Clinical trial results:
An Observer-Blinded, Randomized Study Comparing the Safety and Immunogenicity of HEPLISAV™ to Licensed Vaccine (Engerix-B®) among Adults (18 to 75 Years of Age) with Chronic Kidney Disease (CKD)

Summary

EudraCT number	2009-015877-11
Trial protocol	DE
Global end of trial date	09 January 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-17 synopsis (study-report-dv2-hbv-17 synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	DV2-HBV-17

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00985426
WHO universal trial number (UTN)	-
Other trial identifiers	US IND Number: BB-IND 12692, Canada File Number: 9427-D0897-21C

Notes:

Sponsors

Sponsor organisation name	Dynavax Technologies Corporation
Sponsor organisation address	2929 Seventh Street, Suite 100 Berkeley, Berkeley, California, United States, 94710
Public contact	Referat Klinische Prüfung, Paul-Ehrlich-Institut (PEI), 49 610377 1811, klinpruefung@pei.de
Scientific contact	Referat Klinische Prüfung, Paul-Ehrlich-Institut (PEI), 49 610377 1811, 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	26 June 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2012
Global end of trial reached?	Yes
Global end of trial date	09 January 2012
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the noninferiority of the immune response to a 3-dose regimen of HEPLISAV compared to the standard 4-dose regimen of Engerix-B in subjects with chronic kidney disease (CKD) at 4 weeks after the last injection (Week 28) as measured by the seroprotection rate defined as the percentage of subjects achieving an antibody level to hepatitis B surface antigen (anti-HBsAg) greater than or equal to 10 mIU/mL

Protection of trial subjects:

Injection-site reactions were expected to subside spontaneously. 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 discouraged as it could interfere with the action of the study drug. IMP was not injected into a site if local pain, tenderness, swelling, or pruritus persisted from a previous injection or other cause.
If a subject was stopped from receiving additional study injections, they were to continue to be followed through Week 52.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Canada: 31
Country: Number of subjects enrolled	United States: 452
Worldwide total number of subjects	516
EEA total number of subjects	33

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)	280
From 65 to 84 years	236
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 59 sites: 47 in the US, 3 in Canada and 9 in Germany.

Pre-assignment

Screening details:

The screened population comprised 918 subjects who provided informed consent and began the screening process. Of these subjects, 521 (56.8%) were randomized and 397 (43.2%) were screen failures.

Period 1

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

Blinding implementation details:

The subjects and the study personnel conducting clinical safety evaluations were blinded to treatment assignment. Study drug was not packaged in a blinded manner; therefore, designated study site personnel with no other study responsibilities were not blinded so they could prepare and/or administer the study injections. In addition, an unblinded study monitor with no other study responsibilities confirmed drug accountability.

Arms

Are arms mutually exclusive?	Yes
Arm title	HEPLISAV arm

Arm description:

3 single-dose regimen of HEPLISAV

Arm type	Experimental
Investigational medicinal product name	HBsAg-1018 ISS
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The test product (HEPLISAV) was 20 mcg recombinant HBsAg subtype adw with 3000 mcg 1018 immunostimulatory sequence (ISS) adjuvant. Subjects in the HEPLISAV group received a single IM injection (0.5 mL) in the right or left deltoid muscle at Weeks 0, 4, and 24 (placebo at Week 8).
The reference therapy was Engerix-B (20 mcg recombinant HBsAg combined with 500 mcg alum adjuvant/mL) manufactured by GlaxoSmithKline Biologicals. Subjects in the Engerix-B group received 2 IM injections of 1.0 mL each (for a total dose of 40 mcg HBsAg and 1 mg alum) in the right or left deltoid muscle at Weeks 0, 4, 8, and 24.
The treatment period was 24 weeks (Week 0 to Week 24), with study injections administered at Weeks 0, 4, 8, and 24. Follow-up for safety and immunogenicity was conducted from Week 24 through Week 52.

Arm title	Engerix-B arm

Arm description:

4 double-dose regimen (total of 8 doses) of 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 pen
Routes of administration	Intramuscular use

Dosage and administration details:

The reference therapy was Engerix-B (20 mcg recombinant HBsAg combined with 500 mcg alum adjuvant/mL) manufactured by GlaxoSmithKline Biologicals.
Subjects in the Engerix-B group received 2 IM injections of 1.0 mL each (for a total dose of 40 mcg HBsAg and 1 mg alum) in the right or left deltoid muscle at Weeks 0, 4, 8, and 24.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: This is an observer-blinded study but the subjects are also blinded.

Number of subjects in period 1	HEPLISAV arm	Engerix-B arm
Started	254	262
Completed	215	219
Not completed	39	43
Subject Non-Compliance	3	3
Consent withdrawn by subject	12	16
Adverse event, non-fatal	-	1
Other	7	10
Deaths	7	3
Lost to follow-up	8	10
Protocol deviation	2	-

Baseline characteristics

Reporting groups	
Reporting group title	HEPLISAV arm
Reporting group description:	
3 single-dose regimen of HEPLISAV	
Reporting group title	Engerix-B arm
Reporting group description:	
4 double-dose regimen (total of 8 doses) of Engerix-B	

Reporting group values	HEPLISAV arm	Engerix-B arm	Total
Number of subjects	254	262	516
Age categorical			
The effect of age on immunogenicity was evaluated in 3 age strata: Subjects 18 to 39 years of age (HEPLISAV: n = 2; Engerix-B: n = 11), subjects 40 to 55 years of age (HEPLISAV: n = 57; Engerix-B: n = 46), and subjects 56 to 75 years of age (HEPLISAV: n = 180; Engerix-B: n = 195). TO CONFIRM			
Units: Subjects			
Adults (18 - 64 years)	137	143	280
Adults (65 - 84 years)	117	119	236
Adults (> 84 years)	0	0	0
Age continuous			
Age mean (SD) by treatment group (HEPLISAV vs Engerix-B) Total age mean (SD) including both groups.			
Units: years			
arithmetic mean	61.4	61.3	
standard deviation	± 9.1	± 9.7	-
Gender categorical			
Units: Subjects			
Female	94	104	198
Male	160	158	318

Subject analysis sets	
Subject analysis set title	HEPLISAV mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The primary immunogenicity analysis was based on the mITT population. The mITT population for the immunogenicity analyses comprised all randomized subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation excluding 16 subjects treated at Site 42 - subjects treated with HEPLISAV.	
Subject analysis set title	Engerix-B mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The primary immunogenicity analysis was based on the mITT population. The mITT population for the immunogenicity analyses comprised all randomized subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation excluding 16 subjects treated at Site 42 - subjects treated with Engerix-B.	

Reporting group values	HEPLISAV mITT	Engerix-B mITT	
Number of subjects	239	252	
Age categorical			
The effect of age on immunogenicity was evaluated in 3 age strata: Subjects 18 to 39 years of age (HEPLISAV: n = 2; Engerix-B: n = 11), subjects 40 to 55 years of age (HEPLISAV: n = 57; Engerix-B: n = 46), and subjects 56 to 75 years of age (HEPLISAV: n = 180; Engerix-B: n = 195). TO CONFIRM			
Units: Subjects			
Adults (18 - 64 years)			
Adults (65 - 84 years)			
Adults (> 84 years)	0	0	
Age continuous			
Age mean (SD) by treatment group (HEPLISAV vs Engerix-B) Total age mean (SD) including both groups.			
Units: years			
arithmetic mean	61.4	61.5	
standard deviation	± 9.1	± 9.7	
Gender categorical			
Units: Subjects			
Female	89	101	
Male	150	151	

End points

End points reporting groups

Reporting group title	HEPLISAV arm
Reporting group description:	
3 single-dose regimen of HEPLISAV	
Reporting group title	Engerix-B arm
Reporting group description:	
4 double-dose regimen (total of 8 doses) of Engerix-B	
Subject analysis set title	HEPLISAV mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The primary immunogenicity analysis was based on the mITT population. The mITT population for the immunogenicity analyses comprised all randomized subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation excluding 16 subjects treated at Site 42 - subjects treated with HEPLISAV.	
Subject analysis set title	Engerix-B mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The primary immunogenicity analysis was based on the mITT population. The mITT population for the immunogenicity analyses comprised all randomized subjects who received at least 1 study injection and had at least 1 post-injection immunogenicity evaluation excluding 16 subjects treated at Site 42 - subjects treated with Engerix-B.	

Primary: Noninferiority of the immune response measured by SPR at Week 28

End point title	Noninferiority of the immune response measured by SPR at Week 28[1]
End point description:	
End point type	Primary
End point timeframe:	
Week 28	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive Analysis

End point values	HEPLISAV mITT	Engerix-B mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	219	235		
Units: Number of Subjects				
Week 28	196	191		

Statistical analyses

No statistical analyses for this end point

Secondary: Superiority of the immune response measured by SPR at Week 28

End point title	Superiority of the immune response measured by SPR at Week 28

End point description:

To demonstrate the superiority of the immune response to a 3 single-dose regimen of HEPLISAV compared to the standard 4 double-dose regimen of Engerix-B in subjects with CKD at 4 weeks after the last dose of study treatment (Week 28) as measured by the SPR.

End point type	Secondary

End point timeframe:

Week 28

End point values	HEPLISAV mITT	Engerix-B mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	219	235		
Units: Percentage				
Week 28	196	191		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluate the safety of HEPLISAV compared to Engerix-B

End point title	Evaluate the safety of HEPLISAV compared to Engerix-B

End point description:

Overall number of subjects who reported a local and/or systemic post-injection reaction

End point type	Secondary

End point timeframe:

Overall trial period

End point values	HEPLISAV arm	Engerix-B arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	254	262		
Units: Number of Subjects	117	132		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluate the immune response as measured by SPR of subjects with type 2 diabetes

End point title	Evaluate the immune response as measured by SPR of subjects with type 2 diabetes

End point description:

End point type	Secondary
End point timeframe:	
Week 28	

End point values	HEPLISAV mITT	Engerix-B mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	147	145		
Units: Number of Subjects	131	110		

Statistical analyses

No statistical analyses for this end point

Secondary: Compare the immunogenicity of HEPLISAV and Engerix-B measured by SPR

End point title	Compare the immunogenicity of HEPLISAV and Engerix-B measured by SPR
End point description:	

End point type	Secondary
End point timeframe:	
Weeks 4, 8, 12, 24, 28, 36, 44, 52	

End point values	HEPLISAV mITT	Engerix-B mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	250		
Units: percent				
number (confidence interval 95%)				
Week 4	5.4 (2.9 to 9.1)	6.0 (3.4 to 9.7)		
Week 8	46.8 (40.2 to 53.4)	20.0 (15.2 to 25.5)		
Week 12	64.3 (57.8 to 70.5)	49.8 (43.3 to 59.3)		
Week 24	78 (72 to 83.2)	61.5 (55.0 to 67.7)		
Week 28	89.5 (84.7 to 93.2)	81.3 (75.7 to 86.1)		
Week 36	86.4 (81.1 to 90.7)	79.7 (73.9 to 84.8)		
Week 44	83.3 (77.6 to 88.1)	78.0 (71.9 to 83.4)		
Week 52	83.7 (78.0 to 88.5)	76.6 (70.4 to 82.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Compare the immunogenicity of HEPLISAV and Engerix-B as measured by the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL

End point title	Compare the immunogenicity of HEPLISAV and Engerix-B as measured by the percentage of subjects with anti-HBsAg greater than or equal to 100 mIU/mL

End point description:

Comparison of Percentage of Subjects With Anti-HBsAg Greater Than or Equal to 100 mIU/mL Between HEPLISAV and Engerix-B by Visit (mITT Population)

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 18, 24, 28, 36, 44 and 52

End point values	HEPLISAV mITT	Engerix-B mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	250		
Units: percent				
number (confidence interval 95%)				
Week 4	3.3 (1.5 to 6.5)	2.4 (0.9 to 5.2)		
Week 8	18.9 (14.1 to 24.5)	7.2 (4.3 to 11.1)		
Week 12	26.1 (20.5 to 32.3)	21.6 (16.6 to 27.3)		
Week 18	37.3 (31.0 to 43.9)	24.9 (19.6 to 30.9)		
Week 24	43.6 (37.1 to 50.3)	28.0 (22.4 to 34.2)		
Week 28	72.6 (66.2 to 78.4)	62.1 (55.6 to 68.4)		
Week 36	67.8 (61.0 to 74.0)	57.7 (51.0 to 64.2)		
Week 44	66.7 (59.9 to 73.0)	53.3 (46.3 to 60.1)		
Week 52	65.6 (58.7 to 72.0)	47.7 (40.8 to 54.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluate the immunogenicity of HEPLISAV compared to Engerix-B as measured by serum anti-HBsAg GMC

End point title	Evaluate the immunogenicity of HEPLISAV compared to Engerix-B as measured by serum anti-HBsAg GMC

End point description:

Comparison of Geometric Mean Concentrations Between HEPLISAV and Engerix-B by Visit (mITT Population) (at Weeks 4, 8, 12, 18, 24, 28, 36, 44, and 52).
The Ratio of GMCs HEPLISAV/Engerix-B (95% CI) is used to compare GMC (table 11-4 of CSR).
To add Figure 11-2 of CSR in the 'chart' section in previous interface.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 18, 24, 28, 36, 44 and 52

End point values	HEPLISAV mITT	Engerix-B mITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	239	250		
Units: percent				
number (confidence interval 95%)				
Week4	0.4 (0.3 to 0.5)	0.2 (0.2 to 0.3)		
Week 8	7.3 (5.1 to 10.5)	0.9 (0.6 to 1.2)		
Week 12	15.1 (10.7 to 21.5)	6.8 (4.7 to 10.0)		
Week 18	30.8 (21.7 to 43.7)	11.6 (8.1 to 16.7)		
Week 24	41.8 (29.5 to 59.2)	14.5 (10.1 to 20.8)		
Week 28	526.0 (344.6 to 802.9)	143.4 (94.4 to 217.8)		
Week 36	271.8 (179.1 to 412.4)	96.3 (64.0 to 144.8)		
Week 44	194.3 (130.8 to 288.8)	66.5 (44.6 to 99.1)		
Week 52	155.8 (106.1 to 228.8)	47.5 (32.2 to 70.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting period for all nonserious AEs began at the time of first injection and extended through 4 weeks following the last injection (Week 28).

Adverse event reporting additional description:

All AEs were monitored until resolution or until the subject completed the study. If an AE remained unresolved when the subject discontinued or completed the study, a clinical assessment was made by the investigator and the medical monitor to determine whether continued follow-up of the event was warranted.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	HEPLISAV arm

Reporting group description:

3 single-dose regimen of HEPLISAV

Reporting group title	Engerix-B arm

Reporting group description:

4 double-dose regimen (total of 8 doses) of Engerix-B

Serious adverse events	HEPLISAV arm	Engerix-B arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 254 (26.77%)	76 / 262 (29.01%)	
number of deaths (all causes)	7	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon adenoma			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			

subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
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	0 / 254 (0.00%)	1 / 262 (0.38%)	
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	0 / 254 (0.00%)	1 / 262 (0.38%)	
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 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid cancer			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (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 / 254 (0.39%)	4 / 262 (1.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	2 / 254 (0.79%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 254 (0.39%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant hypertension			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 254 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steal syndrome			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Diarrhoea			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			

subjects affected / exposed	1 / 254 (0.39%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia obstructive			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-Organ failure			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 254 (0.79%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical Device Complication			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Victim of homicide			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 254 (0.39%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchiectasis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 254 (0.39%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	3 / 254 (1.18%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory depression			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
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	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Lipase increased			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
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			
Accidental overdose			

subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
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 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft occlusion			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	3 / 254 (1.18%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	3 / 3	2 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 254 (0.00%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 254 (0.79%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 254 (0.39%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	8 / 254 (3.15%)	8 / 262 (3.05%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 254 (0.00%)	5 / 262 (1.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial infarction			
subjects affected / exposed	3 / 254 (1.18%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 254 (0.39%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			

subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lacunar infarction			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 254 (0.39%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 254 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 254 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 254 (1.57%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			

subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enlarged uvula			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia, obstructive			

subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 254 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 254 (0.39%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 254 (0.00%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal cyst			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst ruptured			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
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	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure acute			
subjects affected / exposed	5 / 254 (1.97%)	7 / 262 (2.67%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure chronic			
subjects affected / exposed	9 / 254 (3.54%)	12 / 262 (4.58%)	
occurrences causally related to treatment / all	0 / 9	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (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			
Gouty arthritis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Bacterial pyelonephritis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 254 (0.39%)	3 / 262 (1.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis staphylococcal			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic tonsillitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	2 / 254 (0.79%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal peritonitis			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 254 (0.79%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 254 (0.39%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			

subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 254 (0.39%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 254 (1.97%)	4 / 262 (1.53%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst infection			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (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	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	2 / 254 (0.79%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (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	1 / 254 (0.39%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	3 / 254 (1.18%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			

subjects affected / exposed	1 / 254 (0.39%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	1 / 254 (0.39%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 254 (0.79%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	2 / 254 (0.79%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 254 (0.00%)	1 / 262 (0.38%)	
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: 2 %

Non-serious adverse events	HEPLISAV arm	Engerix-B arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	140 / 254 (55.12%)	146 / 262 (55.73%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 254 (3.15%)	18 / 262 (6.87%)	
occurrences (all)	8	18	
Hypotension			

subjects affected / exposed	6 / 254 (2.36%)	7 / 262 (2.67%)	
occurrences (all)	6	7	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	16 / 254 (6.30%)	13 / 262 (4.96%)	
occurrences (all)	16	13	
Oedema peripheral			
subjects affected / exposed	16 / 254 (6.30%)	13 / 262 (4.96%)	
occurrences (all)	16	13	
Non-cardiac chest pain			
subjects affected / exposed	5 / 254 (1.97%)	3 / 262 (1.15%)	
occurrences (all)	5	3	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 254 (4.33%)	9 / 262 (3.44%)	
occurrences (all)	11	9	
Dyspnoea			
subjects affected / exposed	8 / 254 (3.15%)	9 / 262 (3.44%)	
occurrences (all)	8	9	
Oropharyngeal pain			
subjects affected / exposed	4 / 254 (1.57%)	6 / 262 (2.29%)	
occurrences (all)	4	6	
Pulmonary oedema			
subjects affected / exposed	6 / 254 (2.36%)	3 / 262 (1.15%)	
occurrences (all)	6	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 254 (2.36%)	1 / 262 (0.38%)	
occurrences (all)	6	1	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 254 (2.76%)	5 / 262 (1.91%)	
occurrences (all)	7	5	
Cardiac disorders			

Cardiac failure congestive			
subjects affected / exposed	12 / 254 (4.72%)	10 / 262 (3.82%)	
occurrences (all)	12	10	
Coronary artery disease			
subjects affected / exposed	1 / 254 (0.39%)	6 / 262 (2.29%)	
occurrences (all)	1	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 254 (1.57%)	8 / 262 (3.05%)	
occurrences (all)	4	8	
Headache			
subjects affected / exposed	9 / 254 (3.54%)	8 / 262 (3.05%)	
occurrences (all)	9	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 254 (3.54%)	11 / 262 (4.20%)	
occurrences (all)	9	11	
Eye disorders			
Cataract			
subjects affected / exposed	7 / 254 (2.76%)	3 / 262 (1.15%)	
occurrences (all)	7	3	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	11 / 254 (4.33%)	11 / 262 (4.20%)	
occurrences (all)	11	11	
Diarrhoea			
subjects affected / exposed	11 / 254 (4.33%)	10 / 262 (3.82%)	
occurrences (all)	11	10	
Nausea			
subjects affected / exposed	11 / 254 (4.33%)	13 / 262 (4.96%)	
occurrences (all)	11	13	
Vomiting			
subjects affected / exposed	6 / 254 (2.36%)	8 / 262 (3.05%)	
occurrences (all)	6	8	
Abdominal pain			
subjects affected / exposed	5 / 254 (1.97%)	5 / 262 (1.91%)	
occurrences (all)	5	5	

Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 254 (0.79%)	8 / 262 (3.05%)	
occurrences (all)	2	8	
Rash			
subjects affected / exposed	5 / 254 (1.97%)	2 / 262 (0.76%)	
occurrences (all)	5	2	
Renal and urinary disorders			
renal failure chronic			
subjects affected / exposed	11 / 254 (4.33%)	13 / 262 (4.96%)	
occurrences (all)	11	13	
Renal failure acute			
subjects affected / exposed	8 / 254 (3.15%)	9 / 262 (3.44%)	
occurrences (all)	8	9	
Renal impairment			
subjects affected / exposed	5 / 254 (1.97%)	4 / 262 (1.53%)	
occurrences (all)	5	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 254 (5.91%)	7 / 262 (2.67%)	
occurrences (all)	15	7	
Back pain			
subjects affected / exposed	3 / 254 (1.18%)	12 / 262 (4.58%)	
occurrences (all)	3	12	
Muscle spasms			
subjects affected / exposed	5 / 254 (1.97%)	10 / 262 (3.82%)	
occurrences (all)	5	10	
Musculoskeletal pain			
subjects affected / exposed	5 / 254 (1.97%)	7 / 262 (2.67%)	
occurrences (all)	5	7	
Myalgia			
subjects affected / exposed	2 / 254 (0.79%)	6 / 262 (2.29%)	
occurrences (all)	2	6	
Pain in extremity			
subjects affected / exposed	8 / 254 (3.15%)	11 / 262 (4.20%)	
occurrences (all)	8	11	

Infections and infestations			
Bronchitis			
subjects affected / exposed	9 / 254 (3.54%)	8 / 262 (3.05%)	
occurrences (all)	9	8	
Gastroenteritis			
subjects affected / exposed	7 / 254 (2.76%)	2 / 262 (0.76%)	
occurrences (all)	7	2	
Nasopharyngitis			
subjects affected / exposed	13 / 254 (5.12%)	18 / 262 (6.87%)	
occurrences (all)	13	18	
Sinusitis			
subjects affected / exposed	7 / 254 (2.76%)	7 / 262 (2.67%)	
occurrences (all)	7	7	
Upper respiratory tract infection			
subjects affected / exposed	11 / 254 (4.33%)	11 / 262 (4.20%)	
occurrences (all)	11	11	
Urinary tract infection			
subjects affected / exposed	12 / 254 (4.72%)	7 / 262 (2.67%)	
occurrences (all)	12	7	
Pneumonia			
subjects affected / exposed	7 / 254 (2.76%)	4 / 262 (1.53%)	
occurrences (all)	7	4	
Cellulitis			
subjects affected / exposed	6 / 254 (2.36%)	3 / 262 (1.15%)	
occurrences (all)	6	3	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	7 / 254 (2.76%)	7 / 262 (2.67%)	
occurrences (all)	7	7	
Hyperphosphataemia			
subjects affected / exposed	4 / 254 (1.57%)	8 / 262 (3.05%)	
occurrences (all)	4	8	
Hypoglycaemia			
subjects affected / exposed	6 / 254 (2.36%)	6 / 262 (2.29%)	
occurrences (all)	6	6	
Hypokalaemia			

subjects affected / exposed	9 / 254 (3.54%)	4 / 262 (1.53%)	
occurrences (all)	9	4	
Metabolic acidosis			
subjects affected / exposed	4 / 254 (1.57%)	6 / 262 (2.29%)	
occurrences (all)	4	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2009	Protocol Amendment 1 - first version of the protocol submitted to ethics committees and implemented at the site level.
23 November 2009	Protocol Amendment 2
05 May 2010	Protocol Amendment 3
14 July 2011	Protocol Amendment 4

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported