Clinical trial results:
A phase II/III, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the immunogenicity and safety of GSK Biologicals' herpes zoster HZ/su candidate vaccine when administered intramuscularly on a 0 and 1 to 2 months schedule to adults 18 years of age with solid tumours receiving chemotherapy.

Summary

EudraCT number	2012-002966-11
Trial protocol	ES GB CZ
Global end of trial date	

Results information

Result version number	v1
This version publication date	02 July 2016
First version publication date	02 July 2016

Trial information

Trial identification

Sponsor protocol code	116427

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01798056
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline Biologicals
Sponsor organisation address	Rue de l'Institut 89, Rixensart, Belgium, B-1330
Public contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 44 2089904466, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	23 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 June 2015
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate anti-gE humoral immune responses at Month 2, following a two-dose administration of the HZ/su vaccine, as compared to placebo in subjects with solid tumours receiving chemotherapy (PreChemo Groups only).
Criteria to be used:
The objective is met if the lower limit of the 95% confidence interval (CI) of the Geometric Mean (GM) ratio (HZ/su PreChemo group over Placebo PreChemo group) in anti-gE ELISA antibody concentrations is greater than 3.

-To evaluate the safety and reactogenicity following administration of the HZ/su vaccine as compared to placebo up to 30 days post last vaccination in subjects with solid tumours receiving chemotherapy.

Protection of trial subjects:

All subjects were supervised for 30 min after vaccination/product administration with appropriate medical treatment readily available. Vaccines/products were administered by qualified and trained personnel. Vaccines/products were administered only to eligible subjects that had no contraindications to any components of the vaccines/products. Subjects were followed-up for 30 days after the last vaccination/product administration.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 170
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Korea, Republic of: 35
Country: Number of subjects enrolled	Canada: 6
Worldwide total number of subjects	266
EEA total number of subjects	225

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	192
From 65 to 84 years	72
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

During the screening the following steps occurred: check for inclusion/exclusion criteria, contraindications/precautions, medical history of the subjects and signing informed consent forms.

Pre-assignment period milestones

Number of subjects started	266
Number of subjects completed	232

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No vaccination received: 34

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK1437173A Group

Arm description:

Subjects receiving the adjuvanted GSK1437173A vaccine according to a 0, 1-2 month schedule.

Arm type	Experimental
Investigational medicinal product name	GSK 1437173A
Investigational medicinal product code	
Other name	HZ/su vaccine
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Arm title	Placebo Group

Arm description:

Subjects receiving saline placebo according to a 0, 1-2 month schedule.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Saline solution
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The placebo was administered intramuscularly into the deltoid muscle of the non-dominant arm.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: This trial was blinded as concerns the subjects, the caregivers and the outcomes assessors.

Number of subjects in period 1[2]	GSK1437173A Group	Placebo Group
Started	117	115
Completed	102	107
Not completed	15	8
Consent withdrawn by subject	11	5
Adverse event, non-fatal	3	2
Unspecified	1	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Some subjects enrolled in the study did not receive any vaccination and were eliminated before starting.

Baseline characteristics

Reporting groups	
Reporting group title	GSK1437173A Group
Reporting group description:	
Subjects receiving the adjuvanted GSK1437173A vaccine according to a 0, 1-2 month schedule.	
Reporting group title	Placebo Group
Reporting group description:	
Subjects receiving saline placebo according to a 0, 1-2 month schedule.	

Reporting group values	GSK1437173A Group	Placebo Group	Total
Number of subjects	117	115	232
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	57.1	58.5	
standard deviation	± 10.8	± 11.7	-
Gender categorical Units: Subjects			
Female	70	69	139
Male	47	46	93

End points

End points reporting groups

Reporting group title	GSK1437173A Group
Reporting group description:	
Subjects receiving the adjuvanted GSK1437173A vaccine according to a 0, 1-2 month schedule.	
Reporting group title	Placebo Group
Reporting group description:	
Subjects receiving saline placebo according to a 0, 1-2 month schedule.	
Subject analysis set title	HZ/su-PreChemo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects receiving the adjuvanted HZ/su vaccine, with the first vaccination at least 10 days (up to 1 month) before the start of a chemotherapy cycle.	
Subject analysis set title	Placeb-PreChemo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects receiving saline placebo, with the first vaccination at least 10 days (up to 1 month) before the start of a chemotherapy cycle.	

