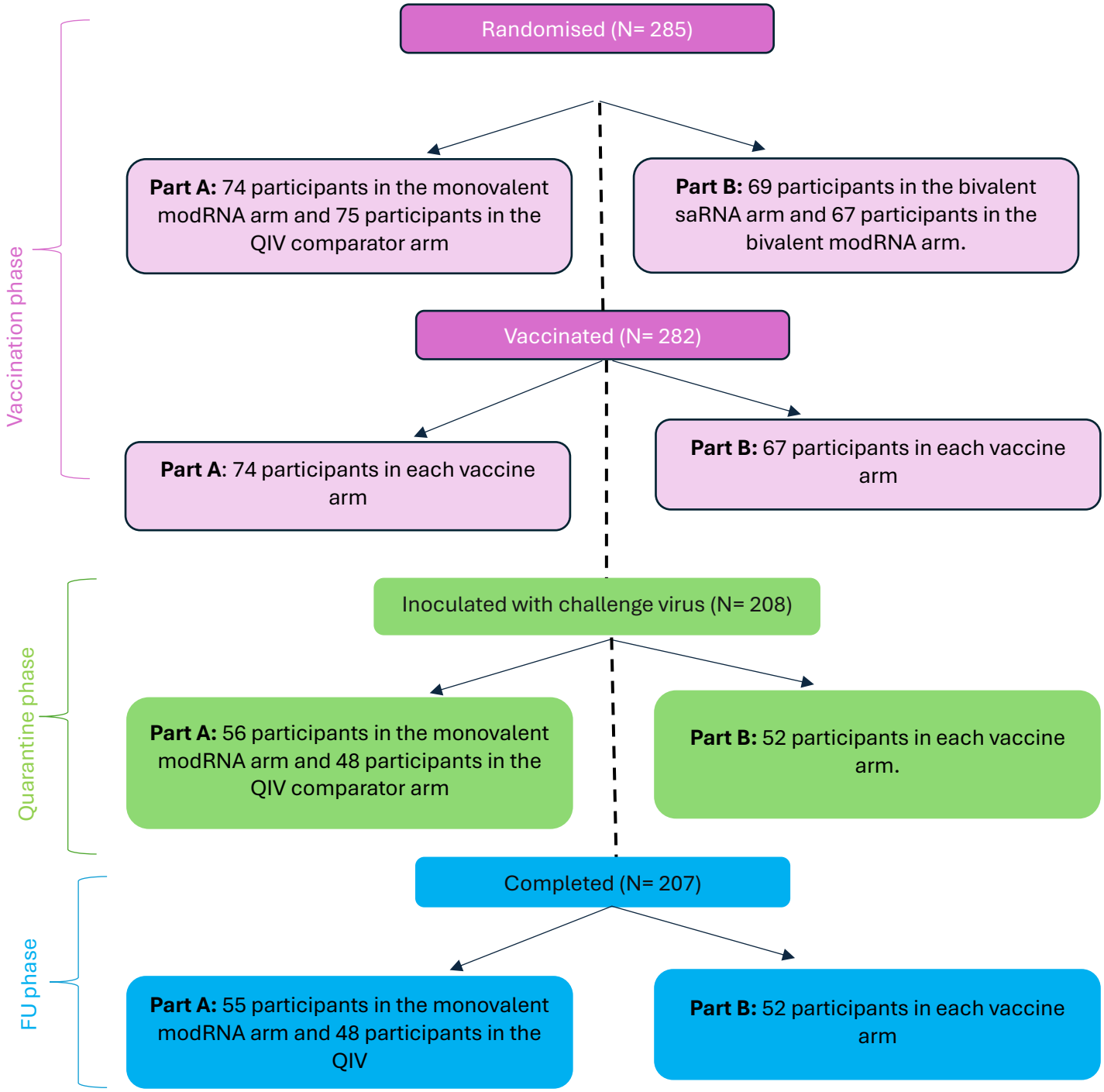
PIR-CSV-001 Number of Participants (Planned and Analysed):

Planned:

Approximately 280 participants (approximately 140 participants in Part A and approximately 140 participants in Part B [i.e., approximately 70 participants in each vaccine arm]) were planned to be vaccinated and 52 participants in each vaccine arm were planned to be inoculated with the challenge virus.

Analysed:



Summary of Results

Demographic and Other Baseline characteristics:

All enrolled participants were randomised to treatment and all randomized participants were vaccinated, except for 1 participant in the QIV comparator arm who withdrew and 2 participants in the bivalent saRNA arm who were withdrawn due to investigator's decision.

Another 54 participants were in a separate control group from a previous study. These individuals were not vaccinated in this study but were included in the data analysis for comparison.

Overall, demographic characteristics were well balanced across the treatment arms, with no notable differences observed in age, ethnicity, or BMI. The proportion of female participants was slightly higher in the QIV comparator arm (35.1%) compared to the other treatment arms (range: 27.8 to 29.7%). Participants were predominantly White across all treatment arms (61.1% to 77.0%). While minor variations in racial distribution were observed across treatment arms, these differences are not expected to have influenced the study outcomes.

Table 10-3: Demographic Characteristics - Safety Population

	Part A		Part A and Part B	Part B	
Description	**Monovalent modRNA N=74**	**QIV Comparator N=74**	**Placebo N=54**	**Bivalent saRNA N=67**	**Bivalent modRNA N=67**
Age at Screening (years)					
Mean (SD)	27.6 (7.79)	26.6 (6.97)	25.6 (6.41)	27.2 (6.42)	28.8 (7.15)
Median	25.0	26.0	24.5	26.0	27.0
Min, Max	18, 53	18, 50	18, 48	18, 50	18, 52
Sex, n (%)					
Male	52 (70.3)	48 (64.9)	39 (72.2)	48 (71.6)	48 (71.6)
Female	22 (29.7)	26 (35.1)	15 (27.8)	19 (28.4)	19 (28.4)
Ethnicity, n (%)					
Hispanic or Latino	0	2 (2.7)	3 (5.6)	4 (6.0)	3 (4.5)
Not Hispanic or Latino	74 (100)	72 (97.3)	51 (94.4)	63 (94.0)	64 (95.5)
Race, n (%)					
American Indian or Alaska native	1 (1.4)	0	1 (1.9)	0	0
Asian	0	11 (14.9)	2 (3.7)	8 (11.9)	9 (13.4)
Black or African American	6 (8.1)	6 (8.1)	9 (16.7)	8 (11.9)	5 (7.5)
White	57 (77.0)	53 (71.6)	33 (61.1)	43 (64.2)	45 (67.2)
Other	10 (13.5)	4 (5.4)	9 (16.7)	8 (11.9)	8 (11.9)
BMI at Screening (kg/m^2)					
Mean (SD)	25.40 (3.573)	24.77 (3.278)	25.94 (3.884)	24.49 (3.138)	25.53 (3.660)
Median	25.10	24.55	25.45	23.80	25.00
Min, Max	18.7, 34.7	19.0, 32.3	18.6, 34.4	19.4, 34.4	18.9, 33.2

BMI=body mass index; Max=maximum; Min=minimum; modRNA=nucleoside-modified messenger ribonucleic acid; N/n=number of participants; QIV=quadrivalent influenza vaccine; saRNA=self-amplifying ribonucleic acid; SD=standard deviation.

Immunogenicity and Efficacy:

All vaccines elicited antigen-specific antibody and cell-mediated immune responses. Vaccination with monovalent modRNA, bivalent modRNA, bivalent saRNA, or QIV prior to inoculation with the challenge virus showed a significant reduction of VL-AUC determined by qRT-PCR and by viral culture following viral challenge compared with placebo (Wilcoxon p-value <0.001; α=0.05 2-sided).

Table 13-1: Vaccine Efficacy for qRT-PCR-confirmed Influenza Infection – PP Population

Vaccine Efficacy (%) (95% CI)[a]	Monovalent modRNA (N=55)	QIV Comparator (N=48)	Bivalent saRNA (N=52)	Bivalent modRNA (N=52)
Moderately severe influenza infection	100.0 (75.2, 100.0)	84.5 (43.4, 96.0)	71.4 (23.7, 89.7)	92.9 (60.1, 98.8)
Febrile influenza infection	100.0 (61.2, 100.0)	100.0 (55.9, 100.0)	66.7 (0.0, 89.9)	88.9 (35.7, 98.2)
Influenza infection	100.0 (85.6, 100.0)	81.9 (55.0, 93.2)	58.3 (23.7, 78.0)	91.7 (70.7, 97.8)
Symptomatic influenza infection	100.0 (84.3, 100.0)	85.2 (57.8, 95.1)	63.6 (28.2, 82.3)	95.5 (75.2, 99.2)

CI=confidence interval; modRNA=nucleoside-modified messenger ribonucleic acid; N=number of participants; PP=per protocol; QIV=quadrivalent influenza vaccine; qRT-PCR=quantitative reverse transcriptase-polymerase chain reaction; saRNA=self-amplifying ribonucleic acid.

[a] The 95% CI for vaccine efficacy is obtained using the Farrington-Manning method.

Safety:

Vaccination with monovalent or bivalent modRNA, bivalent saRNA, or quadrivalent influenza vaccines and subsequent challenge with the study virus was safe and well tolerated. No deaths, AESIs, or SAEs were reported, and none of the AEs led to withdrawal from the study. The incidence of challenge-emergent AEs (CEAEs) or CEAEs related to viral challenge was comparable between the active vaccine arms. Most AEs were of mild intensity and were resolved at the end of the study.

Table 12-2: Number (%) of Participants with Unsolicited Adverse Events - Safety Population

	Monovalent modRNA (N=74) n (%)	QIV Comparator (N=74) n (%)	Placebo (N=54) n (%)	Bivalent saRNA (N=67) n (%)	Bivalent modRNA (N=67) n (%)
VEAEs					
Number of events	48	47	-	61	63
Number of participants with any AE	33 (44.6)	30 (40.5)	-	34 (50.7)	40 (59.7)
Mild	27 (36.5)	21 (28.4)	-	27 (40.3)	34 (50.7)
Moderate	5 (6.8)	7 (9.5)	-	7 (10.4)	6 (9.0)
Severe	1 (1.4)	2 (2.7)	-	0	0
Number of participants with any SAE	0	0	-	0	0
Number of participants with any related AEs	12 (16.2)	7 (9.5)	-	19 (28.4)	23 (34.3)
Number of participants with any AE leading to withdrawal from the study	0	0	-	0	0
CEAEs					
Number of events	18	17	23	15	16
Number of participants with any AE	15 (20.3)	11 (14.9)	20 (37.0)	12 (17.9)	13 (19.4)
Mild	12 (16.2)	9 (12.2)	14 (25.9)	7 (10.4)	12 (17.9)
Moderate	3 (4.1)	1 (1.4)	6 (11.1)	5 (7.5)	1 (1.5)
Severe	0	1 (1.4)	0	0	0
Number of participants with any SAE	0	0	0	0	0
Number of participants with any related AEs	5 (6.8)	2 (2.7)	12 (22.2)	5 (7.5)	1 (1.5)
Number of participants with any AE leading to withdrawal from the study	0	0	0	0	0

AE=adverse event; CEAE=challenge-emergent adverse event; modRNA=nucleoside-modified messenger ribonucleic acid; N/n=number of participants; QIV=quadrivalent influenza vaccine; saRNA=self-amplifying ribonucleic acid; VEAE=vaccine-emergent adverse event.

Notes:

- VEAEs are those events with an onset at or after vaccination.
- CEAEs are those events with an onset at or after viral challenge.
- If a participant experiences >1 event, the event with the worst severity or strongest relationship is included.
- Related = 'possibly related', 'probably related', 'definitely related', or 'not assessed'.
- AE leading to withdrawal from the study = participant withdrew from the study due to an AE.
- Percentages are based on the safety population.

Table 12-3: Number (%) of Participants with Post-vaccination Solicited Local Adverse Events - Safety Population

Number of participants with symptoms	Monovalent modRNA (N=74) n (%)	QIV Comparator (N=74) n (%)	Placebo (N=54) n (%)	Bivalent saRNA (N=67) n (%)	Bivalent modRNA (N=67) n (%)
Pain at injection site	32 (43.2)	32 (43.2)	-	50 (74.6)	52 (77.6)
Redness	0	2 (2.7)	-	1 (1.5)	3 (4.5)
Swelling	0	1 (1.4)	-	2 (3.0)	4 (6.0)
Any local reaction	32 (43.2)	32 (43.2)	-	50 (74.6)	52 (77.6)

modRNA=nucleoside-modified messenger ribonucleic acid; N/n=number of participants; QIV=quadrivalent influenza vaccine; saRNA=self-amplifying ribonucleic acid.

Notes:

- The distinct number of participants with each local reaction is presented. For each participant, the worst incidence of each local reaction is reported (i.e., the largest redness/swelling, the most severe pain).
- Percentages are based on the safety population.

Table 12-4: Number (%) of Participants with Post-vaccination Solicited Systemic Adverse Events - Safety Population

Number of participants with symptoms	Monovalent modRNA (N=74) n (%)	QIV Comparator (N=74) n (%)	Placebo (N=54) n (%)	Bivalent saRNA (N=67) n (%)	Bivalent modRNA (N=67) n (%)
Fever ≥38°C	4 (5.4)	1 (1.4)	-	3 (4.5)	1 (1.5)
Tiredness	17 (23.0)	26 (35.1)	-	31 (46.3)	32 (47.8)
Headache	14 (18.9)	18 (24.3)	-	21 (31.3)	29 (43.3)
Vomiting	1 (1.4)	1 (1.4)	-	0	0
Nausea	3 (4.1)	5 (6.8)	-	6 (9.0)	3 (4.5)
Diarrhea	5 (6.8)	1 (1.4)	-	4 (6.0)	4 (6.0)
Muscle pain	19 (25.7)	17 (23.0)	-	24 (35.8)	27 (40.3)
Joint pain	4 (5.4)	2 (2.7)	-	6 (9.0)	10 (14.9)
Any systemic event	39 (52.7)	43 (58.1)	-	43 (64.2)	47 (70.1)

modRNA=nucleoside-modified messenger ribonucleic acid; N/n=number of participants; QIV=quadrivalent influenza vaccine; saRNA=self-amplifying ribonucleic acid.

Notes:

- The distinct number of participants with each systemic reaction is presented. For each participant, the worst incidence of each local reaction is reported.
- Percentages are based on the safety population.

Overall Conclusion:

Vaccination with monovalent modRNA, bivalent saRNA, or bivalent modRNA induced humoral and cell-mediated immune responses and protected from subsequent challenge with study virus by significantly reducing the incidence of infection, symptomatic infection, febrile infection, viral loads, and clinical disease.

Vaccination with monovalent modRNA, bivalent saRNA, bivalent modRNA, or quadrivalent influenza vaccines and subsequent challenge with the study virus was safe and well tolerated.