Clinical trial results:
An open, prospective, single arm study investigating efficacy and safety of human hepatitis B immunoglobulin Zutectra in liver transplanted patients - the ZEUS Study

Summary

EudraCT number	2012-002516-51
Trial protocol	GB IT ES
Global end of trial date	24 September 2014

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	987

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Biotest AG
Sponsor organisation address	Landsteinerstr. 5, Dreieich, Germany, 63303
Public contact	Vice President Corporate Clinical Research & Development, Biotest AG, 49 61038010, andrea.wartenberg-demand@biotest.com
Scientific contact	Vice President Corporate Clinical Research & Development, Biotest AG, 49 61038010, andrea.wartenberg-demand@biotest.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	24 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 September 2014
Global end of trial reached?	Yes
Global end of trial date	24 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of Zutectra in orthotopic liver transplanted patients with the therapeutic goal to prevent hepatitis B virus re-infection in HBV-DNA negative patients ≥ one week after liver transplantation.

Protection of trial subjects:

To facilitate home administration including patient compliance, patients or caregivers needed to be adequately trained by the investigator/site staff and appropriate control measures were to be performed during the study, i.e. regular checks of anti-HBs levels and of the documentation in the patient diary. Patients or caregivers who complied with the injection technique and patients that presented sufficiently high (> 100 IU/L) trough serum HBs antibody concentrations at fixed dosage regimen could begin home administration after assessments in the transplantation unit during the 4 weeks following Orthotopic Liver Transplantation.

Background therapy:

Concomitant medication other than immunoglobulins could be administered as medically required. The concomitant use of adequate virostatic agents was to be
considered, if appropriate, as standard of hepatitis B re-infection prophylaxis. Virostatic agents were to be used according to the standard of care at each site.

Evidence for comparator:

Not applicable

Actual start date of recruitment	15 December 2012
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	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Italy: 41
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	46
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period (Informed consent initial date) lasted from 15DEC2012 to 01APR2014. Seventeen out of 18 initiated sites in Spain, France, United Kingdom and Italy recruited 75 patients by signing the informed consent form. Of these, 56 patients were screened and 49 patients were eligible for study treatment.

Pre-assignment

Screening details:

Included were male and female adult patients with hepatitis B infection requiring liver transplantation ≥ one week after OLT (also re-transplantation) with undetectable HBV-DNA at time point of informed consent (IC) signature and at OLT, being HBsAg negative at pre-dose, and showing serum HBs antibody concentration ≥ 400 IU/L at pre-dose.

Period 1

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

Blinding implementation details:

Not applicable

Arms

Arm title	Zutectra

Arm description:

Subcutaneous injections of human hepatitis B immunoglobulin Zutectra

Arm type	Experimental
Investigational medicinal product name	Zutectra
Investigational medicinal product code	BT088
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Subcutaneous injections of 500 IU (1mL) or 1,000 IU (2mL) Zutectra were administered weekly or fortnightly until 24 weeks after transplantation, according to the serum anti-HBs concentrations and at the discretion of the physician in charge according to local practice to maintain antibody levels above 100 - 150 IU/L.

Number of subjects in period 1	Zutectra
Started	49
Completed	47
Not completed	2
Adverse event, non-fatal	1
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	49	49	
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)	46	46	
From 65-84 years	3	3	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	41	41	
Male	8	8	

Subject analysis sets	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who received the study medication at least once

Subject analysis set title	Full-Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All patients who received at least one dose of study medication and had at least one post dose efficacy assessment

Subject analysis set title	Per-Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of the FAS who completed the whole study period until assessment of treatment failure or Closing Visit (whichever comes first) without major protocol deviations

Reporting group values	Safety Set	Full-Analysis Set	Per-Protocol Set
Number of subjects	49	49	46
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)	46	46	43
From 65-84 years	3	3	3
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	41	41	7
Male	8	8	39

End points

End points reporting groups

Reporting group title	Zutectra
Reporting group description:	
Subcutaneous injections of human hepatitis B immunoglobulin Zutectra	
Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who received the study medication at least once	
Subject analysis set title	Full-Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients who received at least one dose of study medication and had at least one post dose efficacy assessment	
Subject analysis set title	Per-Protocol Set
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients of the FAS who completed the whole study period until assessment of treatment failure or Closing Visit (whichever comes first) without major protocol deviations	

Primary: Treatment Failure

End point title	Treatment Failure
End point description:	
The definition of treatment failure (primary efficacy variable) is based on any trough level of serum anti-HBs ≤ 100 IU/L and/or diagnosed hepatitis B related re-infection in patients with trough levels of serum anti-HBs > 100 IU/L during the period between first study drug administration and end of study.	
End point type	Primary
End point timeframe:	
Period between first study drug administration and end of study.	

End point values	Zutectra	Full-Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	49	49		
Units: Patient Numbers	0	0		

Statistical analyses

Statistical analysis title	Treatment Failure
Statistical analysis description:	
A two-sided 95% confidence interval (using the Clopper-Pearson method) was calculated for the primary efficacy variable as well as for its components. The time to failure from Day 0 = Day of OLT was to be analyzed for the combined endpoint and its components using survival time methods (Kaplan-Meier).	
Comparison groups	Zutectra v Full-Analysis Set

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.169 [2]
Method	Compared to upper CL of CI
Parameter estimate	rate
Point estimate	0
Confidence interval	
level	95 %
sides	1-sided
upper limit	0.0725

Notes:

[1] - The 95% confidence interval should be below the upper confidence limit (CL) of a 5% failure rate, which would result in a upper CL of 16.9%.

[2] - No P-value was calculated; compared to upper limit of confidence interval

Secondary: Hepatitis B related Infections

End point title	Hepatitis B related Infections

End point description:

The number of all patients with hepatitis B related infection.

End point type	Secondary

End point timeframe:

Period between first study drug administration and end of study.

End point values	Full-Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	49			
Units: Patient Numbers	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During active treatment phase, from first dose until closing visit.

Adverse event reporting additional description:

Patients were asked about adverse events (AEs) that occurred during the SC Zutectra injection or since the last visit. Patients kept a diary to document any discomfort during the course of the trial which was reviewed regularly. Treatment emergent AEs are AEs not present at baseline or present at baseline, but worsening during the treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Zutectra

Reporting group description:

Subcutaneous injections of human hepatitis B immunoglobulin Zutectra

Serious adverse events	Zutectra		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 49 (28.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Biliary anastomosis complication			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar vertebral fracture			

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Status epilepticus			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Spinal pain			
subjects affected / exposed	1 / 49 (2.04%)		
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	3 / 49 (6.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia, obstructive			

subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Localised intraabdominal fluid collection				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Umbilical hernia				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	2 / 49 (4.08%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic artery stenosis				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Psychotic disorder				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Osteoporotic fracture				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Brain abscess				

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peritonitis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4.1 %

Non-serious adverse events	Zutectra		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 49 (87.76%)		
Injury, poisoning and procedural complications			
Biliary anastomosis complication			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Tremor			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Pyrexia			

subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4		
Immune system disorders Liver transplant rejection subjects affected / exposed occurrences (all)	 5 / 49 (10.20%) 5		
Gastrointestinal disorders Aphthous stomatitis subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 2 / 49 (4.08%) 2 2 / 49 (4.08%) 2 4 / 49 (8.16%) 5		
Hepatobiliary disorders Cholangitis subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 3		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	 2 / 49 (4.08%) 2		
Infections and infestations Cytomegalovirus infection subjects affected / exposed occurrences (all) Escherichia urinary tract infection subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all)	 12 / 49 (24.49%) 13 4 / 49 (8.16%) 4 2 / 49 (4.08%) 3		
Metabolism and nutrition disorders Diabetes mellitus			

subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Hypertriglyceridaemia			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		
Hyperuricaemia			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2013	Amendment No. 1 of 28 February 2013 was implemented to clarify inclusion and exclusion criteria, expand the time window for study visits, increase the number of participating countries and sites, correct minor mistakes in the study flowchart and protocol, and adapt the definition of AEs/IRAEs. Main changes were: • The study population could also include hepatocellular carcinoma patients with hepatitis B requiring liver transplantation. Such patients are not always viewed as having liver failure • The time-window for the pre-dose assessment, the start of Zutectra study treatment, and treatment days was extended to allow increased flexibility in study visit arrangements • To improve recruitment into the study, additional centers were included, including centers in Spain
03 April 2014	Amendment No. 2 of 03 April 2014 was implemented to prolong the study duration, decrease the required patient number, adapt inclusion criterion 2, update information on completed studies with Zutectra, change AE reporting requirements before start of treatment with study drug, and introduce some clarifications and administrative changes. Main changes were: • The number of evaluable patients (ITT population) required was decreased to 40 • The study duration was extended due to slow patient recruitment • The time-window for the historical HBV-DNA test required by inclusion criterion 2 was extended to reflect the common practice • To change reporting requirements for AEs before start of treatment with IMP • To change reporting requirements for study procedure related AEs • To delete chloride assessment from the safety parameters • Updated information on studies 974 and 978

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported