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A two-part phase I study to establish and compare the safety and local tolerability of two nasal formulations of XF-73 for decolonization of *Staphylococcus aureus*: A previously investigated 0.5 mg/g viscosified gel formulation versus a modified formulation

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Abstract

OBJECTIVES: There is conflicting data on the success of mupirocin as an effective decolonizing regimen for *Staphylococcus aureus* (SA) carriage, in part due to increasing drug resistance. This multi-center, randomized, open-label, prospective phase 1 study compared the safety and local tolerability of two nasal formulations of XF-73, a novel porphyrinic antibacterial drug with rapid intrinsic activity against *SA*.

METHODS: The study was conducted in 2 dosing cohorts, and enrolled 60 healthy adults. In Part 1, 8 non-SA carriers were randomized to 2 groups of 4 subjects in each arm and were treated with

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DECLARATIONS

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the new formulations of XF-73 in concentrations of 0.5 mg/g 2% gel and 2 mg/g 2% gel, respectively. In Part 2, 52 healthy persistent SA carriers were randomized to 4 groups of 13 subjects in each arm and were treated with three different concentrations of XF-73 (0.5 mg/g 2% gel, 2 mg/g 2% gel and 0.5 mg/g 4% gel) or a 4% viscosified placebo gel, respectively. Plasma pharmacokinetics (PK) and pharmacodynamics (PD) studies were performed. Anti-staphylococcal activity was assessed as the presence or absence of SA and by quantification of the level of colonization using a semi-quantitative scale (SA score).

RESULTS: 56 subjects (8/8 from Part 1 and 48/52 from Part 2) completed the study, with 47/60 comprising the PK population and 48/60 the PD population. There was no measurable systemic absorption of XF-73 from nasal application. Treatment with XF-73 was associated with a rapid diminution in the SA scores in all subjects. The most common treatment emergent adverse events (TEAE) reported were rhinorrhea and nasal dryness (15.5% each in Part 1 and Part 2). TEAEs were mostly mild and resolved spontaneously.

CONCLUSION: XF-73 was found to be safe and was tolerated with minimal side effects at doses of 0.5mg/g 2% gel and 2mg/g 2% gel in healthy volunteers. These findings support moving on to Phase 2 trials to further evaluate the efficacy of XF-73.

Keywords

Staphylococcus aureus; decolonization; XF-73; antimicrobial resistance

INTRODUCTION

Methicillin-susceptible (MSSA) and methicillin-resistant (MRSA) *S. aureus* (SA) strains are the most common causative organisms of healthcare-associated infections worldwide [1]. SA can colonize various body sites; however, the anterior nares have been identified as the most frequent site of carriage. Nasal colonization with *S. aureus* is the single most important determinant of subsequent invasive *S. aureus* infection. Colonization—whether present on admission or hospital-acquired— increases the risk of hospital acquired infections [3–5]. Colonized individuals are at a higher risk of invasive staphylococcal infections following invasive procedures and carry substantial morbidity and mortality, with a significant impact on healthcare costs [6–8].

Several studies have reported that pre-operative use of mupirocin together with skin decontamination with chlorhexidine or triclosan body wash resulted in a significant decrease in nosocomial SA infections in SA carriers [9–11]. There are few antibiotics specifically approved for intranasal use for SA decolonization, with mupirocin being the only topical preparation approved in the United States for eradication of carriage of MRSA. As is the case with other antibiotics, widespread use of mupirocin has been reported to be associated with emergence of mupirocin-resistant MRSA strains [12–16]. There is, therefore, a clinical need for alternative therapies to mupirocin for use in nasal decolonization.

XF-73 is a novel porphyrinic antibacterial drug that was developed for treatment or eradication of SA carriage. Its mechanism of action has not been precisely defined but it has been shown to interfere with several membrane functions. Bacterial cell death induced by

exposure to XF-73 is not accompanied by lysis of the cells, but appears to result from a rapid effect on the integrity of the cytoplasmic membrane with significant loss (>95%) of membrane potential observed within 1 minute [17]. In *in vivo* studies, XF-73 has been shown to exhibit potent and rapid antimicrobial activity against SA and other gram-positive and gram-negative organisms [17–19]. Additionally, its safety and efficacy have been previously evaluated in three preclinical studies in subjects colonized with SA [19]. No serious adverse events (SAEs) were reported and XF-73 was very well tolerated in concentrations up to 2.0 mg/g gel (total maximum dosage / application =1.2 mg) applied to both nares [19]. AEs reversed spontaneously without sequelae.

In this two-part phase I study, we compared the safety and local tolerability of two nasal formulations of XF-73 for decolonization of *S. aureus*—a previously investigated 0.5 mg/g 4% viscosified gel formulation versus a modified formulation at two different concentrations (i.e., 2 mg/g 2% gel and 0.5 mg/g 2% gel, respectively).

MATERIALS AND METHODS

Materials

The investigational drug product, XF-73 gel, was provided by the manufacturer, Destiny Pharma, pic. (Brighton, UK), at three different concentrations, i.e., 0.5 mg/g 2% gel; 2 mg/g 2% gel; and 0.5 mg/g 4% gel. A color-matched placebo gel prepared using the same base, gelling agent and preservative system was also supplied by Destiny Pharma, plc. Sage® 2% chlorhexidine gluconate (CHG) wipes for skin decontamination were supplied by Sage Products, Inc. (Cary, ILTrial design).

Study design and population

This was a multi-center, randomized, open-label, double-blinded placebo controlled prospective study in healthy adult volunteers from October 2012 to October 2015 (Clinicaltrials.gov registration number NCT01592214). The study was conducted in two dosing cohorts—Part 1 and Part 2 respectively (Figure 1). The study was approved by the Institutional Review Boards at UHCMC and ACT and all subjects provided written informed consent prior to participating in the study. Full eligibility (inclusion and exclusion) criteria are provided in Supplementary Material 1.

Sixty healthy adults aged 18 to 45 years inclusive were screened and enrolled. in the study from October 2012 to November 2015. In Part 1, a total of 8 healthy volunteers without *S. aureus* nasal colonization were randomized to 2 groups of a total of 4 subjects each in each arm and were treated with XF-73 at concentrations of 0.5 mg/g 2% gel and 2 mg/g 2% gel, respectively (Table 1). In Part 2, a total of 52 subjects were randomized to 4 groups and treated with three different concentrations of XF-73 or placebo (i.e.,13 received 0.5 mg/g 2% gel; 13 received 2 mg/g 2% gel; 13 received 0.5 mg/g 4% gel and 13 received placebo respectively) (Table 2).

All 8/8 (100%) of subjects in Part 1 and 48/52 (92.3%) of subjects in Part 2 completed the study (Figure 1); 4/52 (7.7%) subjects discontinued (2 subjects due to negative nasal swab at

enrollment, and 2 withdrawn as mandated by the NIH because of a federal government shutdown.

Study objectives

The primary objective of the study was to establish the *safety and tolerability* of 2 concentrations of a modified lower viscosity nasal formulation of XF-73, and to compare them to a previously investigated, thicker, higher viscosity formulation.

The secondary objectives of the study were to (1) establish whether there was any potential *systemic exposure* following administration of the two nasal formulations of XF-73, and (2) to evaluate the anti-staphylococcal efficacy of two concentrations of a lower- and a thicker, higher viscosity nasal formulation of XF-73 (Part 2 only).

Methodology

Figure 1 shows a schematic design of Parts 1 and 2 of the study. In Part 1, the 2 concentrations of the new formulation of XF-73 (0.5 mg/g 2% gel and 2.0 mg/g 2% gel, respectively) were administered twice on Day 1 for total daily dosages of 0.6 mg/g (0.3 mg/g per dose) and 2.4 mg/g (1.2 mg/g per dose), respectively. On Day 2, the subjects were discharged from the inpatient study unit. Local (nasal and nasal passage) safety and tolerability were evaluated, as well as overall safety. All assessments were completed within 24 hours after application of the first intranasal dose and on Day 8 of the study. Safety data from Part 1 were reviewed by a Safety Monitoring Committee before initiating dosing of subjects in Part 2.

In Part 2, the same 2 concentrations of the new gel formulation of XF 73 used in Part 1 were now evaluated and compared to the 0.5 mg/g 4% gel (previously evaluated formulation) in a total dosage of 0.3 mg/g per dose, and to 4% viscosified placebo gel. Each study agent formulation (XF-73 or placebo) was administered daily for 5 days (3 times on Day 1 and twice daily on Days 2 to 5). From Day 1 to Day 5, all subjects underwent body and face (avoiding eyes, ears, mouth, and nostrils) wash with a topical antiseptic, chlorhexidine gluconate (CHG) to prevent nasal contamination from other skin reservoirs. Body wash was completed in the morning of each dosing day, after obtaining a nasal swab for SA culture, but before other baseline assessments and dosing with study drug. On Day 6, the subjects were discharged from the inpatient study unit and followed up on Day 14.

Clinical safety assessments

Laboratory safety assessments, including serum chemistry, hematology, serology, urinalysis, urine drug and alcohol screen, and pregnancy test (female subjects only) were completed at Screening Visit, for both parts of the study. Vital sign measurements (blood pressure, pulse rate, respiratory rate and temperature) were obtained at Screening Visit, admission (Day-1), at 0 hour (prior to dosing) and 4 hours after each dose was administered on treatment days, on discharge, and at final follow-up visit. A standard 12-lead ECG was completed at Screening Visit and discharge.. A full physical examination (skin, head and neck, cardiac, pulmonary, eyes, abdominal, extremities and joints, and neurological examination, but excluding breast, genital, and perineal examination) was performed at Screening Visit,

admission (Day-1), and at discharge (Day 2 in Part 1; Day 6 in Part 2). Safety data from Part 1 were reviewed by a Safety Monitoring Committee before initiating dosing of subjects in Part 2.

In Part 2, an Ear, Nose and Throat (ENT) specialist performed the Smell Identification Test™ according to *Doty* [20] on Admission (Day -1) prior to the first dose of study product, at Discharge (Day 6) and at the Follow-up visit (Day 14) to evaluate for nose and nasal passage treatment-emergent adverse events (TEAEs).

Pharmacokinetic (PK) analysis and measurement of XF-73 plasma level.

Serial blood samples (4 mL) for XF-73 measurement were collected as follows: Part 1 at 0 hour (within 15 min before dosing) and at 15 and 30 min, and 1, 2, 4, 8, and 12 hours after each dose; Part 2: Day 1, within 15 minutes before the first dose and 30, 240, and 480 minutes after the first dose; additional samples were taken on Day 3 30 minutes after the first dose and on Day 5 within 15 minutes before the first dose and 30 and 240 minutes after the first dose. The blood was centrifuged at 2500g within 2 hours of collection and the plasma fraction removed and frozen at −70°C.

XF-73 plasma levels were determined using a validated liquid chromatography/mass spectrometry (LC-MS/MS) method developed in the Department of Bioanalytical Services, Covance Laboratories Limited, Otley Road, Harrogate, North Yorkshire, England, UK (Covance Study number 2569-021). This has a lower limit of quantification (LLOQ) of 0.2 ng/mL of XF-73 using 25 μL of plasma.

The following PK parameters were estimated from the plasma concentration-time data collected from 0 hour to 12 hours on Day 1, Part 1, and following the last dose on Day 5, Part 2: maximum concentration of systemic exposure (Cmax), time of maximum concentration of systemic exposure (Tmax), and area under the concentration time curve from time zero to time t (AUC(O-t)). Additional PK parameters that were calculated as data permitted in the collection period after the last dose in Part 2 of the study included: area under the concentration time curve in the samples matrix during a dosing interval at steady state (AUC(O-tau)), apparent terminal half-life (t1/2), elimination rate constant (Ke1), apparent oral clearance (CL/F), and apparent volume of distribution (Vz/F).

Pharmacodynamic (PD) Analysis of In-Vitro Microbiological Activity

Specimen collection and culture.—Specimens for detection and quantitation of SA were collected from the bilateral anterior nares of subjects, using double-headed nasal swabs (Copan Venturi Transystem (TM) Liquid Amies—Copan Diagnostics Inc). A total of 9 nasal swabs were obtained, 3 per subject each during the Pre-screening, Screening, and on Admission for the diagnosis of SA colonization. In addition, swabs were obtained from Day 1 to Day 5, on Discharge (day 6) and on Follow-up visit (Day 14). All specimens were obtained before CHG body and face wash and before administration of study drug formulation or placebo. Following specimen collection, each swab was placed in an Amies-charcoal gel medium for transfer to the microbiology laboratory at each site for detection, identification, and quantification of SA. Specimens were broth-enriched and plated onto

SaSelect and MRSASelect agar (Bio-Rad Laboratories, Redmond, WA), and BD Trypticase Soy Agar II (Becton, Dickinson and Company, Sparks, MD).

Semi-Quantitative Scale Scores.—Anti-staphylococcal activity was assessed as the presence or absence of SA, by the quantitation of SA in the sample (colony forming units per milliliter [CFU/mL]), by quantification of the level of colonization using a semi-quantitative scale (SA Score) according to *Andriesse et al* [21], and the plate quantitation scale (Table 1).

Upper and Lower Microbial Estimated Microbial Count Range Scores.—Based on the scores on the semi-quantitative scale, lower and upper estimated microbial count-range scores variables (denoted as LECR and UECR, respectively) were determined based on the respective endpoints of the estimated CFU corresponding to the semi-quantitative score (Supplementary Table 1).

Derived AUC Scores.—For the semi-quantitative scores, the LECR scores, and the UECR scores, AUC scores were calculated for each subject using the trapezoidal rule, with separate calculations spanning the following ranges: over the five-day treatment period, (Days 1 to 5); through the five-day treatment and Discharge, (Days 1 to 6); and through the five-day treatment period, at Discharge, and Follow-up (Days 1 to 14). A continuous-data summary of the AUC scores was prepared, and comparisons of these scores across treatment groups were performed using a linear model that included the fixed factor treatment group, and that employed the baseline (Day 1) SA score as a covariable. If parametric analysis of the calculated AUC scores was contraindicated based upon the distribution of scores, a Wilcoxon Rank Sum test was employed to compare treatments with respect to the median AUC scores.

Derived Assessment of Anti-SA Activity.—Anti-staphylococcal activity was assessed as the presence or absence of SA, with semi-quantitative scores of Negative and 0 interpreted as absence, and levels of 1 or greater interpreted as presence (Table 1). The percentage of subjects presenting a positive response to treatment was presented, and compared to the corresponding percentage in the placebo group using a one-sided Fisher's exact test at the 5% significance level. A p value of < 0.05 was considered statistically significant.

RESULTS

Demographic and Other Baseline Characteristics

Subject demographic and other baseline characteristics for Part 1 and Part 2 were generally balanced across treatment groups, except for gender (Table 2). Most subjects were male (from 69.2% to 76.9%) across Treatment Arms (TAs) except in the 0.5 mg/g 2% gel TA (46.2%). In Part 1, the overall mean age was 28.5 years, subjects were mostly male (75%), white (87.5%), of non-Hispanic or Latino ethnicity (87.5%), and the mean BMI was 25.8 kg/m^2. In Part 2, the overall mean age was 26.5 years, subjects were mostly white (69.2%), of non-Hispanic or Latino ethnicity (84.6%), and mean BMI was 25.0 kg/m^2.

Pharmacokinetic analysis

The PK Population included all subjects in the Safety Population who received at least one dose of XF-73 and provided sufficient blood samples for measurement of XF-73 concentration, regardless of the presence of measurable amounts and the ability to calculate PK parameters. Forty-seven subjects in total (47/60, 78.3%) comprised the PK Population, which included all 8 subjects from Part 1 and 39 subjects in Part 2, while the 13 subjects who received placebo were excluded from the PK Population.

Using the method previously validated at Covance Laboratories Limited (Covance Study number 2569-021), there was no measurable systemic absorption of XF-73 from nasal application in Part 1 (single-dose) and Part 2 (multi-dose).

Pharmacodynamics

The PD Population included all subjects who provided microbiological data and received at least one dose of study product. This comprised of all 48 subjects in Part 2 who completed the study. The anti-staphylococcal efficacy was evaluated by assessing the semi-quantitative scores, AUC scores calculated from semi-quantitative scores, and anti-SA activity (described in Methods section).

Semi-Quantitative SA Scores.—The summary and trends of semi-quantitative SA scores are presented in Table 3 and Figure 2. Active treatment with XF-73 was associated with a rapid diminution in mean semi-quantitative SA scores; at least half of the subjects in all 3 active treatment arms achieved a positive response by Day 2. Mean semi-quantitative SA scores showed a consistent bimodal distribution in the placebo arm and a gradual diminution of high scores of the semi-quantitative culture results in the active treatment arms. Continued treatment resulted in little, if any, further diminution in semi-quantitative SA scores. By Day 14, the scores for the subjects treated with the 2 mg/g 2% gel and 0.5 mg/g 4% gel had returned to baseline (Day 1) and only 1 subject had maintained a positive response in this combined treatment group. In contrast, over half of the subjects treated with the 0.5 mg/g 2% gel had sustained a positive response at Day 14.

There also was a diminution in semi-quantitative SA scores among subjects who received the 4% gel without active drug, but the diminution was slower. Half the subjects recorded a positive response at Day 5, but the response was sustained in only 1 subject.

AUC Scores Calculated from Semi-Quantitative Scores.—The mean AUC scores by treatment interval are presented in Table 4 and Figure 3. The AUCs of the SA semi-quantitative culture data showed a trend favoring the higher concentration of XF-73 (2.0 mg/g) in the lower-viscosity (2%) gel. There was a consistent trend for a treatment effect during application (from Day 1 to Day 6) of XF-73 that disappeared when the posttreatment week's data were added into the analysis (from Day 1 to Day 14).

A summary of AUC scores calculated from lower estimated count range scores showed a consistent trend for a treatment effect during application (from Day 1 to Day 6) of XF-73 that disappeared when the posttreatment week's data were added into the analysis (from Day 1 to Day 14) (Supplementary Figure 1 and Supplementary Table 2).

A summary of AUC scores calculated from upper estimated count range scores showed a significant *p* value for a treatment effect during application (from Day 1 to Day 6) of XF-73 (Supplementary Figure 2 and Supplementary Table 3). When the posttreatment week's data were added into the analysis (from Day 1 to Day 14), both doses in the low viscosity formulation had a significant *p* value when compared to placebo. This was not identical to the AUC of the SA semi-quantitative culture data, but very similar to AUC scores calculated from lower estimated count range scores. This apparent discrepancy across analysis styles was most likely due to the bimodal distribution of the primary observations.

Anti-SA Activity.—The anti-SA activity of XF-73 assessed during this study is presented in Table 5. A simple yes/no approach to the data indicated that a treatment effect appeared on Day 2 but did not increase with increasing treatment duration and was observed to return to baseline at the Day 14 Follow-up visit.

Subject safety and tolerability

The Safety Population was defined as all 60 enrolled subjects who received study drug or placebo. A summary of TEAEs by System Organ Class (SOC) is presented in Table 6.

In Part 1, one TEAE of rhinorrhea was reported that was considered mild in severity and related to study drug. Forty-two (80.8%) subjects in Part 2 had at least one TEAE; the majority of TEAEs were seen in the 2.0 mg/g 2% gel treatment arm (12 [92.3%]) and 11 (84.6%) in the placebo treatment arm. Two subjects reported serious AEs (SAEs): one subject each in the 2.0 mg/g 2% gel (treatment-related) treatment arm and one subject in the 0.5 mg/g 4% gel (non-treatment related) treatment arm. Other frequently reported TEAEs were increased blood chlorine, hyposmia, nasal discomfort, nasal mucosal disorder, and nasal edema (6 [11.5%] each).

The majority of TEAEs in Part 2 were mild in severity, 95 (84.8%) (Supplementary Table 4). Moderate TEAEs was greater in the placebo treatment arm (18.5%) compared to 5 (14.3%) in the 2.0 mg/g 2% gel TA. One event (7.7%) of moderate mucosal erosion was noted in the placebo TA. Four severe TEAEs were experienced: 2 (9.1%) in the 0.5 mg/g 2% gel and 2 (7.1%) in the 0.5 mg/g 4% gel TAs, respectively. There was one life-threatening event (3.6%) in the XF-73 in 0.5 mg/g 4% gel TA; one subject attempted suicide that was not considered related to study drug and was resolved with treatment.

No TEAEs caused treatment modification or discontinuation from the study. There were no deaths reported for this study. No subjects in the study met any of the halting criteria.

DISCUSSION

This phase 1 multi-center randomized clinical trial evaluated the safety and local tolerability of two nasal formulations of XF-73 (0.5mg/g 2% gel and 2mg/g 2% gel, respectively) for decolonization of SA in healthy persistently colonized adults. The study met its primary objective. XF-73 in the new nasal formulations was generally well tolerated and the concentration of the carrier gel did not appear to make material difference to the safety profile of the study. Although there was a trend to more TEAEs in those subjects that

received the higher concentration of XF-73 (2% gel 2 mg/g), subjects who received placebo (carrier gel) also reported some TEAEs. These findings indicate that the carrier gel or some of the protocol procedures, rather than XF-73 concentration, might have contributed to the overall profile of the product.

The study also met its secondary objectives. Overall, there was no measurable systemic absorption of XF-73 from nasal application Part 1 (single day) and Part 2 (multiple days of dosing in presence of SA colonization). At least half of the subjects in each of the three active treatment arms achieved a positive response by Day 2 and continued treatment did not increase the number of subjects achieving a positive response. Reduced growth of bacteria after plating in the reference laboratory could have resulted not from reduced colonization, per se, but from the effect of XF-73 in residual gel in the nares to which unaffected colonizing bacteria were exposed for the first time during swabbing and before placement in the neutralizing transport medium. This possibility was not addressed in this study.

As previously discussed, mupirocin is currently the only approved agent for MRSA nasal decolonization by the United States Food and Drug Administration, and while its pre-operative use has shown considerable success in reducing MRSA colonization in select patient populations [9–11], the durability of its effects and the emergence of drug-resistant strains continue to potentially limit its effectiveness [12–16]. Another concern with mupirocin is that it is slow to reach its full effect, generally requiring a five-day, twice-daily application. Patient compliance with this self-application protocol is a common challenge. Furthermore, despite correct application and full course of treatment, eradication of *S. aureus* nasal carrier state and durability of decolonization has been shown to vary widely, ranging from no appreciable change to reducing colonization by up to 59% [14–16]. It was previously demonstrated in pre-clinical studies that XF-73 is faster-acting, rapidly kills S. aureus in vitro, with loss of bacterial membrane potential in 1 minute [17]. The results of this study suggest that XF-73 is an effective and rapidly-acting alternative antibiotic regimen to mupirocin for nasal decolonization of SA.

A potential limitation of the study is the small sample size. The methodology was carefully constructed to minimize bias, although the sample size was small, so only dramatic results would be conclusive. However, the careful selection of subjects with persistent staphylococcal carriage in their nares may allow the use of these data to be generalized to patients as well as healthy subjects for whom a temporary decrease in nasal staphylococcal colonization would be beneficial.

CONCLUSIONS

In this Phase 1 study, XF-73 in 2% gel demonstrated a trend in dose-dependent anti-staphylococcal activity during the treatment of healthy subjects. It demonstrated safety and local tolerability with minimal side effects, thus providing a potentially viable alternative to mupirocin in SA decolonization, thus warranting further investigation of the efficacy of XF-73 in Phase 2 trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- XF-73 led to rapid diminution in semi-quantitative *S. aureus* scores
- Common treatment adverse events were rhinorrhea and nasal dryness
- Demonstrated safety, tolerability, and minimal side effects in healthy volunteers

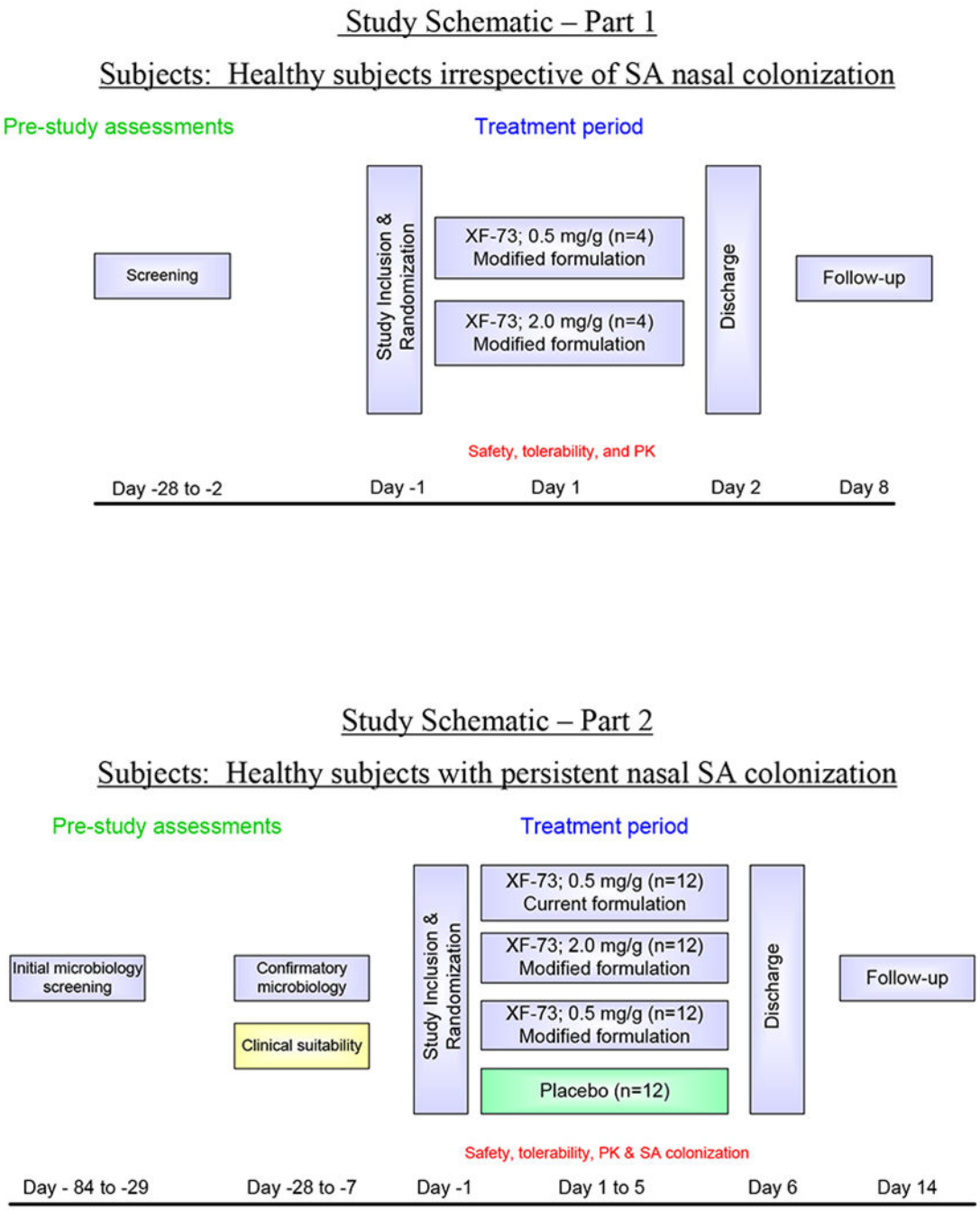

Figure 1. Descriptive Schematic of Study Design

n = number of subjects, PK = pharmacokinetic(s), SA = *Staphylococcus aureus*.

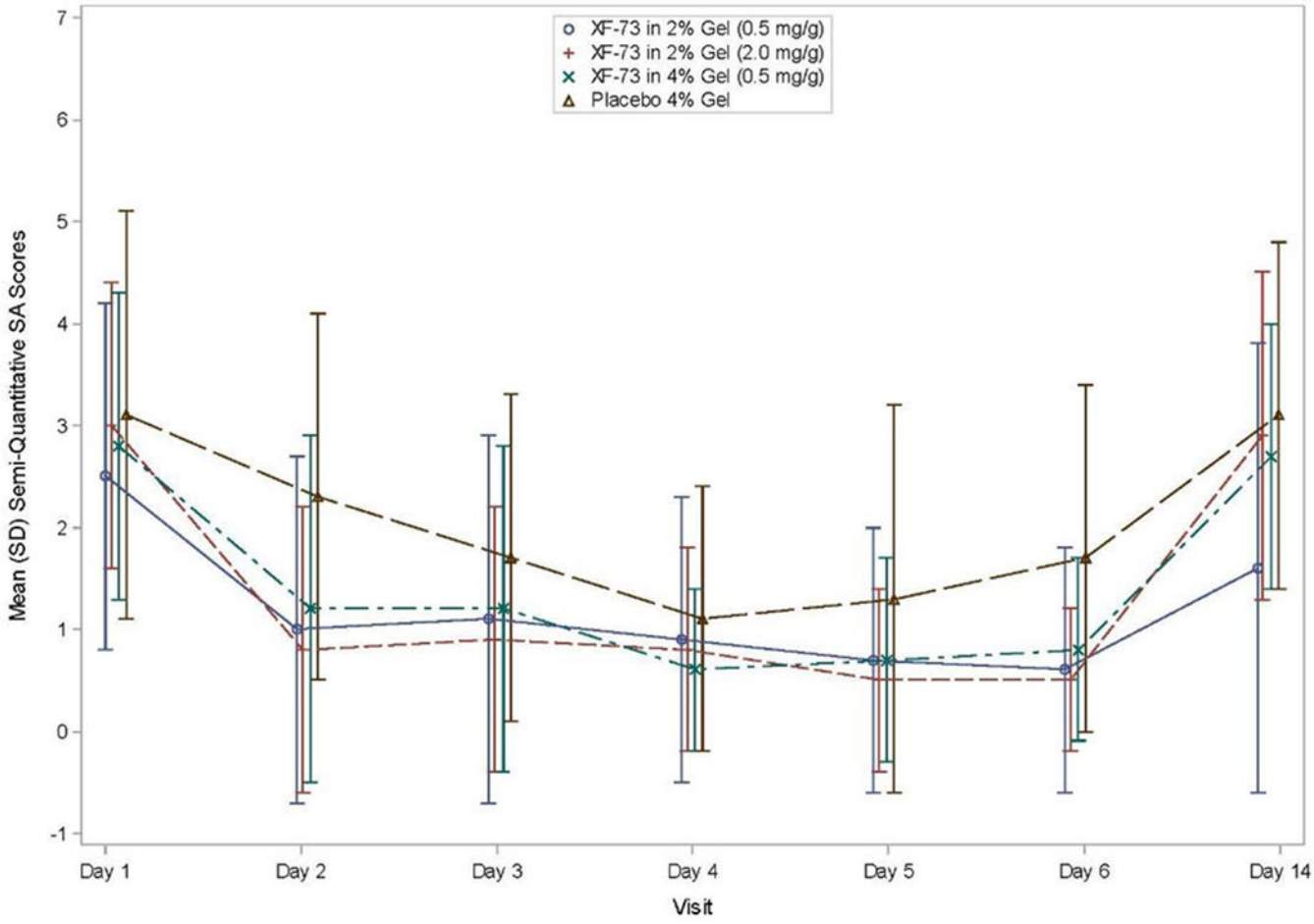

Figure 2. Mean (± SD) Semi-Quantitative SA Scores by Treatment Day – PD Population
PD = pharmacodynamics(s), SA = Staphylococcus aureus, SD = standard deviation

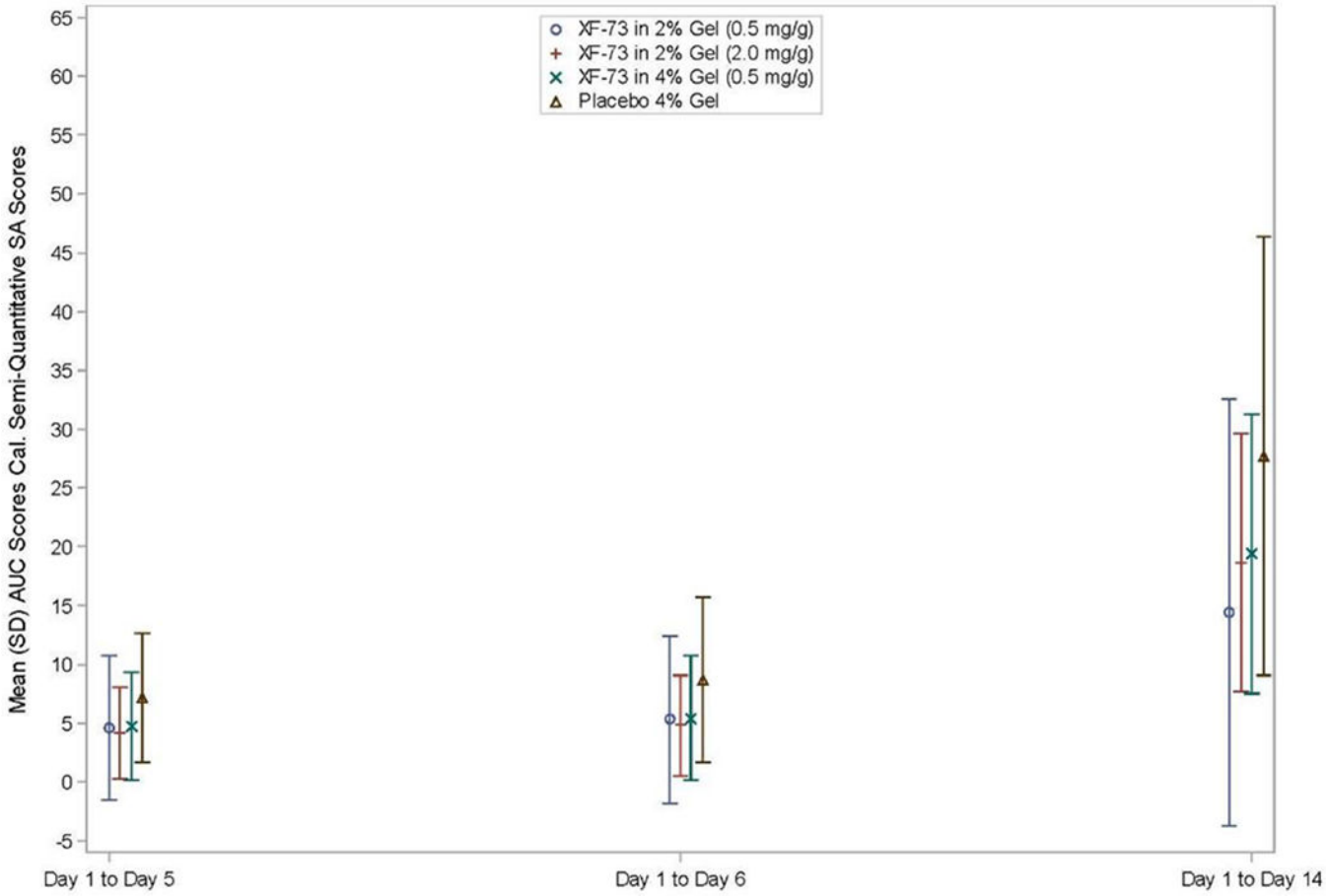

Figure 3. Mean (± SD) AUC Scores by Treatment Interval – PD Population

AUC = area under the curve, PD = pharmacodynamics(s), SD = standard deviation.

Table 1

Semi-quantitative scale for grading level of nasal *Staphylococcus Aureus* Colonization

Growth on the Highest Ranking Plate	Number of Colonies on SSA Plates	Estimated Number of CFUs in Original Swab	Semi-quantitative Scale	Plate Quantitation
No growth on all plates	n/a	0	Negative	Negative (absent)
Growth on plate C only (subculture from liquid medium)	Any number	1–10	0	Growth in liquid medium only
Plate A (original suspension)	1–10	10–100	1	0 (absent) + (scant) ++ (moderate) +++ (heavy)
	11–100	100–1,000	2	
	>100	>1,000	3	
Plate B (1:100 dilution of original suspension)	1–10	1,000–10,000	4	Quantitate as above
	11–100	10,000–100,000	5	
	>100	>100,000	6	

CFU = colony forming unit, n/a = not applicable, SSA = selective staphylococcal agar.

Table 2

Demography and Baseline Characteristics at Screening

Category	Part 1		Part 2			
	XF-73 in 2% Gel 0.5 mg/g (N = 4)	**XF-73 in 2% Gel 2.0 mg/g (N = 4)**	**XF-73 in 2% Gel 0.5 mg/g (N = 13)**	**XF-73 in 2% Gel 2.0 mg/g (N = 13)**	**XF-73 in 4% Gel 0.5 mg/g (N = 13)**	**Placebo in 4% Gel (N = 13)**
Age (years)						
N	4	4	13	13	13	13
Mean (SD)	29.0 (8.5)	28.0 (9.4)	28.7 (10.3)	25.1 (5.3)	24.2 (5.6)	28.1 (8.0)
Median	26.5	24.0	22.0	24.0	21.0	27.0
Min, Max	22, 41	22, 42	19, 45	19, 37	19, 34	18, 41
Subjects with Missing Data	0	0	0	0	0	0
Gender						
Male	3 (75.0%)	3 (75.0%)	6 (46.2%)	10 (76.9%)	9 (69.2%)	10 (76.9%)
Female	1 (25.0%)	1 (25.0%)	7 (53.8%)	3 (23.1%)	4 (30.8%)	3 (23.1%)
Subjects with Missing Data	0	0	0	0	0	0
Race						
White	4 (100%)	3 (75.0%)	11 (84.6%)	9 (69.2%)	8 (61.5%)	8 (61.5%)
Black or African American	0	0	0	1 (7.7%)	2 (15.4%)	2 (15.4%)
Asian	0	1 (25.0%)	2 (15.4%)	3 (23.1%)	3 (23.1%)	3 (23.1%)
Hispanic or Latino	1 (25.0%)	0	4 (30.8%)	1 (7.7%)	3 (23.1%)	0
Non-Hispanic or Latino	3 (75.0%)	4 (100%)	9 (69.2%)	12 (92.3%)	10 (76.9%)	13 (100.0%)
Other	0	0	0	0	0	0
Subjects with Missing Data	0	0	0	0	0	0
Body Mass Index (kg/m^2)						
Mean (SD)	25.8 (5.4)	25.8 (2.0)	25.3 (3.6)	23.5 (3.1)	25.6 (4.5)	25.7 (3.8)
Median	26.0	26.1	24.6	23.0	25.2	26.6
Min, Max	21, 31	23, 28	21, 31	20, 29	19, 35	19, 33
Subjects with Missing Data	0	0	0	0	0	0

BMI = body mass index, Max = maximum, Min = minimum, N = number of subjects, SD = standard deviation.

Note: Percentages were based on the number of subjects in the indicated treatment group.

Table 3

Categorical Summary of Semi-Quantitative SA Scores – PD Population

Semi-Quantitative SA Scores At Each Assessment	XF-73 in 2% Gel 0.5 mg/g (N = 11)	XF-73 in 2% Gel 2.0 mg/g (N = 13)	XF-73 in 4% Gel 0.5 mg/g (N = 12)	Placebo in 4% Gel (N = 12)
Day 1				
Negative	0	0	0	0
0	1 (9.1%)	0	0	1 (8.3%)
1	3 (27.3%)	2 (15.4%)	3 (25.0%)	3 (25.0%)
2	2 (18.2%)	3 (23.1%)	3 (25.0%)	1 (8.3%)
3	0	0	0	0
4	2 (18.2%)	4 (30.8%)	1 (8.3%)	1 (8.3%)
5	1 (9.1%)	1 (7.7%)	3 (25.0%)	1 (8.3%)
6	2 (18.2%)	3 (23.1%)	2 (16.7%)	5 (41.7%)
Day 2				
Negative	2 (18.2%)	0	0	0
0	5 (45.5%)	8 (61.5%)	6 (50.0%)	3 (25.0%)
1	1 (9.1%)	3 (23.1%)	3 (25.0%)	2 (16.7%)
2	1 (9.1%)	1 (7.7%)	1 (8.3%)	1 (8.3%)
3	0	0	0	1 (8.3%)
4	1 (9.1%)	0	0	1 (8.3%)
5	0	0	1 (8.3%)	3 (25.0%)
6	1 (9.1%)	1 (7.7%)	1 (8.3%)	1 (8.3%)
Day 3				
Negative	1 (9.1%)	1 (7.7%)	1 (8.3%)	0
0	5 (45.5%)	6 (46.2%)	5 (41.7%)	4 (33.3%)
1	3 (27.3%)	3 (23.1%)	2 (16.7%)	2 (16.7%)
2	0	1 (7.7%)	2 (16.7%)	2 (16.7%)
3	0	0	0	0
4	0	1 (7.7%)	1 (8.3%)	3 (25.0%)
5	1 (9.1%)	1 (7.7%)	0	0
6	1 (9.1%)	0	1 (8.3%)	1 (8.3%)
Day 4				
Negative	2 (18.2%)	1 (7.7%)	1 (8.3%)	0
0	4 (36.4%)	6 (46.2%)	6 (50.0%)	5 (41.7%)
1	3 (27.3%)	3 (23.1%)	3 (25.0%)	4 (33.3%)
2	0	2 (15.4%)	2 (16.7%)	1 (8.3%)
3	0	0	0	0
4	1 (9.1%)	1 (7.7%)	0	1 (8.3%)
5	1 (9.1%)	0	0	1 (8.3%)
6	0	0	0	0

Semi-Quantitative SA Scores At Each Assessment	XF-73 in 2% Gel 0.5 mg/g (N = 11)	XF-73 in 2% Gel 2.0 mg/g (N = 13)	XF-73 in 4% Gel 0.5 mg/g (N = 12)	Placebo in 4% Gel (N = 12)
Day 5				
Negative	5 (36.4%)	3 (23.1%)	3 (25.0%)	0
0	2 (27.3%)	5 (38.5%)	4 (33.3%)	6 (50.0%)
1	2 (18.2%)	4 (30.8%)	3 (25.0%)	3 (25.0%)
2	1 (9.1%)	0	1 (8.3%)	0
3	0	0	0	0
4	0	1 (7.7%)	1 (8.3%)	0
5	1 (9.1%)	0	0	2 (16.7%)
6	0	0	0	1 (8.3%)
Day 6				
Negative	5 (45.5%)	2 (15.4%)	3 (25.0%)	1 (8.3%)
0	2 (18.2%)	5 (38.5%)	2 (16.7%)	4 (33.3%)
1	3 (27.3%)	5 (38.5%)	5 (41.7%)	0
2	0	1 (7.7%)	1 (8.3%)	4 (33.3%)
3	0	0	0	0
4	0	0	1 (8.3%)	1 (8.3%)
5	1 (9.1%)	0	0	1 (8.3%)
6	0	0	0	1 (8.3%)
Day 14				
Negative	2 (18.2%)	0	0	1 (8.3%)
0	4 (36.4%)	1 (7.7%)	0	0
1	1 (9.1%)	1 (7.7%)	2 (16.7%)	2 (16.7%)
2	0	3 (23.1%)	4 (33.3%)	1 (8.3%)
3	0	0	0	0
4	1 (9.1%)	4 (30.8%)	4 (33.3%)	1 (8.3%)
5	1 (9.1%)	1 (7.7%)	0	5 (41.7%)
6	2 (18.2%)	3 (23.1%)	2 (16.7%)	2 (16.7%)

PD = pharmacodynamics(s), SA = *Staphylococcus aureus*.

Table 4

Summary of AUC Scores Calculated from Semi-Quantitative SA Scores – PD Population

	XF-73 in 2% Gel 0.5 mg/g (N = 11)	XF-73 in 2% Gel 2.0 mg/g (N = 13)	XF-73 in 4% Gel 0.5 mg/g (N = 12)	Placebo in 4% Gel (N = 12)
AUC Based on Scores from Day 1 to Day 5				
Subjects with Non-Missing Data	11	13	12	12
Mean (SD)	4.6 (6.1)	4.2 (3.9)	4.7 (4.6)	7.2 (5.5)
p-value vs. Placebo	0.4786	0.0224	0.1086	n/a
Median	1.5	3.0	3.3	8.5
Min, Max	0, 19	1, 13	1, 16	0, 19
Subjects with Missing Data	0	0	0	0
AUC Based on Scores from Day 1 to Day 6				
Subjects with Non-Missing Data	11	13	12	12
Mean (SD)	5.3 (7.1)	4.8 (4.3)	5.4 (5.3)	8.7 (7.0)
p-value vs. Placebo	0.3628	0.0128	0.0798	n/a
Median	1.5	4.0	3.3	10.0
Min, Max	0, 21	1, 13	1, 19	0, 24
Subjects with Missing Data	0	0	0	0
AUC Based on Scores from Day 1 to Day 14				
Subjects with Non-Missing Data	11	13	12	12
Mean (SD)	14.4(18.1)	18.6(11.0)	19.4(11.9)	27.7(18.6)
p-value vs. Placebo	0.0432	0.0325	0.1031	n/a
Median	5.5	13.0	17.3	30.0
Min, Max	0, 49	1, 35	5, 51	0, 64
Subjects with Missing Data	0	0	0	0

AUC = area under the curve, Max = maximum, Min = minimum, n/a = not applicable, PD = pharmacodynamics(s), SA = *Staphylococcus aureus*, SD = standard deviation.

Note: The calculations of AUC scores employed the value 0 when the semi-quantitative SA score was “Negative.” *P*-values were from pairwise treatment comparisons versus placebo, based on a linear model that included Treatment as a fixed factor, and that employed the baseline semi-quantitative SA score as a covariable (“Negative”=0).

Table 5

Anti-SA Activity – PD Population

	XF-73 in 2% Gel 0.5 mg/g (N = 11)	XF-73 in 2% Gel 2.0 mg/g (N = 13)	XF-73 in 4% Gel 0.5 mg/g (N = 12)	All Active Treatments (N = 36)	Placebo in 4% Gel (N = 12)
Day 1: Absence of SA Colonization					
No	10 (90.9%)	13 (100.0%)	12 (100.0%)	35 (97.2%)	11 (91.7%)
Yes	1 (9.1%)	0	0	1 (2.8%)	1 (8.3%)
p-value vs. Placebo	0.7391	1.0000	1.0000	0.9415	n/a
Day 2: Positive Response to Treatment					
No	4 (36.4%)	5 (38.5%)	6 (50.0%)	15 (41.7%)	9 (75.0%)
Yes	7 (63.6%)	8 (61.5%)	6 (50.0%)	21 (58.3%)	3 (25.0%)
p-value vs. Placebo	0.0736	0.0749	0.2002	0.0467	n/a
Day 3: Positive Response to Treatment					
No	5 (45.5%)	6 (46.2%)	6 (50.0%)	17 (47.2%)	8 (66.7%)
Yes	6 (54.5%)	7 (53.8%)	6 (50.0%)	19 (52.8%)	4 (33.3%)
p-value vs. Placebo	0.2735	0.2655	0.3401	0.2028	n/a
Day 4: Positive Response to Treatment					
No	5 (45.5%)	6 (46.2%)	5 (41.7%)	16 (44.4%)	7 (58.3%)
Yes	6 (54.5%)	7 (53.8%)	7 (58.3%)	20 (55.6%)	5 (41.7%)
p-value vs. Placebo	0.4211	0.4179	0.3421	0.3084	n/a
Day 5: Positive Response to Treatment					
No	4 (36.4%)	5 (38.5%)	5 (41.7%)	14 (38.9%)	6 (50.0%)
Yes	7 (63.6%)	8 (61.5%)	7 (58.3%)	22 (61.1%)	6 (50.0%)
p-value vs. Placebo	0.4067	0.4296	0.5000	0.3649	n/a
Day 6: Positive Response to Treatment					
No	4 (36.4%)	6 (46.2%)	7 (58.3%)	17 (47.2%)	7 (58.3%)
Yes	7 (63.6%)	7 (53.8%)	5 (41.7%)	19 (52.8%)	5 (41.7%)
p-value vs. Placebo	0.2632	0.4179	0.6599	0.3700	n/a
Day 14: Positive Response to Treatment					
No	5 (45.5%)	12 (92.3%)	12 (100.0%)	29 (80.6%)	11 (91.7%)
Yes	6 (54.5%)	1 (7.7%)	0	7 (19.4%)	1 (8.2%)
p-value vs. Placebo	0.0240	0.7800	1.0000	0.3457	n/a

n/a = not applicable, PD = pharmacodynamics(s).

Note: Positive response to treatment was defined as reaching an absence of SA colonization, which was indicated by a semi-quantitative SA score of “Negative” or 0. *P*-values are from pairwise one-sided Fisher’s exact tests versus placebo.

Table 6

Subjects with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Related to Study Treatment – Safety Population

SOC PT	Part 1			Part 2				
	XF-73 in 2% Gel 0.5 mg/g (N = 4)	XF-73 in 2% Gel 2.0 mg/g (N = 4)	Overall Part 1 (N= 8)	XF-73 in 2% Gel 0.5 mg/g (N = 13)	XF-73 in 2% Gel 2.0 mg/g (N = 13)	XF-73 in 4% Gel 0.5 mg/g (N = 13)	Placebo in 4% Gel (N = 13)	Overall Part 2 (N = 52)
Total Number of AEs	1	0	0	22	35	28	27	112
Not Related	0	0		8 (36.4%)	6 (17.1%)	14 (50.0%)	9 (33.3%)	37 (33.0%)
Related	1 (100%)	0	1 (100%)	14 (63.6%)	29 (82.9%)	14 (50.0%)	18 (66.7%)	75 (67.0%)
Number of Subjects with at Least One AE								
Not Related	0	0	0	1 (7.7%)	0	2 (15.4%)	2 (15.4%)	5 (9.6%)
Related	1 (25.0%)	0	1 (12.5%)	9 (69.2%)	12 (92.3%)	7 (53.8%)	9 (69.2%)	37 (71.2%)
General disorders and administration site conditions								
Mucosal erosion	0	0	0	0	0	0	1 (7.7%)	1 (1.9%)
Paresthesia mucosal	0	0	0	0	1 (7.7%)	0	0	1 (1.9%)
Injury, poisoning, and procedural complications								
Excoriation	0	0	0	0	1 (7.7%)	0	0	1 (1.9%)
Scratch	0	0	0	0	1 (7.7%)	0	0	1 (1.9%)
Investigations								
AST increased	0	0	0	0	0	0	1 (7.7%)	1 (1.9%)
Blood bilirubin increased	0	0	0	0	0	0	1 (7.7%)	1 (1.9%)
Blood Ca decreased	0	0	0	1 (7.7%)	1 (7.7%)0	0	0	2 (3.8%)
Blood Cl increased	0	0	0	0	2 (15.4%)	1 (7.7%)	1 (7.7%)	4 (7.7%)
Blood Mg decreased	0	0	0	1 (7.7%)	0	0	0	1 (1.9%)
Protein total decreased	0	0	0	2 (15.4%)	1 (7.7%)	1 (7.7%)	0	4 (7.7%)
WBC count decreases	0	0	0	0	1 (7.7%)	0	0	1 (1.9%)
WBC urine positive	0	0	0	0	0	0	1 (7.7%)	1 (1.9%)
Nervous system disorders								
Headache	0	0	0	0	1 (7.7%)	0	2(15.4%)	3 (5.8%)
Paresthesia	0	0	0	1 (7.7%)		0	0	1 (1.9%)
Sinus headache	0	0	0	0	0	0	1 (7.7%)	1 (1.9%)
Respiratory, thoracic, and mediastinal disorders								
Epistaxis	0	0	0	0	0	0	1 (7.7%)	1 (1.9%)
Hyposmia	0	0	0	3 (23.1%)	1 (7.7%)	0	0	4 (7.7%)

SOC PT	Part 1			Part 2				
	XF-73 in 2% Gel 0.5 mg/g (N = 4)	XF-73 in 2% Gel 2.0 mg/g (N = 4)	Overall Part 1 (N= 8)	XF-73 in 2% Gel 0.5 mg/g (N = 13)	XF-73 in 2% Gel 2.0 mg/g (N = 13)	XF-73 in 4% Gel 0.5 mg/g (N = 13)	Placebo in 4% Gel (N = 13)	Overall Part 2 (N = 52)
Nasal discomfort	0	0	0	2 (15.4%)	1 (7.7%)	1 (7.7%)	2 (15.4%)	6 (11.5%)
Nasal dryness	0	0	0	1 (7.7%)	3 (23.1%)	2 (15.4%)	1 (7.7%)	7 (13.5%)
Nasal inflammation	0	0	0	0	0	1 (7.7%)	0	1 (1.9%)
Nasal mucosal disorder	0	0	0	1 (7.7%)	1 (7.7%)	2 (15.4%)	1 (7.7%)	5 (9.6%)
Nasal edema	0	0	0	0	4 (30.8%)	1 (7.7%)	1 (7.7%)	6 (11.5%)
Nasal septum disorder	0	0	0	0	0	0	1 (7.7%)	1 (1.9%)
Rhinorrhea	1 (25.0%)	0	1 (12.5%)	0	3 (23.1%)	2 (15.4%)	2 (15.4%)	7 (13.5%)
Sneezing	0	0	0	1 (7.7%)	1 (7.7%)	0	0	2 (3.8%)
Throat irritation	0	0	0	0	0	1 (7.7%)	0	1 (1.9%)
Skin and subcutaneous tissue disorders								
Scab	0	0	0	1 (7.7%)	1 (7.7%)	0	0	2 (3.8%)

AE = adverse event, AST = aspartate aminotransferase, Ca = calcium, Cl = chloride, Mg = magnesium, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event, WBC = white blood cell.

Note: The percentage distribution of AEs by relationship was based on the total number of events reported for the indicated treatment group. Subjects may have had more than one AE per SOC and PT. At each level of subject summarization (including individual preferred terms), a subject was counted once under the most relevant event if he/she reported one or more events. AEs with unknown relationship were counted as Related. Percentages for subject summarizations are based on the number of subjects in the indicated treatment group.

Note: The terms “microsmia” and “hyposmia” are considered synonymous in this report. While the term “microsmia” was used in the tables, listings, and graphs (TLGs), the preferred term “hyposmia” was used in the clinical study report (CSR) in place of “microsmia.”