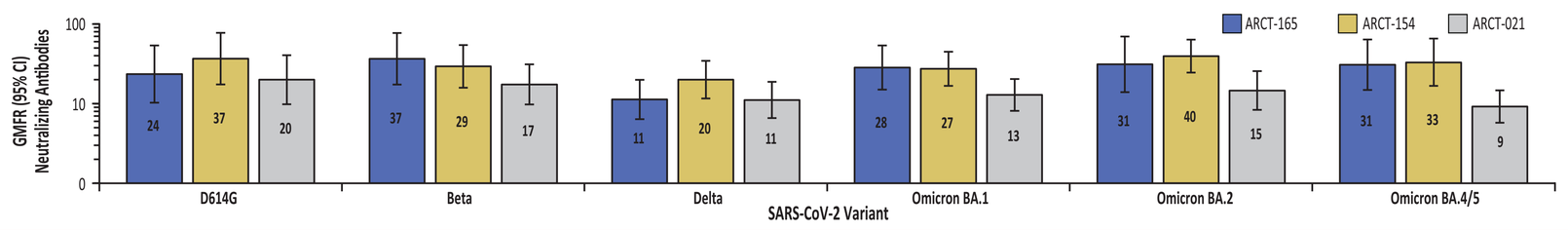
TABLE 2. Summary of Unsolicited Adverse Events.

	ARCT-165 (N=12)	ARCT-154 (N=12)	ARCT-021 (N=12)	Total (N=36)
Participants (%) reporting at least one:				
AE	9 (75%)	10 (83%)	9 (75%)	28 (78%)
Mild	9 (75%)	5 (42%)	5 (42%)	19 (53%)
Moderate	0	4 (33%)	2 (17%)	6 (17%)
Severe	0	1 (8%)	2 (17%)	3 (8%)
Related	2 (17%)	2 (17%)	3 (25%)	7 (19%)
Not Related	7 (58%)	8 (67%)	6 (50%)	21 (58%)
MAAE	1 (8.3%)	0	2 (17%)	3 (8%)
SAE	0	0	1 (8.3%)	1 (2.8%)
Related	0	0	0	0
Not Related	0	0	1 (8.3%)	1 (2.8%)

AE = Adverse Event; MAAE = Medically Attended Adverse Event; SAE = Serious Adverse Event

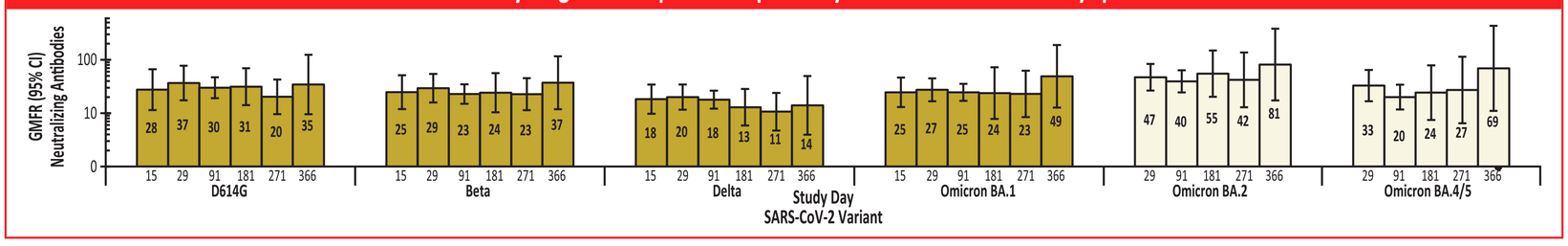
- All three vaccines induced robust neutralizing immune response against ancestral strain with D614G mutation at Day 29 with geometric mean fold rises (GMFR) from pre-booster levels of 20.0, 36.7 and 23.5 after ARCT-021, ARCT-154, and ARCT-165, respectively. **Figure 3**.

FIGURE 3. Geometric mean fold rise of neutralizing antibodies against SARS-CoV-2 variants (versus pre-booster levels) after ARCT-165, ARCT-154, and ARCT-021 booster vaccination at Day 29 measured by pseudoviral microneutralization assay (N=12). Error bars represent the 95% CI. GMFR values are included in black.



- ARCT-154, a leading candidate, induced a broad, cross-neutralizing immune response, which persisted up to 1-year post-booster in absence of other COVID-19 vaccination and diagnosed SARS-CoV-2 infection. **Figure 4**.

FIGURE 4. Geometric mean fold rise of neutralizing antibodies against SARS-CoV-2 variants (versus pre-booster levels) after ARCT-154 booster vaccination measured by pseudoviral microneutralization assay (N=12). Error bars represent the 95% CI. GMFR values are included in black. Dark bars represent validated microneutralization assays. Light bars represent exploratory microneutralization assays performed at NCID.



- Similar trends were observed for other SARS-CoV-2 variants including Beta, Delta, Omicron BA.1, Omicron BA.2, and Omicron BA.4/5.
- Additional testing confirmed cross-neutralization against emergent BQ.1.1 and XBB.1.5 Omicron sub-lineages with GMFRs of 12.8 and 3.4, respectively, at Day 29 post-booster.

CONCLUSIONS

- This study provides evidence that a booster dose of sa-mRNA vaccine induces a robust, broadly cross-reactive, and durable neutralizing immune response, that persists through 12 months post-vaccination.
- Favorable safety and reactogenicity was observed for all three sa-mRNA vaccines.

REFERENCES

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