Clinical trial results:
A randomised controlled trial to assess the clinical and cost effectiveness of topical lactic acid gel for treating second and subsequent episodes of bacterial vaginosis

Summary

EudraCT number	2016-004483-19
Trial protocol	GB
Global end of trial date	26 February 2020

Results information

Result version number	v1 (current)
This version publication date	18 December 2021
First version publication date	18 December 2021

Trial information

Trial identification

Sponsor protocol code	RRK5908

Additional study identifiers

ISRCTN number	ISRCTN14161293
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals Birmingham NHS Foundation Trust
Sponsor organisation address	1st Floor Institute of Translational Medicine, Mindelsohn Way, Edgbaston, Birmingham, United Kingdom, B15 2TH
Public contact	VITA Trial Manager, Nottingham Clinical Trials Unit, vita@nottingham.ac.uk
Scientific contact	Professor Jonathan Ross (Chief Investigator for VITA trial), University Hospitals Birmingham NHS Foundation Trust, Jonathan.Ross@uhb.nhs.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	04 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 February 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The principle objective of the study is to determine whether intravaginal lactic acid gel is better than oral metronidazole for symptomatic resolution of recurrent bacterial vaginosis.

Protection of trial subjects:

None required.

Background therapy:

None.

Evidence for comparator:

The control group received a 7 day course of twice daily 400mg oral metronidazole. This was chosen as the comparator because it is recommended as first line therapy in the UK national BV treatment guideline, active against a wide range of the anaerobic bacteria associated with BV, and commonly used in clinical practice supported by evidence from randomised controlled trials.

Actual start date of recruitment	01 September 2017
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: 518
Worldwide total number of subjects	518
EEA total number of subjects	0

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)	3
Adults (18-64 years)	515
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between October 2017 and June 2019. The original planned end of recruitment was November 2019. Recruitment finished early after the DMC reviewed unblinded trial data at a planned meeting, and recommended early stopping as the primary question had been answered; this was agreed by the TSC. There were no safety concerns.

Pre-assignment

Screening details:

3141 approached. Of these 2618 did not participate: Did not have history of BV = 695; Receiving antibiotics/antifungals = 418; Not interested = 248; Using topical antibiotics/antifungals = 209; Takes too much time = 192; No staff available = 178; No current clinical diagnosis of BV = 83; Other = 595.

Pre-assignment period milestones

Number of subjects started	3141[1]
Number of subjects completed	518

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Did not participate: 2618
Reason: Number of subjects	inclusion criteria: 3

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: These are the numbers initially approached; less people took part in the trial for the reasons given.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Data analyst[2]

Blinding implementation details:

Data analyst remained blinded until after database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Metronidazole

Arm description:

Metronidazole tablets; 400 mg to be taken orally twice daily, approximately 12 hours apart, for 7 days.

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

Dosage and administration details:

Metronidazole tablets; 400 mg to be taken orally twice daily, approximately 12 hours apart, for 7 days.

Arm title	Intravaginal lactic acid gel

Arm description:

Lactic acid gel; 5ml to be inserted into the vagina before bedtime each day for 7 days.

Arm type	Experimental
Investigational medicinal product name	Lactic acid gel 5ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Vaginal gel
Routes of administration	Vaginal use

Dosage and administration details:

5ml gel administered through an intravaginal tube applicator, once daily before bed, for 7 days

Notes:

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This is an open label trial, but the analysing statistician and laboratory staff remained blinded to treatment until after the database lock.

Number of subjects in period 1	Metronidazole	Intravaginal lactic acid gel
Started	259	259
week 2	258	257
month 3	256	256
month 6	256	256
Completed	256	256
Not completed	3	3
Consent withdrawn by subject	3	2
Dissatisfied with efficacy of treatment	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Metronidazole
Reporting group description:	
Metronidazole tablets; 400 mg to be taken orally twice daily, approximately 12 hours apart, for 7 days.	
Reporting group title	Intravaginal lactic acid gel
Reporting group description:	
Lactic acid gel; 5ml to be inserted into the vagina before bedtime each day for 7 days.	

Reporting group values	Metronidazole	Intravaginal lactic acid gel	Total
Number of subjects	259	259	518
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)	3	0	3
Adults (18-64 years)	256	259	515
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Age at consent (must be at least 16)			
Units: years			
arithmetic mean	29.0	29.4	
standard deviation	± 8.41	± 8.12	-
Gender categorical Units: Subjects			
Female	259	259	518
Male	0	0	0
Ethnicity			
Categories were combined to aid anonymity.			
Units: Subjects			
White	125	126	251
Black	89	78	167
Other	45	54	99
Not recorded	0	1	1

End points

End points reporting groups

Reporting group title	Metronidazole
Reporting group description:	
Metronidazole tablets; 400 mg to be taken orally twice daily, approximately 12 hours apart, for 7 days.	
Reporting group title	Intravaginal lactic acid gel
Reporting group description:	
Lactic acid gel; 5ml to be inserted into the vagina before bedtime each day for 7 days.	
Subject analysis set title	Safety set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Treatment received at baseline (metronidazole or lactic acid gel)	
Subject analysis set title	As randomised
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants analysed as randomised (metronidazole or lactic acid gel)	

Primary: Resolution of BV symptoms by week 2

End point title	Resolution of BV symptoms by week 2
End point description:	
BV symptoms resolved within 2 weeks (yes/no)	
End point type	Primary
End point timeframe:	
Week 2 (within 2 weeks of starting treatment)	

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	204[1]	205[2]		
Units: people				
yes	143	97		
no	61	108		

Notes:

[1] - Treatment as randomised, responses by questionnaire and phonecall.

[2] - Treatment as randomised, responses by questionnaire and phonecall

Statistical analyses

Statistical analysis title	Primary outcome adjusted risk difference
Statistical analysis description:	
A generalised estimating equation with site as panel variable and adjusted for number of BV episodes in 12 months before baseline (0, 1-3, >3) and female partner in 12 months before baseline (yes/no).	
Comparison groups	Metronidazole v Intravaginal lactic acid gel

Number of subjects included in analysis	409
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted risk difference
Point estimate	-23.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.3
upper limit	-14
Variability estimate	Standard error of the mean

Secondary: Time to first recurrence of BV

End point title	Time to first recurrence of BV

End point description:

A new episode of BV symptoms in those whose BV symptoms resolved within 2 weeks of starting treatment.

Note: in the analysis the upper confidence bound that was not calculable, due to the censored observations, has been represented by 99999 since the system would not allow it to be left blank.

End point type	Secondary

End point timeframe:

Between 2 weeks and 6 months

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73[3]	50[4]		
Units: days				
median (confidence interval 95%)	92 (71 to 188)	124 (74 to 99999)		

Notes:

[3] - As randomised. Data from questionnaires

[4] - As randomised, data from questionnaires.

Attachments (see zip file)	Kaplan Meier plot: time to recurrence of symptoms/VITA

Statistical analyses

No statistical analyses for this end point

Secondary: Number of episodes of BV symptoms within 6 months

End point title	Number of episodes of BV symptoms within 6 months

End point description:

Number of new episodes of BV symptoms within 6 months for participants whose symptoms resolved within 2 weeks

End point type	Secondary

End point timeframe:

2 weeks to 6 months

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[5]	29[6]		
Units: episodes				
median (inter-quartile range (Q1-Q3))	1 (0 to 3)	1 (0 to 2)		

Notes:

[5] - Only those with episode data at both 3 and 6 months are included.

[6] - Only those with episode data at both 3 and 6 months are included.

Statistical analyses

Statistical analysis title	Comparison of number of new episodes

Statistical analysis description:

Negative binomial regression presenting adjusted incidence rate ratio. Adjusted for: site, number of BV episodes in 12 months before baseline, female partner in 12 months before baseline

Comparison groups	Metronidazole v Intravaginal lactic acid gel
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	Adjusted incidence rate ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.69

Notes:

[7] - Uses medians. Only CI, not p-values presented.

Secondary: Number of BV treatment courses within 6 months

End point title	Number of BV treatment courses within 6 months

End point description:

Number of participant reported BV treatment courses between week 2 and 6 months per participant, for those who resolved by 2 weeks and had treatment data at both 3 and 6 months.

End point type	Secondary

End point timeframe:

2 weeks to 6 months

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	35		
Units: treatment course				
median (inter-quartile range (Q1-Q3))	1 (0 to 3)	1 (0 to 2)		

Statistical analyses

Statistical analysis title	Comparison of number of BV treatment courses
Statistical analysis description:	
Negative binomial regression, presenting adjusted incidence rate ratio. Adjusted for: site, number of BV episodes in 12 months before baseline, female partners in 12 months before baseline.	
Comparison groups	Metronidazole v Intravaginal lactic acid gel
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted incidence rate ratio
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	2.01

Secondary: Microbiological resolution of BV at week 2

End point title	Microbiological resolution of BV at week 2
End point description:	
Microbiological resolution of BV (grade 0, 1, 2 or U) on microscopy of vaginal smears at Week 2 in those with positive baseline smear for BV (grade 3) using central lab results	
End point type	Secondary
End point timeframe:	
week 2, for those with microbiologically confirmed BV (Ison-Hay 3) at baseline	

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	73		
Units: people				
yes	59	31		
no	18	42		

Statistical analyses

Statistical analysis title	Comparison of microbiological resolution of BV

Statistical analysis description:

Generalised estimating equation adjusted for: site and female partners in in 12 months before baseline; adding number of episodes in 12 months before baseline or vaginal douching causes the analysis to not converge.

Comparison groups	Metronidazole v Intravaginal lactic acid gel
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted risk difference
Point estimate	-34.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-49.1
upper limit	-19.5

Secondary: Prevalence of STIs at week 2

End point title	Prevalence of STIs at week 2

End point description:

STIs included are gonorrhoea, chlamydia and trichomoniasis. Yes= have at least one of these STIs. Only includes data from sample kits that were known to be in date.

End point type	Secondary

End point timeframe:

week 2

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108	111		
Units: people				
yes	5	1		
no	103	110		

Statistical analyses

Statistical analysis title	Analysis of prevalence of STI at Week 2

Statistical analysis description:

logit model adjusted for: site (panel variable) and baseline STI (12 in the metronidazole group and 3 in the lactic acid group); these are the only covariates that can be included without collinearity problems.

Comparison groups	Metronidazole v Intravaginal lactic acid gel

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted odds ratio
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	1.6

Secondary: Time to resolution of BV symptoms

End point title	Time to resolution of BV symptoms
End point description:	
Time in days to resolution of BV symptoms.	
End point type	Secondary
End point timeframe:	
6 months	

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	192[8]	179[9]		
Units: days				
median (standard error)	14 (± 0.65)	14 (± 3.41)		

Notes:

[8] - Where resolution known, but date missing time substituted with 14. If not yet resolved time censored

[9] - Where resolution known, but date missing time substituted with 14. If not yet resolved time censored

Statistical analyses

Statistical analysis title	Analysis: median time to resolution of BV symptoms
Statistical analysis description:	
quantile (median) regression adjusted for: site, number of BV episodes in 12 months before baseline, female partner in 12 months before baseline, vaginal douching	
Comparison groups	Metronidazole v Intravaginal lactic acid gel
Number of subjects included in analysis	371
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted median difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	1.9

Secondary: Nausea

End point title	Nausea

End point description:

Nausea in the first 2 weeks as reported on the week 2 participant questionnaire. Incidence, severity, start time, duration and resolution were also reported, but only incidence given here.
Treatment as received.

End point type	Secondary

End point timeframe:

first 2 weeks

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	157		
Units: people				
yes	50	13		
no	103	144		

Statistical analyses

No statistical analyses for this end point

Secondary: vomiting

End point title	vomiting

End point description:

Vomiting in the first 2 weeks as reported on the week 2 participant questionnaire. Incidence, severity, start time, duration and resolution were also reported, but only incidence given here.
Treatment as received.

End point type	Secondary

End point timeframe:

first 2 weeks

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	154		
Units: people				
yes	9	2		
no	141	152		

Statistical analyses

No statistical analyses for this end point

Secondary: Taste changes

End point title	Taste changes

End point description:

Taste changes in the first 2 weeks as reported on the week 2 participant questionnaire. Incidence, severity, start time, duration and resolution were also reported, but only incidence given here. Treatment as received.

End point type	Secondary

End point timeframe:

first 2 weeks

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	158		
Units: people				
yes	28	2		
no	127	156		

Statistical analyses

No statistical analyses for this end point

Secondary: Vaginal irritation

End point title	Vaginal irritation

End point description:

Vaginal irritation in the first 2 weeks as reported on the week 2 participant questionnaire. Incidence, severity, start time, duration and resolution were also reported, but only incidence given here. Treatment as received.

End point type	Secondary

End point timeframe:

within 2 weeks

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: people				
yes	44	34		
no	110	125		

Statistical analyses

No statistical analyses for this end point

Secondary: Abdominal pain

End point title	Abdominal pain

End point description:

Abdominal pain in the first 2 weeks as reported on the week 2 participant questionnaire. Incidence, severity, start time, duration and resolution were also reported, but only incidence given here. Treatment as received.

End point type	Secondary

End point timeframe:

within 2 weeks

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: people				
yes	31	27		
no	123	132		

Statistical analyses

No statistical analyses for this end point

Secondary: Diarrhoea

End point title	Diarrhoea

End point description:

Diarrhoea in the first 2 weeks as reported on the week 2 participant questionnaire. Incidence, severity, start time, duration and resolution were also reported, but only incidence given here. Treatment as received.

End point type	Secondary

End point timeframe:

within 2 weeks

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	159		
Units: people				
yes	31	9		
no	123	150		

Statistical analyses

No statistical analyses for this end point

Secondary: Adherence to treatment

End point title	Adherence to treatment

End point description:

Percentage of treatment received - out of 14 possible doses of metronidazole and 7 of lactic acid - participant reported by questionnaire.
Treatment as received.

End point type	Secondary

End point timeframe:

7 days of treatment (usually starting on day of randomisation)

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	161		
Units: percentage				
arithmetic mean (standard deviation)	94 (± 18.4)	95 (± 12.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality adjusted life years

End point title	Quality adjusted life years

End point description:

SF-6D utility scores were derived from the SF12 responses at baseline, 2 weeks, 3 months and 6 months, and used to obtain QALYs.

End point type	Secondary

End point timeframe:

over 6 months

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	48		
Units: years				
arithmetic mean (standard deviation)	0.351 (± 0.030)	0.348 (± 0.028)		

Statistical analyses

Statistical analysis title	Comparison of QALYs

Statistical analysis description:

Health outcomes (QALYs) were compared between treatment groups, in an ITT analysis of cost utility.

Comparison groups	Metronidazole v Intravaginal lactic acid gel
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference
Point estimate	-0.003
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.013
upper limit	0.009

Secondary: Mean cost per participant at 6 months

End point title	Mean cost per participant at 6 months

End point description:

Mean cost per participant at 6 months (Comparative cost effectiveness of using intravaginal lactic acid gel versus oral metronidazole tablets at 6 months).
No analysis: Cost per QALY gained not presented as ICER dominated (intravaginal lactic acid gel was found to be less effective and more costly than metronidazole at 6 months)

End point type	Secondary

End point timeframe:

6 months

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	54		
Units: pounds sterling				
arithmetic mean (standard deviation)	214.48 (± 302.45)	273.08 (± 366.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cost per participant

End point title	Cost per participant

End point description:

Cost per participant
(Comparative cost effectiveness of using intravaginal lactic acid gel versus oral metronidazole tablets at 2 weeks)

End point type	Secondary

End point timeframe:

2 weeks

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	143	151		
Units: Pounds sterling				
arithmetic mean (standard deviation)	48.00 (± 112.68)	55.38 (± 134.89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cost per participant with resolved BV

End point title	Cost per participant with resolved BV

End point description:

Cost per participant with resolved BV (Comparative cost effectiveness of using intravaginal lactic acid gel versus oral metronidazole tablets at 2 weeks)

End point type	Secondary

End point timeframe:

2 weeks

End point values	Metronidazole	Intravaginal lactic acid gel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	259	259		
Units: Pounds sterling				
arithmetic mean (confidence interval 95%)	86.94 (2.16 to 331.83)	147.00 (3.29 to 548.04)		

Statistical analyses

Statistical analysis title	Cost-effectiveness comparison

Statistical analysis description:

Difference in cost per participant with resolved BV. A sampling distribution for the incremental cost-effectiveness ratio was simulated based on a bootstrapped sample. The 2.5 and 97.5 percentiles for the ratio were used to establish the 95% confidence interval for the distribution.

Comparison groups	Metronidazole v Intravaginal lactic acid gel
Number of subjects included in analysis	518
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Mean difference
Point estimate	60.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-142.94
upper limit	180.54

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Six side effects were collected by questionnaire during the first 2 weeks of the trial - reported as secondary endpoints. Serious adverse events were collected throughout the trial, though there were none.

Adverse event reporting additional description:

Side effects of nausea, vomiting, abnormal taste changes, vaginal irritation, abdominal pain and diarrhoea were recorded by the participant on the 2 week questionnaire - see secondary end points. Serious adverse events were identified from hospitalisations and other healthcare service use reported on all 3 questionnaires during the trial

Assessment type	Systematic

Dictionary used

Dictionary name	No coding required
Dictionary version	N/A

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

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: The safety profiles of the interventions in this trial are well characterised. Metronidazole was used for its licensed indication and lactic acid gel was used within its intended use covered by the CE-mark. In order to provide secondary outcome data to compare tolerability of the two treatments, only specified Adverse Reactions (ARs) experienced during treatment with either lactic acid gel or metronidazole were reported (see secondary outcomes).

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.

The trial was terminated early (518 randomised out of a proposed 1900), because the primary objective had been answered. This meant that data were limited for answering the secondary outcomes.

Notes: