



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 \pm 1 day), V3 (Day 7 \pm 1 day), V4 (Day 11 \pm 2 days) and V5 (D16 \pm 1 day). Patients were called on Day 60 \pm 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 positively 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 standard deviation | 34.09 ± 10.99 | 33.55 ± 10.60 | 34.01 ± 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 standard deviation | 32.24 ± 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 blood 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 occurrences (all) | 0 / 27 (0.00%) 0 | 2 / 26 (7.69%) 2 | 0 / 12 (0.00%) 0 |
| NT-proBNP increased subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 26 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Cardiac disorders Heart pressure subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 12 (0.00%) 0 |
| Nervous system disorders Nervousness subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 0 / 26 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Concentration impaired subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 1 / 26 (3.85%) 1 | 0 / 12 (0.00%) 0 |
| Forgetfulness subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 0 / 26 (0.00%) 0 | 0 / 12 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 6 / 27 (22.22%) 5 | 5 / 26 (19.23%) 5 | 2 / 12 (16.67%) 2 |
| Headache aggravated subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | 1 / 26 (3.85%) 1 | 1 / 12 (8.33%) 1 |
| Light headedness subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | 2 / 26 (7.69%) 2 | 0 / 12 (0.00%) 0 |
| Loss of smell subjects affected / exposed occurrences (all) | 2 / 27 (7.41%) 3 | 0 / 26 (0.00%) 0 | 1 / 12 (8.33%) 1 |
| Loss of taste subjects affected / exposed occurrences (all) | 5 / 27 (18.52%) 5 | 4 / 26 (15.38%) 4 | 0 / 12 (0.00%) 0 |
| Sleepiness | | | |

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

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

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Fibrin D dimer increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| NT-proBNP increased subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Cardiac disorders Heart pressure subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Nervous system disorders Nervousness subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Concentration impaired subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Forgetfulness subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | | |
| Headache subjects affected / exposed occurrences (all) | 4 / 12 (33.33%) 4 | | |
| Headache aggravated subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Light headedness subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Loss of smell subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 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 occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Limb discomfort subjects affected / exposed occurrences (all) Muscle ache subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | | |
| Infections and infestations Acute bacterial bronchitis subjects affected / exposed occurrences (all) Bronchitis bacterial subjects affected / exposed occurrences (all) Cold subjects affected / exposed occurrences (all) Common cold subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Herpes NOS subjects affected / exposed occurrences (all) Sinusitis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 0 / 12 (0.00%) 0 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Appetite lost | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | | |
| occurrences (all) | 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 analysis. After at least 36 patients had completed the study up to day 16, an interim futility 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: