

**Clinical trial results:**

A double-blind, randomized, placebo-controlled Phase III study to assess the efficacy of recMAGE-A3 + AS15 ASCI as adjuvant therapy in patients with MAGE-A3 positive resected stage III melanoma

Summary

EudraCT number	2008-002447-16
Trial protocol	IE DE BE CZ FR NL IT SE EE ES AT GR BG GB
Global end of trial date	15 March 2016

Results information

Result version number	v2 (current)
This version publication date	22 February 2021
First version publication date	15 October 2016
Version creation reason	• Correction of full data set Alignment in the endpoints and safety sections.

Trial information**Trial identification**

Sponsor protocol code	111482
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00796445
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 Disclosure Advisor, GlaxoSmithKline Biologicals, 044 2089-904466, GSKClinicalSupportHD@gsk.com
Scientific contact	Clinical Disclosure Advisor, 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	15 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 September 2015
Global end of trial reached?	Yes
Global end of trial date	15 March 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical efficacy in terms of disease-free survival (DFS) of recMAGE-A3 + AS15 ASCI compared to placebo in the overall study population of patients with completely resected stage III cutaneous melanoma with macroscopic lymph node involvement;
To demonstrate the clinical efficacy in terms of DFS of the recMAGE-A3 + AS15 ASCI compared to placebo in the population presenting the potentially favorable gene expression signature.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 December 2008
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	Argentina: 5
Country: Number of subjects enrolled	Australia: 126
Country: Number of subjects enrolled	Austria: 29
Country: Number of subjects enrolled	Belgium: 25
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Czech Republic: 40
Country: Number of subjects enrolled	Estonia: 10
Country: Number of subjects enrolled	France: 303
Country: Number of subjects enrolled	Germany: 184
Country: Number of subjects enrolled	Greece: 7
Country: Number of subjects enrolled	Ireland: 15
Country: Number of subjects enrolled	Israel: 4
Country: Number of subjects enrolled	Italy: 96
Country: Number of subjects enrolled	Japan: 7
Country: Number of subjects enrolled	Mexico: 3

Country: Number of subjects enrolled	Netherlands: 21
Country: Number of subjects enrolled	Norway: 14
Country: Number of subjects enrolled	Poland: 69
Country: Number of subjects enrolled	Romania: 3
Country: Number of subjects enrolled	Russian Federation: 63
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Ukraine: 44
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	United States: 209
Worldwide total number of subjects	1351
EEA total number of subjects	872

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)	958
From 65 to 84 years	384
85 years and over	9

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of 1351 patients enrolled, 6 did not receive treatment and were excluded, hence 1345 patients were included in the Total treated population (895 in MAGE-A3 Group, 450 in Placebo Group). Between the final and follow-up analyses, 1 patient (in MAGE-A3 Group) had an invalid ICF and was not included in the follow-up analysis, which included 1344 patients

Pre-assignment period milestones

Number of subjects started	1351
Number of subjects completed	1345

Pre-assignment subject non-completion reasons

Reason: Number of subjects	No treatment received: 6
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Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MAGE-A3 (as treated) Group

Arm description:

Patients who received up to 13 doses of recMAGE-A3 + AS15 ASCI.

Arm type	Experimental
Investigational medicinal product name	recMAGE-A3 recombinant protein formulated in AS15 adjuvant
Investigational medicinal product code	recMAGE-A3 + AS15
Other name	GSK 2132231A, ASCI
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The study product was administered intramuscularly in 13 doses over 27 months: 5 doses of placebo at 3-week intervals, followed by 8 doses of placebo at 12-week intervals.

Arm title	Placebo (as treated) Group
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Arm description:

Patients who received up to 13 doses of placebo.

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

Dosage and administration details:

The study product was administered intramuscularly in 13 doses over 27 months: 5 doses of placebo at 3-week intervals, followed by 8 doses of placebo at 12-week intervals.

Number of subjects in period 1^[1]	MAGE-A3 (as treated) Group	Placebo (as treated) Group
Started	895	450
Completed	310	158
Not completed	585	292
Adverse event, serious fatal	10	5
Consent withdrawn by subject	18	9
Adverse event, non-fatal	4	-
Invalid informed consent form	1	-
Unspecified	10	7
Disease progression/recurrence	537	268
Protocol deviation	5	3

Notes:

[1] - 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: Out of the subjects enrolled in the trial, only the ones who received treatment according to the protocol started the study.

Baseline characteristics

Reporting groups

Reporting group title	MAGE-A3 (as treated) Group
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Reporting group description:

Patients who received up to 13 doses of recMAGE-A3 + AS15 ASCI.

Reporting group title	Placebo (as treated) Group
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Reporting group description:

Patients who received up to 13 doses of placebo.

Reporting group values	MAGE-A3 (as treated) Group	Placebo (as treated) Group	Total
Number of subjects	895	450	1345
Age categorical Units: Subjects			

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	56	56.2	
standard deviation	± 13.51	± 13.66	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	345	188	533
Male	550	262	812

End points

End points reporting groups

Reporting group title	MAGE-A3 (as treated) Group
Reporting group description: Patients who received up to 13 doses of recMAGE-A3 + AS15 ASCI.	
Reporting group title	Placebo (as treated) Group
Reporting group description: Patients who received up to 13 doses of placebo.	
Subject analysis set title	GS+ MAGE-A3 Sub-Group
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subset of patients with the pre-specified gene signature, receiving the MAGE-A3 ASCI product. Gene-signature sub-grouping was based on patients having a potentially predictive gene signature, as assessed at screening.	
Subject analysis set title	GS+ Placebo Sub-Group
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subset of patients with the pre-specified gene signature, receiving placebo. Gene-signature sub-grouping was based on patients having a potentially predictive gene signature, as assessed at screening.	
Subject analysis set title	GS- MAGE-A3 Sub-Group
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subset of patients without the pre-specified gene signature, receiving the MAGE-A3 ASCI product. Gene-signature sub-grouping was based on patients having a potentially predictive gene signature, as assessed at screening.	
Subject analysis set title	GS- Placebo Sub-Group
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subset of patients without the pre-specified gene signature, receiving placebo. Gene-signature sub-grouping was based on patients having a potentially predictive gene signature, as assessed at screening.	
Subject analysis set title	MAGE-A3 (as randomized) Group
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who were allocated by the randomization system for receiving up to 13 doses of recMAGE-A3 + AS15 ASCI.	
Subject analysis set title	Placebo (as randomized) Group
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who were allocated by the randomization system for receiving up to 13 doses of placebo.	

Primary: Disease Free Survival (DFS)

End point title	Disease Free Survival (DFS)
End point description: DFS = time to event from randomization to the date of first disease recurrence or the date of death (whatever cause), whichever occurred first. DFS expressed as person-year rate i.e number of patients with at least one event over the sum of follow-up periods (in years), until first occurrence of a recurrence/death. Types of recurrence to be considered as an event included loco-regional and distant metastases. Any death occurring without prior documentation of tumor recurrence was considered as an event. If no event occurred by the time of analysis, then time to event was censored at the last assessment date of the patient. Any new primary cancer at another site, including second primary melanoma, was not considered as a recurrence and had to be reported as a Serious Adverse Event. The analysis was performed on the Total Treated population - as randomized, which included patients in the treatment groups as allocated by the randomization system at the start of the study.	
End point type	Primary

End point timeframe:

At Final analysis (Month 30 = Year 2.5) and at follow-up analysis (up to Year 5)

End point values	GS+ MAGE-A3 Sub-Group	GS+ Placebo Sub-Group	GS- MAGE-A3 Sub-Group	GS- Placebo Sub-Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	200	116	255	126
Units: First events per person-year				
number (not applicable)				
DFS, Final analysis (N=200,116,255,126,893,452)	0.5	0.46	0.437	0.442
DFS, Follow-up analysis(N=200,116,255,126,892,452)	0.345	0.335	0.316	0.319

End point values	MAGE-A3 (as randomized) Group	Placebo (as randomized) Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	893	452		
Units: First events per person-year				
number (not applicable)				
DFS, Final analysis (N=200,116,255,126,893,452)	0.505	0.478		
DFS, Follow-up analysis(N=200,116,255,126,892,452)	0.366	0.345		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: At Final analysis (Month 30 = Year 2.5). The aim of this analysis was to demonstrate the clinical efficacy in terms of disease-free survival (DFS) of recMAGE-A3 + AS15 ASCI compared to placebo in the overall study population of patients with completely resected stage III cutaneous melanoma with macroscopic lymph node involvement.	
Comparison groups	MAGE-A3 (as randomized) Group v Placebo (as randomized) Group
Number of subjects included in analysis	1345
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8566
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.013

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.879
upper limit	1.169

Statistical analysis title	Statistical analysis 2
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Statistical analysis description:

At Final analysis (Month 30 = Year 2.5).

The aim of this analysis was to demonstrate the clinical efficacy in terms of DFS of the recMAGE-A3 + AS15 ASCI compared to placebo in the population presenting the potentially favorable gene expression signature.

Comparison groups	GS+ Placebo Sub-Group v GS+ MAGE-A3 Sub-Group
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4821
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.828
upper limit	1.491

Statistical analysis title	Statistical analysis 3
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Statistical analysis description:

At Final analysis (Month 30 = Year 2.5).

The aim of this analysis was to demonstrate the clinical efficacy in terms of DFS of the recMAGE-A3 + AS15 ASCI compared to placebo in the population without the potentially favorable gene expression signature.

Comparison groups	GS- Placebo Sub-Group v GS- MAGE-A3 Sub-Group
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5375
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.915
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.691
upper limit	1.212

Statistical analysis title	Statistical analysis 4
Statistical analysis description:	
At Follow-up analysis (Up to Year 5). The aim of this analysis was to demonstrate the clinical efficacy in terms of disease-free survival (DFS) of recMAGE-A3 + AS15 ASCI compared to placebo in the overall study population of patients with completely resected stage III cutaneous melanoma with macroscopic lymph node involvement.	
Comparison groups	MAGE-A3 (as randomized) Group v Placebo (as randomized) Group
Number of subjects included in analysis	1345
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7534
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.175

Statistical analysis title	Statistical analysis 5
Statistical analysis description:	
At Follow-up analysis (Up to Year 5). The aim of this analysis was to demonstrate the clinical efficacy in terms of DFS of the recMAGE-A3 + AS15 ASCI compared to placebo in the population presenting the potentially favorable gene expression signature.	
Comparison groups	GS+ Placebo Sub-Group v GS+ MAGE-A3 Sub-Group
Number of subjects included in analysis	316
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5385
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.094
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.821
upper limit	1.457

Statistical analysis title	Statistical analysis 6
Statistical analysis description:	
At Follow-up analysis (Up to Year 5). The aim of this analysis was to demonstrate the clinical efficacy in terms of DFS of the recMAGE-A3 + AS15 ASCI compared to placebo in the population without the potentially favorable gene expression signature.	

Comparison groups	GS- Placebo Sub-Group v GS- MAGE-A3 Sub-Group
Number of subjects included in analysis	381
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5419
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.918
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.698
upper limit	1.207

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) was defined as the time to event from randomization to the date of death, irrespective of the cause of death; OS was expressed as the person-year rate i.e. the number of patients with death over the sum of the follow-up periods in years; Patients alive at the time of the analysis were censored on the date last known to be alive. The analysis was performed on the Total Treated population - as randomized, which included patients in the treatment groups as allocated by the randomization system at the start of the study.	
End point type	Secondary
End point timeframe:	
At final analysis (Month 30 = Year 2.5) and Follow-up analysis (Up to Year 5).	

End point values	GS+ MAGE-A3 Sub-Group	GS+ Placebo Sub-Group	GS- MAGE-A3 Sub-Group	GS- Placebo Sub-Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	200	116	255	126
Units: Events per person-year				
number (not applicable)				
OS, Final analysis (N=200,116,255,126,893,452)	0.172	0.188	0.165	0.151
OS, Follow-up analysis (N=200,116,255,126,892,452)	0.146	0.153	0.132	0.12

End point values	MAGE-A3 (as randomized) Group	Placebo (as randomized) Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	893	452		
Units: Events per person-year				
number (not applicable)				
OS, Final analysis (N=200,116,255,126,893,452)	0.177	0.165		

OS, Follow-up analysis (N=200,116,255,126,892,452)	0.146	0.14		
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Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free specific survival (DFSS)

End point title	Disease-free specific survival (DFSS)
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End point description:

Disease Free Specific Survival (DFSS) was defined as the time to event from randomization to the date of first recurrence of disease or date of death due to melanoma (cause as assessed by investigator), whichever occurred first. DFSS was expressed as the person-year rate i.e. the number of patients with at least one event over the sum of the follow-up periods in years. Patients who died due to a cause other than the disease under study and patients alive at the time of analysis were censored on the date of last assessment (visit or tumor assessment). The analysis was performed on the Total Treated population - as randomized, which included patients in the treatment groups as allocated by the randomization system at the start of the study.

End point type	Secondary
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End point timeframe:

At Final analysis (Month 30 = Year 2.5)

End point values	GS+ MAGE-A3 Sub-Group	GS+ Placebo Sub-Group	GS- MAGE-A3 Sub-Group	GS- Placebo Sub-Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	200	116	255	126
Units: First events per person-year number (not applicable)	0.5	0.46	0.434	0.442

End point values	MAGE-A3 (as randomized) Group	Placebo (as randomized) Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	893	452		
Units: First events per person-year number (not applicable)	0.499	0.478		

Statistical analyses

No statistical analyses for this end point

Secondary: Distant metastasis-free survival (DMFS)

End point title	Distant metastasis-free survival (DMFS)
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End point description:

Distant Metastasis Free Survival (DMFS) was defined as the time to event from randomization to the date of first distant metastasis or date of death, whichever occurred first. DMFS was expressed as the person-year rate i.e. the number of patients with at least one event over the sum of the follow-up periods in year. Patients alive and without distant metastases were censored at the date of last assessment (visit or tumor assessment, or date of last tumor assessment as documented during the yearly contact follow-up period). The analysis was performed on the Total Treated population - as randomized, which included patients in the treatment groups as allocated by the randomization system at the start of the study.

End point type	Secondary
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End point timeframe:

At Final analysis (Month 30 = Year 2.5)

End point values	GS+ MAGE-A3 Sub-Group	GS+ Placebo Sub-Group	GS- MAGE-A3 Sub-Group	GS- Placebo Sub-Group
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	200	116	255	126
Units: First events per person-year				
number (not applicable)	0.388	0.337	0.334	0.307

End point values	MAGE-A3 (as randomized) Group	Placebo (as randomized) Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	893	452		
Units: First events per person-year				
number (not applicable)	0.387	0.342		

Statistical analyses

No statistical analyses for this end point

Secondary: Health-related quality of life

End point title	Health-related quality of life
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End point description:

The assessment of health-related quality of life was restricted to patients who consented to study participation after Protocol Amendment 1 became effective at their study site, and for whom a validated version of the Euro Quality of Life-5D (EQ-5D) questionnaire was available in their native language. The EQ-5D comprises a 5-dimensional descriptive system (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), where each item has 3 levels and together they define 243 possible health states. For each health state, a value (utility) was determined by using an additive algorithm. These utility scores were calculated for each patient at each timepoint at which an EQ-5D questionnaire was completed. The score had a maximum value of 1.0 corresponding to full health level, while lower scores, down to a minimum value of 0.0 reflected degradation in the health-related quality of life.

End point type	Secondary
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End point timeframe:

At Week 0, 6, 12 [on the day of and on the day after treatment administration (TA)], at Month 6, 9, 12, 24, at the Concluding visit (Month 30) + 6 months and +12 Months and at disease recurrence

End point values	MAGE-A3 (as treated) Group	Placebo (as treated) Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	118		
Units: Units on a scale				
arithmetic mean (standard deviation)				
EQ-5D, W0 day of TA (N=245;118)	0.842 (± 0.182)	0.861 (± 0.159)		
EQ-5D, W0 day after TA (N=195;94)	0.773 (± 0.182)	0.873 (± 0.141)		
EQ-5D, W6 day of TA (N=234;118)	0.853 (± 0.183)	0.865 (± 0.173)		
EQ-5D, W6 day after TA (N=198;96)	0.722 (± 0.245)	0.867 (± 0.174)		
EQ-5D, W12 day of TA (N=193;96)	0.873 (± 0.158)	0.887 (± 0.138)		
EQ-5D, W12 day after TA (N=162;77)	0.788 (± 0.17)	0.888 (± 0.126)		
EQ-5D, M6 (N=144;75)	0.879 (± 0.146)	0.9 (± 0.156)		
EQ-5D, M9 (N=130;77)	0.891 (± 0.134)	0.876 (± 0.194)		
EQ-5D, M12 (N=113;67)	0.891 (± 0.157)	0.899 (± 0.149)		
EQ-5D, M24 (N=62;36)	0.894 (± 0.132)	0.881 (± 0.15)		
EQ-5D, Concluding visit + 6 months (N=1;2)	0.727 (± 0)	0.568 (± 0.074)		
EQ-5D, Concluding visit + 12 months (N=30;10)	0.791 (± 0.264)	0.648 (± 0.344)		
EQ-5D, Disease recurrence (N=76;35)	0.752 (± 0.261)	0.815 (± 0.197)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Anti-MAGE-A3 antibody concentrations above the cut-off values

End point title	Number of subjects with Anti-MAGE-A3 antibody concentrations above the cut-off values
End point description: The cut-off value was 27 ELISA units per millilitre (EL.U/mL).	
End point type	Secondary
End point timeframe: At Weeks 0, 6, 12, 36, 48, 72, 120 (Concluding visit) and at Week 120 + 6 months	

End point values	MAGE-A3 (as treated) Group	Placebo (as treated) Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	629	316		
Units: Subjects				
Anti-MAGE-A3, W0 (N=629;316)	25	19		
Anti-MAGE-A3, W6 (N=482;271)	478	22		
Anti-MAGE-A3, W12 (N=425;230)	424	13		
Anti-MAGE-A3, W36 (N=259;131)	259	6		
Anti-MAGE-A3, W48 (N=224;113)	224	5		
Anti-MAGE-A3, W72 (N=178;85)	178	4		
Anti-MAGE-A3, W120 (N=257;140)	257	10		
Anti-MAGE-A3, Concluding visit+6 months (N=70;36)	70	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-MAGE-A3 antibody geometric mean concentration

End point title	Anti-MAGE-A3 antibody geometric mean concentration
End point description: Geometric mean concentration (GMC) was expressed as ELISA units per millilitre (EL.U/mL).	
End point type	Secondary
End point timeframe: At Weeks 0, 6, 12, 36, 48, 72, 120 (Concluding visit) and at Week 120 + 6 months	

End point values	MAGE-A3 (as treated) Group	Placebo (as treated) Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	629	316		
Units: EL.U/mL				
geometric mean (confidence interval 95%)				
Anti-MAGE-A3, W0 (N=629;316)	11 (10.6 to 11.4)	11.4 (10.7 to 12.1)		
Anti-MAGE-A3, W6 (N=482;271)	1451.6 (1290.9 to 1632.3)	11.9 (11 to 12.9)		
Anti-MAGE-A3, W12 (N=425;230)	4031.6 (3738.7 to 4347.4)	11.3 (10.6 to 12.1)		
Anti-MAGE-A3, W36 (N=259;131)	2189.6 (2000.4 to 2396.7)	11.4 (10.4 to 12.4)		
Anti-MAGE-A3, W48 (N=224;113)	2243.4 (2034.4 to 2473.8)	11.3 (10.2 to 12.6)		
Anti-MAGE-A3, W72 (N=178;85)	2489.4 (2221.8 to 2789.4)	11.2 (10 to 12.5)		

Anti-MAGE-A3, W120 (N=257;140)	3109.7 (2827.4 to 3420.2)	12.7 (10.9 to 14.8)		
Anti-MAGE-A3, Concluding visit+6 months (N=70;36)	1293.4 (1056.3 to 1583.7)	10.8 (9.9 to 11.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with Anti-MAGE-A3 antibody response

End point title	Number of subjects with Anti-MAGE-A3 antibody response
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End point description:

Treatment response defined as: - For initially seronegative patients: post-treatment antibody concentration ≥ 27 EL.U/mL; - For initially seropositive patients: post-treatment antibody concentration ≥ 2 fold the pre-treatment antibody concentration.

End point type	Secondary
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End point timeframe:

At Weeks 6, 12, 36, 48, 72, 120 (Concluding visit) and at Week 120 + 6 months

End point values	MAGE-A3 (as treated) Group	Placebo (as treated) Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	482	271		
Units: Subjects				
Anti-MAGE-A3, W6 (N=482;271)	476	9		
Anti-MAGE-A3, W12 (N=425;230)	424	4		
Anti-MAGE-A3, W36 (N=259;131)	259	2		
Anti-MAGE-A3, W48 (N=224;113)	224	2		
Anti-MAGE-A3, W72 (N=178;85)	178	2		
Anti-MAGE-A3, W120 (N=257;140)	257	6		
Anti-MAGE-A3, Concluding visit+6 months (N=70;36)	70	1		

Statistical analyses

No statistical analyses for this end point

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

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

End point type	Secondary
End point timeframe:	
Within the 31-day (Days 0-30) follow-up period after treatment	

End point values	MAGE-A3 (as treated) Group	Placebo (as treated) Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	895	450		
Units: Subjects	822	333		

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of subjects with any serious adverse events (SAEs)	
End point description:		
Serious adverse events (SAEs) assessed include medical occurrences that result in death, are life-threatening, require hospitalization or prolongation of hospitalization or result in disability/incapacity.		
End point type	Secondary	
End point timeframe:		
From Day 0 up to study end (up to 5 years)		

End point values	MAGE-A3 (as treated) Group	Placebo (as treated) Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	895	450		
Units: Subjects	129	64		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with potential immune-mediated disorders(pIMDs)

End point title	Number of subjects with potential immune-mediated disorders(pIMDs)
End point description:	
Potential Immune-Mediated Disorders (pIMDs) were to be collected up to 5 years after first treatment administration or study withdrawal.	
End point type	Secondary
End point timeframe:	
From Day 0 up to study end (up to 5 years)	

End point values	MAGE-A3 (as treated) Group	Placebo (as treated) Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	895	450		
Units: Subjects	33	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with abnormal haematological and biochemical parameters

End point title	Number of subjects with abnormal haematological and biochemical parameters
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End point description:

Laboratory abnormalities belong to hematological and biochemical parameters such as: alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [AP], bilirubin [BIL], creatinine [CREA], hemoglobin [HGB], leukocytes [LEU], lymphopenia [LYMPH], neutrophils [NEU], platelets [PLA]. Parameter grades (Grade [G] 0, 1, 2, 3, 4, Unknown) were compared to each baseline parameter grade (G Unknown, 0, 1, 2, 3), as defined by the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 of August 9, 2006.

End point type	Secondary
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End point timeframe:

Within the 31-day (Days 0-30) post-treatment period

End point values	MAGE-A3 (as treated) Group	Placebo (as treated) Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	894	450		
Units: Subjects				
ALT, Unknown - G0 (N=894,450)	3	2		
ALT, Unknown - G1 (N=894,450)	1	0		
ALT, Unknown - G3 (N=894,450)	0	0		
ALT, Unknown - G4 (N=894,450)	0	0		
ALT, Unknown - Unknown (N=894,450)	2	0		
ALT, G0 - G0 (N=894,450)	625	337		
ALT, G0 - G1 (N=894,450)	98	30		
ALT, G0 - G2 (N=894,450)	10	4		
ALT, G0 - G3 (N=894,450)	3	4		
ALT, G0 - G4 (N=894,450)	0	0		
ALT, G0 - Unknown (N=894,450)	36	18		
ALT, G1 - G0 (N=894,450)	45	22		
ALT, G1 - G1 (N=894,450)	49	25		
ALT, G1 - G2 (N=894,450)	14	4		
ALT, G1 - G3 (N=894,450)	1	2		

ALT, G1 - G4 (N=894,450)	0	0		
ALT, G1 - Unknown (N=894,450)	2	1		
ALT, G2 - G0 (N=894,450)	1	1		
ALT, G2 - G1 (N=894,450)	2	0		
ALT, G2 - G2 (N=894,450)	1	0		
ALT, G2 - G3 (N=894,450)	0	0		
ALT, G2 - G4 (N=894,450)	0	0		
ALT, G2 - Unknown (N=894,450)	0	0		
ALT, G3 - G0 (N=894,450)	0	0		
ALT, G3 - G1 (N=894,450)	0	0		
ALT, G3 - G2 (N=894,450)	0	0		
ALT, G3 - G3 (N=894,450)	0	0		
ALT, G3 - G4 (N=894,450)	0	0		
ALT, G3 - Unknown (N=894,450)	1	0		
ALT, Total - G0 (N=894,450)	674	362		
ALT, Total - G1 (N=894,450)	150	55		
ALT, Total - G2 (N=894,450)	25	8		
ALT, Total - G3 (N=894,450)	4	6		
ALT, Total - G4 (N=894,450)	0	0		
ALT, Total - Unknown (N=894,450)	41	19		
AST, G0 - G0 (N=894,450)	701	356		
AST, G0 - G1 (N=894,450)	88	37		
AST, G0 - G2 (N=894,450)	5	3		
AST, G0 - G3 (N=894,450)	3	4		
AST, G0 - G4 (N=894,450)	0	0		
AST, G0 - Unknown (N=894,450)	40	19		
AST, G1 - G0 (N=894,450)	24	15		
AST, G1 - G1 (N=894,450)	18	11		
AST, G1 - G2 (N=894,450)	3	1		
AST, G1 - G3 (N=894,450)	2	0		
AST, G1 - G4 (N=894,450)	0	0		
AST, G1 - Unknown (N=894,450)	1	1		
AST, G2 - G0 (N=894,450)	0	0		
AST, G2 - G1 (N=894,450)	0	0		
AST, G2 - G2 (N=894,450)	1	0		
AST, G2 - G3 (N=894,450)	0	0		
AST, G2 - G4 (N=894,450)	0	0		
AST, G2 - Unknown (N=894,450)	1	0		
AST, Total - G0 (N=894,450)	728	374		
AST, Total - G1 (N=894,450)	107	48		
AST, Total - G2 (N=894,450)	9	4		
AST, Total - G3 (N=894,450)	5	4		
AST, Total - G4 (N=894,450)	0	0		
AST, Total - Unknown (N=894,450)	45	20		
AP, Unknown - G0 (N=894,450)	9	6		
AP, Unknown - G1 (N=894,450)	0	1		
AP, Unknown - G2 (N=894,450)	1	0		
AP, Unknown - G3 (N=894,450)	0	0		
AP, Unknown - G4 (N=894,450)	0	0		
AP, Unknown - Unknown (N=894,450)	2	0		
AP, G0 - G0 (N=894,450)	749	378		
AP, G0 - G1 (N=894,450)	56	18		

AP, G0 - G2 (N=894,450)	3	4		
AP, G0 - G3 (N=894,450)	2	1		
AP, G0 - G4 (N=894,450)	0	0		
AP, G0 - Unknown (N=894,450)	38	18		
AP, G1 - G0 (N=894,450)	18	13		
AP, G1 - G1 (N=894,450)	14	9		
AP, G1 - G2 (N=894,450)	0	0		
AP, G1 - G3 (N=894,450)	0	0		
AP, G1 - G4 (N=894,450)	0	0		
AP, G1 - Unknown (N=894,450)	2	2		
AP, Total - G0 (N=894,450)	776	397		
AP, Total - G1 (N=894,450)	70	28		
AP, Total - G2 (N=894,450)	4	4		
AP, Total - G3 (N=894,450)	2	1		
AP, Total - G4 (N=894,450)	0	0		
AP, Total - Unknown (N=894,450)	42	20		
BIL, Unknown - G0 (N=894,450)	7	5		
BIL, Unknown - G1 (N=894,450)	1	0		
BIL, Unknown - G2 (N=894,450)	0	0		
BIL, Unknown - G3 (N=894,450)	0	0		
BIL, Unknown - G4 (N=894,450)	0	0		
BIL, Unknown - Unknown (N=894,450)	1	1		
BIL, G0 - G0 (N=894,450)	771	383		
BIL, G0 - G1 (N=894,450)	33	21		
BIL, G0 - G2 (N=894,450)	3	2		
BIL, G0 - G3 (N=894,450)	0	1		
BIL, G0 - G4 (N=894,450)	0	0		
BIL, G0 - Unknown (N=894,450)	44	19		
BIL, G1 -G0 (N=894,450)	11	3		
BIL, G1 - G1 (N=894,450)	10	5		
BIL, G1 -G2 (N=894,450)	9	4		
BIL, G1 - G3 (N=894,450)	0	0		
BIL, G1 - G4 (N=894,450)	0	0		
BIL, G1 - Unknown (N=894,450)	3	2		
BIL, G2 - G0 (N=894,450)	0	0		
BIL, G2 - G1 (N=894,450)	0	2		
BIL, G2 - G2 (N=894,450)	0	2		
BIL, G2 - G3 (N=894,450)	0	0		
BIL, G2 - G4 (N=894,450)	0	0		
BIL, G2 - Unknown (N=894,450)	1	0		
BIL, Total - G0 (N=894,450)	789	391		
BIL, Total - G1 (N=894,450)	44	28		
BIL, Total - G2 (N=894,450)	12	8		
BIL, Total - G3 (N=894,450)	0	1		
BIL, Total - G4 (N=894,450)	0	0		
BIL, Total - Unknown (N=894,450)	49	22		
CREA, Unknown - G0 (N=894,450)	2	1		
CREA, Unknown - G1 (N=894,450)	0	0		
CREA, Unknown - G2 (N=894,450)	0	0		
CREA, Unknown - G3 (N=894,450)	0	0		
CREA, Unknown - G4 (N=894,450)	0	0		

CREA, Unknown - Unknown (N=894,450)	1	0		
CREA, G0 - G0 (N=894,450)	789	391		
CREA, G0 - G1 (N=894,450)	31	19		
CREA, G0 - G2 (N=894,450)	0	1		
CREA, G0 - G3 (N=894,450)	0	1		
CREA, G0 - G4 (N=894,450)	0	0		
CREA, G0 - Unknown (N=894,450)	36	19		
CREA, G1 - G0 (N=894,450)	8	6		
CREA, G1 - G1 (N=894,450)	19	12		
CREA, G1 - G2 (N=894,450)	3	0		
CREA, G1 - G3 (N=894,450)	0	0		
CREA, G1 - G4 (N=894,450)	0	0		
CREA, G1 - Unknown (N=894,450)	4	0		
CREA, G2 - G0 (N=894,450)	0	0		
CREA, G2 - G1 (N=894,450)	0	0		
CREA, G2 - G2 (N=894,450)	1	0		
CREA, G2 - G3 (N=894,450)	0	0		
CREA, G2 - G4 (N=894,450)	0	0		
CREA, G2 - Unknown (N=894,450)	0	0		
CREA, Total - G0 (N=894,450)	799	398		
CREA, Total - G1 (N=894,450)	50	31		
CREA, Total - G2 (N=894,450)	4	1		
CREA, Total - G3 (N=894,450)	0	1		
CREA, Total - G4 (N=894,450)	0	0		
CREA, Total - Unknown (N=894,450)	41	19		
HGB, Unknown - G0 (N=894,450)	2	1		
HGB, Unknown - G1 (N=894,450)	1	0		
HGB, Unknown - G2 (N=894,450)	0	0		
HGB, Unknown - G3 (N=894,450)	0	0		
HGB, Unknown - G4 (N=894,450)	0	0		
HGB, Unknown - Unknown (N=894,450)	0	0		
HGB, G0 - G0 (N=894,450)	636	326		
HGB, G0 - G1 (N=894,450)	78	28		
HGB, G0 - G2 (N=894,450)	7	3		
HGB, G0 - G3 (N=894,450)	2	1		
HGB, G0 - G4 (N=894,450)	0	0		
HGB, G0 - Unknown (N=894,450)	35	17		
HGB, G1 - G0 (N=894,450)	39	27		
HGB, G1 - G1 (N=894,450)	77	41		
HGB, G1 - G2 (N=894,450)	7	2		
HGB, G1 - G3 (N=894,450)	1	0		
HGB, G1 - G4 (N=894,450)	1	0		
HGB, G1 - Unknown (N=894,450)	4	3		
HGB, G2 - G0 (N=894,450)	1	1		
HGB, G2 - G1 (N=894,450)	1	0		
HGB, G2 - G2 (N=894,450)	2	0		
HGB, G2 - G3 (N=894,450)	0	0		
HGB, G2 - G4 (N=894,450)	0	0		
HGB, G2 - Unknown (N=894,450)	0	0		
HGB, Total - G0 (N=894,450)	678	355		
HGB, Total - G1 (N=894,450)	157	69		

HGB, Total - G2 (N=894,450)	16	5		
HGB, Total - G3 (N=894,450)	3	1		
HGB, Total - G4 (N=894,450)	1	0		
HGB, Total - Unknown (N=894,450)	39	20		
LEU, Unknown - G0 (N=894,450)	2	1		
LEU, Unknown - G1 (N=894,450)	1	0		
LEU, Unknown - G2 (N=894,450)	0	0		
LEU, Unknown - G3 (N=894,450)	0	0		
LEU, Unknown - G4 (N=894,450)	0	0		
LEU, Unknown - Unknown (N=894,450)	0	0		
LEU, G0 - G0 (N=894,450)	762	382		
LEU, G0 - G1 (N=894,450)	53	31		
LEU, G0 - G2 (N=894,450)	4	2		
LEU, G0 - G3 (N=894,450)	0	0		
LEU, G0 - G4 (N=894,450)	2	0		
LEU, G0 - Unknown (N=894,450)	39	18		
LEU, G1 - G0 (N=894,450)	13	8		
LEU, G1 - G1 (N=894,450)	15	6		
LEU, G1 - G2 (N=894,450)	1	1		
LEU, G1 - G3 (N=894,450)	0	0		
LEU, G1 - G4 (N=894,450)	0	0		
LEU, G1 - Unknown (N=894,450)	0	1		
LEU, G2 - G0 (N=894,450)	0	0		
LEU, G2 - G1 (N=894,450)	1	0		
LEU, G2 - G2 (N=894,450)	0	0		
LEU, G2 - G3 (N=894,450)	1	0		
LEU, G2 - G4 (N=894,450)	0	0		
LEU, G2 - Unknown (N=894,450)	0	0		
LEU, Total - G0 (N=894,450)	777	391		
LEU, Total - G1 (N=894,450)	70	37		
LEU, Total - G2 (N=894,450)	5	3		
LEU, Total - G3 (N=894,450)	1	0		
LEU, Total - G4 (N=894,450)	2	0		
LEU, Total - Unknown (N=894,450)	39	19		
LYMPH, Unknown - G0 (N=894,450)	8	1		
LYMPH, Unknown - G1 (N=894,450)	2	2		
LYMPH, Unknown - G2 (N=894,450)	0	0		
LYMPH, Unknown - G3 (N=894,450)	0	0		
LYMPH, Unknown - G4 (N=894,450)	0	0		
LYMPH, Unknown - Unknown (N=894,450)	0	0		
LYMPH, G0 - G0 (N=894,450)	633	303		
LYMPH, G0 - G1 (N=894,450)	93	57		
LYMPH, G0 - G2 (N=894,450)	17	8		
LYMPH, G0 - G3 (N=894,450)	4	0		
LYMPH, G0 - G4 (N=894,450)	0	0		
LYMPH, G0 - Unknown (N=894,450)	38	22		
LYMPH, G1 - G0 (N=894,450)	29	9		
LYMPH, G1 - G1 (N=894,450)	49	37		
LYMPH, G1 - G2 (N=894,450)	4	6		
LYMPH, G1 - G3 (N=894,450)	4	0		
LYMPH, G1 - G4 (N=894,450)	0	0		

LYMPH, G1 - Unknown (N=894,450)	4	0		
LYMPH, G2 - G0 (N=894,450)	1	1		
LYMPH, G2 - G1 (N=894,450)	4	1		
LYMPH, G2 - G2 (N=894,450)	2	2		
LYMPH, G2 - G3 (N=894,450)	2	0		
LYMPH, G2 - G4 (N=894,450)	0	0		
LYMPH, G2 - Unknown (N=894,450)	0	0		
LYMPH, G3 - G0 (N=894,450)	0	0		
LYMPH, G3 - G1 (N=894,450)	0	1		
LYMPH, G3 - G2 (N=894,450)	0	0		
LYMPH, G3 - G3 (N=894,450)	0	0		
LYMPH, G3 - G4 (N=894,450)	0	0		
LYMPH, G3 - Unknown (N=894,450)	0	0		
LYMPH, Total - G0 (N=894,450)	671	314		
LYMPH, Total - G1 (N=894,450)	148	98		
LYMPH, Total - G2 (N=894,450)	23	16		
LYMPH, Total - G3 (N=894,450)	10	0		
LYMPH, Total - G4 (N=894,450)	0	0		
LYMPH, Total - Unknown (N=894,450)	42	22		
NEU, Unknown - G0 (N=894,450)	6	1		
NEU, Unknown - G1 (N=894,450)	0	1		
NEU, Unknown - G2 (N=894,450)	0	0		
NEU, Unknown - G3 (N=894,450)	0	0		
NEU, Unknown - G4 (N=894,450)	0	0		
NEU, Unknown - Unknown (N=894,450)	0	0		
NEU, G0 - G0 (N=894,450)	781	393		
NEU, G0 - G1 (N=894,450)	39	16		
NEU, G0 - G2 (N=894,450)	9	2		
NEU, G0 - G3 (N=894,450)	0	0		
NEU, G0 - G4 (N=894,450)	1	0		
NEU, G0 - Unknown (N=894,450)	43	22		
NEU, G1 - G0 (N=894,450)	7	10		
NEU, G1 - G1 (N=894,450)	6	3		
NEU, G1 - G2 (N=894,450)	1	2		
NEU, G1 - G3 (N=894,450)	0	0		
NEU, G1 - G4 (N=894,450)	0	0		
NEU, G1 - Unknown (N=894,450)	0	0		
NEU, G2 - G0 (N=894,450)	0	0		
NEU, G2 - G1 (N=894,450)	1	0		
NEU, G2 - G2 (N=894,450)	0	0		
NEU, G2 - G3 (N=894,450)	0	0		
NEU, G2 - G4 (N=894,450)	0	0		
NEU, G2 - Unknown (N=894,450)	0	0		
NEU, Total - G0 (N=894,450)	794	404		
NEU, Total - G1 (N=894,450)	46	20		
NEU, Total - G2 (N=894,450)	10	4		
NEU, Total - G3 (N=894,450)	0	0		
NEU, Total - G4 (N=894,450)	1	0		
NEU, Total - Unknown (N=894,450)	43	22		
PLA, Unknown - G0 (N=894,450)	4	1		
PLA, Unknown - G1 (N=894,450)	0	0		
PLA, Unknown - G2 (N=894,450)	0	0		

PLA, Unknown - G3 (N=894,450)	0	0		
PLA, Unknown - G4 (N=894,450)	0	0		
PLA, Unknown - Unknown (N=894,450)	0	0		
PLA, G0 - G0 (N=894,450)	796	390		
PLA, G0 - G1 (N=894,450)	34	25		
PLA, G0 - G2 (N=894,450)	0	1		
PLA, G0 - G3 (N=894,450)	0	0		
PLA, G0 - G4 (N=894,450)	1	3		
PLA, G0 - Unknown (N=894,450)	36	17		
PLA, G1 - G0 (N=894,450)	4	1		
PLA, G1 - G1 (N=894,450)	15	10		
PLA, G1 - G2 (N=894,450)	1	0		
PLA, G1 - G3 (N=894,450)	0	0		
PLA, G1 - G4 (N=894,450)	0	0		
PLA, G1 - Unknown (N=894,450)	3	2		
PLA, Total - G0 (N=894,450)	804	392		
PLA, Total - G1 (N=894,450)	49	35		
PLA, Total - G2 (N=894,450)	1	1		
PLA, Total - G3 (N=894,450)	0	0		
PLA, Total - G4 (N=894,450)	1	3		
PLA, Total - Unknown (N=894,450)	39	19		
AST, Unknown - G0 (N=894, 450)	3	3		
AST, Unknown - G1 (N=894,450)	1	0		
AST, Unknown - G2 (N=894,450)	0	0		
AST, Unknown - G3 (N=894,450)	0	0		
AST, Unknown - G4 (N=894,450)	0	0		
AST, Unknown - Unknown (N=894,450)	3	0		
ALT, Unknown - G2 (N=894,450)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs): Within the 31-day (Days 0-30) follow-up period after treatment. Serious Adverse Events: from Day 0 up to study end (up to 5 years).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Placebo (as treated) Group
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Reporting group description:

Patients who received up to 13 doses of placebo.

Reporting group title	MAGE-A3 (as treated) Group
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Reporting group description:

Patients who received up to 13 doses of recMAGE-A3 + AS15 ASCI.

Serious adverse events	Placebo (as treated) Group	MAGE-A3 (as treated) Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 450 (14.22%)	129 / 895 (14.41%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	13 / 450 (2.89%)	25 / 895 (2.79%)	
occurrences causally related to treatment / all	0 / 14	0 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			

subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Focal nodular hyperplasia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna			
subjects affected / exposed	1 / 450 (0.22%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	3 / 450 (0.67%)	9 / 895 (1.01%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ			
subjects affected / exposed	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage i			

subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-hodgkin's lymphoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia vera			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Porocarcinoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 450 (0.22%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			

subjects affected / exposed	3 / 450 (0.67%)	6 / 895 (0.67%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial spreading melanoma stage unspecified			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract neoplasm			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 450 (0.22%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 450 (0.22%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 450 (0.22%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			

subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 450 (0.00%)	3 / 895 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organising pneumonia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			

subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Asbestosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media reaction			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electric shock			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprosthetic fracture			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative hernia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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 / 450 (0.22%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	1 / 450 (0.22%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 450 (0.22%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningism			

subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor skills impaired			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenic purpura			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Retinal detachment			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vascular thrombosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 450 (0.22%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			

subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 450 (0.44%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocholecystis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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			
Actinic elastosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermal cyst			

subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder neck sclerosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basedow's disease			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytic hypophysitis			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyglandular autoimmune syndrome			

type ii			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (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			
Back pain			
subjects affected / exposed	1 / 450 (0.22%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 450 (0.22%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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 limb			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	5 / 450 (1.11%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis enterococcal			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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	5 / 450 (1.11%)	7 / 895 (0.78%)	
occurrences causally related to treatment / all	0 / 5	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			

subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (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	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymph node abscess			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	1 / 450 (0.22%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			

subjects affected / exposed	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis Escherichia coli			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (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	0 / 450 (0.00%)	2 / 895 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 450 (0.22%)	0 / 895 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 450 (0.00%)	1 / 895 (0.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo (as treated) Group	MAGE-A3 (as treated) Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	327 / 450 (72.67%)	819 / 895 (91.51%)	
Nervous system disorders			
Headache			
subjects affected / exposed	55 / 450 (12.22%)	205 / 895 (22.91%)	
occurrences (all)	128	550	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	46 / 450 (10.22%)	149 / 895 (16.65%)	
occurrences (all)	68	354	
Chills			
subjects affected / exposed	15 / 450 (3.33%)	179 / 895 (20.00%)	
occurrences (all)	23	432	
Fatigue			
subjects affected / exposed	63 / 450 (14.00%)	210 / 895 (23.46%)	
occurrences (all)	116	490	
Influenza like illness			
subjects affected / exposed	30 / 450 (6.67%)	261 / 895 (29.16%)	
occurrences (all)	46	902	
Injection site erythema			
subjects affected / exposed	3 / 450 (0.67%)	90 / 895 (10.06%)	
occurrences (all)	3	241	
Injection site oedema			
subjects affected / exposed	3 / 450 (0.67%)	48 / 895 (5.36%)	
occurrences (all)	5	134	
Injection site pain			
subjects affected / exposed	22 / 450 (4.89%)	325 / 895 (36.31%)	
occurrences (all)	37	1057	

Injection site reaction subjects affected / exposed occurrences (all)	6 / 450 (1.33%) 9	160 / 895 (17.88%) 500	
Pain subjects affected / exposed occurrences (all)	19 / 450 (4.22%) 26	191 / 895 (21.34%) 480	
Pyrexia subjects affected / exposed occurrences (all)	35 / 450 (7.78%) 44	380 / 895 (42.46%) 1240	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	19 / 450 (4.22%) 26	46 / 895 (5.14%) 61	
Nausea subjects affected / exposed occurrences (all)	32 / 450 (7.11%) 43	123 / 895 (13.74%) 266	
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all)	10 / 450 (2.22%) 10	138 / 895 (15.42%) 297	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	31 / 450 (6.89%) 43	84 / 895 (9.39%) 165	
Myalgia subjects affected / exposed occurrences (all)	23 / 450 (5.11%) 39	188 / 895 (21.01%) 456	
Pain in extremity subjects affected / exposed occurrences (all)	26 / 450 (5.78%) 28	115 / 895 (12.85%) 207	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 April 2014	Immune related gene signatures have been recently reported as having a possible prognostic value in melanoma [Messina, 2012; Sivendran, 2014]. Similarly, a prognostic gene signature has been identified in the training set (Refer to Figure 4 and Section 10.3) of this study. As this prognostic gene signature is independent from other clinical covariates it will also be included as an additional covariate in the Cox model for the primary analyses in the gene signature sub-group (test set). Other minor corrections have been made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 September 2015	The study was terminated early following assessment of the two co-primary endpoints showed the lack of efficacy of the study product.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated early following assessment of the two co-primary endpoints showed the lack of efficacy of the study product.

Notes: