The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: Herpes Zoster vaccine (GSK1437173A)

Study Number: 116796 (ZOSTER-033)

Title: Immunogenicity and safety of GSK Biologicals' Herpes Zoster vaccine GSK1437173A in adults with a prior episode of herpes zoster.
GSK1437173A (HZV): GSK Biologicals' Herpes Zoster vaccine

Rationale:
The purpose of this study was to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 2 month schedule to adults ≥ 50 years of age (YOA) with a prior episode of herpes zoster.

Phase: III

Study Period: From 10-Jun-2013 to 25-Nov-2014.

Study Design: This was a non-randomized, open-label, multicentre study.

Centres: 4 centres: 2 in Canada and 2 in the Russian Federation

Indication: Prevention of Herpes Zoster (HZ) and related complications.

Treatment: The study groups were as follows:
- HZ/su Group: Subjects who received HZ vaccine according to a 0, 2 months schedule.

The study group was divided into 3 sub-groups, according to age: 50 to 59 YOA, 60 to 69 YOA and ≥ 70 YOA.

Objectives:
- To evaluate anti-gE vaccine response rate one month following a two-dose administration with HZ/su vaccine in all study subjects ≥50 YOA with a previous episode of HZ.

Criteria used:
- The objective is met if the lower limit (LL) of the 95% CI of the vaccine response rate for anti-gE enzyme-linked immunosorbent assay (ELISA) antibody concentrations 1 month after the second dose is at least 60%.

- To evaluate the safety following administration of HZ/su vaccine from the first vaccination up to 30 days post last vaccination in all study subjects ≥50 YOA with a previous episode of HZ.

Primary Outcome/Efficacy Variable:
Immunogenicity
- Anti-gE humoral immunogenicity.
  - Vaccine response for anti-gE humoral immunogenicity, as determined by ELISA, at Month 3.

Safety
- Occurrence of solicited local and general symptoms.
  - Occurrence, intensity and duration of each solicited local symptom within 7 days (Days 0-6) after each vaccination.
  - Occurrence, intensity, duration and relationship to vaccination of each solicited general symptom within 7 days (Day 0-6) after each vaccination.
- Occurrence of unsolicited adverse events.
  - Occurrence, intensity and relationship to vaccination of unsolicited adverse events (AEs) during 30 days (Days 0-29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification.
- Occurrence of Serious Adverse Events (SAEs).
  - Occurrence and relationship to vaccination of all SAEs from first vaccination up to 30 days post last vaccination.
- Occurrence of AEs of specific interest.
  - Occurrence of any potential Immune Mediated Diseases (pIMDs) from first vaccination up to 30 days post last vaccination.

Secondary Outcome/Efficacy Variable(s):
Immunogenicity
- Anti-gE humoral immunogenicity in each of the following age ranges: 50-59 YOA, 60-69 YOA and ≥ 70 YOA.
  - Anti-gE antibody concentrations, as determined by ELISA, at Month 0 and Month 3.

Safety
- Occurrence of SAEs.
  - Occurrence and relationship to vaccination of all SAEs during the period starting after 30 days post last vaccination until study end.

- Occurrence of SAEs considered by the investigator to be related to vaccination during the period starting after 30 days post last vaccination until study end.

• Occurrence of AEs of specific interest.
  - Occurrence of any pIMDs during the period starting after 30 days post last vaccination until study end.

Statistical Methods:

The analyses were performed on the Total Vaccinated cohort and the According-to-Protocol (ATP) cohort for immunogenicity.

- The Total Vaccinated cohort included all subjects with at least one study vaccine administered.
- The ATP cohort for immunogenicity included all evaluable subjects (i.e., those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria during the study) for whom data concerning immunogenicity outcome variables were available.

Analysis of Immunogenicity:

The analysis was performed on the ATP cohort for immunogenicity.

Vaccine response rate (VRR) for anti-gE antibody ELISA concentrations with their exact 95% confidence interval (CI) were calculated by the study group and age group (50-59 YOA, 60-69 YOA and ≥ 70 YOA) at Month 3. Geometric Mean Concentrations (GMCs) and seropositivity rates as determined by ELISA were calculated with their 95% CI by the age group at Months 0 and 3.

Analysis of Safety:

The analysis was performed on the Total Vaccinated cohort.

For each solicited local and general symptom, the percentage of subjects with the symptom reported within 7 days following vaccination was summarized with its exact 95% CI by vaccine group, by dose and across doses. The same tabulation was performed for grade 3 solicited AEs and for solicited general AEs assessed by the investigator as causally related to vaccination. The number of days with each individual solicited local and general AE during the solicited follow-up period was tabulated. The percentage of subjects with at least one unsolicited AEs within 30 days following vaccination was summarized by vaccine group according to the MedDRA preferred terms with exact 95% CI for the vaccine group. The same tabulation was performed for grade 3 unsolicited AEs and unsolicited AEs assessed by the investigator as causally related to vaccination. The percentage of subjects reporting pIMDs from first vaccination up to 30 days post last vaccination and from 30 days post last vaccination until study end were summarized by vaccine group according to MedDRA preferred terms. The percentage of subjects reporting at least one SAE and that of SAEs assessed by the investigators as related to the vaccination classified by MedDRA preferred terms from first vaccination up to 30 days post last vaccination and from 30 days post last vaccination until study end was summarised by group.

Study Population: Healthy male and female subjects aged 50 years or older at the time of enrolment, with a physician-documented history of HZ (documented physician clinical judgment was enough). Female subjects of childbearing potential could be enrolled in the study, if they had practiced adequate contraception for 30 days prior to vaccination, and had a negative pregnancy test on the day of vaccination, and had agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series. Written informed consent was obtained from each subject.

Number of Subjects	**Sub-group**			**HZ/su Group**
	50-59YOA	**60-69YOA**	**≥ 70 YOA**	
Planned, N	32	32	32	96
Enrolled, N (Total Vaccinated Cohort)	32	32	32	96
Completed, n (%)	32 (100)	31 (96.9)	30 (93.8)	93 (96.9)
Total Number Subjects Withdrawn, n (%)	0 (0.0)	1 (3.1)	2 (6.2)	3 (3.1)
Withdrawn due to Adverse Events, n (%)	0 (0.0)	1 (3.1)	0 (0.0)	1 (1.0)
Withdrawn due to Lack of Efficacy, n (%)	Not Applicable	Not Applicable	Not Applicable	Not Applicable
Withdrawn for other reasons, n (%)	0 (0.0)	0 (0.0)	2 (6.2)	2 (2.1)
Demographics	**50-59YOA**	**60-69YOA**	**≥ 70 YOA**	**HZ/su Group**
N (Total Vaccinated Cohort)	32	32	32	96
Gender Females, n (%)	24 (75.0)	19 (59.4)	20 (62.5)	63 (65.6)
Males, n (%)	8 (25.0)	13 (40.6)	12 (37.5)	33 (34.4)
Mean Age, years (SD)	53.7 (2.9)	64.4 (2.8)	76.8 (5.2)	64.9 (10.2)
Median Age, years	54	64	76	64

Minimum, Maximum	50, 59	60, 69	70, 89	50, 89
White - Caucasian / European Heritage, n (%)	31 (96.9)	30 (93.8)	31 (96.9)	92 (95.8)

Primary Efficacy Results: Vaccine response rates for anti-gE antibody ELISA concentrations at Month 3 (ATP cohort for immunogenicity)

			Vaccine response*			
					95% CI	
Antibody	**Sub-group/Group**	**N**	**n**	**%**	**LL****	**UL**
Anti-gE	50-59 YOA	29	26	89.7	72.6	97.8
	60-69 YOA	28	26	92.9	76.5	99.1
	≥ 70 YOA	25	22	88.0	68.8	97.5
	HZ/su*	82	74	90.2	81.7	95.7

Vaccine response defined as :
For initially seronegative subjects, antibody concentration at post-vaccination ≥ 4 fold the cut-off for Anti-gE (4x97 mIU/mL)
For initially seropositive subjects, antibody concentration at post-vaccination ≥ 4 fold the pre-vaccination antibody concentration
N = number of subjects with both pre- and post-vaccination results available
n/% = number/percentage of responders
95% CI = exact 95% confidence interval, LL = Lower Limit, UL = Upper Limit
*Primary Outcome result
**Superiority criterion: LL of the 95% CI of the VRR for anti-gE ELISA is at least 60%

Primary Efficacy Results: Number (%) of subjects reporting solicited local symptoms during the 7-day (Days 0-6) post-vaccination period following each dose and across doses (Total Vaccinated Cohort)

		HZ/su Group				
					95 % CI	
Symptom	**Intensity**	**N**	**n**	**%**	**LL**	**UL**
Dose 1						
Pain	Any	94	61	64.9	54.4	74.5
	Grade 3	94	3	3.2	0.7	9.0
Redness	Any	94	17	18.1	10.9	27.4
	>100 mm	94	0	0.0	0.0	3.8
Swelling	Any	94	12	12.8	6.8	21.2
	>100 mm	94	0	0.0	0.0	3.8
Dose 2						
Pain	Any	86	56	65.1	54.1	75.1
	Grade 3	86	5	5.8	1.9	13.0
Redness	Any	86	22	25.6	16.8	36.1
	>100 mm	86	2	2.3	0.3	8.1
Swelling	Any	86	13	15.1	8.3	24.5
	>100 mm	86	0	0.0	0.0	4.2
Across Doses						
Pain	Any	95	70	73.7	63.6	82.2
	Grade 3	95	8	8.4	3.7	15.9
Redness	Any	95	31	32.6	23.4	43.0
	>100 mm	95	2	2.1	0.3	7.4
Swelling	Any	95	19	20.0	12.5	29.5
	>100 mm	95	0	0.0	0.0	3.8

N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once when the intensity is maximum
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = occurrence of any local symptom regardless of their intensity grade
Grade 3 Pain = Significant pain at rest. Prevented normal every day activities

Primary Efficacy Results: Number (%) of subjects reporting solicited general symptoms during the 7-day (Days 0-6) post-vaccination period following each dose and across doses (Total Vaccinated Cohort)

	HZ/su Group	
		95 % CI

Symptom	Intensity/Relationship	N	n	%	LL	UL
Dose 1						
Fatigue	Any	94	37	39.4	29.4	50.0
	Related	94	29	30.9	21.7	41.2
	Grade 3	94	5	5.3	1.7	12.0
Gastrointestinal*	Any	94	14	14.9	8.4	23.7
	Related	94	6	6.4	2.4	13.4
	Grade 3	94	1	1.1	0.0	5.8
Headache	Any	94	22	23.4	15.3	33.3
	Related	94	15	16.0	9.2	25.0
	Grade 3	94	1	1.1	0.0	5.8
Myalgia	Any	94	25	26.6	18.0	36.7
	Related	94	21	22.3	14.4	32.1
	Grade 3	94	5	5.3	1.7	12.0
Shivering	Any	94	15	16.0	9.2	25.0
	Related	94	14	14.9	8.4	23.7
	Grade 3	94	2	2.1	0.3	7.5
Temperature/(Oral)	≥ 37.5°C	94	7	7.4	3.0	14.7
	Related	94	6	6.4	2.4	13.4
	>39.0°C	94	0	0.0	0.0	3.8
Dose 2						
Fatigue	Any	86	41	47.7	36.8	58.7
	Related	86	28	32.6	22.8	43.5
	Grade 3	86	6	7.0	2.6	14.6
Gastrointestinal*	Any	86	13	15.1	8.3	24.5
	Related	86	6	7.0	2.6	14.6
	Grade 3	86	2	2.3	0.3	8.1
Headache	Any	86	29	33.7	23.9	44.7
	Related	86	20	23.3	14.8	33.6
	Grade 3	86	3	3.5	0.7	9.9
Myalgia	Any	86	27	31.4	21.8	42.3
	Related	86	23	26.7	17.8	37.4
	Grade 3	86	2	2.3	0.3	8.1
Shivering	Any	86	25	29.1	19.8	39.9
	Related	86	21	24.4	15.8	34.9
	Grade 3	86	5	5.8	1.9	13.0
Temperature/(Oral)	≥ 37.5°C	86	14	16.3	9.2	25.8
	Related	86	11	12.8	6.6	21.7
	>39.0°C	86	0	0.0	0.0	4.2
Across Doses						
Fatigue	Any	95	57	60.0	49.4	69.9
	Related	95	43	45.3	35.0	55.8
	Grade 3	95	10	10.5	5.2	18.5
Gastrointestinal*	Any	95	23	24.2	16.0	34.1
	Related	95	11	11.6	5.9	19.8
	Grade 3	95	2	2.1	0.3	7.4
Headache	Any	95	37	38.9	29.1	49.5
	Related	95	28	29.5	20.6	39.7
	Grade 3	95	4	4.2	1.2	10.4
Myalgia	Any	95	35	36.8	27.2	47.4
	Related	95	31	32.6	23.4	43.0
	Grade 3	95	6	6.3	2.4	13.2
Shivering	Any	95	31	32.6	23.4	43.0
	Related	95	26	27.4	18.7	37.5
	Grade 3	95	7	7.4	3.0	14.6
Temperature/(Oral)	≥ 37.5°C	95	19	20.0	12.5	29.5

