

## Supplemental material

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## **Supplemental File S1 - Frailty assessment**

The frailty index (FI) was scored between 0 and 41 as detailed in Supplementary Table S1. The subject's pre-vaccination questionnaires contributed a max score of 29 and the medical history contributed a max score of 12. If a participant had more than 10 missing quality of life components, the FI was treated as missing, unless based on their available data their classification as frail was unquestionable (they already had sufficient deficits to be classified as frail).

The medical history was divided into 12 selected deficits (Supplementary Table S2). The coded combined medical history database from studies ZOE-50 and ZOE-70 were searched and participants with the relevant preferred terms were assigned to 1 or more of the deficits. If a subject had any of the listed events in a deficit category, they were assigned a max score of 1 for that deficit.

**Supplementary Table S1 - Details of components of frailty index**

<b>Item</b>	<b>Scoring method based on response to questionnaire or medical history assessment</b>	<b>Max Contribution to Frailty Index</b>
<i>SF-36 Q1</i>	Poor=1 Fair=0.5 Good=0 Very good=0 Excellent=0	1
<i>SF-36 Q11A-11D</i>	<b>Q11A, Q11C</b> Definitely true=1 Mostly true=0.5 Don't know=0 Mostly false=0 Definitely false=0 <b>Q11B, Q11D</b> Definitely true=0 Mostly true=0 Don't know=0 Mostly false=0.5 Definitely false=1	4
<i>SF-36 Q3A - Q3J</i>	Limited a lot=1 Limited a little=0.5 Not limited at all=0	10
<i>SF-36 Q9A - Q9I</i>	<b>Q9A, Q9D, Q9E, Q9H</b> All of the Time=0 Most of the time=0 Some of the time=0 A little of the time=0.5 None of the time=1 <b>Q9B, Q9C, Q9F, Q9G, Q9I</b> All of the time=1 Most of the time=0.5 Some of the time=0 A little of the time=0 None of the time=0	9
<i>SF-36 Q2</i>	Much worse=1 Somewhat worse=0.5 Same=0 Somewhat better=0 Better=0	1
<i>EQ-5D Mobility</i>	No Problems=0 Some Problems=0.5 Confined to bed=1	1
<i>EQ-5D Anxiety</i>	No Anxiety=0 Moderate Anxiety=0.5 Extreme Anxiety=1	1
<i>EQ-5D Self care</i>	No Problems=0 Some Problems=0.5 Inability to wash or dress himself /herself=1	1
<i>EQ-5D Usual activities</i>	No Problems=0 Some Problems=0.5 Inability to perform usual activities=1	1
<b>Medical history</b>	Cancer Diabetes Mellitus High Blood Pressure Heart Attack Congestive Heart Failure Cerebrovascular Disease Arthritis Chronic Lung Disease Stomach or Intestinal Ulcers Migraine Cataract Glaucoma	1 1 1 1 1 1 1 1 1 1 1 1
<b>Total</b>		<b>41</b>

EQ-5D=EuroQol-5 Dimension; Q=question; SF-36=Short Form Survey-36

## Supplementary Table S2 - Detail of medical history search items

<b>Deficit</b>	<b>MedDRA version 18 Search Terms</b>
<b>Cancer</b>	Malignancy related conditions (SMQ) Malignant tumours (SMQ)
<b>Diabetes Mellitus</b>	Diabetes mellitus (incl subtypes) (HLT) Diabetic complications (HLGT)
<b>High Blood Pressure</b>	Hypertension (SMQ)
<b>Heart Attack</b>	Ischaemic heart disease (SMQ)
<b>Congestive Heart Failure</b>	Cardiac failure (SMQ)
<b>Cerebrovascular Disease</b>	Central nervous system vascular disorders (SMQ)
<b>Arthritis</b>	Arthritis (SMQ)
<b>Chronic Lung Disease</b>	Asthma/bronchospasm (SMQ) Interstitial lung disease (SMQ) Pulmonary hypertension (SMQ) Chronic Obstructive Pulmonary Disease (PT) / Infective exacerbation of chronic obstructive airways disease (PT) Bronchiectasis (PT) / Infective exacerbation of bronchiectasis (PT) Cystic fibrosis (PT) / Cystic fibrosis lung (PT) / Infective pulmonary exacerbation of cystic fibrosis (PT) Chronic respiratory disease (PT) Chronic respiratory failure (PT)
<b>Stomach or Intestinal Ulcers</b>	Gastrointestinal ulceration (SMQ)
<b>Migraine</b>	Migraine headaches (HLT) Migraine prophylaxis (PT)
<b>Cataract</b>	Cataract Conditions (HLT) Cataract operation (PT) Cataract diabetic (PT) Cataract operation complication (PT)
<b>Glaucoma</b>	Glaucoma (SMQ)

HLGT=high level group term; HLT=high level term; PT=preferred term; SMQ=Standardized MedDRA queries

**Supplementary Table S3 - Vaccine efficacy estimates (modified total vaccinated cohort)**

Herpes zoster	RZV group				Placebo group				Vaccine Efficacy
	N	n	T (year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	% (95% CI)
Non-Frail	5545	8	21803	0.4	5551	188	21443	8.8	95.8 (91.6, 98.2)
Pre-Frail	5738	18	21842	0.8	5969	191	22250	8.6	90.4 (84.4, 94.4)
Frail	1449	5	5158	1.0	1348	46	4663	9.9	90.2 (75.4, 97.0)
Unknown	53	0	186	0.0	62	5	194	25.8	100.0 (14.6, 100.0)
Burden of Illness	RZV group				Placebo group				Vaccine Efficacy
	N	n	T (year)	ZBPI BOI	N	n	T (year)	ZBPI BOI	% (95% CI)
Non-Frail	5545	8	21803	0.017	5550	187	21439	1.173	98.6 (97.1, 100.0)
Pre-Frail	5738	18	21842	0.108	5968	190	22248	1.475	92.6 (86.6, 98.7)
Frail	1449	5	5158	0.345	1348	46	4663	2.330	85.2 (62.6, 100.0)
Unknown	53	0	186	0.000	60	3	190	3.303	100.0 (NE)

N=number of participants with follow-up; n=number of participants with a confirmed zoster episode; RZV=adjuvanted recombinant zoster vaccine; T (year)=total years of follow-up for all participants in that subgroup; 95% CI=95% confidence interval using the variance estimate of the vaccine efficacy from the Chang test; ZBPI=Zoster Brief Pain Inventory; BOI=burden of illness; NE=not estimable

“Unknown” refers to participants who could not be assigned a frailty subgroup due to missing data

ZBPI Burden of Illness score was calculated as the sum of the ZBPI worst pain scores for all participants in the group divided by participant years of follow-up. Participants who did not have a confirmed zoster episode were assigned a score of 0. Four participants in the placebo group who had a confirmed zoster episode but who did not have at least one ZBPI assessment were excluded from the analysis of ZBPI BOI efficacy

**Supplementary Table S4 - Number of participants in the various cohorts (total vaccinated cohort)**

	<b>RZV N=13487 n</b>	<b>Placebo N=13489 n</b>	<b>Total N=26976 n</b>
Total vaccinated cohort	13487	13489	26976
Modified total vaccinated cohort	12785	12930	25715
Total vaccinated cohort - diary card subset	4570	4571	9141
ATP cohort for immunogenicity - humoral month 3	1400	1432	2832
ATP cohort for immunogenicity - humoral month 14	1360	1366	2726
ATP cohort for immunogenicity - humoral month 26	1318	1314	2632
ATP cohort for immunogenicity - humoral month 38	1255	1253	2508
ATP cohort for immunogenicity - CMI month 3	196	204	400
ATP cohort for immunogenicity - CMI month 14	187	194	381
ATP cohort for immunogenicity - CMI month 26	185	188	373
ATP cohort for immunogenicity - CMI month 38	174	180	354

ATP=according-to-protocol; CMI=cell-mediated immunogenicity; N=total number of participants; n=number of participants in the given cohort=RZV, adjuvanted recombinant zoster vaccine

**Supplementary Table S5 - Summary of demographic characteristics**

		<b>RZV N=13487</b>	<b>Placebo N=13489</b>	<b>Total N=26976</b>
<b>Age (years)</b>	Mean	68.8	68.8	68.8
	Median	71.0	71.0	71.0
	Minimum	50	48	48
	Maximum	96	95	96
<b>Gender</b>	Female	58.0 %	58.3 %	58.1 %
	Male	42.0 %	41.7 %	41.9 %
<b>Ethnicity</b>	American hispanic or latino	8.8 %	8.8 %	8.8 %
	Not american hispanic or latino	91.2 %	91.2 %	91.2 %
<b>Geographic Ancestry</b>	White - Caucasian / European Heritage	74.6 %	74.5 %	74.6 %
	Asian - East Asian Heritage	15.2 %	15.1 %	15.2 %
	Other	4.7 %	4.8 %	4.8 %

N=total number of participants; RZV=adjuvanted recombinant zoster vaccine

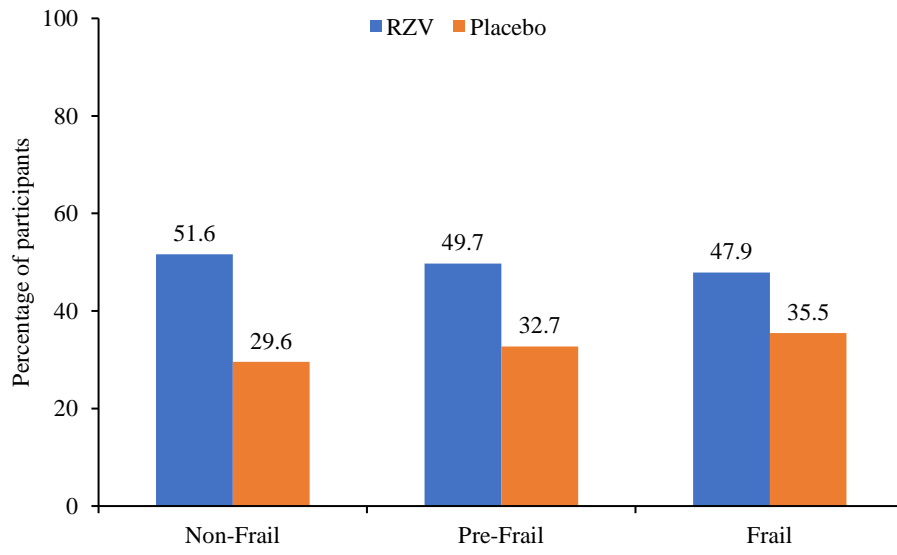
**Supplementary Table S6 - Incidence and nature of symptoms (solicited only) reported during the 7-day (days 0–6) post-vaccination period overall per participant by frailty status (total vaccinated cohort - diary card subset)**

	Sub-group	Group	Any symptom					General symptoms					Local symptoms				
			N	n	%	95% CI		N	n	%	95% CI		N	n	%	95% CI	
						LL	UL				LL	UL				LL	UL
<b>Any Grade</b>	<b>Non-Frail</b>	RZV	2008	1752	87.3	85.7	88.7	2007	1369	68.2	66.1	70.2	2007	1699	84.7	83.0	86.2
		Placebo	2034	654	32.2	30.1	34.2	2034	558	27.4	25.5	29.4	2034	227	11.2	9.8	12.6
	<b>Pre-Frail</b>	RZV	1977	1649	83.4	81.7	85.0	1971	1242	63.0	60.8	65.1	1977	1559	78.9	77.0	80.6
		Placebo	1964	662	33.7	31.6	35.8	1964	575	29.3	27.3	31.3	1964	227	11.6	10.2	13.1
	<b>Frail</b>	RZV	490	360	73.5	69.3	77.3	488	248	50.8	46.3	55.3	489	335	68.5	64.2	72.6
		Placebo	468	169	36.1	31.8	40.6	468	154	32.9	28.7	37.4	468	51	10.9	8.2	14.1
	<b>Unknown</b>	RZV	21	18	85.7	63.7	97.0	21	11	52.4	29.8	74.3	21	17	81.0	58.1	94.6
		Placebo	18	7	38.9	17.3	64.3	18	6	33.3	13.3	59.0	17	2	11.8	1.5	36.4
<b>Grade 3</b>	<b>Non-Frail</b>	RZV	2008	349	17.4	15.7	19.1	2007	240	12.0	10.6	13.5	2007	190	9.5	8.2	10.8
		Placebo	2034	37	1.8	1.3	2.5	2034	36	1.8	1.2	2.4	2034	4	0.2	0.1	0.5
	<b>Pre-Frail</b>	RZV	1977	279	14.1	12.6	15.7	1971	185	9.4	8.1	10.8	1977	172	8.7	7.5	10.0
		Placebo	1964	44	2.2	1.6	3.0	1964	40	2.0	1.5	2.8	1964	6	0.3	0.1	0.7
	<b>Frail</b>	RZV	490	75	15.3	12.2	18.8	488	50	10.2	7.7	13.3	489	50	10.2	7.7	13.3
		Placebo	468	24	5.1	3.3	7.5	468	22	4.7	3.0	7.0	468	5	1.1	0.3	2.5
	<b>Unknown</b>	RZV	21	1	4.8	0.1	23.8	21	0	0.0	0.0	16.1	21	1	4.8	0.1	23.8
		Placebo	18	0	0.0	0.0	18.5	18	0	0.0	0.0	18.5	17	0	0.0	0.0	19.5

CI=confidence interval; LL=lower limit; N=number of participants in each group; n (%)=number (percentage) of participants reporting the adverse event at least once; RZV=adjuvanted recombinant zoster vaccine; UL=upper limit



**Supplementary Figure S1 - Percentages of participants reporting any unsolicited adverse events within the 30-day (days 0-29) post-vaccination by frailty status (total vaccinated cohort)**



RZV= adjuvanted recombinant zoster vaccine