Primary: Adjusted geometric means (GMC) of HZ/su over placebo for anti-glycoprotein E (gE) antibody ELISA concentrations in PreChemo Groups only

End point title	Adjusted geometric means (GMC) of HZ/su over placebo for anti-glycoprotein E (gE) antibody ELISA concentrations in PreChemo Groups only
End point description:	
End point type	Primary
End point timeframe:	
At Month 2	

End point values	HZ/su-PreChemo	Placeb-PreChemo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	65	76		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Adjusted GMC of antibody titers	24501.57 (19051.99 to 31509.94)	1056.77 (990.37 to 1127.62)		

Statistical analyses

Statistical analysis title	Adjusted GMC ratio

Statistical analysis description:

The analysis evaluated the anti-gE humoral immune responses at Month 2, following a two-dose administration of the HZ/su vaccine, as compared to placebo in subjects with solid tumours receiving

chemotherapy (PreChemo Groups only).
Criteria used:
The objective is met if the lower limit of the 95% confidence interval (CI) of the Geometric Mean (GM) ratio (HZ/su PreChemo group over Placebo PreChemo group) in anti-gE ELISA antibody concentrations is greater than 3.

Comparison groups	HZ/su-PreChemo v Placeb-PreChemo
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	Adjusted GMC ratio
Parameter estimate	Ratio
Point estimate	23.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	17.9
upper limit	30

Notes:

[1] - Difference of means between vaccines and placebo were calculated together with 2-sided confidence intervals and back-transformed to the original units to provide GMCs and GM ratios.

Secondary: Number of subjects with anti-gE antibody concentrations as determined by ELISA above the cut-off value (97 mIU/ml)

End point title	Number of subjects with anti-gE antibody concentrations as determined by ELISA above the cut-off value (97 mIU/ml)

End point description:

End point type	Secondary

End point timeframe:

At Month 2

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	98		
Units: Subjects				
Subjects	87	97		

Statistical analyses

No statistical analyses for this end point

Secondary: GMCs for anti-Varicella Zoster Virus (VZV) gE antibodies

End point title	GMCs for anti-Varicella Zoster Virus (VZV) gE antibodies

End point description:

End point type	Secondary

End point timeframe:

At Month 2

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	98		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
GMCs	18291.7 (14432.1 to 23183.5)	1060.5 (873.9 to 1287.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with vaccine responses for anti-gE antibody ELISA concentrations

End point title	Number of subjects with vaccine responses for anti-gE antibody ELISA concentrations

End point description:

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

End point type	Secondary

End point timeframe:

At Months 1 and 2

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	94		
Units: Subjects				
Vaccine responders Month 1 [N=85, 93]	73	0		
Vaccine responders Month 2 [N=87, 94]	75	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells

End point title	Descriptive statistics of the frequency of gE-specific CD4[2+] T-cells

End point description:

Descriptive statistics were tabulated for CD4[2+] cells, which are gE-specific CD4+ T-cells with at least 2 activation markers ([2+]) expressed from the activation markers IFN-γ, IL-2, TNF-α and CD40 L, as determined by intra-cellular staining (ICS) method.

End point type	Secondary

End point timeframe:

At Months 0, 1 and 2

End point values	HZ/su-PreChemo	Placeb-PreChemo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	25		
Units: CD4 T-cells per million T-cells				
median (inter-quartile range (Q1-Q3))				
CD4[2+] T-cells, Month 0 [N=20, 23]	134.5 (42.8 to 329.7)	112 (39.3 to 151.5)		
CD4[2+] T-cells, Month 1 [N=19, 25]	498.1 (336.1 to 652.4)	53.9 (1 to 179.4)		
CD4[2+] T-cells, Month 2 [N=20, 21]	832.1 (536.2 to 1303.6)	58.9 (22.7 to 139.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with vaccine responses for gE-specific CD4[2+] T-cells

End point title	Number of subjects with vaccine responses for gE-specific CD4[2+] T-cells

End point description:

Vaccine response defined as:
For initially subjects with pre-vaccination T cell frequencies below the threshold, at least a 2-fold increase as compared to the threshold (2x320 Events/10E6 CD4+ T cells)
For initially subjects with pre-vaccination T cell frequencies above the threshold, at least a 2-fold increase as compared to pre-vaccination T cell frequencies

End point type	Secondary

End point timeframe:

At Months 1 and 2

End point values	HZ/su-PreChemo	Placeb-PreChemo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	23		
Units: Subjects				
CD4[2+] T-cells, Month 1 [N=19, 23]	5	0		
CD4[2+] T-cells, Month 2 [N=19, 20]	11	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with unsolicited adverse events (AEs)

End point title	Number of subjects with unsolicited adverse events (AEs)

End point description:

An unsolicited AE covers any untoward medical occurrence in a clinical investigation subject temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product and reported in addition to those solicited during the clinical study and any solicited symptom with onset outside the specified period of follow-up for solicited symptoms. Any was defined as the occurrence of any unsolicited AE regardless of intensity grade or relation to vaccination. Grade 3 AE = an AE which prevented normal, everyday activities. Related = AE assessed by the investigator as related to the vaccination.

End point type	Secondary

End point timeframe:

During the 30-day (Days 0-29) post-vaccination period

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	115		
Units: Subjects				
Subjects with any AEs	100	102		

Statistical analyses

No statistical analyses for this end point

Secondary: Number (%) of subjects with serious adverse events (SAEs)

End point title	Number (%) of subjects with serious adverse events (SAEs)

End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.

End point type	Secondary

End point timeframe:

From the first dose up to 30 days post last vaccination period

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	115		
Units: Subjects				
Subjects with any SAEs	16	14		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any potential Immune Mediated Diseases (pIMDs)

End point title	Number of subjects with any potential Immune Mediated Diseases (pIMDs)

End point description:

End point type	Secondary

End point timeframe:

From first vaccination up to 30 days post last vaccination

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	115		
Units: Subjects				
pIMDs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms during the 7-day post-vaccination period; Unsolicited AEs during the 30-day post-vaccination period; SAEs during the entire study period.

Adverse event reporting additional description:

Individual SAEs remain blinded as long as the study is ongoing.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	HZ/su Group

Reporting group description: -

Reporting group title	Placebo Group

Reporting group description: -

Serious adverse events	HZ/su Group	Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 117 (0.00%)	0 / 115 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	HZ/su Group	Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 117 (98.29%)	106 / 115 (92.17%)	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 117 (0.85%)	6 / 115 (5.22%)	
occurrences (all)	1	6	
Headache			
subjects affected / exposed	45 / 117 (38.46%)	41 / 115 (35.65%)	
occurrences (all)	61	52	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	11 / 117 (9.40%)	13 / 115 (11.30%)	
occurrences (all)	12	15	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	30 / 117 (25.64%)	29 / 115 (25.22%)	
occurrences (all)	34	33	
Chills			
subjects affected / exposed	39 / 117 (33.33%)	25 / 115 (21.74%)	
occurrences (all)	48	30	
Fatigue			
subjects affected / exposed	80 / 117 (68.38%)	69 / 115 (60.00%)	
occurrences (all)	118	109	
Mucosal inflammation			
subjects affected / exposed	9 / 117 (7.69%)	6 / 115 (5.22%)	
occurrences (all)	11	8	
Pain			
subjects affected / exposed	90 / 117 (76.92%)	7 / 115 (6.09%)	
occurrences (all)	139	7	
Pyrexia			
subjects affected / exposed	22 / 117 (18.80%)	9 / 115 (7.83%)	
occurrences (all)	23	9	
Swelling			
subjects affected / exposed	18 / 117 (15.38%)	1 / 115 (0.87%)	
occurrences (all)	23	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	16 / 117 (13.68%)	11 / 115 (9.57%)	
occurrences (all)	19	11	
Diarrhoea			
subjects affected / exposed	9 / 117 (7.69%)	10 / 115 (8.70%)	
occurrences (all)	12	10	
Dyspepsia			
subjects affected / exposed	6 / 117 (5.13%)	13 / 115 (11.30%)	
occurrences (all)	6	13	
Gastrointestinal disorder			

subjects affected / exposed	51 / 117 (43.59%)	51 / 115 (44.35%)	
occurrences (all)	74	63	
Nausea			
subjects affected / exposed	31 / 117 (26.50%)	28 / 115 (24.35%)	
occurrences (all)	36	33	
Vomiting			
subjects affected / exposed	10 / 117 (8.55%)	14 / 115 (12.17%)	
occurrences (all)	10	16	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 117 (17.95%)	22 / 115 (19.13%)	
occurrences (all)	21	22	
Erythema			
subjects affected / exposed	43 / 117 (36.75%)	1 / 115 (0.87%)	
occurrences (all)	58	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	62 / 117 (52.99%)	33 / 115 (28.70%)	
occurrences (all)	88	45	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 117 (7.69%)	5 / 115 (4.35%)	
occurrences (all)	12	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 November 2012	The primary objective for immunogenicity response (based on Geometric Mean [GM] ratios) following the HZ/su vaccination compared to placebo will now be evaluated only in the PreChemo Groups. The secondary objectives have now been qualified to evaluate immunogenicity in either the PreChemo Groups (Vaccine Response Rates [VRR] in anti-gE humoral immunogenicity responses and VRR and GM ratio in gE-specific Cellular-Mediated Immunity [CMI]) or in all study subjects (VRR and GM ratio in anti-gE humoral immunogenicity responses). The CMI sub-cohort will now only be recruited in the PreChemo Groups. The timepoint for evaluation of the primary objective for safety/reactogenicity has been reworded for clarity ('up to 30 days post last vaccination' instead of 'up to month 2').
11 August 2014	The cut-off of the gE-specific ELISA assay has been changed from 18 to 97 mIU/mL. The definition of the according-to-protocol (ATP) cohort for safety was updated. (Section 9.4.2) Statistical section was updated to describe the descriptive cell-mediated immune (CMI) response analysis, to clarify other descriptive analysis for immunogenicity and safety. (Section 9.5.3)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported