PROTOCOL: GH001

TITLE:	**An evaluation of the efficacy of HEXI-PREP by Clinell Wipes versus placebo and ChloraPrep, for use in preoperative skin preparation**
Protocol Version and Date:	Version 3.0, 08 November 2017
DRUG:	HEXI-PREP by Clinell Wipes (Chlorhexidine 2%wv/; Isopropyl Alcohol 70%w/v)
EudraCT No.	2016-002692-98
SPONSOR:	GAMA Healthcare Limited 2 Regal Way, Watford WD24 4YJ Telephone: 02079930030
SPONSOR EMERGENCY CONTACT	Dr. Allen Hanouka GAMA Healthcare Limited 2 Regal Way, Watford WD24 4YJ Telephone: 02079930030
PRINCIPAL INVESTIGATOR:	Dr. D. Bendel
Monitoring CRO	Surrey Clinical Research Centre University of Surrey Egerton Road, Guildford, Surrey, GU2 7XP
Projected Start date (first participant first visit FSFV):	December 2017
Projected Finish date (last participant last assessment LSLA):	February 2018

PROTOCOL SIGNATURE PAGE - SPONSOR

Sponsor's Approval

This protocol has been approved by GAMA Healthcare.

Sponsor's Responsible Medical Officer on behalf of the Sponsor:

Dr. A. Hanouka

Signature: **Date: 20/11/2017**

PROTOCOL SIGNATURE PAGE – CHIEF INVESTIGATOR

Principal Investigator's Agreement

I have read GAMA Healthcare's protocol no. GH001

Title: An evaluation of the efficacy of Clinell Chlorhexidine 2%w/v Alcoholic Wipes versus Placebo and Chloraprep, for use in preoperative skin preparation

I have fully discussed the objectives of this trial and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical and regulatory review of the trial, without written authorisation from GAMA Healthcare Ltd. It is, however, permissible to provide information to a potential trial participant in order to obtain consent.

I agree to conduct this trial according to this protocol and to comply with its requirements, participant to ethical and safety considerations and guidelines, and to conduct the trial in accordance with International Conference on Harmonisation Guidelines on Good Clinical Practice and with the applicable regulatory requirements and confirm that any changes in procedures will only be made if necessary to protect the safety, rights and welfare of the participants.

I understand that the Sponsor may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial I will provide the sponsor with a detailed written explanation. In either case I will promptly inform the trial participants and provide appropriate therapy and follow up

Investigator Name and Address: Dr. D. Bendel
Surrey Clinical Research Centre
University of Surrey
Egerton Road,
Guildford,

Signature: _____ **Date:** _____

SUMMARY OF CHANGES	
Protocol Amendments	
An evaluation of the efficacy of HEXI-PREP by Clinell Wipes versus placebo and ChloraPrep, for use in preoperative skin preparation	
HEXI-PREP By Clinell Wipes	
Amendment Number	**Date of Amendment**
Amendment 0 (Version 1.0)	04 November 2016
Amendment 1 (Version 2.0)	10 May 2017
Amendment 2 (Version 3.0)	08 November 2017
Details of the changes follow.	

Amendment 1
The following revisions have been made to the protocol and synopsis as appropriate:
• **Inclusion Criteria:** Qualification of Sexual Abstinence in line with MHRA Review Comments. Unqualified sexual abstinence has been changed to "True abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception]."
Amendment 2
• **Minor (Non-Substantial) Amendments** Several minor amendments were implemented to correct typos, correct identified inconsistencies within the protocol and to provide clarification regarding proposed activities. All proposed changes have been judged to be non-substantial, in that they do not impact on the safety or physical or mental integrity of the subjects, the scientific value of the study, the conduct or management of the study or the quality of safety of the medicinal products used in the clinical trial. • **Substantial Amendment** Change in Principal Investigator to Dr. Bendel

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ABBREVIATIONS AND DEFINITIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ASTM	American Standards & Testing Methodology
BMI	Body Mass Index
CMO	Chief Medical Officer
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
ENT	Ear, Nose & Throat
EPIC	Evidence based project for the Prevention of Infection
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food & Drug Administration (US)
FOCP	Female of Child Bearing Potential
FPFV	First Participant First Visit
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
ICH GCP	International Conference on Harmonisation: Harmonised Tripartite Guideline for Good Clinical Practice
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ITT	Intention-to-Treat Population
IUD	Intra-Uterine Device
LOCF	Last Observation Carried Forward
LPLV	Last Participant Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PP	Per Protocol Population
SAE	Serious Adverse Event
SDV	Source Data Verification
SUSAR	Suspected Unexpected Serious Adverse Reaction

TBD	To Be Determined
TFM	Tentative Final Monograph
TMF	Trial Master File
UK	United Kingdom of Great Britain and Northern Ireland

TRIAL SUMMARY

Protocol number: GH001	**Investigational product:** HEXI-PREP by Clinell Wipes

Title of the trial: An evaluation of the efficacy and safety of HEXI-PREP by Clinell Wipes versus Placebo and ChloraPrep, for use in preoperative skin preparation

Investigator(s): Dr. D. Bendel

Trial centre:
Surrey Clinical Research Centre, University of Surrey, Egerton Road, Guildford, Surrey, GU2 7XP, UK

Trial period (planned): December 2017 to February 2018	**Clinical phase:** III

Objectives:

To evaluate the antimicrobial properties of HEXI-PREP by Clinell versus: (1) a placebo, negative control product, (sterile saline 0.9% w/v and (2) a positive control product, ChloraPrep® Chlorhexidine Gluconate 2% w/v solution (PL31760/004; PA1435/1/2) as per the methodology specified by the Food and Drug Administration Tentative Final Monograph (TFM) for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452)

- Primary Objective: To demonstrate superiority of HEXI-PREP by Clinell Wipe vs placebo (negative control) in reducing immediate bacterial load 1-10 minutes after administration to each test site.
- Secondary Objectives: To demonstrate superiority of HEXI-PREP by Clinell Wipe vs placebo (negative control) in terms of persistence of a reduction in bacterial load at 30 minutes - 24 hours. To also assess the relative efficacy of HEXI-PREP Wipe to ChloraPrep (positive control) in regard to a reduction in bacterial load at 1-10 minutes, 30 minutes -24 hours after administration to the test sites. A further secondary objective is to establish the safety profile (local tolerance) of the administered preparations.

Trial Design:

This is a Good Clinical Practise (GCP) compliant, single centre, double-blind, within participant, randomised, comparator and placebo controlled study to evaluate the immediate and persistent antimicrobial properties of the investigational medicinal product: HEXI-PREP by Clinell Wipes for use in preoperative skin preparation. An active control, ChloraPrep® Chlorhexidine Gluconate 2%w/v solution (PL31760/004; PA1435/1/2) and a placebo, (sterile saline 0.9% w/v) will also be evaluated. Volunteer participants will be randomised to one of three groups at which time the test products will be applied bilaterally to an area of skin up to 15x15cm (i.e. 225cm^2) at four anatomical sites, including the inguinal area (groin), abdomen, the clavicular region and the median cubital region of the arm.

- Group 1: HEXI-PREP by Clinell Wipes vs placebo
- Group 2: HEXI-PREP by Clinell Wipes vs ChloraPrep
- Group 3: ChloraPrep vs placebo

The immediate and persistent antimicrobial effects of the preoperative preparations will be evaluated using the criteria set out in ASTM E1173-15, dated 05 Jan 2015. Using this methodology, all four anatomical test sites on each side of the body (8 in total) will be evaluated by microbiological sampling at:

- Inguina (groin) and Abdomen: time 0 (baseline), 10 minutes, 30 minutes and six hours after the skin preparation.
- Clavicular region and Median Cubital Region of Arm: time 0 (baseline), one minute, six hours and 24 hours after the skin preparation

Number of participants (total and for each treatment arm, if applicable):

Approximately 100 participants will be screened and undergo the pre-treatment test conditioning period to ensure that a total of 60 participants are randomised to the study (20 per group; i.e. 40 data sets per group).

- Group 1: HEXI-PREP by Clinell Wipes vs placebo (N=20)
- Group 2: HEXI-PREP by Clinell Wipes vs ChloraPrep (N=20)
- Group 3: ChloraPrep vs placebo (N=20)

Key Eligibility Criteria:

Inclusion Criteria:

- Male and female participants 18 – 70 years, who have provided written informed consent to participate in the study
- Participants with a bacterial baseline count ≥ 5.0 log10/cm^2 at the groin, ≥4.0 log10/cm^2 on the abdomen, and >3.0 log10/cm^2 at the clavicle and median cubital fossa of the arm on Day -5 of the study.
- Participants, who in the opinion of the Investigator, are in suitable health for inclusion in the study.

Exclusion Criteria:

- Participants who are exposed to topical antimicrobial agents, including medicated soaps, medicated shampoos or medicated lotions, who use biocide treated pools or hot-tubs, use tanning beds or sunbathing during the 14-day pre-test conditioning period or during the test period.
- Exposure of the test sites to strong detergents, solvents or other irritants during the 14-day pre-test conditioning period or during the test period.
- Use of systemic or topical antibiotic medications, steroid medications or any other product known to affect the normal microbial flora of the skin, up to 1 month prior to the screening period, during the 14-day pre-test conditioning period or during the test period.
- Known allergies to latex (rubber), alcohols, tape adhesives or to common antibacterial agents found in soaps, lotions or ointments, particularly chlorhexidine gluconate or chlorine.
- Female patients who are pregnant, become pregnant or are breastfeeding during the pre-test conditioning period or during the test period.
- Active skin rashes or breaks in the skin at the test site
- Active skin diseases or inflammatory skin condition including contact dermatitis within 10cm of the test site
- Showering or bathing after Day-5 baseline sampling and unwilling to refrain from showering or bathing whilst at Surrey CRC (Day 0 to Day 1)
- Participation in another clinical trial within 90 days preceding randomisation
- Any other medical condition, which in the Investigator's opinion, should preclude participation
- Unwillingness to fulfil the performance requirements of the study.

Test product (includes placebo), dose and mode of administration

- HEXI-PREP by Clinell Wipes (3mL fill) applied topically to intact skin
- ChloraPrep 2% w/v / 70% v/v cutaneous solution2% w/v / 70% v/v cutaneous solution (3mL) applied topically to intact skin
- Placebo (0.9% sterile saline) wipes; 3mL applied topically to intact skin.

Duration of treatment:

- Preparations will be administered on a single occasion, bilaterally to a pre-defined treatment area of skin

Evaluation of Endpoints:

- Primary endpoint assessment will be based on a $\log_{10}$ reduction of the immediate baseline bacterial count at 1-10 minutes compared to placebo and ChloraPrep active control.
- Secondary endpoint assessments will be based on persistence of a $\log_{10}$ reduction of the baseline bacterial counts at 30 minutes and 6 hours (inguinal and abdomen test sites) and 6 and 24 hours (clavicular and median cubital region of arm) after application to the test site compared to placebo and ChloraPrep active control. Further secondary endpoints relate to local tolerance of the administered preparations.

Trial schedule(s)

Table 1: Schedule of Assessments

Visit	Screening period (Day -21 to -19)	Conditioning Period (Day -19 to -5)**	Day -5	Time 0	1 min	10 mins	30 mins	6 hours	24 hours
Informed consent	✓								
In/exclusion criteria	✓			✓					
Demographics	✓								
Medical history	✓								
Physical examination	✓								
Urine pregnancy test (FOCP)	✓			✓					
Use of non-medicated personal hygiene products		✓	✓	✓	✓	✓	✓	✓	✓
Diary Card		✓							
Randomisation				✓					
Investigational products dosed				✓					
Adverse events				✓	✓	✓	✓	✓	✓
Concomitant medication	✓			✓					
Hair Clipping			✔						
Microbiological Sampling (Groin and Abdomen)			✔	✓		✓	✓	✓	
Microbiological Sampling (Arm and Clavicle)			✔	✓	✓			✓	✓
**Participants do not attend the Clinical Trial Centre during this period									

1. BACKGROUND INFORMATION

1.1 Condition Background and Current Treatment

One of the most important risk factors for post-operative wound infection is the presence of bacteria in the wound at the time of surgery. Indeed, wound infection rates are directly related to the level of intraoperative bacterial contamination with a range reported from 1-5% for clean surgeries, 3 – 10% for clean-contaminated surgeries, 10-20% for contaminated surgeries and 15-45% for dirty surgeries [1-4]. With respect to clean surgeries, in which endogenous contamination is not expected, exogenous bacteria that enter the open wound during surgery are the most common contaminants of the operative wound and are responsible for the majority of infections [4].

Possible sources of extrinsic bacteria include the skin overlying the operative site, skin from other sites on the patient, from members of the operative team, nasal flora, surgical equipment and other items in the operating room environment. Within this context, skin disinfection, prior to surgery, is now universally accepted as an essential component of surgical practice, in order to reduce the risk of infection.

1.2 Product Background

HEXI-PREP by Clinell Wipes contain both chlorhexidine gluconate 2%w/v and Isopropyl alcohol 70%v/v within a single-use sterile wipe; immediately on opening the sachet, the HEXI-PREP by Clinell Wipe contains sufficient solution (3mL) to treat an area of skin up to 15x15cm (225cm^2) and is intended disinfection of the skin prior to invasive medical procedures.

HEXI-PREP by Clinell Wipes are essentially similar to other commercially available chlorhexidine / isopropyl alcohol wipes including ChloraPrep (PL31760/004; PA1435/1/2) in regards the formulation of solution applied to the skin and which are already licensed for use in disinfection of the skin prior to invasive medical procedures. The only significant difference is the means of application (i.e. a wipe vs an applicator used with ChloraPrep).

1.2.1 Preclinical information

Chlorhexidine Gluconate is a well-established cationic polybiguanide (bisbiguanide), which is widely used in disinfectants, cosmetics and pharmaceutical preparations as both an active substance and preservative.

At physiologic pH, chlorhexidine salts dissociate and release the positively charged chlorhexidine cation. The bactericidal effect is a result of the binding of this cationic molecule to negatively charged bacterial cell walls. At low concentrations of chlorhexidine, this results in a bacteriostatic effect; at high concentrations, membrane disruption results in cell death [5].

Chlorhexidine has been established to be active against Gram-positive and Gram-negative organisms, facultative anaerobes, aerobes, and yeasts [5]. It is particularly effective against Gram-positive bacteria (in concentrations ≥ 1µg/L). Significantly higher concentrations (10 to ≥73µg/mL) are required for Gram-negative bacteria and fungi. Chlorhexidine is ineffective against polioviruses and adenoviruses.

Chlorhexidine, like other cation-active compounds, remains on the skin. It is frequently combined with alcohols (ethanol and isopropyl alcohol) which evaporate rapidly from the skin leaving behind a residue of chlorhexidine on the skin; providing for a persistent antimicrobial effect.

Isopropyl alcohol at a concentration of 70%v/v is however known to have antibacterial properties, in its own right and is well-established as a biocidal disinfectant (particularly in regard to hand washes). Water is required to open up membrane pores of bacteria, which acts as a gateway inside for the isopropyl alcohol. In this context isopropyl alcohol has been reported, in of its own, to be effective against a wide range of bacteria, viruses, protozoa, and fungi, and has a relatively low toxicity to humans. The main effect on microorganisms appears to be the coagulation of essential proteins, rendering them ineffective, and causing cell death or inhibiting reproduction. Isopropyl alcohol may also have a dehydrating effect and may interfere with the functioning of cell membranes. Rapid evaporation, however, means that the effect of the alcohol is very short-lived, and is unlikely to contribute to the prolonged antibacterial action being claimed for Clinell Wipes.

1.2.2 Clinical information

Nationally recognised clinical guidelines, such as EPIC 2, EPIC 3 and NICE Guideline CG74 are clear that antiseptic skin preparation should be routinely undertaken at the surgical site immediately before incision using aqueous or alcohol based preparations; clinical guidance indicates the use of alcoholic chlorhexidine solutions.

1.2.3 Rationale for this Trial

This trial has been designed to demonstrate that HEXI-PREP by Clinell Wipes are superior to placebo (saline 0.9%w/v) in regards to their ability to achieve suitable and clinically acceptable skin disinfection at four anatomical locations. These include moist-skin sites (inguina) in which skin-to-skin contact results in a moist environment conducive to higher populations of microflora and three dry-skin areas; the lower abdomen below the umbilicus, the clavicular region and the median cubital region of the arm. This trial will also assess the relative efficacy of HEXI-PREP by Clinell Wipes with regard to an already licensed preparation (ChloraPrep) for this indication.

The trial is designed based on the principles set out in the US Food & Drug Administration (FDA) Tentative Final Monograph (TFM) for Effectiveness Testing of a Patient Preoperative Skin Preparation. In turn, this TFM uses the methodology set out in the US standard, ASTM E1173-15 "*Standard Test Method for Evaluation of Preoperative, Precatheterization, or Preinjection Skin Preparations",* dated January 2015.

This trial will be conducted in compliance with the trial protocol, International Conference on Harmonisation: Harmonised Tripartite Guidelines for Good Clinical Practice (ICH GCP) and the applicable regulatory requirements.

2. TRIAL OBJECTIVES AND PURPOSE

2.1 Trial Objectives

To evaluate the antimicrobial properties of HEXI-PREP by Clinell Wipe versus: (1) Placebo, negative control, product, (sterile saline 0.9% w/v) and (2) a positive control product, ChloraPrep® Chlorhexidine Gluconate 2% w/v solution (PL31760/004; PA1435/1/2), as per the methodology specified by the Food and Drug Administration Tentative Final Monograph (TFM) for Effectiveness Testing of a Patient Preoperative Skin Preparation (FR 59:116, 17 June 94, pp. 31450-31452).

2.1.1 Primary

To demonstrate superiority of HEXI-PREP by Clinell Wipe vs placebo (negative control) in reducing immediate bacterial load 1-10 minutes after administration to each test site.

2.1.2 Secondary

To demonstrate superiority of HEXI-PREP by Clinell Wipe vs placebo (negative control) in terms of persistence of a reduction in bacterial load at 30 minutes - 24 hours. To also assess the relative efficacy of HEXI-PREP Wipe to ChloraPrep (positive control) in regard to a reduction in bacterial load at 1-10 minutes, 30 minutes - 24 hours after administration to the test sites. A further secondary objective is to establish the safety profile (local tolerance) of the administered preparations.

3. TRIAL DESIGN

3.1 Trial Design

This is a GCP compliant, single-centre, within-participant, double-blind, randomised, placebo and comparator controlled study to evaluate the immediate and persistent antimicrobial properties of the investigational product; HEXI-PREP by Clinell Wipes for use in pre-operative skin preparation. An active control, ChloraPrep Chlorhexidine Gluconate 2%w/v solution (PL31760/004; PA1435/1/2) and a placebo (sterile saline 0.9%w/v) will also be evaluated as positive and negative controls respectively.

Volunteer test participants, who meet the inclusion / exclusion criteria will be randomly assigned to one of three test groups:

- Group 1: HEXI-PREP by Clinell Wipes vs placebo
- Group 2: HEXI-PREP by Clinell Wipes vs ChloraPrep
- Group 3: ChloraPrep vs placebo

Test products will be applied bilaterally to an area of pre-marked skin at four anatomical sites such that the investigational product is randomly applied to skin on one side of the participant's body and the control on the contralateral side. The four anatomical sites are the inguina (groin), in which skin-to-skin contact results in a moist environment conducive to higher populations of microflora and three dry-skin sites; the lower abdomen below the umbilicus, the clavicular region and the median cubital region of the arm.

The immediate and persistent antimicrobial effects of the preoperative preparations will be evaluated using the criteria set out in ASTM E1173-15, dated 05 Jan 2015. Using this methodology, the anatomical test sites will be evaluated by microbiological sampling at:

- Inguinal & Abdominal sites: zero (baseline), ten minutes, 30 minutes and six hours after the skin preparation
- Clavicular & Median Cubital region of Arm: zero (baseline), one minute, six hours and 24 hours after the skin preparation.

3.2 End Points

Co-primary endpoint assessment will be based on a $\log_{10}$ reduction of the immediate (time zero) baseline bacterial count at 1 and 10 minutes (dependent on site) compared to placebo and ChloraPrep active control at each of the four respective test sites. Critical indices (i.e. a clinically relevant reduction in bioburden) are prospectively defined as at least a 2 Log_{10} reduction in microorganisms at the dry sites (abdominal, clavicular and median cubital region of the arm) compared to placebo and at least a 3 Log_{10} reduction in microorganisms at the moist inguinal sites compared to placebo.

Secondary endpoint assessments will be based on persistence of a $\log_{10}$ reduction of the baseline bacterial counts at 30 minutes - 24 hours after application to the respective test sites compared to placebo and ChloraPrep active control.

3.3 Measures to Avoid Bias

Measures taken to avoid bias in this study, include:

1. Randomisation to Group: Participants will be randomly allocated, after confirmation of meeting the inclusion / exclusion criteria to one of three groups as set out in section 3.1, which will define the investigational products to be tested.
2. Randomisation to Test Site: Prior to administration of investigational products, participants will be further randomised such that investigational products will be allocated to the left or right side of the participant.
3. Blinding. The HEXI-PREP by Clinell Wipes and placebo wipes will be comparable in regards visual assessment, such that application of the investigational participant and placebo product will be blinded.
4. Although participants and administering clinicians will not be blinded due to packaging and administration of HEXI-PREP by Clinell Wipe vs ChloraPrep (due to differences in application methods), all clinical assessments will be undertaken blinded, by an assessor not present during product administration. Moreover, the primary efficacy endpoint will be based on an objective assessment of microbiological load, based on a defined sampling procedure (see section 6.3.3). The microbiologists responsible for plating and data collection will also be blinded to product assignment.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Number and Source of Participants

Participants will be recruited from participants registered on a database at the participating investigational site or those who respond to study specific, ethically approved advertising. A total of 60 participants will be randomised to the study (20 per group; i.e. 40 data sets per group).

4.2 Inclusion Criteria

- Male and female participants, aged 18 – 70 years inclusive at time of screening, who have provided written, informed consent to participate in the study.
- Participants with a bacterial baseline count of ≥5.0 $\log_{10}$ /cm^2 at the inguinal (groin) test administration sites. ≥4.0 $\log_{10}$ /cm^2 at the abdominal test site and ≥ 3.0 $\log_{10}$/cm^2 at the clavicular and median cubital regions at Day – 5 of screening.
- Participants, who in the opinion of the Investigator, are in suitable health for inclusion in the study.

4.3 Exclusion Criteria

- Participants who are exposed to topical antimicrobial agents, including medicated soaps, medicated shampoos or medicated lotions, who use biocide treated pools or hot-tubs, use tanning beds or sunbathe during the 14-day pre-test conditioning period or during the test period.
- Exposure of the test sites to strong detergents, solvents or other irritants during the 14-day pre-test conditioning period or during the test period.
- Use of systemic or topical antibiotic medications, steroid medications or any other product known to affect the normal microbial flora of the skin, up to 1 month prior to the screening period, during the 14-day pre-test conditioning period or during the test period.
- Any known allergies to latex (rubber), alcohols, tape adhesives or to common antibacterial agents found in soaps, lotions or ointments, particularly chlorhexidine gluconate or chlorine.
- Active skin rashes or breaks in the skin at the test site.
- Active skin diseases or inflammatory skin conditions including contact dermatitis within 10cm of the test site.
- Showering or bathing after the Day -5 baseline sampling and unwilling to refrain from showering or bathing whilst at Surrey CRC (Day 0 to Day 1).
- Participation in another clinical trial within 90 days preceding randomisation.
- Pregnant or breastfeeding women.
- Any other medical condition, which in the opinion of the Investigator, should preclude participation.

- Unwillingness to fulfil the performance requirements of the study.

4.4 Reproductive Potential

Female participants, recruited to the study should be either:

- post-menopausal, as defined by 12 months with no menses without an alternative medical cause;
- surgically sterile, or
- females of child-bearing potential (FOCP) with a negative urine pregnancy test at screening and Day 0 (prior to randomisation) and who are using or agree to use an effective method of birth control. For the purposes of this study, an effective method has been defined as those that result in a low failure rate (<1 % year). These include:
  - intrauterine devices (IUDs),
  - true abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception].
  - vasectomised partner

Condom use is advised with all of the above forms of contraception.

One of the above methods of birth control must be used throughout the pre-test conditioning period and for at least 30 days after last application of investigational product.

4.5 Withdrawal of Participants

Participants may withdraw their consent to participate in the trial at any time, for any reason without prejudice to their future medical care by the physician.

The Investigator may also withdraw participants from the trial, if they are not compliant with the trial protocol or from IMP treatment in order to protect their safety and well-being.

The reason for withdrawal must be recorded in the participant's medical record and on the Case Report Form (CRF). If a participant is withdrawn for more than one reason, each reason should be documented in the source documents and the most clinically relevant reason should be entered on the CRF.

Participants who are withdrawn will not be replaced. Any comments (spontaneous or elicited) or complaints made by the participant and the reason for termination, date of stopping investigational product and the total amount of investigational product taken must be recorded in the CRF and source documents.

The Sponsor reserves the right to terminate the trial at any time if deemed appropriate. In such an event, the necessary authorities, investigators and institutes will be informed promptly.

5. TREATMENT OF PARTICIPANTS

5.1 Administration of Investigational Product(s)(IMP)

Each participant will receive four test sites pre-marked with a surgical pen, as per Figure 1, by a member of the unblinded team.

- **Test Site 1 - Inguinal (groin) area**: Using a 3.8 x 12.7cm sterile template the treatment sites in the inguina are delineated on the uppermost inner aspects of both thighs, centring the long axis of the template along the inguinal crease, and marking the corners using a surgical skin marker. If, due to a participant's anatomy, the treatment site cannot be centred along the inguinal crease, the site should be positioned on the upper, inner thigh as close to the crease as possible. In no instance should testing be performed on areas not having skin-to-skin contact. The site is then divided on the long axis into 2.5 by 3.8cm sampling areas, allowing for spaces of about 0.9 cm between each of the four areas. Sampling areas are numbered from anterior to posterior, beginning with 1 and proceeding perineally to 4, and then are randomized to sampling for baseline and the three post-treatment sampling times.
- **Test Site 2 - Abdominal treatment sites** are to be located within a 12.7 cm by 12.7 cm site below and to the right or left of the umbilicus, approximately midway between the umbilicus and the pubis. Within this area a sterile template will be used to mark out four 2.5cm x 2.5cm quadrants with a 1.25cm gap between each quadrant in the abdominal region, the corners of each site are numbered 1, 2, 3, and 4 directly on the skin, using a surgical skin marker. Numbering is to be the same for all abdominal sites: number 1 is placed at the top corner to the participant's right, and numbers 2, 3, and 4 are assigned in order clockwise from 1, when looking at the participant. Three quadrants of each site are used for the three different treatment exposure times, and the remaining quadrant is used for a baseline count. The test formulation and reference control material are then randomized to the treatment sites, right and left, and baseline and the three post-treatment sampling times are randomized to the four sampling areas within each site.
- **Test Site 3 – Clavicular region**. A sterile template will be used to mark out four 2.5cm x 2.5cm quadrants with a 1.25cm gap between each quadrant in the clavicular region; the corners of each site are numbered 1, 2, 3, and 4 directly on the skin, using a surgical skin marker. Numbering is to be the same for all clavicular sites: number 1 is placed at the top corner to the participant's right, and numbers 2, 3, and 4 are assigned in order clockwise from 1, when looking at the participant. Three quadrants of each site are used for the three different treatment exposure times, and the remaining quadrant is used for a baseline count. The test formulation and reference control material are then randomized to the treatment sites, right and left, and baseline and the three post-treatment sampling times are randomized to the four sampling areas within each site.
- **Test Site 4** – **Median Cubital Region of Arm**. A sterile template will be used to mark out four 2.5cm x 2.5cm quadrants with a 1.25cm gap between each quadrant in the cubital region of the arm. These are numbered 1 through four at outside corners, beginning proximally and proceeding distally on the arm. Three sampling areas of the site are used for different treatment exposure times and the remaining sampling area is used for a baseline count. The test formulation and reference material should be

randomized to the treatment sites, right or left, and exposure times and baseline should be randomized to the four quadrants of each site.

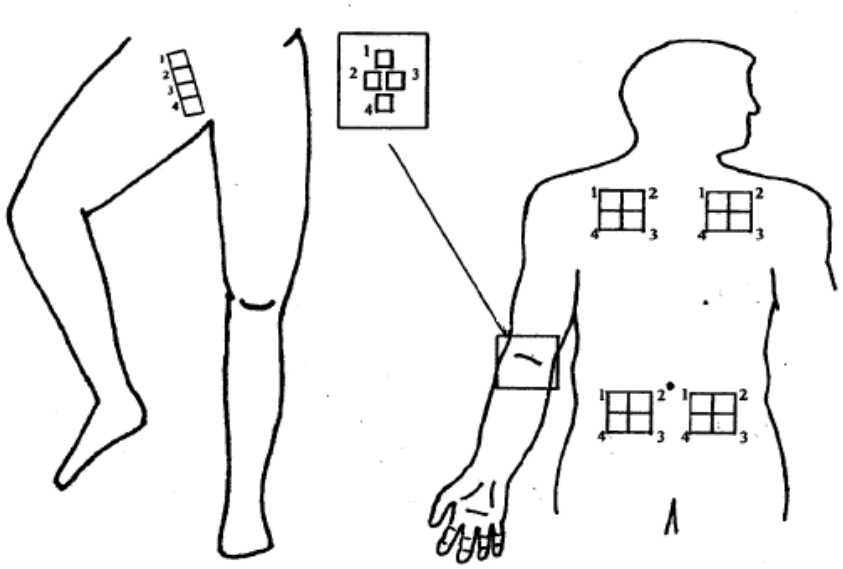

Figure 1: Test sites

The investigator will be responsible for administering the treatments as per the following instructions:

5.2 HEXI-PREP by Clinell Wipes:

Wearing sterile gloves, the investigator /designee should tear open one sachet of HEXI-PREP by Clinell Wipes and remove the wipe. Wipe the marked area using gentle back and forth strokes to prep the site for 30 seconds. The area covered should be allowed to air dry completely. HEXI-PREP by Clinell should not be removed from the test site until after the last efficacy sampling point.

5.2.1 Placebo (Sterile Saline)

Wearing sterile gloves, the investigator /designee should tear open one sachet of placebo Wipes and remove the wipe. Wipe the marked area using gentle back and forth strokes to prep the site for 30 seconds. The area covered should be allowed to air dry completely. The placebo should not be removed from the test site until after the last efficacy sampling point.

5.2.2 ChloraPrep

The applicator should be removed from the wrapper by the Investigator /designee and held with the sponge facing downward. The applicator is squeezed gently to break the ampoule containing the antiseptic solution, which is released onto the sponge in a controlled flow. Pinch wings only once to activate the applicator and release the antiseptic. Do not repeatedly pinch or pump the wings in an attempt to accelerate the saturation of the foam. The broken ampoule

remains safely contained within the applicator. The sponge is gently pressed against the participant's skin in order to apply the antiseptic solution. Once the solution is visible on the skin, use gentle back and forth strokes to wipe the marked area for 30 seconds. The area covered should be allowed to air dry completely. ChloraPrep should not be removed from the test site until after the last efficacy sampling point.

5.3 Allocation to Treatment and Dosage Regimen

A total of 60 participants will be randomised; 20 to each of the following three dosing groups:

- Group 1: HEXI-PREP by Clinell Wipes vs placebo
- Group 2: HEXI-PREP by Clinell Wipes vs ChloraPrep
- Group 3: ChloraPrep vs placebo

During the pre-test conditioning period and prior to randomisation, unique identifiers will be assigned to all participants as they consent to take part in the trial. This number will be assigned to participants according to the sequence of presentation for trial participation and will be used to anonymise participants prior to randomisation.

Randomisation numbers will be allocated sequentially to participants, once eligibility has been confirmed with respect to the inclusion and exclusion criteria. Once a randomisation number has been assigned, that number must not be used again if, for example, a participant is withdrawn from the trial. If a randomisation number is allocated incorrectly, notify the trial monitor and sponsor as soon as the error is discovered.

Code-break information will be held by the designated person at the investigational site.

5.3.1 Accountability

Investigational products must be used only as directed in the protocol. The Investigator / designee must keep accurate, written records of all investigational product received from GAMA Healthcare and the quantities of the investigational products dispensed/distributed, and used on each participant.

The nominated person will record details on the drug accountability log.

Based on entries in the site drug accountability forms, it must be possible to reconcile drug product delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented appropriately.

5.4 Concomitant Therapy

All concomitant medications taken by the participant between -19 days (beginning of the pre-test conditioning period) through to the last efficacy sampling (24 hours post administration of the test site) will be recorded in participant’s Case Record Form (CRF).

Participants who are on stable doses of medications for medical conditions which are not excluded by this protocol, may continue on these medications.

5.5 Rescue Therapy

No rescue therapy is required in this study.

If, in the opinion of the investigator and for the safety of the participant, the investigational product must be removed from the test treatment site prior to the last efficacy assessment, the site can be cleaned with soap, water or alcohol as appropriate. The participant should be documented as withdrawn from the trial.

5.6 Manufacturing, Packaging, Labelling and Storage

5.6.1 Manufacturing and labelling

All HEXI-PREP by Clinell and placebo Investigational Medicinal Products will be manufactured under Good Manufacturing Practice (GMP) for clinical use as a sterile finished Investigational Medicinal Product (IMP). All IMP will be labelled in accordance with GMP and local regulations. Details of the storage conditions for the IMP (including details of any permitted storage deviations) will be agreed with the designated Qualified Person for GMP and provided to the relevant regulatory authorities.

ChloraPrep used in this study will be purchased from a licensed wholesaler or from a pharmacy and will be identical to product placed on the market by the MA Holder (CareFusion UK Ltd).

5.6.2 Storage

The Investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy member of the trial team, but this delegation must be documented.

Investigational product must be stored in accordance with labelled storage conditions (store below 25°C). Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. Excursion from the established range will require site investigation as to cause and remediation. The designated Qualified Person will determine ultimate impact of excursion and will provide supportive documentation.

The Sponsor must be permitted access to audit the supplies storage and distribution procedures and records.

6. TRIAL PROCEDURES

6.1 Visit Schedule

The trial visit schedule and assessments to be undertaken are summarised in Table 1. Details of all trial visits procedures are presented below:

6.1.1 Day -21 to Day -19 (Screening)

The Principal Investigator or his designee must obtain written informed consent from the participant prior to the performance of any the trial related procedures listed below:

- A review of the inclusion / exclusion criteria
- A medical history will be taken, including details of any medication taken
- Participant demographics will be recorded
- The participant will undergo a physical examination
- FOCP will undergo a urine pregnancy test

The participant will be provided with information to avoid antimicrobials.

6.1.2 Day –19 – Day -5 (Start of Pre-Conditioning Period)

- Participants will be provided with non-antibacterial / non-medicated personal hygiene products for use during the pre-conditioning period. Participants will be advised they cannot use conditioner on their hair or moisturisers.
- A diary card will also be provided to record use of personal hygiene products

6.1.3 Day -5

Approximately 120 hours before test initiation, the participant will be asked to attend a non-residential visit to the investigational site, at which time:

- Hair in and slightly outside the test areas (if applicable) will be clipped
- The test sites will be marked with a sterile surgical pen
- A screening microbiological sample will be collected from each of the four test sites on one side of the participant only (Quadrant 1).
- The participant will be advised that no further bathing or showering is permitted until after the last efficacy assessment.

6.1.4 Day 0 /1 (Treatment of Test Sites)

On Day 0, the participant will be asked to attend a visit to the investigational site.

Pre-randomisation:

- The inclusion / exclusion criteria will be re-assessed; in particular screening microbiological results (taken at Day-5) will be assessed for each of the test sites. Participants who do not meet the microbiological requirements for entry into the study, will be invited to re-screen once
- Any changes in concomitant medication will be re-assessed.
- FOCP will undertake a urine pregnancy test.
- If required, the marked test sites may be remarked with a surgical pen, in order to delineate the sites.

Following randomisation:

- A pre-dose (baseline) microbiological sample will be taken
- Investigational Products will be applied to the marked test sites and allowed to air dry
- Any adverse events occurring at the test site will be recorded
- At the Inguinal and Abdominal Test sites:

  - Ten minutes after application of the investigational products a microbiological sample will be taken at each test site
  - Thirty minutes after application of the investigational products a microbiological sample will be taken at each test site
  - Six hours after application of the investigational product a microbiological sample will be taken at each test site.
- At the Clavicular and Median Cubital Region of the Arm:
  - One minute after application of the investigational products a microbiological sample will be taken at each test site
  - Six hours after application of the investigational product a microbiological sample will be taken at each test site
  - Twenty-four hours after application of the investigational product, a microbiological sample will be taken at each test site.
- After the 30 minute sampling time points, participants will be permitted to move around / sit but must remain at the investigational site.
- After the final sampling, the test areas may be cleaned using ordinary soap and water to remove the investigational products. This can be performed either by clinical staff, or participants may be permitted to shower as appropriate.

6.2 End of trial

This trial formally ends after completion of the last efficacy assessment (24 hours after administration of the test products) by the last participant.

6.3 Clinical Procedures

6.3.1 Hair clipping

Prior to delineating test sites and /or microbiological sampling, the hair in and around the proposed sites will be clipped on Day -5, in a manner that preserves skin integrity. Specifically, hair will be clipped against the growth (if the hair is long, it may be clipped in the direction of growth first). Participants will be able to clip themselves, but if they are not efficient enough, a staff member will complete the clipping. Participants must not shave or wax sites whilst out of the Center from Day -9 to Day 0 so that participants do not damage / irritate the sites.

6.3.2 Marking of the Test Sites

Each participant will receive eight test sites as per section 5.1, four on the left of the body and four on the right. Each of the test sites will be marked out using a defined template. The area will be marked using a surgical pen. If the marks are found to have faded, the site marked on day-5 may be renewed on Day 0 using a surgical pen, prior to the application of IMP.

During the marking on Day-5 and during the procedures on Day 0/1 participants will be provided with disposable underwear or other covering and/or can wear their own bikini underwear. Participants will be advised this may be damaged due to the marking, study products or dressings.

6.3.3 Microbiological Sampling

Microbiological samples will be taken on Day-5 for screening purposes; these will be taken from the test sites on only one side of the participant and always from quadrant 1. Additionally, a pre-dose (baseline) microbiological sample will be taken immediately prior to application of the IMP at each of the 8 respective sites. A modesty item may be used during sampling.

The inguinal and abdominal test sites will be sampled at ten minutes ± 1 minute and at 30 minutes ± 2-minute post application of the investigational product (i.e. at the end of the 30 second application time frame), using the Cylinder Sampling Technique as detailed in 6.3.3.1. Following the 30-minute sampling time point, the test sites will be covered with sterile gauze and a semi-occlusive bandage until six hours ± 15 minutes, at which time sampling will be undertaken by the Cylinder Sampling Technique as detailed in 6.3.3.1.

The clavicular and median cubital regions of the arm will be sampled within one minute ± 30 seconds, post application of the investigational product (i.e. at the end of the 30 second application time frame), using the Cylinder Sampling Technique as detailed in 6.3.3.1. Following the 1-minute sampling time point, the test sites will be covered with sterile dressings until six hours ± 15 minutes at which time sampling will be undertaken by the Cylinder Sampling Technique as detailed in 6.3.3.1. Following the six-hour sampling time point, the test sites will again be covered with sterile dressings until 24 hours ± 30 minutes, at which time sampling will be undertaken by the Cylinder Sampling Technique as detailed in 6.3.3.1.

6.3.3.1 Cylinder Sampling Technique

- At the designated time period, a standardised sterile cylinder will be held firmly onto the anatomical site to be sampled. 2.5mL of sterile Stripping Suspending Fluid with appropriate product neutralizers (SSF++) will be instilled into the cylinder and the skin area inside the cylinder will be massaged in a circumferential manner for one minute with a sterile rubber policeman.

- The 2.5mL of SSF++ will be removed with a pipette and transferred to a sterile test tube. A second 2.5mL aliquot of SSF++ will be instilled into the cylinder and the skin area again massaged for one minute with a sterile rubber policeman.

- The second 2.5mL aliquot will then be pooled in the test tube with the first aliquot.

6.3.3.2 Neutralization:

- A separate neutralization study will be performed to assure the neutralizer used in the recovery medium quench the antimicrobial activity of the test and control products. The neutralization will follow guidelines set forth in ASTM E 1054-02, *"Standard Tests for Evaluation of Inactivators of Antimicrobial Agents*" except that the microorganism will be added to the neutralizer prior to the addition of the test and control products. *Staphylococcus epidermidis* (ATCC #12228) will be used as the challenge species in the neutralizer validation study.

6.3.3.3 Diluting & Plating

- Aliquots of the microorganism suspension (10^0 dilution) will be serially diluted in Butterfield's Phosphate Buffer Solution with product neutralizers as appropriate.

- Duplicate spread samples and/or spiral plates will be prepared from each of these dilutions on General Purpose Agar with product neutralizers and incubated at 30°C ± 2°C for approximately 72 hours, or until sufficient growth is observed. Colonies will be counted and data recorded using the Q-COUNT Equivalent.

6.3.3.4 Calculation of Colony Forming Units

- To convert the volumetric measure of the sample into the number of colony forming units per square cm (cm^2) the following formula will be applied:

$$R = Log_{10} \frac{\left[F\left(\frac{\sum ci}{n}\right)10^{-D}\right]}{A}$$

Where:

- R = Average colony forming units in Log_{10} scale /cm^2 of sampling surface
- F = Number of mL of stripping fluid added to the sampling cylinder; in this study F =5mL
- $\frac{\sum ci}{n}$ = Average of the duplicate colony counts used for each sample collected
- D = Dilution factor of the plates
- A = Interior area of the cylinder in cm^2; in this study A = 3.46cm^2

NOTE: The reason that a log_{10} transformation will be performed on the collected data is to obtain a linear scale. A linear scale, more appropriately a log_{10} linear scale, is a basic requirement of the statistical models used in this study.

6.4 Safety Assessments

6.4.1 Local tolerability assessments

At each of the assessment time points (and prior to microbiological sampling), the Investigator will ask the participant to comment on local tolerability, in particular with respect to itch, burn and pain. These will be categorised on five point scales as follows:

Itch as:
-None
-Mild (occasional, slight itching/scratching)
-Moderate (intermittent itching/scratching not affecting sleep/daily activities)
-Marked (constant itching/scratching occasionally affecting sleep/daily activities)
-Severe (persistent itching/scratching affecting sleep/daily activities)

Burn as:
-None
-Mild (occasional, slight burning sensation)
-Moderate (intermittent burning sensation not affecting sleep/daily activities)

-Marked (constant burning sensation occasionally affecting sleep/daily activities)
-Severe (persistent burning sensation affecting sleep/daily activities)

Pain as: -None
-Mild (occasional, slight discomfort)
-Moderate (intermittent pain not affecting sleep/daily activities)
-Marked (constant pain occasionally affecting sleep/daily activities)
-Severe (persistent pain affecting sleep/daily activities)

In addition, the Investigator will record assessments of erythema and oedema according to the following five point scales:

Erythema as: -None (normal skin)
-Mild (faintly detectable erythema, very light pink)
-Moderate (pink and distinguishable)
-Marked (dull red, clearly distinguishable)
-Severe (deep dark red)

Oedema as: -None
-Mild (<2mm swelling)
-Moderate (2-5mm swelling, localised to application site)
-Marked (>5mm swelling, spreading from application site)
-Severe (>5mm swelling, deep oedema, spreading extensively from application site)

6.4.2 Pregnancy test

A urine pregnancy test is performed on all FOCP at screening and immediately prior to randomisation.

6.4.3 Physical examination

A physical examination will be conducted by the physician at the screening visit. This will include assessment of the following systems according to the Investigator's normal clinical practice:

- Cardiovascular
- Ear, Nose and Throat (ENT)
- Respiratory
- Gastrointestinal
- Musculoskeletal
- Neurological
- Dermatological
- Lymphatic

6.4.4 Adverse events (AEs)

The Investigator will assess any AEs experienced by the participant using a general open question such as “How are you feeling?” following each assessment. Local tolerability assessments greater than “none” as described in section 6.4.1 will be recorded as AEs. All AEs will be recorded and assessed as described in Section 7.

6.5 Other Assessments

6.5.1 Demographic data

The following demographic data will be recorded

- Date of birth
- Age
- Sex
- Race
- Height
- Weight
- Body Mass Index
- Fitzpatrick Skin Type

7. AE, SAE AND ADR REPORTING

7.1 Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation participant who has been administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (investigational) product.

Events involving adverse drug reactions (ADRs), illnesses that onset during the trial, or exacerbations of pre-existing illnesses should be recorded. Exacerbation of pre-existing illness is defined as a manifestation (sign or symptom) of the illness that indicates a significant increase in the severity of the illness as compared to the severity noted at the start of the trial. It may include worsening or increase in severity of signs or symptoms of the illness, increase in frequency of signs and symptoms of an intermittent illness, or the appearance of a new manifestation/complication. Exacerbation of a pre-existing illness should be considered when a patient requires new or additional concomitant drug or non-drug therapy for the treatment of that illness during the trial. Lack of or insufficient clinical response, benefit, efficacy, therapeutic effect or pharmacological action, should not be recorded as an AE.

For all AEs, the Investigator must pursue and obtain adequate information both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Sponsor.

For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e. trial drug or other illness). The Investigator is required to assess causality and indicate that assessment on the CRF. Follow-up of the AE, after the date of therapy discontinuation, is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator or their designated representative.

The Investigator/Sponsor must supply all participants with a card detailing the trial protocol number and the Investigator's name. This card should provide details of 24-hour contact numbers that can be called in the event of a medical emergency.

7.2 Severity of Adverse Events

AE severity will be classified according to the following definitions:

MILD: Discomfort noticed but does not interfere with the patient’s daily routines.

MODERATE: Discomfort sufficient to interfere with some aspect of the patient’s daily routines.

SEVERE: Discomfort so severe it prevents patient continuing daily routines. Note that the term ‘serious’ is usually associated with events that pose a threat to the patient’s life or functioning. The term ‘severe’ is used to describe the intensity of a specific event but the event may itself be of minor clinical significance e.g. a headache.

7.3 Relationship of Adverse Event to Investigational Drug or Concomitant Therapy

Deciding the relationship of an AE to the study treatment is the responsibility of the investigating physician and is based on clinical judgement. The following guidelines should be used, which are based on the Karch-Lasagna classification (Clin.Pharm.Ther. (1977), 21:247):

ALMOST DEFINITE

- Distinct temporal relationship with study treatment.
- Known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot be explained by patient's clinical state or other factors.

PROBABLE

- Reasonable temporal relationship with study treatment.
- Likely to be known reaction to agent or chemical group, or predicted by known pharmacology.
- Event cannot easily be explained by patient's clinical state or other factors.

POSSIBLE

- Reasonable temporal relationship with study treatment.
- Event could be explained by patient's clinical state or other factors.

UNLIKELY

- Poor temporal relationship with study treatment and/or
- Event easily explained by participant's clinical state or other factors

UNRELATED

- Event occurred before dosing or
- Event or intercurrent illness due wholly to factors other than drug treatment.

7.4 Recording Adverse Events in the Case Report Form (CRF)

All AEs, which occur between administration of the investigational products and the 24 hour assessment, will be recorded in the CRF. Serious adverse events will be reported according to the procedures given below.

7.5 Serious Adverse Events (SAEs)

All serious adverse events (as defined below) regardless of treatment group or suspected relationship to trial drug must be reported within 24 hours to the sponsor by completing a Serious Adverse Event Form and emailing to the Sponsor’s Responsible Physician.

The Sponsor's Responsible Physician will assess all serious adverse events and report any suspected unexpected serious adverse reactions to the regulatory authorities according to Sponsor standard operating procedures.

A SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening.
- Requires hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability / incapacity.
- Results in a congenital anomaly / birth defect.

Medically significant events that may not result in death, be life-threatening, or require hospitalisation may be considered serious adverse drug experiences when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation or the development of drug dependency or drug abuse.

Serious Adverse Events which have causality assessed as possible, probable or almost definitely related to the IMP and which do not appear as Adverse Events within the Investigator Brochure, will be reported as Suspected Unexpected Serious Adverse Reactions (SUSARs) to the appropriate Competent Authority (s), Ethics Committee (s) and Clinical Investigators. Initial reports of SUSARs will be made within 7 calendar days for deaths or life-threatening conditions and within 15 days for all other SUSARs.

8. STATISTICAL DESIGN

8.1 Sample Size Calculation and Power Considerations

Because the primary purpose of this study is to demonstrate efficacy (defined as a significant reduction in microbial counts from baseline), sample size calculations have been undertaken to determine the number of participants necessary to reliably assess efficacy. The number of participants required depends on the within participant variability in (log10) microbial count change from baseline, the expected efficacy of the test product (in terms of expected reduction from baseline in microbial count (log10)), the desired Power (1-β) and 2-sided Type I error (α).

Moreover, since this clinical trial is intended to provide sole clinical evidence for the efficacy of HEXI-PREP by Clinell Wipes, and in line with the guidance provided in CPMP/EWP/2330/99, dated May 2001, evidence more stringent than p<0.05 is sought. Hence, a reduced α of 0.0125, one-sided is proposed.

Using this information, and in line with the requirements of ASTM E1173-15, the required number of participants has been estimated using the following equation:

$$n \geq S^2 \left[\frac{t_{\alpha/2,n-1} + t_{\beta,n-1}}{\mathrm{D}}\right]^2$$

where:

- S^2 = estimate of the within participant variance for the reduction from baseline in microbial count (log10) at 10 minutes after administration
- t_p = $100(1-p)^{th}$ percentile of the of the centralised t distribution with $n-1$ degrees of freedom
- D = expected efficacy (expected reduction from baseline in microbial count (log10)),)

Using this formula with S^2 estimate of 1.0 (Edmiston et al 2006 [6]) and assuming a 3.5 $\log_{10}$ mean microbial count reduction from baseline on test (being in line with that previously seen with ChloraPrep, Edmiston 2006), with a one-sided α level of 0.0125 a sample size of 20 participants will provide >90% power to test the primary hypothesis.

8.2 Statistical Methods

The basic study design for the testing procedures is a pre- to post-treatment within participant comparative structure. The microbial population determined prior to treatment with test formulation (baseline population) is compared with the population remaining at a specified time after treatment.

- The co-primary analysis will test the hypothesis that HEXI-PREP by Clinell Wipe is superior to placebo at each of the four test sites within the ITT population at 1-10 minutes after administration.

- Secondary analyses will:
  i. Test the hypotheses that HEXI-PREP by Clinell Wipe is superior to placebo at inguinal and abdominal sites within the ITT population at 30 minutes and 6 hours after administration; and within the PP population at 10 minutes, 30 minutes and 6 hours after administration.
  ii. Test the hypotheses that HEXI-PREP by Clinell Wipe is superior to placebo at clavicular and arm sites within the ITT population at 6 hours and 24 hours after administration; and within the PP population at 1 minute, 6 hours and 24 hours after administration.
  iii. Examine the relative effectiveness of HEXI-PREP by Clinell Wipe to ChloraPrep within the ITT and PP populations at the inguinal and abdominal test sites at 10 minutes, 30 minutes and 6 hours after administration. If antimicrobial efficacy of HEXI-PREP by Clinell Wipe in terms of mean change from baseline in microbial count ($\log_{10}$) is not less than 80% of the corresponding antimicrobial efficacy of ChloraPrep, non-inferiority will have been demonstrated.
  iv. Examine the relative effectiveness of HEXI-PREP by Clinell Wipe to ChloraPrep within the ITT and PP populations at the clavicular and arm sites at 1 minute, 6 hours and 24 hours after administration. If antimicrobial efficacy of Clinell in terms of mean change from baseline in microbial count ($\log_{10}$) is not less than 80% of the corresponding antimicrobial efficacy of ChloraPrep, non-inferiority will have been demonstrated
  v. Test the hypothesis that the efficacy of ChloraPrep is superior to placebo (to establish assay sensitivity of the trial protocol and procedures) in the ITT population at 1-10 minutes after administration.

Secondary analyses will be conducted **only** if the co-primary hypotheses are met (i.e. if HEXI-PREP by Clinell Wipe is shown to be superior to placebo at all test sites within the ITT population at 1-10 minutes' post administration). Further, since Groups 1 to 3 represent independent experiments, each with non-overlapping participants and each group addressing different questions, considerations versus alpha control will apply to each of the 3 groups separately.

Therefore, if the primary hypothesis is accepted, the secondary analyses under (i) and (ii) above will be assessed in the following hierarchical order and will be stopped after the first failure: (a) groin at 30 minutes ITT population, (b) abdomen at 30 minutes ITT population (c) groin at 6 hours ITT population, (d) clavicular region at 6 hours in the ITT population (e) median cubital region of the arm at 6 hours in the ITT population (f) abdomen at 6 hours ITT population (g) clavicular region at 24 hours in the ITT population and (h) median cubital region of the arm at 24 hours in the ITT population. A significance level of 0.0125 2-sided will be applied. PP analyses of HEXI-PREP by Clinell Wipe versus placebo are supportive and will not be participant to alpha control.

Similarly, if the primary hypothesis is accepted, the relative efficacy analyses versus ChloraPrep under (iii) and (iv) will be assessed in the following hierarchical order and will be stopped after the first failure (a) groin at 30 minutes PP population, (b) abdomen at 30 minutes PP population (c) groin at 6 hours PP population, (d) clavicular region at 6 hours in the PP population (e) median cubital region of the arm at 6 hours in the PP population (f) abdomen at 6 hours PP population (g) clavicular region at 24 hours in the PP population and (h) median cubital region of the arm at 24 hours in the PP population. ITT relative efficacy analyses of HEXI-PREP by Clinell Wipe versus ChloraPrep are supportive and will not be participant to alpha control.

Finally, as the test ChloraPrep efficacy under (v) does not involve HEXI-PREP by Clinell Wipe and serves only to establish assay sensitivity, no alpha control will be applied.

A matched pair Student's t-test is an appropriate parametric analysis to assess the difference between treatments in terms of change from baseline (pre-to post-treatment) in $\log_{10}$ microbial count. In the event data are found not to conform to a normal distribution a non-parametric statistical approach such as the Wilcoxon signed rank test will be applied. For the assessment of relative efficacy under (iii) and (iv), the lower 98.75% CL for the difference between HEXI-PREP by Clinell Wipe and ChloraPrep in mean microbial count reduction from baseline (Log_{10}) will be expressed as a fraction of the mean microbial reduction on ChloraPrep using Fieller's theorem. If this lower 98.75% CL limit is more than a 20% loss of relative efficacy, HEXI-PREP by Clinell Wipe will be considered non-inferior to ChloraPrep.

The statistical analyses described in this section will be presented in further detail in the Statistical Analysis Plan (SAP) as necessary. The SAP which will be finalised prior to unblinding of the database and will be included as part of the final Clinical Study Report.

8.3 Trial Populations

The Intent to Treat (ITT) population consists of participants who are randomized, receive at least one dose of investigational product, and have at least one follow-up assessment for efficacy measures. This population will be primary for the assessment of HEXI-PREP by Clinell

efficacy versus to placebo and for the assessment of ChloraPrep versus placebo for determination of assay sensitivity.

The Per Protocol (PP) population is a subset of the ITT population and consists of participants who do not have any major protocol violations or missing primary efficacy endpoint data. This population will be primary for the assessment of the relative efficacy of HEXI-PREP by Clinell Wipe versus ChloraPrep.

8.4 Data Handling

Data from the Case Report Forms will be entered into a trial database. Edit checks will fire upon entry and any obvious data entry errors can be corrected. Subsequently, the data will be reviewed (100% of the key safety and efficacy data) and any further errors will be queried and corrected accordingly, within the system.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List which employs the Anatomical Therapeutic Chemical classification system to the Preferred Term and General Term. Medical history and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Microbiological samples will be processed centrally through a pre-specified microbiological laboratory and the results will be sent electronically to Sponsor.

When the database has been declared to be complete and accurate, the database will be locked and unblinded. Any changes to the database after that time can only be made by joint written agreement between the Trial Manager, the Trial Statistician, the Trial Data Manager and the Sponsor.

8.5 Procedures for Handling Missing, Unused or Spurious Data

Procedures for handling missing or spurious data will be documented in the SAP prior to unblinding and outlined in the final clinical trial report.

8.6 Interim Analysis

There is no interim analysis planned for this trial.

9. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This trial will be conducted in accordance with current applicable regulations, ICH guidelines, EU Directive 2001/20/EC or EU Regulation 536/2014 (as appropriate to the timeframe of the clinical trial) and local ethical and legal requirements.

9.1 Sponsor's Responsibilities

9.1.1 ICH GCP compliance

The Sponsor and any third party to whom aspects of the trial management or monitoring have been delegated will undertake their roles for this trial in compliance with all applicable regulations, ICH GCP Guideline E6 and EU Directive 2001/20/EC or EU Regulation 536/2014

(as appropriate to the timeframe of the clinical trial) and in accordance with the Sponsor's (or designee's) Standard Operating Procedures.

The Sponsor will appoint monitors(s) to conduct the monitoring of this clinical trial, which will be conducted according to agreed monitoring conventions. The monitor will review the source documents for accuracy of data recording and for compliance with the protocol, ICH GCP guidelines and applicable regulatory guidelines.

Records and data may additionally be reviewed by auditors or by regulatory authorities.

9.1.2 Regulatory approval

The Sponsor will ensure that Local Regulatory Authority requirements are met before the start of the study. The Sponsor (or a nominated designee) will also be responsible for the preparation, submission and confirmation of receipt of any Regulatory Authority approvals required prior to release of investigational medicinal product for shipment to the trial site.

9.1.3 Indemnity/liability and insurance

The Sponsor will ensure that suitable insurance cover is in place prior to the start of the trial. An insurance certificate will be supplied to the involved parties, including the Principal Investigator and CRO as appropriate.

9.1.4 Protocol management

All protocols and amendments will be prepared by the Sponsor. If it becomes necessary to issue a protocol amendment during the course of the trial the Sponsor (or designee) will notify the Investigators and collect documented Investigator Agreement to the amendment. No changes to the protocol will be initiated without prior written approval of the relevant independent ethics committee and regulatory body. The only exception to this is when the change is necessary to eliminate immediate hazards to the participants or when the change involves only logistical or administrative aspects of the trial.

9.1.5 Submission of summary of Clinical Study Report to competent authorities of Member States concerned and IECs

The Sponsor will provide a summary of the Clinical Study Report within one year of the end of the complete trial to the competent authority of the Member State(s) concerned as required by the regulatory requirement(s) and to comply with the ICH GCP. The Sponsor will additionally provide the IECs with a copy of the same summary.

9.1.6 Study suspension, termination, and completion

The sponsor may suspend or terminate the trial or part of the trial at any time for any reason.

9.2 Investigator's Responsibilities

9.2.1 ICH GCP compliance

The Investigator must undertake to perform the trial in accordance with ICH GCP Guideline E6, EU Directive 2001/20/EC or EU Regulation 536/2014 (as appropriate to the timeframe of the clinical trial) and all applicable regulatory requirements. A copy of the guidelines will be available in the Investigator Site File.

It is the Investigator's responsibility to ensure that adequate time and appropriate resources are available at the trial site prior to commitment to participate in this trial. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant trial-related tasks. *Curriculum vitae* for these individuals as well as the Investigator will be provided to the Sponsor (or designee) before starting the trial.

If the participant has a primary physician the Investigator should, with the participant's consent, inform them of the participant's participation in the trial.

Agreement with the final Clinical Study Report is documented by the signed and dated signature of the Principal Investigator in compliance with Directive 2001/83/EC, Regulation 536/2014 and ICH E3.

9.2.2 Protocol adherence and Investigator agreement

The Investigator must adhere to the protocol as detailed in this document. The Investigator will be responsible for enrolling only those participants who have met protocol eligibility criteria. The Investigators are required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the trial, the investigator will promptly inform the sponsor and the IEC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon trial completion, the investigator will provide the sponsor, IEC, and regulatory agency with final reports and summaries as required by regulations.

9.2.3 Documentation and retention of records

9.2.3.1 Case Report Forms

CRFs are supplied and should be handled in accordance with instructions provided.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information can be transcribed onto CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. CRFs should be filled out completely by the Investigator or delegate as stated in the site delegation log. All CRFs should be completed in a neat legible manner to ensure accurate interpretation of the data and the CRFs must be reviewed, signed and dated by the Investigator.

Once the trial monitor has verified the contents of the completed CRF pages against the source data, the pages are collected and forwarded to the Sponsor (or designee) for data entry. If the data are unclear or contradictory queries are sent for corrections or verifications to data.

9.2.3.2 Recording, access and retention of source data and study documents

The Investigator must permit authorised representatives of the Sponsor, the respective national, local or foreign regulatory authorities, the IEC, and auditors to inspect facilities and records relevant to this trial.

The consent form includes a statement by which the participant agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities or the IEC having access to source data.

Source data to be reviewed during this trial will include, but is not limited to: participant's medical records, and original laboratory reports.

The following source data will be recorded directly into the CRF (unless otherwise agreed with individual trial sites.

- Participant demographics
- Details of physical examination
- Eligibility criteria (excluding baseline microbiological analysis)
- IMP dosing details
- Safety and tolerability assessment

The participant's medical history will be assessed by direct questioning of the participant. Source data verification (SDV) will be carried out in accordance with the SOPs either of Sponsor or the authorised Contract Research Organisation carrying out SDV on Sponsor 's behalf.

All trial records must be retained by the Investigator until authorised for destruction by the Sponsor. The normal period of archiving, will be 15 years or 2 years after the last marketing application in an ICH region.

9.2.3.3 Investigational medicinal product accountability

All investigational medicinal products required for completion of this trial will be provided by the Sponsor. The recipient will acknowledge receipt of the investigational medicinal products, documenting shipment content and condition. Damaged supplies will be replaced. Accurate records of all investigational medicinal product dispensed, used and returned will be maintained.

9.2.3.4 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this trial must be available for inspection upon request by representatives of, for example the UK Medicines and

Healthcare products Regulatory Agency (MHRA), other foreign regulatory authorities, the Sponsor or its representatives, and the IEC for each trial site.

9.2.3.5 Financial disclosure

The Investigator is required to disclose any financial arrangement whereby the value of the compensation for conducting the trial could be influenced by the outcome of the trial.

In consideration of participation in the trial, the Sponsor will pay the Investigator or nominated payee the sums set out in the payment schedule in the study contract.

9.2.4 Compliance to all local, state, and national controlled-substance regulations

When using controlled substances while participating in a Sponsor sponsored clinical trial, the Investigator must at all times comply with all local, state, and national laws pertaining to registration and reporting with the appropriate regulatory body and control and handling of controlled substances.

9.3 Ethical Considerations

This protocol accords with the principles of the 18th World Medical Assembly (Helsinki 1964) and amendments of the 29th (Tokyo 1975), the 35th (Venice 1983), the 41st (Hong Kong 1989) <and> the 48th (Somerset West [South Africa] 1996), 53rd (Washington 2002), 55th (Tokyo 2004) and 59th (Seoul 2008) World Medical Assemblies

9.3.1 Informed consent

It is the responsibility of the Investigator to obtain written Informed Consent from participants in accordance with all applicable local, national and international regulations and guidance. All consent documentation must be in accordance with applicable regulations and ICH GCP. Each participant or the participant's legally authorised representative is requested to sign the Participant Informed Consent Form after the participant has received and read the written participant information and received an explanation of what the trial involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the participant's rights and responsibilities. A copy of the informed consent documentation (Consent Form or Participant Information and the Consent Form, as applicable) must be given to the participant or the participant's legally authorised representative. If applicable, it is provided in a certified translation of the local language. Signed consent forms must remain in each particpant's screening pack and must be available for verification by study monitors at any time.

The Principal Investigator will provide the Sponsor with a copy of the IEC approved consent forms, and a copy of the IEC's written approval, prior to the start of the trial unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to trial start that another party (i.e., sponsor or Chief Investigator) is responsible for this action. Additionally, if the IEC requires modification of the sample Participant Information and Consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

9.3.2 Independent Ethics Committee approval

For all investigational sites this protocol, the informed consent document (approved by the Sponsor or its designate), relevant supporting information and all types of participant recruitment information, will be submitted to the IEC for review and approval prior to site initiation.

Prior to implementing changes in the trial, the Sponsor and the IEC will approve any revised informed consent documents and amendments to the protocol.

On the approval letter, the trial (title, protocol number and version), the documents reviewed (protocol, informed consent material, advertisements and amendments, if applicable) and the date of review and actions taken should be clearly stated.

Investigational product supplies will not be released and the participant recruitment will not begin until the Sponsor has received this written approval, along with copies of all revisions and approved documents.

For all investigational sites, the IEC will be appraised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; according to national provisions. The local IEC will also be informed of any serious and significant adverse events.

9.4 Privacy and Confidentiality

Data collected during this trial may be used to support the development, registration or marketing of Clinell. The Sponsor will control all data collected during the trial, and will abide by the EU Directive on Data Privacy concerning the processing and use of participants' personal data. For the purpose of data privacy legislation, the Sponsor will be the data controller.

After participants have consented to take part in the trial their medical records and the data collected during the trial will be reviewed by the Sponsor and/or its representatives. These records and data may, in addition, be reviewed by the following: independent auditors who validate the data on behalf of Sponsor; third parties with whom Sponsor may develop, register or market Clinell; national or local regulatory authorities and the IEC which gave its approval for this trial to proceed.

Although participants are known by a unique number, their date of birth will also be collected and used to assist the Sponsor to verify the accuracy of the data, for example, that the laboratory results are assigned to the correct participant. The results of this trial containing the unique number, date of birth and relevant medical information may be recorded and transferred to and used in other countries throughout the world, which may not afford the same level of protection that applies within the EU. The purpose of any such transfer would be to support regulatory submissions made by the Sponsor in order to market Clinell in other countries.

9.5 Publication Policy

All manuscripts, abstracts or other modes of presentation arising from the results of the trial must be reviewed and approved in writing by the Sponsor, in advance of submission. The

review is aimed at protecting the Sponsor 's proprietary information existing either at the date of the commencement of the study or generated during the trial.

Communication and/or publication of documents or data relating to this trial is not permitted without the written approval of the CEO of Sponsor.

10. REFERENCES

1. Cruse P. Wound infection surveillance. Rev Infect Dis. 1981;3(4):734-7.
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11. APPENDICES

APPENDIX 1 DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human participants

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975 35th World Medical Assembly, Venice, Italy, October 1983 41st World Medical Assembly, Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human participants must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research, which ultimately must rest in part on experimentation involving human participants.

In the field of biomedical research, a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person participating in the research.

Special caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human participants. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human participants must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human participants should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the

sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human participants should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human participant must always rest with a medically qualified person and never rest on the participant of the research, even though the participant has given his or her consent.

4. Biomedical research involving human participants cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the participant.

5. Every biomedical research project involving human participants should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the participant or to others. Concern for the interests of the participant must always prevail over the interests of science and society.

6. The right of the research participant to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the participant and to minimize the impact of the study on the participant's physical and mental integrity and on the personality of the participant.

7. Physicians should abstain from engaging in research projects involving human participants unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential participant must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the participant's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the participant is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the participant is a minor, permission from the responsible relative replaces that of the participant in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best-proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN

PARTICIPANTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The participant should be a volunteer - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The Investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the participant.

APPENDIX 2 INVESTIGATOR ICH GCP RESPONSIBILITIES

ICH GCP Section 4. Investigator Responsibilities

4.1 Investigator's Qualifications and Agreements

4.1.1 The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the application regulatory requirements(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulator authority(ies).

4.1.2 The Investigator should be thoroughly familiar with the appropriate use of the Investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The Investigator should be aware of, and should comply with, GCP and applicable regulatory requirements.

4.1.4 The Investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority (ies).

4.1.5 The Investigator should maintain a list of appropriately qualified persons to whom the Investigator has delegated significant trial-related duties.

4.2 Adequate Resources

4.2.1 The Investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable participants within the agreed recruitment period.

4.2.2 The Investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The Investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s) and their trial-related duties and functions.

4.3 Medical Care of Trial Participants

4.3.1 A qualified physician (or dentist, when appropriate), who is an Investigator or sub-Investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a participant's participation in a trial, the Investigator/institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The Investigator/intuition should inform a participant when medical care is needed for intercurrent illness (es) of which the Investigator aware.

4.3.3 It is recommended that the Investigator inform the participant's primary physician about the participant's participation in the trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.

4.3.4 Although a participant is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights.

4.4 Communication with IRB/IEC

4.4.1 Before initiating a trial, the Investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g. advertisements), and any other written information to be provided to participants.

4.4.2 As part of the Investigator's / institution's written application to the IRB/IEC, the Investigator / institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the Investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the Investigator/institution should provide to the IRB/IEC all documents participant to review.

4.5 Compliance with Protocol

4.5.1 The Investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority (ies) and which was given approval/favourable opinion by the IRB/IEC. The Investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The Investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/ favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) trial participants, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s)).

4.5.3 The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

4.5.4 The Investigator may implement a deviation from, or a change of, protocol to eliminate an immediate hazard(s) to trial participants without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, protocol amendments should be submitted:

- To the IRB/IEC for review and approval/favourable opinion,
- To the sponsor for agreement and, if required,
- To the regulatory authority (ies).

4.6 Investigational Product's(s)

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the Investigator / institution.

4.6.2 Where allowed/required, the Investigator/institution may/should assign some or all of the Investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the Investigator / institution.

4.6.3 The Investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the Investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor and (see 5.13.2 and 5.14.3) in accordance with applicable regulatory requirement(s).

4.6.5 The Investigator should ensure that the investigational product(s) are used to only in accordance with the approved protocol.

4.6.6 The Investigator, or a person designated by the Investigator / institution, should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instruction properly.

4.7 Randomisation Procedures and Unblinding

The Investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the Investigator should promptly document and explain to the sponsor any premature unblinding (e.g. accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 Informed Consent of Trial Participants

4.8.1 In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the Investigator should have the IRB/IEC's written approval/ favourable opinion of the written informed consent form and any other written information to be provided to participants.

4.8.2 The written informed consent form and any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The participant or the participant's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the Investigator, nor the, trial staff, should coerce or unduly influence a participant to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the participant or the participant's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the Investigator, the institution, the sponsor, or their agents liability for negligence.

4.8.5 The Investigator, or a person designated by the Investigator, should fully inform the participant or, if the participant is unable to provide informed consent, the participant's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including, the written informed consent form, should be as non-technical as practical and should be understandable to the participant or the participant’s legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the Investigator, or a person designated by the Investigator, should provide the participant or the participant's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the participant or the participant's legally acceptable representative.

4.8.8 Prior to a participant's participation in the trial, the written informed consent form should be signed and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.8.1 If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participants, is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the participant's legally acceptable representative from

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants should include explanations of the following:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The participant’s responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks.
- The compensation and/or treatment available to the participant in the event of trial-related injury.
- The anticipated prorated payment, if any, to the participant for participating in the trial.
- The anticipated expenses, if any, to the participant for participating in the trial.
- That the participant’s participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participants is otherwise entitled.
- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority (ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participant to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the participant's legally acceptable representative is authorizing such access
- That records’ identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the participant's identity will remain confidential.
- That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the trial.
- The person(s) to contact for further information regarding the trial and the rights of trial participants, and whom to contact in the event of trial- related injury.
- The foreseeable circumstances and/or reasons under which the participant's unduly participation in the trial may be terminated.

- The expected duration of the participant's participation in the trial.
- The approximate number of participants involved in the trial.

4.8.11 Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the participants. During a participant's participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to participants

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes participants who can only be enrolled in the trial with the consent of the participant's legally acceptable representative (e.g. minors, or patients with severe dementia), the participant should be informed about the trial to the extent compatible with the participants understanding and, if capable, the participant should sign and personally date the written informed consent participant may refuse to participate or withdraw from the trial, at any time,

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the participant), should be conducted in participants who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:

- The objectives of the trial cannot be met by means of a trial in participants who can give informed consent personally.
- The foreseeable risks to the participants are low.
- The negative impact on the participant's well-being is minimized and low.
- The trial is not prohibited by law.
- The approval/favourable opinion of the IRB/IEC is expressly sought on the
- Inclusion of such participants, and the written approval/favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be distressed.

4.8.15 In emergency situations, when prior consent of the participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible, and the participant's legally acceptable representative is not available, enrolment of the participant should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the participant and to ensure compliance with applicable regulatory requirements. The participant or the participant's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 Records and Reports

4.9.1 The Investigator should ensure the accuracy, completeness, legibility, and the timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initiated, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to Investigators and/or the Investigators' designated representatives on

making such corrections. Sponsors should have written procedures to assure that changes or corrections In CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the Investigator. The Investigator should retain records of the changes and corrections.

4.9.4 The Investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The Investigator / institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 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. These documents should be retain or a longer period however if required by the applicant regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the Investigator/institution.

4.9.7.1 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the Investigator/institution should make available for direct access all requested trial-related records.

4.10 Progress Reports

4.10.1 The Investigator should submit written summaries of the trial status to IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The Investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any

changes significantly affecting the conduct of the trial, and/or increasing the risk to participants.

4.11 Safety Reporting

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify participants by unique code numbers assigned to the trial participants rather than by the participants' names, personal identification numbers, and/or addresses. The Investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority (ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the Investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g. autopsy reports and terminal medical reports).

4.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the Investigator/institution should promptly inform the trial participants, should assure appropriate therapy and follow-up for the participants, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority (ies). In addition:

4.12.1 If the Investigator terminates or suspends a trial without prior agreement of the sponsor, the Investigator should inform the institution where applicable, and the Investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the Investigator should promptly inform the institution where applicable and the Investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the Investigator should inform the institution where applicable and the Investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 Final Report(s) by Investigator

Upon completion of the trial, the Investigator, where applicable, should inform the institution; the Investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority (ies) with any reports required.