	Related	95	15	15.8	9.1	24.7
	>39.0°C	95	0	0.0	0.0	3.8

N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once when the intensity is maximum
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
Any = occurrence of any general symptoms regardless of their intensity grade or relationship to vaccination
Grade 3 symptoms = symptoms that prevented normal activity.
Related = general symptom assessed by the investigator as causally related to vaccination
*Gastrointestinal symptoms means nausea, vomiting, diarrhoea and/or abdominal pain

Primary Efficacy Results: Number of days with local symptoms during the solicited post-vaccination period (Total Vaccinated Cohort)

Solicited symptom	Group	Dose	N	Mean	Median
Pain	HZ/su	Dose 1	61	2.9	3.0
		Dose 2	56	3.0	3.0
Redness		Dose 1	17	2.6	3.0
	HZ/su	Dose 2	22	2.9	2.5
Swelling		Dose 1	12	2.9	3.0
		Dose 2	13	2.5	2.0

N = number of doses with the symptom

Primary Efficacy Results: Number of days with general symptoms during the solicited post-vaccination period (Total Vaccinated Cohort)

Solicited symptom	Group	Dose	N	Mean	Median
Fatigue	HZ/su	Dose 1	37	2.9	2.0
		Dose 2	41	2.7	2.0
Gastrointestinal symptoms	HZ/su	Dose 1	14	2.5	1.5
		Dose 2	13	1.9	1.0
Headache	HZ/su	Dose 1	22	2.4	2.0
		Dose 2	29	2.0	2.0
Myalgia	HZ/su	Dose 1	25	3.0	3.0
		Dose 2	27	2.6	2.0
Shivering	HZ/su	Dose 1	15	1.9	1.0
		Dose 2	25	1.7	1.0
Temperature	HZ/su	Dose 1	7	1.1	1.0
		Dose 2	14	1.6	1.5

N = number of doses with the symptom

Primary Efficacy Results: Number (%) of subjects with pIMDs from the first administered dose up to 30 days post vaccination period (Total Vaccinated cohort)

pIMDs	HZ/su Group N = 96
Subjects with any pIMD(s), n (%)	0 (0.0)

Primary Efficacy Results: For the safety outcome results (unsolicited AEs and SAEs), please refer to the Safety section of this CTRS

Secondary Outcome Results: Seropositivity rates and GMCs of anti-gE antibody at Months 0 and 3 (ATP cohort for immunogenicity)

				≥ 97 mIU/mL				GMC (mIU/mL)		
						95% CI			95% CI	
Antibody	Sub-group	Timing	N	n	%	LL	UL	value	LL	UL
anti-gE	50-59 YOA	PRE	29	29	100	88.1	100	2561.4	1531.4	4284.2
		PII(M3)	29	29	100	88.1	100	56413.7	43783.3	72687.6
	60-69 YOA	PRE	28	28	100	87.7	100	2083.5	1357.4	3198.0
		PII(M3)	28	28	100	87.7	100	44470.8	37373.2	52916.2
	≥ 70 YOA	PRE	25	25	100	86.3	100	2600.6	1319.4	5125.9
		PII(M3)	25	25	100	86.3	100	42642.5	34698.8	52404.9

Seropositivity rate = Anti-gE antibody concentration ≥ 97 mIU/mL
GMC = geometric mean antibody concentration calculated on all subjects
N = number of subjects with available results
n/% = number/percentage of subjects with concentration equal to or above specified value
95% CI = 95% confidence interval; LL = Lower Limit, UL = Upper Limit
PRE = Pre-vaccination (Day 0)
PII(M3) = Post-vaccination Dose II (Month 3)

Secondary Outcome Results: Number (%) of subjects with pIMDs from Day 30 post last vaccination up to 12 months post last vaccination period (Total Vaccinated Cohort)

pIMDs	**HZ/su Group N = 96**
Subjects with any pIMD(s), n (%)	0 (0.0)

Safety Results: Number (%) of subjects with unsolicited AEs reported within the 30-day (Days 0-29) post-vaccination period (Total Vaccinated Cohort)

Most frequent adverse events - On-Therapy (occurring within days 0-29 following vaccination)	**HZ/su Group N = 96**
Subjects with any AE(s), n (%)	30 (31.3)
Subjects with grade 3 AE(s), n (%)	11 (11.5)
Subjects with related AE(s), n (%)	12 (12.5)
Back pain	3 (3.1)
Pain in extremity	3 (3.1)
Arthralgia	2 (2.1)
Blood pressure decreased	2 (2.1)
Chills	2 (2.1)
Paraesthesia	2 (2.1)
Post herpetic neuralgia	2 (2.1)
Acarodermatitis	1 (1.0)
Acute stress disorder	1 (1.0)
Blepharospasm	1 (1.0)
Blood pressure increased	1 (1.0)
Bone pain	1 (1.0)
Burning sensation	1 (1.0)
Chronic gastritis	1 (1.0)
Exomphalos	1 (1.0)
Facial neuralgia	1 (1.0)
Gastrooesophageal reflux disease	1 (1.0)
Herpes zoster	1 (1.0)
Hyperaesthesia	1 (1.0)
Hyperhidrosis	1 (1.0)
Hypertension	1 (1.0)
Hypoaesthesia	1 (1.0)
Hypoaesthesia oral	1 (1.0)
Influenza like illness	1 (1.0)
Injection site bruising	1 (1.0)
Injection site mass	1 (1.0)
Injection site pruritus	1 (1.0)
Intertrigo	1 (1.0)
Miliaria	1 (1.0)
Muscle spasms	1 (1.0)
Nasopharyngitis	1 (1.0)
Neck pain	1 (1.0)
Neuralgia	1 (1.0)
Non-cardiac chest pain	1 (1.0)
Osteoarthritis	1 (1.0)
Pain	1 (1.0)

Pain of skin	1 (1.0)
Paraesthesia oral	1 (1.0)
Peripheral coldness	1 (1.0)
Presyncope	1 (1.0)
Procedural pain	1 (1.0)
Rash	1 (1.0)
Sensory disturbance	1 (1.0)
Skin infection	1 (1.0)
Syncope	1 (1.0)
Tremor	1 (1.0)
Vertigo	1 (1.0)

Grade 3 = AE that prevented normal activity
Related = AE assessed by the investigator as causally related to the study vaccination

Safety Results: Number (%) of subjects with SAEs reported from the first administered dose up to 30 days post last vaccination period (Total Vaccinated Cohort)

Serious adverse event, n (%) [n assessed by the investigator to be related to study medication]

All SAEs	**HZ/su Group N = 96**
Subjects* with any SAE(s), n (%) [n assessed by the investigator as related]	1 (1.0) [0]
Chronic gastritis	1 (1.0) [0]
Gastrooesophageal reflux disease	1 (1.0) [0]
Fatal SAEs	**HZ/su Group N = 96**
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]

*The SAEs presented appeared in the same subject.

Safety Results: Number (%) of subjects with SAEs reported from Day 30 post last vaccination up to 12 months post last vaccination period (Total Vaccinated Cohort)

Serious adverse event, n (%) [n assessed by the investigator to be related to study medication]

All SAEs	**HZ/su Group N = 96**
Subjects with any SAE(s), n (%) [n assessed by the investigator as related]	2 (2.1) [0]
Cholecystitis	1 (1.0) [0]
Duodenal ulcer perforation	1 (1.0) [0]
Pancreatitis	1 (1.0) [0]
Fatal SAEs	**HZ/su Group N = 96**
Subjects with fatal SAE(s), n (%) [n assessed by the investigator as related]	0 (0.0) [0]

Conclusion:
The primary objective for the anti-gE vaccine response rate (VRR) one month following a two-dose administration with HZ/su vaccine in all study subjects ≥ 50 YOA with a previous episode of HZ was met since the LL of the 95% CI for the anti-gE ELISA antibody concentrations at Month 3 (81.7%) was > 60%.
There was no apparent clinical difference between age groups in terms of the Geometric Mean fold increase for anti-gE antibody concentrations from pre-vaccination to one month post dose 2 (Month 3).
For the 7-day (Days 0-6) post-vaccination period following each dose, the most frequently reported solicited local symptom was pain reported by 73.7% of subjects with 8.4% of these subjects reporting grade 3 pain.
The most frequently reported solicited general symptoms were fatigue, headache and myalgia, reported by 60.0%, 38.9%, 36.8% of subjects, respectively, out of which Grade 3 symptoms were reported for 10.5%, 4.2% and 6.3% of subjects, respectively.
There were a total of 5 SAEs, with 1 subject having 2 SAEs reported within 30 days post last vaccination. During the remainder of the study up to data lock point (DLP), there was 1 subject with 1 SAE and another subject with 2 SAEs reported. None of the SAEs resulted in a withdrawal or were related to vaccination. None of the SAEs were fatal.

Date Updated: 05-August-2015