



Clinical trial results:

A RANDOMIZED, OPEN-LABEL, MULTICENTER, CONTROLLED STUDY TO ASSESS SAFETY AND EFFICACY OF ELAD IN SUBJECTS WITH SEVERE ACUTE ALCOHOLIC HEPATITIS (SAAH) AND LILLE SCORE FAILURE

Summary

EudraCT number	2013-001884-21
Trial protocol	GB DE ES AT
Global end of trial date	16 September 2015

Results information

Result version number	v1 (current)
This version publication date	09 April 2017
First version publication date	09 April 2017

Trial information

Trial identification

Sponsor protocol code	VTI-210
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01829347
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vital Therapies, Inc.
Sponsor organisation address	15010 Avenue of Science, Suite 200, San Diego, United States, 92128
Public contact	Duane Nash, Vital Therapies, Inc., 001 858-673-6840, dnash@vitaltherapies.com
Scientific contact	Robert Ashley, Chief Technical Officer, Vital Therapies, Inc., 001 858-673-6840, rashley@vitaltherapies.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 September 2015
Global end of trial reached?	Yes
Global end of trial date	16 September 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate safety and efficacy of ELAD with respect to overall survival (OS) in subjects with a clinical diagnosis of severe acute alcoholic hepatitis (sAAH) who are Lille score failures (Lille score >0.45). Follow-up Protocol VTI 210E will provide additional survival data up to a maximum of 5 years that will be included, as available, through VTI-210 study termination (after all enrolled subjects complete Study Day 91, are lost to follow up or withdraw consent, or die before that Study Day). This will be assessed using a Kaplan-Meier survival analysis of the intent-to-treat (ITT) population utilizing a log-rank test to evaluate the null hypothesis of equality of survival curves. The randomization and the analysis model will be stratified by whether or not the clinical diagnosis of sAAH was confirmed with a liver biopsy.

Protection of trial subjects:

Continuous monitoring of the ELAD System by trained ELAD Specialists during ELAD treatment. Administration of diphenhydramine or equivalent immediately prior to initiation of ELAD treatment to prevent hypersensitivity reactions.

Background therapy:

The standard of care (background therapy) for the secondary medical problems associated with alcoholic hepatitis (AH) was derived from the practice guidelines issued by the American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of Liver (EASL). These guidelines were applied to both the ELAD-treated and Control subjects during this study.

Evidence for comparator:

VTI-210 was a randomized, open-label, multicenter, controlled study of subjects with severe acute alcoholic hepatitis (sAAH). Subjects meeting eligibility requirements of the study received either standard of care treatment for sAAH (as defined in the protocol) plus treatment with the ELAD System (ELAD group) or standard of care treatment for sAAH alone (Control group).

Treatment options for patients with sAAH are limited. Patients with severe AH (defined as a Maddrey Discriminant Function of ≥ 32) have a poor prognosis, with 90-day survival of around 50%. Regimens that have been used for the past 40 years, including corticosteroids, theophylline with corticosteroids, pentoxifylline, and infliximab, have had no significant effect on the long-term survival of patients with sAAH.

Of particular importance are the results of the UK NIHR-supported STOPAH study, a study in alcoholic hepatitis reporting out in 2015. Results from this study, which randomized 1103 subjects in 40 clinical sites in the UK, showed that the administration of steroids and pentoxifylline had no effect on survival at 90 days either alone or in combination.

While a sham control is a potential comparator, regulatory and ethical bodies have determined that the administration of a sham extracorporeal therapy without the possibility of benefit is unethical, and therefore could not be considered for study VTI-210. Consequently, the best available standard of care in accord with AASLD and EASL guidelines was recommended in the VTI-210 study protocol for all participants irrespective of treatment arm.

Actual start date of recruitment	30 September 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	18
EEA total number of subjects	13

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)	18
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with clinical (protocol-guided) or biopsy-proven evidence of sAAH who met study inclusion/exclusion criteria, including Lille score >0.45, were eligible for participation in the study. Subjects were recruited from September 2014 through August 2015 in the United States, United Kingdom and Spain.

Pre-assignment

Screening details:

A total of 31 participants diagnosed with alcoholic hepatitis were screened, out of which 13 were screen failures, and 18 were randomized, of which 9 received ELAD treatment. Participants who successfully completed the initial 91-day treatment period were entered into a 5-year extension phase (VTI-210) of the study.

Period 1

Period 1 title	VTI-210
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Investigative staff who carried out follow-up treatment visits were blinded to participant treatment assignment. Home visit staff who carried out weekly home visits for participants discharged from the hospital were also blinded to participant treatment assignment. Sponsor staff, with the exception of those involved in the monitoring of the study safety, were blinded to treatment outcomes. The Data and Safety Monitoring Board was blinded to study outcomes.

Arms

Are arms mutually exclusive?	Yes
Arm title	ELAD Treatment

Arm description:

Participants randomized to the ELAD group received ELAD treatment plus protocol-directed standard of care treatment for a period of up to 10 days followed by standard of care treatment through Study Day 91.

Arm type	Experimental
Investigational medicinal product name	ELAD
Investigational medicinal product code	ELAD System
Other name	VTL C3A cells
Pharmaceutical forms	Living tissue equivalent
Routes of administration	Haemodialysis

Dosage and administration details:

Four cartridges, each containing approximately 110 grams of VTL C3A cells (approximately 440 grams total or approximately 20% to 30% of the native liver, a residual mass necessary for survival). ELAD treatment duration spans for up to 10 days. Continuous extracorporeal circulation by central venous catheter allowing plasma fraction interaction with VTL C3A cells incorporated in ELAD C3A cell cartridges.

Arm title	Control
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Arm description:

Participants randomized to the Control group received protocol-directed standard of care treatment in accord with AASLD and EASL guidelines for up to 91 days.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	ELAD Treatment	Control
Started	9	9
Completed	4	6
Not completed	5	3
Adverse event, serious fatal	4	3
Consent withdrawn by subject	1	-

Period 2

Period 2 title	VTI-210E
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ELAD Treatment

Arm description:

Participants randomized to the ELAD group and who received ELAD treatment plus protocol-directed standard of care treatment for a period of up to 10 days during study VTI-210 were followed up for up to 5 years in VTI-210E.

Arm type	Experimental
Investigational medicinal product name	ELAD
Investigational medicinal product code	ELAD System
Other name	VTL C3A cells
Pharmaceutical forms	Living tissue equivalent
Routes of administration	Haemodialysis

Dosage and administration details:

Four cartridges, each containing approximately 110 grams of VTL C3A cells (approximately 440 grams total or approximately 20% to 30% of the native liver, a residual mass necessary for survival). ELAD treatment duration spans for up to 10 days. Continuous extracorporeal circulation by central venous catheter allowing plasma fraction interaction with VTL C3A cells incorporated in ELAD C3A cell cartridges.

Arm title	Control
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Arm description:

Participants randomized to the Control group and who received protocol-directed standard of care during the VTI-210 study in accord with AASLD and EASL guidelines were followed up for up to 5 years.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	ELAD Treatment	Control
Started	4	6
Completed	0	0
Not completed	4	6
Death	3	2
VTI-210E ongoing	1	4

Baseline characteristics

Reporting groups

Reporting group title	ELAD Treatment
Reporting group description:	
Participants randomized to the ELAD group received ELAD treatment plus protocol-directed standard of care treatment for a period of up to 10 days followed by standard of care treatment through Study Day 91.	
Reporting group title	Control
Reporting group description:	
Participants randomized to the Control group received protocol-directed standard of care treatment in accord with AASLD and EASL guidelines for up to 91 days.	

Reporting group values	ELAD Treatment	Control	Total
Number of subjects	9	9	18
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	9	9	18
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	46.1	50	
standard deviation	± 7.29	± 9.79	-
Gender categorical			
Units: Subjects			
Female	6	3	9
Male	3	6	9
Race			
Units: Subjects			
White	9	9	18
Baseline MELD			
Baseline value of the Model for End-stage Liver Disease score.			
Units: MELD score			
arithmetic mean	27.531	26.323	
standard deviation	± 2.887	± 2.8524	-

End points

End points reporting groups

Reporting group title	ELAD Treatment
Reporting group description: Participants randomized to the ELAD group received ELAD treatment plus protocol-directed standard of care treatment for a period of up to 10 days followed by standard of care treatment through Study Day 91.	
Reporting group title	Control
Reporting group description: Participants randomized to the Control group received protocol-directed standard of care treatment in accord with AASLD and EASL guidelines for up to 91 days.	
Reporting group title	ELAD Treatment
Reporting group description: Participants randomized to the ELAD group and who received ELAD treatment plus protocol-directed standard of care treatment for a period of up to 10 days during study VTI-210 were followed up for up to 5 years in VTI-210E.	
Reporting group title	Control
Reporting group description: Participants randomized to the Control group and who received protocol-directed standard of care during the VTI-210 study in accord with AASLD and EASL guidelines were followed up for up to 5 years.	

Primary: Overall Survival

End point title	Overall Survival
End point description: The primary endpoint of the study was a comparison of overall survival between ELAD-treated and Control groups defined by a Kaplan-Meier analysis of survival up to at least Study Day 91, with protocol VTI-210E providing additional survival data up to a maximum of 5 years, that was included as available at the time of database lock (11 July 2016).	
End point type	Primary
End point timeframe: Up to at least Study Day 91, with protocol VTI-210E providing additional survival data up to 5 years from randomization.	

End point values	ELAD Treatment	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Subjects				
Alive	1	4		
Dead	7	5		
Withdrew Consent	1	0		

Statistical analyses

Statistical analysis title	Kaplan-Meier Analysis of Overall Survival
Statistical analysis description: The primary endpoint was assessed using a Kaplan-Meier survival analysis of the Intent-to-treat (ITT) population utilizing a log-rank test.	
Comparison groups	ELAD Treatment v Control
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.305
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.083
upper limit	1.127

Notes:

[1] - VTI-210E remains ongoing. Subjects were censored at last known time point alive. Data reflects information through 31 December 2016.

Secondary: Proportion of Survivors at Study Day 91

End point title	Proportion of Survivors at Study Day 91
End point description: Proportion of survivors at Study Day 91.	
End point type	Secondary
End point timeframe: Up to Study Day 91.	

End point values	ELAD Treatment	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: Subjects				
Alive	4	6		
Dead	4	3		

Statistical analyses

Statistical analysis title	Proportion of Survivors at Study Day 91
Statistical analysis description: Proportion of Survivors at Study Day 91	
Comparison groups	ELAD Treatment v Control

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Randomization through Study Day 91.

Adverse event reporting additional description:

It should be noted that the outcome of the serious adverse event is recorded as the subject status at Study Day 91. Note, one serious adverse event (melaena) was ongoing at Study Day 91, and ultimately resulted in death of the subject at Study Day 94 at which time the subject had entered VTI-210E.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	ELAD Treatment
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Reporting group description:

Participants received ELAD treatment plus protocol-guided standard of care for a period of up to 10 days followed by standard of care through Study Day 91.

Reporting group title	Control
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Reporting group description:

Subjects randomized to the Control group received protocol-guided standard of care in accord with AASLD and EASL guidelines for up to 91 days.

Serious adverse events	ELAD Treatment	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 9 (66.67%)	5 / 9 (55.56%)	
number of deaths (all causes)	4	3	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Hepatic encephalopathy			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (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	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Alcoholic liver disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis alcoholic			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (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			
Peritonitis bacterial			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (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			
Fluid retention			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	ELAD Treatment	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	9 / 9 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Vascular disorders			
Hypotension			
subjects affected / exposed	6 / 9 (66.67%)	1 / 9 (11.11%)	
occurrences (all)	7	1	
Peripheral venous disease			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Catheter site haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Device malfunction			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Generalised oedema			
subjects affected / exposed	3 / 9 (33.33%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Medical device complication			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	3 / 9 (33.33%)	3 / 9 (33.33%)	
occurrences (all)	4	3	
Pain			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	2 / 9 (22.22%)	2 / 9 (22.22%)	
occurrences (all)	6	3	
Xerosis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Hydrocele			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Scrotal oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Atelectasis			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Bronchospasm			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	3 / 9 (33.33%)	0 / 9 (0.00%)	
occurrences (all)	4	0	
Epistaxis			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	
occurrences (all)	3	1	
Haemoptysis			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pneumonia aspiration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Respiratory failure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Wheezing			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Flat affect			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Injury, poisoning and procedural complications			
Perineal injury			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Periorbital haematoma			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Cardiac disorders Cardiomegaly subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Nervous system disorders Asterixis subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hepatic encephalopathy subjects affected / exposed occurrences (all) Irregular sleep phase subjects affected / exposed occurrences (all) Stupor subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 3 / 9 (33.33%) 4 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 1 / 9 (11.11%) 1	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Coagulopathy subjects affected / exposed occurrences (all) Haemolysis subjects affected / exposed occurrences (all) Leukocytosis	7 / 9 (77.78%) 7 2 / 9 (22.22%) 2 1 / 9 (11.11%) 1	2 / 9 (22.22%) 2 1 / 9 (11.11%) 1 0 / 9 (0.00%) 0	

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Splenomegaly subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Thrombocytopenia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Ear and labyrinth disorders Middle ear effusion subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	0 / 9 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 3	1 / 9 (11.11%) 1	
Abdominal tenderness subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Ascites subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 4	4 / 9 (44.44%) 4	
Colonic pseudo-obstruction subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Constipation subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	1 / 9 (11.11%) 1	
Diarrhoea subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3	2 / 9 (22.22%) 2	
Duodenal ulcer			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	
occurrences (all)	3	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Varices oesophageal			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Decubitus ulcer			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

Dermatitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Ecchymosis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Excoriation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Pruritus generalised			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Skin plaque			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 9 (22.22%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Renal failure			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Renal impairment			

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Critical illness myopathy subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Infections and infestations Bacteraemia subjects affected / exposed occurrences (all)	3 / 9 (33.33%) 7	2 / 9 (22.22%) 4	
Cellulitis subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	2 / 9 (22.22%) 2	
Gingival abscess subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Oesophageal candidiasis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Pneumonia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	
Sepsis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	
Septic shock			

subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	2 / 9 (22.22%)	1 / 9 (11.11%)	
occurrences (all)	2	1	
Urinary tract infection fungal			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Vulval cellulitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Hyperammonaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	2 / 9 (22.22%)	2 / 9 (22.22%)	
occurrences (all)	2	2	
Hypernatraemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Hypocalcaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hypokalaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	
occurrences (all)	1	1	
Hypomagnesaemia			
subjects affected / exposed	2 / 9 (22.22%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

Hypophosphataemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Lactic acidosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Metabolic acidosis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2013	Amendment 1, Version 2 - The number of planned subjects was increased from 100 to 120 in order to increase the power to achieve the planned significance level of 0.05 while maintaining the same assumptions for the treatment effect. Removed the maximum treatment age of 65. Modified the inclusion/exclusion criteria. Added a quality of life questionnaire (EQ-5D-5L). Made clarifications of the Screening Phase of the study.
17 October 2013	Amendment 2, Version 3 - Changes were made to correct the schedule of evaluations tables.
06 August 2014	Amendment 3 - Global harmonization of the protocol to better assist investigators and clinical sites in the conduct of the trial. Significant changes were made to the inclusion/exclusion criteria, the statistical sections, and the overall conduct of the study. However, no subjects were enrolled under any previous versions of the VTI-210 study protocol.
03 December 2014	Amendment 4 - Changes were made as a consequence of the STOPAH study results (Thursz et al., 2014). A change to the study title, inclusion/exclusion criteria, and general conduct of the study. This amendment no longer mandates steroid use during the period of Lille score assessment as an entry criterion, but rather continues to assess subject's mortality risk by Lille score, independent of steroid use.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study was terminated early after enrollment of only 18/150 planned subjects due to findings from previous VTI-208 study. Thus, sample size of VTI-210 was very small leading to statistical analyses that cannot be meaningfully interpreted.

Notes: