CLINICAL STUDY PROTOCOL

A Phase 2 Study to Assess the Effect of a Repeated Dose of Exeporfinium Chloride (XF-73) Nasal Gel on the Microbiological Burden of Commensal *Staphylococcus aureus* Nasal Carriage in Surgical Patients at Risk of Post-Operative Staphylococcal Infections.

Protocol Number:	XF-73B07
Investigational Medicinal Product:	Exeporfinium chloride (XF-73)
Indication:	Prevention of post-operative staphylococcal infections
Phase:	2
Sponsor:	Destiny Pharma plc Sussex Innovation Centre Science Park Square, Falmer Brighton, BN1 9SB United Kingdom
Sponsor Chief Medical Officer:	[redacted]
IND Number:	109303
Protocol Version and Date:	Version 2.1, 04 Jun 2020
	NCT03915470

The study will be conducted according to the protocol and in compliance with versions of Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements in effect during the time of the conduct of the study.

SPONSOR SIGNATURE PAGE

Declaration of Sponsor or Responsible Medical Officer

Title:

A Phase 2 Study to Assess the Effect of a Repeated Dose of Exeporfinium Chloride (XF-73) Nasal Gel on the Microbiological Burden of Commensal *Staphylococcus aureus* Nasal Carriage in Surgical Patients at Risk of Post-Operative Staphylococcal Infections.

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the current version of the Declaration of Helsinki (Brazil 2013), and the guidelines on Good Clinical Practice.

_____ _____

[redacted] Date
Chief Medical Officer
Destiny Pharma plc

_____ _____

[redacted] Date
Director of Clinical Projects
Destiny Pharma plc

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Title:

A Phase 2 Study to Assess the Effect of a Repeated Dose of Exeporfinium Chloride (XF-73) Nasal Gel on the Microbiological Burden of Commensal *Staphylococcus aureus* Nasal Carriage in Surgical Patients at Risk of Post-Operative Staphylococcal Infections.

I have read and understood all sections of the protocol.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the final protocol, the International Conference on Harmonisation Tripartite Guideline: Good Clinical Practice E6 (R2) and all applicable government regulations. I will not make changes to the protocol before consulting with Destiny Pharma plc or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to subjects. I agree to administer study treatment only to subjects under my personal supervision or the supervision of a sub-Investigator.

I will not supply the investigational product to any person not authorized to receive it. Confidentiality will be protected. Subject identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from Destiny Pharma plc.

_____ _____

Signature Date

_____

Print Name (block capitals)

_____

Site Number, Name and Address (block capitals)

1 PROTOCOL SYNOPSIS

<table>
<tr><td>Title:</td><td>A Phase 2 Study to Assess the Effect of Repeated Dose of Exeporfinium Chloride (XF-73) Nasal Gel on the Microbiological Burden of Commensal Staphylococcus aureus Nasal Carriage in Surgical Patients at Risk of Post-Operative Staphylococcal Infections.</td></tr>
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<tr><td>Chief Medical Officer:</td><td>[redacted]</td></tr>
<tr><td>Objectives and Endpoints:</td><td>
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<tr><th>Primary Objective</th><th>Endpoint</th></tr>
<tr><td>To demonstrate the efficacy of a 0.2% XF-73 nasal gel in reducing the microbiological burden of nasal S. aureus measured as change in colony forming units (CFU) per millilitre (mL) from baseline to immediately prior to surgery in a patient population at risk of post-operative staphylococcal infection</td><td>Change in S. aureus log CFU/mL from baseline to pre-surgery</td></tr>
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<tr><th>Secondary Objectives will include</th><th>Endpoint</th></tr>
<tr><td>To determine the effect of a 0.2% XF-73 nasal gel on S. aureus nasal burden from baseline to pre-surgery and from baseline to immediately post-surgery measured as area under the curve (AUC) of S. aureus log CFUs/mL over time.</td><td>• Difference in AUC of S. aureus log CFU/mL from baseline to pre-surgery.
• Difference in AUC of S. aureus log CFU/mL from baseline to immediately post-surgery</td></tr>
<tr><td>To determine the effect of a 0.2% XF-73 nasal gel on S. aureus nasal burden measured as CFUs/mL in follow-up after last administration.</td><td>• Change in S. aureus log CFU/mL from immediately after surgery to 48 hours after surgery
• Change in S. aureus log CFU/mL from immediately after surgery to 7 days after surgery</td></tr>
<tr><td>To explore the efficacy of XF-73 in reducing the burden of S. aureus carriage at the patient level.</td><td>• Percentage of patients reaching a specific reduction in S. aureus carriage prior to surgery, immediately post-surgery and on Day 6 ± 24hrs.</td></tr>
<tr><td>To assess the effect of XF-73 on S. aureus nasal carriage in the prevention of post-operative</td><td>• Difference in the incidence of staphylococcal post-operative infections during the 30-day</td></tr>
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	staphylococcal infections (surgical site infection, blood stream infections, and others) during the 30 days post-surgery (90 days in the case of a foreign implant). — period after surgery (90 days in the case of foreign implant)
	To describe the safety and tolerability of multiple administrations of a 0.2% XF-73 nasal gel in a population of surgical patients at risk of post-operative staphylococcal infections. — • Incidence of treatment-emergent adverse events from the first dose of study medication to 7 days after last dose of study medication. • Changes in vital signs, safety clinical laboratory assessments, nasal examination, and brief smell identification test (B-SIT).
	Exploratory Objective — **Endpoint** To describe the use of post-operative anti-staphylococcal antibiotics, except those provided for prophylaxis as local standard of care (SOC), during the 30-day post-surgery period (90 days in the case of an object implant) reported separately — • Reason for post-operative prescription of anti-staphylococcal antibiotics during the 30-day post-operative period (90 days post-surgery in the case of an object implant)
Design:	This is a Phase 2, multi-centre, randomized, double-blind, parallel, placebo-controlled study conducted in patients undergoing surgical procedures at risk of post-operative staphylococcal infections.
Study Population:	Patients undergoing surgical procedures at risk of post-operative staphylococcal infections.
Inclusion Criteria:	Individuals who meet all of the following criteria are eligible to participate in the study. 1. Male or female patients between 18 and 75 years of age. 2. Patients who are confirmed nasal *S. aureus* carriers by PCR screen assay, and due to undergo a surgical procedure associated with risk of post-operative staphylococcal infections. 3. Patients who are willing to provide written informed consent. 4. Patients who are willing and able (as per Investigator judgement) to complete all protocol specified visits and assessments. 5. Woman of childbearing potential* with a negative urine pregnancy test (sensitive to 25 IU human chorionic gonadotropin [hCG]). ** Women of childbearing potential are defined as those women between menarche and menopause who have not undergone permanent sterilisation. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.*

Exclusion Criteria:	Individuals who meet any of the following criteria are not eligible to participate in the study. 1. Pregnancy (current) currently lactating. 2. Uncontrolled acute or chronic illness (as determined by the Investigator) in addition to those requiring the planned surgical intervention. 3. History of atopy, allergic reaction, or hypersensitivity to the study mediation or its components. 4. Current upper respiratory tract infection, cold or influenza with significant nasal symptoms that might impact on the patient's ability to comply with the gel application procedure. 5. History of photosensitivity. 6. Family history of porphyria. 7. Use of intra-nasal, topical or systemic antibiotics or anti-infectives within the last 4 weeks before screening. (Patients who screen positive for nasal carriage of *S. aureus* and receive topical or systemic antibiotics or anti-infectives which are not part of their prophylactic peri-operative SOC between screening and first dose of IMP will be excluded from the study.) The use of intra-nasal antibiotics or anti-infectives other than the study medication prior to surgery is not allowed. 8. Use of other prescribed or over-the-counter nasal medication in the last 14 days or oral decongestants in the last 7 days before first administration of study drug. 9. Participation in a clinical trial within the last 12 weeks before first administration of study drug. 10. Contemporaneous clinically significant abnormalities in vital signs or laboratory analyses reported within 14 days prior to randomization which in the opinion of the Investigator would preclude from the safety assessment of the medication under study. 11. Nasal polyps or significant anatomical or other nasal abnormality that would prevent from appropriate administration of the study treatment or represent an excessive risk for the patient's participation. 12. History of nasal surgery including cauterization. 13. A recent history of frequent epistaxis and/or an episode of epistaxis within 3 months of the planned surgery. 14. Use of in-situ nasal jewellery or existence of open nasal piercings.
Number of Patients:	It is planned that approximately 125 patients will need to be recruited in order to have around 80 patients with sufficient burden of *S. aureus* nasal carriage which will allow for the detection of an effect of XF-73 nasal gel over placebo.
Countries/Number of Sites:	USA (~ 10 sites), Georgia (~10 sites), Serbia (~5)

Investigational Medicinal Product:	Patients will be randomised in a double-blind manner to either the active or placebo arm. The active and placebo study drugs used in the study are as follows: 0.2% w/w XF-73 Nasal Gel (0.3 ml nasal gel equating to 0.6 mg XF-73 per naris) Placebo to Match XF-73 Nasal Gel (0.3 ml nasal gel per naris)
Duration of Participation:	The study duration will be either up to 6 or 12 weeks for each individual (from screening to last post-study follow-up visit at either 30 or 90 days). The overall duration of the study will be approximately 15 months starting Q3 2019 to Q4 2020
Criteria for Evaluation:	
Efficacy Assessments:	• Measurement of *S. aureus* CFU/mL • Incidence of post-operative staphylococcal infections
Safety Assessments:	• Incidence of TEAEs • Clinical laboratory parameters • Vital signs • Physical examinations • Nasal examination • Brief Smell identification test (B-SIT).
Concomitant Medication:	At randomization, patients will be asked what medications they have taken during the last 30 days. At each subsequent study visit, patients will be asked what concomitant medications they are currently taking. Special attention will be placed in recording the concomitant use of anti-infectives and antibiotics. The use of intra-nasal antibiotics or anti-infectives other than study medication prior to surgery is not allowed. The use of skin decolonization products (e.g. chlorhexidine) and systemic perioperative prophylactic antibiotics (e.g. intravenous vancomycin) as part of the SOC will be recorded.

Statistical Methods:	A Statistical Analysis Plan (SAP) describing the planned final analysis in detail with tables, figures and listings templates will be developed as a separate document Primary analysis will be on the endpoint of change in log_{10} CFU from baseline to pre-surgery using an analysis of covariance (ANCOVA) model including baseline CFU as a covariate. A similar analysis will also be performed for the endpoint of change from baseline to the post-surgery measurement. Secondary efficacy analyses will include; • Change in log_{10} CFU from baseline to post-surgery using an ANCOVA model including baseline CFU as a covariate. • A log_{10} AUC for CFUs will also be undertaken utilising data for all time points up until the pre-surgery assessment. This analysis of log_{10} AUC CFUs will also including baseline log_{10} CFU as a covariate. • A log_{10} AUC for CFUs will also be undertaken utilising data for all time points up until the post-surgery assessment. This analysis of log_{10} AUC CFUs will also including baseline log_{10} CFU as a covariate. • Percentage of patients reaching a specific reduction in *S. aureus* carriage prior to surgery, immediately post-surgery and on Day 6 ± 24hrs. • Proportion of patients with nasal carriage below a set value (value TBD) • Summary of data for nasal carriage according to SQS along with an analysis of proportional odds. • Summary of the proportion of patients with a 2-log drop (TBD) All available data from patients in the Safety Population will be included in the assessment of safety and tolerability. All safety and tolerability data will be listed and summarised by treatment group using appropriate descriptive statistics. Formal statistical comparisons between the different treatment groups will not be conducted. All AEs will be coded using the MedDRA terminology.

Table 1.1: Schedule of Assessments

Assessment	**Screening Visit**	**Randomisation Visit**	**Treatment Period**					**Follow-up Period**		
Study Day	**Day -14 to Day -1***	**Day -10 to Day -1***	**Day -1 to Day 0**					**48h ± 24h post wound closure**	**Day 6± 24h**	**Day 30 (and Day 90) [a]**
			Dose 1	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**			
Screening consent	X									
Nasal Swab for *S. aureus* (quantitative and rapid screen [k])	X [k]		X[i]		X [i]	X [i]	X [i]	X	X	
Study consent		X								
Inclusion/Exclusion Criteria		X	X							
Demographics		X								
Medical /Surgical History		X	X [m]							
Prior Medication History		X	X [m]							
Physical Examination [b]		X	X					X	X	
Examination of Nose and Nasal Passages by ENT [c]		X [c]	X [c]					X		
Vital Signs [d]		X[n]					X	X	X	
Clinical Chemistry and Haematology [e]		X[n]					X (Post dose)	X	X	
Urinalysis [f]		X					X (Post dose)	X		

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			Dose 1	**Dose 2**	**Dose 3**	**Dose 4**	**Dose 5**			
Pregnancy Test		X							X	
Record standard of care in skin decontamination and peri-operative prophylactic regimen		X	X	X	X	X	X	X		
Record blood glucose levels and temperature during surgery [j]						X	X			
Brief Smell Identification Test		X [g]	X [g]						X	
Adverse Events		X[l]	X	X	X	X	X	X	X	
Concomitant medication		X	X	X	X	X	X	X	X	X
Randomisation		X [g]	X [g]							
Study Drug Administration [h]			X	X	X	X	X			
Record staphylococcal infections and use of antibiotics								X	X	X

ENT=Ear, Nose, and Throat specialist

*) All screening and randomisation activity to be completed ahead of Dose 1

a) The Day 90 Follow-up Visit is for patients who have had a foreign implant during surgery.

b) A complete physical examination, including height and weight, (skin; head, eyes, ears, nose, and throat; lymph nodes; heart, lungs, and abdomen; extremities and joints; and neurological examination, but no breast, genital, or rectal examinations) will be done at the Randomisation Visit OR before nasal swab prior to dose 1. Brief symptom-driven physical examinations (including the nose and nasal passages) will be done at other visits.

c) Nasal examination by ENT specialist at randomisation OR before nasal swab prior to dose 1, and again at 48+/-24h (post wound closure nasal swab). Nasal examination by ENT specialist at other timepoints if investigator mandated (*i.e.* symptoms/signs directed)

d) Vital signs including blood pressure and heart rate, taken in supine position.

e) Clinical safety lab tests will consist of the following: Haematology: Complete Blood Count (CBC), including Red blood cell (RBC) count, Haemoglobin, Haematocrit, RBC indices and red cell diameter width (RDW), white blood cell (WBC) total and differential count, and Platelet count; Serum Chemistry: Serum Sodium, Potassium, Carbon dioxide (CO_2) (bicarbonate), Chloride, Blood urea nitrogen (BUN), Creatinine, Glucose (Screening), Glucose (Admission, Discharge and Follow up); record the time the patient last ate for all glucose levels, Calcium, Magnesium, Phosphate, Uric acid, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Total bilirubin, Alkaline phosphatase, Total protein, and Albumin

f) Urinalysis dip-stick for at least test (pH, spec gravity, proteins, glucose, ketones, bilirubin, nitrites, WBC, blood). If there are abnormal findings samples will be sent for microscopic examination Microbiological testing to undertaken at the Investigators decision

g) Baseline Brief Smell Identification Test and Randomization may occur between Day -10 and Day -1 prior to Dose 1.

h) XF-73 or placebo will be administered 4 times into each nostril prior to surgery and then a single application immediately after wound closure.

i) Nasal swabs are taken within 1 hour before the corresponding dose.

j) The number of total glucose/core temperature determinations between admission to hospital for surgery and the period 48±24hours after surgery is determined by how many are over 200 mg/dL for glucose or below 35.5 °Celsius for temperature.

k) Only rapid screen nasal swab required at Screening. No quantitative testing will be performed.

l) Record AEs that according to investigator's judgement are related with the screening procedures.

m) If changes from randomization visit.

n) Standard of care or study mandated vital signs or laboratory analyses reported within 14 days prior to randomization should be used to determine inclusion/exclusion criteria.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BDRM	Blinded data review meeting
BP	Blood pressure
B-SIT	Brief Smell Identification Test™
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CFU	Colony forming units
CHRS	Cardinal Health Research Service
CO_2	Carbon Dioxide
CRA	Clinical Research Associate
CSR	Clinical study report
DNA	Deoxyribonucleic acid
eCRF	electronic Case report form
EDC	Electronic data capture
ENT	Ear, Nose and Throat specialist
FD&C	Food, Drug & Cosmetic
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
HPC	Hydroxypropyl cellulose
IB	Investigator's Brochure
ICF	Informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IDSA	Infectious Disease Society of America
IEC	Independent Ethics Committee
IN	Intranasal
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigational Site File
ITT	Intent-to-treat
JP	Japanese Pharmacopoeia
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *S. aureus*
MSSA	Methicillin-sensitive *S. aureus*
NF	National Formulary
NHSN	National Healthcare Safety Network
PCR	Polymerase chain reaction
Ph Eur	European Pharmacopoeia
PP	Per-protocol
QS	Quantity sufficient
RNA	Ribonucleic acid
S. aureus	*Staphylococcus aureus*
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SHEA	The Society for Healthcare Epidemiology for America
SIS	Surgical Infection Society
SOC	Standard of care
SSI	Surgical site infection
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation	Definition
TBD	To be determined
TEAE	Treatment-emergent adverse event
US	United States
USP	United States Pharmacopoeia
WHO	World Health Organization

4 INTRODUCTION

4.1 Background

Staphylococcus aureus (*S. aureus*) and specially the more antibiotic resistant strain, Methicillin-Resistant *S. aureus* (MRSA), is a common causative organism of nosocomial infections in hospitals across the world[8]. It was estimated that 1% of all hospitalized patients in the United States (US) suffered from *S. aureus* infections, equating to nearly 400,000 patients[19], at an estimated cost of $14.5 billion. Amongst nosocomial infections caused by *S. aureus* (including MRSA), Surgical Site Infections (SSIs) are a major infectious entity and are a cause of significant morbidity and mortality[22,23]. The prevalence of MRSA nosocomial infections in the US ranges from 42.6% to 52.0% depending of the site of the nosocomial infection[23]. The most recent data from the National Healthcare Safety Network (NHSN) in the US showed that despite recent efforts, 42.6% of all reported *S. aureus* surgical site infections were due to MRSA[23]. At least 80% of such infections are caused by the patients' own bacteria[9-11]. *S. aureus* can colonize several body sites - nose, axillae, groin and throat - although the anterior nares are the preferred ecologic niche and are identified as the most frequent site of carriage[11-13], with 25 to 35%[14] of the population being colonized at any given time. *S. aureus* carriers are at a higher risk of staphylococcal infections after invasive medical or surgical procedures than non-carriers, having been estimated to be 2 to 10 times more likely to develop surgical-site/intravenous catheter infections[15-18]. Specifically, *S. aureus* nasal carriage has been identified as a risk factor for the development of infections in orthopaedic, thoracic and general surgery as summarized in a review by Wertheim *et al* (2005)[11].

Standard infection control measures, including hand-washing by staff with antiseptic detergents or 70% alcohol, ward cleaning, disinfecting equipment, correct handling of clinical waste, etc are important for limiting MRSA cross-infection. However, body decolonization procedures (typically nasal decolonization and additional body washes) have been adopted or recommended for at-risk patients in many settings[25].

In 2010, Bode *et al* reported the results of a randomized, double-blind, placebo-controlled study investigating nasal and body decolonization and concluded that hospital-acquired infections with *S. aureus* could be prevented by initiating decolonization treatment (nasal and body) immediately after admission of surgical patients[20]. In a commentary on this study, Bertrand *et al* also concluded that pre-emptive *S. aureus* decolonization should be used in surgery with a high risk of *S. aureus* infection such as open-heart surgery and orthopaedic or neurosurgical implant procedures[9]. In their review of published data on decolonization therapy from 2008 to 2010, Hebert and Robicsek concluded that decolonization therapy was likely to be an effective tool for reducing surgical infection in cardiac and orthopaedic patients[21]. Kim *et al* have reported a study in 7,019 orthopaedic surgical patients, concluding that a program of identification and eradication of both MRSA and methicillin-sensitive *S. aureus* (MSSA) carriage with intranasal mupirocin and chlorhexidine showers can lead to significant reductions in post-operative rates of surgical site infection[5].

In February 2013, a consensus involving the Surgical Infection Society (SIS), Infectious Disease Society of America (IDSA) and The Society for Healthcare Epidemiology for America (SHEA), published guidelines which recommend the use of nasal decolonization of all *S. aureus* in cardiovascular and orthopaedic surgery[26]. They also discussed the risks in other clean surgeries where there was not the level of proof to make a formal recommendation yet. As the only

approved agent for nasal decolonization, mupirocin is cited, with caveats over widespread use, compliance and awareness of potential resistance. The SIS guidelines[26] are likely to increase the number of centres employing *S. aureus* decolonization in the surgeries identified, but this may be affected by the limitations of mupirocin in respect of treatment duration, compliance, concerns over resistance and logistical difficulties associated with pre-admission screening.

Despite these recommendations, existing product approvals do not explicitly exemplify the use of prophylactic intranasal (IN) antibiotics by surgical patients. In the US, Mupirocin (Bactroban®) is indicated for MRSA decolonization during institutional outbreaks; in Europe the indication is worded: 'the elimination of nasal carriage of staphylococci, including MRSA'. In fact, *S. aureus* nasal decolonisation is not universally accepted practice and if practiced it is not done in a standard manner, but with a variety of products and dosing regimens for each product as none of these are approved for the intended indication.

Exeporfinium chloride (XF-73) is a dicationic porphyrin derivative having potent bactericidal properties with a novel mode of action. XF-73 is being developed as a viscous dermal gel for the decolonization of *S. aureus* in the anterior nares (nasal cavity) to prevent post-operative staphylococcal infections.

XF-73 has been investigated against a panel of 101 Gram-positive and Gram-negative organisms selected for susceptibility and cross-resistance testing[2]. The panel comprised 65 Gram-positive isolates (56 aerobic and 9 anaerobic) and 36 Gram-negative isolates (31 aerobic and 5 anaerobic). XF-73 demonstrated excellent bactericidal activity against all Gram-positive strains tested regardless of species, phenotype or genotype, with minimum inhibitory concentrations (MICs) of 0.25 to 4 mg/L. The antibacterial activity against Gram-negative species was lower, with MICs of 1 mg/L to > 64 mg/L. The study indicated that XF-73 is rapidly bactericidal against *S. aureus*, including methicillin-resistant strains (including USA300) [2] (Study R14). Exposure of bacteria to XF-73 resulted in an observed loss of membrane potential within 1 minute, followed by efflux of small molecular weight molecules, ATP and potassium; >99.99% of *S. aureus* are killed within 5 minutes[1]. The mode of action is thus focused on the bacterial cell membrane. Cell death is not accompanied by lysis of the cells, as observed by electron microscopy (Study R39) or resulting in efflux of large molecular weight components (DNA, RNA, proteins) [1].

A multistep study, in which MRSA was passaged 55 times, showed that XF-73 had a very low potential for inducing resistance over the 55 passages. The MIC values showed no more than a 4-fold increase over the starting MIC and the accepted threshold for resistance (≥ 8-fold increase in MIC) was not reached[3].

The speed of onset of anti-staphylococcal activity of XF-73 has also been observed during clinical studies, in which the level of *S. aureus* isolated from heavily colonized, stable *S. aureus* carriers was observed to be reduced dramatically after 1 to 3 doses over 1 day. These characteristics have supported the targeting of a preferred indication of IN administration to prevent post-operative staphylococcal infections. In this setting, the rapidity of action will allow for a short treatment course around surgery.

To date there have been 7 completed clinical studies on XF-73 (5 intranasal and 2 dermal) in 263 patients, of which 241 received XF-73. In the intranasal (i.n.) studies carried without photodymanic therapy, the most common (≥10%) adverse events (AEs) reported with XF-73 gel application are headache (11.4%), nasal discomfort (9.0%), and rhinorrhoea (7.8%). Most of the

treatment-emergent AEs (TEAEs) associated with nasal gel application from previous studies were considered mild to moderate in intensity. Further details can be found in the current version of Investigator's Brochure (IB), which contains comprehensive information on the investigational product.

This is a proof-of-concept study which will assess the efficacy and safety of XF-73 in the decolonisation of nasal carriers of *S. aureus* that will undergo a surgical procedure associated with risk of post-operative staphylococcal infections.

4.2 Rationale

XF-73 provided as a 2 mg/g nasal gel with [redacted] is being developed for the prevention of post-operative staphylococcal infections. Both microbiological and clinical data support the move of XF-73 into this Phase 2 proof-of-concept study to assess the safety and microbiological efficacy of XF-73 in reducing the burden of nasal *S. aureus* before surgery in patients who are undergoing procedures at risk of post-operative staphylococcal infection, the population for which XF-73 is intended.

XF-73 possesses anti-bacterial activity *in vitro* in the 0.5 to 1 mg/L concentration range, against *S. aureus* colonies, including MRSA, as well as for other potentially pathogenic Staphylococci spp. This antibacterial activity is rapid and suggests that a short duration of treatment e.g., 24 to 48 hours will be possible, promoting compliance with the treatment.

Two Phase 1 studies in human volunteers, who were confirmed nasal carriers of *S. aureus,* have already assessed the safety of XF-73 2 mg/g nasal gel and preliminary efficacy in reducing the burden of *S. aureus* in the nose: study XF-73B03 study with 63 healthy volunteers and study DMID11-007 with 56 healthy volunteers. These studies have used different regimens concentrations of XF-73 (0.5 mg/g and 2 mg/g) in different regimens (from 1 IN application every 12 hours for 2 days to 1 IN application every 8 hours for 1 day and then every 12 hours for another 4 days) and have analysed efficacy (burden of nasal *S. aureus*) in various ways (percentage of patients decolonized, evolution of quantitative *S. aureus* scores and area under the curve of quantitative *S. aureus* scores). Although limited in volunteers' numbers, both studies have shown consistent better responses for the XF-73 2mg/g nasal gel compared to placebo. These studies have also allowed to assess the dynamics of nasal burden of *S. aureus* when exposed to XF-73 and inform a dose selection for further development and last but not least, these studies have depicted a favourable safety and tolerability profile for XF-73. XF-73 has also been assessed for safety up to 5.0 mg/g aqueous solution applied to the shoulder in healthy volunteers. These data suggest that XF-73 may also reduce the burden of *S. aureus*, including MRSA, before surgery in patients at risk of post-operative staphylococcal infections.

In summary, the data from previous studies warrant the move of XF-73 into a further step in its development for the prevention of post-operative staphylococcal infections with this Phase 2 proof-of-concept study where the safety and efficacy of XF-73 to decrease the burden of nasal carriage of *S. aureus* will be studied in actual patients who will undergo a procedure at risk of post-operative staphylococcal infections. Please refer to the current IB for further information.

4.3 Risk-Benefit Assessment

The safety of nasal application of XF-73 in concentrations up to 2 mg/g, cumulative doses up to 13.2 mg and for up to 5 days has already been studied in 172 volunteers. The most common AEs reported as related to XF-73 have been nasal discomfort, headache and rhinorrhoea in 17, 14 and

14 patients, respectively. These events were mostly mild in intensity, transient and resolved spontaneously without sequelae. Post-dose nasal examinations have not revealed erythema or increased secretions, so these events seem to be more related with the physical presence and sensation of the gel in the nares rather than a physiological interaction with the nasal mucosa; though a dose response cannot be fully ruled out.

Only one suspected unexpected serious adverse reaction (SUSAR), hyposmia, has been reported; and has also been the only related serious adverse event so far. This was in study DMID11-007 and since this report the remaining 21 volunteers were provided a smell test pre- and post- study. No signal was detected.

XF-73 plasma levels have been determined in all studies up to date showing no evidence of systemic absorption (assay detection limit 0.2 ng/mL), therefore no systemic toxicity from XF-73 is expected in this study. Of note, in the studies with XF-73 nasal gel to date, there have been no AEs leading to treatment or study discontinuation.

XF-73 provided as a nasal gel has been shown to be well tolerated in different healthy volunteer studies; nevertheless in this Phase 2 study, with patients who will undergo surgery, besides the usual safety exams (physical, biochemistry and haematological laboratory tests) a nasal examination by an ear nose and throat (ENT) specialist will be performed pre and post-dosing to further assess the risks from the contact of XF-73 gel and the nasal mucosa as well as a pre-post-dosing smell test to address the possible risk of hyposmia as it was seen in study DMID11-007.

An independent data monitoring committee (IDMC) of experts will be set up which will regularly review the safety information from the study as well as the incidence of post-operative staphylococcal infections. Should these reach an unexpectedly high level, the IDMC can recommend stopping the study. The IDMC charter containing amongst others membership, meetings frequency, structure and procedures produced before randomization of the first patient will be updated implementing the changes introduced in this version 2.1 of the protocol.

A benefit cannot be guaranteed, given the early stage of development if XF-73, however it is expected that the reduction in nasal burden of *S. aureus* seen in the healthy volunteers will reproduce in patients who participate in this study, which may translate in a reduction in the risk of developing post-operative staphylococcal infections. This benefit will be difficult to appreciate in this study as the incidence of these infections is low and the number patients to enrol very limited.

In summary, even though a benefit cannot be guaranteed or measured, only expected; the risks are limited. Additionally, surveillance measures to reassess benefit-risk during the execution of the study such as the nasal examination smell test and an IDMC are in place; so that appropriate action can be taken should an unexpected signal arise. The risk-benefit assessment is therefore thought to be favourable in this study.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Primary Objective and Endpoint

Objective	Endpoint
To demonstrate the efficacy of a 0.2% XF-73 nasal gel in reducing the microbiological burden of nasal *S. aureus* measured as change in colony forming units (CFU) per mL from baseline to immediately prior to surgery in a patient population at risk of post-operative staphylococcal infection	• Change in *S. aureus* log CFU/mL from baseline to pre-surgery

5.2 Secondary Objectives and Endpoint

Objective	Endpoint
To determine the effect of a 0.2% XF-73 nasal gel on *S. aureus* nasal burden from baseline to pre-surgery and from baseline to immediately post-surgery measured as area under the curve (AUC) of *S. aureus* log CFUs/mL over time.	• Difference in AUC of *S. aureus* log CFU/mL from baseline to pre-surgery. • Difference in AUC of *S. aureus* log CFU/mL from baseline to immediately post-surgery.
To determine the efficacy of a 0.2% XF-73 nasal gel in their effect on *S. aureus* nasal burden measured as CFUs/mL in follow-up immediately after surgery, at approximately 48 hours after surgery and 7 days after surgery.	• Change in *S. aureus* log CFU/mL from baseline to immediately after surgery • Change in *S. aureus* log CFU/mL from baseline to 48 hours after surgery • Change in *S. aureus* log CFU/mL from baseline to 7 days after surgery
To explore the efficacy of XF-73 in reducing the burden of *S. aureus* carriage at the patient level.	• Percentage of patients reaching a specific reduction in *S. aureus* carriage prior to surgery, immediately post-surgery and on Day 6 ± 24hrs.
To assess the effect of XF-73 on *S. aureus* nasal carriage in the prevention of post-operative staphylococcal infections (surgical site infections, blood stream infections and others) during the 30 days post-surgery (90days in the case of a foreign implant).	• Difference in the incidence of *S. aureus* post-operative infections during the 30-day period after surgery (90 days in the case of foreign implant)
To describe the safety and tolerability of multiple administrations of a 0.2% XF-73 nasal gel in a population of surgical patients at risk of post-operative staphylococcal infections.	• Incidence of TEAEs from the first dose of study medication to 7 days post last application of study medication • Changes in vital signs, safety clinical

	laboratory assessments, nasal examination, and smell identification test.

5.3 Exploratory Objective and Endpoint

Objective	Endpoint
To describe the use of post-operative anti-staphylococcal antibiotics, except those provided for prophylaxis as local standard of care (SOC), during the 30-day post-surgery period (90 days in the case of an object implant) reported separately.	• Reason for post-operative prescribed anti staphylococcal antibiotic use during the 30-day post-operative period (90 days in the case of an object implant)

6 OVERALL DESIGN AND PLAN OF THE STUDY

6.1 Overview

This is a Phase 2, multi-centre, randomized, double-blind, parallel, placebo-controlled study of multiple applications of a single concentration of XF-73 nasal gel to assess the microbiological effect of XF-73 on commensal *S. aureus* nasal carriage in patients scheduled for surgical procedures deemed to be at high risk of post-operative *S. aureus* infection. The study is divided in 4 periods: screening (Days -14 to -1) randomization (Days -10 to -1), treatment (Days -1 and 0) and follow-up (post-last study dose to Day 30 or Day 90 if an implant is inserted during surgery). Day 0 is the calendar day in which surgery takes place. Only patients who test positive to *S. aureus* by a standardized rapid diagnostic test will be enrolled in the study. Approximately 125 patients will be randomised in a double-blind manner (the investigators and patients are blind to the treatment assignment) in a 1:1 ratio to 0.2% w/w XF-73 nasal gel treatment OR placebo to match XF-73 nasal gel.

The study drug, 0.2% w/w XF-73, or matched placebo will be administered 4 times into each nostril over 24 hours prior to surgery and then a single application immediately upon closure of surgical wound. Additionally, patients may undergo chlorhexidine skin decolonisation ahead of surgery and receive perioperative prophylactic systemic antibiotics in accordance with local practice.

In total 7 nasal swabs will be taken: at screening, 3 times prior to surgery (surgery within 1 hour), post-surgery (right after surgical wound closure), 48 hours post-surgery and 7 days post-surgery.

Efficacy will be assessed by *S. aureus* colonisation from screening to 7 days after surgery as well as by incidence of post-operative staphylococcal infections and use of anti-staphylococcal antibiotics post-surgery. Safety will be assessed by reported AEs from screening up to Day 6 as well as vital signs, physical examination (ENT), clinical laboratory assessments (haematology, clinical chemistry, and urinalysis) and Brief-Smell Identification Tests (B-SIT) at different time points as reflected in Table 1.1.

The maximum study duration will be up to 45 or 105 days for each individual (from screening to post-study follow-up visit) depending on whether a foreign implant was inserted during surgery.

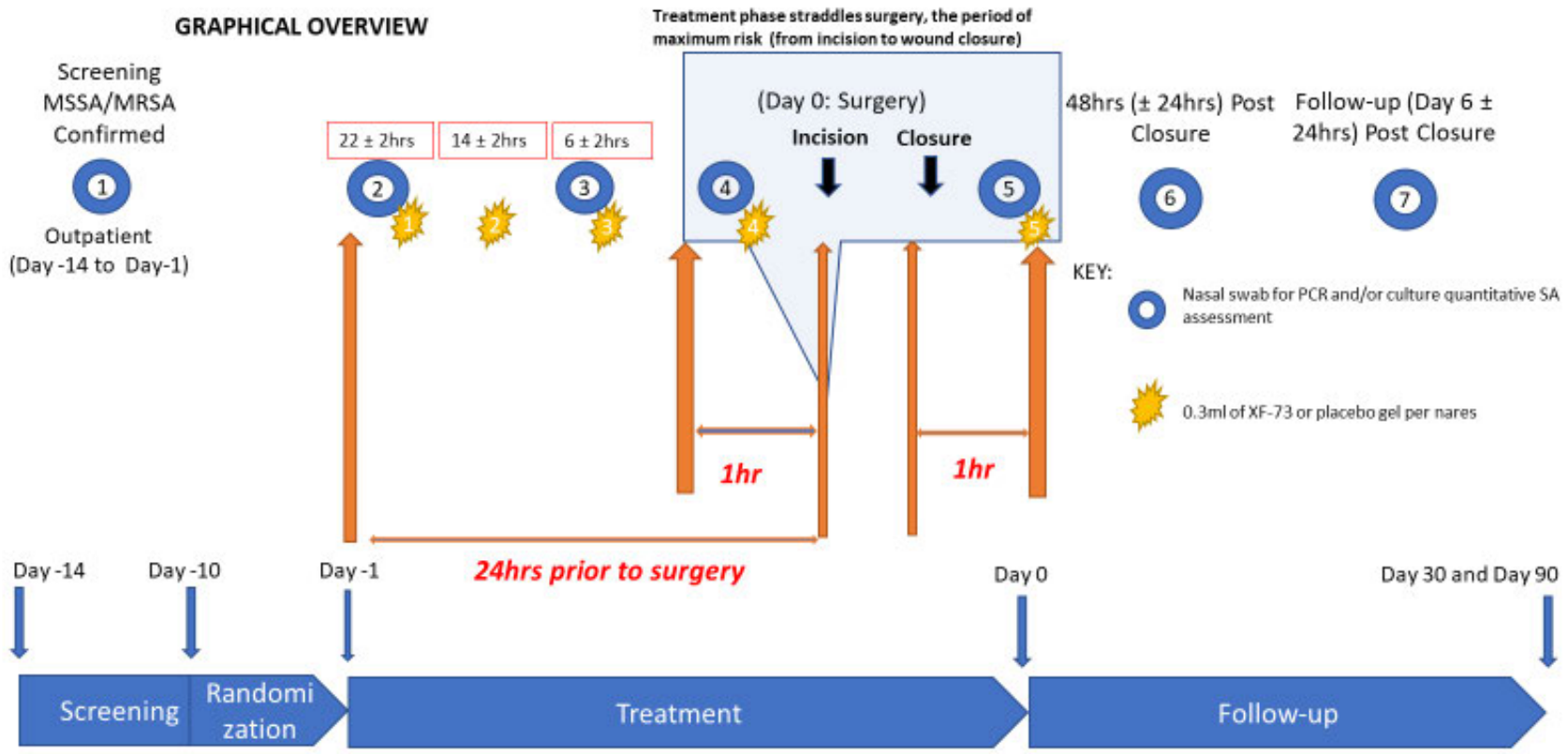
An IDMC will be set up which will review the safety information from the study and the incidence of post-operative staphylococcal infections. Based on the findings from these activities, the IDMC can recommend;

- Stop the study in case of serious concerns on subject's safety.
- Stop the study due to the incidence of post-operative staphylococcal infections.
- Continue as currently described in the protocol
- Continue the study with protocol modifications.

The IDMC charter containing, amongst other things: membership, meetings frequency, stopping criteria, structure and procedures produced before randomization of the first patient will be updated implementing the changes introduced in this version 2.1 of the protocol.

Figure 6.1 presents the study design.

Figure 6.1: Study Design



6.2 Discussion of Study Design

This is a Phase 2, randomised, double-blind, parallel, placebo-controlled, study of a single concentration of XF-73 nasal gel conducted in surgical patients who are at risk of post-operative staphylococcal infections. Patients will be randomised in a double-blind manner to either the active or placebo arm on a 1:1 basis.

6.2.1 Rationale for the Dosage of XF-73

The dosing regimen to be assessed in this study, four 0.3 mL applications in each naris of a 2 mg/g XF-73 [redacted] nasal gel 24 hours before surgery and a 5th application right after surgery (a cumulative dose of 6 mg of XF-73), is supported by microbiological and clinical data from XF-73 Phase 1 studies. Microbiological data showed that XF-73 has a rapid antibacterial activity and suggests that a short duration of treatment may be possible, facilitating compliance with this treatment.

In study XF-73B03, 63 healthy volunteers (safety population) who were nasal persistent carriers of *S. aureus* were randomly assigned to receive XF-73 nasal gel (0.5 mg/gr) or XF-73 nasal gel (2.0 mg/gr), both with [redacted], or placebo in each naris every 12 hours for 2 days; 27, 12 and 24 volunteers per group respectively. Burden of *S. aureus* in the naris was measured as semiquantitative *S. aureus* scores during the 2-day treatment period and up to discharge (Day 4) and follow-up (up to Day 6).

The efficacy data for the treatment period showed consistent better responses for the 2 XF-73 groups than for placebo in different efficacy measures: eradication rates of *S. aureus* from participants' noses; semiquantitative *S. aureus* scores; time to first clearance and mean differences in AUC. In many instances these differences were statistically significant in favour of XF-73. In the efficacy data at discharge (Day 4), on the other hand, only the AUC analysis showed statistically significant differences in favour of XF-73 groups for the discharge. No differences between study groups were detected during the follow-up period (Days 7 and 14). XF-73 was well tolerated at all dose levels used in this study.

Results for eradication of *S. aureus* during the treatment period (i.e., after 2 doses to each naris in the first 24-hour period and after 4 doses to each naris in the first 48-hour period), are described in the Table 6.1 below. In summary, for the XF-73 2.0 mg/g group there was a 41.7% (10 out of 24, P = 0.0087) clearance of *S. aureus* carriage at 24 hours after 2 doses (total dose 2.4 mg of XF-73) and a 37.5% (9 out of 24, P = 0.0965) clearance of *S. aureus* carriage at 48 hours after 4 doses (total dose 4.8 mg of XF-73) over placebo. For the XF-73 0.5 mg/g [redacted] group the was a 33.3% (4 out of 12, P = 0.0804) clearance of *S. aureus* carriage at 24 hours after 2 doses (total dose 0.6 mg of XF-73) and a 50% (6 out of 16, P = 0.0455) clearance of *S. aureus* carriage at 48 hours after 4 doses (total dose 1.2 mg of XF-73) over placebo.

Table 6.1: Analysis of Direct Plating Score Response Rate (ITT Population) – Study XF73-B03

Time Point	XF-73 2.0 mg/g [redacted] (2d) N=24	XF-73 0.5 mg/g [redacted] (2d) N=12	Placebo (2d) N=24
Day 2	10[2] (a total of 2.4 mg XF-73) 41.7% 7.86 (1.32, 80.65) 0.0087	4[2] (a total of 0.6 mg XF-73) 33.3% 5.50 (0.61, 68.03) 0.0804	2[1] 8.3%
EOT+12h	9[2] (a total of 4.8 mg XF-73) 37.5% 3.0 (0.66, 15.63) 0.0965	6[2] (a total of 1.2 mg XF-73) 50.0% 5.0 (0.82, 31.8) 0.0455	4[1] 16.7%

CI=confidence interval; EOT=end of treatment; HPC=hydroxypropyl cellulose

[1] Number of Responders, Response Rate

[2] Number of Responders, (total dose), Response Rate; Comparisons v Placebo - Odds Ratio (Exact 95% CI), One-sided Fisher Exact Test p-value using 2.5% significance level.

In addition, the analysis of semi-quantitative *S. aureus* scores during the treatment period also showed a more marked decrease from baseline in the 2 XF-73 treatment groups than in the placebo group. This same difference was shown in the analysis of mean differences in AUC during the treatment period and it was statistically significant with better responses for the XF-73 groups. Moreover, statistical AUC analysis and the change from baseline in the reduction in *S. aureus* semi-quantitative scores there was an apparent dose response relationship with the higher 2.0 mg/g XF-73 dosage performing better than the 0.5 mg/g dosage.

In conclusion, these data from the study suggest that the highest concentration of XF-73 (i.e., 2.0 mg/g) should be used to get a maximum response and that an efficient dose should be provided right before the point of highest risk for development of post-operative infections (i.e., right before surgery).

In the healthy volunteer study DMID11-007, 52 healthy volunteers (safety population) who were nasal persistent carriers of *S. aureus* received XF-73 nasal gel (0.5 mg/gr) [redacted] or XF-73 nasal gel (2.0 mg/gr) [redacted] or XF-73 nasal gel (0.5 mg/gr) [redacted] or placebo in each naris every 8 hours on Day 1 and every 12 hours Days 2 to 5; this provided cumulative doses of XF-73 of 3.3 mg, 13.2 mg and 3.3 mg respectively. Thirteen volunteers were randomly assigned to each group. Burden of *S. aureus* in the naris was measured as semiquantitative *S. aureus* scores during the 5-day treatment period and up to discharge (up to Day 6).

The efficacy data for the treatment period supported the conclusions from study XF73-B03. Early in treatment there were important differences in the number of volunteers achieving eradication of *S. aureus* from their nose between placebo and XF-73

groups. These differences were already seen at Day 2, after 3 nasal gel applications (i.e., 0.9 mg or 3.6 mg of XF-73 depending on 0.5 mg/g or 2 mg/g concentration in gel respectively), and in the case of the nasal gel with highest concentration of XF-73 reached statistical significance (data shown in Table 6.2 below). The AUC and semiquantitative *S. aureus* scores analysis confirmed this early effect of XF-73 at Day 2 in favour of the highest concentration of XF-73 over placebo and lower concentration of XF-73. The semiquantitative *S. aureus* scores analysis showed little effect, if any, in continued treatment beyond 3 doses to further diminish the burden of *S. aureus* in the nose.

In conclusion the data suggests that providing 3 applications of the gel with the highest concentration of XF-73, the effect on *S. aureus* burden plateaued with no significant extra effect with continued treatment. There were no differences in efficacy between the two gels with the same concentration of XF-73 (0.5%) and different concentration of HPC. All XF-73 doses provided in this study were well tolerated regardless of the HPC concentration in the gel.

Table 6.2: Response Rate (SQSA Score = negative/zero) (PD Population; Baseline Responders Removed) – Study DMID11-0007

Time Point	XF-73 0.5 mg/g [redacted] HPC Gel N=10	XF-73 2.0 mg/g [redacted] HPC Gel N=13	XF-73 0.5 mg/g [redacted] HPC Gel N=12	Placebo in [redacted] HPC Gel N=11
Day 2[1]	6 60% 0.0635	8 62% 0.0402	6 50% 0.1224	2 18%

HPC=hydroxypropyl cellulose

[1] Number of responders, response rate, one-sided Fisher Exact Test p-value v placebo

In summary, the differences observed in the XF-73 arms versus placebo in reduction and elimination of *S. aureus* nasal burden in healthy volunteers, the suggested trend of dose-effect in favour of the XF-73 2mg/g [redacted] gel along with the positive safety and tolerability profile at the different doses used, warrant further evaluation of the efficacy of 2 mg/g XF-73 [redacted] nasal gel in Phase 2 clinical trials (i.e. in patients who will undergo a procedure at risk of post-operative staphylococcal infections). At least 3 applications should be provided right before surgery to achieve maximum effect and the efficacy should be maintained during surgery, the time at highest risk for the development of post-operative staphylococcal infections. Accordingly, in this study, patients will receive four 0.3 mL applications in each naris of a 2 mg/g XF-73 [redacted] nasal gel 24 hours before surgery and a 5th application right after surgery (a cumulative dose of 6 mg of XF-73) in order to maximize the reduction in *S. aureus* burden right before surgery and keep it during surgery and a few hours after surgery.

6.2.2 Use of Placebo

The use of a placebo control arm is considered appropriate for a reliable assessment of the efficacy of XF-73 based on the following:

- There is no approved drug for *S. aureus* nasal decolonization to prevent post-operative staphylococcal infections, the indication under study
- Studies of nasal decolonisation of *S. aureus* show a significant variability in the microbiological measurements and an important placebo effect (up to 50%-60%) which supports the need for a placebo to appropriately assess the effect of XF-73.
- *S. aureus* nasal decolonisation prior to surgery is not universally accepted practice and when practiced it is not done in a standard way, but with considerable variation in the products and dosing regimens used of each product; as these products are not approved for the intended indication.
- The study's primary endpoint is based on microbiological data, not clinical. No impact is expected on post-operative staphylococcal infections from the use of placebo as their incidence is low and the sample size not enough to detect it.
- The IDMC will assess the incidence of post-operative staphylococcal infections.
- Patients will receive skin decontamination prior to surgery and peri-prophylactic systemic antibiotics according to SOC at their centre.

7 STUDY POPULATION

Patients undergoing surgical procedures who are at risk of post-operative *S. aureus* infection due to patient carriage status are eligible to participate in the study. Only patients who test positive to *S. aureus* (MSSA or MRSA) by standardized rapid diagnostic test will be enrolled in the study.

7.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible to participate in the study.

1. Male or female patients between 18 and 75 years of age.
2. Patients who are confirmed nasal *S. aureus* carriers by polymerase chain reaction (PCR) screen assay, and due to undergo surgical procedure.
3. Patients who are willing to provide written informed consent.
4. Patients who are willing and able (as per Investigator judgment) to complete all protocol specified visits and assessments.
5. Woman of childbearing potential* with a negative urine pregnancy test (sensitive to 25 IU human chorionic gonadotropin [hCG]).

   * Women of childbearing potential are defined as those women between menarche and menopause who have not undergone permanent sterilisation. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy

7.2 Exclusion Criteria

Individuals who meet any of the following criteria are not eligible to participate in the study.

1. Pregnancy (current) or currently lactating.
2. Uncontrolled acute or chronic illness (as determined by the investigator) in addition to those requiring the planned surgical intervention.
3. History of atopy, allergic reactions or hypersensitivity to the study medication or its components.
4. Current upper respiratory tract infection, cold or influenza with significant nasal symptoms that might impact on the patient's ability to comply with the gel application procedure.
5. History of photosensitivity.
6. Family history of porphyria.
7. Use of intra-nasal topical or systemic antibiotics or anti-infectives within the last 4 weeks before screening. (Patients who screen positive for nasal carriage of *S. aureus* and receive topical or systemic antibiotics or anti-infectives which are not part of their prophylactic peri-operative SOC between screening and

first dose of IMP will be excluded from the study.) The use of intra-nasal antibiotics or anti-infectives other than the study medication prior to surgery is not allowed.

8. Use of other prescribed or over the counter nasal medication in the last 14 days, or oral decongestants in the last 7 days before first administration of study drug.
9. Participation in a clinical trial within the last 12 weeks before first administration of study drug.
10. Contemporaneous clinically significant abnormalities in vital signs or laboratory analyses reported within 14 days prior to randomization which in the opinion of the Investigator would preclude from the safety assessment of the medication under study.
11. Nasal polyps or significant anatomical or other nasal abnormality that would prevent from appropriate administration of the study treatment or represent an excessive risk for the patient's participation.
12. History of nasal surgery including cauterization.
13. A recent history of frequent epistaxis and/or an episode of epistaxis within 3 months of the planned surgery.
14. Use of *in situ* nasal jewellery or existence of open nasal piercings.

7.3 Patient Withdrawal

7.3.1 Reasons for Withdrawal

Participation is strictly voluntary. Patients must be withdrawn from the study for any of the following reasons:

- Withdrawal of informed consent;
- Pregnancy;
- Investigator's opinion that it is in the best interests of the patient;
- Patient is not willing or able to comply with study requirements

If a patient withdraws from a trial prematurely, the Investigator must determine the primary reason for this and record it in the electronic case report form (eCRF). For patients who are lost to follow up, the Investigator should show due diligence by documenting in the source documents steps taken to contact the patient.

7.3.2 Replacement of Patients

Patients who withdraw or who are prematurely withdrawn from the study having received study medication will not be replaced but will be followed-up for safety as far as practical for inclusion into the safety dataset.

7.4 Patient Identification and Randomization

At screening, each patient will be given a unique 5-digit number to facilitate anonymous identification within the study. The first 2 digits of the number is the centre number (i.e.,

01, 02, etc.). The following 3 digits will be enrolment order number (i.e., first patient at centre number 01 is number 01-001 then 01-002, etc). Once assigned to a patient, a patient number will not be re-used. This number will be used throughout the study as the subject identifier.

A randomisation schedule will be prepared by an independent statistician and provided to Interactive Response Technology System (IRT) personnel prior to commencement of the study. This list will be maintained in the IRT system, under restricted access, until after study unblinding occurs. Patients will be randomly allocated in a 1:1 ratio as follows: 0.2% w/w XF-73 nasal gel treatment OR placebo to match XF-73 nasal gel treatment.

At randomisation, the IRT will assign an investigational product (IP) pack number. The pharmacist or qualified designee will retrieve the appropriate cardboard carton with the corresponding number. If a second bottle is needed, *e.g.* because syringe time to use has exceeded 48 hours from preparation, the pharmacist or qualified designee will use the IRT system to ascertain the second IP pack number required for the subject. Detailed instructions will be provided in the Pharmacy and IRT Manuals.

7.5 Stopping and Discontinuation

An IDMC will be set up which will review the safety information from the study as well as the incidence of post-operative staphylococcal infections. Should these reach an unexpectedly high level, the IDMC can recommend stopping the study, the decision will be communicated to the sponsor as well as investigator sites, competent authorities, and ethics committees/IRBs. The IDMC charter containing, amongst other things, membership, meetings frequency, stopping criteria, structure and procedures produced before randomization of the first patient will be updated implementing the changes introduced in this version 2.1 of the protocol.

8 STUDY DRUG

The investigational products are 0.2% w/w XF-73 Nasal Gel and placebo to Match XF-73 Nasal Gel.

8.1 Identity of Study Drugs

8.1.1 0.2% w/w XF-73 Nasal Gel

XF-73 is presented as a nasal gel for topical application to the anterior nares at a concentration of 0.2%w/w XF-73 (base). It is a clear, dark red gel. The consistency of the gel is such that it should not drip out of the nose and remains in the anterior nares, the principal site of carriage, with minimal spread to the more absorbent mucosal surfaces further up the nostril.

XF-73 is formulated with the excipients [redacted] in water. The formulation is summarised in Table 8.1.

Table 8.1: Components of 0.2% w/w XF-73 Nasal Gel

Component	Content (%w/w)	Function	Reference to Quality Standards
Exeporfinium chloride (XF-73)	0.22% [a]	Drug substance	Internal specification
[redacted]	[redacted]	Gelling agent	NF, Ph Eur, JP
[redacted]	[redacted]	Solvent/Humectant	USP, Ph Eur, JP
[redacted]	[redacted]	Solvent	USP, Ph Eur, JP
[redacted]	[redacted]	Metal chelator	USP, Ph Eur, JP
Water for irrigation	QS to 100.0	Solvent	Ph Eur

JP=Japanese Pharmacopoeia; NF=National Formulary; Ph Eur =European Pharmacopoeia; QS=quantity sufficient; USP = United States Pharmacopeia.

[a] Equivalent to 0.2% w/w XF-73 base. Actual drug substance amount corrected for water content (at time of production).

8.1.2 Placebo to Match XF-73 Nasal Gel

Placebo to match XF-73 nasal gel is a clear, dark red topical gel comprising the excipients in 0.2% w/w XF-73 Nasal Gel formulations, minus the active ingredient. To colour match the active study medication, a commercially available Food, Drug and Cosmetic (FD&C) compliant blend of [redacted], is included in the formulation at a concentration of [redacted]. The quantity of [redacted] in the placebo is [redacted] w/w as opposed to [redacted] w/w in the active. This is to compensate for the viscosity contribution of the XF-73 in the active gel and produce a placebo product with similar viscosity to the active. The rest of the

excipients are at the same level as used in the active product. [redacted] have the additional role of preservatives in the placebo product.

The placebo formulation is summarised in Table 8.2.

Table 8.2: Components of Placebo to Match XF-73 Nasal Gel

Component	Content (%w/w)	Function	Standards
[redacted]	[redacted]	Placebo dye to colour match XF-73	FD&C
[redacted]	[redacted]	Gelling agent	NF, Ph Eur, JP
[redacted]	[redacted]	Solvent/humectant	USP, Ph Eur, JP
[redacted]	[redacted]	Solvent/preservative	USP, Ph Eur, JP
[redacted]	[redacted]	Metal chelator/preservative	USP, Ph Eur, JP
Water for irrigation	QS to 100.0	Solvent	Ph Eur

FD&C=Food, drug and cosmetics; JP = Japanese Pharmacopoeia; NF = National Formulary; Ph Eur=European Pharmacopoeia; QS=quantity sufficient.

8.2 Maintenance of the Blind

Study staff participating in patient care or clinical evaluations, and patients will be blinded to study drug assignment until all patients have completed the study and the database is locked. In order to maintain the blind, patients will receive either XF-73 or matched placebo (in color and viscosity). If a possible risk for unblinding or introducing bias in pharmacy staff is identified, these personnel will be considered unblinded and managed as such. Unblinded study staff (not participating in patient care) will be responsible for maintaining accountability and preparing the blinded study drug, ensuring that all syringes are appropriately labelled according to the pharmacy manual. If needed, an unblinded monitor will be assigned to confirm drug accountability. The double-blind (investigator and participant blinded to IMP received) will be maintained throughout the study until database lock and unblinding. Additional details regarding blinding of the investigational products can be found in the pharmacy manual.

8.3 Administration of Study Drug

Patients will be randomised in a double-blind manner to either the active or placebo arm in a 1:1 ratio.

Each individual dose of gel for application to the patient will be removed using a 1 mL sterile BD slip tip syringe. A 0.3 mL volume of 0.2% XF-73 (equating to 0.6 mg XF-73) or placebo gel will be withdrawn from the bottle using the syringe, the exterior of the syringe wiped down with a sterile wipe and the dose carefully applied directly from the syringe to the epithelium within a naris, ensuring all the gel remains on withdrawal. The dose is massaged in the nose by pinching/massaging the nose for approximately 30 seconds to uniformly distribute the gel inside the nose. The process will be repeated

and an additional 0.3mL dose applied to the contralateral naris. The total volume of study drug dispensed on each dose occasion will be 0.6 mL (2 × 0.3 mL equating to 1.2 mg of XF-73). Each bottle contains sufficient gel to withdraw 10 × 0.3 mL volumes (5 administrations to each nares). The nasal gels are preserved, but care must be taken during the opening of the bottle, withdrawal of doses and closing of the bottle to ensure the integrity of the product is maintained and not contaminated. If necessary, the syringes can be prepared up to 48 hours in advance of dosing. It is expected that doses 1, 2, 3, and 4 will be prepared at the same time.

Detailed instructions for the preparation and handling of the syringes from the supplied study drug will be provided in the Pharmacy Manual. Detailed instructions for the application of the nasal gel to the anterior nares will be provided in the Administration Manual.

8.4 Packaging, Labelling and Storage

0.2% w/w XF-73 Nasal Gel and placebo to Match XF-73 Nasal Gel will be provided in [redacted] bottles with screw top caps. Each bottle contains [redacted] s of gel, sufficient to allow removal of at least 10 × 0.3 mL of gel as per protocol. The label on each bottle/kit does not identify the treatment arm (active or placebo) the nasal gel is assigned to. The bottles will be packaged in individual cardboard cartons as part of a patient kit. Each kit contains 1 bottle of nasal gel (active or placebo) 1 mL luer slip tip syringes, syringes caps, sterile wipes, syringe labels and a zip-lock foil bag in which filled syringes can be stored until use. Each bottle/kit will include a pack number which will be allocated to a single patient using the IRT system. Study drug will be labelled in accordance with applicable regulatory requirements.

The study drugs must be stored at room temperature, below 25˚C and protected from light (by storing in the cardboard carton). The study drug must not be refrigerated or frozen. Each bottle and kit containing study drug is labelled with an expiry date. The shelf life of the study drug is under constant review based on data availability from ongoing stability studies on the batches used in the study and previous batches produced, and it is expected to be at least 12 months for each product. Until dispensed, the study drug must be stored in a securely locked area, accessible to authorized pharmacy or qualified designee personnel only.

Syringes prepared for the administration of the study drug can be prepared up to 48 hours in advance of dosing, in accordance with instruction in the Pharmacy Manual and should be stored in the foil zip-lock bag provided until use. It is expected that doses 1, 2, 3, and 4 will be prepared at the same time.

Packaging and labelling of study drug will comply with Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) rules, and country specific regulatory requirements; this information will be available in the local language.

8.5 Drug Accountability

The pharmacist or qualified designee must keep a record of the dates and amounts of study drug received, dispensed and left unused at the end of the study. He or she will also have responsibility for ensuring the correct pack number is assigned to each patient based

on the IRT assignment. The pharmacist or qualified designee is responsible for maintaining accurate study drug accountability records throughout the study.

Each dispensing of study drug will be documented in the Pharmacy File and the time of administration should be captured in the eCRF. Any unused prepared syringes will be kept in their zip-lock foil bag at pharmacy for accountability and reconciliation.

The study drug records must be available for inspection by the Sponsor's representative and is subject to inspection by a regulatory agency at any time. Copies of the records will be provided to the Sponsor at the end of the study. A Clinical Research Associate (CRA) will review the study drug records. Any remaining study drug will be either returned to the Sponsor or destroyed at site in accordance with the site's Standard Operating Procedures following final accountability by the CRA.

8.6 Compliance

Patients will be considered compliant if they receive the 5 scheduled applications (4 prior to surgery and 1 after surgery) of randomized study drug.

8.7 Concomitant Medications

Any medication the patient takes other than the study drug is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At randomization, patients will be asked what medications they have taken during the last 30 days. Changes to concomitant medications will be captured throughout the study and follow-up periods.

The use of intra-nasal antibiotics or anti-infectives other than the study mediation prior to surgery is not allowed.

8.8 Treatment of Overdose

There have been no reports of XF-73 overdose or off-target application and under the conditions of the study protocols, the possibility has been minimised, as site staff administer the product. Please see the Pharmacy and Administration Manual for additional information about overdose or off-target application.

9 PARAMETERS AND METHODS OF ASSESSMENT

9.1 Microbiological Assessments

9.1.1 Screening

Potentially suitable patients who provide written informed consent to nasal swabbing and microbiological analysis will be assessed for nasal *S. aureus* carriage.

Specimens for detection of *S. aureus* will be collected using commercial nasal swabs. Each specimen will be collected from the anterior naris, and the swab will be immersed in the accompanying transport medium container for transfer to the microbiological laboratory. PCR will be used for the rapid detection and identification of *S. aureus* at screening. The swab will be processed by a standardized laboratory process using an FDA-cleared commercial rapid diagnostic test, the [redacted] to confirm *S. aureus* and identify whether it is MSSA or MRSA. This test will confirm presence or absence of MSSA or MRSA in nasal swab and will be used for inclusion in the study.

Only subjects who are *S. aureus* positive by the rapid diagnostic test (and meeting other criteria) will be enrolled to the study.

9.1.2 Treatment and Follow-up Periods

Patients who test positive for *S. aureus* at screening and provide consent for the main study will have nasal swabs taken at the following times

1. Prior to Dose 1 (22 hours (± 2 hours) prior to surgery; quantitative).
2. Prior to Dose 3 (6 hours (± 2 hours) prior to surgery; quantitative)
3. Prior to Dose 4 (Up to 1 hour prior to incision; quantitative)
4. Prior to Dose 5 (Up to 1 hour post wound closure; quantitative)
5. 48 hours (± 24 hours) after surgery (quantitative)
6. 6 days (± 24 hours) after surgery (quantitative)

Swabs will be transferred to the microbiological laboratory and standard microbiology culture techniques will be used to quantify the number of bacteria in CFU/mL at each timepoint.

In order to appropriately assess the incidence of post-operative staphylococcal infections investigators will take all reasonable efforts to obtain microbiological documentation and a bacterial isolate when the suspicion of post-operative infection is raised. This includes but is not limited to the collection and culture of exudates, blood, implant or other specimens according to the suspected site of infection. Isolates of *Staphylococcus* spp. obtained from these cultures will be kept for further analysis and characterization (e.g., genotypic and phenotypic characterization).

These samples as well as those bacterial isolates obtained from the nasal swabs during the study will kept for up to 10 years after the completion of the study for further phenotypic

and genotypic analysis and characterization. The details of these tests are not known at this time. No subject identifying information will be retained for these samples. The Informed Consent Form explains the storage and future use of specimens and subjects will be asked to consent for future testing of samples.

The Sponsor and Sponsor contracted vendors will have access to the samples and will perform microbiological work on behalf of the sponsor. Additionally, bacterial isolates may be shared with academic researchers.

As these are bacterial samples, no human genetic testing will be performed.

9.1.3 Microbiological Specimen Collection and Culture for S. aureus

The Laboratory Manual of Microbial Procedures will describe the details of collection and processing methods for microbiological samples, including type of nasal swab and transport tube, microbiological culture methods, and reporting of results.

9.2 Efficacy Parameters

Efficacy will be assessed by measuring CFUs/mL at the time points outlined in the Schedule of Assessments (Table 1.1) the incidence of post-operative staphylococcal infections as well as use of post-operative anti-staphylococcal antibiotics.

Any staphylococcal post-operative infections arising between study treatment and up to 30 or 90 days (if foreign implant) included but not limited to SSI, bloodstream infections, catheter-related infections, and implant infections are to be captured as events indicating lack of efficacy. These should NOT be captured as safety TEAEs.

9.3 Safety Parameters

Safety will be assessed by incidence of AEs, clinical laboratory parameters, vital signs, physical examinations, nasal examination, and the B-SIT.

9.3.1 Adverse Events

All AEs, whether identified by the Investigator or the study patient from screening to Day 6, will be recorded in the eCRF. Measurement of vital signs and clinical laboratory parameters will be performed pre- and post-study and clinically significant values will be captured as AEs. For AEs occurring after Day 6, see section 9.3.1.2 of this protocol.

9.3.1.1 Definitions

Per ICH, an AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. The AE may be any of the following:

- A new illness

- An exacerbation of a sign or symptom or the underlying condition or of a concomitant illness under treatment
- Unrelated to participation in the clinical study or an effect of the study medication or comparator drug
- A combination of 1 or more of the above factors

No causal relationship with the study medication is implied by the use of the term AE.

Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.

When an AE occurs after written consent has been obtained but before the first dose of study drug, the AE will be considered a non-treatment emergent AE. An AE that occurs from the time the patient receives his/her first dose of study drug until his/her last study visit will be considered a TEAE regardless of the assessed relationship to the administration of the study drug.

Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that:

- Results in death
- Is life-threatening (Note: the term "life-threatening" refers to any AE that, as it occurs, puts the patient at immediate risk of death. It does not refer to an AE that hypothetically might have caused death if it were more severe).
- Requires hospitalization or prolongation of existing hospitalization (not including hospitalization for a pre-existing condition that has not increased in severity or frequency from the patient's underlying medical condition prior to entry into the study). Hospitalization for an elective procedure, or routinely scheduled treatment for a pre-existing condition that has not worsened, is not an SAE.
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is another medically important condition

An important medical event that is not immediately life threatening or will result in death or hospitalization, but which may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above, should be reported as "serious" as well.

Medical and scientific judgment should be exercised in deciding whether a case is serious.

"Occurring at any dose" does not imply that the patient is receiving study drug at the time of the event.

Severity of Adverse Event:

Refers to the extent to which an AE affects the patient's daily activities. Severity will be categorized according to the following criteria:

Mild:	The AE does not interfere with the patient’s routine activities.
Moderate:	The AE interferes with the patient’s daily routine, but usual routine activities can still be carried out.
Severe:	The AE results in the inability to perform routine activities.

The term "severity" is used to describe the intensity of an event. This is not the same as "serious". Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

Causality of Adverse Event:

Refers to the relationship of the AE to study drug. Causality will be reported according to the following criteria:

Not related:	Adverse events for which a reasonable explanation for an alternative cause is considered plausible, e.g., no study drug taken, plausible clinical alternative like accidental injury, expected progression of underlying or concomitant disease, pharmacologically incompatible temporal relationship, or intercurrent illness.
Related:	Adverse events for which a reasonably possible clinical and/or pharmacological relationship to study drug cannot be excluded, e.g., lacking plausible alternatives.

9.3.1.2 Recording Adverse Events

Patient Enrolment to the First Administration of Study Drug: Non-treatment emergent AEs will be recorded from the time when the patient is enrolled into the study (date of signature of the screening informed consent) until first administration of study drug. These events will be recorded in the medical history section of the eCRF.

First Administration of Study Drug to Patient's Day 6 visit: Thereafter, all AEs are TEAEs and will be recorded until Day 6 visit has been performed.

After Day 6: Only AEs that meet SAE criteria and are considered related with the study medication by the investigator will be recorded after Day 6 through the final follow up visit.

If an AE (serious or not) started during the study but did not end before the final follow-up visit, the Investigator should make a reasonable effort to establish the outcome and the end date. If this is not possible, the outcome recorded at the final follow-up visit will be assumed to be the final outcome.

If an event stops and later restarts, all the occurrences must be reported. If in a patient the same event changes in intensity over time (e.g., diarrhoea starting as mild turns into

severe), only the most severe intensity will be recorded. All AEs assessed as related to study medication by the Investigator and all SAEs must be followed up until resolution. (e.g., value back to baseline value) or stabilization or until final database lock.

Signs/symptoms should be documented if a definite diagnosis cannot be established. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. If a diagnosis is accompanied by unusual symptoms, both the diagnosis itself and the symptoms will be reported.

After Patient's Last Study Visit: The Investigator records and forwards to the Sponsor all SAEs that she or he becomes aware of and she or he considers related to the study drug.

Laboratory values that are outside the normal range and considered clinically relevant in the opinion of the Investigator are also defined as AEs.

If abnormal laboratory values are signs of an AE (e.g., an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE.

Wherever reasonable the reporting Investigator will use the clinical term rather than the laboratory term (e.g., anaemia versus low haemoglobin value).

9.3.1.3 Responsibilities of the Investigator

The AE data should be obtained through observation of the patient, from any information volunteered by the patient, or through patient questioning. The general type of question asked could be similar to: “Do you have any health problems?” or “Have you had any health problems since your last clinic visit?”

All AEs are to be documented/recorded accurately and completely on the AE pages of the respective eCRF and in the patient's source data.

All non-treatment and TEAEs will be recorded through Day 6.

This is true even if the study drug was not administered according to the study protocol.

For conditions leading to unplanned surgical procedures the underlying condition, should be documented as an AE, but not the procedure. **For withdrawals due to AEs** these should be captured in the CRF. If the AE meets the criteria of an SAE, it should be reported to [redacted] as normal.

Overdose needs to be captured as an AE in the CRF and reported to [redacted] if the AE meets the criteria of an SAE.

9.3.1.4 Responsibilities of the Sponsor

For purposes of safety analyses all AEs will be recorded in the clinical database. To ensure expedited and periodic notification of authorities, SAEs will also be recorded in the drug safety database.

9.3.1.5 Evaluation of Adverse Events

The Investigator will assess the seriousness, severity, and causality of each AE in accordance with the definitions in Section 9.3.1.

For all AEs a causality assessment must be provided and documented on the respective form (eCRF AE page for all AEs, SAE form for SAEs and eCRF page "Study completion / termination form" for withdrawals due to AEs) even if it is preliminary information.

The Sponsor will not downgrade the causality assessment provided by the Investigator. If the Sponsor disagrees with the Investigator's causality assessment, both the opinion of the Investigator and the Sponsor will be recorded in clinical study report (CSR) and IB.

9.3.1.6 Notifying of Adverse Events

For SAEs the Investigator must inform [redacted] via e-mail or fax using the SAE report/ eCRF page within 24 hours of the study site being informed.

Serious Adverse Event Reporting Contact:

[redacted]

Investigators or other site personnel should inform [redacted] of any follow-up information that becomes available for a previously reported SAE immediately but no later than 24 hours of becoming aware of the information. Follow-up reports (as many as required) should be completed and faxed or e-mailed following the same procedure above. Any requested supporting documentation (e.g., laboratory results, autopsy report) should be sent to the PrimeVigilance Ltd.

Prior to forwarding any personal data for safety reporting, the documents need to be coded in a way that keeps the patient's identity confidential (e.g., by using the patient's identification code, randomisation number, etc.).

For fatal and life-threatening SAEs, [redacted] will work with the Investigator to ensure that any additional information is provided by the Investigator within 1 business day of availability. The Investigator will ensure that all the necessary information for all other SAEs will be actively sought and submitted as soon as it becomes available.

Follow-up reports relative to the subject's subsequent course must be submitted until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

The Investigator is responsible for informing local Independent Ethics Committee (IECs) / Institutional Review Board (IRBs) of safety reports, unless otherwise required and documented by the IRB/IEC, in compliance with applicable regulatory requirements. Copies of all correspondence relating to reporting of any safety reports to the IEC/IRB should be maintained in the Investigational Site File (ISF) / Regulatory Binder.

Following-up AEs / SAEs:

Patients that have unresolved AEs, clinically relevant laboratory parameters or SAEs after Day 6 (including the Early Termination Visit), should be followed by the Investigator until satisfactory resolution (e.g., value back to baseline value) or stabilization or until final database lock. If necessary, in order to obtain the additional information, the Investigator may request additional physical examinations to be completed or additional blood or urine samples to be taken. The assessments measured will be determined by the Investigator. All data must be documented in the eCRF.

Destiny Pharma's regulatory advisors [redacted] are responsible for fulfilling all sponsor obligations regarding notification of the FDA according to applicable regulatory requirements (expedited and periodic reporting, e.g., SUSARs, Development Safety Update Report). In addition, [redacted] will provide safety information arising from the authorities of countries other than the US and to Investigators according to the current regulations and ensure that the Investigators notify their IEC/IRB.

9.3.2 Pregnancy

If a female patient or the female partner of a male patient becomes pregnant during the study or 30 days after study completion, the patient should notify the Investigator immediately, who will report the event to [redacted]. The pregnancy will be followed until termination or birth of the baby.

9.3.3 Laboratory Parameters

Laboratory references from certified central laboratories will be used. All results of laboratory tests will be entered in the study database.

The tests listed in Table 9.1 will be conducted on samples collected and analysed by standard laboratory procedures at the time points designated on the Schedule of Assessments (Table 1.1). Tests that are not done must be reported as such on the eCRFs.

Table 9.1: Laboratory Parameters

Haematology		
Complete blood count including Red blood cell (RBC) count Haemoglobin	RBC indices and red cell diameter width (RDW) Haematocrit,	White blood cell (WBC) total and differential count Platelet count
Clinical Chemistry		
Serum sodium (bicarbonate) Creatinine Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase	Potassium Chloride Glucose (screening), Glucose; Record the time the patient last ate for all glucose levels Total protein, and Albumin Total bilirubin	Carbon dioxide (CO_2) Blood urea nitrogen (BUN) Calcium Magnesium Phosphate Uric Acid
Urine		

Table 9.1: Laboratory Parameters

Dipstick with reflex urine microscopic examination may be done at the investigator's discretion if the dipstick test is positive for blood, nitrites, protein, and/or leukocyte esterase.	
Pregnancy Testing (female patients only)	Urine human chorionic gonadotropin (hCG)

All laboratory reports will be reviewed and any values outside the normal range will be commented on by the Investigator or qualified designee. The reports will then be signed and dated. The laboratory reports will remain with the source documents and the Investigator's comments will be recorded in the eCRF along with the date and time of the sample collection.

9.3.4 Vital Signs

Vital signs will be measured and recorded at the time points designated on the Schedule of Assessments (Table 1.1). All measurements will be recorded on the vital signs eCRF. Abnormal test results may be repeated at the discretion of the Investigator and must be reported on the corresponding eCRF. When vital signs and/or blood sample collection occur at the same time, vital signs should be performed before blood sample collection.

9.3.5 Physical Examinations

The Investigator or qualified designee will perform a complete physical examination (including nose and nasal passages) at the Randomisation Visit (Table 1.1). Pre-dose abnormal findings will be reported on the medical history eCRF. After that, brief, symptom-driven physical examinations (including nose and nasal passages) will be done. Any adverse change from the baseline physical examination at Randomisation Visit will be documented on the AE eCRF (except those occurring prior to first study medication application which will be reported in the medical history eCRF).

A complete physical examination will include inspection of general appearance, skin, neck (including thyroid), eyes, ears, nose and nasal passages, throat, heart, lungs, abdomen, lymph nodes, extremities, musculoskeletal system, and nervous system.

9.3.6 Assessment of Nose, Nasal Passages, and Sense of Smell

9.3.6.1 Nasal Examination by ENT specialist

Nose and nasal passage examinations will be conducted by an ear nose and throat (ENT) specialist at the time points designated on the Schedule of Assessments (Table 1.1).

The standard nasal examination will consist of evaluation of both nares and the nasal passages for mucosal erythema, oedema, and secretions. Note that the test article is a red, viscous gel, and as such, this should be considered during assessments.

9.3.6.2 Brief Smell Identification Test™

In the study, patients are required to complete the B-SIT, also known as the University of Pennsylvania B-SIT at the time points designated on the Schedule of Assessments (Table 1.1).

The B-SIT is self-administered and consists of 1 enveloped-sized booklet containing 12 “scratch and sniff” odorants. Each odorant strip has a multiple-choice question with 4 alternative responses. The patient is required to mark one of the 4 alternatives even if no smell is perceived. These scores will be recorded in the eCRF.

A percentile score is established which measures an individual’s olfactory diagnosis. Both patients scores will be reviewed by an Investigator. If the patient’s olfactory diagnosis at Follow-Up (Day 6) has significantly worsened, this will be recorded as an AE and relationship determined.

10 STUDY CONDUCT

10.1 Observations by Visit

10.1.1 Screening Visit (Day -14 to Day -1)

Patients will be asked to sign a screening informed consent form (ICF) prior to undergoing nasal swabbing for rapid *S. aureus* testing. Patients will be given a full explanation of the nature of the study and the main study ICF will be provided. As the results from the standardized [redacted] rapid test will take a few hours, the patient will have time to become familiar with the main study ICF and compose questions if the swab result is positive for *S. aureus*.

10.1.2 Randomization Visit (Day -10 to Day -1)

If the patient is tested *S. aureus* positive, the following procedures are to be completed (Table 1.1):

- Obtain consent for the main study. Patient's informed consent to the study will be documented before any Randomization Visit study-specific assessments or procedures are performed.
- Verify eligibility (inclusion/exclusion criteria)
- Record demographic data including sex, age, race, and ethnicity
- Record medical/surgical history (including any risk factors for *S. aureus* carriage) (Risk factors include: HIV infection, obesity, diabetes, granulomatosis with polyangiitis, rheumatoid arthritis, skin and soft tissue infections, recurrent furunculosis, atopic dermatitis, smoking, hormonal contraception use, hospital workers, haemoglobin in nasal secretions, histocompatibility antigen phenotype HLA-DR3, and polymorphisms in genes encoding for the glucocorticoid receptor, interleukin-4, C-reactive proteins and complement inhibitor proteins.) Any potential AEs related to the screening swab (in the investigator's judgment) should be recorded as medical history.
- Record previous (4 weeks prior) and current medications
- Perform a complete physical examination
- Examination of the nose and nasal passages by an ENT specialist
- Measure and record vital signs (heart rate and supine blood pressure [BP])
- Draw blood for haematology and clinical chemistry
- Collect urine sample for urinalysis and pregnancy test
- Record SOC in skin decontamination and peri-operative prophylactic regimen
- Record AEs
- -B-SIT

- Randomization to study drug after eligibility is verified (may occur from Day - 7 to Day -1 prior to dose 1)

10.1.3 Treatment Period (Days -1 to Day 0)

Patients who meet the entry criteria will undergo the following treatment visits and assessments at timepoints designated on the Schedule of Assessments (Table 1.1). All assessments should be completed prior to the dose of study drug. Treatment visits will normally occur in hospital, however if more convenient for the patient, home visits by qualified staff working to an agreed process will be allowed.

It is normally expected that patients will continue as planned to their pre-determined surgery time and date after the initial pre-surgical doses of IMP in the previous 24 hours. However, in clinical practice surgery can be postponed at any point in the lead up to the planned surgery time and date for different reasons and would not be considered a protocol deviation. If surgery is delayed, then the following steps should be followed.

- If the delay to the planned incision timepoint is less than or equal to 48 hours, the patient should continue with the remaining doses as per protocol to the new timeframe. The remaining IMP must be checked to be within its own 48hr expiry window or replaced with a new kit assigned by the IRT system.
- If the delay to the planned incision timepoint is greater than 48 hours but the patient's new surgery date and time is still within their screening window, then existing IMP should be replaced and a new kit assigned to the patient and full dosing regimen provided according to the protocol to the new timeframe.
- If the delay to the planned incision timepoint is greater than 48 hours and the patient's new surgery date and time is outside their screening window, then the patient should be withdrawn. If time permits, the patient can be re-screened using a new screening number.

10.1.3.1 First dose visit (Day -1)

- Verify eligibility (inclusion/exclusion criteria)
- Randomization to study drug if not completed prior to Day -1
- Record changes in medical history and concomitant medications from randomization visit.
- Perform a brief symptom-driven physical examination or a complete medical examination if it was not performed at randomization visit.
- Examination of the nose and nasal passages by the ENT specialist (only if not performed during randomization visit) before drug application.
- Nasal swabbing for quantification of *S. aureus* within 1 hour prior to drug application
- Record SOC in skin decontamination and peri-operative prophylactic regimen

- B-SIT before drug application if not performed during randomization visit.
- Record AEs
- Record concomitant medications.
- First application of assigned study drug at 22h ±2h before surgery (estimated incision time)

10.1.3.2 Second dose visit (Day -1)

- Record SOC in skin decontamination and peri-operative prophylactic regimen
- Second application of assigned study drug at 14h±2h before surgery (estimated incision time)
- Record AEs
- Record concomitant medications.

10.1.3.3 Third dose visit (Day 0)

- Nasal swabbing for quantification *S. aureus* within 1 hour prior to drug application
- Record SOC in skin decontamination and peri-operative prophylactic regimen
- Third application of assigned study drug at 6h±2h before surgery (estimated incision time)
- Record AEs
- Record concomitant medications.

10.1.3.4 Fourth dose visit (Day 0)

- Nasal swabbing for quantification of *S. aureus* within 1 hour prior to drug application
- Record SOC in skin decontamination and peri-operative prophylactic regimen
- Application of fourth dose of study medication within one hour before incision (e.g. in the operating room).
- Record number of blood glucose records from time of admission to hospital for surgery and how many were over 200 mg/dL.
- Record number of body temperature measurements from time of admission to hospital for surgery and how many were under 35.5º C.
- Record AEs
- Record concomitant medications

10.1.3.5 Fifth dose visit (Day 0)

- Measure and record vital signs (heart rate and supine BP)

- Nasal swabbing for quantification of *S. aureus* within 1 hour prior to drug application
- Record SOC in skin decontamination and peri-operative prophylactic regimen
- Application of fifth dose of study medication within 1 hour after closure of incision (e.g. in the operating room)
- Record number of blood glucose records from visit dose 1 and how many were over 200 mg/dL.
- Record number of body temperature measurements from visit dose 1 and how many were under 35.5º C.
- Draw blood for haematology and clinical chemistry after study medication application
- Collect urine sample for urinalysis after study medication application.
- Record AEs
- Record concomitant medication

10.1.4 Follow-up Period

10.1.4.1 Post-surgical visit (48h ± 24h post closure of surgical incisions)

- Complete brief symptom-driven physical examination
- Examination of the nose and nasal passages by the ENT specialist
- Nasal swabbing for *S. aureus*
- Record SOC in skin decontamination and peri-operative prophylactic regimen
- Measure and record vital signs (heart rate and supine BP)
- Draw blood for haematology and clinical chemistry
- Collect urine sample for urinalysis
- Record concomitant medications
- Record AEs
- Record staphylococcal infections and use of antibiotics from visit dose 5.

10.1.4.2 Follow Up (Day 6 (± 24 hours)

- Complete brief symptom-driven physical examination (including nose and nasal passages)
- Nasal swabbing for *S. aureus*
- Measure and record vital signs (heart rate and supine BP)
- Draw blood for haematology and clinical chemistry
- Collect urine for pregnancy test

- B-SIT
- Record concomitant medications.
- Record AEs
- Record staphylococcal infections and use of antibiotics

10.1.4.3 Follow-up (Day 30)

- Record staphylococcal infections and use of antibiotics
- Record suspected IP related SAEs, only
- Record concomitant medications

10.1.4.4 Follow-up Day 90 (Only if object implant in surgery)

- Record staphylococcal infections and use of antibiotics
- Record suspected IP related SAEs, only
- Record concomitant medications

11 STATISTICAL METHODS

11.1 Disposition of Patients

The numbers and percentages of patients enrolled, randomized, treated, discontinued with associated reasons and completed in the Safety, Intent-to-treat (ITT) and Per-protocol (PP) will be tabulated for each treatment group.

The reasons for patient exclusions from each of the populations of interest will be listed.

11.2 Protocol Deviations

Major protocol deviations are compliance issues that have an impact on patient safety or the scientific integrity of the study data. All deviations will be evaluated and classified as major or minor before database lock and unblinding.

11.3 Analysis Populations

11.3.1 All Enrolled Patients

All enrolled patients include all patients that completed main study informed consent (i.e., has a non-missing informed consent date).

11.3.2 Safety Population

The Safety Population will consist of all patients who received at least 1 dose of study drug. Patients will be presented in the actual treatment group that they received. The primary population for the safety analyses will be the Safety population.

11.3.3 Intent-To-Treat Population

The ITT Population will consist of all patients who were randomized.

11.3.4 Modified Intent-To-Treat Population

The modified ITT Population will consist of all patients who were randomized, received at least 1 dose of study drug and have at least 1 post-baseline assessment of *S. aureus* log10 CFU/mL. Patients will be presented in the treatment group that they were randomly assigned.

11.3.5 Microbiological Intent-To-Treat Population

The microbiological Intent-To-Treat (micro ITT) set will consist of all patients in the mITT set who have a log CFU/mL result at baseline greater than 0, i.e. all patients in the mITT set with a quantifiable baseline microbiological result. The primary population for the efficacy analyses will be the Micro ITT.

11.3.6 Per-protocol Population

The PP Population will consist of all patients in the micro ITT population without major protocol deviations. Supportive efficacy analyses will also be performed on the PP population for key endpoints and at key time points, as specified in Section 5.

11.4 General Considerations

A Statistical Analysis Plan (SAP) describing the planned final analysis up to Day 6 and separately for the 30-day and 90-day follow-up periods and including detail with tables, figures and listings templates will be developed as a separate document.

- Continuous variables will be summarised using the number of patients with evaluable data, mean, standard deviation (SD), median, minimum and maximum.
- Categorical variables will be summarised using the number of observations (n), frequency and percentage of patients. All percentages will be presented as one-decimal point, unless otherwise specified. Percentages equal to 100 will be presented as 100% and percentages will not be presented for zero frequencies.

11.5 Demographics, Baseline Characteristics and Concomitant Medications

Demographic and baseline characteristic data will be summarised and listed by treatment groups by means of descriptive statistics. Further details will be provided in the SAP.

Concomitant medications will be coded by using the World Health Organisation (WHO) Drug Dictionary and will be summarised by treatment group with the number and percentage of patients receiving concomitant medication by drug class and preferred drug name. A listing of all medications will be produced indicating whether the medication was taken prior to, during and/or after treatment.

11.6 Treatment Compliance

Treatment exposure will be summarised and listed by treatment group by means of descriptive statistics for categorical data (counts and percentages). The number of doses taken (range 1 to 5) will be reported for the Safety Population.

11.7 Efficacy Analyses

Primary analysis will be on the endpoint of change in $\log_{10}$ CFU from baseline to pre-surgery using an analysis of covariance (ANCOVA) model including baseline CFU as a covariate. A similar analysis will also be performed for the endpoint of change from baseline to the post-surgery measurement.

Secondary efficacy analyses will include;

- Change in $\log_{10}$ CFU from baseline to post-surgery using an ANCOVA model including baseline CFU as a covariate.
- A $\log_{10}$ AUC for CFUs will also be undertaken utilising data for all time points up until the pre-surgery assessment. This analysis of $\log_{10}$ AUC CFUs will also including baseline $\log_{10}$ CFU as a covariate.

- A log_{10} AUC for CFUs will also be undertaken utilising data for all time points up until the post-surgery assessment. This analysis of log_{10} AUC CFUs will also including baseline log_{10} CFU as a covariate.
- Percentage of patients reaching a specific reduction in *S. aureus* carriage prior to surgery, immediately post-surgery and on Day 6 ± 24hrs
- Proportion of patients with nasal carriage below a set value (value to be determined [TBD])
- Summary of data for nasal carriage according to SQS along with an analysis of proportional odds.
- Summary of the proportion of patients with a 2-log drop (TBD)

In addition to the planned analysis in the PP population which requires patients to receive 4 doses of pre-surgery treatment, and additional sensitivity analysis will be performed which will include all patients who receive 3 doses of pre-surgery treatment.

Analysis of post-operative infections and antibiotic use at Day30 and Day 90 will be performed separately to the main analysis period of randomisation Day 0 to follow-up at Day 6 and can be reported separately.

11.8 Safety Analyses

Safety will be determined by AEs, clinical laboratory parameters, physical examination, vital signs, microbiological specimen collection and nasal examination.

All available data from patients in the Safety Population will be included in the assessment of safety and tolerability. All safety and tolerability data will be listed and summarised by treatment group using appropriate descriptive statistics. Formal statistical comparisons between the different treatment groups will not be conducted.

All AEs will be coded using the MedDRA terminology.

Further details will be provided in the SAP.

11.9 Interim Analyses

An interim analysis will be performed, depending on recruitment projections, when approximately 60% evaluable subjects have been recruited. The aims of this interim analysis are to:

- Review the Safety data generated to date.
- Review the incidence of post-operative staphylococcal infections.
- Stop the study in case of serious concerns on subject's safety
- Stop the study due to the incidence of post-operative staphylococcal infections.

The interim analyses will be performed by an independent statistician and will be performed using similar methodology to that for the main analysis. This approach will be described in further detail in the IDMC SAP.

All study staff including the Sponsor will remain blinded until the end of the study.

Full details of these analyses and the role of the IDMC will be provided in the new version of the IDMC charter implementing the changes introduced in this version 2.1 of the protocol.

11.10 Determination of Sample Size

Individual CFU data is presented in the study of Verhoeven 2012[27] in the absence of treatment. As the primary population for the efficacy analysis is the micro-ITT, those values with zero CFU have been excluded and the resulting data have been converted to the $\log_{10}$ CFU scale. The SD of these values has been used as the estimate of variability for an analysis of change from baseline whilst including baseline $\log_{10}$ CFU as a covariate. As a result, a trial including 80 evaluable patients (40 per arm) would have a greater than 90% power to detect a true treatment effect of a 2 $\log_{10}$ CFU difference and an 90% power to detect a true treatment effect of a 1.5 $\log_{10}$ CFU difference between XF-73 and placebo, assuming 2-sided alpha=0.05, a between patient SD of 2 $\log_{10}$ CFUs taken from the Verhoeven study.

We estimate that approximately 125 patients will need to be recruited in order to have around 80 patients with a burden *S. aureus* nasal carriage which will allow for the detection of an effect of XF-73 nasal gel.

12 DATA MANAGEMENT

12.1 Data Collection

The trained Investigator site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture tools as needed) directly into the study database on a central server. All information in the eCRFs must be traceable to these source documents. Data recorded directly into the eCRFs will be defined before study start and the eCRFs will be considered the source data. Clinical Research Associates and a Data Manager will review eCRFs entered by investigational staff for completeness and accuracy. Automatic quality programs check for data discrepancies in the eCRFs and the resulting queries will be notified to the investigational site using an electronic data query process within the electronic data capture (EDC) system. Designated Investigator site staff are required to respond to queries and make any necessary changes to the data. Details of the data correction process will be specified in the Data Management Plan.

A validated, electronic database will be employed from the EDC system. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study.

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a data handling plan/ data management plan together with a description of the personnel responsible for data entry.

12.2 Data Correction

Automatic and manual queries will be defined according to the data validation plan. These queries will be generated by the Destiny's data management provider [redacted] and sent through the EDC system for clarification. Corrections will be entered directly into the system. This procedure will be repeated until all queries are resolved. All query forms will be linked to the eCRF in the EDC system.

12.3 Data Handling

The final data will be transferred to the SAS-system for data analyses in accordance with the SAP. The MedDRA dictionary will be used for coding of AEs and concomitant diseases. Concomitant medication will be coded using the WHO Drug Dictionary **A**(natomical) **T** (herapeutical **C**(hemical) code.

12.3.1 Deviations from the Protocol

Deviations from the protocol will be judged during the study and/or when an individual patient's eCRF is completed (monitored).

Before unblinding the data, a blinded data review meeting (BDRM) will take place where protocol deviations will be classified (major/minor protocol deviations) for statistical analysis.

12.4 Data Quality Assurance

Destiny Pharma will conduct a site visit to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRFs for this study must be consistent with the patients' source documentation (i.e., medical records).

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Study Initiation Activities

The Investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures at a Pre-Study Visit by the monitor (if necessary), an Investigators' meeting, and during the Site Initiation Visit by the monitor.

13.2 Training of Site Staff

The Investigator will ensure that everyone assisting with the clinical study is adequately informed about the protocol, the investigational product(s), and their study-related duties and functions. Furthermore, the Investigator will maintain a list of qualified persons to whom the Investigator has delegated study-related duties.

13.3 Documentation and Filing

13.3.1 eCRF System

All data recorded according to this study protocol must be documented in an eCRF. The Investigator and persons authorized by the Investigator will be instructed about how to complete the eCRF. Entries in the eCRF must only be made by the Investigator or persons authorized by the Investigator. A list of all persons who are allowed to make entries in the eCRF must be available in each study site.

The Investigator must verify that all data entries in the eCRF are accurate and correct. Entries will be checked against appropriate source documentation by the monitor.

13.3.2 List of Patients (patient identification log)

The Investigator will keep a confidential list of names of all patients participating in the study, so that the patients' records can be identified if necessary.

In addition, the Investigator will keep a list of all patients screened on a screening log to document identification of patients who entered pre-study screening. If someone is not eligible to participate in the study, a reason must be provided.

13.3.3 Source Data

Per ICH, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

13.3.4 Investigator Site File / Regulatory Binder

Before site initiation [redacted] will provide an ISF/ Regulatory Binder to each site. The ISF will include essential documents as defined by the ICH GCP guideline and applicable local requirements.

The Investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by the monitor(s). These documents will be reviewed during an audit by the Sponsor or an inspection by the Regulatory Authorities.

All study-related documents are to be archived and stored according to legal requirements.

Prior to destruction of study-related documents, the Investigator will contact the Sponsor for approval and conformation.

13.4 Monitoring

The CRA is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Additionally, the CRA ensures that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

The interval between monitoring visits will depend on the recruitment rate and the complexity of the study.

Source data verification is an essential part of the monitoring process and the Investigator must grant direct access to the patient's source data.

The extent and nature of monitoring will be described in detail in the monitoring plan.

13.5 Audits and Inspections

Audits will be performed according to the corresponding audit program. The Sponsor's Quality Assurance Department may visit the investigative site to audit the performance of the study, as well as all study documents. Audits may also be performed by contract auditors who will be instructed about the timing and extent of the audits. In the event of an audit at the investigational site, the monitor will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and IECs/IRBs are possible at any time, even after the end of study. The Investigator is to notify the Sponsor immediately of any such inspection. The Investigator and institution will permit study-related monitoring, audits, reviews by the IEC/IRB and/or Regulatory Authorities and will allow direct access to source data and source documents for monitoring, audits, and inspections.

14 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

14.1 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by the principles of the GCP guidelines of the ICH, and of the current version of the Declaration of Helsinki (Brazil 2013). The study also will be carried out in keeping with local legal requirements.

14.2 Informed Consent

Before each patient is admitted to the study, a pre-screening nasal swab informed consent will be obtained from the patient (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country (i.e., the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Patients (21 Code Federal Regulation [CFR] 50.25 (a) and (b), CFR 50.27, and CFR Part 56, Subpart A), and other applicable local regulations). If the patient is *S. aureus* positive, he/she will be asked to sign the main ICF. This consent form must be dated and retained by the Investigator as part of the study records. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

14.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

14.4 Archiving Study Records

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

14.5 Premature Termination of the Study

If the Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study;
- Failure to enrol patients at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

14.6 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to [redacted] by their patient number, initials and/or birth date, not by name. Documents not to be submitted to Pharm-Olam that identify the patient (e.g., the signed ICF) must be maintained in confidence by the Investigator.

14.7 Future Use of Stored Specimens

In order to appropriately assess the incidence of post-operative staphylococcal infections investigators will take all reasonable efforts to obtain microbiological documentation and a bacterial isolate when the suspicion of a staphylococcal post-operative infection is raised. This includes but is not limited to the collection and culture of exudates, blood, implant or other specimens according to the suspected site of infection.

The Sponsor is planning to store these samples as well as those bacterial isolates obtained from the nasal swabs after the completion of the study for up to 10 years for further analysis and characterization. The details of these tests are not known at this time. No subject identifying information will be retained for these samples. The Informed Consent Form explains the storage and future use of specimens and subjects will be asked to consent for future testing of samples.

14.8 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

14.9 Publication Policy

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications and extent of involvement.

An Investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

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16 APPENDICES

16.1 List of Organizations Involved in the Study

Sponsor	Destiny Pharma plc Sussex Innovation Centre Science Park Square, Falmer Brighton, BN1 9SB UK
Chief Medical Monitor	[redacted]
Contract Research Organization	[redacted]
Safety Reporting	[redacted]
Data Management, Statistics and Medical Writing	[redacted]
Central Laboratory	Blood samples, Nasal Swabs and Bacterial Isolate storage: [redacted]

	Nasal Swabs, post-operative infection sample processing and bacterial isolate storage:
	[redacted]
	[redacted]
IP Supply & IRT	[redacted]
Regulatory Unblinding Service	[redacted]