Clinical trial results:
Tick Test & Prophylaxis Proof

Summary

EudraCT number	2012-005101-51
Trial protocol	NL
Global end of trial date	09 December 2016

Results information

Result version number	v1 (current)
This version publication date	13 December 2023
First version publication date	13 December 2023
Summary attachment (see zip file)	published article (1-s2.0-S016344532030414X-main_TTPP_article.pdf)

Trial information

Trial identification

Sponsor protocol code	EPI-303

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NTR: NL3787

Notes:

Sponsors

Sponsor organisation name	RIVM
Sponsor organisation address	Antonie van Leeuwenhoeklaan 9, Bilthoven, Netherlands, 3720 MA
Public contact	Secretariat Epid. and Surveillance, National Institute of Health and the Environment (Dutch acronym: RIVM), +31 88 6892910, kees.van.den.wijngaard@rivm.nl
Scientific contact	Secretariat Epid. and Surveillance, National Institute of Health and the Environment (Dutch acronym: RIVM), +31 88 6892910, kees.van.den.wijngaard@rivm.nl

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	12 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 December 2016
Global end of trial reached?	Yes
Global end of trial date	09 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of antibiotic prophylaxis after a tick bite in the Dutch setting in relation to Borrelia infection of the tick, tick engorgement and attachment time.

Protection of trial subjects:

In the non-treatment group there is no additional health risk, as not taking prophylaxis after a tick bite is standard procedure in the current CBO guideline. In the prophylaxis group, the participants are likely to have a smaller risk of developing Lyme disease after the tick bite and a small possible risk of AEs by the prophylaxis. People who voluntarily report a recent tick bite on the web portal Tekenradar.nl will be included in the study if they meet the inclusion criteria and provide informed consent. People are randomly assigned to the prophylaxis group and this group will receive a letter by internet to inform their GP. The GP decides, in consultation with the participant, whether it is safe to prescribe prophylaxis regarding the medical history of the participant. Prophylaxis is prescribed as one dose 200mg doxycycline, following the draft CBO-guideline. If the participant has a contraindication for doxycycline, the GP may decide to prescribe a different antibiotic as prophylaxis although this is not part of the study. Doxyxycline is a bacteriostatic antibiotic belonging to the class of tetracyclines. For this study a single dose of 200 mg in tablet form of the generic product is prescribed. Any registered doxycycline from any marketing authorisation holder (MAH) is allowed. A single dose of 200 mg doxycycline is dispensed by the subjects' local pharmacy via the GP's prescription according to common health care practice. Any subjects in the study are advised to seek medical advice as soon as they develop possible symptoms of Lyme disease; the RIVM will facilitate additional advice and diagnostics upon request. The burden for the participants of sending in ticks and filling-in questionnaires will be minimal, as all questionnaires will be online and ticks can be sent in by mail.

Background therapy:

-

Evidence for comparator:

-

Actual start date of recruitment	01 April 2013
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: 2844
Worldwide total number of subjects	2844
EEA total number of subjects	2844

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)	182
Adolescents (12-17 years)	138
Adults (18-64 years)	2079
From 65 to 84 years	443
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were recruited nationwide in the Netherlands through the website www.tekenradar.nl when reporting a tick bite on this website. Recruitment was between April 11th, 2013 and June 10th, 2015.

Pre-assignment

Screening details:

Individuals of at least 8 years old were eligible for the study if they, or their parents/guardians for them, reported a tick bite within 72 h after removal and collection of the tick. Age and time since removal were screened in the online reporting questionnaire.

Period 1

Period 1 title	prophylaxis after a tick bite (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was not blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	prophylaxis after a tick bite

Arm description:

After randomization, participants in the prophylaxis group were asked to visit their general practitioner with an information letter in which we requested the prescription of a single dose of 200 mg doxycycline (or with a body weight below 50 kg a lower dose of 4 mg/kg body weight) to be taken within 72 h after tick
removal, after checking for contra-indications. For adequate treatment, if needed, we instructed all participants (prophylaxis and no-treatment group) to contact their general practitioner if symptoms possibly related to Lyme borreliosis occurred. One week and one month after inclusion participants filled out online follow up questionnaires inquiring about the use and timing of antibiotic prophylaxis, development and antibiotic treatment of possible Lyme borreliosis, and development of adverse events.

Arm type	Experimental
Investigational medicinal product name	doxycycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Suspension for oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

A single dose of 200 mg doxycycline (or with a body weight below 50 kg a lower dose of 4 mg/kg body weight) to be taken within 72 h after tick removal, upon subscription of the participant's own GP.

Arm title	no-treatment group

Arm description:

All participants that report a tick bite on www.tekenradar.nl within 72 h after removal, that then were randomized in the no-treatment arm, see further details in the prophylaxis group.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	prophylaxis after a tick bite	no-treatment group
Started	1754	1090
Completed	1041	648
Not completed	713	442
Lost to follow-up	213	144
Protocol deviation	500	298

Baseline characteristics

Reporting groups

Reporting group title	prophylaxis after a tick bite

Reporting group description:

After randomization, participants in the prophylaxis group were asked to visit their general practitioner with an information letter in which we requested the prescription of a single dose of 200 mg doxycycline (or with a body weight below 50 kg a lower dose of 4 mg/kg body weight) to be taken within 72 h after tick
removal, after checking for contra-indications. For adequate treatment, if needed, we instructed all participants (prophylaxis and no-treatment group) to contact their general practitioner if symptoms possibly related to Lyme borreliosis occurred. One week and one month after inclusion participants filled out online follow up questionnaires inquiring about the use and timing of antibiotic prophylaxis, development and antibiotic treatment of possible Lyme borreliosis, and development of adverse events.

Reporting group title	no-treatment group

Reporting group description:

All participants that report a tick bite on www.tekenradar.nl within 72 h after removal, that then were randomized in the no-treatment arm, see further details in the prophylaxis group.

Reporting group values	prophylaxis after a tick bite	no-treatment group	Total
Number of subjects	1754	1090	2844
Age categorical			
age categories			
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)	102	80	182
Adolescents (12-17 years)	85	53	138
Adults (18-64 years)	1286	793	2079
From 65-84 years	279	164	443
85 years and over	2	0	2
Age continuous			
Units: years			
arithmetic mean	45.8	45.4	
standard deviation	± 17.7	± 18.0	-
Gender categorical			
Units: Subjects			
Female	887	552	1439
Male	865	538	1403
unknown	2	0	2

Subject analysis sets

Subject analysis set title	modified intention-to-treat prophylaxis group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

For the modified-ITT analysis participants were excluded if they: a) reported chronic complaints attributed to Lyme borreliosis at t = 0; b) did not timely finish their questionnaire at t = 0; c) missed

both of the questionnaires at t = 1 week and t = 1 month; d) missed both of the questionnaires at t = 3 and 6
months; e) reported new tick bites within 3 months after inclusion unless Lyme borreliosis developed before these new tick bites; f) at t = 0 reported medication use – other than the prescribed study prophylaxis – which might have had an effect on the development of Lyme borreliosis, such as immunosuppressants, other antibiotic prescriptions than the study prophylaxis, or erroneously prescribed study prophylaxis (i.e. other antibiotics than doxycycline, wrong dosage or taking the prophylaxis more than 72 h after removing the tick); g) at t = 0 reported medication use that possibly had an effect on the efficacy of the prophylaxis such as antacids and anti-epileptics.

Subject analysis set title	Per-protocol prophylaxis group
Subject analysis set type	Per protocol

Subject analysis set description:

For the per-protocol analysis, compared to the mITT population we additionally excluded all participants that reported crossover between study groups. Some of the participants in the prophylaxis group reported crossover to the no-treatment group due to erythema migrans developed within 72 h after tick removal, which called for an immediate full antibiotic treatment instead of the study prophylaxis. To balance the per-protocol study groups, we therefore excluded all participants diagnosed with Lyme borreliosis within 72 h after tick removal.

Subject analysis set title	modified intention-to-treat no-treatment group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

For the modified-ITT analysis participants were excluded if they: a) reported chronic complaints attributed to Lyme borreliosis at t = 0; b) did not timely finish their questionnaire at t = 0; c) missed both of the questionnaires at t = 1 week and t = 1 month; d) missed both of the questionnaires at t = 3 and 6
months; e) reported new tick bites within 3 months after inclusion unless Lyme borreliosis developed before these new tick bites; f) at t = 0 reported medication use – other than the prescribed study prophylaxis – which might have had an effect on the development of Lyme borreliosis, such as immunosuppressants, other antibiotic prescriptions than the study prophylaxis, or erroneously prescribed study prophylaxis (i.e. other antibiotics than doxycycline, wrong dosage or taking the prophylaxis more than 72 h after removing the tick); g) at t = 0 reported medication use that possibly had an effect on the efficacy of the prophylaxis such as antacids and anti-epileptics.

Subject analysis set title	Per-protocol no-treatment group
Subject analysis set type	Per protocol

Subject analysis set description:

For the per-protocol analysis, compared to the mITT population we additionally excluded all participants that reported crossover between study groups. Some of the participants in the prophylaxis group reported crossover to the no-treatment group due to erythema migrans developed within 72 h after tick removal, which called for an immediate full antibiotic treatment instead of the study prophylaxis. To balance the per-protocol study groups, we therefore excluded all participants diagnosed with Lyme borreliosis within 72 h after tick removal.

Reporting group values	modified intention-to-treat prophylaxis group	Per-protocol prophylaxis group	modified intention-to-treat no-treatment group
Number of subjects	1041	794	648
Age categorical			
age categories			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)	68	43	48
Adolescents (12-17 years)	50	37	36
Adults (18-64 years)	774	599	471
From 65-84 years	149	115	93
85 years and over	0	0	0

Age continuous			
Units: years			
arithmetic mean	44.8	45.0	44.7
standard deviation	± 17.6	± 17.1	± 18.2
Gender categorical			
Units: Subjects			
Female	526	396	318
Male	515	398	330
unknown			

Reporting group values	Per-protocol no-treatment group		
Number of subjects	630		
Age categorical			
age categories			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)	46		
Adolescents (12-17 years)	36		
Adults (18-64 years)	458		
From 65-84 years	90		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	44.6		
standard deviation	± 18.1		
Gender categorical			
Units: Subjects			
Female	308		
Male	322		
unknown			

End points

End points reporting groups

Reporting group title	prophylaxis after a tick bite

Reporting group description:

After randomization, participants in the prophylaxis group were asked to visit their general practitioner with an information letter in which we requested the prescription of a single dose of 200 mg doxycycline (or with a body weight below 50 kg a lower dose of 4 mg/kg body weight) to be taken within 72 h after tick
removal, after checking for contra-indications. For adequate treatment, if needed, we instructed all participants (prophylaxis and no-treatment group) to contact their general practitioner if symptoms possibly related to Lyme borreliosis occurred. One week and one month after inclusion participants filled out online follow up questionnaires inquiring about the use and timing of antibiotic prophylaxis, development and antibiotic treatment of possible Lyme borreliosis, and development of adverse events.

Reporting group title	no-treatment group

Reporting group description:

All participants that report a tick bite on www.tekenradar.nl within 72 h after removal, that then were randomized in the no-treatment arm, see further details in the prophylaxis group.

Subject analysis set title	modified intention-to-treat prophylaxis group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

For the modified-ITT analysis participants were excluded if they: a) reported chronic complaints attributed to Lyme borreliosis at t = 0; b) did not timely finish their questionnaire at t = 0; c) missed both of the questionnaires at t = 1 week and t = 1 month; d) missed both of the questionnaires at t = 3 and 6
months; e) reported new tick bites within 3 months after inclusion unless Lyme borreliosis developed before these new tick bites; f) at t = 0 reported medication use – other than the prescribed study prophylaxis – which might have had an effect on the development of Lyme borreliosis, such as immunosuppressants, other antibiotic prescriptions than the study prophylaxis, or erroneously prescribed study prophylaxis (i.e. other antibiotics than doxycycline, wrong dosage or taking the prophylaxis more than 72 h after removing the tick); g) at t = 0 reported medication use that possibly had an effect on the efficacy of the prophylaxis such as antacids and anti-epileptics.

Subject analysis set title	Per-protocol prophylaxis group
Subject analysis set type	Per protocol

Subject analysis set description:

For the per-protocol analysis, compared to the mITT population we additionally excluded all participants that reported crossover between study groups. Some of the participants in the prophylaxis group reported crossover to the no-treatment group due to erythema migrans developed within 72 h after tick removal, which called for an immediate full antibiotic treatment instead of the study prophylaxis. To balance the per-protocol study groups, we therefore excluded all participants diagnosed with Lyme borreliosis within 72 h after tick removal.

Subject analysis set title	modified intention-to-treat no-treatment group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

For the modified-ITT analysis participants were excluded if they: a) reported chronic complaints attributed to Lyme borreliosis at t = 0; b) did not timely finish their questionnaire at t = 0; c) missed both of the questionnaires at t = 1 week and t = 1 month; d) missed both of the questionnaires at t = 3 and 6
months; e) reported new tick bites within 3 months after inclusion unless Lyme borreliosis developed before these new tick bites; f) at t = 0 reported medication use – other than the prescribed study prophylaxis – which might have had an effect on the development of Lyme borreliosis, such as immunosuppressants, other antibiotic prescriptions than the study prophylaxis, or erroneously prescribed study prophylaxis (i.e. other antibiotics than doxycycline, wrong dosage or taking the prophylaxis more than 72 h after removing the tick); g) at t = 0 reported medication use that possibly had an effect on the efficacy of the prophylaxis such as antacids and anti-epileptics.

Subject analysis set title	Per-protocol no-treatment group
Subject analysis set type	Per protocol

Subject analysis set description:

For the per-protocol analysis, compared to the mITT population we additionally excluded all participants

that reported crossover between study groups. Some of the participants in the prophylaxis group reported crossover to the no-treatment group due to erythema migrans developed within 72 h after tick removal, which called for an immediate full antibiotic treatment instead of the study prophylaxis. To balance the per-protocol study groups, we therefore excluded all participants diagnosed with Lyme borreliosis within 72 h after tick removal.

Primary: Development of physician-confirmed Lyme borreliosis (LB)

End point title	Development of physician-confirmed Lyme borreliosis (LB)

End point description:

Our primary outcome measure was development of Lyme borreliosis within 6 months after inclusion, in line with the clinical case definitions for Lyme borreliosis described by Stanek et al. 2011.

End point type	Primary

End point timeframe:

Within 6 months after inclusion

End point values	prophylaxis after a tick bite	no-treatment group	modified intention-to-treat prophylaxis group	Per-protocol prophylaxis group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	1754	1090	1041	794
Units: participants with physician-confirmed LB	10	19	10	5

End point values	modified intention-to-treat no-treatment group	Per-protocol no-treatment group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	648	630		
Units: participants with physician-confirmed LB	19	17		

Statistical analyses

Statistical analysis title	modified-intention-to-treat

Statistical analysis description:

For both the modified-intention-to-treat and per-protocol analysis, we used the Newcombe-Wilson method to estimate the absolute risk in both groups, relative risk, relative risk reduction and number-needed-to-treat to prevent one case of Lyme borreliosis.

Comparison groups	modified intention-to-treat prophylaxis group v modified intention-to-treat no-treatment group

Number of subjects included in analysis	1689
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003 [1]
Method	Newcombe-Wilson
Parameter estimate	Risk ratio (RR)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	6.5

Notes:

[1] - This is for the mITT analysis.

Statistical analysis title	per-protocol analysis

Statistical analysis description:

For both the modified-intention-to-treat and per-protocol analysis, we used the Newcombe-Wilson method to estimate the absolute risk in both groups, relative risk, relative risk reduction and number-needed-to-treat to prevent one case of Lyme borreliosis.

Comparison groups	Per-protocol prophylaxis group v Per-protocol no-treatment group
Number of subjects included in analysis	1424
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [2]
Method	Newcombe-Wilson
Parameter estimate	Risk ratio (RR)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.59
upper limit	11.55

Notes:

[2] - This is for the per-protocol analysis.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The IMP being a registered product and given as a single dose, we limited the period of AE collection to one month after exposure, because no related AEs are reasonably expected after that time period.

Adverse event reporting additional description:

There were no SAEs and SUSARs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Prophylaxis group

Reporting group description:

This group was requested to consult their GP for prescription of a single dose of doxycycline, to be taken within 72 h after tick removal. AE's were recorded in the questionnaires at t=1 week and t=1 months after baseline.

Serious adverse events	Prophylaxis group		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1754 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Prophylaxis group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	128 / 1754 (7.30%)		
Gastrointestinal disorders			
Adverse drug reaction	Additional description: PT: Adverse drug reaction SOC: General disorders and administrative site conditions		
subjects affected / exposed	128 / 1754 (7.30%)		
occurrences (all)	128		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 April 2013	In the first 10 days of the study it has occurred around 10 times out of 24 (about 40%) that a potential subject initially agreed on the webportal to consent for participation by clicking 'I agree' (in Dutch: 'Ik ga akkoord'), was then randomized into the treatment group, and subsequently clicked on 'I do not agree' (in Dutch: 'Ik ga niet akkoord'). In most cases subjects indicated that the reason for discontinuation is that they are not able to visit their GP in a timely manner. As we already described in the protocol, we had planned to continue following subjects in the treatment group that do not go and visit their GP, in order to understand whether this group is a confounding factor. We had not foreseen that these subjects would end their participation immediately. We proposed to enable these subjects to remain in the study. In questionnaire 1 on the webportal, 'Tick bite reporting and start participation', an extra announcement is added in case a subject clicks 'Ik ga niet akkoord' after initial 'Ik ga akkoord' and randomization in the treatment group (text translated from Dutch): "You indicate that you do not agree to the declaration of consent after you have been assigned to the treatment group. We would like to ask you to continue to participate in the study. Even if you are not able to or if you do not want to go to the GP for preventive antibiotics, your participation is of great value for the study. You then submit the declaration of consent and your tick, but do not go to the doctor and do not take preventative antibiotics. You complete the follow-up questionnaires by filling in that you do not have taken preventive antibiotics. If you still want to continue with the research, please click "I agree" again above."
03 April 2014	Raising the number of included subjects a. For the sample size calculation a 2% Lyme disease incidence was assumed in the not-treated group. Interim results of the first year seem to indicate that this risk is slightly lower, i.e. 1.8%. In order to compensate for the lower risk and still be able to detect a risk reduction of 58%, the total number of subjects should be increased to 2800 resulting in 1400 evaluable subjects per group. b. A substantial number of the included subjects is not treated according to the randomization assignment. These are referred to as cross-overs. Furthermore some subjects are lost-to-follow-up. The drop-out incidence due to cross-over and lost-to-follow-up turned out to be approximately 35% in the first year: of 1400 randomized subjects, 900 are treated according to protocol. If all drop-outs are to be replaced, the total number of included subjects should be increased to approximately 4200 in order to obtain 1400 subjects in both the treatment and the control groups. The inclusion rate of approximately 1400 subjects in the first year and a total inclusion period of 3.5 years suggests the number to be included is feasible. We propose to include up to a maximum of 4500 subjects to account for inaccuracy in the predicted numbers. Inclusion will be ended earlier if the targeted number of evaluable subjects is achieved.
03 April 2014	Frequency of SAE reporting Some pre-defined SAEs are exempted from expedited reporting and instead reported in a line listing every half year, as described in section 9.2.2 of the protocol. So far no SAEs have been identified in the first year of the study. Therefore we propose to report these SAEs, in the event of any occurring, in the upcoming years of the study together with the annual report.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32565073