Clinical trial results:
A double-blind, placebo-controlled multicenter trial on the effect of clindamycin and a live biotherapeutic on the reproductive outcomes of IVF patients with abnormal vaginal microbiota

Summary

EudraCT number	2016-002385-31
Trial protocol	DK
Global end of trial date	16 August 2023

Results information

Result version number	v1 (current)
This version publication date	30 August 2024
First version publication date	30 August 2024
Summary attachment (see zip file)	RCT Manuscript (RCT_Manuscript.pdf)

Trial information

Trial identification

Sponsor protocol code	2015/582

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	The Fertility Clinic Skive, Skive regional Hopsital
Sponsor organisation address	Resenvej 25, Skive, Denmark, 7800
Public contact	Peter Humaidan, The Fertility Clinic Skive, Skive regional Hopsital, peter.humaidan@midt.rm.dk
Scientific contact	Peter Humaidan, The Fertility Clinic Skive, Skive regional Hopsital, peter.humaidan@midt.rm.dk

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 August 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2023
Global end of trial reached?	Yes
Global end of trial date	16 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the present trial is to investigate the effect of antibiotic and probiotic treatment on the reproductive outcome of IVF patients with abnormal vaginal microbiota (AVM). The aim is to investigate whether treatment of AVM improve the success-rate of IVF patients.

Protection of trial subjects:

The study was approved by the scientific Ethics Committee of the Central Denmark Region - Project ID: M-2017-157-17

Written informed consent was obtained from all participants prior to inclusion.

Background therapy: -

Evidence for comparator: -

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	Denmark: 338
Worldwide total number of subjects	338
EEA total number of subjects	338

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)	338
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled in December 2017 and the last patient was enrolled in september 2022. Patients were recruited from four danish fertility clinics.

Pre-assignment

Screening details:

A total of 1535 patients were screened and 338 patient were randomized. However, 72 patients were not included in the modified intention to treat (mITT) analysis. This resulted in 94 CLLA, 88 CLPL, and 84 PLPL patients included in the primary mITT analysis.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Treatment 1

Arm description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V (2 x 109 CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration, but patients are allowed to use all 21 applicators

Arm type	Experimental
Investigational medicinal product name	Clindamycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

300 mg 2 times per day for 7 days

Investigational medicinal product name	LACTIN-V
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for vaginal solution
Routes of administration	Vaginal use

Dosage and administration details:

LACTIN-V (2 x 109 CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration.

Arm title	Active Treatment 2

Arm description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V placebo (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. The LACTIN-V placebo regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum

of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of Lactin-V placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

Arm type	Experimental
Investigational medicinal product name	Clindamycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

300 mg 2 times per day for 7 days

Arm title	Inactive treatment (placebo)

Arm description:

Matching clindamycin placebo 2 times per day for 7 days followed by LACTIN-V placebo (Osel Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V placebo regimen is once daily from clindamycin stop and the following 7 days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of live biotherapeutic placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

Arm type	Placebo
Investigational medicinal product name	Clindamycin (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

300 mg 2 times per day for 7 days

Investigational medicinal product name	LACTIN-V (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for vaginal solution
Routes of administration	Vaginal use

Dosage and administration details:

LACTIN-V (2 x 109 CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration.

Number of subjects in period 1[1]	Active Treatment 1	Active Treatment 2	Inactive treatment (placebo)
Started	94	88	84
Completed	94	88	84

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 338 patients were randomized however, 72 patients were not included in the modified intention to treat (mITT) analysis. This resulted in a total of 266 patients.

Baseline characteristics

Reporting groups	
Reporting group title	Active Treatment 1

Reporting group description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V (2 x 109 CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration, but patients are allowed to use all 21 applicators

Reporting group title	Active Treatment 2

Reporting group description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V placebo (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. The LACTIN-V placebo regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of Lactin-V placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

Reporting group title	Inactive treatment (placebo)

Reporting group description:

Matching clindamycin placebo 2 times per day for 7 days followed by LACTIN-V placebo (Osel Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V placebo regimen is once daily from clindamycin stop and the following 7 days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of live biotherapeutic placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

Reporting group values	Active Treatment 1	Active Treatment 2	Inactive treatment (placebo)
Number of subjects	94	88	84
Age categorical Units: Subjects			
Adults (18-64 years)	94	88	84
Age continuous Units: years			
median	31.5	31.8	31.4
standard deviation	± 4.7	± 4.5	± 4.7
Gender categorical Units: Subjects			
Female	94	88	84

Reporting group values	Total		
Number of subjects	266		
Age categorical Units: Subjects			
Adults (18-64 years)	266		
Age continuous Units: years			
median			
standard deviation	-		

Gender categorical Units: Subjects			
Female	266		

Subject analysis sets

Subject analysis set title	Full analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Primary analysis was modified intention to treat (mITT) defined as all patients with embryo transfer less than 63 days from the active treatment start until day 1 in the embryo transfer cycle.

Reporting group values	Full analysis		
Number of subjects	266		
Age categorical Units: Subjects			
Adults (18-64 years)	266		
Age continuous Units: years median standard deviation	 ±		
Gender categorical Units: Subjects			
Female	266		

End points

End points reporting groups

Reporting group title	Active Treatment 1

Reporting group description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V (2 x 109 CFU/dose, 200 mg) regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then LACTIN-V treatment is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant (negative hCG test), then LACTIN-V treatment can be stopped after at least 7 days Lactin-V administration, but patients are allowed to use all 21 applicators

Reporting group title	Active Treatment 2

Reporting group description:

Oral Clindamycin 300 mg 2 times per day for 7 days followed by LACTIN-V placebo (Osel, Inc.) until completion of the clinical pregnancy scan at week 7-9. The LACTIN-V placebo regimen is once daily from the clindamycin stop for 7 consecutive days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of Lactin-V placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

Reporting group title	Inactive treatment (placebo)

Reporting group description:

Matching clindamycin placebo 2 times per day for 7 days followed by LACTIN-V placebo (Osel Inc.) until completion of the clinical pregnancy scan at week 7-9. LACTIN-V placebo regimen is once daily from clindamycin stop and the following 7 days. If there are embryos to transfer (90%), then Lactin-V placebo administration is continued twice weekly until clinical pregnancy scan, however with a maximum of 21 applicators per patient. If the patient has no embryos to transfer or is confirmed not pregnant, then administration of live biotherapeutic placebo can be stopped after at least 7 days Lactin-V placebo administration, but patients are allowed to use all 21 applicators

Subject analysis set title	Full analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Primary analysis was modified intention to treat (mITT) defined as all patients with embryo transfer less than 63 days from the active treatment start until day 1 in the embryo transfer cycle.

Primary: Clinical pregnancy rate

End point title	Clinical pregnancy rate

End point description:

End point type	Primary

End point timeframe:

Gestational week 7-9

End point values	Active Treatment 1	Active Treatment 2	Inactive treatment (placebo)	Full analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	94	88	84	266
Units: Fetal heart beat	39	41	38	118

Statistical analyses

Statistical analysis title	Fisher's exact test

Statistical analysis description:

For each treatment group CLLA, CLPL and PLPL the estimated proportions, risk ratios (RR) and their confidence intervals were calculated using uni- and multivariate logistic regression analyses by generalized linear models with log-link function. The significance level for the final analysis was set at 4.9% (95.1% confidence intervals) due to the preplanned interim analysis where an alpha of 0.1% was used.

Comparison groups	Active Treatment 1 v Active Treatment 2 v Inactive treatment (placebo)
Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.49
Method	Fisher exact
Parameter estimate	Risk ratio (RR)

Secondary: Live birth rate

End point title	Live birth rate

End point description:

End point type	Secondary

End point timeframe:

Birth

End point values	Active Treatment 1	Active Treatment 2	Inactive treatment (placebo)	Full analysis
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	94	88	84	266
Units: Birth	37	40	34	111

Statistical analyses

Statistical analysis title	Fisher’s exact test

Statistical analysis description:

For each treatment group CLLA, CLPL and PLPL the estimated proportions, risk ratios (RR) and their confidence intervals were calculated using uni- and multivariate logistic regression analyses by generalized linear models with log-link function. The significance level for the final analysis was set at 4.9% (95.1% confidence intervals) due to the preplanned interim analysis where an alpha of 0.1% was used.

Comparison groups	Active Treatment 2 v Inactive treatment (placebo) v Active Treatment 1

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.49
Method	Fisher exact
Parameter estimate	Risk ratio (RR)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 14 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23

Reporting groups	
Reporting group title	CLLA
Reporting group description: -	
Reporting group title	CLPL
Reporting group description: -	
Reporting group title	PLPL
Reporting group description: -	

Serious adverse events	CLLA	CLPL	PLPL
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 94 (3.19%)	1 / 88 (1.14%)	3 / 84 (3.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Surgical and medical procedures			
Appendicitis			
subjects affected / exposed	3 / 94 (3.19%)	1 / 88 (1.14%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Obs apoplexia, not confirmed			
subjects affected / exposed	3 / 94 (3.19%)	1 / 88 (1.14%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Arthrogryposis multiplex congenita=> late abortion			
subjects affected / exposed	3 / 94 (3.19%)	1 / 88 (1.14%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foetus mors			

subjects affected / exposed	3 / 94 (3.19%)	1 / 88 (1.14%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrauterine pregnancy			
subjects affected / exposed	3 / 94 (3.19%)	1 / 88 (1.14%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trisomi 21=> abortion			
subjects affected / exposed	3 / 94 (3.19%)	1 / 88 (1.14%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius hypoplasia, normal amniocentesis => live birth			
subjects affected / exposed	3 / 94 (3.19%)	1 / 88 (1.14%)	3 / 84 (3.57%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	CLLA	CLPL	PLPL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 94 (24.47%)	24 / 88 (27.27%)	22 / 84 (26.19%)
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	8 / 94 (8.51%)	16 / 88 (18.18%)	17 / 84 (20.24%)
occurrences (all)	8	16	17
Fatigue			
subjects affected / exposed	12 / 94 (12.77%)	11 / 88 (12.50%)	15 / 84 (17.86%)
occurrences (all)	12	11	15
Bloating			
subjects affected / exposed	23 / 94 (24.47%)	24 / 88 (27.27%)	19 / 84 (22.62%)
occurrences (all)	23	24	19
Headache			
subjects affected / exposed	4 / 94 (4.26%)	6 / 88 (6.82%)	7 / 84 (8.33%)
occurrences (all)	4	6	7

Urticaria			
subjects affected / exposed	0 / 94 (0.00%)	1 / 88 (1.14%)	0 / 84 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	12 / 94 (12.77%)	11 / 88 (12.50%)	15 / 84 (17.86%)
occurrences (all)	12	11	15
Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	13 / 94 (13.83%)	14 / 88 (15.91%)	22 / 84 (26.19%)
occurrences (all)	13	14	22
Vaginal itching			
subjects affected / exposed	8 / 94 (8.51%)	2 / 88 (2.27%)	2 / 84 (2.38%)
occurrences (all)	8	2	2
Vaginal pain			
subjects affected / exposed	2 / 94 (2.13%)	2 / 88 (2.27%)	2 / 84 (2.38%)
occurrences (all)	2	2	2
Vaginal smell			
subjects affected / exposed	1 / 94 (1.06%)	1 / 88 (1.14%)	1 / 84 (1.19%)
occurrences (all)	1	1	1
Vaginal bleeding			
subjects affected / exposed	0 / 94 (0.00%)	3 / 88 (3.41%)	0 / 84 (0.00%)
occurrences (all)	0	3	0
Vaginal rash			
subjects affected / exposed	2 / 94 (2.13%)	1 / 88 (1.14%)	0 / 84 (0.00%)
occurrences (all)	2	1	0
Vaginal candida			
subjects affected / exposed	4 / 94 (4.26%)	2 / 88 (2.27%)	0 / 84 (0.00%)
occurrences (all)	4	2	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 94 (2.13%)	1 / 88 (1.14%)	1 / 84 (1.19%)
occurrences (all)	2	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

None reported