Clinical trial results:
A prospective controlled proof-of-concept trial to demonstrate anti-viral effects of oral bromelaine in COVID-19 positive patients

Summary

EudraCT number	2020-005523-37
Trial protocol	DE
Global end of trial date	14 February 2022

Results information

Result version number	v1 (current)
This version publication date	09 February 2023
First version publication date	09 February 2023

Trial information

Trial identification

Sponsor protocol code	BromCO

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ursapharm Arzneimittel GmbH
Sponsor organisation address	Industriestr. 35, Saarbrücken, Germany, 66129
Public contact	Medical Scientific Department , Ursapharm Arzneimittel GmbH, +49 68059292105, peter.meiser@ursapharm.de
Scientific contact	Medical Scientific Department , Ursapharm Arzneimittel GmbH, +49 68059292105, peter.meiser@ursapharm.de

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	03 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 February 2022
Global end of trial reached?	Yes
Global end of trial date	14 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to assess the clinical impact of the treatment with bromelaine tablets with regard to COVID-19 symptoms via a patient diary.

Protection of trial subjects:

Due to the COVID-19 pandemic, participating patients had to undergo quarantine. Therefore, patients were visited by a member of the study team at their homes on visits V1 (Day 1), V2 (Day 4 ±1 day), V3 (Day 7 ±1 day), V4 (Day 11 ±2 days) and V5 (D16 ±1 day). Patients were called on Day 60±4 days (V6) for a safety follow up.

Background therapy:

no background therapy given

Evidence for comparator:

n.a.

Actual start date of recruitment	15 May 2021
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	Germany: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	77
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

COVID-19 postively tested subjects interested in study participation were asked to contact the study hotline for receiving information regarding the trial and for pre-screening of eligibility. If a subject agreed to participate, he/she was visited at home by a study investigator for the baseline visit (V1).

Pre-assignment

Screening details:

main inclusion/non-inclusion criteria:
- aged 18-60 years
- PCR documented SARS-CoV-2 infection and at least on typical symptom present
- no enrolment permitted if COVID-19 testing performed >48 hours ago
- no enrolment permitted if presence of coagulation disorders or being on risk for serious course of the disease

Pre-assignment period milestones

Number of subjects started	77
Number of subjects completed	77

Period 1

Period 1 title	overall period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Placebo and verum tablets were indistinguishable regarding their appearance. The list with the assignment of treatment number was kept at the production facility until the end of the trial. No person involved in the conduct or evaluation of the study did know the treatment assignment of the individual patients.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bromelaine tablets hysan (1-0-1)

Arm description:

Bromelaine low dose group

Arm type	Experimental
Investigational medicinal product name	Bromelaine tablets hysan (1-0-1)
Investigational medicinal product code	Bromelaine low dose
Other name	
Pharmaceutical forms	Gastro-resistant tablet
Routes of administration	Oral use

Dosage and administration details:

Application: two tablets per day (1-0-1: one tablet in the morning and the evening), to be swallowed with sufficient amount of liquid approximately ½ hour before meals.

Arm title	Bromelaine tablets hysan (2-1-1)

Arm description:

Bromelaine high dose

Arm type	Experimental

Investigational medicinal product name	Bromelaine tablets hysan (2-1-1)
Investigational medicinal product code	Bromelaine high dose
Other name	
Pharmaceutical forms	Gastro-resistant tablet
Routes of administration	Oral use

Dosage and administration details:

Application: four tablets per day (2-1-1: two tablets in the morning, one tablet at midday, and one tablet in the evening), to be swallowed with sufficient amount of liquid approximately ½ hour before meals.

Arm title	Placebo (1-0-1)

Arm description:

Placebo low dose

Arm type	Placebo
Investigational medicinal product name	Placebo tablets (1-0-1)
Investigational medicinal product code	Placebo low dose
Other name	
Pharmaceutical forms	Gastro-resistant tablet
Routes of administration	Oral use

Dosage and administration details:

Application: two tablets per day (1-0-1: one tablet in the morning and the evening), to be swallowed with sufficient amount of liquid approximately ½ hour before meals.

Arm title	Placebo (2-1-1)

Arm description:

Placebo high dose

Arm type	Placebo
Investigational medicinal product name	Placebo tablets (2-1-1)
Investigational medicinal product code	Placebo high dose
Other name	
Pharmaceutical forms	Gastro-resistant tablet
Routes of administration	Oral use

Dosage and administration details:

Application: four tablets per day (2-1-1: two tablets in the morning, one tablet at midday and one tablet in the evening), to be swallowed with sufficient amount of liquid approximately ½ hour before meals.

Number of subjects in period 1	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)
Started	27	26	12
Completed	27	26	12

Number of subjects in period 1	Placebo (2-1-1)
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	Bromelaine tablets hysan (1-0-1)
Reporting group description: Bromelaine low dose group	
Reporting group title	Bromelaine tablets hysan (2-1-1)
Reporting group description: Bromelaine high dose	
Reporting group title	Placebo (1-0-1)
Reporting group description: Placebo low dose	
Reporting group title	Placebo (2-1-1)
Reporting group description: Placebo high dose	

Reporting group values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)
Number of subjects	27	26	12
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)	27	26	12
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.74	33.92	33.42
standard deviation	± 9.925	± 12.309	± 12.161
Gender categorical Units: Subjects			
Female	11	13	8
Male	16	13	4

Reporting group values	Placebo (2-1-1)	Total	
Number of subjects	12	77	
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)	12	77	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	33.67		
standard deviation	± 10.360	-	
Gender categorical			
Units: Subjects			
Female	5	37	
Male	7	40	

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population refers to all randomized patients who have been exposed to the investigational medicinal product at least once

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

Subject analysis set description:

The ITT population refers to all randomized patients who meet key eligibility and evaluability criteria and have diary data of at least day 1.

Subject analysis set title	PP population
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population refers to all evaluable patients who comply with the protocol in all points relevant to the analysis and deliver a complete data set of measurements for the evaluation of the primary efficacy variable.

Subject analysis set title	futility population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

A planned interim analysis for futility was performed based on patient diary data, blood tests and adverse event reporting data of 41 enrolled and randomized patients

Reporting group values	Safety population	ITT population	PP population
Number of subjects	77	75	72
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)	77	75	72
From 65-84 years	0	0	0
85 years and over	0	0	0

Age continuous			
Units: years			
arithmetic mean	34.09	33.55	34.01
standard deviation	± 10.99	± 10.60	± 10.94
Gender categorical			
Units: Subjects			
Female	37	36	34
Male	40	39	38

Reporting group values	futility population		
Number of subjects	41		
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)	41		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	32.24		
standard deviation	± 10.30		
Gender categorical			
Units: Subjects			
Female	17		
Male	24		

End points

End points reporting groups

Reporting group title	Bromelaine tablets hysan (1-0-1)
Reporting group description: Bromelaine low dose group	
Reporting group title	Bromelaine tablets hysan (2-1-1)
Reporting group description: Bromelaine high dose	
Reporting group title	Placebo (1-0-1)
Reporting group description: Placebo low dose	
Reporting group title	Placebo (2-1-1)
Reporting group description: Placebo high dose	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description: The safety population refers to all randomized patients who have been exposed to the investigational medicinal product at least once	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT population refers to all randomized patients who meet key eligibility and evaluability criteria and have diary data of at least day 1.	
Subject analysis set title	PP population
Subject analysis set type	Per protocol
Subject analysis set description: The PP population refers to all evaluable patients who comply with the protocol in all points relevant to the analysis and deliver a complete data set of measurements for the evaluation of the primary efficacy variable.	
Subject analysis set title	futility population
Subject analysis set type	Sub-group analysis
Subject analysis set description: A planned interim analysis for futility was performed based on patient diary data, blood tests and adverse event reporting data of 41 enrolled and randomized patients	

Primary: change in COVID-19 symptom severity score

End point title	change in COVID-19 symptom severity score
End point description: The primary objective of this study was to assess the change in COVID-19 symptom severity reported by the patients daily via a patient diary. The following symptoms assessed from day 1 (baseline) to day 11 (V4): anosmia, ageusia, fever, cough, sore throat, shortness of breath, coryza, general weakness, headache, aching limbs, loss of appetite, nausea, abdominal pain, vomiting, diarrhoea, conjunctivitis, rash, lymph node swelling, apathy and somnolence.	
End point type	Primary
End point timeframe: day 1 (baseline / V1) to day 11 (V4)	

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	11	11
Units: symptom score				
arithmetic mean (standard deviation)	-11.39 (± 8.29)	-11.02 (± 10.33)	-11.23 (± 7.01)	-12.64 (± 7.42)

Statistical analyses

Statistical analysis title	Statistical analysis BromCO

Statistical analysis description:

The analysis of the data was performed by using descriptive and exploratory statistics. Subgroups were analysed exploratorily (e.g., subgroups regarding the sex, age, severity, etc.).
Continuous data was be described by statistical estimates (number all cases and valid cases, mean, standard deviation, median, Q1, Q3, minimum, and maximum values), whereby categorical data was described by absolute frequencies and percentage of valid cases.

Comparison groups	Bromelaine tablets hysan (1-0-1) v Bromelaine tablets hysan (2-1-1) v Placebo (1-0-1) v Placebo (2-1-1)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05 [2]
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Notes:

[1] - Primary and secondary study endpoints were not analysed by confirmatory statistics. As there was no formal testing of a given hypothesis, data was analysed descriptively and exploratively. Normally distributed data were compared with the One-Way ANOVA and t-tests to perform pairwise comparisons. In case of non-normally distributed data, the Kruskal-Wallis and the Mann-Whitney tests were used to compare the groups. The comparison of categorial variables between groups were performed by chi-square

[2] - A two-sided p value of less than 0.05 was considered to indicate statistical significance.

Secondary: clinical improvement of the patient state (WHO score)

End point title	clinical improvement of the patient state (WHO score)

End point description:

assessment of the clinical improvement of the patient state via an 11-category ordinal score as proposed by the WHO

End point type	Secondary

End point timeframe:

day 1 (v1)

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	12	11
Units: WHO score				
number (not applicable)	2	2	2	2

Statistical analyses

No statistical analyses for this end point

Secondary: clinical improvement of the patient state (WHO score)

End point title	clinical improvement of the patient state (WHO score)

End point description:

To assess the clinical improvement of the patient state via a World Health Organisation (WHO) ordinal scale

End point type	Secondary

End point timeframe:

d60 (V6)

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	24	12	11
Units: WHO score				
number (not applicable)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: body temperature V1

End point title	body temperature V1

End point description:

clinical improvement of the patient state via measurement of body temperature (fever)

End point type	Secondary

End point timeframe:

day 1 (V1) to day 11 (V4)

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	11	11
Units: degree celsius				
arithmetic mean (standard deviation)	36.59 (± 0.58)	36.77 (± 0.56)	36.71 (± 0.45)	36.77 (± 0.32)

Statistical analyses

No statistical analyses for this end point

Secondary: baseline-adjusted mean oxygen saturation of blood

End point title	baseline-adjusted mean oxygen saturation of blood

End point description:

clinical improvement of the patient state via measurement of blood oxygen saturation

End point type	Secondary

End point timeframe:

day 1 (V1) to day 11 (V4)

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	11	11
Units: percentage				
arithmetic mean (standard deviation)	0.15 (± 1.37)	0.43 (± 1.01)	-0.48 (± 1.25)	0.45 (± 0.73)

Statistical analyses

No statistical analyses for this end point

Secondary: baseline-adjusted Ct values

End point title	baseline-adjusted Ct values

End point description:

The assessment of the clinical improvement of the patient state via measurement of SARS-CoV-2 virus load in nasopharyngeal swabs (Cycle threshold [Ct] value at V1, V2, V3 and V4).

End point type	Secondary

End point timeframe:

day 1 (V1) to day 11 (V4)

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	11	11
Units: Ct value				
arithmetic mean (standard deviation)	18.97 (± 6.63)	20.34 (± 5.58)	20.54 (± 4.11)	22.34 (± 3.68)

Statistical analyses

No statistical analyses for this end point

Secondary: change in quality of life (SF-36)

End point title	change in quality of life (SF-36)

End point description:

The change in quality of life as assessed by the SF-36 generic quality of life questionnaire

End point type	Secondary

End point timeframe:

day 1 (V1) to day 11 (V4)

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	12	11
Units: SF-36 score				
arithmetic mean (standard deviation)	4.05 (± 9.34)	4.40 (± 9.62)	4.63 (± 7.95)	2.32 (± 8.11)

Statistical analyses

No statistical analyses for this end point

Secondary: adverse events

End point title	adverse events

End point description:

Safety assessment (occurrence of adverse events), including a safety follow-up call 60 days after the start of the treatment

End point type	Secondary

End point timeframe:

day 1 (V1) to day 60 (V6)

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	12	12
Units: total number				
number (not applicable)	71	88	28	28

Statistical analyses

No statistical analyses for this end point

Secondary: body temperature V4

End point title	body temperature V4

End point description:

The assessment of the clinical improvement of the patient state via measurement of body temperature (fever)

End point type	Secondary

End point timeframe:

day 1 (V1) to day 11 (V4)

End point values	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)	Placebo (2-1-1)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	25	11	11
Units: degree celsius				
arithmetic mean (standard deviation)	36.31 (± 0.41)	36.13 (± 0.44)	36.38 (± 0.43)	36.47 (± 0.43)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
day 1 (V1) to day 60 (V6)	
Adverse event reporting additional description:	
Safety assessment (occurrence of adverse events), including a safety follow-up call 60 days after the start of the treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Bromelaine tablets hysan (1-0-1)
Reporting group description:	
Bromelaine low dose group	
Reporting group title	Bromelaine tablets hysan (2-1-1)
Reporting group description:	
Bromelaine high dose	
Reporting group title	Placebo (1-0-1)
Reporting group description:	
Placebo low dose	
Reporting group title	Placebo (2-1-1)
Reporting group description:	
Placebo high dose	

Serious adverse events	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Placebo (2-1-1)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Bromelaine tablets hysan (1-0-1)	Bromelaine tablets hysan (2-1-1)	Placebo (1-0-1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 27 (88.89%)	21 / 26 (80.77%)	9 / 12 (75.00%)
Vascular disorders			
Blood pressure increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	4 / 27 (14.81%)	2 / 26 (7.69%)	1 / 12 (8.33%)
occurrences (all)	4	2	1
General disorders and administration site conditions			
Chest pressure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Exhaustion			
subjects affected / exposed	3 / 27 (11.11%)	3 / 26 (11.54%)	0 / 12 (0.00%)
occurrences (all)	3	4	0
Fever			
subjects affected / exposed	1 / 27 (3.70%)	3 / 26 (11.54%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Flu like symptoms			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Mucosal dryness			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Weakness			
subjects affected / exposed	3 / 27 (11.11%)	2 / 26 (7.69%)	1 / 12 (8.33%)
occurrences (all)	3	2	1
Weakness worsened			
subjects affected / exposed	1 / 27 (3.70%)	2 / 26 (7.69%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Respiratory, thoracic and mediastinal disorders			
Breath shortness			
subjects affected / exposed	2 / 27 (7.41%)	3 / 26 (11.54%)	0 / 12 (0.00%)
occurrences (all)	2	3	0

Cough			
subjects affected / exposed	1 / 27 (3.70%)	2 / 26 (7.69%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Cough aggravated			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Increased shortness of breath			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pain throat			
subjects affected / exposed	2 / 27 (7.41%)	1 / 26 (3.85%)	1 / 12 (8.33%)
occurrences (all)	6	1	1
Tonsillar inflammation			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tonsillitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Disorder sleep			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Restlessness			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood pressure systolic increased			
subjects affected / exposed	2 / 27 (7.41%)	2 / 26 (7.69%)	3 / 12 (25.00%)
occurrences (all)	2	2	3
Diastolic blodd pressure increased			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fibrin D dimer increased			

subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
NT-proBNP increased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Heart pressure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Nervousness			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Concentration impaired			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Forgetfulness			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	0 / 12 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	6 / 27 (22.22%)	5 / 26 (19.23%)	2 / 12 (16.67%)
occurrences (all)	5	5	2
Headache aggravated			
subjects affected / exposed	1 / 27 (3.70%)	1 / 26 (3.85%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Light headedness			
subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Loss of smell			
subjects affected / exposed	2 / 27 (7.41%)	0 / 26 (0.00%)	1 / 12 (8.33%)
occurrences (all)	3	0	1
Loss of taste			
subjects affected / exposed	5 / 27 (18.52%)	4 / 26 (15.38%)	0 / 12 (0.00%)
occurrences (all)	5	4	0
Sleepiness			

subjects affected / exposed	2 / 27 (7.41%)	4 / 26 (15.38%)	1 / 12 (8.33%)
occurrences (all)	2	4	1
Smell loss			
subjects affected / exposed	4 / 27 (14.81%)	6 / 26 (23.08%)	1 / 12 (8.33%)
occurrences (all)	4	6	1
Gastrointestinal disorders			
Belly ache			
subjects affected / exposed	2 / 27 (7.41%)	5 / 26 (19.23%)	2 / 12 (16.67%)
occurrences (all)	2	5	2
Diarrhoea			
subjects affected / exposed	3 / 27 (11.11%)	3 / 26 (11.54%)	4 / 12 (33.33%)
occurrences (all)	3	3	4
Esophageal reflux			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 27 (7.41%)	3 / 26 (11.54%)	2 / 12 (16.67%)
occurrences (all)	2	3	2
Vomiting			
subjects affected / exposed	0 / 27 (0.00%)	2 / 26 (7.69%)	1 / 12 (8.33%)
occurrences (all)	0	2	1
Skin and subcutaneous tissue disorders			
Hair loss			
subjects affected / exposed	1 / 27 (3.70%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Localised itching			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Localised skin reaction			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Skin rash			
subjects affected / exposed	1 / 27 (3.70%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Limb discomfort			
subjects affected / exposed	2 / 27 (7.41%)	4 / 26 (15.38%)	1 / 12 (8.33%)
occurrences (all)	2	4	1
Muscle ache			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Acute bacterial bronchitis			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bronchitis bacterial			
subjects affected / exposed	0 / 27 (0.00%)	0 / 26 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Cold			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	1 / 12 (8.33%)
occurrences (all)	2	0	1
Common cold			
subjects affected / exposed	2 / 27 (7.41%)	3 / 26 (11.54%)	1 / 12 (8.33%)
occurrences (all)	2	3	1
Conjunctivitis			
subjects affected / exposed	1 / 27 (3.70%)	0 / 26 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Herpes NOS			
subjects affected / exposed	0 / 27 (0.00%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	1 / 27 (3.70%)	1 / 26 (3.85%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Metabolism and nutrition disorders			
Appetite lost			
subjects affected / exposed	4 / 27 (14.81%)	4 / 26 (15.38%)	0 / 12 (0.00%)
occurrences (all)	4	4	0

Non-serious adverse events	Placebo (2-1-1)		
Total subjects affected by non-serious adverse events subjects affected / exposed	12 / 12 (100.00%)		
Vascular disorders			
Blood pressure increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Chest pressure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Exhaustion			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Fever			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Flu like symptoms			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Mucosal dryness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Weakness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Weakness worsened			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Breath shortness			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cough aggravated			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Increased shortness of breath			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Pain throat			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Tonsillar inflammation			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Disorder sleep			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Restlessness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Investigations			
Blood pressure systolic increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Diastolic blodd pressure increased			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fibrin D dimer increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
NT-proBNP increased			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Heart pressure			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Nervousness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Concentration impaired			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Forgetfulness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Headache aggravated			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Light headedness			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Loss of smell			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Loss of taste			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Sleepiness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Smell loss			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Gastrointestinal disorders			
Belly ache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Esophageal reflux			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Hair loss			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Localised itching			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Localised skin reaction			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Skin rash			

subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Limb discomfort			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Muscle ache			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Acute bacterial bronchitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Bronchitis bacterial			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Cold			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Common cold			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Herpes NOS			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			

Appetite lost subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2021	Implementation of CAPAs from the findings of an inspection of another COVID-19 study in a similar setting, resulting in protocol version V2.0 dated 21.07.2021
03 November 2021	The measurement of immunologic blood parameters will only be analysed in the subgroup of patients who will be included in the futility analysis (at least 36 patients). This amendment resulted in protocol version V3.0 dated 14.10.2021

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 November 2021	Upon approval of the study protocol Version V3.9 dated 14.10.2021 (date of approval: 03.11.2021), the immunologic blood parameters were only analysed in a subgroup of patients who were included in the futility analyisis. After at least 36 patients had completed the study up to day 16, an interim futiliy analysis based on patient diary data, patient status (via measurement of blood parameters) and adverse event reporting was performed.	03 November 2021

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Recruitment of patients was stopped after the inclusion of 77 patients (instead of planned 120 patients) based on results of the futility analysis results.

Notes: