Clinical trial results:
A randomised controlled trial to compare the safety and effectiveness of doxycycline (200 mg/day) with prednisolone (0.5 mg/kg/day) for initial treatment of bullous pemphigoid

Summary

EudraCT number	2007-006658-24
Trial protocol	GB DE
Global end of trial date	31 October 2014

Results information

Result version number	v1 (current)
This version publication date	10 March 2019
First version publication date	10 March 2019
Summary attachment (see zip file)	A randomised controlled trial to compare the safety, effectiveness and cost-effectiveness of doxycycline (200 mg/day) with that of oral prednisolone (0.5 mg/kg/day) for initial treatment of bullous pe (blister HTA final.pdf)

Trial information

Trial identification

Sponsor protocol code	08024

Additional study identifiers

ISRCTN number	ISRCTN13704604
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Research and Innovation, Jubilee Conference Centre, Triumph Road, Nottingham, United Kingdom, NG8 1DH
Public contact	Professor Hywel Williams, University of Nottingham , +44 1158231048, hywel.williams@nottingham.ac.uk
Scientific contact	Ms Angela Shone, University of Nottingham , +44 1158467906, sponsor@nottingham.ac.uk

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	16 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2014
Global end of trial reached?	Yes
Global end of trial date	31 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To evaluate the effectiveness, safety and cost-effectiveness of a strategy of initiating BP treatment with oral doxycycline or oral prednisolone. We hypothesised that starting treatment with doxycycline gives acceptable short-term blister control while conferring long-term safety advantages over
starting treatment with oral prednisolone.

Protection of trial subjects:

Trial oversight was by a Trial Steering Committee and an independent Data Monitoring Committee. Ethics permission was granted for all participating sites.

Background therapy:

To reflect clinical practice additional application of potent topical corticosteroids (up to 30 g/week, preferably mometasone furoate) to affected areas (or if in the doxycycline arm a switch to oral corticosteroids if symptoms and blister control were inadequate) was permitted except between weeks 3 and 6.
Moisturiser applied to blisters and erosions at any time was permitted.

Evidence for comparator:

Oral prednisolone is thought to be effective at reducing the blisters in BP, but it has many side effects as indicated in previous trials comparing topical corticosteroids with oral corticosteroids (1-3). Doxycycline is perceived to be less effective but probably has fewer side effects.

(1) Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med 2002;346:321–7.http://dx.doi.org/10.1056/NEJMoa011592
(2) Joly P, Roujeau JC, Benichou J, Delaporte E, D'Incan M, Dreno B, et al. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid:
a multicenter randomized study. J Invest Dermatol 2009;129:1681–7. http://dx.doi.org/10.1038/jid.2008.412
(3) Fuertes de Vega I, Iranzo-Fernandez P, Mascaro-Galy JM. Bullous pemphigoid: clinical practiceguidelines. Actas Dermosifiliogr 2014;105:328–46. http://dx.doi.org/10.1016/j.ad.2012.10.022

Actual start date of recruitment	02 March 2009
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	United Kingdom: 241
Country: Number of subjects enrolled	Germany: 12
Worldwide total number of subjects	253
EEA total number of subjects	253

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)	22
From 65 to 84 years	167
85 years and over	64

Subject disposition

Recruitment

Recruitment details:

UK - 1st March 2009 - 31st October 2013
Germany - 1st February 2010 - 31st October 2013

Pre-assignment

Screening details:

Inclusion
Adults capable of consent
Clinical diagnosis of BP
Min 3 significant blisters in past week (at least 2 body sites)
Positive direct or indirect immunofluorescence
No blisters/treatment for BP in past year
Exclusion
Systemic medication for current BP
Oral prednisolone/doxycycline past 12 weeks
Mostly/entirely mucosal pemphigoid

Period 1

Period 1 title	Weeks 0 to 6
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

Investigator and analyst blinded to the treatment allocation for this period

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention: doxycycline

Arm description:

200 mg/day of doxycycline taken as a single, daily dose (brand not specified).

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

Dosage and administration details:

200 mg/day of doxycycline taken as a single, daily dose (brand not specified).

Arm title	Comparator: prednisolone

Arm description:

0.5 mg/kg/day of prednisolone taken as a single, daily dose (brand not specified).

Arm type	Active comparator
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg/kg/day of prednisolone taken as a single, daily dose (brand not specified).

Number of subjects in period 1	Intervention: doxycycline	Comparator: prednisolone
Started	132	121
Completed	112	101
Not completed	20	20
Consent withdrawn by subject	16	10
Died prior to visit	2	5
Missed assessment	2	5

Period 2

Period 2 title	Weeks 7 to 52
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention: doxycycline

Arm description:

200 mg/day of doxycycline taken as a single, daily dose (brand not specified).

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

Dosage and administration details:

200 mg/day of doxycycline taken as a single, daily dose (brand not specified).

Arm title	Comparison: prednisolone

Arm description:

0.5 mg/kg/day of prednisolone taken as a single, daily dose (brand not specified).

Arm type	Active comparator
Investigational medicinal product name	Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg/kg/day of prednisolone taken as a single, daily dose (brand not specified).

Number of subjects in period 2	Intervention: doxycycline	Comparison: prednisolone
Started	112	101
Completed	78	78
Not completed	36	28
Consent withdrawn by subject	20	13
Died prior to visit	12	14
Lost to follow-up	4	1
Joined	2	5
Missed visit period 1	2	5

Baseline characteristics

Reporting groups

Reporting group title	Intervention: doxycycline
Reporting group description:	
200 mg/day of doxycycline taken as a single, daily dose (brand not specified).	
Reporting group title	Comparator: prednisolone
Reporting group description:	
0.5 mg/kg/day of prednisolone taken as a single, daily dose (brand not specified).	

Reporting group values	Intervention: doxycycline	Comparator: prednisolone	Total
Number of subjects	132	121	253
Age categorical			
Age at entry to period 1			
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)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	14	22
From 65-84 years	89	78	167
85 years and over	35	29	64
Gender categorical Units: Subjects			
Female	63	57	120
Male	69	64	133

Subject analysis sets

Subject analysis set title	Period 1 Difference pred-doxy week 6 success
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Non-inferiority comparison, week 6. Treatment success defined as 3 or fewer blisters at week 6 regardless of treatment modification. Percentage difference between prednislone and doxycylcine	
Subject analysis set title	Primary Safety outcome: proportion difference
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Superiority comparison. The proportion of participants with grade 3 (severe), 4 (life-threatening) and 5 (death) adverse events that were possibly, probably or definitely related to the treatment in the 52 weeks following randomisation, comparison prednisolone - doxycycline.	

Reporting group values	Period 1 Difference pred-doxy week 6 success	Primary Safety outcome: proportion difference	
Number of subjects	169	234	

Age categorical			
Age at entry to period 1			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)			
From 65-84 years			
85 years and over			
Gender categorical			
Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Intervention: doxycycline
Reporting group description:	
200 mg/day of doxycycline taken as a single, daily dose (brand not specified).	
Reporting group title	Comparator: prednisolone
Reporting group description:	
0.5 mg/kg/day of prednisolone taken as a single, daily dose (brand not specified).	
Reporting group title	Intervention: doxycycline
Reporting group description:	
200 mg/day of doxycycline taken as a single, daily dose (brand not specified).	
Reporting group title	Comparison: prednisolone
Reporting group description:	
0.5 mg/kg/day of prednisolone taken as a single, daily dose (brand not specified).	
Subject analysis set title	Period 1 Difference pred-doxy week 6 success
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Non-inferiority comparison, week 6. Treatment success defined as 3 or fewer blisters at week 6 regardless of treatment modification. Percentage difference between prednislone and doxycylcine	
Subject analysis set title	Primary Safety outcome: proportion difference
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Superiority comparison. The proportion of participants with grade 3 (severe), 4 (life-threatening) and 5 (death) adverse events that were possibly, probably or definitely related to the treatment in the 52 weeks following randomisation, comparison prednisolone - doxycycline.	

Primary: Primary endpoint: Three or less blisters at 6 weeks

End point title	Primary endpoint: Three or less blisters at 6 weeks
End point description:	
Proportion of participants who achieved treatment success (three or less blisters) at 6 weeks	
End point type	Primary
End point timeframe:	
Treatment success at 6 weeks	

End point values	Intervention: doxycycline	Comparator: prednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	101		
Units: Percentage	78	91		

Statistical analyses

Statistical analysis title	Difference in proportions: prednis - doxycycli
Comparison groups	Intervention: doxycycline v Comparator: prednisolone

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	18.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	9.8
upper limit	27.6
Variability estimate	Standard error of the mean

Primary: Primary endpoint: proportion of grade 3 or above AEs 52 weeks

End point title	Primary endpoint: proportion of grade 3 or above AEs 52 weeks
End point description:	
Grade 3, 4 and 5 side effects (treatment-related severe, life-threatening or fatal (as per CTC criteria) v3.0 by 52 weeks	
End point type	Primary
End point timeframe:	
52 weeks	

End point values	Intervention: doxycycline	Comparison: prednisolone	Primary Safety outcome: proportion difference	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	112	101	234	
Units: Percentage	112	101	234	

Statistical analyses

Statistical analysis title	Primary o/c: period 2, week 52, superiorty compar
Comparison groups	Intervention: doxycycline v Comparison: prednisolone v Primary Safety outcome: proportion difference
Number of subjects included in analysis	447
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	18.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	6
upper limit	30.85

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 0-52	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Individual adverse vents were not reported. Grade categorisation of all adverse events were collected and analysed as part of the primary safety outcome. Details in the attached summary paper.

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

None reported