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 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 Units: years			
arithmetic mean	38.0		
standard deviation	± 14.3	-	
Gender categorical 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 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 10008531 10072005			
subjects affected / exposed	1 / 234 (0.43%)	1 / 236 (0.42%)	
occurrences (all)	1	1	
Eye disorders 10010741 10010694			
subjects affected / exposed	2 / 234 (0.85%)	1 / 236 (0.42%)	
occurrences (all)	2	1	
Gastrointestinal disorders 10038263 10000055 10017865 10028813			
subjects affected / exposed	5 / 234 (2.14%)	14 / 236 (5.93%)	
occurrences (all)	5	14	
Musculoskeletal and connective tissue disorders 10059671 10023477 10048412			
subjects affected / exposed	2 / 234 (0.85%)	1 / 236 (0.42%)	
occurrences (all)	2	1	
Infections and infestations 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