Clinical trial results:
A phase III, randomised, observer-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' herpes zoster gE/AS01B candidate vaccine when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients

Summary

EudraCT number	2012-000138-20
Trial protocol	BE ES DE FI EE IT CZ GB FR NL GR
Global end of trial date	01 February 2017

Results information

Result version number	v1 (current)
This version publication date	04 January 2018
First version publication date	04 January 2018

Trial information

Trial identification

Sponsor protocol code	115523

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01610414
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, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Trials Call Center, GlaxoSmithKline Biologicals, 044 2089-904466, 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	Final
Date of interim/final analysis	09 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate Vaccine Efficacy (VE) in the prevention of HZ in autologous HCT recipients 18 years of age and older.
Criterion: Clinically meaningful overall HZ VE was demonstrated if the lower limit of the 95% confidence interval (CI was) is above 0%.

Protection of trial subjects:

All subjects were supervised after vaccination/product administration with appropriate medical treatment readily available. Vaccines were administered by qualified and trained personnel. Vaccines were administered only to eligible subjects that had no contraindications to any components of the vaccines.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	28 September 2012
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	United Kingdom: 86
Country: Number of subjects enrolled	United States: 278
Country: Number of subjects enrolled	Australia: 97
Country: Number of subjects enrolled	Belgium: 55
Country: Number of subjects enrolled	Bulgaria: 23
Country: Number of subjects enrolled	Canada: 55
Country: Number of subjects enrolled	Czech Republic: 68
Country: Number of subjects enrolled	Estonia: 8
Country: Number of subjects enrolled	Finland: 43
Country: Number of subjects enrolled	France: 111
Country: Number of subjects enrolled	Germany: 110
Country: Number of subjects enrolled	Greece: 17
Country: Number of subjects enrolled	Hong Kong: 15
Country: Number of subjects enrolled	Israel: 55
Country: Number of subjects enrolled	Italy: 154
Country: Number of subjects enrolled	Japan: 83
Country: Number of subjects enrolled	Korea, Republic of: 148
Country: Number of subjects enrolled	Malaysia: 24

Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Panama: 11
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 35
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Spain: 361
Country: Number of subjects enrolled	Taiwan: 30
Country: Number of subjects enrolled	Turkey: 73
Worldwide total number of subjects	2000
EEA total number of subjects	1080

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)	1560
From 65 to 84 years	440
85 years and over	0

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	2000
Number of subjects completed	1846

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Study vaccine dose not administered: 154

Period 1

Period 1 title	Study start - Month 13
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK1437173A Group

Arm description:

Subjects received 2 doses of the candidate HZ vaccine GSK1437173A, administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Arm type	Experimental
Investigational medicinal product name	Herpes Zoster vaccine GSK1437173A
Investigational medicinal product code	HZ/su
Other name	gE/AS01B
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly (IM) in deltoid region of non-dominant arm, according to a 0, 1-2 Months schedule.

Arm title	Placebo Group

Arm description:

Subjects received 2 doses of placebo (saline solution), administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Arm type	Placebo
Investigational medicinal product name	Herpes Zoster vaccine GSK1437173A
Investigational medicinal product code	HZ/su
Other name	gE/AS01B
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly (IM) in deltoid region of non-dominant arm, according to a 0, 1-2 Months schedule.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Roles blinded presented as per protocol

Number of subjects in period 1[2]	GSK1437173A Group	Placebo Group
Started	922	924
Completed	807	795
Not completed	115	129
Suspected HZ episode	1	3
Consent withdrawn by subject	23	30
Adverse event, non-fatal	14	14
Migrated/moved from study area	2	4
Other reasons for withdrawal	3	4
Lost to follow-up	4	6
Serious Adverse Event	65	67
Protocol deviation	3	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 of the enrolled subjects were allocated subject numbers, but were not administered all doses of study vaccine, hence they did not start the study.

Period 2

Period 2 title	Month 13 - Month 25
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[3]
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK1437173A Group

Arm description:

Subjects received 2 doses of the candidate HZ vaccine GSK1437173A, administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Arm type	Experimental
Investigational medicinal product name	Herpes Zoster vaccine GSK1437173A
Investigational medicinal product code	HZ/su
Other name	gE/AS01B
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly (IM) in deltoid region of non-dominant arm, according to a 0, 1-2 Months schedule.

Arm title	Placebo Group

Arm description:

Subjects received 2 doses of placebo (saline solution), administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Arm type	Placebo

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

Dosage and administration details:

2 doses administered IM in deltoid region of non-dominant arm, according to a 0, 1-2 Months schedule.

Notes:

[3] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Roles blinded presented as per protocol

Number of subjects in period 2	GSK1437173A Group	Placebo Group
Started	807	795
Completed	742	725
Not completed	65	70
Consent withdrawn by subject	7	8
Adverse event, non-fatal	8	4
Migrated/moved from study area	4	2
Other reasons for withdrawal	6	7
Lost to follow-up	5	9
Serious Adverse Event	35	38
Protocol deviation	-	2

Period 3

Period 3 title	After Month 25
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind[4]
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	GSK1437173A Group

Arm description:

Subjects received 2 doses of the candidate HZ vaccine GSK1437173A, administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Arm type	Experimental
Investigational medicinal product name	Herpes Zoster vaccine GSK1437173A
Investigational medicinal product code	HZ/su
Other name	gE/AS01B
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

2 doses administered intramuscularly (IM) in deltoid region of non-dominant arm, according to a 0, 1-2 Months schedule.

Arm title	Placebo Group

Arm description:

Subjects received 2 doses of placebo (saline solution), administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

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

Dosage and administration details:

2 doses administered IM in deltoid region of non-dominant arm, according to a 0, 1-2 Months schedule.

Notes:

[4] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Roles blinded presented as per protocol

Number of subjects in period 3	GSK1437173A Group	Placebo Group
Started	742	725
Completed	694	672
Not completed	48	53
Study end not reached	48	53

Baseline characteristics

Reporting groups	
Reporting group title	GSK1437173A Group
Reporting group description:	
Subjects received 2 doses of the candidate HZ vaccine GSK1437173A, administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.	
Reporting group title	Placebo Group
Reporting group description:	
Subjects received 2 doses of placebo (saline solution), administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.	

Reporting group values	GSK1437173A Group	Placebo Group	Total
Number of subjects	922	924	1846
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	54.8	55.1	
standard deviation	± 11.7	± 11.4	-
Gender categorical Units: Subjects			
Female	342	346	688
Male	580	578	1158
Race/Ethnicity, Customized Units: Subjects			
African Heritage/African American	15	25	40
American Indian or Alaskan Native	2	0	2
Asian - Central/South Asian Heritage	6	5	11
Asian - East Asian Heritage	83	91	174
Asian - Japanese Heritage	43	38	81
Asian - South East Asian Heritage	18	16	34
White - Arabic/North African Heritage	9	12	21
White - Caucasian/European Heritage	715	712	1427
Mixed Origin	31	25	56

End points

End points reporting groups

Reporting group title	GSK1437173A Group

Reporting group description:

Subjects received 2 doses of the candidate HZ vaccine GSK1437173A, administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Reporting group title	Placebo Group

Reporting group description:

Subjects received 2 doses of placebo (saline solution), administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Reporting group title	GSK1437173A Group

Reporting group description:

Subjects received 2 doses of the candidate HZ vaccine GSK1437173A, administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Reporting group title	Placebo Group

Reporting group description:

Subjects received 2 doses of placebo (saline solution), administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Reporting group title	GSK1437173A Group

Reporting group description:

Subjects received 2 doses of the candidate HZ vaccine GSK1437173A, administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Reporting group title	Placebo Group

Reporting group description:

Subjects received 2 doses of placebo (saline solution), administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2-Months schedule.

Subject analysis set title	no group
Subject analysis set type	Per protocol

Subject analysis set description:

Subjects who were not assigned to any group (subjects from pre-vaccination visit).

Primary: Number of subjects with confirmed Herpes Zoster (HZ) episode

End point title	Number of subjects with confirmed Herpes Zoster (HZ) episode

End point description:

A suspected case of HZ was defined as (1) a new rash characteristic of HZ (e.g., unilateral, dermatomal and accompanied by pain broadly defined to include allodynia, pruritus or other sensations), or a vesicular rash suggestive of VZV infection regardless of the distribution, and no alternative diagnosis; or (2) a clinical presentation (symptoms and/or signs) and specific laboratory findings* suggestive of VZV infection in the absence of characteristic HZ or VZV rash. A suspected case of HZ was confirmed either: by Polymerase Chain Reaction (PCR) or by the HZ Ascertainment Committee (HZAC), consisting of physicians with HZ expertise. This analysis does not include HZ cases occurring after the start of the treatment for relapse.

End point type	Primary

End point timeframe:

From Month 0 until the cut-off date for final analysis (median follow up was of 21 months)

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	870	851		
Units: Participants				
Participants	49	135		

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Vaccine efficacy (VE) was evaluated in the prevention of Herpes Zoster (HZ) in autologous haematopoietic stem cell transplant (HCT) recipients 18 years of agee and older.

Comparison groups	GSK1437173A Group v Placebo Group
Number of subjects included in analysis	1721
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Poisson method
Parameter estimate	Vaccine efficacy
Point estimate	68.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.56
upper limit	77.53

Notes:

[1] - Criterion: The lower limit (LL) of the 95% confidence interval (CI) for overall HZ vaccine efficacy was above 0%.

Secondary: Duration of 'worst' HZ-associated pain

End point title	Duration of 'worst' HZ-associated pain

End point description:

Duration of HZ-associated pain rated as 3 or greater on the 'worst pain' Zoster Brief Pain Inventory (ZBPI) question, following the onset of a confirmed HZ rash over the entire pain reporting period in subjects with confirmed HZ; presented as T (day) [=the sum of follow-up period (for subjects without severe worst pain T is 1, for subjects with severe worst pain T is the duration of severe worst pain) expressed in days].

End point type	Secondary

End point timeframe:

From Month 0 until the cut-off date for final analysis (median follow up was of 21 months), from the onset of a confirmed HZ rash over the entire pain reporting period

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	135		
Units: T (day)				
number (not applicable)				
T (day)	892.0	6275.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with confirmed HZ-associated complications

End point title	Number of subjects with confirmed HZ-associated complications

End point description:

This analysis excluded complications that were linked to a confirmed HZ case that occurred after the start of the relapse treatment. This analysis does not include HZ cases occurring after the start of the treatment for relapse.

End point type	Secondary

End point timeframe:

From Month 0 until the cut-off date for final analysis (median follow up was of 21 months)

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	870	851		
Units: Participants				
Participants	3	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Postherpetic Neuralgia (PHN)

End point title	Number of subjects with Postherpetic Neuralgia (PHN)

End point description:

This analysis excluded PHN episodes that were linked to a confirmed HZ case that occurred after the start of the relapse treatment.

End point type	Secondary

End point timeframe:

From Month 0 until study end (21 months median follow up)

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	870	851		
Units: Participants				
Participants	1	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Antigen-glycoprotein E (gE) antibody concentrations in a sub-cohort of subjects

End point title	Antigen-glycoprotein E (gE) antibody concentrations in a sub-cohort of subjects

End point description:

Anti-gE antibody concentrations were determined by enzyme-linked immunosorbent assay (ELISA), presented as geometric mean concentrations (GMCs) and expressed in milli-international units per milliliter (mIU/mL). The seropositivity cut-off value was greater than or equal to (≥) 97 mIU/mL.

End point type	Secondary

End point timeframe:

At Months 0, 1, 2, 13 and 25

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	76		
Units: mIU/mL				
geometric mean (confidence interval 95%)				
Anti-gE, Month 0	762.8 (568.6 to 1023.5)	555.0 (404.3 to 761.8)		
Anti-gE, Month 1	1844.2 (1282.2 to 2652.4)	556.6 (407.3 to 760.6)		
Anti-gE, Month 2	12753.2 (7973.0 to 20399.4)	443.8 (330.8 to 595.4)		
Anti-gE, Month 13	3183.8 (1869.8 to 5421.2)	503.6 (307.8 to 824.1)		
Anti-gE, Month 25	2819.0 (1387.1 to 5729.1)	527.0 (274.3 to 1012.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any and Grade 3 solicited local symptoms

End point title	Number of subjects with any and Grade 3 solicited local symptoms

End point description:

Assessed solicited local symptoms were pain, redness and swelling. Any = occurrence of the symptom regardless of intensity grade. Grade 3 pain = pain that prevented normal activity. Grade 3 redness/swelling = redness/swelling spreading beyond 100 millimeters (mm) of injection site.

End point type	Secondary

End point timeframe:

During the 7-day (Days 0-6) post-vaccination period following each dose and across doses

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	901	892		
Units: Participants				
Any Pain, Dose 1	688	56		
Grade 3 Pain, Dose 1	59	3		
Any Redness, Dose 1	187	5		
Grade 3 Redness, Dose 1	7	0		
Any Swelling, Dose 1	101	7		
Grade 3 Swelling, Dose 1	1	0		
Any Pain, Dose 2	638	45		
Grade 3 Pain, Dose 2	63	0		
Any Redness, Dose 2	231	4		
Grade 3 Redness, Dose 2	24	0		
Any Swelling, Dose 2	132	3		
Grade 3 Swelling, Dose 2	12	0		
Any Pain, Across doses	756	83		
Grade 3 Pain, Across doses	99	3		
Any Redness, Across doses	301	9		
Grade 3 Redness, Across doses	28	0		
Any Swelling, Across doses	168	9		
Grade 3 Swelling, Across doses	13	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, Grade 3 and related solicited general symptoms

End point title	Number of subjects with any, Grade 3 and related solicited general symptoms

End point description:

Assessed solicited general symptoms were fatigue, gastrointestinal symptoms, headache, myalgia, shivering and fever [defined as axillary/tympanic temperature equal to or above 37.5 degrees Celsius (°C) or rectal temperature equal to or above 38.0 °C]. Any = occurrence of the symptom regardless of intensity grade. Grade 3 symptom = symptom that prevented normal activity. Grade 3 fever = fever > 39.5 °C. Related = symptom assessed by the investigator as related to the vaccination.

End point type	Secondary

End point timeframe:

During the 7-day (Days 0-6) post-vaccination period following each dose and across doses

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	901	894		
Units: Participants				
Any Fatigue, Dose 1	356	282		
Grade 3 Fatigue, Dose 1	30	16		
Related Fatigue, Dose 1	124	55		
Any Gastrointestinal, Dose 1	150	134		
Grade 3 Gastrointestinal, Dose 1	6	7		
Related Gastrointestinal, Dose 1	41	22		
Any Headache, Dose 1	156	121		
Grade 3 Headache, Dose 1	2	3		
Related Headache, Dose 1	51	32		
Any Myalgia, Dose 1	340	170		
Grade 3 Myalgia, Dose 1	22	11		
Related Myalgia, Dose 1	170	50		
Any Shivering, Dose 1	116	73		
Grade 3 Shivering, Dose 1	6	6		
Related Shivering, Dose 1	56	27		
Any Temperature, Dose 1	60	28		
Grade 3 Temperature, Dose 1	1	0		
Related Temperature, Dose 1	27	7		
Any Fatigue, Dose 2	395	212		
Grade 3 Fatigue, Dose 2	48	20		
Related Fatigue, Dose 2	153	41		
Any Gastrointestinal, Dose 2	142	98		
Grade 3 Gastrointestinal, Dose 2	13	12		
Related Gastrointestinal, Dose 2	51	13		
Any Headache, Dose 2	232	88		
Grade 3 Headache, Dose 2	24	8		
Related Any Headache, Dose 2	95	20		
Any Myalgia, Dose 2	374	153		
Grade 3 Myalgia, Dose 2	42	9		
Related Myalgia, Dose 2	208	47		
Any Shivering, Dose 2	185	59		
Grade 3 Shivering, Dose 2	29	1		
Related Shivering, Dose 2	102	16		
Any Temperature, Dose 2	150	28		
Grade 3 Temperature, Dose 2	2	1		
Related Temperature, Dose 2	8	8		
Any Fatigue, Across doses	508	340		
Grade 3 Fatigue, Across doses	66	31		
Related Fatigue, Across doses	210	79		
Any Gastrointestinal, Across doses	238	183		

Grade 3 Gastrointestinal, Across doses	18	17		
Related Gastrointestinal, Across doses	79	30		
Any Headache, Across doses	302	166		
Grade 3 Headache, Across doses	26	10		
Related Headache, Across doses	123	46		
Any Myalgia, Across doses	484	234		
Grade 3 Myalgia, Across doses	56	19		
Related Myalgia, Across doses	279	83		
Any Shivering, Across doses	237	115		
Grade 3 Shivering, Across doses	35	7		
Related Shivering, Across doses	131	38		
Any Temperature, Across doses	183	50		
Grade 3 Temperature, Across doses	3	1		
Related Temperature, Across doses	101	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any, Grade 3 and related unsolicited adverse events (AEs)

End point title	Number of subjects with any, Grade 3 and related 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	922	924		
Units: Participants				
Any AE(s)	360	353		
Grade 3 AE(s)	60	47		
Related AE(s)	31	23		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Potential immune-mediated diseases (pIMDs) are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurologic disorders of interest which may or may not have an autoimmune aetiology.

End point type	Secondary

End point timeframe:

From Month 0 up to 365 days post last vaccination

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	922	924		
Units: Participants				
Any pIMDs	13	8		
Related pIMDs	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any relapse

End point title	Number of subjects with any relapse

End point description:

Relapse was defined as the occurrence of the underlying malignancy or disease for which the HCT was undertaken.

End point type	Secondary

End point timeframe:

From Month 0 until study end (approximate median of 29 months follow-up - minimum of 1 year and maximum of 4 years)

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	922	924		
Units: Participants				
Participants	239	253		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with any SAE and Related SAEs to GSK study vaccine/placebo

End point title	Number of subjects with any SAE and Related SAEs to GSK study vaccine/placebo

End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or is a congenital anomaly/birth defect in the offspring of a study subject. This enpoint also presents SAES related to the GSK study vaccine/placebo.

End point type	Secondary

End point timeframe:

From Month 0 up to 365 days post last vaccination (approximate median of 29 months follow-up - minimum of 1 year and maximum of 4 years)

End point values	GSK1437173A Group	Placebo Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	922	924		
Units: Participants				
Any SAEs, up to Month 13	263	241		
Related SAEs, up to Month 13	3	4		
Any SAEs, up to Study End	329	310		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Fatal SAEs and SAEs related to study participation or to a GSK concomitant medication or vaccination

End point title	Number of subjects with Fatal SAEs and SAEs related to study participation or to a GSK concomitant medication or vaccination

End point description:

Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life threatening, require hospitalization or prolongation of hospitalization, result in disability/incapacity or is a congenital anomaly/birth defect in the offspring of a study subject. This endpoint presents fatal SAEs and SAEs related to study participation or to a concurrent GSK medication/vaccine.

End point type	Secondary

End point timeframe:

From the Pre-vaccination visit (Up to 110 days prior Month 0) until study end (approximate median of 29 months follow-up - minimum 1 year and maximum 4 years)

End point values	GSK1437173A Group	Placebo Group	no group	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	922	924	3	
Units: Participants				
Fatal SAEs	118	124	0	
Related SAEs	37	43	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Solicited symptoms: Days 0-6 post-vaccination; Unsolicited adverse events (AEs): Days 0-29 post-vaccination; SAEs: during the entire study period, up to 365 days post last vaccination (minimum 1 year and maximum 4 years).

Adverse event reporting additional description:

SAEs: Any SAE, up to 365 days post last vaccination; Fatal & Related SAEs: during the entire study period (approximate median of 29 months follow up - minimum 1 year and maximum 4 years)
pIMDs: up to 365 days post last vaccination; Relapses: the entire study period (approximate median of 29 months follow up - minimum 1 year and maximum 4 years)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo Group

Reporting group description:

Subjects received 2 doses of placebo (saline solution), administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2 Months schedule.

Reporting group title	GSK1437173A Group

Reporting group description:

Subjects received 2 doses of the candidate HZ vaccine GSK1437173A, administered intramuscularly (IM) in deltoid region of the non-dominant arm, according to a 0, 1-2 Months schedule.

Serious adverse events	Placebo Group	GSK1437173A Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	310 / 924 (33.55%)	329 / 922 (35.68%)	
number of deaths (all causes)	124	118	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myeloid leukaemia			
subjects affected / exposed	8 / 924 (0.87%)	6 / 922 (0.65%)	
occurrences causally related to treatment / all	0 / 8	0 / 6	
deaths causally related to treatment / all	0 / 6	0 / 3	
Acute promyelocytic leukaemia			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angiocentric lymphoma			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioimmunoblastic t-cell lymphoma			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	11 / 924 (1.19%)	12 / 922 (1.30%)	
occurrences causally related to treatment / all	0 / 11	0 / 12	
deaths causally related to treatment / all	0 / 5	0 / 3	
Benign breast neoplasm			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct cancer			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Burkitt's lymphoma			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system lymphoma			
subjects affected / exposed	2 / 924 (0.22%)	5 / 922 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 3	
Diffuse large b-cell lymphoma			
subjects affected / exposed	11 / 924 (1.19%)	13 / 922 (1.41%)	
occurrences causally related to treatment / all	0 / 11	0 / 14	
deaths causally related to treatment / all	0 / 4	0 / 8	
Epstein-barr virus associated lymphoproliferative disorder			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ewing's sarcoma metastatic			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hairy cell leukaemia			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hodgkin's disease			
subjects affected / exposed	3 / 924 (0.32%)	10 / 922 (1.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 2	
Leiomyosarcoma			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoma			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	13 / 924 (1.41%)	13 / 922 (1.41%)	
occurrences causally related to treatment / all	0 / 13	0 / 13	
deaths causally related to treatment / all	0 / 10	0 / 7	
Malignant melanoma			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant ovarian cyst			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle cell lymphoma			
subjects affected / exposed	4 / 924 (0.43%)	6 / 922 (0.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 4	
Marginal zone lymphoma			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma malignant			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to adrenals			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastatic carcinoma of the bladder			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloid leukaemia			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-hodgkin's lymphoma			
subjects affected / exposed	9 / 924 (0.97%)	4 / 922 (0.43%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 7	0 / 1	
Non-small cell lung cancer			

subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Peripheral t-cell lymphoma unspecified			
subjects affected / exposed	0 / 924 (0.00%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Plasma cell leukaemia			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Plasma cell myeloma			
subjects affected / exposed	70 / 924 (7.58%)	90 / 922 (9.76%)	
occurrences causally related to treatment / all	0 / 71	0 / 95	
deaths causally related to treatment / all	0 / 43	0 / 43	
Plasmacytoma			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Precursor t-lymphoblastic lymphoma/leukaemia			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Prostate cancer			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyosarcoma			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma			
subjects affected / exposed	3 / 924 (0.32%)	7 / 922 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 3	
Testicular cancer metastatic			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Testis cancer			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	3 / 924 (0.32%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Adverse drug reaction			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	2 / 924 (0.22%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac death			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Fatigue			
subjects affected / exposed	0 / 924 (0.00%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
General physical health deterioration			
subjects affected / exposed	3 / 924 (0.32%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pain			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 924 (0.87%)	10 / 922 (1.08%)	
occurrences causally related to treatment / all	0 / 9	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amyloidosis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic graft versus host disease			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease			
subjects affected / exposed	0 / 924 (0.00%)	6 / 922 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 2	
Graft versus host disease in gastrointestinal tract			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in liver			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Graft versus host disease in skin			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute promyelocytic leukaemia differentiation syndrome			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	3 / 924 (0.32%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthmatic crisis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 924 (0.32%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoptysis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	0 / 924 (0.00%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 924 (0.22%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 924 (0.43%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 924 (0.32%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug use disorder			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Immunoglobulins decreased			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 924 (0.00%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 924 (0.00%)	4 / 922 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fibula fracture			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis chemical			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	0 / 924 (0.00%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Subdural haemorrhage			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 924 (0.11%)	4 / 922 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac amyloidosis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardiac disorder			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 924 (0.22%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiac failure congestive			
subjects affected / exposed	3 / 924 (0.32%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pulseless electrical activity			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular dysfunction			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral thrombosis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal fistula			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Demyelinating polyneuropathy			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disturbance in attention			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-barre syndrome			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	0 / 924 (0.00%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hemiparesis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinsonism			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post herpetic neuralgia			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radicular pain			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	3 / 924 (0.32%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Spinal cord compression			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	3 / 924 (0.32%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vith nerve paralysis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	3 / 924 (0.32%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytopenia			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	12 / 924 (1.30%)	14 / 922 (1.52%)	
occurrences causally related to treatment / all	0 / 13	0 / 16	
deaths causally related to treatment / all	0 / 2	0 / 2	
Haemolytic anaemia			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 924 (0.32%)	5 / 922 (0.54%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	6 / 924 (0.65%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Thrombocytopenia			

subjects affected / exposed	4 / 924 (0.43%)	4 / 922 (0.43%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 1	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematotympanum			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tympanic membrane perforation			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 924 (0.32%)	5 / 922 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			

subjects affected / exposed	0 / 924 (0.00%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery thrombosis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal achalasia			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bile duct obstruction			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis cholestatic			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertension			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parapsoriasis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			

subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 924 (0.43%)	12 / 922 (1.30%)	
occurrences causally related to treatment / all	0 / 4	0 / 12	
deaths causally related to treatment / all	0 / 3	0 / 6	
Bladder neck obstruction			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 924 (0.22%)	4 / 922 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Renal impairment			
subjects affected / exposed	0 / 924 (0.00%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Kyphosis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 924 (0.11%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic scleroderma			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Abscess			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	3 / 924 (0.32%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	6 / 924 (0.65%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			

subjects affected / exposed	2 / 924 (0.22%)	4 / 922 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 924 (0.43%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	3 / 924 (0.32%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Device related infection			
subjects affected / exposed	3 / 924 (0.32%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 924 (0.00%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-barr viraemia			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 924 (0.00%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal pharyngitis			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Furuncle			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 924 (0.22%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis salmonella			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1n1 influenza			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis b			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis b reactivation			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes simplex			

subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	5 / 924 (0.54%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster cutaneous disseminated			
subjects affected / exposed	10 / 924 (1.08%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	1 / 10	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningitis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningoencephalitis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Influenza			
subjects affected / exposed	7 / 924 (0.76%)	11 / 922 (1.19%)	
occurrences causally related to treatment / all	0 / 7	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	2 / 924 (0.22%)	6 / 922 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	4 / 924 (0.43%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis meningococcal			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis pneumococcal			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis viral			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningoencephalitis herpetic			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycoplasma infection			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	3 / 924 (0.32%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media chronic			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	4 / 924 (0.43%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 924 (0.11%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	41 / 924 (4.44%)	55 / 922 (5.97%)	
occurrences causally related to treatment / all	0 / 46	0 / 64	
deaths causally related to treatment / all	0 / 10	0 / 4	
Pneumonia bacterial			

subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia necrotising			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			

subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchitis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	1 / 924 (0.11%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	10 / 924 (1.08%)	7 / 922 (0.76%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory tract infection bacterial			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	8 / 924 (0.87%)	15 / 922 (1.63%)	
occurrences causally related to treatment / all	0 / 9	0 / 15	
deaths causally related to treatment / all	0 / 4	0 / 10	
Septic shock			
subjects affected / exposed	5 / 924 (0.54%)	7 / 922 (0.76%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 4	0 / 7	
Serratia sepsis			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinusitis			
subjects affected / exposed	2 / 924 (0.22%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis bacterial			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Spinal cord abscess			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal abscess			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal scalded skin syndrome			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 924 (0.11%)	4 / 922 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 924 (0.22%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 924 (0.22%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Viral infection			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 924 (0.22%)	2 / 922 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	2 / 924 (0.22%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 924 (0.00%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 924 (0.00%)	4 / 922 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 924 (0.11%)	1 / 922 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 924 (0.11%)	3 / 922 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	1 / 924 (0.11%)	0 / 922 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo Group	GSK1437173A Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	485 / 924 (52.49%)	813 / 922 (88.18%)	
Nervous system disorders			
Headache			
subjects affected / exposed	170 / 924 (18.40%)	304 / 922 (32.97%)	
occurrences (all)	215	391	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	117 / 924 (12.66%)	238 / 922 (25.81%)	
occurrences (all)	134	303	
Fatigue			
subjects affected / exposed	341 / 924 (36.90%)	509 / 922 (55.21%)	
occurrences (all)	496	754	
Pain			
subjects affected / exposed	84 / 924 (9.09%)	757 / 922 (82.10%)	
occurrences (all)	103	1327	
Pyrexia			
subjects affected / exposed	57 / 924 (6.17%)	192 / 922 (20.82%)	
occurrences (all)	66	224	
Swelling			
subjects affected / exposed	9 / 924 (0.97%)	168 / 922 (18.22%)	
occurrences (all)	10	233	
Gastrointestinal disorders			

Gastrointestinal disorder			
subjects affected / exposed	185 / 924 (20.02%)	238 / 922 (25.81%)	
occurrences (all)	235	293	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	11 / 924 (1.19%)	304 / 922 (32.97%)	
occurrences (all)	11	422	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	236 / 924 (25.54%)	485 / 922 (52.60%)	
occurrences (all)	327	718	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2012	• To address a request from FDA, the conditions for final triggered analysis include that all subjects need to have completed Visit 4 (Month 13). Aligned with this update, the definition of study end has been clarified, i.e., study end will take place when the conditions for final triggered analysis are met and follow-up is completed for each suspected HZ case that occurs up to and including the cut-off date for final analysis. The synopsis, Sections 3, 5.4.2.3, 5.4.2.4, 5.5, 5.6.4.12, 5.6.4.16 and 8.3.1 have been updated accordingly. A clarification has been added in the Synopsis, Sections 3 and 10.7.1 that the end of study analysis, if performed, will be descriptive. • To address a request from FDA, the following study objectives (tertiary objectives) have been added in the Synopsis and in Section 2.3. To evaluate VE in the prevention of HZ in autologous HCT recipients 18 years of age and older when all subjects reach 1 year post-HCT; To evaluate VE in the prevention of PHN in autologous HCT recipients 18 years of age and older with confirmed HZ. Endpoints related to these objectives have been added in the Synopsis and in Section 10.3 and information regarding additional statistical analyses in Sections 10.8.2.1 and 10.8.2.2. Wording in Section 5.4.2.1.3 has been updated accordingly. • To address a request from FDA, the allowed interval between Visit 2 (Month 1, the day of the second dose of study vaccine/placebo) and Visit 4 (Month 13, approximately 12 months after the second dose of study vaccine/placebo) has been modified (Section 5.5).
16 May 2012	• At the European Medicines Agency's (EMA) request, GSK Biologicals has updated its procedure for emergency unblinding during the conduct of a clinical study. According to the revised procedure, the responsibility and the decision to break the treatment code in emergency situations resides solely with the investigator and consequently, the investigator will have full authority to break the treatment code. Section 8.8 and the Sponsor Information page has been updated accordingly. • To improve data collection, changes have been made in instructions for Zoster Brief Pain Inventory (ZBPI) completion. Subjects should start completing a ZBPI questionnaire with the appearance of symptoms suggestive of HZ and continue daily with ZBPI completion, instead of completing retrospectively a ZBPI questionnaire at Visit HZ-1 for the elapsed time between the HZ onset and 24 hours before Visit HZ-1 (Sections 5.4.1, 5.4.2.3, 5.5, 5.6.4.13 and 10.8.2.5); • On request from some sites, for women of childbearing potential, prior to vaccination a serum pregnancy test instead of a urine pregnancy test can be performed if this is required by country, local or ethics committee regulations. In case a serum pregnancy test is required, a blood sample will be collected and used for the test as per local guidance (Synopsis, Sections 3, 5.5, 5.6.3.4, 5.6.4.5 and 5.7.2); • A clarification has been added that certain required signatories on the Protocol Amendment Investigator Agreement page are country-specific; • Study entry occurs at the pre-vaccination visit. Therefore it has been detailed that subjects should be 18 years of age or above at study entry (Section 4.2, Section 12.1); • For clarification, further details have been added regarding the prophylactic antiviral therapy to take into account as exclusion criterion at study entry (Section 4.3) and as medication that may lead to the elimination of a subject from ATP analyses (Section 6.6.1).

31 July 2012	• At the Medicines and Healthcare products Regulatory Agency (MHRA) request (MHRA Reference 19842/0215/001-0001), the occurrence of herpes zoster (HZ) with characteristic Varicella Zoster Virus [VZV] or HZ rash (protocol criterion 1) and postherpetic neuralgia (PHN) associated with a case of HZ will be considered as adverse events (AEs). These events will be recorded in HZ-specific eCRF screens. If these occurrences meet the definition of a serious adverse event (SAE), then they will be reported as such. (Sections 5.4.2.1.3, 5.4.2.3, 6.7, 8.1.1, 8.2.1, 8.3.1 and 8.4.1) • As the occurrence of HZ and PHN are efficacy endpoints, cases of HZ with characteristic VZV or HZ rash and PHN associated with a case of HZ will be considered Population-Related Events (PREs). If they meet the definition of a SAE, they will be reported via the specific SAE screens only if they meet the criteria for expedited reporting (Sections 5.4.2.1.1, 5.4.2.1.3, 5.4.2.3, 8.1.1, 8.2.1, 8.3.1 and 8.4.1) • Cases of HZ without characteristic VZV or HZ rash (protocol criterion 2) will continue to be reported as SAEs. It will be added that they will be specified on the SAE screen to be related to HZ (and not "a case of HZ without characteristic VZV or HZ rash") (Sections 5.4.2.1.1, 5.4.2.4 and 8.3.1) • HZ complications different from PHN will continue to be reported as AEs or SAEs (as appropriate). It will be added that they will be specified on the AE or SAE screen to be related to HZ (and not as "a HZ complication"). (Section 8.3.1)
01 August 2012	• In response to FDA/CBER's 25MAY2012 comments on the protocol, cases of suspected HZ will not be considered a confirmed case of HZ for the efficacy analysis if they potentially could constitute a primary VZV infection (varicella). For subjects born in 1980 or later or before 1980 in a tropical region, and with no serological evidence of prior VZV infection at the time of Visit 1, a case of suspected HZ with a disseminated onset or a VZV infection without characteristic rash (criterion 2) may in reality represent a primary VZV infection. For such subjects, blood samples collected at Visit 1 (prior to vaccination) will now be tested for VZV serological status. (Sections 5.4.2.1.2, 5.5, 5.7.2, 5.7.3, 5.7.4, Appendix 1, Appendix 2) • In response to FDA/CBER's 25MAY2012 comments on the protocol, it is now been added that pIMDs, relapses and HZ complications other than PHN may be serious AEs. (Section 8.5.1) • In response to FDA/CBER's 25MAY2012 comments on the protocol, clarifications have been made to indicate what study procedures the subject would have to complete if a case which had been clinically diagnosed as HZ is no longer considered HZ by the investigator. (Section 5.4.2.3) • In response to FDA/CBER's 25MAY2012 comments on the protocol, clarifications have been made to explain when follow-up of HZ with characteristic VZV or HZ rash is completed for cases accrued close to the end of the study. Modifications have been made to increase the likelihood of detecting cases of PHN occurring close to the end of the study. (Synopsis and Sections 3, 5.4.2.3, 5.4.2.4, 5.6.4.12, 5.6.4.16, 10.7.1) • In response to FDA/CBER's 25MAY2012 comments on the protocol, clarifications have been made to indicate that illiterate subjects should have a designated person to provide assistance with the "real time" completion of questionnaires and diary cards. (Section 5.4.1)
26 August 2012	• To address a concern of the Independent Data Monitoring Committee (IDMC), it has been specified that thrombocytopenia that in the judgment of the investigator would make intramuscular injection unsafe, constitutes a contraindication to administration of gE/AS01B study vaccine or placebo at that point in time (Section 6.5). The wording 'subsequent ' has been removed from the title of the section to indicate that the section also includes contraindications to be checked prior to the first vaccination. The order of the paragraphs has been changed to describe firstly the contraindications to be checked prior to the first and second vaccination, and secondly the absolute contraindications to be checked prior to the second vaccination. • In a footnote to the study design overview diagram (Section 3) and in a footnote to the List of study procedures (Section 5.5, Table 5) it has been clarified that each subject will be followed at least until he/she completes Visit 4. If conditions for study end are met, monthly contacts after Visit 4, Visit 5, and monthly contacts after Visit 5 may not take place in some subjects. A typographical error has been corrected.

05 May 2014	• The randomization system (SBIR application) takes into account minimization factors for the randomized allocation of subjects into the study groups. These factors are taken into account by the system to decrease the risk of having unbalanced groups in the subjects' characteristics at baseline and in this way increase the robustness of the groups' comparison. During the set-up of the SBIR application, the minimization factors center and gender were included but were not specified in the protocol. They have now been specified in the protocol (Section 3, Section 5.2.2.2). • The sample size increase is the result of the review of original study assumptions related to incidence rate of herpes zoster cases after autologous stem cell transplant and recalculation of the non evaluability rate of subjects based on observed data. The increase in the sample size is needed to ensure accrual of the necessary number of cases needed to perform the finalanalysis. Furthermore, this protocol amendment allows earlier termination of enrolment if the target number of HZ cases for the final analysis is reached (Section 3, Table 1, Section 4.1, Section 10.4.4, and Table 24). • The number of HZ cases required to trigger the interim analysis has been increased from 46 to 60. This increases the probability to demonstrate vaccine efficacy at the moment of the interim analysis, while maintaining the alpha spent for the interim analysis at an acceptable level (Section 10.4.4, Table 24, Section 10.7.2) • List of potential immune-mediated diseases has been updated (Section 8.1.5.1, Table 19). • The cut-off of the gE-specific ELISA assay has been changed from 18 to 97 mIU/mL.
24 July 2015	• The interim analyses (IA) for efficacy, safety and immunogenicity have been cancelled. • Due to the cancellation of the efficacy interim analysis, the type I error (alpha) used for final analysis (FA) has changed from 4.4% to 5% (combining both previously calculated alpha for interim and final analysis). This lead to a change of the two-sided confidence interval for final analysis from 95.6% to 95.0%. • As the final analysis is expected to be triggered by last subject having Visit 4, it is anticipated that some subjects from the sub-cohorts for CMI and humoral immunogenicity will not have reached their Visit 5 time point for their last blood sampling. As the end of study criteria are triggered by the FA data cut-off, CMI and humoral immunogenicity analysis blood sampling will not be performed for these subjects at this timepoint. Sections related to sampling and analysis have been modified. • The intervals between vaccinations (dose 1 to dose 2) and between dose 2 and blood sampling at Visit 3 (i.e. the 1 month post dose 2 visit) for inclusion in the According to Protocol cohort for immunogenicity/persistence phase are being enlarged to respectively 30-84 days and 21-63 days. The observation and interpretation of the immunogenicity/persistence data are not anticipated to be compromised by this modification. The increased flexibility will allow meaningful analysis of the data collected in this immunocompromised populations, where the underlying disease and implications of its treatment (such as cancer treatment schedule, side effects of the concomitant treatment) lead to a higher number of out of window visits compared to what is observed in a healthy population.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported