Apr 28, 2023

A multicenter, open label, non-comparative, 3 months study to assess the performance and safety of the new medical device Polybactum® in reducing the frequency of Recurrent Bacterial Vaginosis

JMIR Research Protocols

DOI
dx.doi.org/10.17504/protocols.io.81wgbybbqvpk/v1

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DOI: https://dx.doi.org/10.17504/protocols.io.81wgbybbqvpk/v1

Protocol Citation: Filippo Murina, Dionisio Franco Barattini, Dumitru-Emanuel Dogaru 2023. A multicenter, open label, non-comparative, 3 months study to assess the performance and safety of the new medical device Polybactum® in reducing the frequency of Recurrent Bacterial Vaginosis. **protocols.io** https://dx.doi.org/10.17504/protocols.io.81wgbybbqvpk/v1

Protocol status: Working
We used this protocol and it worked

Created: April 28, 2023

Last Modified: April 28, 2023

Protocol Integer ID: 81133

Keywords: results of bacterial vaginosis treatment, bacterial vaginosis treatment, frequency of recurrent bacterial vaginosis medical literature, recurrent bacterial vaginosis medical literature, recurrent bacterial vaginosi, bacterial vaginosis diagnosis, gardnerella vaginali, antibiotic administration, months after antibiotic administration, barrier effect against the biofilm, biofilm, treatment with plgg, bv, treatment, lauryl glucoside, period without treatment, containing polycarbophil

Abstract

Medical literature has evidenced in recurrent bacterial vaginosis a relapse rate of 35% within 3 months and 60% within 12 months after antibiotic administration. The products able to create a barrier effect against the biofilm produced by
Gardnerella vaginalis could play a role in improving the results of bacterial vaginosis treatment.
This research project (composed by a main study plus a follow-up study) aimed to test the performance and the safety of a medical device containing polycarbophil, lauryl glucoside, and glycerides (PLGG) in reducing the rate of recurrence of BV.
The project included two phases: in the first one (according to an open-label, non-controlled design) the treatment with
PLGG was administered for three cycles and it was followed by a 1-month of follow-up without treatment. In the second phase of the study a 9-month follow-up period was envisaged. This entailed that, for each patient, a 10-months follow-up period without treatment was planned. Bacterial vaginosis diagnosis was performed using Amsel criteria. The 55 planned patients were enrolled in five centres (two in Italy and three in România).

Attachments

POLARIS main study.p... 582KB

POLARIS PMCF study 519KB

Troubleshooting

A multicenter, open label, non-comparative, 3 months study to assess the performance and safety of the new medical device Polybactum® in reducing the frequency of Recurrent Bacterial Vaginosis *followed by PMCF protocol* Observational, non-randomized, not controlled, multicentre post marketing clinical follow up (PMCF) study to evaluate the safety and performance of the medical device Polybactum® in reducing the frequency of Recurrent Bacterial Vaginosis

1 **A multicenter, open label, non-comparative, 3 months study to assess the performance and safety of the new medical device Polybactum® in reducing the frequency of Recurrent Bacterial Vaginosis**
Short Title: Polaris – Polybactum to assess Recurrent Bacterial Vaginosis

Followed by PMCF protocol
Observational, non-randomized, not controlled, multicentre post marketing clinical follow up (PMCF) study to evaluate the safety and performance of the medical device Polybactum®in reducing the frequency of Recurrent Bacterial Vaginosis

2 **A multicenter, open label, non-comparative, 3 months study to assess the performance and safety of the new medical device Polybactum® in reducing the frequency of Recurrent Bacterial Vaginosis**
Short Title: Polaris – Polybactum to assess Recurrent Bacterial Vaginosis

3 **ClinicalTrials.gov Identifier:** NCT02863536
Study type: Interventional prospective trial
Indication studied: Recurrent Bacterial Vaginosis
Design: Interventional, non-controlled, multicenter trial with a prospective design on one cohort of patients
Name and address of Sponsor: EFFIK Italia S.p.A Via dei Lavoratori, 54 Milano (Italy)
Name and address of CRO: Opera Contract Research Organization (Opera CRO)
10 Cozia Street, Building B 300209 Timișoara (Romania)
Principal Investigator of Coordinating Centre: Dr. Filippo Murina Servizio di Patologia Tratto Genitale Inferiore U.O. Ostetricia e Ginecologia Ospedale Vittore Buzzi - Università degli Studi di Milano (Italy)
Statement of Compliance: the trial was in accordance to standard UNI EN ISO 14155:2011, the Guidelines for Good Clinical Practices and complied with the current Italian and Romanian legislation concerning the medical device

