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Concise Communication

Exeporfinium chloride (XF-73) nasal gel significantly reduces *Staphylococcus aureus* nasal carriage in cardiac surgery patients throughout surgery and the early recovery period: results from a randomized placebo-controlled Phase 2 study

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Abstract

Staphylococcus aureus nasal carriers were randomized (1:1) to XF-73 or placebo nasal gel, administered 5x over ~24hrs pre-cardiac surgery. *S. aureus* burden rapidly decreased after 2 doses (–2.2log$_{10}$ CFU/mL; placebo –0.01log$_{10}$ CFU/mL) and was maintained to 6 days post-surgery. Among XF-73 patients, 46.5% received post-operative anti-staphylococcal antibiotics versus 70% in placebo ($P = 0.045$).

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Staphylococcus aureus nasal carriage is established as an important risk factor for the development of surgical site infections (SSIs) in cardio-thoracic procedures.[1] The decolonization of *S. aureus* nasal carriage prior to cardio-thoracic surgery was classified as an "essential practice" with a high level of evidence in the 2022 SHEA/IDSA/APIC update.[2] Between 1 and 3% of healthy adults are nasally colonized with methicillin-resistant *S. aureus* (MRSA) and 15 and 30% are colonized with methicillin-sensitive *S. aureus* (MSSA).[3] *S. aureus* carriers are at higher risk of SSI than non-carriers and are up to nine times more likely to develop an SSI.[4]

Mupirocin is widely used as a nasal antibiotic for the elimination/eradication of nasal carriage of MSSA and MRSA, although not listed as a formal indication for the prevention of SSIs. Warnings to limit the widespread use of mupirocin due to concerns of generating mupirocin-resistant strains of *S. aureus* are present in surgical infection prevention guidelines for *S. aureus* decolonization,[5] and global mupirocin-resistant *S. aureus* prevalence rates have increased to 7.6% and mupirocin-resistant MRSA to 13.8%.[6] Exeporfinium chloride (XF-73), is a rapid bactericidal di-cationic porphyrin derivative with a novel mechanism of action,[7] with a low propensity for engendering bacterial resistance[8] is in clinical development as an intranasal gel for decolonization of *S. aureus,* (including MRSA), to prevent post-operative SSIs.

We have previously reported results from a Phase 2 multicenter, randomized, placebo-controlled study assessing the effect of XF-73 nasal gel versus placebo on *S. aureus* nasal burden in patients undergoing cardiac surgery. In the study (reference NCT03915470), the primary endpoint demonstrated a highly statistically significant, ($P < 0.0001$) reduction of 2.5 log$_{10}$ CFU/mL in nasal *S. aureus* burden with XF-73 nasal gel compared to placebo at 1 hour prior to surgery.[9] We now report on our secondary endpoints, including the impact on nasal *S. aureus* burden at additional timepoints and the use of post-operative anti-staphylococcal antibiotics.

Methods

Details of the Phase 2 study have been previously reported[9] and detailed at www.clinicaltrials.gov (study NCT03915470). *S. aureus* nasal carriage status was determined by a screening polymerase chain reaction (PCR) assay (Cepheid Xpert *S. aureus* Nasal Complete Assay, Cepheid, USA). PCR positive carriers were consented and randomized (1:1) to receive 0.2% (w/w) XF-73 nasal gel or matched placebo gel 4 times (at ~ 6-hour intervals), prior to and once immediately after cardiac surgery over ~24 hours (Figure 1). Nasal swabs for culture were obtained at 6 time-points and were taken just prior to the next application of XF-73 or placebo (Figure 1); both application of nasal gel and cultures were performed by research personnel. Nasal burden of *S. aureus* is expressed as log$_{10}$ CFU/mL. All patients underwent clinical follow-ups at 30 and 90 days, if a foreign implant (ie, mechanical or tissue prosthetic valve, rings, and grafts) was inserted. Concomitant medications, whole body skin decontamination, peri-operative (<48 hours,) and post-operative (≥48 hours) antibiotics and treatment emergent adverse events were recorded.[9]

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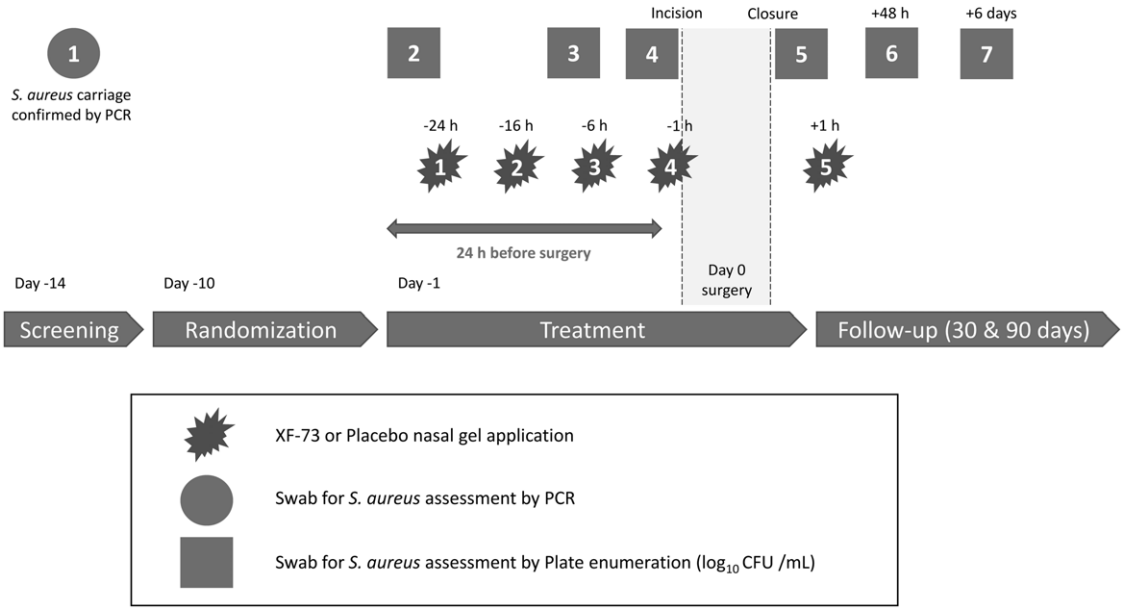

Figure 1. Study schematic. Patients who screened positive for *S. aureus* by PCR [Swab 1] and met entry criteria were randomized. Efficacy was analyzed in patients who were confirmed positive for nasal *S. aureus* carriage at baseline by *S. aureus* culture [Swab 2]. This population represented the microbiological intention-to-treat (micro-ITT) set. Patients were followed for 30 and 90 days, respectively, without and with foreign material placed at the time of surgery.

The Statistical Analysis Plan is available within NCT03915470. Secondary endpoint analysis included the assessment of change in $\log_{10}$ CFU/mL from baseline to all of the additional time points and was assessed using a mixed model for repeated measures. It was fitted with visit, treatment group, country, and the treatment group by visit interaction as fixed effects, and the baseline *S. aureus* $\log_{10}$ CFU/mL value as a covariate.

Results

100% of enrolled patients received all prescribed doses of placebo or XF-73 (Figure A; Supplementary Material); demographics, risk factors, etc. are shown in Table 1; Supplementary Material. A rapid reduction in *S. aureus* nasal burden was seen at approximately 18 hours, after 2 applications of XF-73 [Swab 3] with a mean −2.2 $\log_{10}$ CFU/mL decrease observed compared to baseline (placebo −0.01 $\log_{10}$ CFU/mL). At 48 hours and 6 days after surgery, *S. aureus* nasal burden decrease versus baseline were 2.7 and 3.1 $\log_{10}$ CFU/mL, respectively [Swabs 6 and 7] for XF-73. For placebo, the decrease was −1.5 and −2.4 $\log_{10}$ CFU/mL.

Prior to either arm's third dose, there was a least square mean (LSM) difference of −2.1 $\log_{10}$ CFU/mL, ($P = 0.0001$) between XF-73 and placebo. At 48 hours post-surgery, the LSM difference was −0.9 $\log_{10}$ CFU/mL, ($P = 0.0021$) and at day 6 post-surgery it was −0.4 $\log_{10}$ CFU/mL, ($P = 0.2369$).

The percentage of patients exhibiting zero nasal *S. aureus* carriage, (ie, decolonization), or a ≥2 $\log_{10}$ CFU/mL reduction, (Figure 2) after 2 doses was 62.8% for XF-73 versus 15% for placebo. At 48 hours post-operatively, XF-73 treated patients remained similarly decolonized, or had ≥2 log reduction (76.7%), while the placebo's nasal decolonization had increased to 47.5%. By day 6 post-operatively, 86.1% of the XF-73 treated patients were decolonized versus a similar level of 82.5% in placebo.

In this micro-ITT population (n = 83), 100% of patients received peri-operative (<48 hours) prophylactic antibiotics. For post-operative (≥48 hours) antibiotic use, 48/83 patients (57.8%) received anti-staphylococcal antibiotics, most commonly with second-generation cephalosporins (33.7%). An assessment of post-operative anti-staphylococcal antibiotics between groups demonstrated fewer patients in the XF-73 arm versus the placebo received post-operative antibiotics (20/43, 46.5% vs 28/40, 70%), respectively; post-hoc analysis $P = 0.045$). The mean durations of post-operative anti-staphylococcal antibiotics were 7.57 days [SD = 5.530] in the XF-73 group and 7.77 days [SD = 7.045] in the placebo group.

Discussion

XF-73 nasal gel applied within 24 hours prior to surgery rapidly and significantly reduced nasal *S. aureus* burden from baseline after only 2 doses and throughout the early post-operative period (48 hours post-surgery). By day 6, the nasal *S. aureus* burden in the placebo arm had declined to a similar level as the XF-73 arm [Figure 2]. Reductions in nasal *S. aureus* were previously reported in other studies and attributed to the delayed impact of peri- and post-operative systemic, anti-staphylococcal antibiotics.[10] Clinically, the impact of anti-staphylococcal antibiotics on nasal *S. aureus* in the placebo arm was not observed before, during or immediately within 1 hour of incision closure.[9] This demonstrates that anti-staphylococcal antibiotics had little impact on the reduction in nasal *S. aureus* during and immediately following surgery.

Fewer patients in the XF-73 treatment arm received post-operative anti-staphylococcal antibiotics compared to the placebo arm. These antibiotics may have been prescribed as an early rescue intervention to mitigate against an SSI, yet clinical staff were blinded. No SSIs were reported in either arm; XF 73 may be able to prevent the spread of *S. aureus* from the nose to the incision within the first post-operative week. The prolonged post-operative antibiotic use may have been due to a number of reasons, but was not a focus in the protocol. Prolonged post-operative antibiotic use has not shown efficacy and is not recommended in SSI prevention guidance. Preoperative infection prevention processes such as whole-body skin and nasal decolonization remain crucial to preserve antibiotic long-term efficacy.

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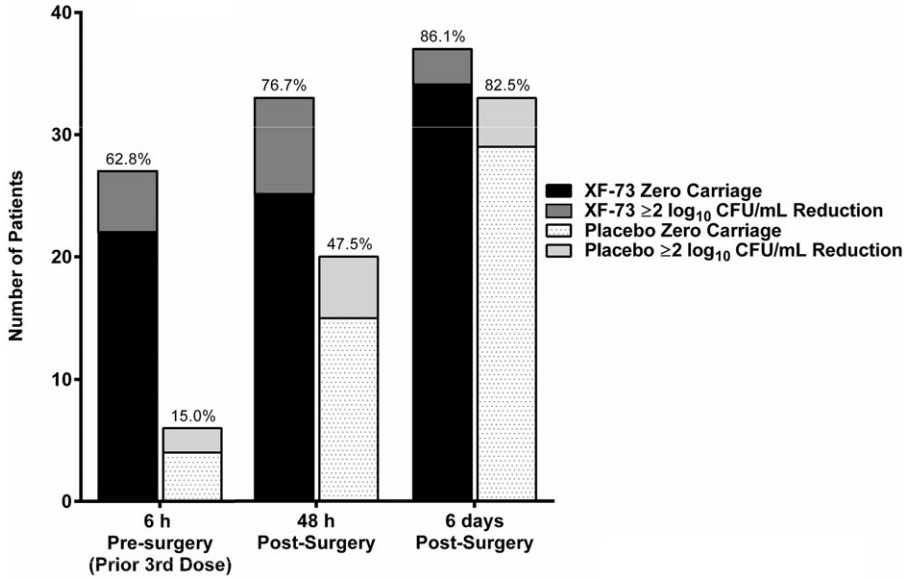

Figure 2. Percentage of patients with zero nasal *S. aureus* carriage or ≥2 $\log_{10}$ CFU/mL reduction. When assessing the percentage of patients exhibiting zero nasal *S. aureus* carriage, (decolonization), or a ≥2 $\log_{10}$ CFU/ml reduction, 62.8% of patients treated with XF-73 met this metric after only 2 doses of XF-73 versus 15% of placebo. At 48 hours post-operatively, XF-73 treated patients remained similarly decolonized (76.7%); while placebo had increased to 47.5%. By day 6 post-operatively, 86.1% XF-73 treated patients were decolonized versus a similar level of 82.5% on placebo. CFU, colony forming units; h, hour.

The rapid anti-staphylococcal action of XF-73 allows for a short administration course pre-operatively, (ie, 1 day vs 5 days for mupirocin); is an excellent fit with clinical practice, could enable infection risk reduction peri-operatively, (ie, for emergency procedures), may enhance surgical scheduling flexibility and could augment infection prevention efforts. Phase 3 studies are being planned to further evaluate the efficacy of XF-73 in the prevention of SSI's in at risk surgeries. The Phase 3 study designs have been discussed with the FDA and comply with ethical, regulatory, and current standard of infection prevention care practices within hospitals for the at risk surgeries to be studied.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/ice.2024.122.

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Competing interests. JPL, JMG, YM, WGL, DB, and WRW are, or were, employed by Destiny Pharma plc. WGL, JL, and WRW have stock/stock options in Destiny Pharma plc. AD received consultancy fees from Destiny Pharma plc for statistical consultancy and support for the present study. JEM and MSF served as consultants and received funding from the Sponsor to serve on the Data Monitoring Committee for the present study in 2020 and 2021.

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