ACOG VIRTUAL Annual Clinical and Scientific Meeting April 30–May 2, 2021

Phase 3 Study of a Single-Dose Bioadhesive Clindamycin 2% Gel for Bacterial Vaginosis

S. Chavoustie[1], A. Goldstein[2], J. Gendreau[2], C. Mauck[2], D. Friend[2], S. Hillier[3]

[1]Segal Trials, Medical Director Women's Health

[2]Daré Bioscience, San Diego, CA

[3]University of Pittsburgh and the Magee-Women's Research Institute, Pittsburgh, PA

daré bio

INTRODUCTION

Bacterial vaginosis (BV) is the most common cause of vaginal discharge in women of childbearing age. It is a "dysbiosis" or imbalance in the vaginal microbiota characterized by a reduction in normally dominant hydrogen peroxide-producing lactobacilli and an increase in other organisms, especially anaerobic Gram-negative rods. BV can lead to a thin white or gray vaginal discharge and an unpleasant "fishy smell" that may be more noticeable after sexual intercourse and during menses. BV may also contribute to pelvic inflammatory disease, preterm birth, and increased risk of sexually transmitted infections. Currently, in the US, oral and intravaginal metronidazole, intravaginal clindamycin, oral tinidazole, and oral secnidazole are available for the treatment of BV.

DARE-BV1 is a thermosetting bioadhesive intravaginal gel formulated with 2% clindamycin phosphate designed to release the active ingredient for approximately 7 days. Research has shown that effective drug delivery is essential to optimizing drug therapy for BV.

AIMS OF STUDY

Primary Objective:

Assess the efficacy of a single dose of DARE-BV1 for the treatment of BV

Secondary Objective:

Assess the safety and acceptability of DARE-BV1

METHODS

Design: Randomized, multicentered, double-blind, placebo-controlled trial of a single-dose of DARE-BV1 vs. placebo

Eligibility: Presence of all 4 Amsel's criteria (Amsel 1983):

- Off-white (milky or gray), thin, homogeneous **discharge** with minimal or absent pruritus and inflammation of the vulva and vagina
- Cl**ue cells > 20**% of total epithelial cells on microscopic exam of saline wet mount
- Vaginal secretion **pH of > 4.5**
- Fishy odor of the vaginal discharge with a drop of 10% KOH (**positive whiff test**)

Primary Efficacy Endpoint:

- Proportion of patients with **Clinical cure**[1] at the test-of-cure visit (TOC) 21-30 days after dosing in the modified intent-to-treat population (mITT).[4]

Secondary Efficacy Endpoints:

- Proportion of patients with **bacteriological cure**[2] and proportion with **therapeutic cure**[3] at the TOC visit (Day 21 to 30) in mITT.[4]
- Proportion of patients with **clinical cure**, proportion with **bacteriological cure**, and proportion with **therapeutic cure** at the interim assessment visit (Day 7 to 14) in the mITT.[4]

[1] **Clinical cure:** resolution of BV discharge and whiff test, and clue cells <20%.

[2] **Bacteriological cure:** Nugent score < 4 (Nugent 1991)

[3] **Therapeutic cure:** both a clinical cure and bacteriological cure.

[4] ITT: all randomized subjects; **mITT:** ITT minus subjects with Nugent Score <7 or concomitant infection at randomization. **NOTE: Previous studies followed an earlier FDA Guidance (pre-2016 and 2019 versions) that allowed subjects with baseline Nugent scores ≥4 (i.e., those with baseline intermediate Nugent scores) to be in the mITT rather than requiring the current stricter criterion of >7 (i.e. bacterial vaginosis Nugent scores). In addition, unlike previous studies, patients were cultured for vaginal yeast at baseline and those with positive results were excluded from the mITT to ensure compliance with FDA guidance for absence of other infections.**

RESULTS

Participant characteristics

- 307 women enrolled at 32 U.S. centers, randomized 2:1 to a single intravaginal dose:
  - 204 DARE-BV1
  - 103 Placebo

	DARE-BV1 (N = 204)	Placebo (N = 103)	Total (N = 307)
Age			
Mean (SD)	34.6 (8.79)	35.2 (8.96)	34.8 (8.84)
Min, Max	15, 56	19, 59	15, 59
Race, n (%)			
Black or African American	116 (56.9)	56 (54.4)	172 (56.0)
White	82 (40.2)	44 (42.7)	126 (41.0)
Asian, Native Hawaiian, Other Pacific Islander, American Indian, Alaska Native, not reported	6 (2.9)	3 (2.9)	9 (2.9)
History of BV in past 12 months, n (%)	158 (77.4%)	76 (73.8%)	234 (76.2%)

Primary Objective: Assess the Efficacy of a Single Dose of DARE-BV1 for Treatment of BV

Modified Intent-to-Treat (mITT) Population (= ITT subjects minus those with Nugent Score <7 or concomitant infection at randomization)		DARE-BV1 (N = 122) n (%)	Placebo (N = 59) n (%)	Total (N = 181) n (%)
At the Test of Cure Visit (day 21-30)	**Clinical Cure - PRIMARY ENDPOINT**	**86 (70.5)**	**21 (35.6)**	**107 (59.1)**
	Bacteriological Cure	53 (43.4)	3 (5.1)	56 (30.9)
	Therapeutic Cure	45 (36.9)	3 (5.1)	48 (26.5)
At the Interim Visit (day 7-14)	Clinical Cure	93 (76.2)	14 (23.7)	107 (59.1)
	Bacteriological Cure	50 (41.0)	2 (3.4)	52 (28.7)
	Therapeutic Cure	43 (35.2)	0	43 (23.8)

Per Protocol Population (= mITT subjects who had no major protocol violations that impacted the primary or secondary endpoints)		DARE-BV1 (N = 102) n (%)	Placebo (N = 47) n (%)	Total (N = 149) n (%)
At the Test of Cure Visit (day 21-30)	Clinical Cure	79 (77.5)	20 (42.6)	99 (66.4)
At the Interim Visit (day 7-14)	Clinical Cure	83 (81.4)	14 (29.8)	97 (65.1)

All p values <0.001

Secondary Objective: Assess the Safety and Acceptability of DARE-BV1

Subjects with AEs that were possibly, probably or definitely related to study treatment		DARE-BV1 (N = 204) n (%)	Placebo (N = 103) n (%)	Total (N = 307) n (%)
All product-related AEs		31 (15.3)	10 (9.7)	41 (13.4)
Most common product-related AEs in DARE-BV1 group:	Vulvovaginal candidiasis	19 (9.3)	1 (1.0)	20 (6.2)
	Vulvovaginal pruritus	4 (2.0)	1 (1.0)	5 (1.6)

The relationship between the use of antibiotics like clindamycin and the development of candidiasis is well-known; it appears that having a positive yeast culture prior to receiving drug may predispose to candidiasis. In both groups at least half of the candidiasis occurred in patients who exhibited a positive yeast culture prior to dosing, [18/35 (51.4%)] in the DARE-BV1 group and exactly half of those reported in the placebo group [2/4 (50%)].

The majority of patients in the DARE-BV1 group (66.3% at the interim visit and 75.3% at the TOC) rated their overall experience with the study drug as "**very satisfied.**"

The majority of patients in the DARE-BV1 group (71.9% at the interim visit and 73.2% at the TOC) reported that they would be "**very likely" to recommend** the study drug to a friend who had BV.

CONCLUSIONS

DARE-BV1 clindamycin 2% was **highly effective** and **well-tolerated**.

The study used a **rigorous study design** that excluded from the mITT patients with intermediate Nugent scores and/or positive yeast cultures at baseline.

The study's **two treatment arms were well balanced** in terms of age, race, ethnicity, and BV history. Patients who are disproportionately affected by BV (Black patients and those with recurrent BV) were well-represented.

DARE-BV1 delivered **better clinical cure rates** at the Test-of-Cure visit than currently marketed branded FDA-approved single-dose vaginal products for treatment of bacterial vaginosis:

- **DARE-BV1, mITT: 70.5%**
  - **Per-protocol population: 77.5%**
- Clindamycin vaginal cream 2% (Clindesse®), mITT: 41.0-53.4%
  - Per-protocol population: 64.3%
- Metronidazole gel 1.3% (Nuvessa™): 37.0%

REFERENCES

- Amsel R, Totten PA, Spiegel CA, Chen KC, Eschenbach D, Holmes KK. Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations. Am J Med. 1983;74(1):14-22.
- Centers for Disease Control and Prevention (CDC). (2017, June). Bacterial Vaginosis - CDC Fact Sheet. https://www.cdc.gov/std/bv/BV-FS.pdf. Retrieved 29 May 2019.
- Nugent RP, Krohn MA, and Hillier SL. Reliability of diagnosing bacterial vaginosis is improved by a standardized method of gram stain interpretation. J Clin Microbiol. 1991;29(2):297-301.
- https://www.clindesse.com/pdf/PI.pdf
- https://www.nuvessa.com/nuvessa_files/Nuvessa%20PI%202018-08.pdf

ACKNOWLEDGEMENTS

Daré Bioscience wishes to thank May Beamer and Michele Austin from Magee-Women's Research Institute for their collaboration in training and Nugent scoring, both integral components of this trial.

CONTACT INFORMATION

Andrew Goldstein MD,
agoldstein@darebioscience.com