Clinical trial results:
A randomized, placebo controlled, double-blind, multi-center, phase II trial investigating the efficacy and safety of trimodulin (BT588) as add-on therapy to standard of care in adult subjects with severe COVID-19

Summary

EudraCT number	2020-002345-42
Trial protocol	ES FR
Global end of trial date	29 June 2021

Results information

Result version number	v1 (current)
This version publication date	29 June 2023
First version publication date	29 June 2023

Trial information

Trial identification

Sponsor protocol code	998

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04576728
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)	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	25 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 June 2021
Global end of trial reached?	Yes
Global end of trial date	29 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of trimodulin as add-on therapy to standard of care (SoC) compared with placebo treatment in adult hospitalized subjects with severe Coronavirus Disease 2019 (COVID-19). Additionally, pharmacodynamic (PD) and pharmacokinetic (PK) properties of trimodulin were evaluated in all subjects.

Protection of trial subjects:

To mitigate previously identified and potential (class) risks certain exclusion criteria were implemented. Furthermore these risks were monitored through (1) defined adverse events of special interest (AESI), (2) general AE reporting and (3) through regular assessment of local clinical laboratory parameters.

A Data Safety Monitoring Board (DSMB) was convened to review cumulative safety and efficacy data, and to monitor demographics and balance between treatment groups.

Background therapy:

Standard of care

Evidence for comparator:

Placebo

Actual start date of recruitment	06 October 2020
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	Russian Federation: 86
Country: Number of subjects enrolled	Brazil: 40
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	France: 32
Worldwide total number of subjects	166
EEA total number of subjects	40

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)	111
From 65 to 84 years	55
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first subject's first visit (date of first enrollment) was on 06-OCT-2020 and the last subject's last visit (date of last completed) was on 29-JUN-2021

Pre-assignment

Screening details:

Laboratory-confirmed SARS-CoV-2 infection, diagnosis of community-acquired severe COVID-19 within 10 days after hospital-admission, age ≥18 years, subject must receive SoC treatment for COVID-19.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The matching placebo had similar appearance to trimodulin which enabled maintaining the treatment blinding. To ensure blinding, vials were covered with transparent colored foils in accordance with studyspecific guidance for coating of vials with green foil.

Arms

Are arms mutually exclusive?	Yes
Arm title	Trimodulin

Arm description:

Trimodulin (BT588; normal polyvalent immunoglobulin M [IgM], immunoglobulin A [IgA] and immunoglobulin G [IgG] from human plasma) was administered via intravenous infusion (IV) at a dose volume of 3.65 mL/kg body weight (BW)/day (corresponding to a dose of 182.6 mg trimodulin/kg BW/day). The approximate concentration of IgM in trimodulin was 18-28%, IgA was 15-27% and IgG was 48-66%.

Arm type	Experimental
Investigational medicinal product name	Trimodulin
Investigational medicinal product code	BT588
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trimodulin volume administered was 3.65 mL/kg body weight (BW)/day, corresponding to 182.6 mg trimodulin/kg BW/day. Each subject received the trimodulin once daily on 5 consecutive days (day 1 through day 5). On day 1 of infusion, the initial infusion rate was set to 0.1 mL/min. The rate was to be raised in steps of 0.1 mL every 10 minutes until the target infusion rate of a maximum 0.5 mL/min was reached, if it was well tolerated by the subject. For subsequent infusions (day 2 through day 5) the infusion was started with the maximum tolerated infusion rate determined on day 1 for that subject, usually the target rate of 0.5 mL/min (30 mL/hour).

Arm title	Placebo

Arm description:

Subjects were treated with placebo containing 1% human albumin solution. The dose to be administered was 3.65 mL/kg body weight (BW)/day, corresponding to a dose of 36.5 mg albumin/kg BW/day, administered as intravenous infusion on 5 consecutive days.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The placebo volume administered was 3.65 mL/kg body weight (BW)/day. Each subject received placebo once daily on 5 consecutive days (day 1 through day 5). On day 1 of infusion, the initial infusion rate was set to 0.1 mL/min. The rate was to be raised in steps of 0.1 mL every 10 minutes until the target infusion rate of a maximum 0.5 mL/min was reached, if it was well tolerated by the subject. For subsequent infusions (day 2 through day 5) the infusion was started with the maximum tolerated infusion rate determined on day 1 for that subject, usually the target rate of 0.5 mL/min (30 mL/hour).

Number of subjects in period 1	Trimodulin	Placebo
Started	84	82
Completed	64	63
Not completed	20	19
Adverse event, serious fatal	18	15
Consent withdrawn by subject	1	1
Adverse event, non-fatal	1	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups

Reporting group title	Trimodulin

Reporting group description:

Trimodulin (BT588; normal polyvalent immunoglobulin M [IgM], immunoglobulin A [IgA] and immunoglobulin G [IgG] from human plasma) was administered via intravenous infusion (IV) at a dose volume of 3.65 mL/kg body weight (BW)/day (corresponding to a dose of 182.6 mg trimodulin/kg BW/day). The approximate concentration of IgM in trimodulin was 18-28%, IgA was 15-27% and IgG was 48-66%.

Reporting group title	Placebo

Reporting group description:

Subjects were treated with placebo containing 1% human albumin solution. The dose to be administered was 3.65 mL/kg body weight (BW)/day, corresponding to a dose of 36.5 mg albumin/kg BW/day, administered as intravenous infusion on 5 consecutive days.

Reporting group values	Trimodulin	Placebo	Total
Number of subjects	84	82	166
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)	55	56	111
From 65-84 years	29	26	55
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	34	32	66
Male	50	50	100

Subject analysis sets

Subject analysis set title	Deterioration/mortality rate:
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) included all subjects of the safety analysis set (SAF), who had at least one post-dose assessment. Subjects were analyzed as randomized. Assessment of primary efficacy was based on a composite of two parameters assessed by the 9-category ordinal scale: the clinical deterioration rate (score of 6 or 7, assessed between day 6 and day 29) plus the 28-day all-cause mortality rate (score of 8, assessed between day 1 and day 29).

Reporting group values	Deterioration/mortality rate:		
Number of subjects	166		

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)	111		
From 65-84 years	55		
85 years and over	0		
Gender categorical Units: Subjects			
Female	66		
Male	100		

End points

End points reporting groups

Reporting group title	Trimodulin

Reporting group description:

Trimodulin (BT588; normal polyvalent immunoglobulin M [IgM], immunoglobulin A [IgA] and immunoglobulin G [IgG] from human plasma) was administered via intravenous infusion (IV) at a dose volume of 3.65 mL/kg body weight (BW)/day (corresponding to a dose of 182.6 mg trimodulin/kg BW/day). The approximate concentration of IgM in trimodulin was 18-28%, IgA was 15-27% and IgG was 48-66%.

Reporting group title	Placebo

Reporting group description:

Subjects were treated with placebo containing 1% human albumin solution. The dose to be administered was 3.65 mL/kg body weight (BW)/day, corresponding to a dose of 36.5 mg albumin/kg BW/day, administered as intravenous infusion on 5 consecutive days.

Subject analysis set title	Deterioration/mortality rate:
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set (FAS) included all subjects of the safety analysis set (SAF), who had at least one post-dose assessment. Subjects were analyzed as randomized. Assessment of primary efficacy was based on a composite of two parameters assessed by the 9-category ordinal scale: the clinical deterioration rate (score of 6 or 7, assessed between day 6 and day 29) plus the 28-day all-cause mortality rate (score of 8, assessed between day 1 and day 29).

Primary: Composite: Clinical Deterioation/Mortality

End point title	Composite: Clinical Deterioation/Mortality

End point description:

Composite endpoint of clinical deterioration rate plus 28-day all-cause mortality rate

End point type	Primary

End point timeframe:

Clinical deterioration rate (score=6 to 7) between day 6 and day 29
28-day all-cause mortality rate (score=8) between day 1 and day 29

End point values	Trimodulin	Placebo	Deterioration/ mortality rate:	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	84	82	166	
Units: Number/Percentage of Subjects				
Number of Subjects Analysed	28	28	56	
Percentage of Subjects Analysed	33	34	33	

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Trimodulin v Placebo

Number of subjects included in analysis	166
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.912
Method	Chi-squared
Parameter estimate	Difference in Proportion
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.56
upper limit	15.74

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From time of informed consent until the end-of-follow-up visit on day 29 [+3].	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24

Reporting groups	
Reporting group title	Safety Analysis Set (SAF)
Reporting group description:	
All subjects, who have been randomized and received at least one dose of IMP. Subjects were analyzed according to the treatment received.	

Serious adverse events	Safety Analysis Set (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	64 / 166 (38.55%)		
number of deaths (all causes)	33		
number of deaths resulting from adverse events	33		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	8 / 166 (4.82%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 6		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			

subjects affected / exposed	15 / 166 (9.04%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 7			
Acute respiratory failure				
subjects affected / exposed	4 / 166 (2.41%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Aspiration				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Organising pneumonia				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	2 / 166 (1.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	7 / 166 (4.22%)			
occurrences causally related to treatment / all	1 / 7			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				

subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	19 / 166 (11.45%)			
occurrences causally related to treatment / all	0 / 21			
deaths causally related to treatment / all	0 / 4			
Investigations				
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glomerular filtration rate decreased				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphocyte count decreased				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Platelet count decreased				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Transfusion-related acute lung injury				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Weaning failure				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	3 / 166 (1.81%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Cardiac failure			
subjects affected / exposed	2 / 166 (1.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	6 / 166 (3.61%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 6		
Cardiovascular insufficiency			
subjects affected / exposed	6 / 166 (3.61%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 6		
Myocardial infarction			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular failure			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			

Quadriparesis			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 166 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haemolytic anaemia			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal ischaemia			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	2 / 166 (1.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	9 / 166 (5.42%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	2 / 166 (1.20%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Acinetobacter sepsis				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterobacter pneumonia				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterobacter sepsis				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterococcal infection				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Klebsiella infection				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				

subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 166 (1.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia acinetobacter				
subjects affected / exposed	2 / 166 (1.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia staphylococcal				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia klebsiella				
subjects affected / exposed	2 / 166 (1.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pseudomonal bacteraemia				
subjects affected / exposed	1 / 166 (0.60%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	3 / 166 (1.81%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	4 / 166 (2.41%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		
Staphylococcal sepsis			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection enterococcal			
subjects affected / exposed	1 / 166 (0.60%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	1 / 166 (0.60%)		
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 Analysis Set (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	134 / 166 (80.72%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	16 / 166 (9.64%)		
occurrences (all)	16		
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 166 (7.83%)		
occurrences (all)	15		
Electrocardiogram QT prolonged			
subjects affected / exposed	37 / 166 (22.29%)		
occurrences (all)	38		
Fibrin D dimer increased			

subjects affected / exposed occurrences (all)	22 / 166 (13.25%) 22		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	17 / 166 (10.24%) 19		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	9 / 166 (5.42%) 9		
Blood and lymphatic system disorders Lymphopenia subjects affected / exposed occurrences (all)	25 / 166 (15.06%) 27		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	10 / 166 (6.02%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2020	The original protocol (Version 1.0) dated 06-JUL-2020 was amended once. An amended protocol (Version 2.0, dated 10-NOV-2020) was instituted after the first subject was enrolled.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported