Clinical trial results:
“Phase II clinical trial of doxycycline 50 mg or 100 mg daily for the prevention of skin toxicity in patients with metastatic colorectal cancer treated with Anti-EGFR and chemotherapy"

Summary

EudraCT number	2017-004413-98
Trial protocol	ES
Global end of trial date	06 April 2020

Results information

Result version number	v1 (current)
This version publication date	14 June 2021
First version publication date	14 June 2021

Trial information

Trial identification

Sponsor protocol code	DERMIA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03448731
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	APICES SOLUCIONES S.L
Sponsor organisation address	Avenida Antonio López 16, 1ªA, Pinto, Madrid , Spain, 28320
Public contact	Clinical Operations Department, APICES, +34 918166804100, ana.moreno@apices.es
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Sponsor organisation name	Fundación CRIS de Investigación para Vencer el Cáncer
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Scientific contact	Marta Cardona, Fundación CRIS de Investigación para Vencer el Cáncer, +34 91 116 1312, mcardona@criscancer.org

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	25 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 April 2020
Global end of trial reached?	Yes
Global end of trial date	06 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to describe the efficacy of doxycycline 50 or 100 mg daily in the prevention of skin toxicity in patients with metastatic CRC (mCRC) treated with FOLFOX or FOLFIRI + anti-EGFR.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	19
From 65 to 84 years	15

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in the study from 9th May 2018 until 22th january 2020

Pre-assignment

Screening details:

The patients underwent wild-type RAS tumor status analysys before signing the study informed consent form in order to check its eligibility. Patients undergoing FOLFOX or FOLFIRI + anti-EGFR treatment as first-line treatment of mCRC were eligible to receive study treatment.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Study treatment

Arm description:

Patients received doxycycline 50 mg (or 100 mg, if applicable, in the second cohort) daily for 6 weeks beginning on Day -1 (one day before the administration of the first anti-EGFR dose). In a first stage, 10 patients entered the study at a dose of doxycycline 50 mg/day and an interim analysis were performed once 10 patients have finished the 6 weeks of treatment. If more than three patients presented ≥ grade 2 skin toxicities the dose of doxycycline will be increased to 100 mg/day for the next 30 patients to be recruited.

Arm type	Experimental
Investigational medicinal product name	Doxycycline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

50 or 100 mg (if applicable) daily for 6 weeks

Number of subjects in period 1	Study treatment
Started	34
Completed	32
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	34	34	
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)	19	19	
From 65-84 years	15	15	
85 years and over	0	0	
Age continuous Units: years			
median	60.8		
full range (min-max)	39 to 79	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	21	21	
ECOG-PS Units: Subjects			
ECOG-PS 0	28	28	
ECPG-PS 1	5	5	
ECPG-PS 2	1	1	
Initial Diagnosis Per Patient according to location Units: Subjects			
Left colon	13	13	
Rectum	12	12	
Transverse colon	6	6	
Right colon	2	2	
Left colon + Rectum	1	1	
Previous Treatments for Cancer: Surgery Units: Subjects			
Yes	15	15	
No	19	19	
Previous Treatments for Cancer: Radiotherapy Units: Subjects			

Yes	4	4	
No	30	30	
Previous Treatments for Cancer: Chemotherapy Units: Subjects			
XELOX	8	8	
FOLFOX	3	3	
Capecitabine	3	3	
NO	20	20	
Antineoplastic Treatment Administered			
Of the 34 patients with information on the antineoplastic treatment administered, 94.1% (32) indicated as anti-EGFR panitumumab.			
Units: Subjects			
FOLFOX + Panitumumab	27	27	
FOLFIRI + Panitumumab	5	5	
FOLFIRI + Cetuximab	2	2	
Number of Patients Treated with Doxycycline According to Weeks of Treatment Units: Subjects			
Six (6)	32	32	
Four (4)	1	1	
Three (3)	1	1	
Metastatic Diagnosis According to Location: Liver			
Percentages calculated on total patients (N=34). Patients may have more than one metastatic site.			
Units: Subjects			
Yes	27	27	
No	7	7	
Metastatic Diagnosis According to Location: Distant Lymph Nodes			
Percentages calculated on total patients (N=34). Patients may have more than one metastatic site.			
Units: Subjects			
Yes	5	5	
No	29	29	
Metastatic Diagnosis According to Location: Peritoneum			
Percentages calculated on total patients (N=34). Patients may have more than one metastatic site.			
Units: Subjects			
Yes	4	4	
No	30	30	
Metastatic Diagnosis According to Location: Lung			
Percentages calculated on total patients (N=34). Patients may have more than one metastatic site.			
Units: Subjects			
Yes	7	7	
No	27	27	
Weight			
Weight not available in two patients of Doxycycline 100 mg subject analysis set.			
Units: Kg			
median	62.5		
full range (min-max)	51.0 to 120.0	-	
Height			
Height not available in 3 patients of Doxycycline 100 mg subject analysis set.			

Units: Cm			
median	169.0		
full range (min-max)	155.0 to 181.0	-	
Respiratory Frequency			
Respiratory Frequency not available in two patients of Doxycycline 50 mg subject analysys set and four patients of Doxycycline 100 mg subject analysis set.			
Units: Breaths per minute			
median	18.5		
full range (min-max)	12.0 to 28.0	-	
Temperature			
Temperature Not available in three patients of Doxycycline 100 mg subject analysis set.			
Units: °C			
median	36.5		
full range (min-max)	35.5 to 37.0	-	
Systolic Blood Pressure			
Systolic Blood Pressure Not available in two patients of Doxycycline 100 mg subject analysis set.			
Units: mm Hg			
median	130.5		
full range (min-max)	107.0 to 182.0	-	
Diastolic Blood Pressure			
Diastolic Blood Pressure Not available in two patients of doxycycline 100 mg subject analysis set.			
Units: mm Hg			
median	74.0		
full range (min-max)	57.0 to 94.0	-	
Heart Rate			
Heart rate not available in three patients of Doxycycline 100 mg subject analysis set.			
Units: Bpm			
median	74.0		
full range (min-max)	60.0 to 122.0	-	
Time Since Initial Diagnosis			
Units: Months			
median	2.0		
full range (min-max)	0.4 to 53.9	-	
Time Since Metastic Diagnosis			
Time between the date of metastatic diagnosis and the date of informed consent.			
Units: Months			
median	1.5		
full range (min-max)	0.3 to 39.8	-	

Subject analysis sets	
Subject analysis set title	Doxycycline 50 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The 10 patients belonging to this subject analysys set received 50 mg of doxycycline.	
Subject analysis set title	Doxycycline 100 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The 24 patients belonging to this subject analysys set received 100 mg of doxycycline.	

Reporting group values	Doxycycline 50 mg	Doxycycline 100 mg	
Number of subjects	10	24	
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)	6	13	
From 65-84 years	4	11	
85 years and over	0	0	
Age continuous Units: years			
median	57.7	62.0	
full range (min-max)	39.0 to 74.0	43.0 to 79.0	
Gender categorical Units: Subjects			
Female	4	9	
Male	6	15	
ECOG-PS Units: Subjects			
ECOG-PS 0	7	21	
ECPG-PS 1	3	2	
ECPG-PS 2	0	1	
Initial Diagnosis Per Patient according to location Units: Subjects			
Left colon	3	10	
Rectum	5	7	
Transverse colon	1	5	
Right colon	1	1	
Left colon + Rectum	0	1	
Previous Treatments for Cancer: Surgery Units: Subjects			
Yes	5	10	
No	5	14	
Previous Treatments for Cancer: Radiotherapy Units: Subjects			
Yes	1	3	
No	9	21	
Previous Treatments for Cancer: Chemotherapy Units: Subjects			
XELOX	2	6	
FOLFOX	1	2	
Capecitabine	0	3	
NO	7	13	

Antineoplastic Treatment Administered			
Of the 34 patients with information on the antineoplastic treatment administered, 94.1% (32) indicated as anti-EGFR panitumumab.			
Units: Subjects			
FOLFOX + Panitumumab	7	20	
FOLFIRI + Panitumumab	3	2	
FOLFIRI + Cetuximab	0	2	
Number of Patients Treated with Doxycycline According to Weeks of Treatment Units: Subjects			
Six (6)	10	22	
Four (4)	0	1	
Three (3)	0	1	
Metastatic Diagnosis According to Location: Liver			
Percentages calculated on total patients (N=34). Patients may have more than one metastatic site.			
Units: Subjects			
Yes	7	27	
No	3	0	
Metastatic Diagnosis According to Location: Distant Lymph Nodes			
Percentages calculated on total patients (N=34). Patients may have more than one metastatic site.			
Units: Subjects			
Yes	1	5	
No	9	19	
Metastatic Diagnosis According to Location: Peritoneum			
Percentages calculated on total patients (N=34). Patients may have more than one metastatic site.			
Units: Subjects			
Yes	0	4	
No	10	28	
Metastatic Diagnosis According to Location: Lung			
Percentages calculated on total patients (N=34). Patients may have more than one metastatic site.			
Units: Subjects			
Yes	2	7	
No	8	17	
Weight			
Weight not available in two patients of Doxycycline 100 mg subject analysis set.			
Units: Kg			
median	78.0	78.5	
full range (min-max)	63.0 to 105.0	51.0 to 120	
Height			
Height not available in 3 patients of Doxycycline 100 mg subject analysis set.			
Units: Cm			
median	169.0	165.0	
full range (min-max)	160.0 to 181.0	155.0 to 180.0	
Respiratory Frequency			
Respiratory Frequency not available in two patients of Doxycycline 50 mg subject analysys set and four patients of Doxycycline 100 mg subject analysis set.			
Units: Breaths per minute			
median	16.0	18.5	
full range (min-max)	12.0 to 26.0	12.0 to 28.0	

Temperature			
Temperature Not available in three patients of Doxycycline 100 mg subject analysis set.			
Units: °C			
median	36.2	36.5	
full range (min-max)	35.5 to 37.0	36.1 to 37.0	
Systolic Blood Pressure			
Systolic Blood Pressure Not available in two patients of Doxycycline 100 mg subject analysis set.			
Units: mm Hg			
median	124.5	138.0	
full range (min-max)	114.0 to 140.0	107.0 to 182.0	
Diastolic Blood Pressure			
Diastolic Blood Pressure Not available in two patients of doxycycline 100 mg subject analysis set.			
Units: mm Hg			
median	72.0	75.0	
full range (min-max)	65.0 to 81.0	57.0 to 94.0	
Heart Rate			
Heart rate not available in three patients of Doxycycline 100 mg subject analysis set.			
Units: Bpm			
median	70.0	75.0	
full range (min-max)	60.0 to 80.0	62.0 to 122.0	
Time Since Initial Diagnosis Units: Months			
median	1.5	2.2	
full range (min-max)	0.4 to 46.0	0.7 to 53.9	
Time Since Metastic Diagnosis			
Time between the date of metastatic diagnosis and the date of informed consent.			
Units: Months			
median	0.6	1.9	
full range (min-max)	0.3 to 1.9	0.7 to 39.8	

End points

End points reporting groups

Reporting group title	Study treatment
Reporting group description:	
Patients received doxycycline 50 mg (or 100 mg, if applicable, in the second cohort) daily for 6 weeks beginning on Day -1 (one day before the administration of the first anti-EGFR dose). In a first stage, 10 patients entered the study at a dose of doxycycline 50 mg/day and an interim analysis were performed once 10 patients have finished the 6 weeks of treatment. If more than three patients presented ≥ grade 2 skin toxicities the dose of doxycycline will be increased to 100 mg/day for the next 30 patients to be recruited.	
Subject analysis set title	Doxycycline 50 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The 10 patients belonging to this subject analysys set received 50 mg of doxycycline.	
Subject analysis set title	Doxycycline 100 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The 24 patients belonging to this subject analysys set received 100 mg of doxycycline.	

Primary: Percentage of patients who develop skin toxicity (≥ grade 2) during dermatological treatment

End point title	Percentage of patients who develop skin toxicity (≥ grade 2) during dermatological treatment[1]
End point description:	
Efficacy of doxycycine to prevent skin toxicity in patients with metastatic colorectal cancer (mCRC) treated with FOLFOX or FOLFIRI + anti-EGFR.	
End point type	Primary
End point timeframe:	
After 6 weeks treatment doxycycline	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: One arm non-controlled clinical trial. Only descriptive analyses performed. No comparisons.	

End point values	Study treatment	Doxycycline 50 mg	Doxycycline 100 mg	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	10	24	
Units: Patients				
Grade 2	9	5	4	
Grade 3	2	1	1	
Grade ≥ 2	11	6	5	

Statistical analyses

No statistical analyses for this end point

Secondary: Median time to first occurrence of specific skin toxicity (≥ grade 2) during the skin treatment period

End point title	Median time to first occurrence of specific skin toxicity (≥ grade

	2) during the skin treatment period

End point description:

Time to first onset of toxicity has been calculated as the number of days from the start of treatment with doxycycline to the onset of the first grade ≥ 2 skin toxicity during the 6-week treatment period.

End point type	Secondary

End point timeframe:

After 6 weeks of treatment with doxycycline

End point values	Study treatment	Doxycycline 50 mg	Doxycycline 100 mg	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8[2]	10	24	
Units: Days				
median (full range (min-max))	28.0 (14.0 to 34.0)	21.5 (15.0 to 29.0)	28.0 (14.0 to 34.0)	

Notes:

[2] - 8 patients experienced ≥ grade 2 skin toxicities

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from baseline in DLQI score at week 7

End point title	Mean change from baseline in DLQI score at week 7

End point description:

Evaluate the quality of life (QoL) of patients treated with doxycycline, 50 or 100 mg per day. QoL was evaluated using the dermatology life quality index (DLQI) at screening and at week 7.

The following were considered:
- Score 0-1: the skin problem has no effect on the patient's life.
- Score 2-5: the skin problem has a slight effect on the patient's life.
- Score 6-10: the skin problem has a moderate effect on the patient's life.
- Score 11-20: the skin problem has a significant effect on the patient's life.
Score 21-30: the skin problem has an extremely important effect on the patient's life.

End point type	Secondary

End point timeframe:

From baseline to week 7

End point values	Study treatment	Doxycycline 50 mg	Doxycycline 100 mg	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	30	10	20[3]	
Units: Score				
median (full range (min-max))	2.0 (0.0 to 10.0)	2.0 (0.0 to 10.0)	1.5 (0.0 to 5.0)	

Notes:

[3] - 4 patients of doxycycline 100 mg cohort did not have the DLQI questionnaire of week 7.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with grade 1-4 NCI-CTCAE adverse events related to doxycycline.

End point title	Number of patients with grade 1-4 NCI-CTCAE adverse events related to doxycycline.

End point description:

Safety and tolerability of doxycycline was based on all patients that received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From baseline until week 7

End point values	Study treatment	Doxycycline 50 mg	Doxycycline 100 mg	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	10	34	
Units: Patients				
Epigastralgia Grade 1	1	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients who received topical, oral or IV antibiotics to treat skin or nail adverse reactions.

End point title	Number of patients who received topical, oral or IV antibiotics to treat skin or nail adverse reactions.

End point description:

Type of medication for skin or nail indications. Percentages for total number of patients in each group, doxycycline 50 mg/day (N=10), doxycycline 100 mg/day (N=24) and total analysed (N=34). Patients may have received more than one drug to treat skin or nail adverse reactions.

End point type	Secondary

End point timeframe:

From baseline until week 7.

End point values	Study treatment	Doxycycline 50 mg	Doxycycline 100 mg	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	34	10	24	
Units: Skin adverse reaction				
Corticosteroid (Prednicarbate)	5	3	2	
Corticosteroid (Hydrocortisone)	2	2	0	
Corticosteroid (Clobetasol)	1	1	0	

Corticosteroid (Betamethasone)	1	1	0	
Antibacterial (Erythromycin)	3	1	2	
Antibacterial (Mupirocin)	1	0	1	
Antibacterial (Doxycycline)	1	0	1	
Antibacterial (Clindamycin)	1	1	0	
Antibacterial (Fusidic acid)	1	1	0	
Antifungal (Nystatin)	1	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline until end of treatment.

Adverse event reporting additional description:

The analysis of adverse events was performed for total number of patients who received at least one dose of doxycycline treatment. Adverse events were coded using the latest available version of MedDRA dictionary and presented by system organ class (SOC) and preferred term (PT). To obtain adverse events by PT and patient, the maximum grades of each

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Doxycycline 50 mg
Reporting group description: -	
Reporting group title	Doxycycline 100 mg
Reporting group description: -	
Reporting group title	Doxycycline treatment
Reporting group description: -	

Serious adverse events	Doxycycline 50 mg	Doxycycline 100 mg	Doxycycline treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	1 / 24 (4.17%)	3 / 34 (8.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Overdose	Additional description: Overdose grade 1		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic thrombosis	Additional description: Aortic thrombosis grade 4		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea	Additional description: Diarrhoea grade 3		

subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Doxycycline 50 mg	Doxycycline 100 mg	Doxycycline treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	24 / 24 (100.00%)	34 / 34 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma	Additional description: Lipoma grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Vascular disorders			
Hypotension	Additional description: Hypotension grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Epistaxis	Additional description: Epistaxis grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Xerosis	Additional description: 2 Xerosis grade 1		
subjects affected / exposed	2 / 10 (20.00%)	0 / 24 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Mucosal inflammation	Additional description: Doxycycline 50 mg: 4 mucosal inflammation grade 1, 2 grade 2 and 1 grade 3. Doxycycline 100 mg: 5 mucosal inflammation grade 1 and 5 grade 2.		
subjects affected / exposed	7 / 10 (70.00%)	11 / 24 (45.83%)	18 / 34 (52.94%)
occurrences (all)	7	11	18
Asthenia	Additional description: Doxycycline 50 mg: 3 Asthenia grade 1, 2 grade 2 and 1 grade 3. Doxycycline 100 mg: 13 Asthenia grade 1 and 2 grade 2.		
subjects affected / exposed	6 / 10 (60.00%)	15 / 24 (62.50%)	21 / 34 (61.76%)
occurrences (all)	6	15	21
Chest pain	Additional description: Chest pain grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal			

disorders			
Oropharyngeal pain	Additional description: Oropharyngeal pain grade 1		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Bronchospasm	Additional description: Bronchospasm grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Investigations			
Reduced platelet count	Additional description: Reduced platelet count grade 2.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Elevated blood creatinine	Additional description: Elevated blood creatinine grade 2.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Weight loss	Additional description: Weight loss grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Accidental exposure to product	Additional description: Accidental exposure to product grade 1.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Nervous system disorders			
Neurotoxicity	Additional description: Doxycycline 50 mg: 2 neurotoxicity grade 1. Doxycycline 100 mg: 8 neurotoxicity grade 1 and 1 grade 1.		
subjects affected / exposed	2 / 10 (20.00%)	8 / 24 (33.33%)	10 / 34 (29.41%)
occurrences (all)	2	8	10
Peripheral neuropathy	Additional description: Doxycycline 50 mg: Peripheral neuropathy grade 1. Doxycycline 100 mg: Peripheral neuropathy grade 1.		
subjects affected / exposed	1 / 10 (10.00%)	1 / 24 (4.17%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Dysgeusia	Additional description: 1 dysgeusia grade 1 and 1 grade 3.		
subjects affected / exposed	2 / 10 (20.00%)	0 / 24 (0.00%)	2 / 34 (5.88%)
occurrences (all)	2	0	2
Dysaesthesia	Additional description: 3 Dysaesthesia grade 1.		
subjects affected / exposed	3 / 10 (30.00%)	0 / 24 (0.00%)	3 / 34 (8.82%)
occurrences (all)	3	0	3
Syncope	Additional description: Syncope grade 1.		

subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Neutropenia	Additional description: 4 neutropenia grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	4 / 24 (16.67%)	4 / 34 (11.76%)
occurrences (all)	0	4	4
Anaemia	Additional description: 2 anaemia grade 1 and 1 grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	3 / 24 (12.50%)	3 / 34 (8.82%)
occurrences (all)	0	3	3
Eye disorders			
Increased fluid production	Additional description: Increased fluid production grade 1		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Eyelid oedema	Additional description: Eyelid oedema grade 1		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Vomiting	Additional description: Doxycycline 50 mg: 2 Vomiting grade 1, 1 grade 2 and 1 grade 3. Doxycycline 100 mg: Vomiting grade 1		
subjects affected / exposed	4 / 10 (40.00%)	1 / 24 (4.17%)	5 / 34 (14.71%)
occurrences (all)	4	1	1
Aphthous ulcer	Additional description: Doxycycline 50 mg: Aphthous ulcer grade 1 Doxycycline 100 mg: 1 Aphthous ulcer grade 1 and 1 grade 2.		
subjects affected / exposed	1 / 10 (10.00%)	2 / 24 (8.33%)	3 / 34 (8.82%)
occurrences (all)	1	2	3
Nausea	Additional description: Doxycycline 50 mg: 2 Nausea grade 1 and 2 grade 2. Doxycycline 100 mg: 8 Nausea grade 1.		
subjects affected / exposed	4 / 10 (40.00%)	8 / 24 (33.33%)	12 / 34 (35.29%)
occurrences (all)	4	8	12
Constipation	Additional description: Doxycycline 50 mg: 3 constipation grade 1. Doxycycline 100 mg: 6 constipation grade 1.		
subjects affected / exposed	3 / 10 (30.00%)	6 / 24 (25.00%)	9 / 34 (26.47%)
occurrences (all)	3	6	9
Dyspepsia	Additional description: Doxycycline 50 mg: dyspepsia grade 1 Doxycycline 100 mg: dyspepsia grade 1		

subjects affected / exposed	1 / 10 (10.00%)	1 / 24 (4.17%)	2 / 34 (5.88%)
occurrences (all)	1	1	2
Diarrhoea	Additional description: Doxycycline 50 mg: 4 Diarrhoea grade 1 and 1 grade 2. Doxycycline 100 mg: 8 Diarrhoea grade 1 and 2 grade 2.		
subjects affected / exposed	6 / 10 (60.00%)	10 / 24 (41.67%)	16 / 34 (47.06%)
occurrences (all)	6	10	16
Rectal tenesmus	Additional description: Rectal tenesmus grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Stomatitis	Additional description: Stomatitis grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Abdominal pain	Additional description: 4 Abdominal pain grade 1 and 1 grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	5 / 24 (20.83%)	5 / 34 (14.71%)
occurrences (all)	0	5	5
Bloating	Additional description: Bloating grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Frequent defecation	Additional description: Frequent defecation grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Dry skin	Additional description: Doxycycline 50 mg: 1 Dry skin grade 2. Doxycycline 100 mg: 2 Dry skin grade 1.		
subjects affected / exposed	1 / 10 (10.00%)	2 / 24 (8.33%)	3 / 34 (8.82%)
occurrences (all)	1	2	3
Skin fissures	Additional description: Doxycycline 100 mg: 2 Skin fissures grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	2 / 24 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Rash	Additional description: Doxycycline 50 mg: 2 Rash grade 2. Doxycycline 100 mg: 3 Rash grade 1 and 3 grade 2.		
subjects affected / exposed	2 / 10 (20.00%)	6 / 24 (25.00%)	8 / 34 (23.53%)
occurrences (all)	2	6	8
Acneiform dermatitis	Additional description: 2 Acneiform dermatitis grade 2 and 1 grade 3.		
subjects affected / exposed	3 / 10 (30.00%)	0 / 24 (0.00%)	3 / 34 (8.82%)
occurrences (all)	3	0	3
Skin toxicity	Additional description: 2 Skin toxicity grade 1.		

subjects affected / exposed	0 / 10 (0.00%)	2 / 24 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Vulvovaginal pruritus	Additional description: Vulvovaginal pruritus grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Pruritus	Additional description: 2 Pruritus grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	2 / 24 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Skin exfoliation	Additional description: Skin exfoliation grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Erythema	Additional description: Erythema grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Eczema	Additional description: Eczema grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Perioral dermatitis	Additional description: Perioral dermatitis grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Scab	Additional description: Scab grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Acne	Additional description: 2 Acne grade 1 and 1 grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	3 / 24 (12.50%)	3 / 34 (8.82%)
occurrences (all)	0	3	3
Paronychia	Additional description: Paronychia grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Folliculitis	Additional description: 4 Folliculitis grade 1, 1 grade 2 and 1 grade 3.		
subjects affected / exposed	0 / 10 (0.00%)	6 / 24 (25.00%)	6 / 34 (17.65%)
occurrences (all)	0	6	6
Cellulitis	Additional description: Cellulitis grade 3.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	0 / 34 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue			

disorders			
Arthralgia	Additional description: Arthralgia grade 1.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Back pain	Additional description: Back pain grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Infections and infestations			
Rhinitis	Additional description: Rhinitis grade 1.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Oral candidiasis	Additional description: Oral candidiasis grade 1.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Conjunctivitis	Additional description: 2 Conjunctivitis grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	2 / 24 (8.33%)	2 / 34 (5.88%)
occurrences (all)	0	2	2
Metabolism and nutrition disorders			
Hyposideraemia	Additional description: Hyposideraemia grade 1.		
subjects affected / exposed	1 / 10 (10.00%)	0 / 24 (0.00%)	1 / 34 (2.94%)
occurrences (all)	1	0	1
Decreased appetite	Additional description: Doxycycline 50 mg: 1 Decreased appetite grade 1 and 1 grade 2. Doxycycline 100 mg: 5 Decreased appetite grade 1.		
subjects affected / exposed	2 / 10 (20.00%)	5 / 24 (20.83%)	7 / 34 (20.59%)
occurrences (all)	2	5	7
Hypomagnesaemia	Additional description: Hypomagnesaemia grade 1.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1
Hypokalaemia	Additional description: Hypokalaemia grade 2.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 24 (4.17%)	1 / 34 (2.94%)
occurrences (all)	0	1	1

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.

Estimated sample size was not reached, which may affect the accuracy of the study results. Not controlled study design.

Notes: