Clinical trial results:
A randomised controlled trial to compare the clinical effectiveness and safety of gentamicin and ceftriaxone in the treatment of gonorrhoea.

Summary

EudraCT number	2014-001823-56
Trial protocol	GB
Global end of trial date	20 January 2017

Results information

Result version number	v1 (current)
This version publication date	26 January 2020
First version publication date	26 January 2020

Trial information

Trial identification

Sponsor protocol code	RRK5104

Additional study identifiers

ISRCTN number	ISRCTN51783227
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Birmingham NHS Foundation Trust
Sponsor organisation address	Queen Elizabeth Hospital Birmingham, Middelsohn Way, Birmingham, United Kingdom, B15 2WB
Public contact	G-ToG Study manager, Nottingham Clinical Trials Unit, g-tog@nottingham.ac.uk
Scientific contact	G-ToG Study manager, Nottingham Clinical Trials Unit, g-tog@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	22 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 January 2017
Global end of trial reached?	Yes
Global end of trial date	20 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principle objective of the study is to determine whether gentamicin is an acceptable alternative to ceftriaxone, in the treatment of gonorrhoea. This will be done by determining whether the clearance rate of gonorrheoa in participants receiving gentamicin is no worse than the rate in participants receiving ceftriaxone. In parallel, the safety of both treatments will be assessed.

Protection of trial subjects:

In previous trials a 240 mg dose of gentamicin was most commonly used and the use of different doses has not demonstrated a significant dose-response effect across studies. The dose of ceftriaxone was chosen to be consistent with current UK gonorrhoea treatment guidelines 29.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2014
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: 720
Worldwide total number of subjects	720
EEA total number of subjects	720

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)	13
Adults (18-64 years)	701
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment, across 14 sexual health clinics in England, commenced in October 2014 and continued until November 2016 when the recruitment target was met.

Pre-assignment

Screening details:

1762 participants who had a provisional or confirmed diagnosis of gonorrhoea were asked if they were interested in participating in the study. If they indicated interest, an appropriately qualified member of the research team provided them with a patient information leaflet, explained the study procedures.

Period 1

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

Blinding implementation details:

Only the nurse/doctor administering the treatment will know what treatment the participant has been randomised to. Members of the research team who are aware of the treatment allocation will not have any role in data collection. The participant and staff involved in the care and assessment of the participant will not know what treatment they have been randomised to. This should ensure the minimisation of any bias in assessment due to knowledge of the treatment administered.

Arms

Are arms mutually exclusive?	Yes
Arm title	gentamicin

Arm description:

- Gentamicin (240mg) administered as a single intramuscular injection.

Arm type	Experimental
Investigational medicinal product name	gentamicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

a single intramuscular injection (IM) of gentamicin (240mg)

Arm title	ceftriaxone

Arm description:

- Ceftriaxone (500mg) administered as a single intramuscular injection.

Arm type	Active comparator
Investigational medicinal product name	ceftriaxone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

a single dose (500mg) of intramuscular injection

Number of subjects in period 1	gentamicin	ceftriaxone
Started	358	362
Completed	358	362

Baseline characteristics

Reporting groups	
Reporting group title	gentamicin
Reporting group description:	
• Gentamicin (240mg) administered as a single intramuscular injection.	
Reporting group title	ceftriaxone
Reporting group description:	
• Ceftriaxone (500mg) administered as a single intramuscular injection.	

Reporting group values	gentamicin	ceftriaxone	Total
Number of subjects	358	362	720
Age categorical 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)	6	7	13
Adults (18-64 years)	350	351	701
From 65-84 years	2	4	6
85 years and over	0	0	0
Age continuous			
summary of age at randomisation in years			
Units: years			
arithmetic mean	30.4	30.2	
standard deviation	± 9.9	± 10.1	-
Gender categorical			
summary of gender			
Units: Subjects			
Female	66	69	135
Male	292	293	585

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
number of participants randomised, without imputation of missing data	

Reporting group values	ITT		
Number of subjects	720		
Age categorical 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)	13		
Adults (18-64 years)	701		
From 65-84 years	6		
85 years and over	0		
Age continuous			
summary of age at randomisation in years			
Units: years			
arithmetic mean	30.3		
standard deviation	± 10		
Gender categorical			
summary of gender			
Units: Subjects			
Female	135		
Male	585		

End points

End points reporting groups

Reporting group title	gentamicin
Reporting group description:	
• Gentamicin (240mg) administered as a single intramuscular injection.	
Reporting group title	ceftriaxone
Reporting group description:	
• Ceftriaxone (500mg) administered as a single intramuscular injection.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
number of participants randomised, without imputation of missing data	

Primary: Clearance of gonorrhoeae at 2 weeks

End point title	Clearance of gonorrhoeae at 2 weeks
End point description:	
The primary outcome measure is clearance of N. gonorrhoeae at all infected sites confirmed by a negative NAAT, two weeks post treatment (as recommended by the British Association for Sexual Health and HIV). The results from the AC NAAT will be considered primary. Infection sites include genital, rectal and pharyngeal sites. Note that urine and urethra are interchangeable genital samples and as are vagina and cervix.	
End point type	Primary
End point timeframe:	
gonorrhoeae clearance at 2 weeks post randomisation	

End point values	gentamicin	ceftriaxone	ITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	292	306	598	
Units: number	267	299	566	

Statistical analyses

Statistical analysis title	generalised estimating equations
Statistical analysis description:	
The primary approach to between-group comparative analyses will be by intention-to-treat without imputation of missing outcome data for clearance of gonorrhoea at 2 weeks. The evaluation of the proportion of participants with clearance of gonorrhoea at 2 weeks will be performed using a generalised estimating equations (GEE) for binary outcomes adjusted by recruiting centre as a random effect.	
Comparison groups	ceftriaxone v gentamicin

Number of subjects included in analysis	598
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.002
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	-0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	-0.024
Variability estimate	Standard error of the mean

Notes:

[1] - Gentamicin will be regarded as non-inferior if the lower 95% confidence limit for the risk difference (Gentamicin group versus Ceftriaxone group) in confirmed clearance is -5 percentage points or greater.

Secondary: resolution of symptom (genital discharge)

End point title	resolution of symptom (genital discharge)

End point description:

End point type	Secondary

End point timeframe:

at 2 weeks post randomisation

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	129		
Units: number	139	122		

Statistical analyses

Statistical analysis title	generalised estimating equations
Comparison groups	gentamicin v ceftriaxone
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	-0.001
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.055
upper limit	0.052

Secondary: resolution of symptom (dysuria)	
End point title	resolution of symptom (dysuria)
End point description:	

End point type	Secondary
End point timeframe:	
2 weeks post randomisaiton	

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	106		
Units: number	116	104		

Statistical analyses

Statistical analysis title	generalised estimating equations
Comparison groups	gentamicin v ceftriaxone
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	-0.077
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.136
upper limit	0.019

Secondary: resolution of symptom (anorectal pain)	
End point title	resolution of symptom (anorectal pain)
End point description:	

End point type	Secondary
End point timeframe:	
2 weeks post randomisation	

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	13		
Units: number	5	12		

Statistical analyses

Statistical analysis title	generalised estimating equations
Comparison groups	gentamicin v ceftriaxone
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	-0.244
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.625
upper limit	0.137

Secondary: resolution of symptom (sore thoat)

End point title	resolution of symptom (sore thoat)

End point description:

End point type	Secondary

End point timeframe:

2 weeks post randomisation

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	45	47		
Units: number	42	42		

Statistical analyses

Statistical analysis title	generalised estimating equations
Comparison groups	gentamicin v ceftriaxone
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.074
upper limit	0.154

Secondary: resolution of symptom (rectal bleeding)	
End point title	resolution of symptom (rectal bleeding)
End point description:	
End point type	Secondary
End point timeframe:	
2 weeks post randomisation	

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: number	7	7		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	gentamicin v ceftriaxone
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.125

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	0.354

Secondary: resolution of symptom (rectal discharge)

End point title	resolution of symptom (rectal discharge)
End point description:	

End point type	Secondary
End point timeframe:	
2 weeks post randomisation	

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	12		
Units: number	6	11		

Statistical analyses

Statistical analysis title	generalised estimating equations
Comparison groups	gentamicin v ceftriaxone
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	-0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.437
upper limit	0.239

Secondary: resolution of symptom (tenesmus)

End point title	resolution of symptom (tenesmus)
End point description:	

End point type	Secondary

End point timeframe:
2 weeks post randomisation

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: number	3	7		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	gentamicin v ceftriaxone
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.104
upper limit	0.354

Secondary: resolution of symptom (intermentrual bleeding)

End point title	resolution of symptom (intermentrual bleeding)

End point description:

End point type	Secondary

End point timeframe:
2 weeks post randomisation

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	9		
Units: number	5	8		

Statistical analyses

Statistical analysis title	Fisher's exact test
Comparison groups	gentamicin v ceftriaxone
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.111
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.094
upper limit	0.316

Secondary: resolution of symptom (constipation)	
End point title	resolution of symptom (constipation)
End point description:	
End point type	Secondary
End point timeframe:	
2 weeks post rando	

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: number	3	10		

Statistical analyses

Statistical analysis title	generalised estimating equations
Comparison groups	ceftriaxone v gentamicin
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Risk difference (RD)
Point estimate	-0.126

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.578
upper limit	0.326

Secondary: side effect (nausea)

End point title	side effect (nausea)

End point description:

End point type	Secondary

End point timeframe:

2 weeks post rando

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	320		
Units: number	41	38		

Statistical analyses

No statistical analyses for this end point

Secondary: side effect (vomitting)

End point title	side effect (vomitting)

End point description:

End point type	Secondary

End point timeframe:

2 weeks post rando

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	320		
Units: number	12	3		

Statistical analyses

No statistical analyses for this end point

Secondary: side effect (reduction in hearing)

End point title	side effect (reduction in hearing)

End point description:

End point type	Secondary

End point timeframe:

2 weeks post rando

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	320		
Units: number	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: side effect (dizziness and unsteadiness)

End point title	side effect (dizziness and unsteadiness)

End point description:

End point type	Secondary

End point timeframe:

2 weeks post rando

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	320		
Units: number	21	24		

Statistical analyses

No statistical analyses for this end point

Secondary: side effect (skin rash)

End point title	side effect (skin rash)

End point description:

End point type	Secondary

End point timeframe:

2 weeks post rando

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	320		
Units: number	12	5		

Statistical analyses

No statistical analyses for this end point

Secondary: side effect (injection pain)

End point title	side effect (injection pain)

End point description:

End point type	Secondary

End point timeframe:

2 weeks post rando

End point values	gentamicin	ceftriaxone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	320		
Units: number	294	315		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 2 weeks post randomisation	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1
Reporting groups	
Reporting group title	gentamicin
Reporting group description: -	
Reporting group title	ceftriaxone
Reporting group description: -	

Serious adverse events	gentamicin	ceftriaxone	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 298 (0.00%)	1 / 320 (0.31%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 298 (0.00%)	1 / 320 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	gentamicin	ceftriaxone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 298 (12.75%)	48 / 320 (15.00%)	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	3 / 298 (1.01%)	10 / 320 (3.13%)	
occurrences (all)	3	10	
General disorders and administration site conditions			
general disorder			

subjects affected / exposed	3 / 298 (1.01%)	6 / 320 (1.88%)	
occurrences (all)	3	6	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed[1]	22 / 298 (7.38%)	14 / 230 (6.09%)	
occurrences (all)	22	14	
Infections and infestations			
infection and infestations			
subjects affected / exposed	5 / 298 (1.68%)	6 / 320 (1.88%)	
occurrences (all)	5	6	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.
Justification: number exposed for reporting group is the total randomised however number exposed to adverse event is the total who received treatment as randomised and who provided adverse event information at 2 week follow up.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2014	Summary of changes: • Inclusion/exclusion criteria amended to clarify meaning of untreated gonorrhoea, exclude patients with bacterial vaginosis and Trichomonas vaginalis and diagnosis of gonorrhoea must be within 4 weeks of trial entry • Removal of the pharmacokinetic sub-study • Clarification of Visit 2 timelines (as close as possible to 14 days, not before, but up to Day 60) • SAE reporting required for events of dizziness and hearing loss of grade 3 or above,

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported