Clinical trial results:
An open-label, prospective, multicenter study investigating clinical efficacy, safety, and pharmacokinetic properties of the human normal immunoglobulin for intravenous administration BT595 as replacement therapy in patients with primary immunodeficiency disease (PID)

Summary

EudraCT number	2015-003652-52
Trial protocol	DE ES GB
Global end of trial date	01 April 2020

Results information

Result version number	v1 (current)
This version publication date	27 August 2021
First version publication date	27 August 2021

Trial information

Trial identification

Sponsor protocol code	991

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02810444
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biotest AG
Sponsor organisation address	Landsteinerstr. 5, Dreieich, Germany, 63303
Public contact	Dr med Andrea Wartenberg-Demand, Biotest AG, +49 61038010, andrea.wartenberg-demand@biotest.com
Scientific contact	Dr med Andrea Wartenberg-Demand, Biotest AG, +49 61038010, andrea.wartenberg-demand@biotest.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002092-PIP01-16
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	07 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2020
Global end of trial reached?	Yes
Global end of trial date	01 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate that the rate of acute serious bacterial infections (i.e., the mean number of acute serious bacterial infections per subject year) is less than 1.0 to provide substantial evidence of efficacy.

Protection of trial subjects:

To monitor the safety data from adult subjects and provide advice and recommendations on the enrollment of pediatric subjects, a DSMB consisting of independent experts has been implemented.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	Russian Federation: 11
Worldwide total number of subjects	67
EEA total number of subjects	35

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)	12
Adolescents (12-17 years)	6
Adults (18-64 years)	44

From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first enrolment: 04-Oct-2016; First IMP administration: 03-Nov-2016; Date of last completed: 01-Apr-2020

Pre-assignment

Screening details:

Male or female, aged 2 through 75 years.
Diagnosis of PID with impaired antibody production.
Established replacement therapy with any intravenous immunoglobulin (IVIg) reference preparation during the previous 6 months.
Established replacement therapy with a single IVIg reference preparation for at least 3 months prior to treatment start.

Period 1

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

Arms

Arm title	Full analysis set (FAS)

Arm description:

3- or 4-week schedule for a treatment period of approximately 12 months according to the subject's prestudy IVIg treatment.

Arm type	Experimental
Investigational medicinal product name	IgG Next Generation
Investigational medicinal product code	BT595
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

BT595 will be administered at 3- or 4-week intervals for a treatment period of approximately 12 months. The initial dose and dosage intervals must be consistent with the subject's prestudy IVIg treatment and the initial dose and dosage interval will only be changed if medically indicated.
The planned dose of BT595 is 0.2 to 0.8 g/kg body weight (bw) (2 to 8 mL/kg bw) administered as intravenous infusions at 3- or 4-week intervals for a treatment period of approximately 12 months.

Number of subjects in period 1	Full analysis set (FAS)
Started	67
Completed	60
Not completed	7
Consent withdrawn by subject	4
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups

Reporting group title	Full analysis set (FAS)

Reporting group description:

3- or 4-week schedule for a treatment period of approximately 12 months according to the subject's prestudy IVIg treatment.

Reporting group values	Full analysis set (FAS)	Total	
Number of subjects	67	67	
Age categorical Units: Subjects			
Adolescents (12-17 years)	6	6	
Adults (18-75 years)	49	49	
Children (6-11 years)	9	9	
Young Children (2-5 years)	3	3	
Gender categorical Units: Subjects			
Female	30	30	
Male	37	37	

Subject analysis sets

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects following the principle of intention to treat. The FAS comprised all subjects who received ≥1 dose of study medication. Subjects were analyzed according to the treatment planned. The FAS was used for all analyses of efficacy endpoints. For this nonrandomized study, FAS and SAF were identical and included all subjects who received ≥1 dose of BT595.

Reporting group values	Full analysis set (FAS)		
Number of subjects	67		
Age categorical Units: Subjects			
Adolescents (12-17 years)	6		
Adults (18-75 years)	49		
Children (6-11 years)	9		
Young Children (2-5 years)	3		
Gender categorical Units: Subjects			
Female	30		
Male	37		

End points

End points reporting groups

Reporting group title	Full analysis set (FAS)

Reporting group description:

3- or 4-week schedule for a treatment period of approximately 12 months according to the subject's prestudy IVIg treatment.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects following the principle of intention to treat. The FAS comprised all subjects who received ≥1 dose of study medication. Subjects were analyzed according to the treatment planned. The FAS was used for all analyses of efficacy endpoints. For this nonrandomized study, FAS and SAF were identical and included all subjects who received ≥1 dose of BT595.

Primary: Number of acute serious bacterial infections (SBI)

End point title	Number of acute serious bacterial infections (SBI)

End point description:

The primary endpoint of this study was the SBI rate, defined as the mean number of acute serious bacterial infections (SBIs) per subject-year, according to EMA and FDA guidance for IVIg studies.
Acute serious bacterial infections included the following (based on specific diagnostic criteria as per FDA guidance (FDA, 2008):

- Bacteremia or sepsis.
- Bacterial meningitis.
- Osteomyelitis/septic arthritis.
- Bacterial pneumonia.
- Visceral abscess.

End point type	Primary

End point timeframe:

Start of treatment until close out.

End point values	Full analysis set (FAS)	Full analysis set (FAS)		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	67	67		
Units: Number of SBI	1	1		

Statistical analyses

Statistical analysis title	Rate of SBI

Statistical analysis description:

According to EMA and FDA guidelines for IVIG studies: The null hypothesis (SBI rate ≥1.0 per subject-year at the 1% level of significance using a computed
one-sample Poisson model) was tested. Therefore, the full analysis set was compared only to a fixed rate.

Comparison groups	Full analysis set (FAS) v Full analysis set (FAS)

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.01 [2]
Method	one-sample Poisson CI
Parameter estimate	annual rate (SBI)
Point estimate	0.015
Confidence interval	
level	Other: 99 %
sides	1-sided
upper limit	0.151

Notes:

[1] - According to EMA and FDA guidelines for IVIG studies: The null hypothesis (SBI rate ≥1.0 per subject-year at the 1% level of significance using a computed
one-sample Poisson model) was tested

[2] - Rate of SBI was tested according to Guidelines against 1.0. Only upper Confidence Limit was calculated.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Only Treatment-emergent AEs (TEAEs) are displayed. TEAEs were recorded from start of Treatment until Follow-up visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Full analysis set (FAS)

Reporting group description:

All subjects following the principle of intention to treat. The FAS comprised all subjects who received ≥1 dose of study medication. Subjects were analyzed according to the treatment planned. The FAS was used for all analyses of efficacy endpoints. For this nonrandomized study, FAS and SAF were identical and included all subjects who received ≥1 dose of BT595.

Serious adverse events	Full analysis set (FAS)		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 67 (13.43%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Meniscus injury			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thermal burn			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			

subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis toxic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Systemic scleroderma			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic sinusitis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal viral infection			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Full analysis set (FAS)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 67 (89.55%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	4		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	10		
Pyrexia			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	4		
Chills			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	3		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain subjects affected / exposed occurrences (all)	6 / 67 (8.96%) 9		
Rhinorrhoea subjects affected / exposed occurrences (all)	5 / 67 (7.46%) 5		
Cough subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 5		
Epistaxis subjects affected / exposed occurrences (all)	3 / 67 (4.48%) 28		
Asthma subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		
Nasal congestion subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 3		
Nasal polyps subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		
Sinus congestion subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		
Psychiatric disorders Mood swings subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		
Investigations Blood pressure increased subjects affected / exposed occurrences (all)	3 / 67 (4.48%) 3		
C-reactive protein increased subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 3		
Injury, poisoning and procedural complications			

Extra dose administered subjects affected / exposed occurrences (all) Ligament sprain subjects affected / exposed occurrences (all)	4 / 67 (5.97%) 4 2 / 67 (2.99%) 2		
Congenital, familial and genetic disorders Phimosis subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		
Nervous system disorders headache subjects affected / exposed occurrences (all)	17 / 67 (25.37%) 41		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 3		
Eye disorders Noninfective conjunctivitis subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 3		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain	7 / 67 (10.45%) 8 4 / 67 (5.97%) 6 4 / 67 (5.97%) 4		

subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	4		
Dental caries			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Gastrointestinal inflammation			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	5		
Back pain			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 67 (23.88%)		
occurrences (all)	24		
Upper respiratory tract infection			

subjects affected / exposed	13 / 67 (19.40%)			
occurrences (all)	24			
Bronchitis				
subjects affected / exposed	8 / 67 (11.94%)			
occurrences (all)	12			
Sinusitis				
subjects affected / exposed	8 / 67 (11.94%)			
occurrences (all)	11			
Pharyngitis				
subjects affected / exposed	7 / 67 (10.45%)			
occurrences (all)	8			
Viral upper respiratory tract infection				
subjects affected / exposed	7 / 67 (10.45%)			
occurrences (all)	7			
Influenza				
subjects affected / exposed	6 / 67 (8.96%)			
occurrences (all)	6			
Urinary tract infection				
subjects affected / exposed	6 / 67 (8.96%)			
occurrences (all)	8			
Conjunctivitis				
subjects affected / exposed	4 / 67 (5.97%)			
occurrences (all)	6			
Oral herpes				
subjects affected / exposed	3 / 67 (4.48%)			
occurrences (all)	9			
Acute sinusitis				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences (all)	2			
Ear infection				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences (all)	3			
Gastroenteritis viral				
subjects affected / exposed	2 / 67 (2.99%)			
occurrences (all)	3			
Respiratory tract infection viral				

subjects affected / exposed occurrences (all) Skin infection subjects affected / exposed occurrences (all) Viral infection subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 4 2 / 67 (2.99%) 3 2 / 67 (2.99%) 2		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2016	The requirement for additional blood sampling for Coombs test and serum haptoglobin for the first 10 (adult) subjects who received ≥2 BT595 infusions was added (due to DSMB request)
02 June 2017	The option of homecare service for the PK sampling in pediatric subjects was added. An additional specification regarding vital sign assessment was added: In any case where a change in infusion rate occurred sooner than within a 15 minute interval, vital signs had to be measured prior to the change (to avoid further protocol deviations). A clarification that every infusion had to start at an initial rate of 0.3 mL/kg/h was added (to avoid further protocol deviations).
21 March 2018	The IND Number was corrected from 128413 to 17046. Note: Former IND number was mistakenly assigned by the Center for Drug Evaluation and Research (CDER) and not by the Center for Biologics Evaluation and Research (CBER). The number of planned subjects was increased from approximately 60 to approximately 70 subjects, to ensure a sufficient number of pediatric subjects was enrolled and to meet the FDA and EMA requirements for the clinical studies of immunoglobulins for intravenous administration. The date for the expected last subject last visit was moved from FEB 2018 to NOV 2019 due to shifted timelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported