ARCTURUS® therapeutics

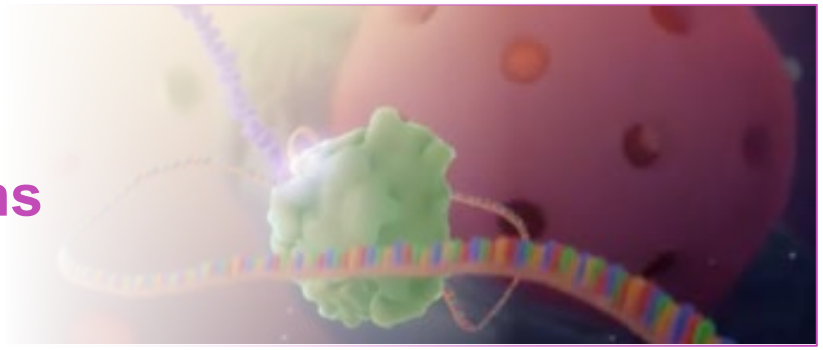
Self-amplifying RNA platform: Growing evidence from pivotal clinical studies

Igor Smolenov

Berlin, 01 November 2023

Arcturus Therapeutics and ARCT-154

Platforms



- **LUNAR** - a lipid-mediated multi-component nucleic acid delivery system with our library of over 250 proprietary lipids
- **The STARR™** Technology platform combines self-replicating RNA with LUNAR® into a single solution to produce proteins inside the human body.

mRNA Development Candidates

LUNAR-COV19	COVID-19 Vaccine (Primary and Booster)
LUNAR-OTC	Ornithine Transcarbamylase Deficiency
LUNAR-CF	Cystic Fibrosis
LUNAR-FLU	Influenza

Additional Earlier Stage Programs

Building Strategic Partnerships: Johnson & Johnson, VINBIOCARE, Takeda, ultragenyx pharmaceutical, CYSTIC FIBROSIS FOUNDATION, DukeNUS Medical School, Catalent, Recipharm

…AND MORE

Arcturus COVID-19 Self-amplifying RNA vaccines

Vaccine candidate	SARS-CoV-2 variant	# of subjects exposed
ARCT-021	Ancestral SARS-CoV-2 strain (native)	~700 (completed)
ARCT-154	Ancestral strain with D614G, double proline substitutions, and furin cleavage site modification (optimized)	~17,300 (completed)
ARCT-165	Beta variant	~65 (completed)
ARCT-2301	Bivalent (ancestral strain with D614G and Omicron BA.4/5)	~425 (ongoing)
ARCT-2303	XBB.1.5	~1680 (planned)

Overall, more than 18,000 adult subjects received at least one dose of sa-RNA COVID-19 vaccines as a primary vaccination series or booster dose

- *Self-amplifying* RNA vaccine: **5** micrograms/dose for administration

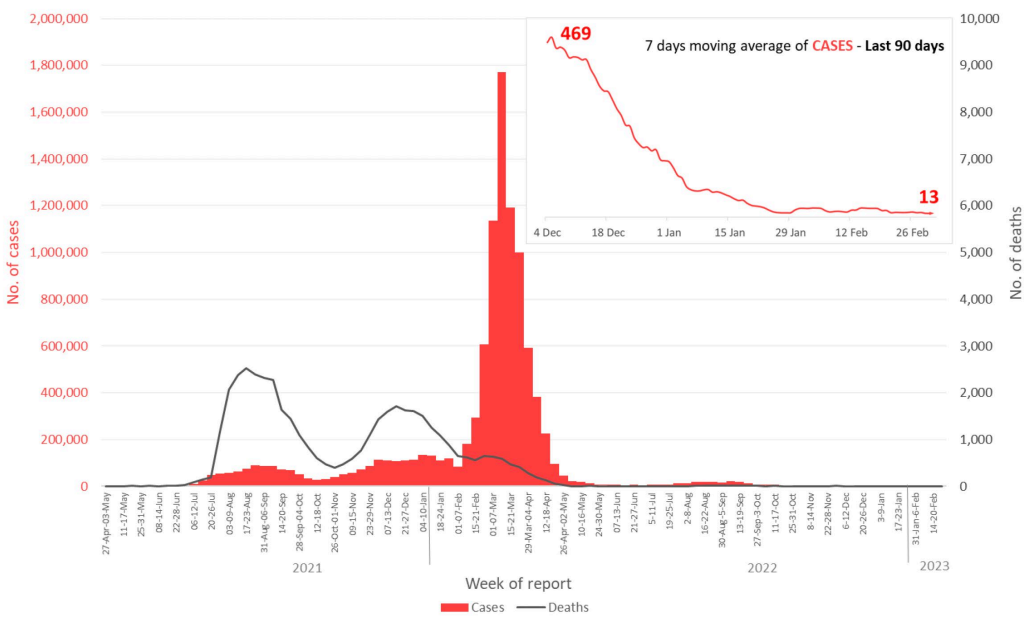
ARCT-154-01: Study Design

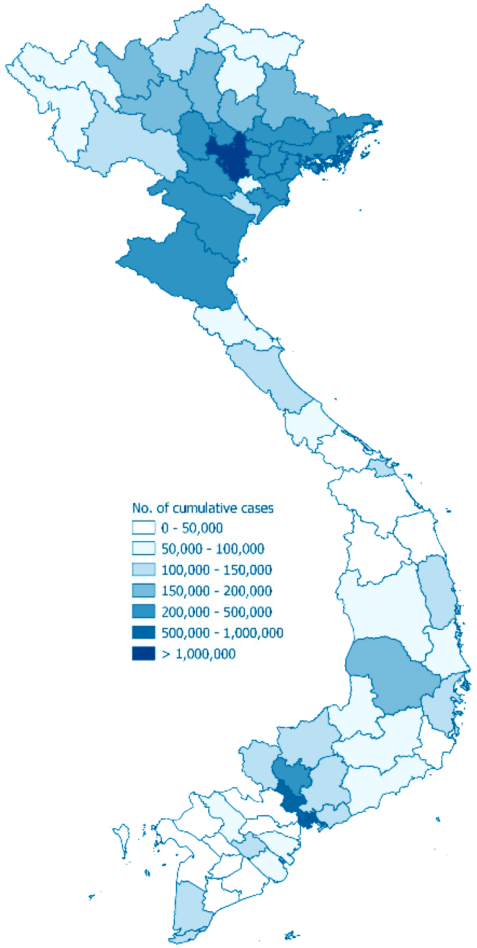
PHASE 1	PHASE 2	PHASE 3a	PHASE 3b	PHASE 3c
• Randomized (3:1) • Placebo-controlled • Healthy volunteers ≥18 to <60 y.o.	• Randomized (3:1) • Placebo-controlled • Healthy and "at risk" volunteers ≥18 y.o.	• Randomized (3:1) • Placebo-controlled • Healthy and "at risk" volunteers ≥18 y.o	• Randomized (1:1) • Placebo-controlled • Healthy and "at risk" volunteers ≥18 y.o	• Randomized (1:1) • Active-controlled (ChAdOx-1) • Healthy and "at risk" volunteers ≥18 y.o.
VACCINE ADMINISTRATIONS 2 doses (Day 1, 29) CROSSOVER 2 doses (Day 92, 120)	**VACCINE ADMINISTRATIONS** 2 doses (Day 1, 29) CROSSOVER 2 doses (Day 92, 120) OR 3 doses (Day 1, 29, 92) CROSSOVER 1 dose (Day 120)	**VACCINE ADMINISTRATIONS** 2 doses (Day 1, 29) CROSSOVER 2 doses (Day 92, 120) OR 3 doses (Day 1, 29, 92) CROSSOVER 1 dose (Day 120)	**VACCINE ADMINISTRATIONS** 2 doses (Day 1, 29) CROSSOVER 2 doses (Day 92, 120)	**VACCINE ADMINISTRATIONS** 2 doses (Day 1, 29) NO CROSSOVER
PRIMARY OBJECTIVES **Pooled Phase 1/2/3a** Safety and Immunogenicity			**PRIMARY OBJECTIVES** **Phase 3b** Safety and Efficacy	**PRIMARY OBJECTIVES** **Phase 3c** Safety and Immunogenicity
PRIMARY OBJECTIVES **Pooled Phase 1/2/3a/3b** Safety and Efficacy				**ALL PARTICIPANTS FOLLOWED THROUGH DAY 394**

ARCT-154-01 Enables Arcturus to Evaluate Efficacy Against Delta variant in a Randomized Clinical Trial

- **Study start: 15 Aug 2021**
- **Cut-off date for efficacy analysis: 12 Jan 2022**
- **14 sites in Vietnam**
- **More than 19,400 adult participants**

- Most participants (98%) were naive to SARS-CoV-2 at the time of the recruitment
- The study was conducted during the dominant circulation of the Delta variant (88% of all sequenced strains)
- The National COVID-19 immunization campaign was rolling during the study conduct, as such, a switchover vaccination on Day 92 was implemented





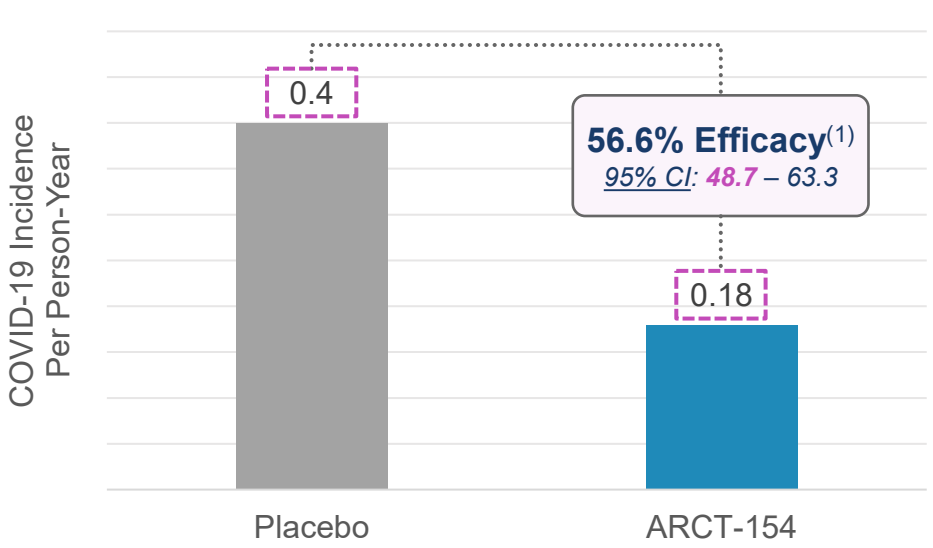
[1] Viet Nam Coronavirus Disease 2019 (COVID-19) Situation Report #107 28 February 2023. Report on 3 March 2023
https://www.who.int/docs/default-source/wpro---documents/countries/viet-nam/covid-19/viet-nam-moh-who-covid-19-sitrep--107_28feb2023.pdf?sfvrsn=9e29ab75_1&download=true

ARCT-154: Primary and Key Secondary Endpoints are met

- **Primary Endpoint is met:** VE against COVID-19 of any severity is 56.6% (LL of 95% CI >30%)
- **Key Secondary Endpoint is met:** VE against severe COVID-19 is 93.3% (LL of 95% CI >0%)

COVID-19 of Any Severity

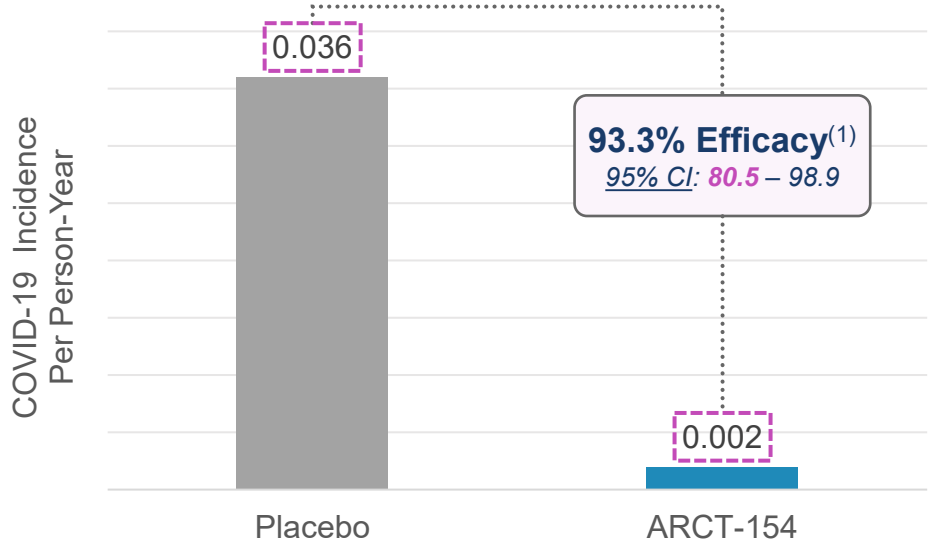
Any Strain



	Placebo	ARCT-154
# at risk	7283	7587
# of cases	440	200

Severe COVID-19

Any Strain



	Placebo	ARCT-154
# at risk	7682	7585
# of cases	41	2

Notes: Figures show data for virologically-confirmed COVID-19 from 7 days after the second dose up to Day 92.

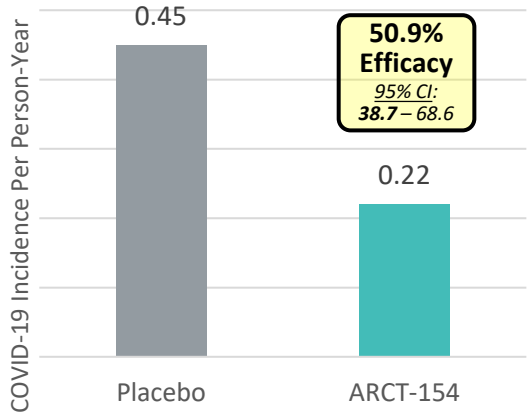
1. Predefined success criteria for primary endpoint: Lower Limit of 95% confidence interval exceeds 30%.
2. Predefined success criteria for key secondary endpoint: Lower Limit of 96% confidence interval exceeds 0%.

Tạ Thành Văn et al, 2023 https://doi.org/10.21203/rs.3.rs-3329097/v1

ARCT-154-01: Consistent Efficacy in High-Risk Populations

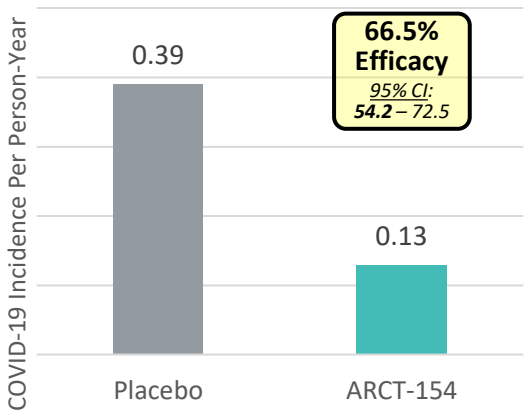
Vaccine Efficacy against Any COVID-19

Healthy 18-59 years



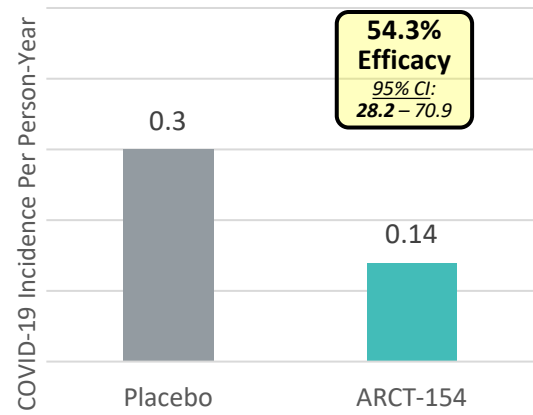
	Placebo	ARCT-154
# at risk	3701	3704
# of cases	235	119

At Risk 18-59 years



	Placebo	ARCT-154
# at risk	2690	2719
# of cases	148	53

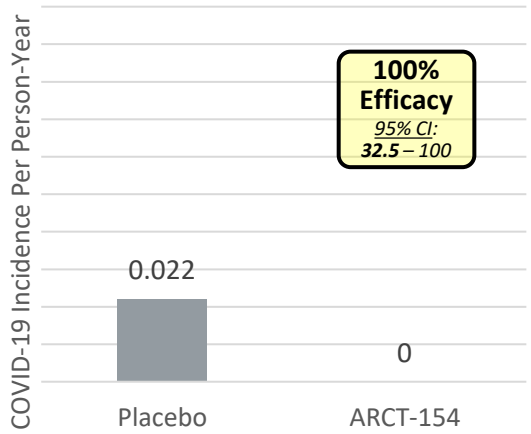
≥60 years



	Placebo	ARCT-154
# at risk	1322	1364
# of cases	57	28

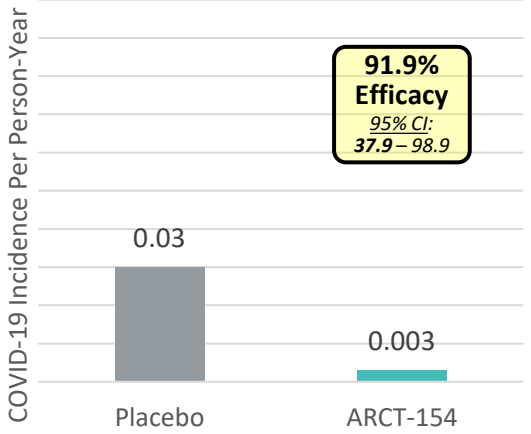
Vaccine Efficacy against Severe COVID-19

Healthy 18-59 years



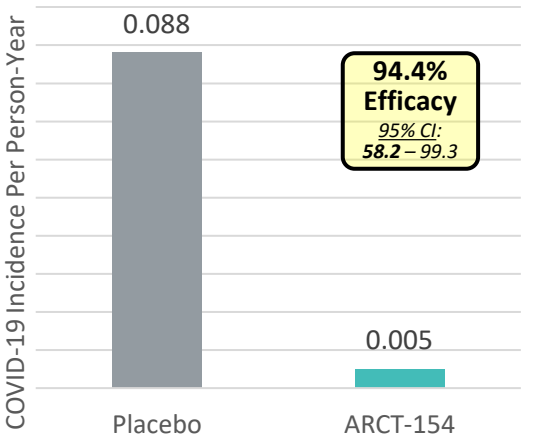
	Placebo	ARCT-154
# at risk	3701	3704
# of cases	12	0

At Risk 18-59 years



	Placebo	ARCT-154
# at risk	2690	2719
# of cases	12	1

≥60 years



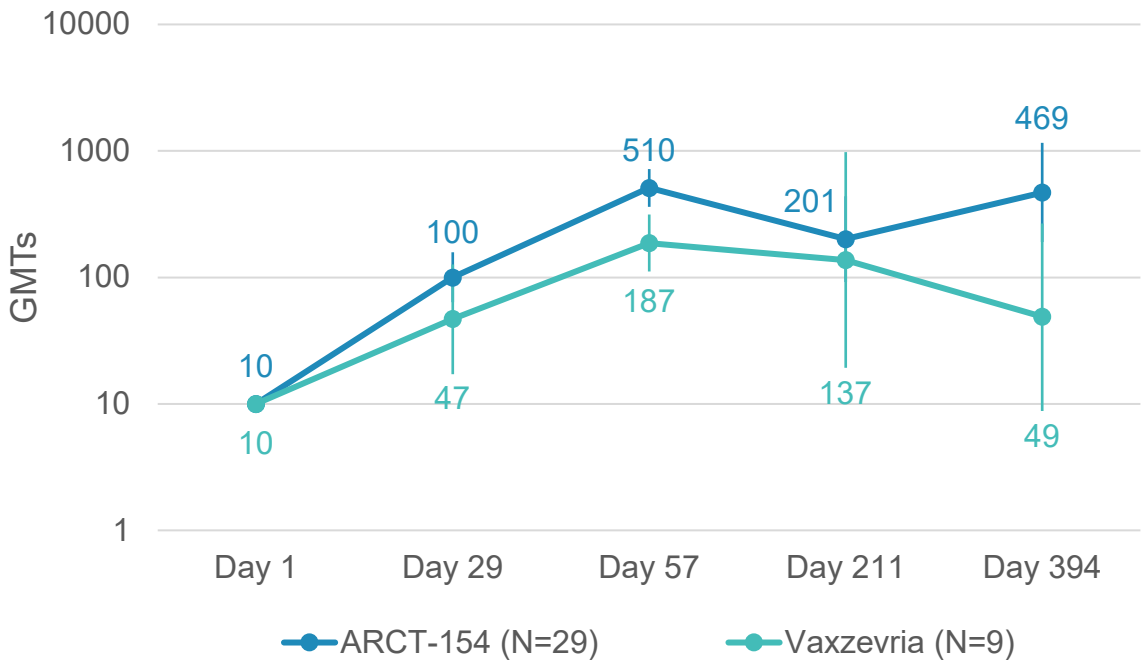
	Placebo	ARCT-154
# at risk	1322	1364
# of cases	17	1

Tạ Thành Văn et al, 2023
https://doi.org/10.21203/rs.3.rs-3329097/v1

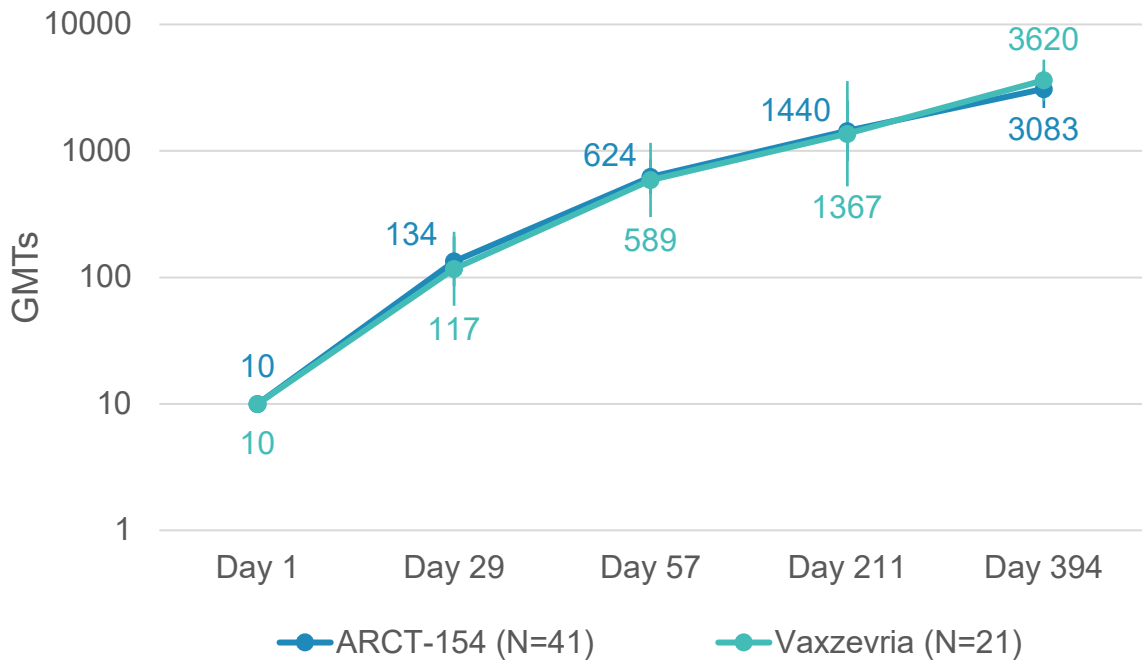
ARCT-154: Favorable 12-month antibody persistence profile vs. Vaxzevria

- The primary vaccination series of ARCT-154 appears to induce a higher and more rapid immune response than Vaxzevria in SARS-CoV-2 naïve individuals
- In subjects with evidence of asymptomatic infection within 12 months post-vaccination, a robust hybrid immune response was observed in both groups

Vaccine-induced immunity only (anti-N negative)



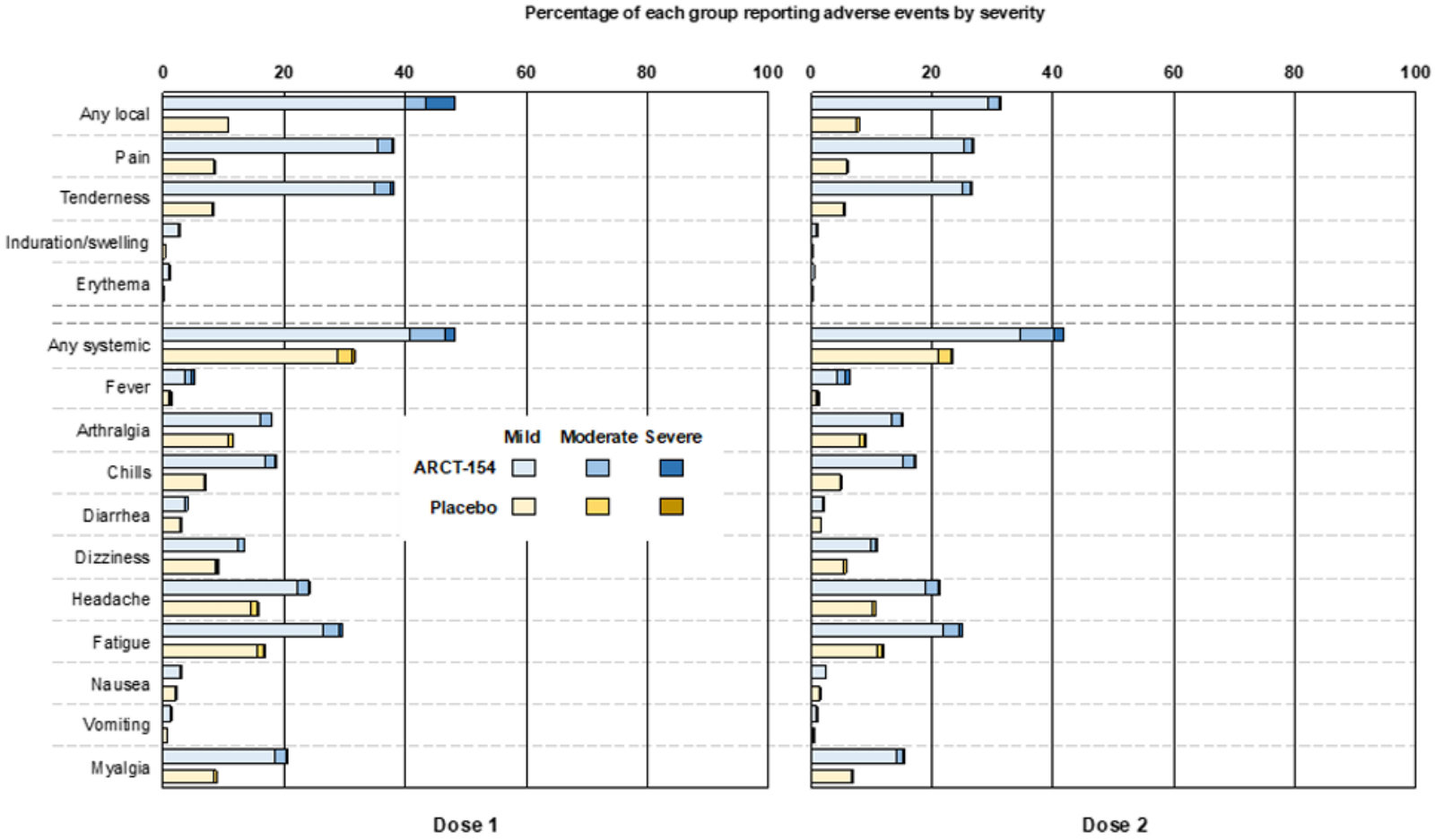
Hybrid immunity (vaccine + infection; anti-N positive)



ARCT-154-01 study; post-hoc analysis, preliminary results

ARCT-154: Reactogenicity profile

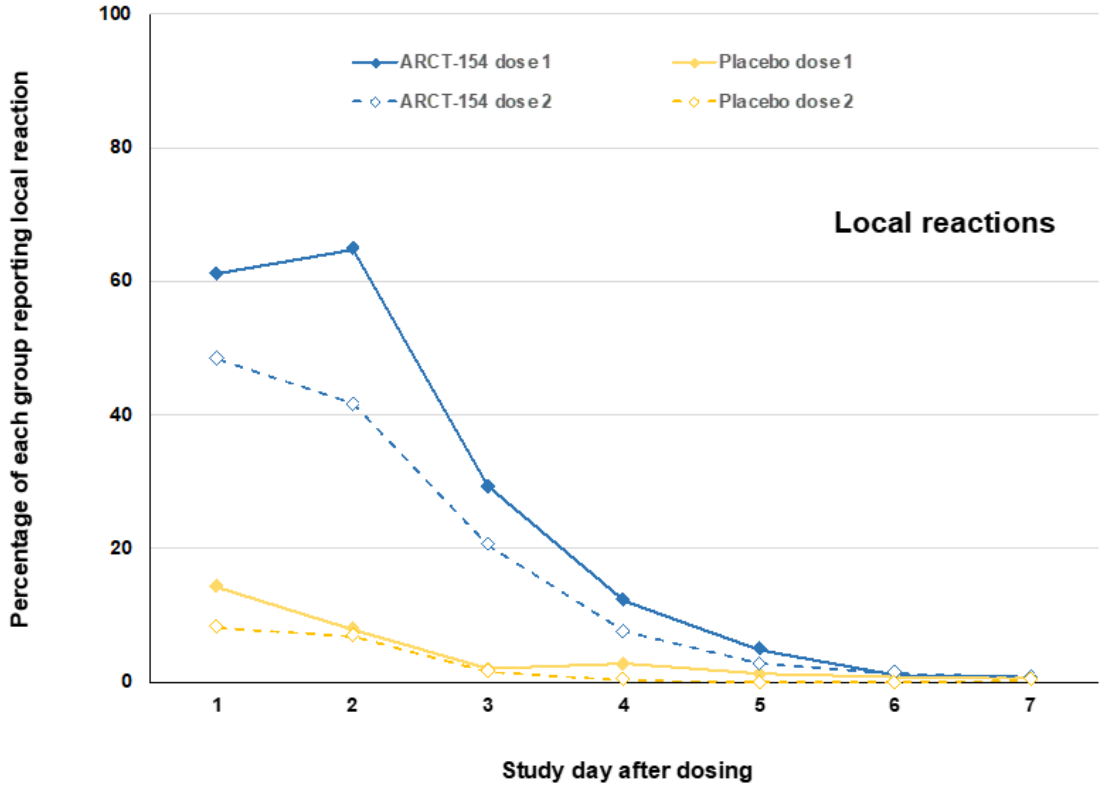
- ✓ Local and systemic solicited AEs: Mostly mild and transient
- ✓ A trend to lower reactogenicity after the second and third (data not shown) vaccination
- ✓ A lower frequency of solicited AEs in older adults
- ✓ Comparable safety profile in subjects with and without comorbidities, across genders and races

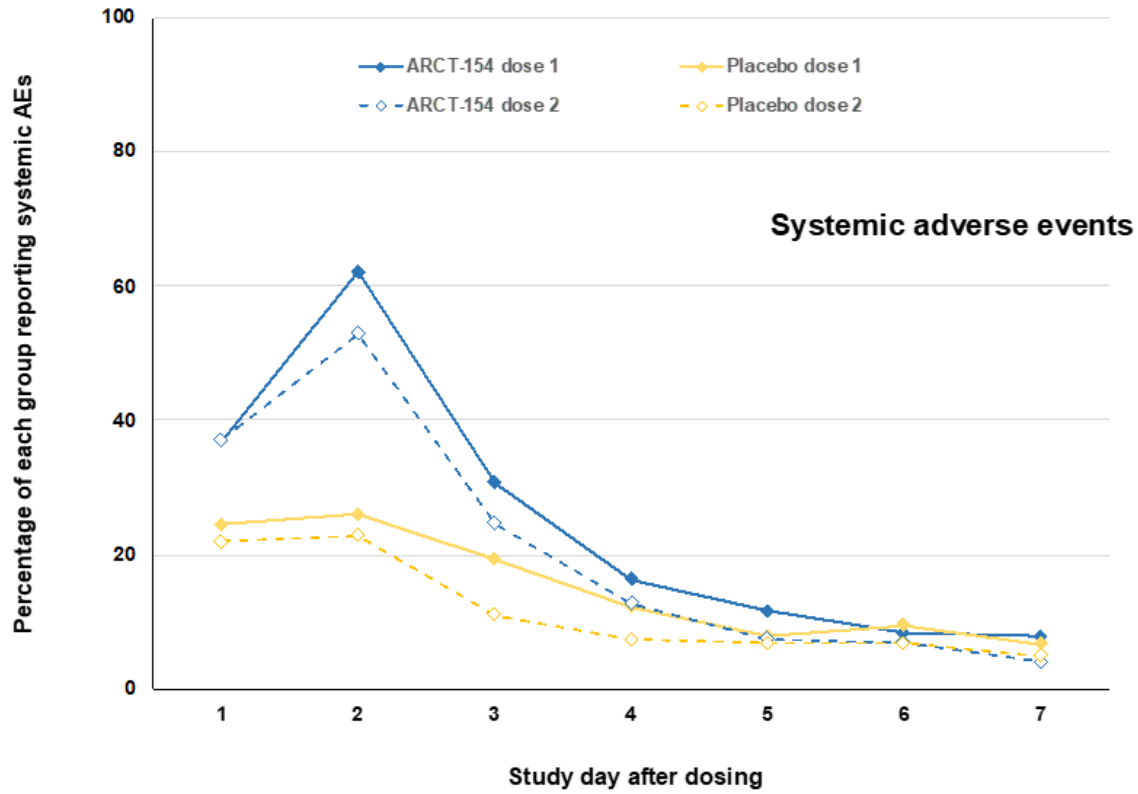


Tạ Thành Văn et al, 2023
https://doi.org/10.21203/rs.3.rs-3329097/v1

Duration of solicited AE after each vaccination

- ✓ Solicited AEs reported mainly on Days 1 and 2 post-vaccination
- ✓ The mean duration of post-vaccination reactions was 2 days
- ✓ The intensity of reactions appeared to reduce after the second dose
- ✓ Post-vaccination reactions resolved within a 7-day follow-up period





*Days post-vaccination on which local reactions and systemic adverse events were reported

Tạ Thành Văn et al, 2023
https://doi.org/10.21203/rs.3.rs-3329097/v1

ARCT-154: Favorable Safety Profile Up to 6 months after Primary Vaccination

N = first dose / second dose		Phases 1, 2 and 3a ARCT-154 (N = 748 / 732)	Phases 1, 2 and 3a Placebo (N = 253 / 245)	Phase 3b ARCT-154 (N = 8059 / 7867)	Phase 3b Placebo (N = 8041 / 7822)
Any adverse event within 28 days [a]	Dose 1	177 (23·7)	71 (28·1)	1125 (14·0)	1101 (13·7)
	Dose 2	124 (16·9)	45 (18·4)	1096 (13·9)	1241 (15·9)
Related adverse event within 28 days, n (%)	Dose 1	27 (3·6)	11 (4·3)	202 (2·5)	184 (2·3)
	Dose 2	19 (2·6)	5 (2·0)	130 (1·7)	107 (1·4)
Severe adverse event within 28 days, n (%)	Dose 1	1 (0·1)	0	38 (0·5)	48 (0·6)
	Dose 2	3 (0·4)	5 (2·0)	13 (0·2)	13 (0·2)
Serious adverse event (SAE) to Day 210 [b]	n (%)	14 (1·9)	16 (6·3)	118 (1·5)	201 (2·5)
Related serious adverse event		0	2 (0·8)	10 (0·1)	5 (0·1)
SAE leading to discontinuation		0	2 (0·8)	8 (0·1)	15 (0·2)
Medically-attended adverse event to Day 210 [b]	n (%)	14 (1·9)	16 (6·3)	118 (1·5)	201 (2·5)
Related Medically-attended adverse event		0	2 (0·8)	10 (0·1)	5 (0·1)
Death	n (%)	0	0	5 (0·1)	16 (0·2)

a: Adverse events reported within 28 days of each vaccination.

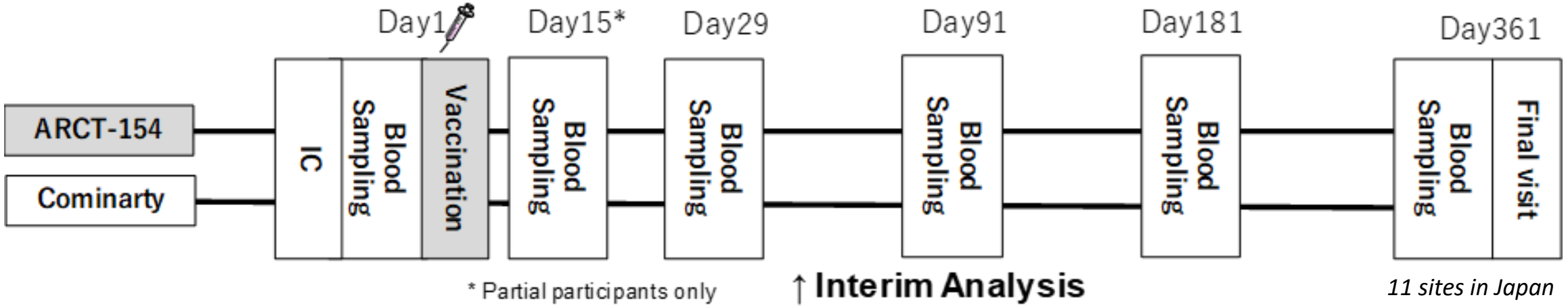
b: Serious and medically-attended adverse events recorded from Day 1 to Day 210 (data up to Day 92/switchover presented in this table).

- ✓ **Frequency and severity of any unsolicited AEs, related unsolicited AEs, and severe unsolicited AEs were similar among ARCT-154 and placebo recipients**
- ✓ **SAEs, MAAEs, and death cases were reported by ARCT-154 recipients at a lower frequency than by placebo recipients, possibly reflecting a lower frequency of AEs categorized under Preferred Terms related to COVID-19**

Tạ Thành Văn et al, 2023
https://doi.org/10.21203/rs.3.rs-3329097/v1

ARCT-154 as a Booster Dose in mRNA-primed population

ARCT-154-J01: A randomized, multicenter, phase 3, double-blind, controlled study of ARCT-154 vs. Comirnaty (Pfizer) in Japan



- **Primary Objective:**
  - **Non-inferiority of ARCT-154 vs. Comirnaty as measured by neutralizing antibodies against the Wuhan-Hu1 strain for:**
    - GMT ratio
    - Seroresponse (SRR) difference
- **Key Secondary Objective:**
  - **Non-inferiority/superiority of ARCT-154 vs. Comirnaty as measured by neutralizing antibodies against Omicron BA.4/5 subvariant for:**
    - **GMT ratio**
    - **SRR difference**
- **Secondary Safety Objectives:**
  - **Solicited AE (systemic & local), within 7 days after vaccination**
  - **Unsolicited AEs (up to D28)**
  - **SAEs, AEs of special interest, medically significant AEs**
  - **Symptoms potentially associated with myocarditis ('featured symptoms')**
  - **Laboratory abnormalities**

- **Immunogenicity and Efficacy** (Secondary/Exploratory)
  - **Neutralizing Antibodies** (other variants of concern)
  - **Persistence of neutralizing antibodies** (Days 29, 91, 181, and 361)
  - **Cell-Mediated Immunity** (ICS Flow)
  - **Efficacy** (reported RT-PCR+ cases)
- **Interim/final analysis**
  - **Day 29: Immunogenicity, reactogenicity, and safety**

Key Timelines:

✓ **Study Initiation:**	**13-Dec-2022**
✓ **Recruitment completed:**	**25-Feb-2023**
✓ **Day 29 Interim Report:**	**June 2023**
Submission to PMDA:	**30-Jun-2023**
3-months safety data:	**06-Sep-2023**
6-month safety data:	**04-Dec-2023**
Final CSR (12 months):	**June 2024**

https://medrxiv.org/cgi/content/short/2023.07.13.23292597v1; Yoshiaki Oda et al. Lancet Infectious Disease, 2023 (accepted)

ARCT-154-J01: Study population

Parameter		ARCT-154	Comirnaty	Total
		N = 417	N = 408	N = 825
Age, years	Mean (± SD)	**45·2** (12·0)	**46·2** (11·6)	**45·7** (11·8)
	[Range]	[18·0, 77·0]	[18·0, 76·0]	[18·0, 77·0]
< 65 years	n (%)	405 (97·1)	400 (98·0)	805 (97·6)
≥ 65 years	n (%)	12 (2·9)	8 (2·0)	20 (2·4)
Gender, n (%)	Female	246 (59·0)	239 (58·6)	485 (58·8)
	Male	171 (41·0)	169 (41·4)	340 (41·2)
Time since 3rd vaccination, n (%)	< 5 months	11 (2·6)	4(1·0)	15 (1·8)
	≥ 5 months	406 (97·4)	404 (99·0)	810 (98·2)
Participants requiring caution in vaccination, n (%)	Underlying disease	72 (17·3)	62 (15·2)	134 (16·2)
	Previous symptoms indicative of allergic reaction #	90 (21·6)	88 (21·6)	178 (21·6)
	History of convulsions	6 (1·4)	1 (0·2)	7 (0·8)
Neutralising antibodies at baseline				
Wuhan-Hu-1, n (%)	Seronegative	5 (1·2)	3 (0·7)	8 (1·0)
	Seropositive	412 (98·8)	405 (99·3)	817 (99·0)
Omicron BA.4/5, n (%)	Seronegative	84 (20·1)	87 (21·3)	171 (20·7)
	Seropositive	333 (79·9)	321 (78·7)	654 (79·3)
SARS-CoV-2 nucleocapsid antibody, n (%)	Seronegative	388 (93·0)	381 (93·4)	769 (93·2)
	Seropositive	29 (7·0)	27 (6·6)	56 (6·8)
Previous brands of vaccine received, n (%) *	C + C + C	329 (78·9)	329 (80·6)	658 (79·8)
	C + S + C	0 (0)	0 (0)	0 (0)
	S + C + C	1 (0·2)	0 (0)	1 (0·1)
	S + S + C	87 (20·9)	79 (19·4)	166 (20·1)

- ✓ In total, 828 subjects were recruited and received a booster dose
- ✓ Mean age was 45.7 years, range 18 to 77 years
- ✓ 97.6% of subjects <65 years of age
- ✓ 58.8% of female subjects
- ✓ Most subjects received three doses of Comirnaty (79.8%), or two doses of Spikevax and Comirnaty booster (20.1%)
- ✓ 98.2% received the last booster dose of Comirnaty ≥5 months before recruitment
- ✓ 99.0% subjects with pre-booster neutralizing Abs against Wuhan strain; 79.3% - against Omicron BA.4/5
- ✓ 6.8% of subjects with anti-nucleocapsid antibodies
- ✓ No differences between study groups in demographic and baseline characteristics

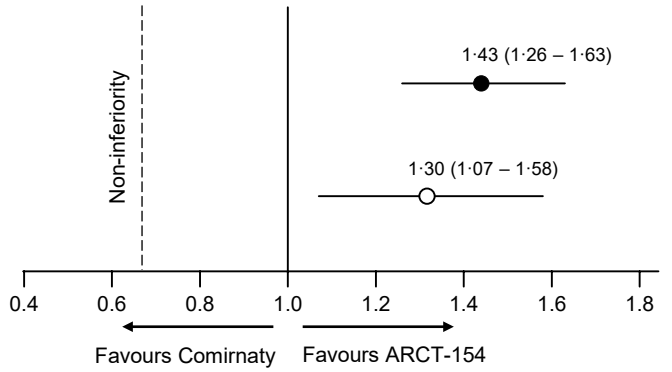
https://medrxiv.org/cgi/content/short/2023.07.13.23292597v1; Yoshiaki Oda et al. Lancet Infectious Disease, 2023 (accepted)

ARCT-154-J01: Immunological non-inferiority/superiority vs a non-replicating mRNA vaccine

A) GMT

	ARCT-154 (N = 385)	COMIRNATY (N = 374)
Wuhan		
GMT Day 1	813 (716 – 924)	866 (755 – 993)
GMT Day 29	5641 (4321 – 7363)	3934 (2993 – 5169)
GMFR Day 1 : Day 29	6·7 (6·0 – 7·5)	4·4 (4·0 – 4·8)
Omicron		
GMT Day 1	275 (227 – 335)	292 (236 – 360)
GMT Day 29	2551 (1687 – 3859)	1958 (1281 – 2993)
GMFR Day 1 : Day 29	8·0 (7·0 – 9·1)	5·7 (5·0 – 6·4)

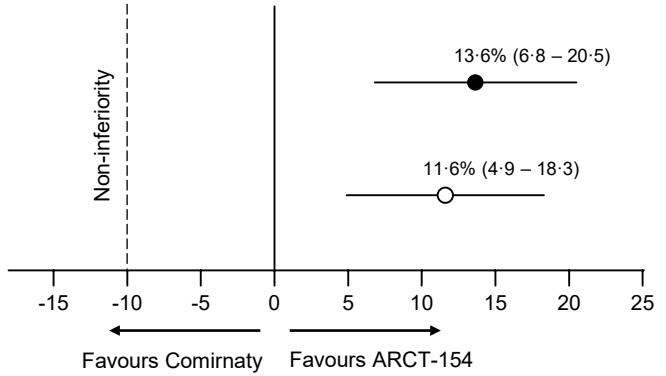
B) GMT RATIO



C) SRR

	ARCT-154	COMIRNATY
Wuhan		
SRR Day 29	65·2% (60·2 – 69·9)	51·6% (46·4 – 56·8)
Omicron		
SRR Day 29	69·9% (65·0 – 74·4)	58·0% (52·8 – 63·1)

D) SRR DIFFERENCE



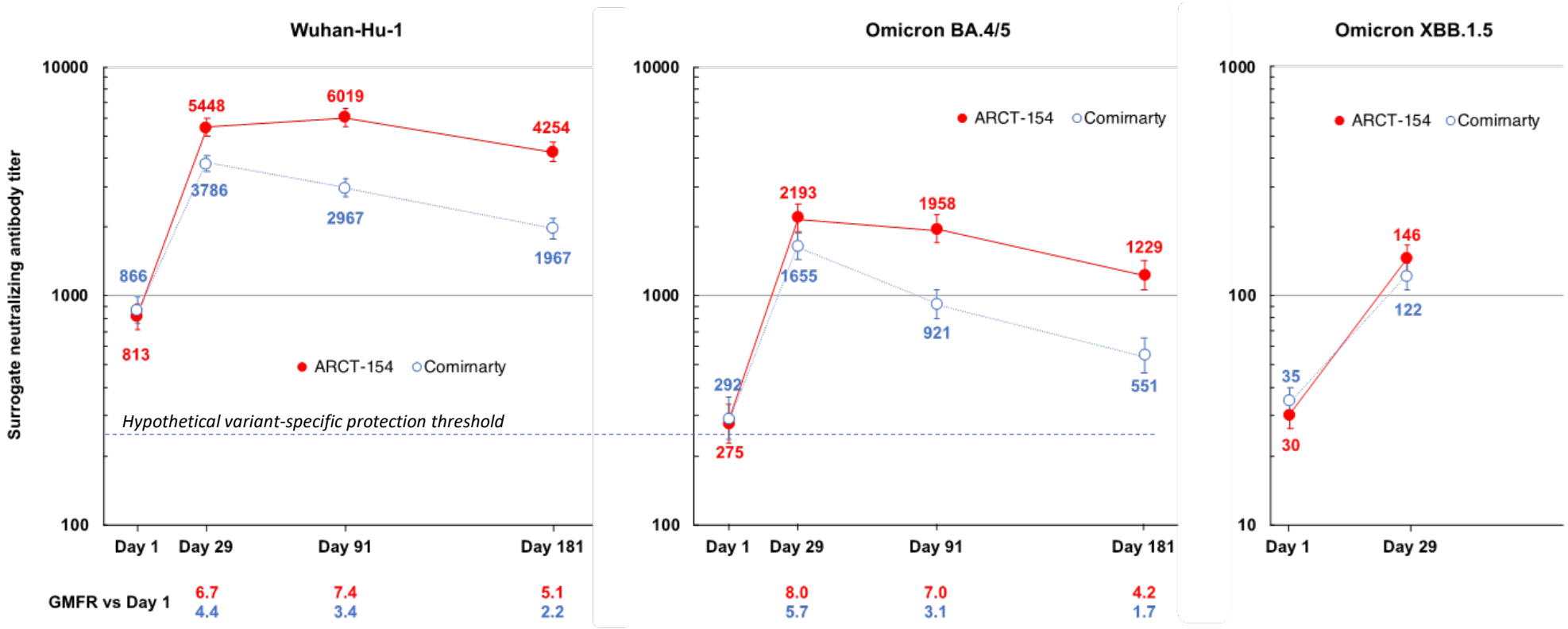
Abbreviations: GMT – geometric mean titer; SRR – seroresponse rate; GMFR – geometric mean fold raise; LL –lower limit; CI – confidence interval

- ✓ Primary study objective – non-inferiority of ARCT-154 vs. Comirnaty as measured by neutralizing Abs against Wuhan strain was demonstrated:
  - ✓ LL of 95% CI for GMT ratio (ARCT-154/Comirnaty) > 0.67
  - ✓ LL of 95% CI for SRR difference (ARCT-154 minus Comirnaty) > -10%
- ✓ Secondary study objective – superiority of ARCT-154 vs. Comirnaty as measured by neutralizing Abs against Omicron BA.4/5 was demonstrated:
  - ✓ LL of 95% CI for GMT ratio (ARCT-154/Comirnaty) > 1.0
  - ✓ LL of 95% CI for SRR difference (ARCT-154 minus Comirnaty) > 0%
- ✓ Post-hoc analysis demonstrated superiority of ARCT-154 vs. Comirnaty for Wuhan strain

https://medrxiv.org/cgi/content/short/2023.07.13.23292597v1;
Yoshiaki Oda et al. Lancet Infectious Disease, 2023 (accepted)

ARCT-154: More durable post-booster immune response

- ✓ Preliminary antibody persistence data at Day 180 post-vaccination indicate higher durability of immune response after ARCT-154 compared to conventional mRNA vaccines
- ✓ The observed antibody persistence trend is consistent with early results of the ARCT-165-01 study and recently published data for another sa-RNA vaccine [1]

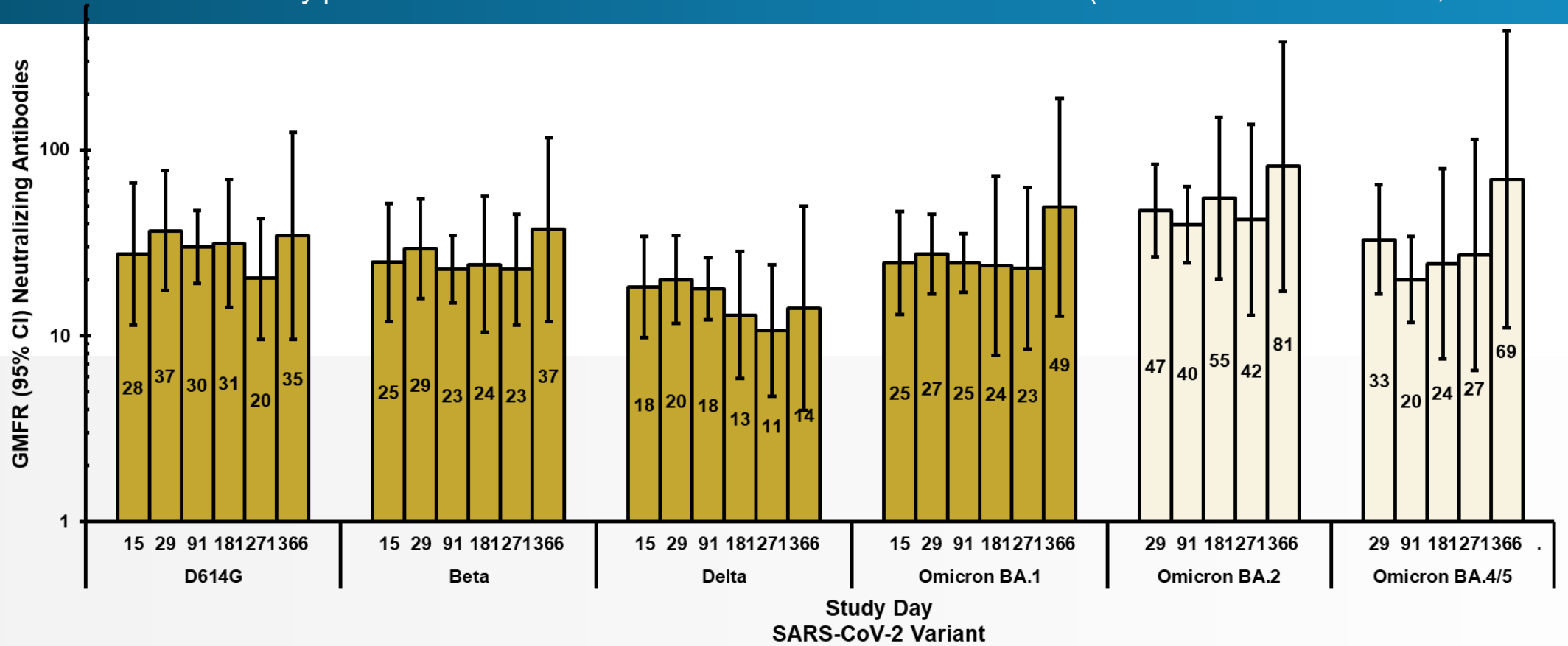


Preliminary data

[1] Palmer, C.D., Scallan, C.D., Kraemer Tardif, L.D. et al. GRT-R910: a self-amplifying mRNA SARS-CoV-2 vaccine boosts immunity for ≥6 months in previously-vaccinated older adults. Nat Commun 14, 3274 (2023). https://doi.org/10.1038/s41467-023-39053-9

ARCT-154 induces broad and long-lasting neutralizing antibodies against SARS-CoV-2

- A booster dose of ARCT-154 induces a durable neutralizing immune response that persists through 12 months post-vaccination.
- Similar trend for antibody persistence showed for other LUNAR-COVID-19 vaccines (ARCT-021 and ARCT-165, data not shown)



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 white. Dark bars represent validated microneutralization assays. Light bars represent exploratory microneutralization assays performed at NCID.

Guek-Hong Low et al. A self-amplifying mRNA SARs-CoV-2 vaccine (ARCT-154) elicits a broadly neutralizing and long-lasting booster response in previously vaccinated adults. ESWI, Barcelona, September 2023

nature communications

Article

https://doi.org/10.1038/s41467-023-39053-9

GRT-R910: a self-amplifying mRNA SARS-CoV-2 vaccine boosts immunity for ≥6 months in previously-vaccinated older adults

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Check for updates

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SARS-CoV-2 has resulted in high levels of morbidity and mortality world-wide, and severe complications can occur in older populations. Humoral immunity induced by authorized vaccines wanes within 6 months, and frequent boosts may only offer transient protection. GRT-R910 is an investigational self-amplifying mRNA (samRNA)-based SARS-CoV-2 vaccine delivering full-length Spike and selected conserved non-Spike T cell epitopes. This study reports interim analyses for a phase I open-label dose-escalation trial evaluating GRT-R910 in previously vaccinated healthy older adults (NCT05148962). Primary endpoints of safety and tolerability were assessed. Most solicited local and systemic adverse events (AEs) following GRT-R910 dosing were mild to moderate and transient, and no treatment-related serious AEs were observed. The secondary endpoint of immunogenicity was assessed via IgG binding assays, neutralization assays, interferon-gamma ELISpot, and intracellular cytokine staining. Neutralizing antibody titers against ancestral Spike and variants of concern were boosted or induced by GRT-R910 and, contrasting to authorized vaccines, persisted through at least 6 months after the booster dose. GRT-R910 increased and/or broadened functional Spike-specific T cell responses and primed functional T cell responses to conserved non-Spike epitopes. This study is limited due to small sample size, and additional data from ongoing studies will be required to corroborate these interim findings.

The COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has resulted in high levels of morbidity and mortality throughout the world, accounting for more than 600 million cases and 6.5 million deaths by October 2022[1]. While many of those infected only develop either mild respiratory symptoms or remain asymptomatic, severe complications such as pneumonia, acute respiratory distress syndrome, and death can occur, particularly in populations ≥60 years of age and those with certain co-morbidities[2]. Although the rollout of authorized vaccines has helped reduce the severity, morbidity, and mortality associated with COVID-19[3,4],

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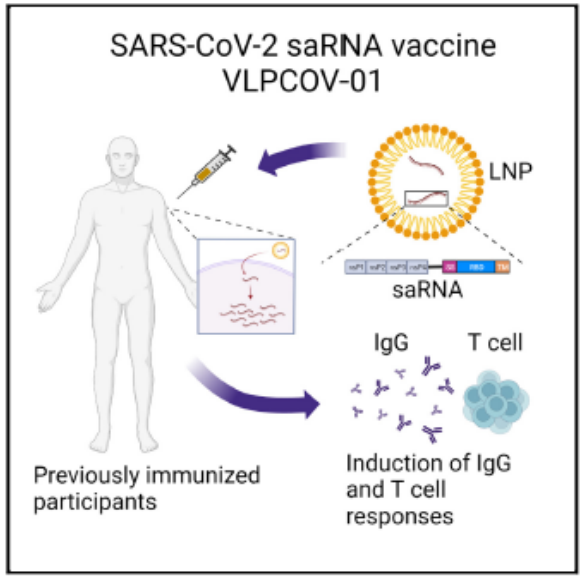
Cell Reports Medicine

Article

Safety and immunogenicity of SARS-CoV-2 self-amplifying RNA vaccine expressing an anchored RBD: A randomized, observer-blind phase 1 study

Graphical abstract



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In brief

Akahata et al. conduct a phase 1 study in which 96 healthy participants who completed two doses of the BNT162b2 mRNA vaccine are boosted with the SARS-CoV-2 saRNA vaccine VLPCOV-01 or BNT162b2. Equivalent or longer-duration antibody responses are observed with VLPCOV-01 at quantitatively lower RNA doses than BNT162b2.

Highlights

- Booster study of an saRNA SARS-CoV-2 vaccine expressing membrane-anchored RBD
- Robust IgG and T cell responses are induced
- Duration of immunity is equivalent to or longer than that of commercially available vaccines

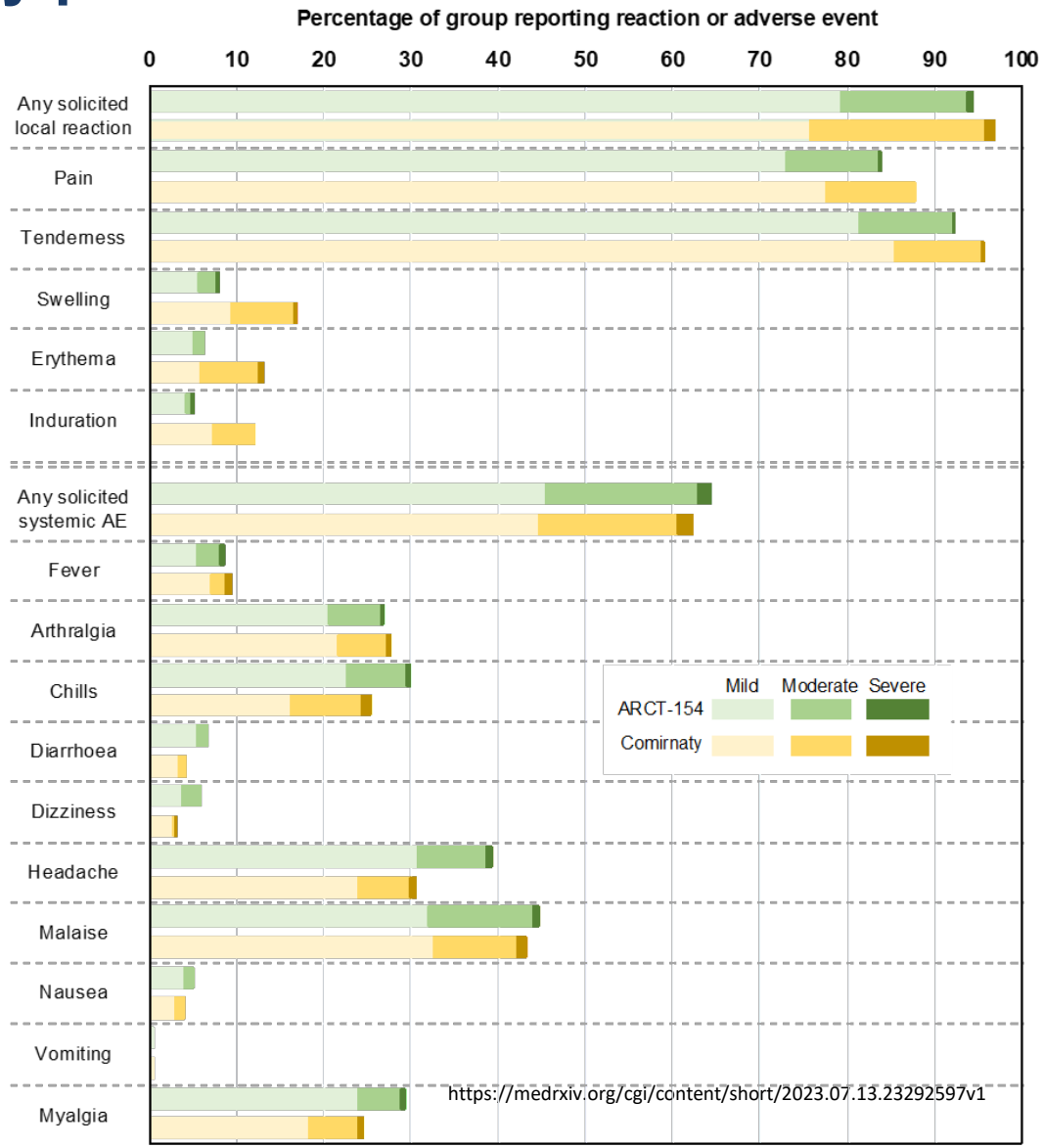
Akahata et al., 2023, Cell Reports Medicine 4, 101134
August 15, 2023
https://doi.org/10.1016/j.xcrm.2023.101134

CellPress

ARCT-154: Favorable tolerability and safety profile after booster dose

- ✓ Both vaccines were well tolerated as booster doses
- ✓ Solicited local and systemic AEs were described as mild or moderate in severity and transient. Swelling, erythema, and induration were reported more frequently after Comirnaty than ARCT-154
- ✓ No solicited AEs were associated with medically attended visits, and no Grade 4 solicited AEs were reported
- ✓ Frequency and severity of any unsolicited AEs, related unsolicited AEs, and severe unsolicited AEs were similar among ARCT-154 and Comirnaty recipients
- ✓ No AESI and medically significant AEs were reported in the study up to Day 90

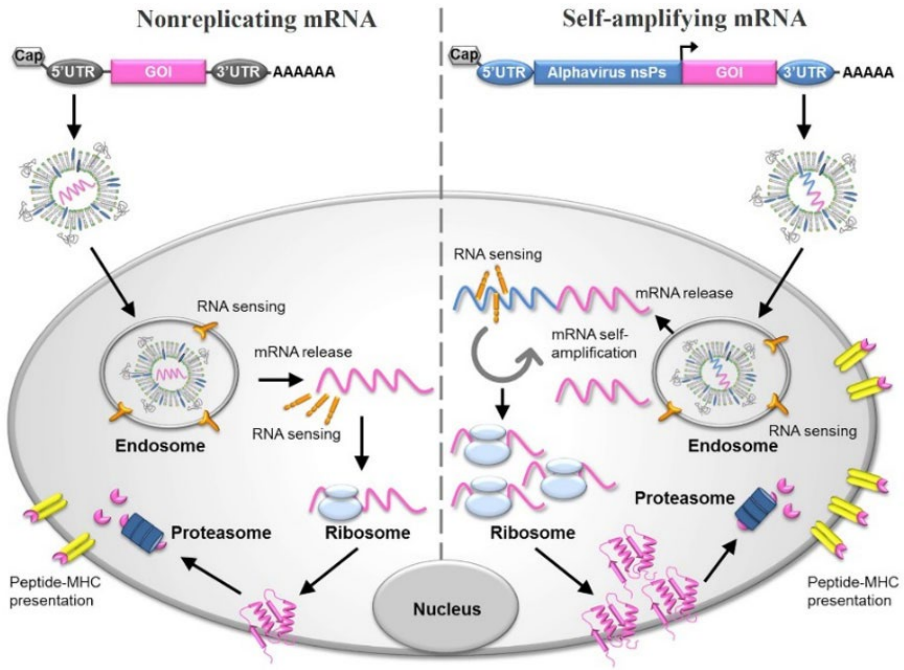
	ARCT-154 (N=420)		Comirnaty (N=408)	
	N	%	N	%
Any unsolicited AEs (Days 1-28)	81	**19.3**	111	**27.2**
Any related unsolicited AE	55	**13.1**	68	**16.7**
Any severe (Grade 3) AEs	1	**0.2**	6	**1.5**
Any SAEs	0	**0.0**	1	**0.2**
Any related SAEs	0	**0.0**	0	**0.0**
AEs of special interest	0	**0.0**	0	**0.0**
Medically-significant AEs	0	**0.0**	0	**0.0**
Any deaths	0	**0.0**	0	**0.0**



https://medrxiv.org/cgi/content/short/2023.07.13.23292597v1; Lancet Infectious Disease (in presss)

Self-amplifying mRNA Platform for Infectious Diseases

Well-tolerated, scalable platform with proven clinical efficacy that provides potential advantages compared to non-replicating conventional mRNA



mRNA replicates in the cell, leading to high and durable antigen expression

Superior Immune Response
→ Potential to increase clinical protection

Durable Immune Response
→ Requires less frequent boosters

Broad Immune Response
→ Additional protection against antigenic escape viruses

Low mRNA dose
→ High potential for the development of combined vaccines

Sa-RNA platform creates additional opportunities for the development of vaccines against multiple viral and bacterial targets

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