# Clinical trial results:
# MULTICENTRIC RANDOMIZED PLACEBO-CONTROLLED DOUBLE-BLIND 2-ARM PIVOTAL STUDY ON EFFICACY AND SAFETY OF ARHAMA®-TINKTUR N IN PATIENS WITH ACUTE DIARRHEA

## Summary

| | |
|---|---|
| EudraCT number | 2011-001776-19 |
| Trial protocol | DE |
| Global end of trial date | 29 April 2014 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 25 November 2021 |
| First version publication date | 25 November 2021 |
| Summary attachment (see zip file) | ISR2014 (5.3.4-07_Wolf_2014.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | 2010-19 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | CardioSec Clinical Research GmbH |
| Sponsor organisation address | Dalbergsweg 21, Erfurt, Germany, D-99084 |
| Public contact | Project manager, CardioSec Clinical Research GmbH, 0049 36178919740, info@cardiosec.de |
| Scientific contact | Project manager, CardioSec Clinical Research GmbH, 0049 36178919740, info@cardiosec.de |
| Sponsor organisation name | Bombastus-Werke AG |
| Sponsor organisation address | Wilsdruffer Str. 170, Freital, Germany, D-01705 |
| Public contact | Mathias Solf, Head of R&D, 0049 3516580354, m.solf@bombastus-werke.de |
| Scientific contact | Mathias Solf, Head of R&D, 0049 3516580354, m.solf@bombastus-werke.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 | 29 April 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 April 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 April 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Superiority of oral treatment with Arhama®-Tinktur N (7,5 ml oral per 48 hours) compared to placebo

Protection of trial subjects:

exclusion of severe cases

Background therapy:

individual possible, was recorded

Evidence for comparator:

Similar to Verum in colour and taste but without effect

| | |
|---|---|
| Actual start date of recruitment | 01 September 2011 |
| 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: 470 |
| Worldwide total number of subjects | 470 |
| EEA total number of subjects | 470 |

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) | 447 |
| From 65 to 84 years | 23 |

| | |
|---|---|
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

26 investigation partners in Germany were involved. They included patients according to the determined criteria.

### Pre-assignment

Screening details:

checking diagnosis, Inclusion and exclusion criteria.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 472[1] |
| Intermediate milestone: Number of subjects | pre assignment: 472 |
| Intermediate milestone: Number of subjects | Randomisation: 472 |
| Number of subjects completed | 470 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Consent withdrawn by subject: 1 |
| Reason: Number of subjects | Pregnancy: 1 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 472-2=470, this are the real numbers before and after randomisation

### Period 1

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

Blinding implementation details:

Verum- / Placebo- Solutions were filled in identical 100-ml- glass bottles. They were individualised with labels with the "randomisation number". The corresponding list of the numbers and relation to the study-arms was unknown to patients and investigators.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Verum |

Arm description:

Dosing of 7.5 ml Verum preparation at initialisation and than in Intervals of 48 h until end of diarrhea

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Arhama-Tinktur N |
| Investigational medicinal product code | |
| Other name | Verum preparation |
| Pharmaceutical forms | Oral liquid |
| Routes of administration | Oral use |

Dosage and administration details:

Dosing of 7.5 ml Verum preparation at initialisation and than in Intervals of 48 h until end of diarrhea

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Dosing of 7.5 ml Placebo preparation at initialisation and than in Intervals of 48 h until end of diarrhea

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | Placebo |
| Pharmaceutical forms | Oral liquid |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo

| **Number of subjects in period 1** | Verum | Placebo |
|---|---|---|
| Started | 234 | 236 |
| Completed | 223 | 231 |
| Not completed | 11 | 5 |
| Adverse event, non-fatal | 3 | - |
| Lost to follow-up | 6 | 1 |
| Lack of efficacy | 2 | 4 |

## Baseline characteristics

### Reporting groups

| Reporting group title | preparation |
|---|---|

Reporting group description: -

| Reporting group values | preparation | Total | |
|---|---|---|---|
| Number of subjects | 470 | 470 | |
| Age categorical<br>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) | 447 | 447 | |
| From 65-84 years | 23 | 23 | |
| 85 years and over | 0 | 0 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 38.0 | | |
| standard deviation | ± 14.3 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 248 | 248 | |
| Male | 222 | 222 | |

### Subject analysis sets

| Subject analysis set title | PPS |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:
Patients without distinct protocol deviations

| Subject analysis set title | FAS |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:
all included patients

| Reporting group values | PPS | FAS | |
|---|---|---|---|
| Number of subjects | 432 | 470 | |
| Age categorical<br>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) | 412 | 447 | |
| From 65-84 years | 20 | 23 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 38.1 | 38.0 | |
| standard deviation | ± 14.1 | ± 14.3 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 227 | 248 | |
| Male | 205 | 222 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Verum |
| Reporting group description: Dosing of 7.5 ml Verum preparation at initialisation and than in Intervals of 48 h until end of diarrhea | |
| Reporting group title | Placebo |
| Reporting group description: Dosing of 7.5 ml Placebo preparation at initialisation and than in Intervals of 48 h until end of diarrhea | |
| Subject analysis set title | PPS |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Patients without distinct protocol deviations | |
| Subject analysis set title | FAS |
| Subject analysis set type | Full analysis |
| Subject analysis set description: all included patients | |

### Primary: duration of diarrhoea

| | |
|---|---|
| End point title | duration of diarrhoea |
| End point description: | |
| End point type | Primary |
| End point timeframe: 15.11.2011 - 04.09.2013 | |

| End point values | Verum | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 234 | 236 | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | 23.9 (± 11.8) | 24.5 (± 11.9) | | |

### Statistical analyses

| Statistical analysis title | Duration of diarrhoea |
|---|---|
| Comparison groups | Verum v Placebo |
| Number of subjects included in analysis | 470 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence[1] |
| P-value | > 0.0038 [2] |
| Method | Kaplan-Meier-Analyse |

Notes:

[1] - zero-Hypothesis: The Duration of diarrhoea is equal in both study arms.

[2] - p=0.067 => the zero-Hypothesis is true

## Post-hoc: Duration of diarrhoea (DD) for patients with DD>48h

| | |
|---|---|
| End point title | Duration of diarrhoea (DD) for patients with DD>48h |

End point description:

for patients with Duration of diarrhoea >48h revealed an benefit for Verum with statistical relevance

| | |
|---|---|
| End point type | Post-hoc |

End point timeframe:

15.11.2011 - 04.09.2013

| End point values | Verum | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 97 | 94 | | |
| Units: hours | | | | |
| median (confidence interval 5%) | 99.7 (68.3 to 131.1) | 113.5 (65.0 to 162.0) | | |

| | |
|---|---|
| **Attachments (see zip file)** | post-hoc-graph/posthoc2014.pdf |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: 15.11.2011 - 04.09.2013 | |
| Assessment type | Systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |
| **Reporting groups** | |
| Reporting group title | Verum |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Serious adverse events | Verum | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 236 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| 10044552, 10009900 | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 0 / 236 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Verum | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 234 (8.55%) | 27 / 236 (11.44%) | |
| Investigations | | | |
| 10048553 10008578 10018644 10026972 | | | |
| subjects affected / exposed | 4 / 234 (1.71%) | 4 / 236 (1.69%) | |
| occurrences (all) | 4 | 4 | |
| Nervous system disorders | | | |
| 10013649 10019211 | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 234 (0.85%) | 4 / 236 (1.69%) | |
| occurrences (all) | 2 | 4 | |
| General disorders and administration site conditions<br>10008531 10072005 | | | |
| subjects affected / exposed | 1 / 234 (0.43%) | 1 / 236 (0.42%) | |
| occurrences (all) | 1 | 1 | |
| Eye disorders<br>10010741 10010694 | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 1 / 236 (0.42%) | |
| occurrences (all) | 2 | 1 | |
| Gastrointestinal disorders<br>10038263 10000055 10017865 10028813 | | | |
| subjects affected / exposed | 5 / 234 (2.14%) | 14 / 236 (5.93%) | |
| occurrences (all) | 5 | 14 | |
| Musculoskeletal and connective tissue disorders<br>10059671 10023477 10048412 | | | |
| subjects affected / exposed | 2 / 234 (0.85%) | 1 / 236 (0.42%) | |
| occurrences (all) | 2 | 1 | |
| Infections and infestations<br>10046544 10033078 10047463 10061735 | | | |
| subjects affected / exposed | 4 / 234 (1.71%) | 2 / 236 (0.85%) | |
| occurrences (all) | 4 | 2 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 24 April 2012 | -additional blood sample for the immune subset |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported