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.
• The initial studies involved the drug clindamycin hydrochloride (CLD-HCl), several grades of poloxamer and xanthan gum\textsuperscript{1}

• The thermosetting property was demonstrated:

\[\text{Viscosity Profile}\]

\[\begin{array}{c}
\text{Temperature (°C)} \\
0 & 5 & 10 & 15 & 20 & 25 & 30 & 35 & 40 \\
\hline
\text{Viscosity (cP)} \\
0 & 200,000 & 400,000 & 600,000 & 800,000 & \text{Body temperature} & \text{Room temperature} & \\
\end{array}\]

• Theses gels demonstrated the ability to release CLD·HCl over a 7 to 8 day period\textsuperscript{1}

# TRL-726 Clinical Proof of Concept Study

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7 - 14</th>
<th>Day 21 - 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Visit</td>
<td>Test-of-Cure Visit</td>
<td>Continued Clinical Response Visit</td>
</tr>
<tr>
<td>• Single dose administered</td>
<td>• Patients questioned regarding comfort level and re-examined</td>
<td>• Patients questioned regarding comfort level and re-examined</td>
</tr>
<tr>
<td>• Tests performed</td>
<td>• Tests performed</td>
<td>• Tests performed</td>
</tr>
<tr>
<td>• Amsel (Primary)</td>
<td>• Clinical Cure (Primary)¹</td>
<td>• Clinical Cure (Primary)</td>
</tr>
<tr>
<td>• Nugent (Secondary)</td>
<td>• Bacteriologic Cure (Nugent, Secondary)</td>
<td>• Bacteriologic Cure (Nugent, Secondary)</td>
</tr>
<tr>
<td>• Urine pregnancy (if needed)</td>
<td>• Urine pregnancy (if needed)</td>
<td>• Urine pregnancy (if needed)</td>
</tr>
</tbody>
</table>

- 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

¹Clinical cure: resolution of BV discharge and whiff test, and clue cells <20%
• 28 of 30 women enrolled completed the study

• 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

<table>
<thead>
<tr>
<th>Product</th>
<th>Clinical (Amsel) Cure</th>
<th>Bacteriologic (Nugent) Cure</th>
<th>Therapeutic Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>DARE-BV1</td>
<td>86%</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>Solesec®2</td>
<td>53-68%</td>
<td>40-46%</td>
<td>35-40%</td>
</tr>
<tr>
<td>Clindesse®3</td>
<td>41-64%</td>
<td>45-57%</td>
<td>30-42%</td>
</tr>
<tr>
<td>Metrogel®, 1.3%4</td>
<td>37%</td>
<td>20%</td>
<td>17%</td>
</tr>
</tbody>
</table>

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

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
**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):

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** at the test-of-cure visit (TOC) 21-30 days after dosing in the modified intent-to-treat population (mITT).

**Secondary Efficacy Endpoints:**
- Proportion of patients with **bacteriological cure** and proportion with **therapeutic cure** at the TOC visit (Day 21 to 30) in mITT.
- 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.

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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

## 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)

<table>
<thead>
<tr>
<th></th>
<th>DARE-BV1 (N = 122) n (%)</th>
<th>Placebo (N = 59) n (%)</th>
<th>Total (N = 181) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At the Test of Cure Visit (day 21-30)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Cure - PRIMARY ENDPOINT</td>
<td>86 (70.5)</td>
<td>21 (35.6)</td>
<td>107 (59.1)</td>
</tr>
<tr>
<td>Bacteriological Cure</td>
<td>53 (43.4)</td>
<td>3 (5.1)</td>
<td>56 (30.9)</td>
</tr>
<tr>
<td>Therapeutic Cure</td>
<td>45 (36.9)</td>
<td>3 (5.1)</td>
<td>48 (26.5)</td>
</tr>
<tr>
<td><strong>At the Interim Visit (day 7-14)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Cure</td>
<td>93 (76.2)</td>
<td>14 (23.7)</td>
<td>107 (59.1)</td>
</tr>
<tr>
<td>Bacteriological Cure</td>
<td>50 (41.0)</td>
<td>2 (3.4)</td>
<td>52 (28.7)</td>
</tr>
<tr>
<td>Therapeutic Cure</td>
<td>43 (35.2)</td>
<td>0</td>
<td>43 (23.8)</td>
</tr>
</tbody>
</table>

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

**Subjects with AEs that were possibly, probably or definitely related to study treatment**

<table>
<thead>
<tr>
<th></th>
<th>DARE-BV1 (N = 204) n (%)</th>
<th>Placebo (N = 103) n (%)</th>
<th>Total (N = 307) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All product-related AEs</td>
<td>31 (15.3)</td>
<td>10 (9.7)</td>
<td>41 (13.4)</td>
</tr>
<tr>
<td>Most common product-related AEs in DARE-BV1 group:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal candidiasis</td>
<td>19 (9.3)</td>
<td>1 (1.0)</td>
<td>20 (6.2)</td>
</tr>
<tr>
<td>Vulvovaginal pruritus</td>
<td>4 (2.0)</td>
<td>1 (1.0)</td>
<td>5 (1.6)</td>
</tr>
</tbody>
</table>

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DARE-BV1-001 Phase 3 Efficacy Trial

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%

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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