Clinical trial results:
An Open-Label, Randomized, Multi-Center Study Comparing the Safety and Immunogenicity of HEPLISAV™ to Engerix-B® and Fendrix® in Adults on Hemodialysis Who Have Previously Received Hepatitis B Vaccination and Are Not Seroprotected

Summary

EudraCT number	2010-019633-10
Trial protocol	DE
Global end of trial date	23 April 2012

Results information

Result version number	v1 (current)
This version publication date	25 August 2021
First version publication date	25 August 2021
Summary attachment (see zip file)	study-report-dv2-hbv-18 synopsis (study-report-dv2-hbv-18 synopsis.docx)

Trial information

Trial identification

Sponsor protocol code	DV2-HBV-18

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01195246
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dynavax Technologies Corporation
Sponsor organisation address	2929 Seventh Street, Suite 100, Berkeley, California, United States, 94710
Public contact	Referat Klinische Prüfung, Paul-Ehrlich-Institut (PEI), +49 6103771811, klinpruefung@pei.de
Scientific contact	Referat Klinische Prüfung, Paul-Ehrlich-Institut (PEI), +49 6103771811, klinpruefung@pei.de

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	14 March 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2012
Global end of trial reached?	Yes
Global end of trial date	23 April 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the immune response of HEPLISAV with Engerix-B and Fendrix as measured by seroprotection rate (SPR) defined as the percentage of subjects with a serum antibody concentration to hepatitis B surface antigen (anti-HBs) ≥ 10 mIU/mL in subjects at 4 weeks after the booster injection

Protection of trial subjects:

Injection site reactions were expected to spontaneously subside. Local pruritus and pain could be treated with oral medications. If significant symptoms of pain and induration persisted for more than 12 hours, an ice pack could be applied locally for 30 minutes every 2 hours, as needed. Use of an ice pack prior to 12 hours after the onset of symptoms was discourages as it could interfere with the action of the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2010
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	Germany: 155
Worldwide total number of subjects	155
EEA total number of subjects	155

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)	52
From 65 to 84 years	95

85 years and over	8

Subject disposition

Recruitment

Recruitment details:

A total of 155 adult subjects (18 years of age or older with ESRD who were receiving hemodialysis and had previously received hepatitis B vaccinations, but were not seroprotected at enrollment) were enrolled at 20 sites in Germany and randomized as follows: HEPLISAV: n = 54; Engerix-B: n = 50; Fendrix: n = 51.

Pre-assignment

Screening details:

Approximately 150 subjects were planned and 155 subjects were enrolled. At visit 0 the subject was asked to sign an informed consent form, asked for a medical and medication history, given a physical exam with vital signs taken, hepatitis and HIV screen, serum and urine pregnancy test and Anti-HBsAg and stored serum aliquot.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This study is an open-label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	HEPLISAV arm

Arm description:

Subjects received HEPLISAV.

Arm type	Experimental
Investigational medicinal product name	Hepatitis B Surface Antigen (HBsAg)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The test product (HEPLISAV) comprised 20 mcg recombinant HBsAg subtype adw with 3000 mcg 1018 ISS (immunostimulatory sequence) Adjuvant (0.5 mL) manufactured by Rentschler Biotechnologie GmbH (Germany).
Subjects in the HEPLISAV group received a single intramuscular (IM) injection of HEPLISAV (0.5 mL) into the right or left deltoid muscle at Day 1 (Week 0).

Subjects remained in the study for up to 16 weeks. The study had a screening period of up to 4 weeks prior to administration of study treatment and a follow-up period of 12 weeks after administration of study treatment.

Arm title	Engerix B

Arm description:

Subjects received Engerix-B.

Arm type	Active comparator
Investigational medicinal product name	Hepatitis B (rDNA) vaccine (adsorbed) (HBV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intramuscular use

Dosage and administration details:

Each 1-mL adult Engerix-B dose contains 20 mcg of HBsAg adsorbed on 500 mcg aluminum as aluminum hydroxide. Engerix-B is manufactured by GlaxoSmithKline Biologicals.
Subjects in the Engerix-B group received 2 IM injections of 1 mL each (a total injection volume of 2 mL) into the right or left deltoid muscle at Day 1 (Week 0).

Subjects remained in the study for up to 16 weeks. The study had a screening period of up to 4 weeks prior to administration of study treatment and a follow-up period of 12 weeks after administration of study treatment.

Arm title	Fendrix

Arm description:

Subjects received Fendrix.

Arm type	Active comparator
Investigational medicinal product name	Hepatitis B (rDNA) vaccine (adjuvanted, adsorbed).
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Each 0.5-mL adult Fendrix dose contains 20 mcg of HBsAg adsorbed on 500 mcg aluminum as aluminum phosphate and combined with 50 mcg monophosphoryl lipid A. Fendrix is manufactured by GlaxoSmithKline Biologicals.
Subjects in the Fendrix group received a single IM injection (0.5 mL) into the right or left deltoid muscle at Day 1 (Week 0).

Subjects remained in the study for up to 16 weeks. The study had a screening period of up to 4 weeks prior to administration of study treatment and a follow-up period of 12 weeks after administration of study treatment.

Number of subjects in period 1	HEPLISAV arm	Engerix B	Fendrix
Started	54	50	51
Completed	52	46	51
Not completed	2	4	0
Adverse event, serious fatal	2	4	-

Baseline characteristics

Reporting groups	
Reporting group title	HEPLISAV arm
Reporting group description:	
Subjects received HEPLISAV.	
Reporting group title	Engerix B
Reporting group description:	
Subjects received Engerix-B.	
Reporting group title	Fendrix
Reporting group description:	
Subjects received Fendrix.	

Reporting group values	HEPLISAV arm	Engerix B	Fendrix
Number of subjects	54	50	51
Age categorical Units: Subjects			
Adults (18 - 64 years)	22	12	18
Adults (65 - 84 years)	31	33	31
Adults (> 84 years)	1	5	2
Age continuous			
Age is calculated by comparing the date of informed consent signed to the date of birth. The prior nonresponder group (n = 117) mean age was 70.2 years (range, 36 to 91 years). The prior responder group (n = 38) mean age was 65.1 years (range, 23 to 85 years).			
Units: years			
arithmetic mean	66.9	71.1	69.0
standard deviation	± 11.77	± 11.90	± 12.77
Gender categorical Units: Subjects			
Female	19	20	18
Male	35	30	33

Reporting group values	Total		
Number of subjects	155		
Age categorical Units: Subjects			
Adults (18 - 64 years)	52		
Adults (65 - 84 years)	95		
Adults (> 84 years)	8		
Age continuous			
Age is calculated by comparing the date of informed consent signed to the date of birth. The prior nonresponder group (n = 117) mean age was 70.2 years (range, 36 to 91 years). The prior responder group (n = 38) mean age was 65.1 years (range, 23 to 85 years).			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	57		
Male	98		

End points

End points reporting groups

Reporting group title	HEPLISAV arm
Reporting group description: Subjects received HEPLISAV.	
Reporting group title	Engerix B
Reporting group description: Subjects received Engerix-B.	
Reporting group title	Fendrix
Reporting group description: Subjects received Fendrix.	
Subject analysis set title	Prior Nonresponders - HEPLISAV (mITT population)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Prior non-responder who was treated with HEPLISAV - mITT population	
Subject analysis set title	Prior Responders - HEPLISAV (mITT population)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Prior responder who was treated with HEPLISAV - mITT population	
Subject analysis set title	Prior Nonresponders - Engerix-B (mITT population)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Prior non-responder who was treated with Engerix-B - mITT population	
Subject analysis set title	Prior Nonresponders - Fendrix (mITT population)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Prior non-responder who was treated with Fendrix - mITT population	
Subject analysis set title	Prior Responders - Engerix-B (mITT population)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Prior responder who was treated with Engerix-B - mITT population	
Subject analysis set title	Prior Responders - Fendrix (mITT population)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: Prior responder who was treated with Fendrix - mITT population	

Primary: Primary Immunogenicity Analysis: Seroprotection Rate (SPR) at 4 Weeks After Study Injection (mITT Population)

End point title	Primary Immunogenicity Analysis: Seroprotection Rate (SPR) at 4 Weeks After Study Injection (mITT Population)
End point description:	
End point type	Primary
End point timeframe: 4 weeks post study injection	

End point values	Prior Nonresponders - HEPLISAV (mITT population)	Prior Responders - HEPLISAV (mITT population)	Prior Nonresponders - Engerix-B (mITT population)	Prior Nonresponders - Fendrix (mITT population)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	15	37	41
Units: percent				
number (confidence interval 95%)	42.1 (26.3 to 59.2)	80.00 (51.9 to 95.7)	18.9 (8.0 to 35.2)	29.3 (16.1 to 45.5)

End point values	Prior Responders - Engerix-B (mITT population)	Prior Responders - Fendrix (mITT population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	10		
Units: percent				
number (confidence interval 95%)	90.9 (58.7 to 99.8)	100 (69.2 to 100)		

Statistical analyses

Statistical analysis title	HEPLISAV vs Engerix-B - prior nonresponders

Statistical analysis description:

The difference in SPRs between the HEPLISAV and Engerix-B groups (HEPLISAV minus Engerix-B) at Week 4 and its two-sided 95% confidence intervals (CIs) were computed using the Wilson score method with continuity correction as described by Newcombe (Newcombe 1998). HEPLISAV was to be declared noninferior to Engerix-B with respect to SPR if the lower limit of the 95% CI from the above analysis was greater than -10% and declared superior if the lower limit of the 95% CI was greater than 0%.

Comparison groups	Prior Nonresponders - HEPLISAV (mITT population) v Prior Nonresponders - Engerix-B (mITT population)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	23.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	43.1
Variability estimate	Standard deviation

Notes:

[1] - Two-sided 95% confidence intervals (CIs) of the difference in seroprotection rates (SPR) between the HEPLISAV-B group and the Engerix-B group was computed using the Newcombe score method with continuity correction.
All statistical tests were performed at the 2-sided 0.05 level of significance.

Statistical analysis title	HEPLISAV vs Fendrix - prior nonresponders

Statistical analysis description:

The difference in SPRs between the HEPLISAV and Fendrix groups (HEPLISAV minus Fendrix) at Week 4 and its two-sided 95% confidence intervals (CIs) were computed using the Wilson score method with continuity correction as described by Newcombe (Newcombe 1998). HEPLISAV was to be declared noninferior to Fendrix with respect to SPR if the lower limit of the 95% CI from the above analysis was greater than -10% and declared superior if the lower limit of the 95% CI was greater than 0%.

Comparison groups	Prior Nonresponders - HEPLISAV (mITT population) v Prior Nonresponders - Fendrix (mITT population)
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Mean difference (final values)
Point estimate	12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	34.1
Variability estimate	Standard deviation

Notes:

[2] - Two-sided 95% confidence intervals (CIs) of the difference in seroprotection rates (SPR) between the HEPLISAV-B group and the Fendrix group was computed using the Newcombe score method with continuity correction.
All statistical tests were performed at the 2-sided 0.05 level of significance.

Statistical analysis title	Engerix-B vs Fendrix - prior nonresponders

Statistical analysis description:

The difference in SPRs between the Engerix-B and Fendrix groups (Engerix-B minus Fendrix) at Week 4 and its two-sided 95% confidence intervals (CIs) were computed using the Wilson score method with continuity correction as described by Newcombe (Newcombe 1998). Engerix-B was to be declared noninferior to Fendrix with respect to SPR if the lower limit of the 95% CI from the above analysis was greater than -10% and declared superior if the lower limit of the 95% CI was greater than 0%.

Comparison groups	Prior Nonresponders - Engerix-B (mITT population) v Prior Nonresponders - Fendrix (mITT population)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Mean difference (final values)
Point estimate	-10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-29.4
upper limit	9.4
Variability estimate	Standard deviation

Notes:

[3] - Two-sided 95% confidence intervals (CIs) of the difference in seroprotection rates (SPR) between the Engerix-B group and the Fendrix group was computed using the Newcombe score method with continuity correction.
All statistical tests were performed at the 2-sided 0.05 level of significance.

Statistical analysis title	HEPLISAV vs Engerix-B - prior responders

Statistical analysis description:

The difference in SPRs between the HEPLISAV and Engerix-B groups (HEPLISAV minus Engerix-B) at Week 4 and its two-sided 95% confidence intervals (CIs) were computed using the Wilson score method with continuity correction as described by Newcombe (Newcombe 1998). HEPLISAV was to be declared noninferior to Engerix-B with respect to SPR if the lower limit of the 95% CI from the above analysis

was greater than -10% and declared superior if the lower limit of the 95% CI was greater than 0%.

Comparison groups	Prior Responders - HEPLISAV (mITT population) v Prior Responders - Engerix-B (mITT population)
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	Mean difference (final values)
Point estimate	-10.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.3
upper limit	23.5
Variability estimate	Standard deviation

Notes:

[4] - Two-sided 95% confidence intervals (CIs) of the difference in seroprotection rates (SPR) between the HEPLISAV-B group and the Engerix-B group was computed using the Newcombe score method with continuity correction.
All statistical tests were performed at the 2-sided 0.05 level of significance.

Statistical analysis title	HEPLISAV vs Fendrix - prior responders

Statistical analysis description:

The difference in SPRs between the HEPLISAV and Fendrix groups (HEPLISAV minus Fendrix) at Week 4 and its two-sided 95% confidence intervals (CIs) were computed using the Wilson score method with continuity correction as described by Newcombe (Newcombe 1998). HEPLISAV was to be declared noninferior to Fendrix with respect to SPR if the lower limit of the 95% CI from the above analysis was greater than -10% and declared superior if the lower limit of the 95% CI was greater than 0%.

Comparison groups	Prior Responders - HEPLISAV (mITT population) v Prior Responders - Fendrix (mITT population)
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Mean difference (final values)
Point estimate	-20
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.6
upper limit	11.8
Variability estimate	Standard deviation

Notes:

[5] - Two-sided 95% confidence intervals (CIs) of the difference in seroprotection rates (SPR) between the HEPLISAV-B group and the Fendrix group was computed using the Newcombe score method with continuity correction.
All statistical tests were performed at the 2-sided 0.05 level of significance.

Statistical analysis title	Engerix-B vs Fendrix - prior responders

Statistical analysis description:

The difference in SPRs between the Engerix-B and Fendrix groups (Engerix-B minus Fendrix) at Week 4 and its two-sided 95% confidence intervals (CIs) were computed using the Wilson score method with continuity correction as described by Newcombe (Newcombe 1998). Engerix-B was to be declared noninferior to Fendrix with respect to SPR if the lower limit of the 95% CI from the above analysis was greater than -10% and declared superior if the lower limit of the 95% CI was greater than 0%.

Comparison groups	Prior Responders - Engerix-B (mITT population) v Prior Responders - Fendrix (mITT population)

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Mean difference (final values)
Point estimate	-9.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.3
upper limit	23.4
Variability estimate	Standard deviation

Notes:

[6] - Two-sided 95% confidence intervals (CIs) of the difference in seroprotection rates (SPR) between the Engerix-B group and the Fendrix group was computed using the Newcombe score method with continuity correction.
All statistical tests were performed at the 2-sided 0.05 level of significance.

Secondary: Secondary Immunogenicity Analysis: Seroprotection Rate at 12 Weeks After Study Injection (mITT Population)

End point title	Secondary Immunogenicity Analysis: Seroprotection Rate at 12 Weeks After Study Injection (mITT Population)

End point description:

End point type	Secondary

End point timeframe:

At 12 weeks after the study injection.

End point values	Prior Nonresponders - HEPLISAV (mITT population)	Prior Responders - HEPLISAV (mITT population)	Prior Nonresponders - Engerix-B (mITT population)	Prior Nonresponders - Fendrix (mITT population)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	15	36	41
Units: Percentage				
number (confidence interval 95%)	24.3 (11.8 to 41.2)	86.7 (59.5 to 98.3)	13.9 (4.7 to 29.5)	26.8 (14.2 to 42.9)

End point values	Prior Responders - Engerix-B (mITT population)	Prior Responders - Fendrix (mITT population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: Percentage				
number (confidence interval 95%)	50.0 (18.7 to 81.3)	100 (69.2 to 100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity Analysis: Anti-HBsAg GMC at Week 4 After Study Injection (mITT Population)

End point title	Secondary Immunogenicity Analysis: Anti-HBsAg GMC at Week 4 After Study Injection (mITT Population)

End point description:

End point type	Secondary

End point timeframe:

Anti-HBsAg serum Geometric Mean Concentration (GMC) at Week 4

End point values	Prior Nonresponders - HEPLISAV (mITT population)	Prior Responders - HEPLISAV (mITT population)	Prior Nonresponders - Engerix-B (mITT population)	Prior Nonresponders - Fendrix (mITT population)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	15	37	41
Units: mIU/mL				
geometric mean (confidence interval 95%)	3.8 (1.6 to 9.2)	99.6 (27.5 to 360.1)	1.2 (0.5 to 2.9)	1.9 (0.8 to 4.3)

End point values	Prior Responders - Engerix-B (mITT population)	Prior Responders - Fendrix (mITT population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	10		
Units: mIU/mL				
geometric mean (confidence interval 95%)	79.5 (17.7 to 357.7)	278.1 (57.6 to 1343.0)		

Statistical analyses

Statistical analysis title	Ratio HEPLISAV/Engerix-B (Week 4) - non responders

Statistical analysis description:

Comparisons of the adjusted anti-HBsAg GMC at Week 4 and Week 12 by treatment group (mITT

population).

Comparison groups	Prior Nonresponders - HEPLISAV (mITT population) v Prior Nonresponders - Engerix-B (mITT population)
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Ratio
Point estimate	3.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	10.88

Notes:

[7] - Ratio of Anti-HBsAg Geometric Mean Concentrations ((95% CI) measured at Week 4 (mITT Population) for HEPLISAV/Engerix-B.

Secondary: Secondary Immunogenicity Analyses: Percentage of Subjects With Anti-HBsAg Concentration Greater Than or Equal to 100 mIU/mL at Week 4 (mITT Population)

End point title	Secondary Immunogenicity Analyses: Percentage of Subjects With Anti-HBsAg Concentration Greater Than or Equal to 100 mIU/mL at Week 4 (mITT Population)

End point description:

End point type	Secondary

End point timeframe:

Measured at Week 4

End point values	Prior Nonresponders - HEPLISAV (mITT population)	Prior Responders - HEPLISAV (mITT population)	Prior Nonresponders - Engerix-B (mITT population)	Prior Nonresponders - Fendrix (mITT population)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	38	15	37	41
Units: Percentage				
number (confidence interval 95%)	10.5 (2.9 to 24.8)	66.7 (38.4 to 88.2)	8.1 (1.7 to 21.9)	14.6 (5.6 to 29.2)

End point values	Prior Responders - Engerix-B (mITT population)	Prior Responders - Fendrix (mITT population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	10		
Units: Percentage				
number (confidence interval 95%)	36.4 (10.9 to 69.2)	70 (34.8 to 93.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Post-Injection Reactions within 7 Days post-injection

End point title	Post-Injection Reactions within 7 Days post-injection

End point description:

End point type	Secondary

End point timeframe:

7-days post-injection

End point values	HEPLISAV arm	Engerix B	Fendrix	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	49	51	
Units: Number of Subjects	13	8	20	

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Immunogenicity Analysis: Anti-HBsAg GMC at Week 12 After Study Injection (mITT Population)

End point title	Secondary Immunogenicity Analysis: Anti-HBsAg GMC at Week 12 After Study Injection (mITT Population)

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	Prior Nonresponders - HEPLISAV (mITT population)	Prior Responders - HEPLISAV (mITT population)	Prior Nonresponders - Engerix-B (mITT population)	Prior Nonresponders - Fendrix (mITT population)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	37	15	36	41
Units: mIU/mL				
geometric mean (confidence interval 95%)	2.7 (1.3 to 5.8)	73.2 (24.4 to 219.5)	0.7 (0.3 to 1.4)	1.4 (0.7 to 3.0)

End point values	Prior Responders - Engerix-B (mITT population)	Prior Responders - Fendrix (mITT population)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	10	10		
Units: mIU/mL				
geometric mean (confidence interval 95%)	24.9 (6.5 to 95.4)	105.5 (27.5 to 404.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of AEs at Week 4

End point title	Incidence of AEs at Week 4

End point description:

End point type	Secondary

End point timeframe:

Week 4

End point values	HEPLISAV arm	Engerix B	Fendrix	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	50	51	
Units: Number of Subjects	24	22	22	

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of AESIs at Week 12

End point title	Incidence of AESIs at Week 12

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	HEPLISAV arm	Engerix B	Fendrix	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	54	50	51	
Units: Number of Subjects	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were entered into CRFs from the time of first dose of study treatment at Day 1 (Week 0) through Week 4. AEs were recorded as medical history if they occurred before injection. AESIs and SAEs were recorded from the Screening Visit through Week 12.

Adverse event reporting additional description:

The safety and tolerability assessments included monitoring and recording of local and systemic post-injection reactions (reactogenicity), AEs, AESIs, SAEs, and deaths. Post-injection reactions were entered into the CRFs for 6 days following the administration of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	HEPLISAV arm

Reporting group description:

Subjects received 3 dose of HEPLISAV.

Reporting group title	Engerix B

Reporting group description:

Subjects received Engerix-B.

Reporting group title	Fendrix

Reporting group description:

Subjects received Fendrix.

Serious adverse events	HEPLISAV arm	Engerix B	Fendrix
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 54 (18.52%)	9 / 50 (18.00%)	7 / 51 (13.73%)
number of deaths (all causes)	2	4	0
number of deaths resulting from adverse events	2	4	0
Injury, poisoning and procedural complications			
Shunt occlusion			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-operative thrombosis			
subjects affected / exposed	2 / 54 (3.70%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shunt thrombosis			

subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shunt aneurysm			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acetabulum fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery occlusion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral vascular disorder			

subjects affected / exposed	0 / 54 (0.00%)	2 / 50 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Nervous system disorders			
Cerebellar infarction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	0 / 54 (0.00%)	2 / 50 (4.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Multi-organ failure			
subjects affected / exposed	0 / 54 (0.00%)	2 / 50 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Cholecystitis infective			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Constipation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Azotaemia			

subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bladder neck sclerosis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis staphylococcal			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			

subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	HEPLISAV arm	Engerix B	Fendrix
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 54 (25.93%)	13 / 50 (26.00%)	15 / 51 (29.41%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm skin			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Vascular disorders			
Extremity necrosis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Femoral artery occlusion			

subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Haematoma			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Hypotension			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	2 / 51 (3.92%)
occurrences (all)	1	0	2
Peripheral vascular disorder			
subjects affected / exposed	0 / 54 (0.00%)	2 / 50 (4.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
General physical health deterioration			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Impaired healing			
subjects affected / exposed	0 / 54 (0.00%)	3 / 50 (6.00%)	1 / 51 (1.96%)
occurrences (all)	0	3	1
Injection site erythema			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Injection site haematoma			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Injection site reaction			

subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	2 / 54 (3.70%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	2	0	1
Multi-organ failure			
subjects affected / exposed	0 / 54 (0.00%)	2 / 50 (4.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	3 / 54 (5.56%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pneumothorax			

subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Productive cough			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Pulmonary haemorrhage			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Femoral neck fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences (all)	0	1	1
Haemodialysis-induced symptom			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Laceration			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Postoperative thrombosis			
subjects affected / exposed	2 / 54 (3.70%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	2	0	0
Procedural hypertension			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Procedural hypotension			
subjects affected / exposed	4 / 54 (7.41%)	1 / 50 (2.00%)	2 / 51 (3.92%)
occurrences (all)	4	1	2
Procedural vomiting			

subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Rib fracture			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Shunt aneurysm			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Shunt occlusion			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Shunt stenosis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Shunt thrombosis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Upper limb fracture			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 54 (3.70%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	2	0	0
Atrioventricular block complete			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Ataxia			

subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Carotid artery occlusion			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Cerebellar infarction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Cerebral ischaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	2 / 51 (3.92%)
occurrences (all)	0	0	2
Grand mal convulsion			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	2 / 51 (3.92%)
occurrences (all)	0	1	2
Hypoaesthesia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Syncope			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Nephrogenic anaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Vertigo positional			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Intestinal ischaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	2 / 54 (3.70%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences (all)	2	1	1
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Bladder neck sclerosis			

subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Bone pain			
subjects affected / exposed	0 / 54 (0.00%)	2 / 50 (4.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Muscle spasms			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Myalgia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Pain in extremity			
subjects affected / exposed	3 / 54 (5.56%)	2 / 50 (4.00%)	0 / 51 (0.00%)
occurrences (all)	3	2	0
Tendon pain			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	3 / 51 (5.88%)
occurrences (all)	0	0	3
Cholecystitis infective			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Cystitis			

subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Endocarditis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Endocarditis staphylococcal			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Erysipelas			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	1	0	1
Gastroenteritis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Localised infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 54 (0.00%)	2 / 50 (4.00%)	1 / 51 (1.96%)
occurrences (all)	0	2	1
Pneumonia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Septic shock			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection bacterial			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			

Hypercalcaemia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Hyperkalaemia			
subjects affected / exposed	0 / 54 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0
Hyponatraemia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences (all)	1	0	0
Hypovolaemia			
subjects affected / exposed	0 / 54 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 December 2011	Protocol Amendment 1 - included changes that occurred since the study began. Number of sites increased from 15 to 20 in order to reach the enrollment goal of approx. 150 subjects

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported