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A Phase 1 pharmacokinetic study of a single-dose bioadhesive clindamycin 2% gel for bacterial vaginosis

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Objectives: To evaluate pharmacokinetics (PK) of a single dose of an investigational 2% clindamycin phosphate vaginal gel in healthy women by assessment of plasma and vaginal clindamycin concentrations over 7 days, and assess safety.

Methods: Single-centre, Phase 1, single-dose PK study. Blood and vaginal samples were collected daily and safety was evaluated through to Day 7.

Results: Twenty-one subjects were enrolled; 20 completed the study. Plasma clindamycin concentrations demonstrated quantifiable values in all subjects through to 24 h post-dose, remaining above the limits of quantification (LOQ) through to 48 h for the majority of subjects. Systemic exposure (AUC_{0-t}) was 1179 (range 62–3822) h·ng/mL. Arithmetic mean AUC_{0-24} was 818 (range 51–3287) h·ng/mL. Vaginal clindamycin phosphate levels were relatively high 24 h following administration in 15/21 subjects (6 subjects had values >400 μg/g and 9 had values of 100–400 μg/g). The levels dropped in most participants to below the LOQ 2 days following dosing. In a few participants, levels remained elevated for several days. Maximal amounts of vaginal clindamycin occurred on Day 2 with a mean value of 30.3 μg. One treatment-emergent adverse event (TEAE) of moderate-severity headache not related to study drug was reported and resolved on Day 1. No TEAEs were related to physical examinations, pelvic examinations, laboratory values or vital signs.

Conclusions: The vaginal concentrations of clindamycin phosphate plus the clindamycin plasma profile over time are consistent with release of drug from the investigational gel over 24 to 72 h. A single dose was well tolerated.

Introduction

Bacterial vaginosis (BV) is the most common vaginal infection in postmenarchal females of childbearing age. It is associated with a disruption in the normal vaginal microbiota, with a decrease in lactic acid-producing bacteria and an increase in various anaerobes.[1] Symptoms include vaginal discharge, pain, itching, burning, and odour, as well as dysuria.[2] BV is associated with an increased risk of pelvic inflammatory disease, infertility, adverse pregnancy outcomes and sexually transmitted infections including HIV.[1]

Currently, in the USA, oral and intravaginal metronidazole, oral and intravaginal clindamycin, oral tinidazole and oral secnidazole are available for the treatment of BV.[2] Topical application, safety and efficacy of vaginally delivered clindamycin phosphate have been widely demonstrated in published literature.[3] Clindamycin can be classified as a time-dependent antibiotic, whereby maximizing the amount of drug and the exposure time to the bacteria is recommended to improve efficacy. Xaciato™ ('zah-she-AH-toe,' Daré Bioscience, Inc., San Diego, CA, USA) is a clear, colourless, thermosetting bioadhesive intravaginal gel containing clindamycin at a concentration of 2%. A single-dose user-filled disposable applicator delivers 5 g of vaginal gel containing 100 mg of clindamycin (present as 119 mg of clindamycin phosphate). At room temperature, the investigational product is a viscous liquid that transitions to a temporary self-forming polymeric gel at body temperature with no alteration in the product's chemical composition. This gelling phase change in the vaginal space renders it immobile, which is designed to reduce leakage, improve vaginal retention time and provide a platform from

which the clindamycin is slowly released over approximately 7 days, based on *in vitro* data.[4] By slowly releasing the clindamycin, the amount available for systemic uptake and bioavailable drug exposure to the patient is minimized. These factors should result in better user compliance, higher cure rates and potentially reduced systemic side effects. Results of a double-blind, placebo-controlled, randomized study comparing the investigational product's efficacy and safety are reported elsewhere, and the results supported the theoretical advantages of the product design.[5] A clinical cure rate of 70% was observed, higher than that seen with other marketed BV treatments, with excellent safety.

This study's primary objective was to evaluate the pharmacokinetics (PK) of a single dose of the investigational product in healthy female subjects by assessment of plasma and vaginal clindamycin concentrations over 7 days. The secondary objective was to further assess the investigational product's safety and tolerability.

Methods

This was a single-centre, Phase 1, single-dose, open-label PK study of the investigational product in healthy women in the USA. The flow diagram summarizes the enrolment and participation of subjects (Figure 1). Healthy female subjects ≥18 years of age who met the following criteria were eligible to enrol in the study: had not used any other investigational product within 30 days of the screening visit; did not have a history of regional enteritis, ulcerative colitis or *Clostridioides difficile*-associated diarrhoea or sensitivity to clindamycin phosphate, other lincosamides, or any

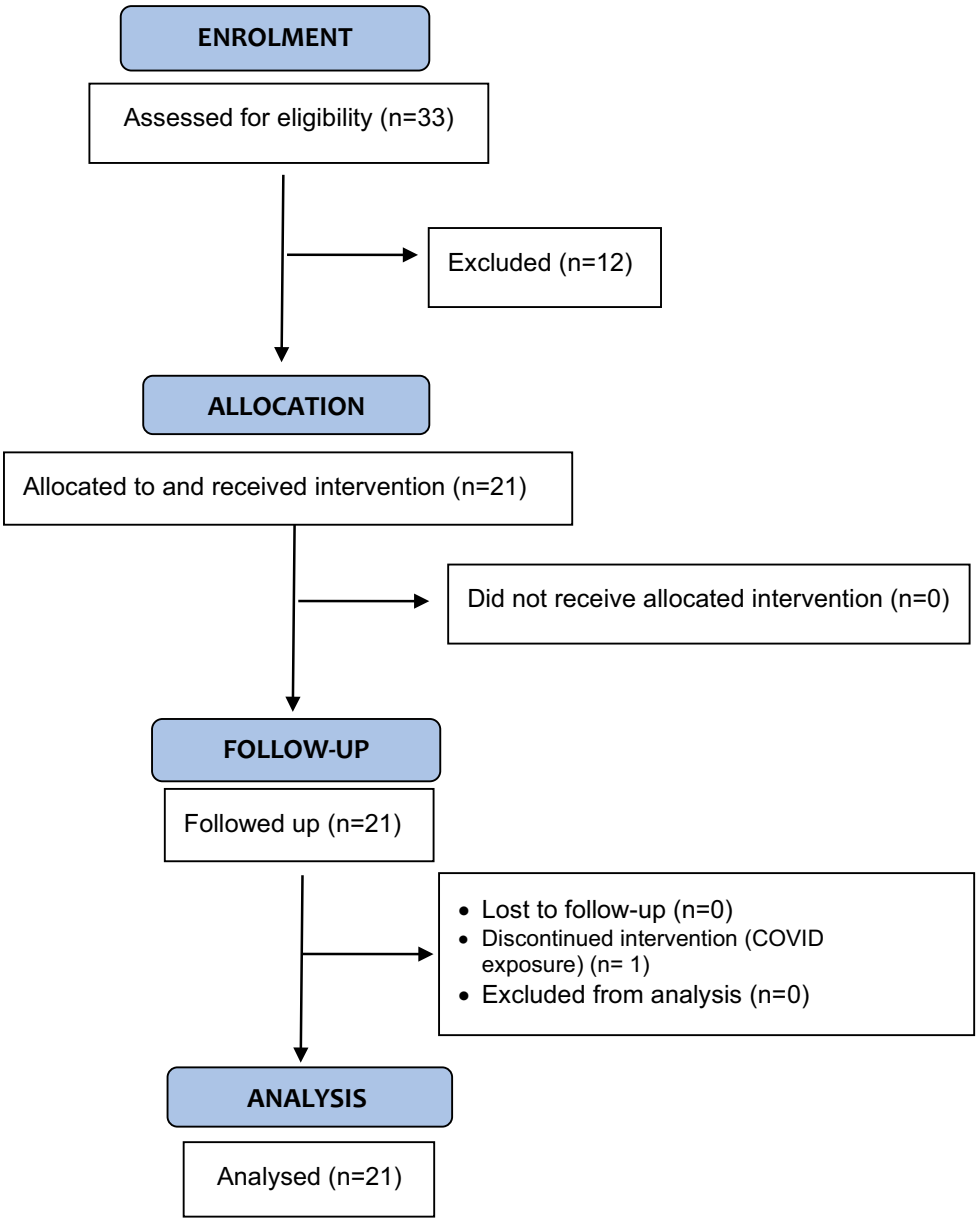

Figure 1. Flow diagram.

Table 1. Summary of demographic data and baseline physical measurements (safety population)

Parameter	Overall ($N=21$)
Age (years)	
Mean (SD)	56.7 (15.65)
Median (min–max)	58.0 (28–80)
Sex, *n* (%)	
Female	21 (100.0)
Ethnicity, *n* (%)	
Hispanic or Latino	11 (52.4)
Not Hispanic or Latino	10 (47.6)
Race, *n* (%)	
Black or African American	6 (28.6)
White	15 (71.4)
Weight (kg)	
Mean (SD)	71.3 (12.1)
Median (min–max)	70.5 (53.3–99.7)
Height (cm)	
Mean (SD)	159.0 (8.1)
Median (min–max)	159.8 (139–177)
BMI (kg/m^2)	
Mean (SD)	28.4 (3.7)
Median (min–max)	27.9 (21.8–35.3)
Menopausal status, *n* (%)	
Premenopausal	6 (28.6)
Postmenopausal	15 (71.4)

Max = maximum; min = minimum; *n* = number of subjects in the respective category; *N* = number of subjects in the enrolled or safety set. Percentages were based on the number of subjects included in the enrolled or safety set in each treatment sequence.

of the inactive ingredients in the study drug; did not have human papillomavirus (HPV) 16 or 18 at screening (performed on subjects >25 years old); did not have active BV, vulvovaginitis or other active infectious causes of cervicitis, vaginitis, vulvitis or urinary tract infection at screening; were not pregnant, breastfeeding or at risk for pregnancy; and were willing to refrain from use of all other intravaginal products. A total of 22 subjects were planned to obtain at least 20 evaluable subjects. The sample size was based on practical considerations since hypothetical inferences were not required.

The study included seven scheduled in-clinic visits. At the Screening Visit, written informed consent was obtained, past medical and gynaecological history was collected, and the following tests were performed: Affirm™ Vaginal Pathogens DNA Direct Probe test (VAGDNA) for *Candida* species, *Gardnerella vaginalis* and *Trichomonas vaginalis*, tests for gonorrhoea and chlamydia, HPV test with reflex cytology (for subjects >25 years old), urine pregnancy test (for women of childbearing potential), blood sample for chemistry and haematology, and urinalysis. These were repeated at both the Visit 2 (Day 1) and End-of-Study (EOS) Visit 7/(Day 7), with the exception of HPV testing, which was done only at the Screening Visit and Visit 2. Urine pregnancy tests, urinalyses and assessment of local site reactions were also done on Days 3 to 6.

The investigational product was supplied in 25 g tubes with accompanying applicators and instructions. One applicator dispensed 5 g of study product [100 mg clindamycin, the same dose delivered by marketed vaginal clindamycin BV treatments (Cleocin®, Clindesse®)]. One full applicator was administered intravaginally to the subject by site staff as a single dose on Day 1 at the study site. The weight of the study drug

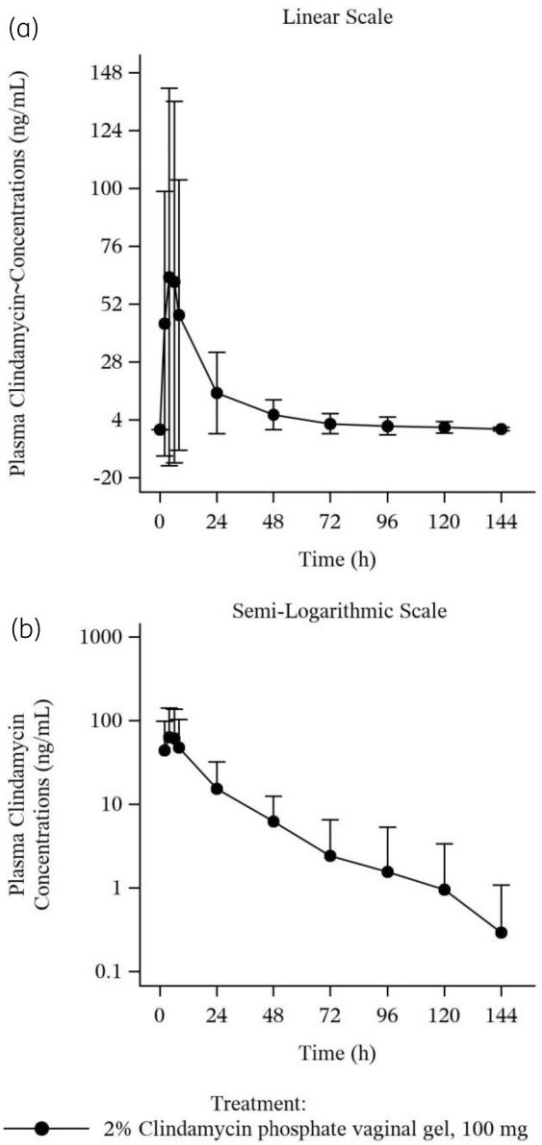

Figure 2. Mean (±SD) plasma clindamycin concentrations (ng/mL) over time (PK evaluable set): a) linear scale, b) semilogarithmic scale. BLQ, below the LLOQ; ND, not detectable. BLQ values prior to the first measurable concentration are set to zero (0). All other BLQ and ND values are set as missing. Red solid line represents the average profile (geometric mean).

tube and applicator prior to and after dispensing from the study drug tube were recorded. Subjects agreed to abstain from sexual activity throughout the 7 days following treatment.

Subjects had blood draws for plasma clindamycin assessment taken at 0 h (pre-dose) and then post-dose at 2, 4, 6 and 8 h (±15 min) on Day 1 and at 24, 48, 72, 96, 120 and 144 h (±2 h, Days 2 to 7). Subjects remained resident in the clinical research unit until discharged after the 24 h post-dose PK sample collection on Day 2. The subjects returned to the clinic for Outpatient Visits on Days 3 to 7/EOS for PK sample collections and safety assessments. Assessment and documentation of adverse events (AEs) and concomitant medications occurred at each visit. A review of subject-reported and investigator-assessed local site reactions occurred at each visit after treatment.

Table 2. Summary of plasma clindamycin PK parameters (PK evaluable set)

Parameter/statistic	Overall $N=21$
C_{max} (ng/mL)	
Mean	69.2
GM	31.4
CV (%)	113
AUC_{0-t} (h·ng/mL)	
Mean	1179
GM	754
CV (%)	85.1
AUC_{inf} (h·ng/mL)	($n=9$)
Mean	1975
GM	1610
CV (%)	53.2
AUC_{0-24} (h·ng/mL)	
Mean	818
GM	415
CV (%)	112
T_{max} (h)	
Median	6.00
Min–max	4.00–95.83
$t_{½}$ (h)	($n=10$)
Mean	20.0
GM	11.8
CV (%)	151
T_{last} (h)	
Median	48.4
Min–max	24.00–145.15
C_{last} (ng/mL)	
Mean	3.54
GM	2.27
CV (%)	104

CV (%) = coefficient of variation; %extrap = AUC extrapolated from time t to infinity as a percentage of total AUC; GM = geometric mean; Inf = infinity; max = maximum; min = minimum; n = number of subjects in the respective category; R^2 = square of the correlation coefficient. The $t_{½}$ for subjects with adjusted $R^2 < 0.8$ was not summarized. The AUC_{inf} for subjects with the adjusted $R^2 < 0.8$ or $AUC_{\%extrap} > 20\%$ were not summarized. AUC_{inf} and $t_{½}$ could not be determined for several subjects due to less than three points in the elimination phase.

Table 3. Summary of plasma clindamycin PK parameters by menopausal status (PK evaluable set)

Parameter/ statistic	Pre ($n=6$, unless otherwise stated)	Post ($n=15$, unless otherwise stated)
C_{max} (ng/mL)		
Mean	11.3	92.3
GM	10.6	48.6
CV (%)	37.7	89.0
AUC_{0-t} (h·ng/mL)		
Mean	564	1426
GM	447	930
CV (%)	87.2	74.5
AUC_{inf} (h·ng/mL)	($n=1$)	($n=8$)
Mean	251	2190
GM	251	2031
CV (%)	NC	40.4
AUC_{0-24} (h·ng/mL)		
Mean	188	1070
GM	163	603
CV (%)	47.5	91.3
T_{max} (h)		
Median	16.00	6.00
Min–max	6.00–48.38	4.00–95.83
$t_{½}$ (h)	($n=1$)	($n=9$)
Mean	16.9	20.4
GM	16.9	11.4
CV (%)	NC	158
T_{last} (h)		
Median	72.00	48.07
Min–max	48.03–145.15	24.00–144.10
C_{last} (ng/mL)		
Mean	3.30	3.64
GM	1.49	2.69
CV (%)	170	77.9

CV (%) = coefficient of variation; %extrap = AUC extrapolated from time t to infinity as a percentage of total AUC; GM = geometric mean; Inf = infinity; max = maximum; min = minimum; n = number of subjects in the respective category; NC = not calculable; R^2 = square of the correlation coefficient. The $t_{½}$ for subjects with adjusted $R^2 < 0.8$ was not summarized. The AUC_{inf} for subjects with the adjusted $R^2 < 0.8$ or $AUC_{\%extrap} > 20\%$ was not summarized. AUC_{inf} and $t_{½}$ could not be determined for several subjects due to fewer than three points in the elimination phase.

In addition, samples for vaginal clindamycin concentrations were collected once daily on Days 1 to 7 (with the Day 1 sampling done pre-dose). Swabs were removed from the transport tube and used to obtain a sample of the vaginal pool, ensuring the swab head was fully saturated. Swabs were then withdrawn and placed back into the transport tube, which was re-capped and stored at −20°C until shipment.

An analytical method to determine concentrations of clindamycin in human plasma (K_2EDTA) was developed and validated by Pyxant Labs Inc. (Colorado Springs, CO, USA). Validation samples were prepared by a protein precipitation extraction procedure. Extracts were analysed by LC-MS/MS in multiple reaction monitoring (MRM) mode under optimized conditions for detection of clindamycin and clindamycin-^{13}C, D_3 (internal standard) positive ions formed by electrospray ionization (ESI). The method was validated with concentrations that ranged from 0.500 to 500 ng/mL. Quality control (QC) samples were prepared at concentrations of 0.500, 1.50, 15.0, 150, 375 and 1500 ng/mL (for dilution purposes). Thus, the lower limit of quantitation (LLOQ) was 0.500 ng/mL and the upper limit of quantitation was 1500 ng/mL.

Vaginal clindamycin phosphate concentrations were analysed by Avomeen (Ann Arbor, MI, USA) as follows. Frozen swabs received from the clinical site were allowed to thaw for approximately 1–3 h to avoid change in moisture. Swabs were weighed and the tip of each swab was cut off into an amber HPLC vial. One millilitre of Cytoloid (a mucolytic reagent with dithiothreitol) was added to the vial and it was briefly vortexed to mix well. The vial was placed in a heat block at 70°C for 2 h. The vial was removed from the heat and 0.5 mL of tetrahydrofuran was added and the vial was vortexed briefly to mix well. The vial was placed in sonication for approximately 10 min. The contents of the vial were quantitatively transferred to a

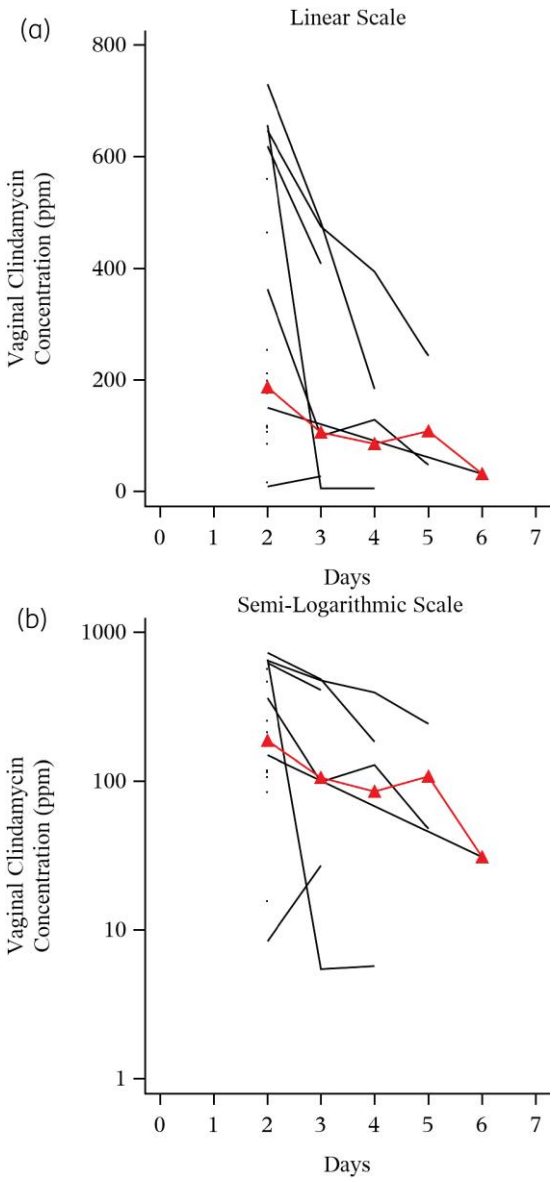

Figure 3. Spaghetti plot of vaginal clindamycin concentrations versus time (PK full set): a) linear scale, b) semilogarithmic scale. BLQ, below the LLOQ; ND, not detectable. Day 1 is the day of dosing. Day 2 is 24 h after dosing. Day 3 is 48 h after dosing. BLQ values prior to the first measurable concentration are set to zero (0). All other BLQ and ND values are set as missing. Red solid line represents the average profile (geometric mean).

scintillation vial using 1.5 mL of diluent [77.5% potassium phosphate monobasic (0.07 M): 22.5% acetonitrile, pH 2.5], vortexed briefly to mix well, and then returned to sonication for approximately 10 additional minutes. The samples were then analysed using a validated HPLC method on an Agilent 1100 Infinity HPLC system. The column used was a Phenomenex Prodigy C8, 150 Å, 250 mm × 4.6 mm, 5 µm. The mobile phase was 77.5% potassium phosphate monobasic (0.07 M): 22.5% acetonitrile, pH 2.5. The flow rate was 1.0 mL/min (isocratic). The detection was UV (210 nm). An injection volume of 20 µL at 30°C was used. The LLOQ of this method was 2.24 µg/mL.

The data were exported in the form of SAS® (SAS Institute, Cary, NC, USA) datasets following database lock. ICON SAS programmers applied validated electronic programs on the data using SAS Version 9.4 to produce tables, figures and listings. PK variables were calculated from the plasma clindamycin concentrations and, when data permitted, for vaginal clindamycin concentrations using non-compartmental methods (Phoenix WinNonlin®, Version 8.0.0.3176) and actual sampling times. Following administration, C_{min}, C_{max} and T_{max} were obtained directly from the experimental observations. AUC_{0-t} was calculated using the linear/log trapezoidal rule.

The analysis populations included the enrolled set, which included all subjects who were screened and enrolled, and was used for disposition and demography summaries. The safety set consisted of subjects who received one dose of the investigational product and was used for safety data and baseline characteristic summaries. The PK full set included all subjects who received one dose of the investigational product, had at least one plasma concentration data point, and was used for the analysis of concentration summaries and figures. The PK evaluable set included all subjects who received one dose of the investigational product and had a sufficient plasma PK profile to derive at least one primary PK endpoint; it was used for the PK parameter endpoint summaries.

The study followed the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and was approved by the IntegReview Institutional Review Board of Austin, TX, USA on 28 October 2020. The study's ClinicalTrials.gov identifier is NCT05354050.

Results

The first participant consented on 03 November 2020 and the last participant visit was on 02 December 2020. Twenty-one subjects were enrolled, dosed and analysed, and 20 subjects (95.2%) completed the study. One subject (4.8%) was dosed on 18 November 2020 and discontinued the study early on 21 November 2020 due to a COVID-19 exposure. The discontinued subject returned to the site on Day 15 to complete EOS procedures. Demographics are shown in Table 1.

Plasma clindamycin concentrations were quantifiable post-dose in all but one subject by the first sample at 2 h, in all subjects by 4 h, and in all subjects through to 24 h. At 48, 72 and 96 through to 144 h post-dose, 18, 10 and 3 subjects, respectively, had measurable concentrations. The mean plasma concentrations over time are shown in Figure 2.

The arithmetic mean peak plasma concentrations were 69.2 ng/mL and were highly variable, with CV (%) of 113% (the range of individual C_{max} values was 3.8 to 236 ng/mL) (Table 2). The median T_{max} occurred at 6.00 h, with individual values ranging from 4 to 96 h. Exposure to clindamycin was also highly variable [CV (%) = 85.1% for AUC_{0-t} and 112% for AUC_{0-24}). The arithmetic mean AUC_{0-t} was 1179 h·ng/mL, with a range of values from 62 to 3822 h·ng/mL, and the arithmetic mean AUC_{0-24} was 818 h·ng/mL, with a range of values from 51 to 3287 h·ng/mL. The arithmetic mean AUC_{inf} was 1975 h·ng/mL and the arithmetic mean $t_{½}$ of clindamycin in plasma was 20.0 h but could only be determined for 9 of the 21 and 10 of the 21 subjects, respectively.

To explore the variability found in the results seen among all participants taken together, the PK parameters were summarized after dividing women by menopausal status (Table 3). The vaginal atrophy resulting from menopause can be expected to allow greater absorption of intravaginally applied drugs,[6] with resulting higher plasma levels shown by higher C_{max} and greater AUC. This effect was observed in this study, with premenopausal women having an arithmetic mean C_{max} of 11.3 ng/mL and

AUC_{0-24} of 188 h·ng/mL, compared with 92.3 ng/mL and 1070 ng·h/mL, respectively, among postmenopausal women.

A spaghetti plot of vaginal clindamycin phosphate concentrations versus time is shown in Figure 3. Vaginal clindamycin phosphate concentrations were not quantifiable in three of the subjects. Clindamycin phosphate levels, measured as the weight of swabs containing vaginal fluid minus their pre-swabbing weight, indicated that in nearly all subjects (15 of 21), the levels were relatively high 24 h following administration of the investigational product (6 subjects had values >400 μg/g and 9 had values between 100 and 400 μg/g). The levels dropped in most participants to below the limit of quantitation 2 days following dosing. In a few participants, levels remained elevated for several days. Maximal amounts of vaginal clindamycin occurred on Day 2, with a mean value of 30.3 μg. The mean amount decreased by approximately 50% on Day 3.

No serious AEs (SAEs) were reported, and no treatment-emergent AEs (TEAEs) led to the discontinuation of study drug. Two subjects (9.5%) reported one AE each. One AE of skin abrasion unrelated to study drug was reported by a subject prior to Day 1 dosing. One TEAE of headache that was of moderate severity and considered by the investigator to not be related to study drug was reported and resolved on Day 1. No abnormalities in physical examination or pelvic examination findings were noted after Day 1 dosing. No local site reactions were noted at any timepoint. A few sporadic abnormalities in laboratory values and vital sign data were noted but none was deemed clinically significant by the investigator and no TEAEs were related to laboratory values or vital signs.

Discussion

The primary objective of this study was to evaluate the PK of a single dose of the investigational product in healthy female subjects by assessment of plasma and vaginal clindamycin concentrations.

Plasma clindamycin concentrations demonstrated quantifiable values in all subjects through to 24 h post-dose, remaining above the limits of quantification through to 48 h for the majority of subjects. The mean C_{max} of clindamycin for Xaciato was approximately 0.5% of that observed after the IV infusion of clindamycin phosphate in 0.9% sodium chloride with 900 mg clindamycin, every 8 h.[7] Postmenopausal women showed greater systemic absorption of clindamycin than premenopausal women, owing most likely to the vaginal atrophy characteristic of the postmenopausal state. To our knowledge, this was the first study to compare the absorption profile of clindamycin in pre- and postmenopausal women.

Vaginal clindamycin phosphate levels indicated that in nearly all subjects, the levels were relatively high 24 h following administration, with maximal amounts of vaginal clindamycin occurring on Day 2, dropping in most subjects to below the limit of quantitation 2 days following dosing. In a few participants, levels remained elevated for several days. These data support the original design of the product, which was to provide an extended duration of clindamycin exposure for improved efficacy in treating BV. The local concentrations of clindamycin phosphate plus the clindamycin plasma profile over time are consistent with release of drug from the gel over 24 to 72 h.

The secondary objective of this study was to assess the safety and tolerability of the investigational product. A single dose of the investigational product was found to be safe and well tolerated in this group of healthy women.

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Transparency declarations

C.K.M. and D.R.F. are employees of Daré Bioscience, Inc. and receive cash compensation and stock options in the company in connection with their employment. N.Z. was previously employed by the company and received cash compensation and stock options in the company during her employment. G.J.A., who was the principal investigator in the study, L.R. and J.M. are or were employed by ICON, which was contracted to conduct the study. J.M. is a medical writer who wrote the clinical study report for the study.

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