Rationale and Research Hypothesis

Bacterial Vaginosis (BV) is a polymicrobial disease occurring when the protective lactobacillus vaginal microbiota is impaired and allows an overgrowth of anaerobes and other pathogens, such as *Gardnerella vaginalis* and *Mycoplasma hominis*. Because of the several BV-determining risk factors, the etiology and pathogenesis of this disease are not completely understood, the treatment is not always effective, resulting in high recurrence rates. Recurrent Bacterial Vaginosis (RBV) is generally defined as 2-3 episodes of BV per year. The recurrence rates are up to 35% at 1 month, 50% at 3 months, and 70% at 12 months.
The Research Hypothesis for the present study is that rate of recurrence after 3 months of administration with Polybactum® shall significantly decreas in comparison to the baseline condition of the patients. In addition, we hypothesize that the proportion of normal vaginal microbiota will be significantly higher receiving Polybactum® for 3-cycle month.

Objectives

The primary objective is to evaluate the efficacy of Polybactum® in reducing the rate of recurrence of BV after a 3-cycle month treatment, compared to what reported by appropriate selected international literature.
The secondary objectives of the trial are:
- to evaluate the rate of return to normality of vaginal microflora, defined as vaginal microflora with numerous pleiomorphic lactobacilli, no other bacteria or clue cells or hyphae after a 3-month therapy;
- to evaluate the safety of Polybactum®.

Outcomes

Primary outcomes:
- Recurrence of BV identified by Amsel criteria (vaginal pH, whiff test, homogenous vaginal discharge and clue cells at optical microscopy by phase-contrast; see Annex 3).
Secondary outcome:
- Treatment effects on Lactobacillus microbiota evaluated by vaginal swab (see Annex 4);
- Signs and symptoms of BV (vaginal discharge, burning, erythema, dyspareunia);
- Global Assessment of Efficacy by patient's diary.
Secondary safety outcomes:
- ADE/SADE/USADE and AE/SAE;
- Global Assessment of Safety.

Inclusion criteria

- Women above 18 years.
- BV diagnosed by Amsel criteria (see Annex 3) in the 6-9 days before study, and cured with metronidazole vaginal formulation (gel for 5 days or ovules for 7 days).

- Diagnosis of RBV (at least 2 episodes of BV in the last 12 months including the BV cured before baseline).
- Non lactating women or lactating non amenorrheic women.
- Read and signed informed consent.

Exclusion criteria

- Pregnancy.
- Candidiasis or mixed vaginitis.
- HIV or other immunodeficiency.
- Known allergy to metronidazole or to Polybactum® ingredients.
- Sex workers.
- Menstruation or pre-menopause/menopause.
- Patients concomitantly included in different interventional clinical trials.
- Unwillingness to provide the informed consent to the trial.
- Time between the last day of last menses and baseline visit > 16 days or ≤5 days.

Concomitant care and interventions not allowed during the trial

- Vaginal tampons.
- Use of an etonogestrel/ethinyl estradiol vaginal ring (Nuvaring®) or an intrauterine device.
-Ora l or vaginal probioticstic therapy or other vaginal therapies (like douching, spermicide).
- Oral or vaginal probiotics.

Sample size

Forty-three (43) evaluable patients (55 enrolled).
In medical literature, the mean recurrence rates without treatment is from 30% to 50% within 3 months. Considering to be realistic to have a 40% as mean recurrence rates without treatment also in the present study, using the current medical literature and in addition the recently collected data on recurrence rates pre-post treatment with Polybactum® (data on file, Effik Italia SpA), and assuming that 40% and 15% of the pairs are positive at the first and the second observation, respectively, the correlation between paired observation is 2% and after applying continuity correction, the study required a sample size of 44 pairs to achieve a power of 80% and a one sided significance of 5% for detecting a difference of -0.25 between marginal proportions. Taking into account of a possible 15% screening failure and 20% drop-out rate, 65 patients had to be screened and 55 enrolled (one group chi square test than a proportion equals user specified value non-inferiority. In this multicenter study, the enrolment was performed in a competitive way in the involved Centers. Therefore, each site should have been recruited and treated from 5 to 15 patients. Patients with a recurrence during the study period were considered as treatment failure and not replaced

Number of Centers
Five (5) Centers (2 in Italy and 3 in Romania).

Statistical analysis
Quantitative variables (i.e. demographic) if normally distributed were described through mean ± Standard Deviation (SD), otherwise median, minimum, maximum and interquartile range were showed. Qualitative variables were evaluated using frequencies and percentages.
In order to evaluate changes over time before and after the treatment, Paired t-test (if applicable) or Wilcoxon signed rank sum test were performed for quantitative variables, while McNemar test were used in order to evaluate changes for binary variables, while symmetry test was performed in order to evaluate changes for qualitative (not binary) variables.
The quality and completeness of the collected data were evaluated preliminarily compared to data analysis. If a subject is missing information for one or more variables, even after the resolution of its query, the missing data were not replaced. If a subject was involved in violation of inclusion/exclusion criteria, the respective data were excluded from the analysis.

Treatment
Polybactum® (medical device Class IIa).
Three (3) cycles treatment one per month. Duration of one cycle: 1 week; administration for each cycle: 1 ovule at Day 1, 1 ovule at Day 4; 1 ovule at Day 7.
In the 1st cycle the treatment started immediately after the end of metronidazole treatment (the maximum acceptable interval between the two treatments is 24 hrs; the minimum 12 hrs).
In the two following cycles, the same treatment was repeated immediately after the end of the first and second menstrual bleeding.

Procedures
a) Screening and Baseline Visit (day 1)
The visit must be performed from 12 to 24 hrs after the end of metronidazole treatment.
- physical examination and medical history;
- Amsel criteria (vaginal pH, whiff test, homogenous vaginal discharge and clue cells at optical microscopy by phase-contrast);
- vaginal swab (lactobacilli determination);
- Nugent Score (not mandatory);
- Polybactum given to the patient (in any case the maximum acceptable interval between metronidazole and Polybactum treatment is 24 hrs).

b)1st contact by phone
The initial phone interview must be done in concomitance with the 1st Polybactum® ovule administration in the 2nd cycle (28±1 days after the last day of last menses); to check

adherence to the treatment, and BV symptoms; visit and Amsel criteria only in suspect of BV recurrence.

c) 2nd contact by phone

The intermediate phone interview must be done in concomitance with the 1st Polybactum ovule administration in the 3rdcycle (28±1 days after the 1st phone contact); to check adherence to treatment, and BV symptoms; visit and Amsel criteria only in suspect of BV recurrence.

d) 3rdcontact by phone

This phone interview must be done the day following the last day of 3rd menses (28±1 days after the 2nd phone contact);
- The patient confirm the end of 3 cycles of Polybactum® ;
- The Investigator indicates the patient to avoid sexual intercourses during the 3 days before the Final Visit;
- No visit is requested at this date.

e) Final Visit

The visit must be performed 4±1 day after the 3rdphone contact (day 72 to day 84 from Baseline):
- physical examination;
- evaluation with Amsel criteria, (see above);
- vaginal swab (see above);
- Global Assessment of Safety performed by Investigator;
- Collection of data reported by patient in the Patient Diary (symptoms, adherence and Global Assessment of Efficacy);
- Polybactum® packages returned to the Investigator
- Nugent Score (not mandatory)

f) Follow-up period (12- 15 months, not mandatory)

- Phone Contact after 3 months
- Follow-up visit after 6 months after the Final Visit was performed at site (or 12-15 months from the start of the study).

The final visit will be performed in the timeframe of 12-15 months after the final visit of the study.

4 **Follow-up protocol**

Observational, non-randomized, not controlled, multicentre post marketing clinical follow up (PMCF) study to evaluate the safety and performance of the medical device Polybactum®in reducing the frequency of Recurrent Bacterial Vaginosis

5 **Study type:** Observational, Post Marketing Clinical Follow-Up
Indication studied: Recurrence of Bacterial Vaginosis
Design: observational, non-randomized, multicentre study
Name and address of Sponsor: EFFIK Italia S.p.A Via dei Lavoratori, 54 Milano (Italy)

Name and address of CRO: Opera Contract Research Organization (Opera CRO)
10 Cozia Street, Building B 300209 Timișoara (Romania)
Principal Investigator of Coordinating Centre: Dr. Filippo Murina Servizio di Patologia Tratto Genitale Inferiore U.O. Ostetricia e Ginecologia Ospedale Vittore Buzzi - Università degli Studi di Milano (Italy)
Statement of Compliance: Clinical Investigation Protocol performed in accordance with International Standard ISO14155 (Second edition 2011-02-01)

Objectives
The main objective of this PMCF study was to assess the safety, performance and long-term efficacy of Polybactum®.
Additional objectives were to detect potential emerging risks related to safety on the basis of eventual clinical evidence, through the extended follow up of patients who have used Polybactum® in the previous clinical trial, OPEFF/0116/MD (POLARIS).®

Methodology
This was an observational, non-randomized, multicentre study. This design was chosen to avoid that the protocol therapeutic strategy influenced the Investigator.
This follow-up study aimed to assess the safety, performance and long-term efficacy of Polybactum®. Furthermore, it permitted to detect potential emerging risks related to safety on the basis of eventual clinical evidence, through the extended follow up of patients who used Polybactum® in the previously performed clinical trial OPEFF/0116/MD (POLARIS).

Planned visits:
A = Screening and Baseline visit.
- physical examination;
- concomitant medications/treatments recordings;
- confirmation of BV absence by a negative test with Amsel criteria. This means that only 0 or 1 variable is met;
- ADE/ SADE/ USADE recordings.

This visit matched the final visit of OPEFF/0116/MD study
B = Phone contact with interview.
- assessment of BV symptoms;
- concomitant medications/treatments checking;
- ADE/ SADE/ USADE recordings;

If the patient had any of the BV symptoms after baseline, the Investigator could decide to perform an unscheduled visit to verify the BV recurrence by Amsel criteria.
C = Final visit (gynaecological examination and Amsel criteria check).
- physical examination;
- concomitant medications/treatments recordings;

- confirmation of BV absence by a negative test with Amsel criteria. This means that only 0 or 1 variable is met;
- ADE/ SADE/ USADE recordings;

If was not possible to perform the visit, a phone call with interview should have been done.

Evaluations included:
- Amsel criteria (vaginal pH, whiff test, homogenous vaginal discharge, and clue cells at optical microscopy by phase-contrast)
- Nugent Score (optional)
- Vaginal swab (Lactobacillus determination)

Sample size
Thirty-five (35) enrolled subjects belonging to OPEFF/0116/MD study in Romania (no d.o. or patients with recurrence in this study were included in the follow up). The patients belonging from Italian sites of OPEFF/0116/MD study were not included due to administrative reasons in the follow up observational study.

Inclusion criteria
- Women above 18 years.
- Patients who have completed the study OPEFF/0116/MD (last visit performed) without any recurrence.
- Subjects who voluntarily decide to participate in this observational study and sign the Informed Consent Form

Exclusion criteria
- Patients who do not want to visit for long-term follow-up observation.
- Patients who need/want to receive other procedures or treatments for prevention of recurrence of BV after participating in the previous study Protocol No OPEFF/0116/MD.
- Patients concomitantly included in different interventional clinical trials.
- Patients who are or become ineligible to participate in the present observational study for other reasons, as assessed by Investigator.

Criteria for efficacy evaluations
Primary Efficacy Assessments
The primary efficacy endpoint will be the evaluation of BV recurrence identified by Amsel criteria.
Secondary Efficacy Assessments
The secondary efficacy endpoints included:
- Vaginal Lactobacillus microbiota.
- Signs and symptoms of BV (vaginal discharge, burning, erythema, dyspareunia).

Criteria for safety evaluations

AE/SAE and ADE/SADE/USADE

Statistical Methods

Statistical analyses wad conducted on all patients entered in the study. The quality and completeness of the collected data were evaluated preliminarily compared to data analysis. If a patient had missing information for one or more variables, the missing data were not substituted. Quantitative variables (i.e. demographic) if normally distributed were described through mean, standard deviation (SD); variables non-normally distributed were described using median and range of interquartile. The Student's t-test and the Mann-Whitney U were employed to perform comparative analysis in accordance to the distribution of these variables. In order to evaluate changes over time before and after the treatment, Paired t-test (if applicable) or Wilcoxon signed rank sum test were planned to be performed for quantitative variables, while McNemar test was planned to be used in order to evaluate changes for binary variables, while symmetry test was performed in order to evaluate changes for qualitative (not binary) variables. Categorical variables were described using frequencies and percentages and comparative analysis using a Chi^2 test. All statistical analyses were performed using the R statistical software v 3.5. The final analysis (including performance and safety data) was completed after all CRFs was filled, and the database locked.

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