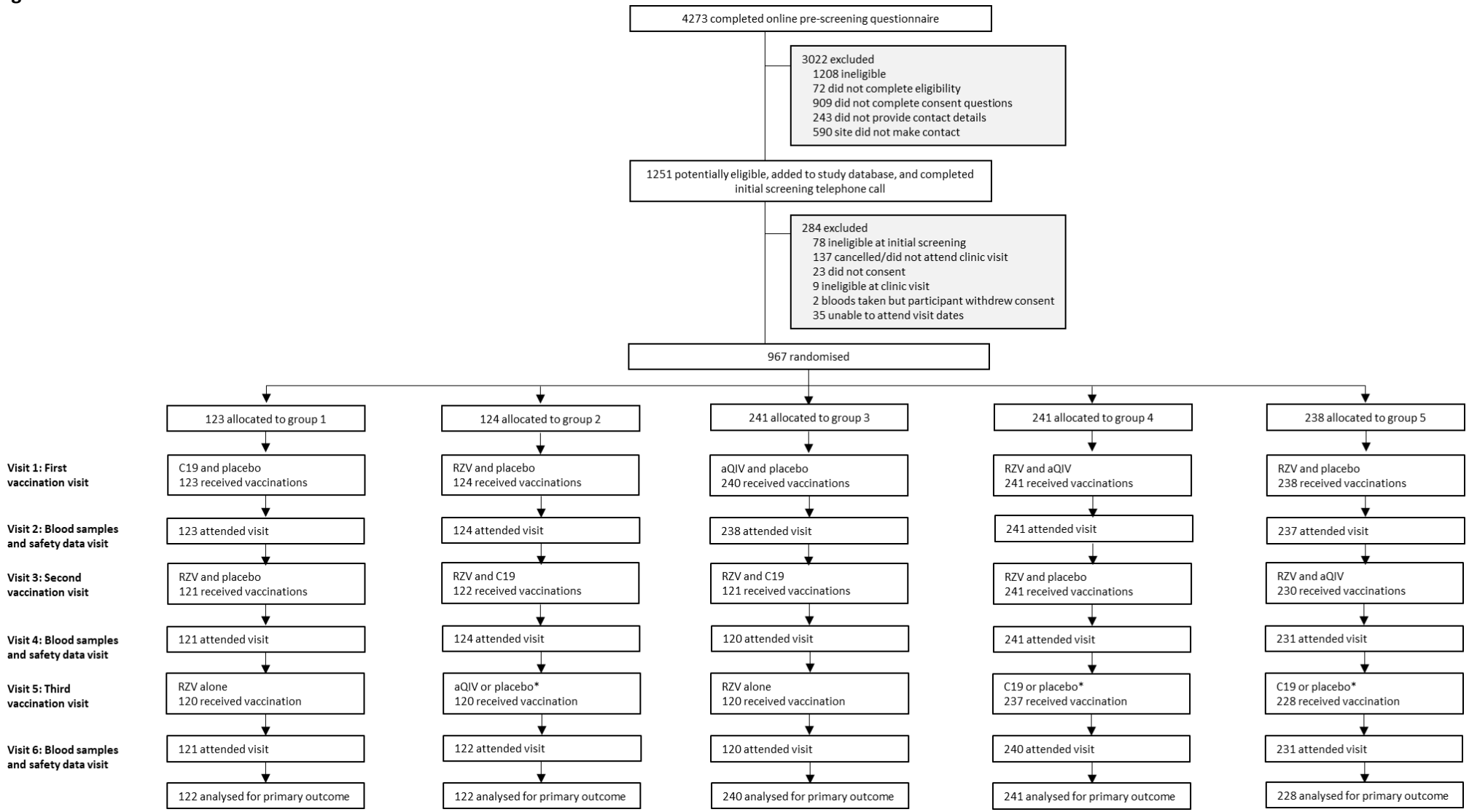
ZosterFluCov ISRCTN26495549

Figure 1 Flow chart



*aQIV or C19 received if visit occurred in winter vaccination season

Table 1 Baseline characteristics and comorbidities

	Group 1 (n=123)	Group 2 (n=124)	Group 3 (n=241)	Group 4 (n=241)	Group 5 (n=238)
Baseline characteristics					
Age at screening (years)	60.8 (55.5, 65.5)	60.8 (56.6, 65.6)	60.8 (57.3, 65.5)	59.8 (56.3, 64.5)	60.5 (56.8, 64.9)
Gender					
Male	58/123 (47.2%)	59/124 (47.6%)	112/241 (46.5%)	101/241 (41.9%)	108/238 (45.4%)
Female	65/123 (52.8%)	65/124 (52.4%)	129/241 (53.5%)	140/241 (58.1%)	129/238 (54.2%)
Non-binary or transgender	0/123 (0.0%)	0/124 (0.0%)	0/241 (0.0%)	0/241 (0.0%)	1/238 (0.4%)
Body-mass index (kg/m^2)	26.3 (24.0, 30.8)	27.6 (24.0, 31.2)	27.2 (24.0, 31.2)	27.0 (24.4, 31.2)	27.1 (24.2, 30.5)
Ethnic origin					
White	121/123 (98.4%)	122/124 (98.4%)	233/241 (96.7%)	227/241 (94.2%)	231/238 (97.1%)
Mixed	0/123 (0.0%)	1/124 (0.8%)	4/241 (1.7%)	4/241 (1.7%)	3/238 (1.3%)
Asian	2/123 (1.6%)	1/124 (0.8%)	2/241 (0.8%)	4/241 (1.7%)	4/238 (1.7%)
Black	0/123 (0.0%)	0/124 (0.0%)	1/241 (0.4%)	1/241 (0.4%)	0/238 (0.0%)
Other	0/123 (0.0%)	0/124 (0.0%)	1/241 (0.4%)	4/241 (1.7%)	0/238 (0.0%)
Prefers not to give	0/123 (0.0%)	0/124 (0.0%)	0/241 (0.0%)	1/241 (0.4%)	0/238 (0.0%)
Employment status					
Employed	73/122 (59.8%)	74/124 (59.7%)	138/241 (57.3%)	149/241 (61.8%)	133/238 (55.9%)
Unemployed	2/122 (1.6%)	3/124 (2.4%)	8/241 (3.3%)	8/241 (3.3%)	10/238 (4.2%)
Student	0/122 (0.0%)	0/124 (0.0%)	0/241 (0.0%)	0/241 (0.0%)	1/238 (0.4%)
Retired	47/122 (38.5%)	47/124 (37.9%)	95/241 (39.4%)	84/241 (34.9%)	94/238 (39.5%)
Participant received influenza vaccination in 2023–24 programme	65/123 (52.8%)	68/124 (54.8%)	131/241 (54.4%)	126/241 (52.3%)	125/238 (52.5%)
Participant previously received shingles vaccine	0/123 (0.0%)	4/124 (3.2%)	7/241 (2.9%)	5/241 (2.1%)	5/238 (2.1%)
Comorbidities					
Any cardiovascular disorder	30/123 (24.4%)	40/124 (32.3%)	69/241 (28.6%)	62/241 (25.7%)	66/238 (27.7%)
Any respiratory disorder	14/123 (11.4%)	22/124 (17.7%)	28/241 (11.6%)	24/241 (10.0%)	30/238 (12.6%)
Any diabetes	3/123 (2.4%)	4/124 (3.2%)	9/241 (3.7%)	9/241 (3.7%)	11/238 (4.6%)
Any renal disorder	3/123 (2.4%)	4/124 (3.2%)	7/241 (2.9%)	10/241 (4.1%)	7/238 (2.9%)
Any history of stroke or TIA	0/123 (0.0%)	3/124 (2.4%)	4/241 (1.7%)	2/241 (0.8%)	2/238 (0.8%)
Any gastrointestinal disorder	19/123 (15.4%)	29/124 (23.4%)	45/241 (18.7%)	41/241 (17.0%)	45/238 (18.9%)
Any liver disorder	4/123 (3.3%)	2/124 (1.6%)	8/241 (3.3%)	6/241 (2.5%)	5/238 (2.1%)
Any endocrine disorder (other than diabetes)	3/123 (2.4%)	14/124 (11.3%)	24/241 (10.0%)	23/241 (9.5%)	24/238 (10.1%)
Any neurological disorder	11/123 (8.9%)	11/124 (8.9%)	23/241 (9.5%)	26/241 (10.8%)	30/238 (12.6%)
Any past or current cancer diagnosis	10/123 (8.1%)	12/124 (9.7%)	28/241 (11.6%)	15/241 (6.2%)	17/238 (7.1%)
Any psychiatric history	24/123 (19.5%)	24/124 (19.4%)	39/241 (16.2%)	38/241 (15.8%)	32/238 (13.4%)

ZosterFluCov ISRCTN26495549

Data are median (IQR) or n/N (%). COPD=Chronic obstructive pulmonary disease. TIA=transient ischaemic attack. Vaccinations received at vaccination visits 1, 2 and 3: group 1 received C19 and placebo, RZV and placebo, RZV; group 2 received RZV and placebo, RZV and C19, aQIV or placebo; group 3 received aQIV and placebo, RZV and C19 , RZV; group 4 received RZV and aQIV, RZV and placebo, C19 or placebo; group 5 received RZV and placebo, RZV and aQIV, C19 or placebo.

Table 2 Primary and secondary safety outcomes

	RZV alone	RZV + C19	RZV + aQIV
	Groups 1 - 5	**Groups 2 & 3**	**Groups 4 & 5**
Primary safety outcome			
One or more grade 3 or 4 solicited systemic reaction following first or second RZV dose*	12/765 (1.6%)	7/213 (3.3%)	11/445 (2.5%)
Secondary safety outcomes			
One or more solicited systemic reaction following first or second RZV dose*	719/818 (87.9%)	219/234 (93.6%)	420/462 (90.9%)
One or more unsolicited adverse event up to 30 days following first or second RZV doses*	197/844 (23.3%)	55/243 (22.6%)	114/469 (24.3%)
One or more local adverse reaction following first or second RZV dose*	797/840 (94.9%)	232/241 (96.3%)	447/468 (95.5%)
	Groups 1, 2 & 5	**Group 3**	**Group 4**
One or more grade 3 or 4 solicited systemic reaction following first RZV dose^	6/465 (1.3%)	0/103 (0%)	6/234 (2.6%)
One or more solicited systemic reaction following first RZV dose^	399/474 (84.2%)	106/115 (92.2%)	215/241 (89.2%)
One or more local adverse reaction following first RZV dose^	459/484 (94.8%)	118/119 (99.2%)	234/242 (96.7%)
	Groups 1, 3 & 4	**Group 2**	**Group 5**
One or more grade 3 or 4 solicited systemic reaction following second RZV dose×	6/419 (1.4%)	7/110 (6.4%)	5/211 (2.4%)
One or more solicited systemic reaction following second RZV dose×	404/462 (87.5%)	113/119 (95.0%)	205/221 (92.8%)
One or more local adverse reaction following second RZV dose×	443/478 (92.7%)	114/122 (93.4%)	213/226 (94.3%)

Data are n/N (%). Denominators differ due to missing data. For comparison, grade 3 or 4 solicited systemic reaction event rates following non-RZV vaccines are 1.2% (C19 alone) and 1.9% (aQIV alone). Similarly, any solicited systemic reaction event rates following non-RZV vaccines are 66.9% (C19 alone) and 66.4% (aQIV alone). * For outcomes following first or second RZV dose, RZV alone includes group 1 following vaccinations 2 & 3, groups 2 & 5 following vaccination 1, group 3 following vaccination 3, and group 4 following vaccination 2; RZV + C19 includes groups 2 & 3 following vaccination 2; RZV + aQIV includes group 4 following vaccination 1 and group 5 following vaccination 2. ^ For outcomes following first RZV dose, RZV alone includes group 1 following vaccination 2 and groups 2 & 5 following vaccination 1; RZV + C19 includes group 3 following vaccination 2; RZV + aQIV includes group 4 following vaccination 1. × For outcomes following second RZV dose, RZV alone includes groups 1 & 3 following vaccination 3 and group 4 following vaccination 2; RZV + C19 includes group 2 following vaccination 2; RZV + aQIV includes group 5 following vaccination 2.

Table 3 Part A immunogenicity outcomes

Outcome	Time	Reference group	Comparator
		RZV alone (n=123)	**C19 + RZV (n=244)**
Anti-gE Ig concentrations	Baseline, prior to 1st RZV vaccination¥	21.8 (20.3, 23.3)	21.1 (20.1, 22.2)
	One month after 2nd RZV vaccination§	103.7 (98.4, 109.3)	104.8 (100.4, 109.5)
Vaccine response rate to RZV		113/115 (98.3%)	230/236 (97.5%)
		C19 alone (n=123)	**C19 + RZV (n=244)**
Anti-S Ig	Baseline, prior to C19 vaccination*	64.2 (59.6, 69.3)	61.6 (58.8, 64.6)
	One month after C19 vaccination^	90.5 (85.6, 95.7)	85.3 (82.3, 88.5)

Data are geometric mean concentration (95% CI) or n/N (%). Missing data: ¥ 5 participants with missing data (0 C19 alone, 5 C19 + RZV), § 5 participants with missing data (1 C19 alone, 4 C19 + RZV), * 16 participants with missing data (8 RZV alone, 8 RZV + aQIV), ^ 12 participants with missing data (7 RZV alone, 5 RZV + aQIV). Missing baseline data imputed using median of cohort as a whole. Data below lower limit of quantification (LLOQ) imputed using midpoint between 0 and the LLOQ.

Table 4 Part B Immunogenicity outcomes

Outcome	Time	Reference group	Comparator
		RZV alone (n=123)	**RZV + aQIV (n=479)**
Anti-gE Ig concentrations	Baseline, prior to 1st RZV vaccination¥	21.8 (20.3, 23.3)	21.6 (20.8, 22.5)
	One month after 2nd RZV vaccination§	103.7 (98.4, 109.3)	101.9 (98.9, 104.9)
Vaccine response rate to RZV		113/115 (98.3%)	443/458 (96.7%)
		aQIV alone (n=241)	**aQIV + RZV (n=479)**
HAI A/H1N1	Baseline, prior to aQIV dose*	3.5 (3.3, 3.8)	3.6 (3.5, 3.8)
	One month after aQIV dose^	4.3 (4.1, 4.6)	4.2 (4.0, 4.3)
HAI A/H3N2	Baseline, prior to aQIV dose×	4.8 (4.5, 5.1)	4.6 (4.4, 4.8)
	One month after aQIV dose†	5.5 (5.1, 5.8)	5.4 (5.2, 5.7)
HAI B/Austria	Baseline, prior to aQIV dose*	4.0 (3.7, 4.3)	3.8 (3.7, 4.0)
	One month after aQIV dose^	4.5 (4.2, 4.8)	4.3 (4.1, 4.5)

Data are geometric mean concentration (95% CI) or n/N (%). Missing data: ¥ 29 participants with missing data (8 RZV alone, 21 RZV + aQIV), § 22 participants with missing data (7 RZV alone, 15 RZV + aQIV), * 54 participants with missing data (6 aQIV alone, 48 RZV + aQIV), ^ 87 participants with missing data (21 aQIV alone, 66 RZV + aQIV), × 55 participants with missing data (6 aQIV alone, 49 RZV + aQIV), † 88 participants with missing data (21 aQIV alone, 67 RZV + aQIV). Missing baseline anti-gE Ig values imputed using median of cohort as a whole. Anti-gE Ig values below lower limit of quantification (LLOQ) imputed using midpoint between 0 and the LLOQ. Multiple imputation used to impute HAI values below LLOQ, and missing baseline and post-randomisation HAI values. Upper limit of quantification imputed for HAI values greater than the upper limit of quantification.