Clinical trial results:
The Qure study: Q-fever fatigue syndrome - response to treatment

Summary

EudraCT number	2011-000643-25
Trial protocol	NL
Global end of trial date	10 September 2015

Results information

Result version number	v1 (current)
This version publication date	13 January 2021
First version publication date	13 January 2021
Summary attachment (see zip file)	The Qure study: Q-fever fatigue syndrome - response to treatment (1471-2334-13-157.pdf) Effectiveness of Long-term Doxycycline Treatment and Cognitive-Behavioral Therapy on Fatigue Severity in Patients with Q Fever Fatigue Syndrome (Qure Study): A Randomized Controlled Trial (cix013.pdf)

Trial information

Trial identification

Sponsor protocol code	205520003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01318356
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trial Register (NTR): NTR2797

Notes:

Sponsors

Sponsor organisation name	Radboud University Nijmegen Medical Centre
Sponsor organisation address	Geert Grooteplein 10, Nijmegen, Netherlands, 6500 HB
Public contact	Department of Internal Medicine, Radboud University Nijmegen Medical Centre, +31 243668256, Stephan.Keijmel@radboudumc.nl
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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	10 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 September 2015
Global end of trial reached?	Yes
Global end of trial date	10 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of two treatment strategies for fatigue and disabilities in QFS: long term treatment with doxycycline or cognitive behavioral therapy (CBT). Both interventions will be compared to a placebo group. Primary outcome measure will be fatigue severity measured with the Checklist Individual Strength (CIS).

Protection of trial subjects:

For safety considerations all participants in the medication condition will visit the Q fever outpatient clinic 4, 8, and 16 weeks after start of the treatment. Furthermore, liver enzymes will be checked, and drug utilization will be recorded. Therefore, patients are required to bring the study medication to all visits. In addition, blood samples drawn 8 weeks after start of treatment will be stored by the study pharmacist, who performed the double-blinded randomization. For patients allocated to CBT, AEs were monitored at 8 weeks after start of therapy and at EOT.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 May 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	Netherlands: 156
Worldwide total number of subjects	156
EEA total number of subjects	156

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)	156
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Eligible patients will be asked to participate in the Qure study after receiving verbal and written information about the study. If patients are willing to participate, written informed consent will be obtained.

Pre-assignment

Screening details:

Male/non-pregnant,-lactating females above 18, proven acute Q fever since 2007 and/or positive serology fitting a past infection with C. burnetii, being severly fatigued, being fatigued for >6m, being disabled because of fatigue
+inclusion based on Dutch QFS algorithm
+absence of fatigue before Q fever/increase of fatigue since Q fever infection

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Doxycycline

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Doxycycline Disp 100 PCH
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients were treated with doxycycline 200 mg or placebo, orally administered once daily, for 24 weeks. Doxycycline was reencapsulated and placebo was prepared as capsules with identical appearance.

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

Patients were treated with placebo, orally administered once daily, for 24 weeks. Placebo was prepared as capsules with identical appearance as doxycycline.

Arm title	Cognitive behavioural therapy (CBT)

Arm description:

Patients allocated to CBT received approximately 24 weeks of individual CBT, based on the manual of CBT for CFS, by trained and supervised cognitive-behavioral therapists. Treatment frequency was determined on individual basis, with intended sessions once every 2 weeks.

Arm type	Experimental without product

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)
Started	52	52	51
Completed	52	52	50
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: One subject refused double-blind randomization after inclusion. Therefore, this subject enrolled in the trial but was not allocated medication.

Baseline characteristics

Reporting groups	
Reporting group title	Doxycycline
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Cognitive behavioural therapy (CBT)

Reporting group description:

Patients allocated to CBT received approximately 24 weeks of individual CBT, based on the manual of CBT for CFS, by trained and supervised cognitive-behavioral therapists. Treatment frequency was determined on individual basis, with intended sessions once every 2 weeks.

Reporting group values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)
Number of subjects	52	52	51
Age categorical Units: Subjects			
Adults (18-64 years)	52	52	51
Gender categorical Units: Subjects			
Female	29	20	25
Male	23	32	26

Reporting group values	Total		
Number of subjects	155		
Age categorical Units: Subjects			
Adults (18-64 years)	155		
Gender categorical Units: Subjects			
Female	74		
Male	81		

End points

End points reporting groups	
Reporting group title	Doxycycline
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Cognitive behavioural therapy (CBT)
Reporting group description:	
Patients allocated to CBT received approximately 24 weeks of individual CBT, based on the manual of CBT for CFS, by trained and supervised cognitive-behavioral therapists. Treatment frequency was determined on individual basis, with intended sessions once every 2 weeks.	

Primary: Fatigue severity at EOT	
End point title	Fatigue severity at EOT
End point description:	
End point type	Primary
End point timeframe:	
End of treatment (EOT) is 26 weeks.	

End point values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	50	
Units: CIS subscale Fatigue Severity				
arithmetic mean (confidence interval 95%)	40.8 (37.3 to 44.3)	37.8 (34.2 to 41.2)	31.6 (28.0 to 35.1)	

Statistical analyses

Statistical analysis title	Doxycycline vs. placebo
Comparison groups	Doxycycline v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	CBT vs. placebo
Comparison groups	Placebo v Cognitive behavioural therapy (CBT)

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Secondary: Questionnaires, SIP8 total score

End point title	Questionnaires, SIP8 total score

End point description:

End point type	Secondary

End point timeframe:

End of treatment (EOT) is after 26 weeks.

End point values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	50	
Units: SIP8 total score				
arithmetic mean (confidence interval 95%)	1101.5 (933.5 to 1269.6)	963.8 (795.8 to 1131.9)	786.8 (615.3 to 958.3)	

Statistical analyses

Statistical analysis title	Doxycycline vs. placebo
Comparison groups	Doxycycline v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	CBT vs. placebo
Comparison groups	Placebo v Cognitive behavioural therapy (CBT)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Secondary: Questionnaires, SCL90 total score

End point title	Questionnaires, SCL90 total score

End point description:

End point type	Secondary

End point timeframe:

End of treatment (EOT) is after 26 weeks.

End point values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	50	
Units: SCL90 total score				
arithmetic mean (confidence interval 95%)	149.2 (141.6 to 156.7)	142.6 (135.1 to 150.1)	127.1 (119.4 to 134.7)	

Statistical analyses

Statistical analysis title	Doxycycline vs. placebo
Comparison groups	Doxycycline v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	CBT vs. placebo
Comparison groups	Placebo v Cognitive behavioural therapy (CBT)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Secondary: Serology and PCR, IgM phase I

End point title	Serology and PCR, IgM phase I

End point description:

End point type	Secondary
End point timeframe: End of treatment (EOT) after 26 weeks.	

End point values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	50	
Units: Positive subjects	24	28	20	

Statistical analyses

Statistical analysis title	Doxycycline vs. placebo
Comparison groups	Doxycycline v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	CBT vs. placebo
Comparison groups	Placebo v Cognitive behavioural therapy (CBT)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Secondary: Serology and PCR, IgM phase II

End point title	Serology and PCR, IgM phase II
End point description:	

End point type	Secondary
End point timeframe: End of treatment (EOT) was after 26 weeks.	

End point values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	50	
Units: Positive subjects	27	32	29	

Statistical analyses

Statistical analysis title	Doxycycline vs. placebo
Comparison groups	Doxycycline v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	CBT vs. placebo
Comparison groups	Placebo v Cognitive behavioural therapy (CBT)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Secondary: Serology and PCR, IgG phase I

End point title	Serology and PCR, IgG phase I

End point description:

End point type	Secondary

End point timeframe:

End of treatment (EOT) was after 26 weeks.

End point values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	50	
Units: Positive subjects	43	39	37	

Statistical analyses

Statistical analysis title	Doxycycline vs. placebo
Comparison groups	Doxycycline v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	CBT vs. placebo
Comparison groups	Placebo v Cognitive behavioural therapy (CBT)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Secondary: Serology and PCR, IgG phase II

End point title	Serology and PCR, IgG phase II

End point description:

End point type	Secondary

End point timeframe:

End of treatment (EOT) was after 26 weeks.

End point values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	50	
Units: Positive subjects	51	50	46	

Statistical analyses

Statistical analysis title	Doxycycline vs. placebo
Comparison groups	Doxycycline v Placebo

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	CBT vs. placebo
Comparison groups	Placebo v Cognitive behavioural therapy (CBT)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Secondary: Negative C. burnetii PCR	
End point title	Negative C. burnetii PCR
End point description:	

End point type	Secondary
End point timeframe:	
End of treatment (EOT) was after 26 weeks.	

End point values	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	52	52	50	
Units: Negative subjects	52	52	50	

Statistical analyses

Statistical analysis title	Doxycycline vs. placebo
Comparison groups	Doxycycline v Placebo
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Statistical analysis title	CBT vs. placebo
Comparison groups	Placebo v Cognitive behavioural therapy (CBT)
Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs in the medication condition were recorded during the study visits, and during the trial when reported by the patient. For patients allocated to CBT, AEs were monitored at 8 weeks after start and at EOT.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups

Reporting group title	Doxycycline
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Cognitive behavioural therapy (CBT)

Reporting group description: -

Serious adverse events	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 52 (0.00%)	2 / 52 (3.85%)	0 / 50 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Cardiological symptoms			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 52 (0.00%)	1 / 52 (1.92%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Doxycycline	Placebo	Cognitive behavioural therapy (CBT)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 52 (98.08%)	45 / 52 (86.54%)	42 / 50 (84.00%)
Nervous system disorders			
Neurological			
subjects affected / exposed	13 / 52 (25.00%)	10 / 52 (19.23%)	6 / 50 (12.00%)
occurrences (all)	13	11	8
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	31 / 52 (59.62%)	27 / 52 (51.92%)	5 / 50 (10.00%)
occurrences (all)	51	33	5
Skin and subcutaneous tissue disorders			
Skin			
subjects affected / exposed	20 / 52 (38.46%)	10 / 52 (19.23%)	5 / 50 (10.00%)
occurrences (all)	29	12	5
Musculoskeletal and connective tissue disorders			
Musculoskeletal			
subjects affected / exposed	22 / 52 (42.31%)	17 / 52 (32.69%)	14 / 50 (28.00%)
occurrences (all)	28	22	18
Bone and teeth			
subjects affected / exposed	3 / 52 (5.77%)	2 / 52 (3.85%)	1 / 50 (2.00%)
occurrences (all)	4	2	1
Infections and infestations			
Infection			
subjects affected / exposed	22 / 52 (42.31%)	26 / 52 (50.00%)	29 / 50 (58.00%)
occurrences (all)	33	46	54

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study was not designed to compare doxycycline and CBT directly, due to limited number of available patients.
Masking for CBT was not possible.
It was not possible to include a control group without any form of treatment.
Longterm effects unknown

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23536997

http://www.ncbi.nlm.nih.gov/pubmed/28329131