



## Clinical trial results:

**An open, randomised parallel study investigating efficacy and safety of the human hepatitis B immunoglobulin BT088 after subcutaneous or intramuscular application for perinatal prophylaxis in infants born to HbsAg positive women**

### Summary

EudraCT number	2006-000110-21
Trial protocol	DE
Global end of trial date	25 January 2011

### Results information

Result version number	v1 (current)
This version publication date	11 September 2021
First version publication date	11 September 2021

### Trial information

#### Trial identification

Sponsor protocol code	959
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#### 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	Landsteinerstraße 5, Dreieich, Germany, 63303
Public contact	Dr. med. Andrea Wartenberg-Demand, Biotest AG, andrea.wartenberg-demand@biotest.com
Scientific contact	Dr. med. Andrea Wartenberg-Demand, Biotest AG, 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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	21 February 2011
Is this the analysis of the primary completion data?	No

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Global end of trial reached?	Yes
Global end of trial date	25 January 2011
Was the trial ended prematurely?	No

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Notes:

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**General information about the trial**

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Main objective of the trial:

The purpose of the present study is the investigation on efficacy and safety regarding two types of administration (subcutaneous and intramuscular injection) of the new human hepatitis B immunoglobulin BT088 in neonates of HBsAg positive mothers to prevent perinatal transmission of hepatitis B.

The primary study objective is to demonstrate efficacy which will be assessed by evaluation of the serum anti-HBs concentration prior to injection of BT088 and afterwards during an interval of 72 hours after birth.

Protection of trial subjects:

non

Background therapy:

non

Evidence for comparator:

not applicable

Actual start date of recruitment	19 April 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Hungary: 4
Worldwide total number of subjects	35
EEA total number of subjects	35

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Notes:

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**Subjects enrolled per age group**

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In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	35
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

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Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment took place in Germany and Hungary only.

Number of countries: 2

Number of centers : 5

Date of first visit of the first subject: 19Apr2007

Date of last visit of the last subject: 30Apr2010

Date last surveillance visit of last subject: 25Jan2011

### Pre-assignment

Screening details:

Inclusion Criteria: Male or female neonate of gestational week  $\geq 37+0$ , Body weight  $\geq 2500$  g, Apgar score, 5 minutes value  $> 7$ , Confirmation of HBsAg positive mother, Available written informed consent of parents or legal guardian

### Pre-assignment period milestones

Number of subjects started	35
Number of subjects completed	34

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Evidence of exclusion criteria -Birth weight $<2500$ : 1
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### Period 1

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

### Arms

Arm title	Full Analysis Set
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Arm description:

BT088 (human hepatitis B immunoglobulin [HBIG] containing 500 IU/mL) as single dose, administered either by subcutaneous (SC) or intramuscular (IM) injection of 200 IU (0.4 mL) within the first 12 hours after birth.

Arm type	Experimental
Investigational medicinal product name	Human hepatitis B immunoglobulin
Investigational medicinal product code	BT088
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use, Subcutaneous use

Dosage and administration details:

Single dose intramuscular (i.m.) or subcutaneous injection of about 200 IU (0.4 mL) BT088 within the first 12 hours after birth

<b>Number of subjects in period 1<sup>[1]</sup></b>	Full Analysis Set
Started	34
Completed	31
Not completed	3
Passive vaccination was done twice by mistake	1
Lost to follow-up	2

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 35 pregnant women have been enrolled into the study before giving birth. 1 of 35 newborns met the exclusion criteria " infant is too small for gestational age (i.e., < 2500g) after birth (screening failure) and therefore just 34 newborns have been randomized and treated (baseline period).

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial (overall period)
Reporting group description:	
All subjects have been randomized and treated who met the Inclusion criteria:	
<ul style="list-style-type: none"><li>- Male or female neonate of gestational week <math>\geq 37+0</math></li><li>- Body weight <math>\geq 2500</math> g</li><li>- Apgar score, 5 minutes value <math>&gt; 7</math></li><li>- Confirmation of HBsAg positive mother</li><li>- Available written informed consent of parents or legal guardian</li></ul>	

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	34	34	
Age categorical			
Units: Subjects			
Newborns (0-27 days)	34	34	
Not recorded- no age information	0	0	
Gender categorical			
Units: Subjects			
Female	11	11	
Male	23	23	

### Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set will consist of all infants in the all subjects treated set who have a value of anti-HBs concentration at the initial visit and at least one value of anti-HBs concentration determined after the single injection of BT0BB during an interval of 72 hours post partum.	

Reporting group values	Full Analysis Set		
Number of subjects	31		
Age categorical			
Units: Subjects			
Newborns (0-27 days)	31		
Not recorded- no age information	0		
Gender categorical			
Units: Subjects			
Female	10		
Male	21		

## End points

### End points reporting groups

Reporting group title	Full Analysis Set
Reporting group description: BT088 (human hepatitis B immunoglobulin [HBIG] containing 500 IU/mL) as single dose, administered either by subcutaneous (SC) or intramuscular (IM) injection of 200 IU (0.4 mL) within the first 12 hours after birth.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set will consist of all infants in the all subjects treated set who have a value of anti-HBs concentration at the initial visit and at least one value of anti-HBs concentration determined after the single injection of BT0BB during an interval of 72 hours post partum.	

### Primary: anti-HBs concentration responder rate

End point title	anti-HBs concentration responder rate
End point description: The responder rate is the proportion of infants with an initial pre-dose anti-HBs concentration of < 10 IU/L and with at least one anti-HBs concentration $\geq$ 100 IU/L determined after BT088 injection during an interval of 72 hours post partum.	
End point type	Primary
End point timeframe: Time interval of 72 hours post partum	

End point values	Full Analysis Set	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	31	31		
Units: percent				
number (confidence interval 95%)	96.77 (83.30 to 99.92)	96.77 (83.30 to 99.92)		

### Statistical analyses

Statistical analysis title	2-sided 95% confidence interval
Comparison groups	Full Analysis Set v Full Analysis Set
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
Parameter estimate	responder rate
Point estimate	0.9677
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.833
upper limit	0.9992

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Notes:

[1] - Efficacy was assessed by exploratory analysis regarding the 'full analysis set' of treated infants in terms of the primary efficacy variable by calculating a 2-sided 95% confidence interval (CI; Clopper-Pearson) for the overall response rate.



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE reporting has to be continued until 4 weeks after the last administration of the study drug(s). In case Biotest receives information about the death of an infant within 4 weeks after study termination, this must be reported as an SAE.

Adverse event reporting additional description:

In case Biotest receives information about the death of an infant within four weeks after study termination, this must be reported as an SAE (see section 15.4.8) and documented in the CRF including possible autopsy results.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	12

### Reporting groups

Reporting group title	subcutaneous injection
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Reporting group description:

subcutaneous injection

Reporting group title	intramuscular injection
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Reporting group description:

intramuscular injection

Reporting group title	Overall period
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Reporting group description: -

Serious adverse events	subcutaneous injection	intramuscular injection	Overall period
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 17 (0.00%)	3 / 17 (17.65%)	3 / 34 (8.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal skin infection			

subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	subcutaneous injection	intramuscular injection	Overall period
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 17 (35.29%)	5 / 17 (29.41%)	11 / 34 (32.35%)
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 17 (5.88%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Glutamate dehydrogenase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Pregnancy, puerperium and perinatal conditions			
Jaundice neonatal			
subjects affected / exposed	2 / 17 (11.76%)	1 / 17 (5.88%)	3 / 34 (8.82%)
occurrences (all)	2	1	3
Cephalhaematoma			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 17 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Hepatobiliary disorders			
Hyperbilirubinaemia neonatal			
subjects affected / exposed	1 / 17 (5.88%)	2 / 17 (11.76%)	3 / 34 (8.82%)
occurrences (all)	1	2	3
Infections and infestations			
Staphylococcal skin infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 17 (5.88%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Metabolism and nutrition disorders			

Hyperglycaemia neonatal subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1	0 / 17 (0.00%) 0	1 / 34 (2.94%) 1
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2007	<p>This protocol amendment is designed for the introduction of a new batch of BT088 in the trial due to the expiry of the current study medication. In the production process of the respective batch an additional filtration step through a 20 nm virus filter was implemented.</p> <p>All plasma derived products manufactured by Biotest are virus safe as demonstrated by virus validation studies and clinical experience. As a result of demonstrated viral safety according to the Note for Guidance "Virus Validation Studies (Revised) (CPMP/BWP/268/95) Biotest products (e.g. Intratect, Hepatect CP) are licensed by regulatory authorities world wide.</p> <p>The requirements on virus removal/inactivation are different in EU countries. Some regulatory authorities thus require an additional step for virus inactivation or virus removal especially for non enveloped viruses.</p> <p>For the European harmonisation of viral safety requirements Biotest will establish an additional step of virus removal by 20 nm virus filtration. This step further improves the margin of safety of our products.</p> <p>The modified manufacturing scheme and the pharmaceutical properties of BT088 are displayed in section 4 of the Amendment No. 1 to the Investigator's Brochure. SA dated 20April2007 has been integrated in the protocol version 3.0 dated 02 January 2007.</p>
19 December 2007	<p>This protocol amendment is designed for subsequent extension of the expiry date of the current batch.</p> <p>Extension of expiry date of the current batch (A098027)</p> <p>Stability tests for BT088 were performed and the stability indicating parameters which were assessed admit an extension of the expiry date until August 2008. The study medication will be labelled according to § 5 (in particular paragraph 7) GCP-Ordinance (GCP-Verordnung).</p> <p>An (additional) label will be affixed on the blister and to the outer packaging presenting the new expiry date and the batch identification number, respectively.</p> <p>Formal adaptations to the study protocol are not applicable for extension of the expiry date as an (additional) label will be provided according to the GCP-Ordinance presenting the following data: Batch number: A098027A; Expiry date: 31.08.2008</p> <p>SA dated 19Dec2007 has been integrated in the protocol version 3.0 dated 02 January 2007.</p>
05 March 2008	<p>Replacement of the current study medication which expires in August 2008 (Batch number: A098027A).</p> <p>This protocol amendment is designed for the introduction of a second nanofiltered batch of BT 088 (Batch number: A098047 - Expiry date: 31.05.2009) as replacement of the current study medication which expires in August 2008 (Batch number: A098027A).</p> <p>The study medication will be labelled according to § 5 (in particular §7) GCP-Ordinance (GCP-Verordnung).</p> <p>The alterations referring to the Substantial Amendment No 2, dated 19th December 2007, page 5 of 5, "Formal Aspects of the Amendment_Batch No.: A098027A; Expiry date: 31.08.2008".</p> <p>SA dated 05Mar2008 has been integrated in the protocol version 3.0 dated 02 January 2007.</p>

25 June 2008	<p>This protocol amendment is designed for the introduction of a subsequent version 3 of Investigational Medicinal Product Dossier (IMPD) and the respective Investigator's Brochure (IB) Version 3.</p> <p>The scope of changes comprises an update of the stability data of the drug substance and drug product and a change of material of syringe tip cap (rubber composition).</p> <p>Furthermore, planned study dates in the study protocol and in the patient informed consent had to be actualised due to slow recruitment rates.</p> <p>This amendment refers to the batch number A=) (= \$/ with expiry date 31.05.2009 (Substantial Amendment, dated 5th March 2008).</p>
27 November 2008	<p>Only for Hungary : This protocol amendment is designed for the introduction of a central laboratory in Hungary for the determination of serology parameters in Hungarian subjects - determinations for hep. serology (HU subjects) will be performed at InterLab GmbH (central lab.).</p> <p>Furthermore, administrative changes are implemented - contact details of Biotest Drug Safety Department were changed.</p> <p>The trial conduct is not affected by the updated IMPD and IB.</p> <p>SA dated 27Nov2008 has been integrated in the protocol version 3.0 dated 02 January 2007.</p>
26 February 2009	<p>Only for Germany - Inclusion of additional investigative sites in Germany</p> <p>SA dated 26Feb2009 has been integrated in the protocol version 3.0 dated 02 January 2007.</p>
24 April 2009	<p>Shelf life extension of BT088 until 30.11.2009.</p> <p>Change of trial coordinating investigator.</p> <p>SA dated 24April2009 has been integrated in the protocol version 3.0 dated 02 January 2007.</p>
17 September 2009	<p>Shelf live extension to 31.10.2010.</p> <p>SA dated 17 September 2009 has been integrated in the protocol version 4.0 dated 21 April 2009.</p>
17 March 2010	<p>The present study protocol amendment is prepared to implement a new statistical approach in terms of the study-specific patient sample size and the previously planned confirmatory analysis. Furthermore, a change of the planned dates concerning termination is necessary. In December 2008, the reasons for the change in sample size and statistical approach were presented to the German competent authority Paul-Ehrlich-Institut (PEI). Recruitment in Germany was hampered by the following difficulties: Many mothers have foreign nationalities and fathers tend to withdraw already given informed consent. Mothers do not want to stay in the hospital for three days. The collaboration between gynaecologists and paediatricians in the study centres has not always been satisfactory. There are not many children eligible for the study due to a particular patient population. Considering the recruitment rate in December 2008 and the required number of patients, even with the inclusion of Hungarian centres, the study would have required at least another two years of recruitment. Hence, it could not be granted if the study would be finalised at all under these conditions. Due to a prolonged regulatory procedure, approval in Hungary was finally received on 17.02.2009, and enrolment started not until 16.09.2009. Biotest proposed to finalise the clinical trial with a smaller sample size (n=25) to achieve a national marketing authorisation in Germany, and suggested a non-confirmatory statistical analysis. The studies used as supportive data have also been analysed with non-confirmatory statistical analyses so far. The PEI emphasized that a patient number of 25 is not optimal, but would be acceptable if data of the other clinical studies on BT088, especially study 956 and 952, will be considered. The PEI agreed that study 959 will be continued until 25 patients have been enrolled, then the study is allowed to be stopped and analysed. SA dated 17Mar2010 integrated into protocol V.4.0, 21.04.2009.</p>

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.

N.A.

Notes:

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22752776>