Clinical trial results:
Modulating the Vaginal Microbiome after Implantation Failure - A randomized placebo controlled study of lactobacilli supplements

Summary

EudraCT number	2018-002376-41
Trial protocol	DK
Global end of trial date	27 February 2021

Results information

Result version number	v1 (current)
This version publication date	08 March 2022
First version publication date	08 March 2022

Trial information

Trial identification

Sponsor protocol code	¨noMICINT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	The Fertility Clinic, Zealand Region
Sponsor organisation address	Lykkebaekvej 14, Koege, Denmark,
Public contact	Fertilitetsklinikken, University Hospital Zealand, 0045 59484270,
Scientific contact	Fertilitetsklinikken, University Hospital Zealand, 0045 59484270,

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 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2021
Global end of trial reached?	Yes
Global end of trial date	27 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Investigate change of microbiome in population after treatment with Vivag Plus or placebo over the course of two months.

Protection of trial subjects:

We used an intervention with a known side-effect profile and known harmless side-effects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2019
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: 77
Worldwide total number of subjects	77
EEA total number of subjects	77

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)	77
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patient with an unfavourable vaginal microbiome were offered to participate in the study.

Pre-assignment

Screening details:

Study population
Women aged 18–40 years referred to the Fertility Clinic who prior to fertility treatment had been diagnosed with an unfavorable vaginal microbiome were invited to participate in the study

Pre-assignment period milestones

Number of subjects started	77
Number of subjects completed	74

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Pregnancy: 1
Reason: Number of subjects	COVID-19: 1
Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Overall trial 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

Blinding implementation details:

The pharmacy of the Capital Region of Denmark conducted the randomization using a computer-based randomization program (www.randomization.com) and labeled all drug packages
to ensure blinding of both clinicians and participants to the content of the packages. Unblinding was not carried out until after completion of the study when all data had been entered and the statistical analysis plan c

Arms

Are arms mutually exclusive?	Yes
Arm title	lactobacillus treatment

Arm description:

The intervention consisted of gelatin capsules containing more than 108 CFU of Lactobacillus gasseri EB01 DSM14869 and more than 108 CFU Lactobacillus rhamnosus PB01 DSM14870.

Arm type	Active comparator
Investigational medicinal product name	Vivag
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Vaginal use

Dosage and administration details:

1 vaginal capsule pr day (before nighttime) for 10 days

Arm title	placebo group

Arm description:

The placebo formulation was identical in appearance and texture to the study intervention but devoid of bacterial strains.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Vaginal use

Dosage and administration details:

1 vaginal capsule pr day (before nighttime) for 10 days.

Number of subjects in period 1[1]	lactobacillus treatment	placebo group
Started	38	36
Completed	38	36

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: 77 patients were included in the study but three patient dropped out before the intervention. Therefor did they neither received the intervention og had the first and second sample (primary- and secondary outcome), and they were not included in the analyses. This according to the prespecified protocol.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial period

Reporting group description: -

Reporting group values	Overall trial period	Total	
Number of subjects	74	74	
Age categorical Units: Subjects			
adults (19-39)	74	74	
Age continuous Units: years			
arithmetic mean	31		
standard deviation	± 4.2	-	
Gender categorical Units: Subjects			
Female	74	74	
Baseline vaginal microbiome profile Units: Subjects			
low	56	56	
medium	18	18	
Partner status Units: Subjects			
Male partner	59	59	
Female partner	2	2	
No partner	13	13	
Etnicity Units: Subjects			
Caucasian	72	72	
Mediterranean	2	2	
Cause of infertility Units: Subjects			
Ideopathic	23	23	
Male factor	27	27	
Cycle disorder	2	2	
Combination	3	3	
Other	2	2	
No partner/female partner	14	14	
Missing	3	3	
Penile-vaginal intercourse Units: Subjects			
None	11	11	
Yes, 1-4 per month	25	25	
Yes, 5-12 per month	28	28	
Yes, >12 per month	9	9	
Yes, frequency n.a.	1	1	
Self-assessed vaginal discharge			

Units: Subjects			
Normal	57	57	
Increase	16	16	
Missing	1	1	
Vaginal odour complaints Units: Subjects			
Yes	56	56	
No	17	17	
missing	1	1	
BMI			
(kg/m2)			
Units: units			
arithmetic mean	26.4		
standard deviation	± 5.6	-	

End points

End points reporting groups

Reporting group title	lactobacillus treatment
Reporting group description:	
The intervention consisted of gelatin capsules containing more than 108 CFU of Lactobacillus gasseri EB01 DSM14869 and more than 108 CFU Lactobacillus rhamnosus PB01 DSM14870.	
Reporting group title	placebo group
Reporting group description:	
The placebo formulation was identical in appearance and texture to the study intervention but devoid of bacterial strains.	

Primary: Improvement in the vaginal microbiome after intervention

End point title	Improvement in the vaginal microbiome after intervention
End point description:	
The primary outcome measure was dichotomous: improvement or no improvement in vaginal microbiome profile occurring in the period between the baseline sample and the first sample after the intervention. An improvement was defined as a shift in profile from low to medium, medium to high, or low to high, whereas no improvement was defined as no change, high to medium, or medium to low	
End point type	Primary
End point timeframe:	
For each patient the timeframe was from 1-3 month: From baseline sample to the first sample after intervention. This covering the 15th of April 2019 to the 27th of February 2021.	

End point values	lactobacillus treatment	placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	35[1]		
Units: 38				
Improvement of vaginal microbiome profil	11	14		
No improvement of vaginal microbiome profil	27	21		

Notes:

[1] - One sample could not be analysed.

Statistical analyses

Statistical analysis title	Chi-square
Comparison groups	lactobacillus treatment v placebo group
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.72

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.38
Variability estimate	Standard deviation

Secondary: Improvement in the vaginal microbiome after intervention one menstrual cycle after intervention

End point title	Improvement in the vaginal microbiome after intervention one menstrual cycle after intervention

End point description:

Improvement in the vaginal microbiome was defined as a change in the microbiome profile from low to medium, low to high, or medium to high from the baseline sample to the second sample (secondary outcome) or from the baseline sample to the second sample (secondary outcome), whereas no improvement was defined as no change or deterioration.

End point type	Secondary

End point timeframe:

For each patient the timeline was from baseline sample to the second sample (the menstrual cycle after the intervention).
This covering from the 15th of April 2019 to the 27th of February 2021.

End point values	lactobacillus treatment	placebo group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[2]	36		
Units: 2				
Improvement in the vaginal microbiome	11	12		
No improvement in the vaginal microbiome	25	24		

Notes:

[2] - One sample could not be analysed and one sample could not be collected due to COVID-19.

Statistical analyses

Statistical analysis title	Chi-square
Comparison groups	lactobacillus treatment v placebo group
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.8
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the inclusion of the first patient to the last patients last visit (=finished with the study), which was the second sample visit (secondary outcome):
15th of april 2019 to 27th of February 2021.

Adverse event reporting additional description:

Throughout the study participants will be questioned about adverse events (AE=an unexpected medical event) and adverse reactions (AR= an unexpected/unintended response to a medical product) at every visit to the clinic. AE and AR will be registered in the trial clinical case reports and reported to the Sponsor within 24 hours.

Assessment type	Systematic

Dictionary used

Dictionary name	The Danish Medicines
Dictionary version	89,stk 2.

Reporting groups

Reporting group title	Lactobacillus group

Reporting group description:

The lactobacillus treatment will consist of Vivag Plus vaginal supplements. The vaginal capsules consist of cultures of Lactobacillus gasseri and Lactobacillus rhamnosus.

Reporting group title	Placebo group

Reporting group description:

The placebo formulation was identical in appearance and texture to the study intervention but devoid of bacterial strains.

Serious adverse events	Lactobacillus group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Reproductive system and breast disorders			
Tubo-ovarian abscess	Additional description: Patient developed tubo-ovarian abscess after a hysterosalpingography which was not related to the study.		
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	
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: 0.8 %

Non-serious adverse events	Lactobacillus group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
Gastrointestinal disorders			
perianal abscess	Additional description: Patient developed perianal abscess during the study period, not related to the study.		
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	
occurrences (all)	1	0	

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