Clinical trial results:
Comparative study of the efficacy and safety of vaginally applied Dequalinium Chloride (10 mg) and orally applied Metronidazole (2 x 500 mg) in the treatment of bacterial vaginosis

Summary

EudraCT number	2020-002489-15
Trial protocol	CZ SK
Global end of trial date	25 August 2022

Results information

Result version number	v1 (current)
This version publication date	05 December 2024
First version publication date	05 December 2024
Summary attachment (see zip file)	Article (Raba_2024_Flu vs Mtz.pdf)

Trial information

Trial identification

Sponsor protocol code	380119

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05788991
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medinova AG
Sponsor organisation address	Eggbühlstrasse 28, Zurich, Switzerland, 8050
Public contact	Anahí Hurtado Chong, Medinova AG, 0041 44306 1396, hurtado.anahi@medinova.ch
Scientific contact	Anahí Hurtado Chong, Medinova AG, 0041 44306 1396, hurtado.anahi@medinova.ch

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	01 June 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 August 2022
Global end of trial reached?	Yes
Global end of trial date	25 August 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether vaginal tablets containing 10 mg dequalinium chloride (Fluomizin) are comparable in clinical efficacy to metronidazole 500 mg oral tablets in women suffering from bacterial vaginosis

Protection of trial subjects:

The study was conducted in accordance with the protocol and the following:
• Consensus ethical principles derived from international guidelines including the Declaration of Helsinki 1996 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
• Applicable ICH Good Clinical Practice (GCP) Guidelines
• All applicable national and international laws, regulations, and standards
• EU directive 2005/28/EC
Data protection was handled in compliance with national/local regulations.

Background therapy:

Metronidazole is is a nitroimidazole antibiotic and one of the first line recommended treatments for bacterial vaginosis with a posology of 500 mg twice daily for 7 days. Metronidazole is well tolerated in general, however after oral use, a bitter, metallic taste in the mouth and gastrointestinal adverse effects (abdominal cramps, nausea) are observed in up to 30% of the patients. In combination with alcohol, it is known to induce vomiting, heartburn, stomach pains, i.e. its typical (disulfiram) effect. According to some studies, Metronidazole is claimed not to be teratogenic in humans, even when used in the first trimester of pregnancy. Due to the difference in taste, it creates in milk, its use is not advised during lactation. Metronidazole is contraindicated in a first trimester (pregnancy category B) and breastfeeding is not possible since Metronidazole is excreted in milk. In general, Metronidazole has a good efficacy profile against all relevant BV associated pathogens.

Evidence for comparator:

Fluomizin® is available as vaginal tablets, containing 10 mg Dequalinium chloride. It was first marketed in Germany in 1993 and is currently approved in 69 countries. Dequalinium chloride 10 mg vaginal tablet (Fluomizin®) has been developed as a directly compressed vaginal tablet to ensure fast disintegration of the tablet and rapid dissolution of the active substance. As soon as the vaginal tablet comes into contact with the vaginal secretion, it begins to disintegrate and Dequalinium chloride is released. After dissolution of the Dequalinium chloride 10 mg tablet in an estimated 2.5 – 5 ml of vaginal fluid, the Dequalinium chloride concentration is estimated at 2000 – 4000 µg/ml, assuming negligible absorption. This concentration is 4 to 8-fold higher than the minimal inhibitory concentration (MIC) of the least susceptible isolate (MIC = 512 µg/ml). The broad-spectrum antimicrobial activity covering all relevant pathogens for vaginal infections and the negligible systemic absorption are the key factors of dequalinium chloride that make it suitable for the treatment of most vaginal infections. The treatment of BV with a 6-day course of 10 mg Dequalinium chloride vaginal tablets had equal efficacy as a 7-day course of Clindamycin vaginal cream. The current formulation Dequalinium chloride 10 mg vaginal tablets (Fluomizin®) as 6-day therapy with its broad antimicrobial spectrum and excellent tolerability offers a safe and effective option for empiric therapy of different vaginal infections in daily practice.

Actual start date of recruitment	29 July 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 71
Country: Number of subjects enrolled	Slovakia: 56
Country: Number of subjects enrolled	Czechia: 24
Worldwide total number of subjects	151
EEA total number of subjects	151

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)	151
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with symptomatic BV were recruited from July 29, 2021, to August 25, 2022, in Poland, the Czech Republic, and Slovakia from 11 gynecology practices and 1 hospital

Pre-assignment

Screening details:

Premenopausal women 18 years or older with BV (defined as 4 positive Amsel criteria) were eligible to participate. Exclusion criteria were uterine/vaginal bleeding of unknown origin, ulcerations or erosions of the vaginal mucosa or cervix, candidiasis, aerobic vaginitis, sexually transmitted infections, hypersensitivity to a study medication

Period 1

Period 1 title	Entry visit (Day 0)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Dequalinium Chloride

Arm description:

Dequalinium chloride 10-mg vaginal tablets (Fluomizin, Medinova AG).

Arm type	Experimental
Investigational medicinal product name	Dequalinium chloride
Investigational medicinal product code	
Other name	Fluomizin
Pharmaceutical forms	Tablet + vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Vaginal tablets (containing either 10 mg dequalinium chloride or placebo) were applied once a day for 6 days

Arm title	Metronidazole

Arm description:

Metronidazole, 500-mg oral tablets

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:

Oral tablets (containing 500 mg metronidazole or placebo) were taken twice a day for 7 days

Number of subjects in period 1	Dequalinium Chloride	Metronidazole
Started	73	78
Treated	72	75
Completed	72	75
Not completed	1	3
Consent withdrawn by subject	1	3

Period 2

Period 2 title	Visit 1 (Day 7-11)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Double-dummy medication kits prepared by an independent contractor contained vaginal and oral tablets, with placebo and active medication. The randomization sequence was prepared by an independent statistician using block randomization with variable block sizes stratified by center. An interactive randomization tool in the electronic case report form provided the medication kit number, ensuring allocation concealment. Patients, investigators, and outcome assessors were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dequalinium Chloride

Arm description:

10-mg vaginal tablets (Fluomizin, Medinova AG).

Arm type	Experimental
Investigational medicinal product name	Dequalinium chloride
Investigational medicinal product code	
Other name	Fluomizin
Pharmaceutical forms	Tablet + vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Vaginal tablets (containing either 10 mg dequalinium chloride or placebo) were applied once a day for 6 days

Arm title	Metronidazole

Arm description:

Metronidazole, 500-mg oral tablets

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:

500 mg twice a day for 7 days

Number of subjects in period 2	Dequalinium Chloride	Metronidazole
Started	72	75
Completed	70	75
Not completed	2	0
Lost to follow-up	1	-
Protocol deviation	1	-

Period 3

Period 3 title	Visit 2 (Day 20-40)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Double-dummy medication kits prepared by an independent contractor contained vaginal and oral tablets, with placebo and active medication. The randomization sequence was prepared by an independent statistician using block randomization with variable block sizes stratified by center. An interactive randomization tool in the electronic case report form provided the medication kit number, ensuring allocation concealment. Patients, investigators, and outcome assessors were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dequalinium Chloride

Arm description:

10-mg vaginal tablets (Fluomizin, Medinova AG).

Arm type	Experimental
Investigational medicinal product name	Dequalinium chloride
Investigational medicinal product code	
Other name	Fluomizin
Pharmaceutical forms	Tablet + vaginal tablet
Routes of administration	Vaginal use

Dosage and administration details:

Vaginal tablets (containing either 10 mg dequalinium chloride or placebo) were applied once a day for 6 days

Arm title	Metronidazole

Arm description:

Metronidazole, 500-mg oral tablets

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:
500 mg twice a day for 7 days

Number of subjects in period 3	Dequalinium Chloride	Metronidazole
Started	70	75
Completed	70	72
Not completed	0	3
Adverse event, non-fatal	-	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Dequalinium Chloride
Reporting group description:	
Dequalinium chloride 10-mg vaginal tablets (Fluomizin, Medinova AG).	
Reporting group title	Metronidazole
Reporting group description:	
Metronidazole, 500-mg oral tablets	

Reporting group values	Dequalinium Chloride	Metronidazole	Total
Number of subjects	73	78	151
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)	0	0	0
Adults (18-64 years)	73	78	151
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	36.0	37.5	
standard deviation	± 9.2	± 8.9	-
Gender categorical Units: Subjects			
Female	73	78	151
Male	0	0	0

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population included all randomized and treated patients allocated according to their randomization.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population included patients without major protocol violations.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included patients who took at least 1 dose of study medication.	

Reporting group values	ITT	PP	Safety
Number of subjects	147	101	147
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)	0	0	0
Adults (18-64 years)	147	101	147
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Dequalinium Chloride
Reporting group description:	
Dequalinium chloride 10-mg vaginal tablets (Fluomizin, Medinova AG).	
Reporting group title	Metronidazole
Reporting group description:	
Metronidazole, 500-mg oral tablets	
Reporting group title	Dequalinium Chloride
Reporting group description:	
10-mg vaginal tablets (Fluomizin, Medinova AG).	
Reporting group title	Metronidazole
Reporting group description:	
Metronidazole, 500-mg oral tablets	
Reporting group title	Dequalinium Chloride
Reporting group description:	
10-mg vaginal tablets (Fluomizin, Medinova AG).	
Reporting group title	Metronidazole
Reporting group description:	
Metronidazole, 500-mg oral tablets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT population included all randomized and treated patients allocated according to their randomization.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
The PP population included patients without major protocol violations.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population included patients who took at least 1 dose of study medication.	

Primary: Clinical cure rate

End point title	Clinical cure rate
End point description:	
Resolution of the abnormal vaginal discharge, negative whiff test, and less than 20% clue cells	
End point type	Primary
End point timeframe:	
One week	

End point values	Dequalinium Chloride	Metronidazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	74		
Units: Number of cured	64	69		

Attachments (see zip file)	Primary analysis.tiff

Statistical analyses

Statistical analysis title	Primary endpoint- non inferiority

Statistical analysis description:

The difference in proportions between groups (with 95%CIs) for clinical cure, bacteriologic cure, and therapeutic cure were analyzed using a Farrington-Manning test with a 1-sided significance level of α = .025 and a noninferiority margin of 15 percentage points

Comparison groups	Metronidazole v Dequalinium Chloride
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	≤ 0.025 [1]
Method	Farrington-Manning
Parameter estimate	Difference in proportion
Confidence interval	
level	95 %
sides	1-sided
lower limit	15

Notes:

[1] - 1 sided significance level

Secondary: Clinical cure rate

End point title	Clinical cure rate

End point description:

Clinical cure was defined as the resolution of abnormal vaginal discharge, whiff test, and clue cells (ie, all 3 criteria must be negative)

End point type	Secondary

End point timeframe:

1 month

End point values	Dequalinium Chloride	Metronidazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: Number of cured	55	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Bacteriological cure rate

End point title	Bacteriological cure rate

End point description:

Bacteriologic cure was defined as a Nugent score of 3 or less.

End point type	Secondary

End point timeframe:

1 week

End point values	Dequalinium Chloride	Metronidazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	74		
Units: Number of cured	35	51		

Statistical analyses

No statistical analyses for this end point

Secondary: Bacteriologic cure rate

End point title	Bacteriologic cure rate

End point description:

End point type	Secondary

End point timeframe:

1 month

End point values	Dequalinium Chloride	Metronidazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: Number of cured	28	38		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical improvement

End point title	Clinical improvement

End point description:

Clinical improvement was defined as 2 or more negative Amsel criteria at both visits.

End point type	Secondary

End point timeframe:

1 month

End point values	Dequalinium Chloride	Metronidazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	70		
Units: Number of improved	59	65		

Statistical analyses

No statistical analyses for this end point

Secondary: Tolerability (assessed by the patient)

End point title	Tolerability (assessed by the patient)

End point description:

Subjective tolerability to the treatment were rated by patients as very good, good, moderate, or poor.

End point type	Secondary

End point timeframe:

1 month

End point values	Dequalinium Chloride	Metronidazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	54		
Units: Percentage				
Very good	30	21		
Good	17	26		
Moderate	3	4		
Poor	0	3		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Standard Amsel Criteria

End point title	Standard Amsel Criteria

End point description:

The standard Amsel criteria define BV as the presence of 3 or more criteria.5 Conversely, 2 or more negative criteria are considered BV negative.

End point type	Post-hoc

End point timeframe:

1 week

End point values	Dequalinium Chloride	Metronidazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	74		
Units: Number of cured	68	73		

Statistical analyses

No statistical analyses for this end point

Post-hoc: Standard Amsel Criteria

End point title	Standard Amsel Criteria

End point description:

End point type	Post-hoc

End point timeframe:

1 month

End point values	Dequalinium Chloride	Metronidazole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	71		
Units: Number of cured	61	67		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse events within 24 days of randomization were defined as treatment emergent.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.1
Reporting groups	
Reporting group title	Dequalinium Chloride
Reporting group description: 10-mg vaginal tablets (Fluomizin, Medinova AG).	
Reporting group title	Metronidazole
Reporting group description: Metronidazole, 500-mg oral tablets	

Serious adverse events	Dequalinium Chloride	Metronidazole	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 72 (0.00%)	0 / 75 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Dequalinium Chloride	Metronidazole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 72 (11.11%)	15 / 75 (20.00%)	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 72 (1.39%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 72 (1.39%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Vulvovaginal burning sensation			
subjects affected / exposed	0 / 72 (0.00%)	3 / 75 (4.00%)	
occurrences (all)	0	3	
Vulvovaginal swelling			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Pharyngeal swelling			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Catarrh			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 72 (1.39%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Vulvovaginal candidiasis			
subjects affected / exposed	3 / 72 (4.17%)	5 / 75 (6.67%)	
occurrences (all)	3	5	
Bacterial vaginosis			
subjects affected / exposed	1 / 72 (1.39%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
COVID-19			
subjects affected / exposed	1 / 72 (1.39%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Vaginal infection			

subjects affected / exposed	1 / 72 (1.39%)	1 / 75 (1.33%)	
occurrences (all)	1	0	
Genital infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 April 2022	One protocol amendment (v2.0 13-April-2022) was made to change the analysis sets definition. The analysis set mITT was restricted to subjects who were treated and had the Nugent score value at baseline ≥7 and was going to be used for the main efficacy analysis. The mITT was replaced with the ITT, i.e. all patients randomized and treated, regardless of the Nugent score value. A clarification to describe exactly when a subject is considered treated was also added, to avoid any ambiguity. Nugent scores results were only received after several days at which time the subject was already enrolled in the study. Considering the unexpectedly high rate of low Nugent score values, there was a risk of lack of power in the analysis because the primary analysis was planned on the mITT analysis set, although the primary endpoint bacterial vaginosis status was based on the Amsel Criteria and not on the Nugent score values. Therefore, it seemed more meaningful to consider the Nugent score in a sensitivity analysis than in the primary analysis. With this change, the analysis set for the primary endpoint changed from the mITT to the new ITT analysis set defined. To include a differentiation dependent on the Nugent score value in the analysis as was originally intended, subjects were categorised into subgroups by Nugent score value at baseline, and the primary and secondary endpoint analyses were performed also by subgroup. The change in the analysis set population for the primary endpoint also affected the drop-out rate considered from 30% to 5%, and consequently the planned global sample size was reduced from 160 to 118 patients per treatment arm.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

12 November 2021	Metronidazole Batch Nr. 906351 was recalled by the manufacturer on 11-Nov-2021 due to deviations from the specified release of active ingredient parameters detected during planned stability testing. There were no patient safety concerns linked to the recall of the medication. Recruitment was initially paused at all sites starting 12-Nov-2021. IL-CSM, which packaged the IMP for the study, together with the unblinded statistician at GCP-Service responsible for the randomization list clarified that only the kits at site 3815 (first delivery), at sites 3805 and 3806 (second deliveries), as well as all IMP stock in the depot at that time were affected. Affected kits were identified, removed and destroyed. Recruitment was resumed at the unaffected sites on 19-Nov-2021, and at the affected sites after resupply with new IMP was performed.	19 November 2021

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The limitations of the study are the short follow-up; the reduced sample size, which hindered subgroup analyses; and the patient population limited to White European individuals

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/38696172