Clinical trial results:
EFFICACY AND SAFETY OF NIULIVA FOR THE PREVENTION OF HEPATITIS B VIRUS RECURRENCE IN NEWLY ORTHOTOPIC LIVER TRANSPLANT RECIPIENTS

Summary

EudraCT number	2010-020931-37
Trial protocol	IT
Global end of trial date	16 June 2014

Results information

Result version number	v1 (current)
This version publication date	31 December 2016
First version publication date	31 December 2016

Trial information

Trial identification

Sponsor protocol code	IG0907

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01131065
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Instituto Grifols S.A.
Sponsor organisation address	C/ Can Guasch 2, Parets del Vallés, Spain, 08150
Public contact	Michael K. Woodward, Grifols Therapeutics Inc., michael.woodward@grifols.com
Scientific contact	Michael K. Woodward, Grifols Therapeutics Inc., michael.woodward@grifols.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	10 November 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 June 2014
Global end of trial reached?	Yes
Global end of trial date	16 June 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the percentage of patients that present HBV recurrence, after the administration of Niuliva in newly liver transplanted patients due to HBV induced liver disease, during the first six months after transplantation

Protection of trial subjects:

Trial subjects were informed of the advantages, risk and constraints of the study before signing the informed consent form.
Precautions were taken in case any patient had presented an episode of infection associated with fever, chills or nausea at the time of the infusion, the infusion would have been interrupted until the infection was under control.
Precautions were also taken in case intolerance problems had occurred, the admininstration rate would have been reduced or even temporarily stopped. Suspicion of allergic or anaphylactic type reactions would have required immediate discontinuation of the infusion. In the case of shock, the current medical treatment protocols must have been followed.
The dose administration frequency established for each subject could be modified according to clinical criteria and should have been justified in the case report form.

Background therapy: -

Evidence for comparator:

Not applicable

Actual start date of recruitment	26 July 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	Italy: 15
Worldwide total number of subjects	15
EEA total number of subjects	15

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifteen subjects (newly liver transplanted due to HBV induced liver disease) were screened in the study in a total of four centers in Italy.
First subject enrolled - 26 July 2010 Last subject completed - 16 June 2014

Pre-assignment

Screening details:

Subjects participating in this study were selected among subjects that were to undergo orthotopic liver transplantation due to HBV infection-related disease. Baseline visit (screening visit) will be performed within 3 months (maximum) prior to transplanstation

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Day 3

Arm description:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm title	Day 4

Arm description:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm title	Day 5

Arm description:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm type	Experimental

Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm title	Day 6

Arm description:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm title	Day 7

Arm description:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 10,000 IU

Arm title	Week 2

Arm description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm title	Week 3

Arm description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details: Hepatitis B immune globulin intravenously dose of 5,000 IU	

Arm title	Week 4
Arm description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm title	Month 2
Arm description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm title	Month 3
Arm description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm title	Month 4
Arm description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm title	Month 5

Arm description:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm title	Month 6
Arm description:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm title	Month 7
Arm description:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm title	Month 8
Arm description:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm title	Month 9
Arm description:	
Hepatitis B immune globulin intravenously dose of 5,000 IU	
Arm type	Experimental

Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm title	Month 10

Arm description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm title	Month 11

Arm description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm title	Month 12

Arm description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Arm type	Experimental
Investigational medicinal product name	Niuliva
Investigational medicinal product code	
Other name	Hepatitis B immune globulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Number of subjects in period 1	Day 3	Day 4	Day 5
Started	15	15	15
Completed	15	15	15

Number of subjects in period 1	Day 6	Day 7	Week 2
Started	15	15	15
Completed	15	15	15

Number of subjects in period 1	Week 3	Week 4	Month 2
Started	15	15	15
Completed	15	15	15

Number of subjects in period 1	Month 3	Month 4	Month 5
Started	15	15	15
Completed	15	15	15

Number of subjects in period 1	Month 6	Month 7	Month 8
Started	15	3	3
Completed	15	3	3

Number of subjects in period 1	Month 9	Month 10	Month 11
Started	3	3	3
Completed	3	3	3

Number of subjects in period 1	Month 12
Started	3
Completed	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall study

Reporting group description: -

Reporting group values	Overall study	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	55.27		
standard deviation	± 10.51	-	
Gender categorical Units: Subjects			
Female	3	3	
Male	12	12	
Race Units: Subjects			
white	15	15	
black	0	0	
asian	0	0	
other	0	0	
Alcohol consumption Units: Subjects			
Abstemious	15	15	
Currently uses	0	0	
History of alcohol abuse (Exclusion criteria)	0	0	
Hepatitis History Units: Subjects			
chronic HBV	15	15	
fulminant HBV	0	0	
Adequate Birth control Units: Subjects			
Yes	1	1	
No	1	1	
Not applicable	13	13	

Pregnancy test Units: Subjects			
negative	1	1	
Not applicable	14	14	
E-Antigen (HBeAg) Units: Subjects			
negative	14	14	
positive	1	1	
HBV-DNA Units: Subjects			
negative	14	14	
positive	1	1	
Height Units: centimeters			
arithmetic mean	170.33		
standard deviation	± 8.08	-	
Weight Units: kilogram(s)			
arithmetic mean	73.73		
standard deviation	± 12.05	-	

Subject analysis sets

Subject analysis set title	ITT set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects enrolled in the clinical trial and treated with at least 1 administration of the investigational drug

Reporting group values	ITT set		
Number of subjects	15		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	14		
From 65-84 years	1		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	55.27		
standard deviation	± 10.51		
Gender categorical Units: Subjects			
Female	3		
Male	12		

Race Units: Subjects			
white	15		
black	0		
asian	0		
other	0		
Alcohol consumption Units: Subjects			
Abstemious	15		
Currently uses	0		
History of alcohol abuse (Exclusion criteria)	0		
Hepatitis History Units: Subjects			
chronic HBV	15		
fulminant HBV	0		
Adequate Birth control Units: Subjects			
Yes	1		
No	1		
Not applicable	13		
Pregnancy test Units: Subjects			
negative	1		
Not applicable	14		
E-Antigen (HBeAg) Units: Subjects			
negative	14		
positive	1		
HBV-DNA Units: Subjects			
negative	14		
positive	1		
Height Units: centimeters			
arithmetic mean	170.33		
standard deviation	± 8.08		
Weight Units: kilogram(s)			
arithmetic mean	73.73		
standard deviation	± 12.05		

End points

End points reporting groups

Reporting group title	Day 3
Reporting group description: Hepatitis B immune globulin intravenously dose of 10,000 IU	
Reporting group title	Day 4
Reporting group description: Hepatitis B immune globulin intravenously dose of 10,000 IU	
Reporting group title	Day 5
Reporting group description: Hepatitis B immune globulin intravenously dose of 10,000 IU	
Reporting group title	Day 6
Reporting group description: Hepatitis B immune globulin intravenously dose of 10,000 IU	
Reporting group title	Day 7
Reporting group description: Hepatitis B immune globulin intravenously dose of 10,000 IU	
Reporting group title	Week 2
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Week 3
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Week 4
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Month 2
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Month 3
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Month 4
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Month 5
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Month 6
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Month 7
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Month 8
Reporting group description: Hepatitis B immune globulin intravenously dose of 5,000 IU	
Reporting group title	Month 9

Reporting group description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Reporting group title	Month 10

Reporting group description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Reporting group title	Month 11

Reporting group description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Reporting group title	Month 12

Reporting group description:

Hepatitis B immune globulin intravenously dose of 5,000 IU

Subject analysis set title	ITT set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All subjects enrolled in the clinical trial and treated with at least 1 administration of the investigational drug

Primary: HBV recurrence at six months

End point title	HBV recurrence at six months[1]

End point description:

HBV recurrence is measured by seroconversion or reappearance of HBsAg and HBV DNA positivity

End point type	Primary

End point timeframe:

First six months after liver transplantation

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: HBV recurrence at six months after liver transplantation was descriptively evaluated by proportion of subjects estimated together with its confidence interval calculated by means of the Clopper-Pearson method, which inverts the equal-tailed test based on the binomial distribution. There is no comparison statistical analysis for this primary endpoint.

End point values	ITT set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: subjects				
Month 6	0			

Statistical analyses

No statistical analyses for this end point

Primary: HBV recurrence at twelve months

End point title	HBV recurrence at twelve months[2]

End point description:

HBV recurrence is measured by seroconversion or reappearance of HBsAg and HBV DNA positivity

End point type	Primary

End point timeframe:

First twelve months after liver transplantation

Notes:

[2] - 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: HBV recurrence at twelve months after liver transplantation was descriptively evaluated by proportion of subjects estimated together with its confidence interval calculated by means of the Clopper-Pearson method, which inverts the equal-tailed test based on the binomial distribution. There is no comparison statistical analysis for this primary endpoint.

End point values	ITT set			
Subject group type	Subject analysis set			
Number of subjects analysed	3			
Units: subjects	0			

Statistical analyses

No statistical analyses for this end point

Primary: HBsAg pre-infusion levels

End point title	HBsAg pre-infusion levels[3]

End point description:

Trough levels before each Niuliva administration

End point type	Primary

End point timeframe:

Days 3 to 7, Weeks 2 to 4, Months 2 to 6, Months 7 to 12

Notes:

[3] - 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: HBsAb titer (i.e. immediately pre-infusion) was descriptively evaluated at relevant visits by mean, standard deviation (SD), median, minimum and maximum values and 95% Confidence Interval (CI) of the mean computed using a t-distribution. There is no comparison statistical analysis for this primary endpoint

End point values	Day 3	Day 4	Day 5	Day 6
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	10	10	12
Units: IU/L				
arithmetic mean (standard deviation)	764.7 (± 375.91)	910.7 (± 282.39)	969.6 (± 96.13)	1000 (± 0)

End point values	Day 7	Week 2	Week 3	Week 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	11	13	14
Units: IU/L				
arithmetic mean (standard deviation)	1000 (± 0)	1073.6 (± 244.21)	945.2 (± 250.38)	1029.2 (± 175.21)

End point values	Month 2	Month 3	Month 4	Month 5
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	14	15	15
Units: IU/L				
arithmetic mean (standard deviation)	592.5 (± 260.14)	439.2 (± 218.22)	398.1 (± 272.68)	351.9 (± 179.01)

End point values	Month 6	Month 7	Month 8	Month 9
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	3	3	3
Units: IU/L				
arithmetic mean (standard deviation)	369 (± 182.75)	277.7 (± 89.14)	304.3 (± 50.24)	266 (± 34.7)

End point values	Month 10	Month 11	Month 12	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: IU/L				
arithmetic mean (standard deviation)	301 (± 61.99)	273.3 (± 117.93)	284.3 (± 137.47)	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and Tolerance

End point title	Safety and Tolerance

End point description:

Safety and tolerance to the product administration will be measured by the detection of adverse events or clinically relevant changes in vital signs

End point type	Secondary

End point timeframe:

During and after each product administration (up to 12 month of treatment period)

End point values	ITT set			
Subject group type	Subject analysis set			
Number of subjects analysed	15			
Units: subjects				
Well-tolerared	15			
Very slight discomfort	0			
Discomfort	0			

Early cessation of infusion	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events data was collected up to 12 month following orthotopic liver transplant

Adverse event reporting additional description:

The duration of treatment was 6 months after which subjects were offered the option to be treated for an additional 6 months (12 months total)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups

Reporting group title	Safety

Reporting group description: -

Serious adverse events	Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 15 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Liver function test abnormal	Additional description: Liver function test abnormal was also associated with hepatic artery thrombosis		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia	Additional description: Pyrexia event was also associated with possible cholangitis		
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Liver transplant rejection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Biliary fistula			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Immune system disorders			
Transplant rejection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Blood bilirubin increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood glucose increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac murmur			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatic enzyme increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Kell blood group positive			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pharyngeal culture positive			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Aphonia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypokinesia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neuropathy peripheral			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Hemorrhagic anemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pancytopenia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Aphthous stomatitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Localized intraabdominal fluid collection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pancreatitis acute			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Biliary fistula			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hepatic function abnormal			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Portal vein thrombosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal failure acute			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Renal impairment			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Biliary tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Herpes virus infection subjects affected / exposed occurrences (all) Postoperative wound infection subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 November 2011	There were no important modifications of the study protocol that could potentially alter the interpretation of the study. The modifications made to the study protocol were administrative to reflect the change of the Coordinating Investigator of the study (Pisa).
23 April 2012	Amendment No. 2 was classified as relevant as one of the Exclusion criteria #6 (i.e. Evidence of hepatocellular carcinoma in the transplanted liver, or metastatic disease, at time of inclusion in the clinical trial) was removed from the protocol. The latter criteria was originally placed to reduce bias and inter-subject variability as the presence of hepatocellular carcinoma was a well-known risk factor for postoperative HBV recurrence. However, the participating Investigators indicated that this criteria was an important barrier to subject enrollment as approximately 80% of their current liver transplantations were performed on subjects presenting with concomitant hepatocellular carcinoma. On the other hand, subjects with simple HBV-related cirrhosis were progressively being managed with new and more effective antiviral drugs which in most cases avoided the need for transplantation. This modification potentially could have had a negative effect on the primary efficacy and safety variables due to an elevated risk of HBV reinfection in these subjects. However, all participating subjects with hepatocellular carcinoma successfully completed the study and did not present a higher reinfection rate as no subjects presented HBV recurrence at the end of the study.
19 October 2012	Amendment No. 3 was also classified as relevant as modifications were made to the previous treatment regimen and follow-up period duration. Specifically, the monthly maintenance dose of 5,000 IU of Niuliva was optionally extended from 6 to 12 months and the final follow-up phone call visit was scheduled at month 13 post-OLT. Accordingly, the primary efficacy and safety variables were to be determined at both month 6 and 12 in order to provide a better insight of the Niuliva's long-term efficacy.
25 October 2013	There were no important modifications of the study protocol that could potentially alter the interpretation of the study. The modifications made to the study protocol were administrative to reflect changes in the CRO contact numbers and a change of the Principal Investigator at one investigational site (Modena).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported