DARE-BV1, a Novel Single Dose 2% Clindamycin Phosphate Vaginal Gel

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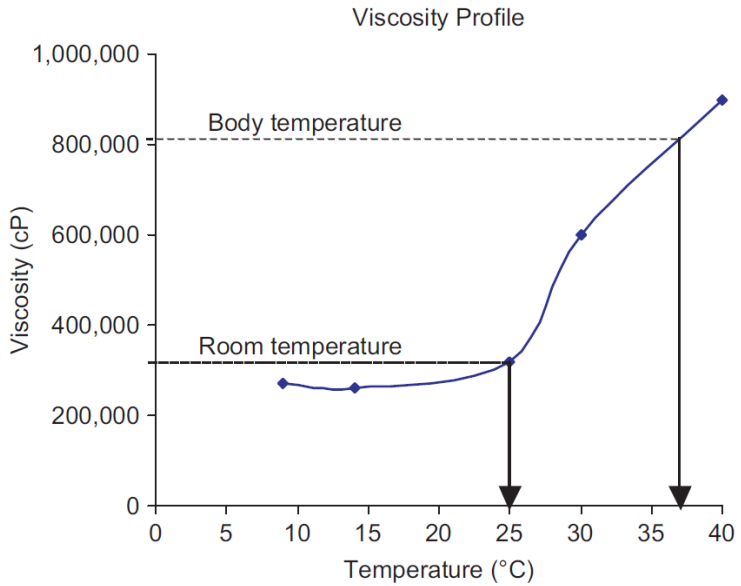
DARE-BV1 Background

- DARE-BV1 is a single dose 2% clindamycin phosphate vaginal gel for the treatment of bacterial vaginosis in adult women
- It began development in the late 2000s as a means to apply antibiotic gels to various locations in the body for the human and veterinary applications
- The technology was originally developed as a drug delivery matrix at the University of Missouri-Kansas City (T. P. Johnston) and Trilogic Pharma (H. Alur) and was called TRI-726
- A key design feature was the use of poloxamer to create a reversible in situ thermosetting gel
- It also contains xanthan gum designed to provide mucoadhesive properties
- The gel demonstrates high viscosity at body temperature which leads to in vitro sustained release characteristics

Initial Studies

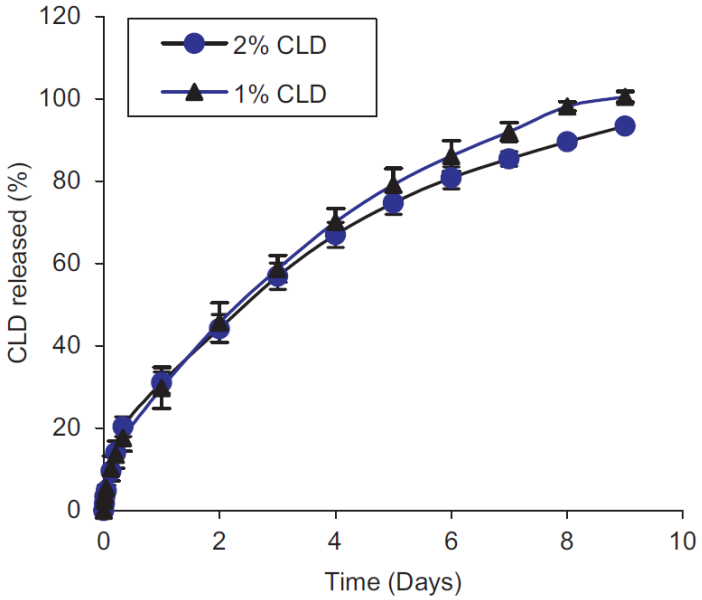
- The initial studies involved the drug clindamycin hydrochloride (CLD·HCl), several grades of poloxamer and xanthan gum[1]
- The thermosetting property was demonstrated:

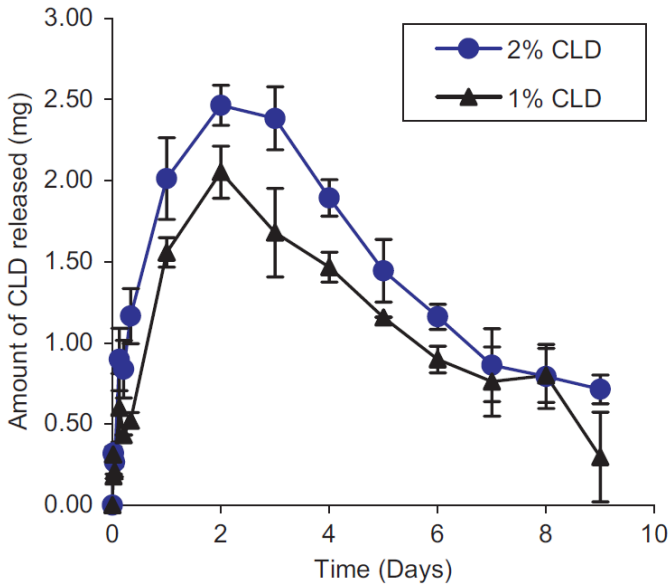


[1]M. Pravakar, H. Alur, T. P. Johnston, *Drug Dev. Indus. Pharm.*, **37**, 995-1001 (2011)

Initial Studies

- Theses gels demonstrated the ability to release CLD·HCl over a 7 to 8 day period[1]





[1]M. Pravakar, H. Alur, T. P. Johnston, *Drug Dev. Indus. Pharm.*, **37**, 995-1001 (2011)

TRL-726 Clinical Proof of Concept Study

Day 1
Baseline Visit

- Single dose administered
- Tests performed
  - Amsel (Primary)
  - Nugent (Secondary)
  - Urine pregnancy (if needed)

Day 7 - 14
Test-of-Cure Visit

- Patients questioned regarding comfort level and re-examined
- Tests performed
  - Clinical Cure (Primary)[1]
  - Bacteriologic Cure (Nugent, Secondary)
  - Urine pregnancy (if needed)

Day 21 - 30
Continued Clinical Response Visit

- Patients questioned regarding comfort level and re-examined
- Tests performed
  - Clinical Cure (Primary)
  - Bacteriologic Cure (Nugent, Secondary)
  - Urine pregnancy (if needed)

- Gel contained 2.0% clindamycin phosphate in 5 g dose (100 mg clindamycin)
- Single site, open-label investigator-initiated efficacy study (OBGYN Associates of Montgomery, Montgomery, AL)
- Eligibility: Female subjects 18 years or older with confirmed diagnosis of BV
- Primary endpoint: Clinical cure at Test-of-Cure Visit (defined as resolution of clinical findings from baseline visit based on Amsel Criteria)[1]
- Secondary endpoint: Proportion of women with Bacteriologic (Nugent score) and Therapeutic (combination of clinical and bacteriologic) Cures
- Safety: Women were questioned about their comfort level and any adverse reactions experienced

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

TRL-276 Clinical Proof of Concept Study

- 28 of 30 women enrolled completed the study[1]
- Test-of-Cure Visit (Day 7 – 14)
  - **24 of 28 (86%) achieved clinical cure based on Amsel Criteria**
  - 4 of 7 women had bacteriologic cure and 4 of 7 had therapeutic cure (subset of 10 women)
- Continued clinical response visit (Day 21 – 30)
  - **23 of 24 (96%) women showed continued clinical cure**
  - 7 of 9 women have bacteriologic cure and 6 of 9 had therapeutic cure

Product	Clinical (Amsel) Cure	Bacteriologic (Nugent) Cure	Therapeutic Cure
DARE-BV1	86%	57%	57%
Solesec®[2]	53-68%	40-46%	35-40%
Clindesse®[3]	41-64%	45-57%	30-42%
Metrogel®, 1.3%[4]	37%	20%	17%

A single dose of TRL-278 gel containing 2% clindamycin phosphate demonstrated high clinical cure rate compared to other approved products

1. A. Dupre, H. H. Alur, and D. R. Friend, Clin. Exp. Obstet. Gynecol., **47**, 516-518 (2020).
2. https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=551e43d5-f700-4d6e-8029-026f8a8932ff&type=display. Cure rate range reflects low and high cure rates across multiple studies.
3. http://www.clindesse.com/pdf/PI.pdf. Cure rate range reflects low and high cure rates across multiple studies
4. http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205223s000lbl.pdf

DARE-BV1

- Daré Bioscience acquired the rights to TRL -726 in late 2018 and renamed the product DARE-BV1
- Initiated transfer and scale-up of gel manufacture to DPT (San Antonio, TX) in early 2019
  - Final product configuration was a tube with a user-filled applicator (5 g dose of 2% clindamycin phosphate)
- Conducted a pre-IND meeting in mid 2019 to align with FDA on CMC, nonclinical, and clinical study requirements
- CMC
  - No substantive issues raised
- Nonclinical
  - Genotoxicity studies (in vitro and in vivo) for three excipients not previously administered vaginally in an approved prescription drug product
    - Poloxamer 407
    - Sodium citrate
    - Xanthan gum
  - Segment 1, 2 and 3 reproductive toxicology studies of vaginally administered DARE-BV1
  - DMPK study in rats (poloxamer 407)
  - 28-day vaginal and systemic toxicology study in rabbits of once-daily vaginally administered DARE-BV1
- Clinical
  - Reached agreement that a single, double-blind, placebo-controlled Phase 3 pivotal trial was acceptable as a registration study
- Requested and received a Qualified Infectious Disease Product (QIDP) status
  - Given Fast Track designation with the potential for expedited regulatory review (6 months rather than 10 months)
  - Five additional years of market exclusivity

DARE-BV1-001 Phase 3 Efficacy Trial[1]

- **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
- **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[2]):
  1. Off-white (milky or gray), thin, homogeneous discharge with minimal or absent pruritus and inflammation of the vulva and vagina
  2. Clue cells > 20% of total epithelial cells on microscopic exam of saline wet mount
  3. Vaginal secretion pH of > 4.5
  4. Fishy odor of the vaginal discharge with a drop of 10% KOH (positive whiff test)
- **Primary Efficacy Endpoint:**
  - Proportion of patients with **Clinical cure**[3] 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** and proportion with **therapeutic cure** 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. S. Chavoustie, A. Goldstein, J. Gendreau, C. Mauck, D. R. Friend, S. Hillier, American College of Obstetricians and Gynecologists Annual Meeting, 31 May 2021.
2. R. Amsel, P.A. Totten, C.A. Spiegel, K.C. Chen, D. Eschenbach, K.K. Holmes. Am. J. Med., **74**, 14-22 (1983).
3. **Clinical cure:** resolution of BV discharge and whiff test, and clue cells <20%.
4. **mITT:** ITT minus subjects with Nugent Score <7 or concomitant vaginal infection at randomization

DARE-BV1-001 Phase 3 Efficacy Trial[1]

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)

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)

1. S. Chavoustie, A. Goldstein, J. Gendreau, C. Mauck, D. R. Friend, S. Hillier, American College of Obstetricians and Gynecologists Annual Meeting, 31 May 2021.

DARE-BV1-001 Phase 3 Efficacy Trial[1]

DARE-BV1 clindamycin phosphate 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%

1. S. Chavoustie, A. Goldstein, J. Gendreau, C. Mauck, D. R. Friend, S. Hillier, American College of Obstetricians and Gynecologists Annual Meeting, 31 May 2021.

DARE-BV1 Final Points

- A New Drug Application was filed with FDA in June 2021 (505(b)(2) application)
- The Phase 3 was conducted in 2020 and despite COVID-19, the trial enrolled very quickly
- Attempted to enroll pediatric patients (age 12-17) but were unable to do so
- Demonstrated that it is possible to develop a novel product based on use of new delivery technology even in crowded therapeutic space

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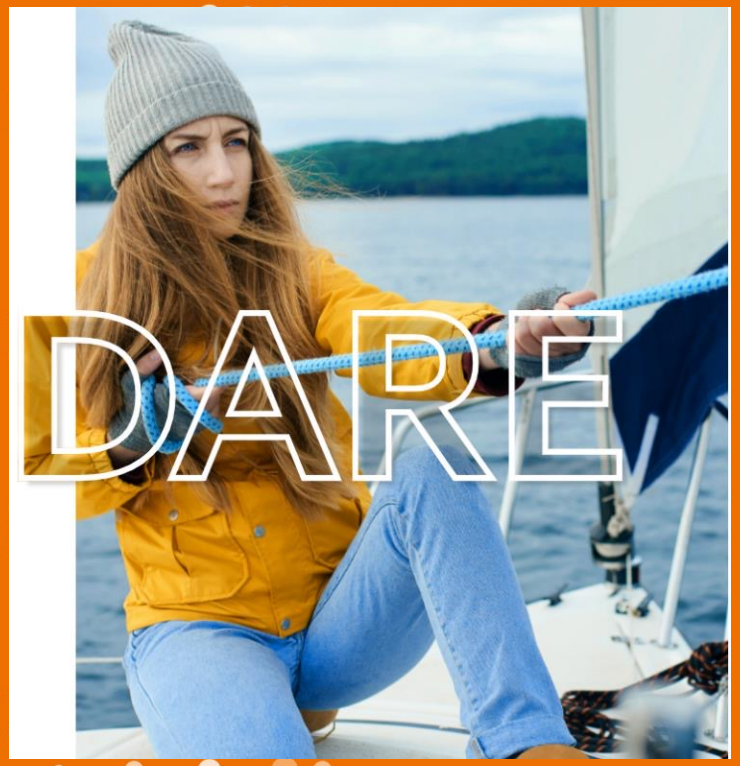

www.darebioscience.com