Medline Industries, Inc.
www.medline.com

Three Lakes Drive
Northfield, IL 60093

1.847.949.5500
Toll Free: 1.800.MEDLINE

SINGLE DOSE PHARMACOKINETIC STUDY TO ASSESS THE SYSTEMIC EXPOSURE OF CHLORHEXIDINE FROM ReadyPrep® CHG (2% CHLORHEXIDINE GLUCONATE CLOTH)

Algorithme Pharma Protocol Number:	MDL-P2-670
Medline Protocol Number	R17-023
Investigational Product:	ReadyPrep® CHG (2% Chlorhexidine Gluconate Cloth)
Regulations:	FDA
Sponsor:	Medline Industries, Inc. Three Lakes Drive Northfield, IL 60093
Sponsor's contact person:	Alannah Minarcik Clinical Research Associate II Tel.: 847-643-3515 Fax: 866-758-4660 Email: AMinarcik@medline.com

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations.

Protocol Version	Date
1.0 (Original)	**2017/06/14**
2.2 (Amendment 01)	**2017/07/13**

TABLE OF CONTENTS

LIST OF TABLES

STUDY SYNOPSIS

Title of Study: Single Dose Pharmacokinetic Study to Assess the Systemic Exposure of Chlorhexidine from ReadyPrep® CHG (2% Chlorhexidine Gluconate Cloth)

Phase: Phase I study

Investigational Product: ReadyPrep® CHG (2% Chlorhexidine Gluconate Cloth)
Manufacturer: Medline Industries, Inc., USA

Treatments: Treatment-1: Abdominal application of ReadyPrep® CHG

Treatment-2: Groin application of ReadyPrep® CHG

Treatment-3: Control treatment with no application

Objective: The primary objective of this study is to demonstrate that no or negligible systemic exposure occurs after a single topical application of ReadyPrep® CHG.

The secondary objective of this study is to determine the safety and tolerability of a single topical application of ReadyPrep® CHG in healthy volunteers after a single topical application.

Study Design: Single center, randomized, single dose, laboratory-blinded, 3-period, 3-sequence, crossover design.

Subjects: Twelve (12) subjects will be included in the study

Main Inclusion Criteria: Male and female volunteers, non- or ex-smokers, ≥ 18 and ≤ 60 years of age (inclusive) with a body mass index (BMI) greater than or equal to 19.00 and below or equal to 32.00 kg/m^2 and a body weight ≥ 55 kg will be selected according to the inclusion and exclusion criteria. They will be healthy according to medical history, complete physical examination (including vital signs and skin examination) and laboratory tests (general biochemistry, hematology, urinalysis) including negative Human Immunodeficiency Virus (HIV), Hepatitis B and Hepatitis C tests as well as negative drug screening of alcohol, and drugs of abuse. For female subjects, a pregnancy test must be negative.

Administration: In Treatment-1 and -2, a single topical application of ReadyPrep® CHG consisting of a 3-minute vigorous rub followed by a 1 minute dry time will be done at the application site. In one study period, the application site

will be the abdomen (surface area of approximately 5 x 5 inches) and in the other study period, the application site will be the groin (surface area of approximately 5 x 2 inches).

Treatment-3 will consist of a control treatment where the same procedures as Treatment-1 and -2 will be performed, but without the topical application of ReadyPrep® CHG.

Subjects will remain seated for at least the first 4 hours following each treatment.

Blood Sampling: In each study period, 12 blood samples will be collected. Baseline levels will be assessed before each treatment. For baseline assessment, 3 blood samples will be collected prior to each treatment while the others will be collected up to 24 hours after each treatment.

Housing: From at least 10 hours prior to each treatment until 24 hours following each treatment.

Wash-out: The treatment will be separated by at least 7 calendar days.

Tests during study: Drug and alcohol screening will be performed before each period of the study.

For female subjects, a pregnancy test will be performed before each period of the study.

General biochemistry tests will be performed before each period of the study.

Vital signs will be measured prior to and approximately 12 and 24 hours following each treatment.

Visual skin evaluation at the application site will be performed prior to and approximately 4, 8 and 24 hours after treatment.

Poststudy Tests: Hematology, general biochemistry tests (including a pregnancy test for female subjects) and urinalysis will be repeated at the end of the study.

A complete physical examination (including vital signs) will be performed.

Safety data: Safety will be evaluated through the assessment of adverse events (AE), laboratory tests, vital signs, visual skin evaluation and physical examination.

Bioanalysis: Chlorhexidine plasma concentrations will be measured by a validated bioanalytical method.

Pharmacokinetics: In the event that chlorhexidine levels are measurable, the pharmacokinetic parameters will be estimated with and without baseline adjustment. Main absorption and disposition parameters will be assessed using a non-compartmental approach with a log-linear terminal phase assumption. Trapezoidal rule will be used to estimate the area under the curve. The pharmacokinetic parameters of interest will be C_{max}, AUC_{0-T} and $AUC_{0-\infty}$. Other parameters including T_{max}, $AUC_{0-T/\infty}$, $\lambda_{Z,}$ $T_{half,}$ Cl/F and V_d/F will be calculated and provided for information purposes only.

Statistics: No statistical analysis will be performed.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	Adverse Event
ALT:	Alanine Aminotransferase
ANDA:	Abbreviated New Drug Application
ASA:	Acetylsalicylic Acid
AST:	Aspartate Aminotransferase
BLQ:	Below Limit of Quantitation
BMI:	Body Mass Index
BPM:	Beats Per Minute
BUN:	Blood Urea Nitrogen
CV:	Coefficient of Variation
CFR:	Code of Federal Regulations
CRF:	Case Report Form
CYP:	Cytochrome P450
EDTA:	Ethylene Diamine Tetraacetic Acid
EMA:	European Medicines Agency
FDA:	Food and Drug Administration
g:	Relative Centrifugal Force
GCP:	Good Clinical Practice
GLP:	Good Laboratory Practice
GMP:	Good Manufacturing Practice
h:	Hour
HBsAG (B):	Hepatitis B Surface Antigen
HCV (C):	Hepatitis C Virus
HIV:	Human Immunodeficiency Virus
ICF:	Informed Consent Form
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
kg:	Kilogram
L:	Liter
ln:	Neperian log transformation
LOQ:	Limit of Quantitation
MCV:	Mean Corpuscular Volume
MedDRA:	Medical Dictionary for Regulatory Activities
mg:	Milligram
min:	Minute
mL:	Milliliters
mmHg:	Millimeter of Mercury
NDA:	New Drug Application
ng:	Nanograms
NSAIDs:	Non-steroidal Anti-inflammatory Drugs
OTC:	Over-the-counter

pH:	The Logarithm, On The Base 10, of The Reciprocal of The Hydrogen Ion Concentration
PK:	Pharmacokinetic
PR:	Time between P and R wave
PT:	Preferred Term
QA:	Quality Assurance
QC:	Quality Control
QRS:	Complex between Q and S wave
QTc:	QT Interval Corrected for Heart Rate
SAE:	Serious Adverse Event
SOC:	System Organ Class
SOP:	Standard Operating Procedure
SRA:	Scientific and Regulatory Affairs
ST:	ST segment of the Electrocardiogram
T:	T wave of the Electrocardiogram
ULQ:	Upper Limit of Quantitation

FACILITIES

AUTHOR OF THE PROTOCOL:	Julie Basque, MSc., Senior Clinical Research Scientist Algorithme Pharma 575 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4B3
CLINICAL FACILITY:	James Carlson, PharmD, Principal Investigator Jeffrey Peterson, MD, Medical Investigator Algorithme Pharma USA LLC 4837 Amber Valley Pkwy S Fargo, ND 58104
PHARMACY:	Retain Pharmacy Solutions 4837 Amber Valley Pkwy S Fargo, ND 58104
BIOMEDICAL FACILITY:	Sanford Health 737 Broadway Fargo, ND 58122
BIOANALYTICAL FACILITY:	Yves Moras, V-P, Bioanalytical Services Algorithme Pharma 575 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4B3
PHARMACOKINETIC FACILITY:	Marc Lefebvre, PhD, V-P, Scientific and Regulatory Affairs Algorithme Pharma 575 Armand-Frappier Blvd. Laval, Quebec, Canada H7V 4B3
STATISTICAL FACILITY:	Pascal Guibord, MSc, Senior Director, Biometrics Algorithme Pharma 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1
DATA MANAGEMENT FACILITY:	David Cote, Specialist, Data Management Algorithme Pharma 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1

PROJECT MANAGEMENT: Joanna Pohl, PhD., Project Manager
Algorithme Pharma
575 Armand-Frappier Blvd.
Laval, Quebec, Canada
H7V 4B3

PROTOCOL APPROVAL

ALGORITHME PHARMA PROTOCOL NUMBER: MDL-P2-670
MEDLINE PROJECT N° R17-023

TITLE: SINGLE DOSE PHARMACOKINETIC STUDY TO ASSESS THE SYSTEMIC EXPOSURE OF CHLORHEXIDINE FROM ReadyPrep® CHG (2% CHLORHEXIDINE GLUCONATE CLOTH)

We have carefully read this study protocol and agree it contains all necessary information required to conduct this study. We agree to conduct the study according to this protocol and in accordance with Good Clinical Practices and the applicable regulatory requirements:

James Carlson, PharmD
Principal Investigator
Algorithme Pharma USA LLC

2017/07/20
Date (yyyy/mm/dd)

MD

Jeffrey Peterson, MD
Medical Investigator
Algorithme Pharma USA LLC

Dr Instro for Peterson

2017/07/20
Date (yyyy/mm/dd)

PROTOCOL APPROVAL

ALGORITHME PHARMA PROTOCOL NUMBER: MDL-P2-670
MEDLINE PROJECT N° R17-023

TITLE: SINGLE DOSE PHARMACOKINETIC STUDY TO ASSESS THE SYSTEMIC EXPOSURE OF CHLORHEXIDINE FROM ReadyPrep® CHG (2% CHLORHEXIDINE GLUCONATE CLOTH)

I have carefully read this study protocol and agree it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with Good Clinical Practices and the applicable regulatory requirements:

Marc Lefebvre, PhD
Vice-President, Scientific and Regulatory Affairs
Altasciences Company Inc. (doing business as Algorithme Pharma)

2017/07/20
Date (yyyy/mm/dd)

PROTOCOL APPROVAL

ALGORITHME PHARMA PROTOCOL NUMBER: MDL-P2-670
MEDLINE PROJECT N^{o} R17-023

TITLE: SINGLE DOSE PHARMACOKINETIC STUDY TO ASSESS THE SYSTEMIC EXPOSURE OF CHLORHEXIDINE FROM ReadyPrep® CHG (2% CHLORHEXIDINE GLUCONATE CLOTH)

On behalf of the sponsor, I am aware of, and agree to comply with, all of the procedures contained within this protocol:

Alannah Minarcik

Digitally signed by Alannah Minarcik
DN: cn=Alannah Minarcik, o=Medline Industries, Inc., ou=Research and Development, email=aminarcik@medline.com, c=US
Date: 2017.07.20 14:51:29 -05'00'

Alannah Minarcik
Sponsor's Representative
Medline Industries, Inc.

Date (yyyy/mm/dd)

1. INTRODUCTION

Chlorhexidine [CHD; 1,1'-hexamethylenebis[5-(4-chlorophenyl) biguanide]] has a wide spectrum of bactericidal and antiviral activity and is a common ingredient in various formulations ranging from skin disinfectants in healthcare products to antiplaque agents in dentistry. The presence of two symmetrically positioned basic chlorophenyl guanide groups attached to a lipophilic hexamethylene chain aid in rapid absorption through the outer bacterial cell wall, causing irreversible bacterial membrane injury, cytoplasmic leakage, and enzyme inhibition. Chlorhexidine exists as various forms of salts: diacetate, dihydrochloride, or digluconate, mainly differing by their solubilizing abilities in aqueous or oily media. Chlorhexidine digluconate (or gluconate), as most soluble in water or alcohol, is the most used form in topical dermatology or cosmetic preparations.[1,2]

As chlorhexidine is not significantly absorbed through intact skin[3] no systemic adverse events are expected. However, skin reaction could occur.

ReadyPrep® CHG is composed of 2% chlorhexidine gluconate (CHG) solution on a single fiber, polyester cloth. Each cloth contains 500 mg CHG. The sponsor is developing ReadyPrep® CHG (2% Chlorhexidine Gluconate Cloth) for patient preoperative skin preparation.

In order to better understand and control for the presence of chlorhexidine in the environment, baseline levels will be assessed in each study period and a control treatment arm will be included.

2. STUDY OBJECTIVES

The primary objective of this study is to demonstrate that no or negligible systemic exposure occurs after a single topical application of ReadyPrep® CHG.

The secondary objective of this study is to determine the safety and tolerability of a single topical application of ReadyPrep® CHG in healthy volunteers after a single topical application.

3. STUDY TREATMENTS

3.1. INVESTIGATIONAL PRODUCT

ReadyPrep® CHG (2% Chlorhexidine Gluconate Cloth)
Manufacturer: Medline Industries Inc., USA

DOSAGE FORM: Cloth for topical application.

DOSAGE: Single topical application of ReadyPrep® CHG (2% Chlorhexidine Gluconate Cloth) on either the abdomen or the groin.

The investigational product will be provided by the sponsor. The lot number and the measured content of the dosage form (when available) will be included in the final report.

3.2. PACKAGING AND LABELING

The sponsor will be responsible for ensuring the investigational product is manufactured in accordance with Good Manufacturing Practice (GMP); the labeling should also comply with applicable regulatory requirement(s).

The investigational products will be dispensed according by Algorithme Pharma, unless the sponsor supplies Algorithme Pharma with pre-labeled individual dosing samples.

3.3. RANDOMIZATION AND UNBLINDING PROCEDURES

3.3.1. Treatment assignment

Algorithme Pharma will generate the randomization code with a computer program according to the study design, the number of subjects and the sequence

of treatment. The random allocation of each sequence of treatment to each subject will be done in such a way that the study is balanced. Once generated, the randomization code will be final and will not be modifiable.

3.3.2. Un-blinding procedure

The randomization code will not be available to the personnel of the bioanalytical facility until the bioanalytical tables have been finalized and audited by the Quality Assurance (QA) department.

3.4. DRUG ACCOUNTABILITY

Algorithme Pharma will maintain an inventory record of the investigational products received, stored in a secure restricted area, and dispensed as per State law. Investigational products will be provided to study subjects only.

At the conclusion of the study, all unused investigational products and all medication containers will be returned to the sponsor unless the sponsor has approved other arrangements. A final report of investigational product accountability will be prepared and maintained.

4. STUDY DESIGN AND DURATION

In two study periods, the ReadyPrep® CHG formulation will be administered as a single topical application to either the abdomen or the groin. Another study period will consist of a control treatment without topical application of ReadyPrep® CHG.

Treatment-1: Abdominal application of ReadyPrep® CHG

Treatment-2: Groin application of ReadyPrep® CHG

Treatment-3: Control treatment with no application

Twelve (12) healthy male or female subjects will be included in the studyaccording to the following randomized, 3-sequence, 3-period, crossover design:

	Period 1	**Period 2**	**Period 3**
Sequence 1 (n= 4)	Treatment-1	Treatment-2	Treatment-3
Sequence 2 (n= 4)	Treatment-2	Treatment-3	Treatment-1
Sequence 3 (n= 4)	Treatment-3	Treatment-1	Treatment-2

The drug applications will be separated by at least 7 calendar days. The duration of the clinical part of this study is expected to be approximately 17 days. The actual overall study duration may vary.

5. SELECTION OF STUDY POPULATION

5.1. NUMBER OF SUBJECTS

Twelve (12) subjects will be selected for inclusion in the study. A subject who withdraws subsequent to the pre-trial evaluations but before the application of the investigational product will not be considered as a drop-out and will not be included in the database. Standbys should be recruited and be available to replace a subject who withdraws prior to the first drug application. Drop-outs will not be replaced. Justification for the number of subjects is presented in section 9.4.

An effort will be made to include similar proportions of males and females in the study.

5.2. INCLUSION CRITERIA

Volunteers meeting all of the following criteria will be considered for enrollment in the study. A signed copy of the informed consent form will be provided to each subject.

1. Availability for the entire study

2. Motivated volunteer and absence of intellectual problems likely to limit the validity of consent to participate in the study or the compliance with protocol requirements; ability to cooperate adequately; ability to understand and observe the instructions of the physician or designee

3. Healthy adult volunteer

4. A female volunteer must meet one of the following criteria:
   a) Participant is of childbearing potential and agrees to use one of the accepted contraceptive regimens from at least 28 days prior to the first administration of the study drug, during the study and for at least 30 days after the last dose of the study drug. An acceptable method of contraception includes one of the following:
      - Abstinence from heterosexual intercourse
      - Systemic contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)

- Intrauterine device (with or without hormones)
- Condom with spermicide

or

b) Participant is of non-childbearing potential, defined as surgically sterile (i.e. has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or in a menopausal state (at least 1 year without menses)

5. Volunteer aged ≥ 18 and ≤ 60 years (inclusive)

6. Volunteer with a BMI greater than or equal to 19.00 kg/m^2 and below or equal to 32.00 kg/m^2

7. Volunteer with a body weight ≥ 55 kg

8. Non- or ex-smokers; an ex-smoker being defined as someone who completely stopped smoking for at least 3 months before study day 1

9. Clinical laboratory values within the laboratory's stated normal range; if not within this range, they must be without any clinical significance as determined by the medical investigator

10. Have no clinically significant diseases captured in the medical history or evidence of clinically significant findings on physical examination and/or clinical laboratory evaluations (hematology, general biochemistry, and urinalysis) as determined by the medical investigator

11. Willingness to adhere to the protocol requirements as evidenced by the informed consent form (ICF) duly read, signed and dated by the volunteer

The informed consent form must be signed by all volunteers prior to their participation in the study.

5.3. EXCLUSION CRITERIA

Volunteers presenting any of the following will not be included in the study:

1. Females who are pregnant or are lactating

2. Seated pulse rate less than 45 Beats per Minute (bpm) or more than 100 bpm at screening, unless deemed non-significant by the medical investigator.

3. Seated blood pressure below 100/60 mmHg or higher than 140/90 mmHg at screening, unless deemed non- significant by the medical investigator

4. History of significant hypersensitivity to chlorhexidine or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs

5. Presence of significant gastrointestinal, liver or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism or excretion of drugs or known to potentiate or predispose to undesired effects

6. History of significant gastrointestinal, liver or kidney disease that may affect drug bioavailability

7. Presence of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease

8. Volunteers who have presence of a skin condition, excessive hair, scar tissue, tattoo, piercing, skin coloration, open sores or sunburn at the application site that would interfere with application, or reactions to drug

9. Any method of hair removal (e.g. waxing, shaving, epilating, laser) at the application site 7 days prior to the first application as well as hair removal with tweezers at the application site 58 hours prior to the first application

10. Sunbathing and using tanning beds at the application site 7 days prior to the first application

11. Use of topical product containing medication for application (including creams, lotions, ointments, gels, topical solutions, patches; including salicylate-based topical creams or ointments) at the application site 14 days prior to the first application

12. Use of topical product without medication (including make-up, sunscreen, creams, lotions, powders, alcohol) at the application site 7 days prior the first application

13. Use of oral acetylsalicylic acid (ASA) and salicylic acid or any oral product containing ASA or salicylic acid, in the previous 7 days before study day 1

14. History of or disposition to seizures, state of confusion, clinically relevant psychiatric diseases

15. Maintenance therapy with any drug or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic)

16. Any clinically significant illness in the previous 28 days before study day 1

17. Use of any enzyme-modifying drugs, including strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) and strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin and St John's Wort), in the previous 28 days before study day 1

18. Any history of tuberculosis and/or prophylaxis for tuberculosis

19. Positive screening of alcohol, and/or drugs of abuse

20. Positive results from the hepatitis serology, except for vaccinated subjects or subjects with past but resolved hepatitis, at screening.

21. Positive results from the HIV serology at screening

22. Volunteers who have already been included in one group of this clinical study.
23. Volunteers who took chlorhexidine in the previous 28 days before study day 1

24. Volunteers who took an Investigational Product in the previous 28 days before study day 1

25. Volunteers who donated plasma in the previous 14 days before study day 1

26. Donation of 1 blood donation unit (American Red Cross, etc.) in the previous 56 days before study day 1

5.4. CRITERIA FOR REMOVAL OF A SUBJECT

Subjects will be allowed to discontinue their participation in the study at any time.

Subjects will be discontinued from the clinical study and/or period for any of the following reasons:

1. Use of oral ASA and salicylic acid or any oral product containing ASA or salicylic acid during the study
2. Sunburn, sunbathing and/or use of topical medication/product at the application site during the study
3. Hair removal at the application site during the study
4. Presence of any skin condition that would interfere with the application of the study medication
5. Females who are pregnant according to a positive pregnancy test
6. Clinically significant laboratory values before each period, as judged by the Principal Investigator or designee
7. Positive screening of alcohol and/or drugs of abuse

Furthermore, participation in the clinical study and/or period could be discontinued by the physician in charge of the study or by the sponsor for any of the following reasons:

1. Adverse events;
2. Significant protocol violation;
3. Difficulties with blood collection;
4. The subject is uncooperative during the study

The PK facility can, with sponsor's approval, also remove a subject from the study due to an unanticipated event that could result in an inadequately characterized pharmacokinetic profile, such as a missed blood draw, an adverse event, meal deviations or concomitant medications.

Details of reasons for removal of subjects will be recorded, reported to the sponsor and documented in the clinical study report.

5.5. RESTRICTIONS

Each subject will be questioned on the specific points listed below prior to each treatment. If a subject admits non-compliance with any of these restrictions, the Principal Investigator (or designee) and/or the sponsor will decide whether the subject will be permitted to remain in the study. Non-compliance with these restrictions will be noted.

5.5.1. Medications

In addition to the drugs prohibited as per the exclusion criteria, subjects will be requested to abstain from taking any other prescription medications used with the intention to treat a condition for 28 days prior to the first treatment and during the study, unless judged differently by the Principal Investigator or designee.

Systemic contraceptives and hormone replacement therapy will be permitted.

Subjects will also be requested to abstain from taking any over-the-counter (OTC) products for 7 days prior to the first treatment and during the study. They will be specifically reminded that this includes cold preparations, non-steroidal anti-inflammatory drugs (NSAIDs), vitamins and natural products used for therapeutic benefits and antacid preparations.

Vitamins used as nutritional supplements in non-therapeutic doses (as judged by the Principal Investigator or designee) may be accepted, but they must be stopped at least 48 hours prior to the first treatment and during the study.

Subjects will be instructed not to apply topical products without medication (including make-up, sunscreen, creams, lotions, powders, alcohol) to the skin area where the drug will be applied from 7 days prior to the first treatment until the end of the study.

Subjects will be instructed not to apply topical product containing medication for application (including creams, lotions, ointments, gels, topical solutions, patches; including salicylate-based topical creams or ointments) to the skin area where the drug will be applied from 14 days prior to the first treatment until the end of the study.

If a medication (including OTC) other than those specified in the protocol is used after the first treatment or at any time before the end of the study, the Principal Investigator or designee and/or the sponsor will decide whether the subject will be permitted to remain in the study, depending on the drug used, the time of drug intake, etc. The drug and dose will be noted.

5.5.2. Alcohol

Subjects will be requested to abstain from alcohol for 58 hours prior to each treatment and during each study period. Throughout the study in case of any doubt about alcohol consumption, a test for alcohol may be performed if requested by the physician.

5.5.3. Xanthines

Subjects will be requested to avoid food or beverages containing xanthines (i.e. tea, coffee, cola drinks, energy drinks or chocolate) for 58 hours prior to each treatment and during each study period.

5.5.4. Fluids

Fluid intake other than water will be controlled for each housing period and for all subjects. Water will be provided *ad libitum* during the housing periods.

Non-carbonated, non-xanthine and non-grapefruit fluids will be provided during the housing periods.

5.5.5. Food

Food will be controlled and standardized for all subjects for each housing period. Meals and snacks will be served at appropriate times.

5.5.6. Grapefruit, Seville Oranges, poppy-seed and pomelo-containing beverages and food

Subjects will be instructed to avoid food or beverages containing grapefruit, Seville oranges and/or pomelo for 7 days prior to the first treatment and during the study.

Food or beverages containing poppy-seeds should also be avoided for 36 hours prior to the first treatment and during the study.

5.5.7. Posture and physical activities

Subjects will remain seated for at least the first 4 hours following each treatment. However, should adverse events occur, subjects may be placed in an appropriate position. During this interval subjects will be permitted, under supervision, to leave their seats for brief periods, e.g. to use the washroom facilities or for blood sampling (if necessary). After this 4-hour period, subjects may get up, but only under supervision. Subjects will not engage in strenuous activity at any time during the housing periods.

5.5.8. Contraceptive regimen throughout the study

Female volunteers of childbearing potential will have to take appropriate measures to prevent pregnancy for at least 28 days prior to the first treatment, during the study and for at least 30 days after the last treatment, as described in section 5.2.

5.5.9. Other Activities

Subjects will be instructed that sunbathing and using tanning beds at the area intended for drug application is not allowed from 7 days prior to the first treatment and throughout the study in order to avoid sunburn at the application site.

Subjects will be instructed not to shave, wax, epilate or laser (for hair removal) the skin area where the drug will be applied from 7 days prior to the first treatment until the end of the study. Moreover, subjects will be instructed not to remove hair with tweezers to the skin area where the drug will be applied for 58 hours prior to the first treatment until the end of the study.

In each study period, subjects will be required to not take a shower for 2 hours prior to the treatment until departure from the clinical site.

6. CLINICAL PROCEDURES

Unless otherwise stated in this protocol, SOPs of the clinical site, which are available for all activities relevant to the quality of the study, will be followed during this study. The different parts of this study are summarized in Table 1 and explained in the following sections.

6.1. DESCRIPTION OF STUDY DAYS

6.1.1. Pre-trial evaluation

Potential study volunteers will be examined before the start of the study to determine their eligibility for participation. These tests are to be conducted no more than 28 days before the start of the study. The following examinations will be performed:

6.1.1.1. Medical history

The medical history will include evaluation of ears, nose, throat and any ophthalmological, cardiovascular, respiratory, musculoskeletal, gastrointestinal, genitourinary, neurological, endocrine, psychiatric, immunological or allergic, dermatological, hematological, family history disorder or disease.

6.1.1.2. Physical examination

The physical examination will include measurement of vital signs (blood pressure, pulse rate, respiratory rate and body temperature) and a review of the following: head and neck, heart, lungs, abdomen and general appearance. Skin examination at the application sites will be performed.

Demographic data (age, gender, race, ethnicity, body weight adjusted for indoor clothing, height, BMI), and alcohol and smoking habits will be recorded.

6.1.1.3. Laboratory tests

General Biochemistry: Sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, bilirubin total, alkaline phosphatase, AST, ALT, albumin, calcium, carbon dioxide, inorganic phosphate, magnesium, total protein and uric acid

Hematology: White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and

basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), and platelets count

Urinalysis: Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein

6.1.1.4. Other laboratory tests

Serology: HIV Ag/Ab Combo, Hepatitis B (HBsAg (B)) and Hepatitis C (HCV (C))

Drug Screen: Alcohol, amphetamines, barbiturates, cannabinoids, cocaine, opiates, oxycodone and benzodiazepine

A pregnancy test will be performed on female subjects.

6.1.1.5. Other tests

Additional laboratory tests may be also performed by the medical laboratory as part of larger standard tests panels although not required for the subject's safety. All test results will be assessed by physician for clinical significance. Only test results required by the protocol and/or abnormal results will be entered in the clinical database and reported in the Clinical Study Report, based on the report requirement.

6.1.2. Study days

The following procedures will be applied for each period of the study:

Subjects will be admitted to the clinical site up until at least 10 hours prior to drug administration.

Screening of alcohol and drugs of abuse will be performed at the subjects' arrival, prior to drug application.

A pregnancy test will be performed at the female subject's arrival, prior to drug application.

General biochemistry tests will be performed before each period of the study.

The first baseline blood sample will be collected 10 hours prior to each treatment (T = -10.00). After a supervised overnight fast, the subjects will be awakened, vital signs (blood pressure, pulse rate, respiratory rate and body temperature) will be measured, visual skin evaluation at the application site will be performed and the 2 other baseline blood samples (T= -2.00 and -0.50) will be collected. *Pre-dose vital signs should be done within 120 minutes of drug application.*

Serial blood sampling will follow drug administration (details in section 6.2.1).

Vital signs (blood pressure and pulse rate) will be assessed twice after treatment (details in section 6.3).

Visual skin evaluation at the application site will be performed several times after treatment (details in section 6.3).

Subjects may leave the clinical site at least 24 hours after treatment. However, they will be advised to stay at the clinical site, if judged necessary by the physician in charge, for safety reasons. A card identifying the medication 'Chlorhexidine Gluconate' will be distributed to all subjects prior to departure from the clinical site in period 1. This card is given to subjects in order for them to inform the hospital / doctors they are participating in a clinical trial in case of a medical emergency.

6.1.2.1. Drug administration procedure

ReadyPrep® CHG Application (Treatment-1 and Treatment-2):

In two Treatment-1 and -2, a single topical application of ReadyPrep® CHG will be done on either the abdomen (surface area of approximately 5 x 5 inches) or the groin (surface area of approximately 5 x 2 inches) according to the randomization scheme.

The drug will be applied to a clean, dry, non-irritated, normal skin area. Possible hairs will be removed by means of scissors (no shaving) on the morning of dosing.

Approximately 30 minutes prior to any application, the site should be gently washed with room temperature water and dried without rubbing or heavy pressure with a gauze or similar cotton soft material. The application site must be allowed to dry for at least 15 minutes before drug application. After drying, the application site will be marked for dose location.

The topical application of ReadyPrep® CHG will consist of a 3-minute vigorous rub followed by a 1 minute dry time at the application site. The

1-minute dry time will be air drying without dabbing or rubbing. The time of dosing will be defined as the start time of the drug application on the skin.

Control Treatment (Treatment-3):

In Treatment-3, the same procedures as Treatment-1 and -2 will be performed, but without the topical application of ReadyPrep® CHG or placebo (no placebo ReadyPrep® cloth will be provided or used). Therefore, approximately 30 minutes prior, the site should be gently washed with room temperature water and dried without rubbing or heavy pressure with a gauze or similar cotton soft material. The application site must be allowed to dry for at least 15 minutes and after drying, the skin site will be marked. Subjects should be placed in the same position, for the same length of time, in the same area as they would be dosed.

The physician will remain at the clinical site for at least the first 4 hours following each treatment and will remain available at all times during the entire period of the study.

6.1.3. End of the study

The following poststudy tests will be performed at the end of the study.

For subjects whose participation in this clinical study is discontinued during the course of the trial, every effort will be made to perform the poststudy tests as soon as possible after discontinuation.

6.1.3.1. Physical Examination

The physical examination will include measurement of vital signs (blood pressure, pulse rate, respiratory rate and body temperature) and a review of the following: head and neck, heart, lungs, abdomen and general appearance

6.1.3.2. Laboratory tests

General Biochemistry: Sodium, potassium, chloride, glucose (random), blood urea nitrogen (BUN), creatinine, bilirubin total, alkaline phosphatase, AST, ALT, albumin, calcium, carbon dioxide, inorganic phosphate, magnesium, total protein and uric acid

Hematology: White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and

basophil), red cell count, hemoglobin, hematocrit, MCV, and platelets count

Urinalysis: Color, clarity, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if dipstick test is outside the reference range for leukocyte, blood, nitrite or protein

Additional laboratory tests may be also performed by the medical laboratory as part of larger standard tests panels although not required for the subject's safety. All test results will be assessed by physician for clinical significance. Only test results required by the protocol and/or abnormal results will be entered in the clinical database and reported in the Clinical Study Report, based on the report requirement.

6.1.3.3. Other laboratory tests

A pregnancy test will be performed on female subjects at the end of the study.

6.1.3.4. Other tests

No other tests will be performed at the end of the study.

6.2. SAMPLING DURING THE STUDY

6.2.1. Blood sampling

In order to better understand and control for the presence of chlorhexidine in the environment, baseline levels will be assessed in each study period.

For baseline assessment, 3 blood draws will be performed prior to each treatment. A total of 12 blood samples will be collected (one tube of 6 mL each) in each study period. Samples will be collected into labeled tubes containing the appropriate anticoagulant as specified by the bioanalytical facility.

The complete schedule for each study period is presented in Table 2. The time of blood sample collection will be calculated according to the drug application schedule. The clock time of all blood draws will be recorded and reported for all subjects. For postdose samples, all deviations from the scheduled sampling time of 2 minutes or more will be reported in the final report.

The total volume of blood withdrawn, including ~20 mL required for screening, pre-dose and poststudy tests, should be approximately 236 mL per subjects. The total blood donation may be higher if repeat blood samples are required for safety assessments.

6.2.2. Urine sampling

No urine samples will be collected during the course of this study, other than for screening prior to each drug administration, as well as for safety reasons at the end of the study.

6.2.3. Sample processing, storage and shipping

Blood samples will be processed, split, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

6.3. SAFETY MONITORING

6.3.1. Vital signs

Blood pressure, pulse rate, respiratory rate and body temperature will be recorded within 120 minutes prior to each treatment, and at approximately 12 and 24 hours after each treatment. Vital signs will be monitored subsequently, if judged necessary by the medical investigator or designee.

6.3.2. ECG records

ECG will be recorded if judged necessary by the physician in charge.

6.3.3. Visual skin evaluation

Visual skin evaluation of the application site will be performed by the physician in charge or designee as follows:

Application site verification (for redness, markings, scars, etc.) will be documented prior to and approximately 4, 8 and 24 hours after each treatment.

6.3.4. Other measurements

General biochemistry tests will be performed before each period of the study.

7. ADVERSE EVENTS

7.1. DEFINITIONS

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

An adverse event may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study medication including comparator; it could be an abnormal laboratory value as well as a significant shift from baseline within normal range which the Medical Investigator considers to be clinically important

Abnormalities in laboratory tests, in the measurements of vital signs, in visual skin evaluation or in other measurements performed after drug application or at the end of the study are to be recorded as adverse events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to study discontinuation and/or fulfilling a seriousness criterion. If asymptomatic, but with a suspected underlying process, the Medical Investigator may consider the abnormalities to be medically relevant.

Surgical procedures themselves are not adverse events. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an adverse event, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A serious adverse event (SAE) or reaction is any untoward medical occurrence that at any dose:

- Results in death

- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions)
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the Medical Investigator)

7.2. SEVERITY ASSESSMENT

All adverse events will be graded as mild, moderate, or severe according to the following definitions:

Mild: Causing no limitation of usual activities; the subject may experience slight discomfort.

Moderate: Causing some limitation of usual activities; the subject may experience annoying discomfort.

Severe: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

Every effort will be made to obtain an adequate evaluation of the severity.

7.3. CAUSALITY ASSESSMENT

The Medical Investigator will determine the relationship of any adverse event to the Investigation Product according to the following criteria:

TERM	DEFINITION
Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the investigational product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational product. In case of cessation or reduction of the dose the AE may abate or resolve and it may reappear upon rechallenge.
No Reasonable Possibility	Evidence exists that the adverse event has an etiology other than the investigational product. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

7.4. DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

For the purposes of this study, the period of observation of adverse events extends from the pre-trial evaluation until the end of the study. From screening to the first dose of the study, they will be recorded as screening events or as part of the medical history, as applicable. When AEs occur after initiation of study medication, they will be indicated as treatment-emergent AEs in the clinical study report. During the study, all adverse events spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded for all subjects and reported in the CRF.

If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw early from the study, they will be advised of the safety precautions to be taken.

Subjects will be questioned on their health status at the beginning of each study period and before each departure from the clinical site. Open-ended questions will be asked.

Classification will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or higher.

7.5. SERIOUS ADVERSE EVENT REPORTING REQUIREMENTS

The clinical site will notify any SAE to the sponsor, without regard to causality, within 24 hours after becoming aware of its occurrence. This notification will contain a description of the observed symptoms and an assessment of causality. A detailed report will be sent in the following days.

The notification, in English, should be directed to the following sponsor representative:

Alannah Minarcik, Clinical Research Associate II
Medline Industries, Inc.
Tel. (847) 643-3515 (Working hours)
Tel. (630) 327-0532 (nights, weekends, and holidays)
Fax. (866) 758-4660

Email:aminarcik@medline.com

A SAE will be considered as "unexpected" when the nature or severity is not consistent with information in the relevant source document(s).

Algorithme Pharma will determine whether any serious unexpected related adverse event must be reported to the IRB. If so, the event will be reported via fax or email within 15 calendar days of the investigator or staff becoming aware of the event.

The sponsor will be responsible for notifying FDA and all participating investigators of any SAE observed during conduct of the study, regardless of whether the event is considered drug related, as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence. If the adverse event is fatal or life-threatening, the sponsor must also notify the Clinical Safety Coordinator in CDER's Office of Generic Drugs as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence.

7.6. PREGNANCY

Pregnancy in a female subject in the study shall be reported to the sponsor within 24 hours of the knowledge of its occurrence by the clinical site (for pregnancies occurring during the course of the study or immediately following the end of the study). Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the clinical site to the sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on a SAE Report Form.

8. METHODS OF EVALUATION

8.1. DRUG CONCENTRATIONS

8.1.1. Bioanalytical assays

Chlorhexidine plasma concentrations will be measured according to a validated bioanalytical method.

The validated range can be truncated when less than 5 calibration standards appear to be below the expected C_{max}, provided that this new calibration curve range is validated prior to use.

In the event that the study is conducted in multiple groups, sample analysis will begin only after completion of the clinical portion of the last group (i.e. after the last sample is collected).

Where possible, all samples from each subject will be analyzed on the same standard curve. Quality control samples will be distributed through each batch of study samples assayed. Samples with drug concentrations greater than the upper limit of quantification (ULQ) of the assay range will be diluted with the appropriate drug-free biological fluid and re-assayed; those which are below the lower limit of this range will be reported as being below limit of quantitation concentrations (BLQ). The analysts will not have access to the randomization scheme.

8.1.2. Aberrant values and retested samples

Unacceptable values attributable to bioanalytical reasons will be determined by the bioanalytical facility. Such re-assayed samples will be termed “repeats”. All cases of re-assay will be reported in the final report.

No samples will be repeated for pharmacokinetic reasons.

8.1.3. Incurred sample reproducibility

In order to establish the reproducibility of the assay with incurred samples, at least 10% of the total analyzable study samples will be selected and re-assayed. The replicate measurement is not to be averaged with the original one, but both values will be presented in the bioanalytical report with the initial value being used for PK calculations. The concentrations of the original and replicate samples will be tabulated, along with the percent difference between the two values.

8.2. SAFETY DATA

The safety population will include all subjects who received at least one treatment under study.

Descriptive statistics will be used to summarize adverse events, safety results and demographic variables (age, height, weight and BMI).

The laboratory tests and the measurements of vital signs, visual skin evaluation and other safety parameters performed after treatment are mainly performed for safety reasons, and changes may occur without any clinical symptoms. Therefore, any significant changes will be recorded as adverse events only if they are judged clinically significant by the Medical Investigator.

The laboratory tests will be carried out according to the standard operating procedures of the licensed medical laboratory. Abnormal results will be verified to rule out laboratory error. Persistent relevant abnormal values should be followed up until the cause is determined or until the values return to the pre-medication value.

9. PHARMACOKINETICS AND STATISTICS

9.1. SUBJECTS TO ANALYZE

Samples from all subjects who received at least one treatment and for whom sufficient number of blood samples was taken for pharmacokinetic analysis will be assayed and included in the pharmacokinetic analysis.

Subjects who do not complete the sampling schedule of one or more study periods may be included in the pharmacokinetic analysis for only the PK parameters that are judged not to be affected by the missing sample(s). This decision is to be documented by the SRA department and approved by the sponsor before the start of the sample analysis by the bioanalytical facility.

9.2. PHARMACOKINETIC ANALYSIS

No or negligible plasma levels of chlorhexidine are expected following a single topical application of ReadyPrep® CHG. Chlorhexidine plasma concentrations produced by each treatment will be determined in order to establish the pharmacokinetic profile of the drug product. Below limit of quantitation concentrations (coded BLQ) will be treated as zero for all statistical analyses. In the event that chlorhexidine levels are measurable, the pharmacokinetic parameters that will be derived from the plasma concentrations *versus* time profiles are listed in Table 3. All reported sampling time deviations (see Section 6.2.1) will be taken into consideration for evaluation of PK parameters.

In the case where concentrations of chlorhexidine cannot be determined due to bioanalytical or clinical reasons, these values will be set to missing for the pharmacokinetic analysis.

In the case where less than 3 consecutive measurable concentrations of chlorhexidine are observed, the AUC parameters will not be estimated for that specific study period.

In order to better understand and control for the presence of chlorhexidine in the environment, baseline levels will be assessed in each study period. The pharmacokinetic parameters for chlorhexidine will be presented both adjusted for baseline and unadjusted. The baseline adjustment will consist of the following:

- Baseline concentrations will be measured approximately 10.00, 2.00 and 0.50 hours prior to each treatment. The mean of these 3 pre-dose concentrations will be used for baseline adjustment.

- Concentrations post-dose will be adjusted for each subject during each period by subtracting the mean baseline value corresponding to that subject. Baseline adjustment will therefore be subject- and period- specific.

If subtraction leads to values of adjusted profile that would be below the LOQ, these values will be reported without any change and they will not be reported as BLQ. However, if a negative plasma concentration value results after baseline adjustment, this value will be set to 0 prior to calculating the baseline-adjusted AUC.

For baseline adjusted calculations, concentrations at time T= -0.50 h will be set to zero given that no concentration provided by the given treatment is expected to be present at this time point. Unadjusted baseline PK estimation will use the observed concentration value at time T=-0.50 h.

The main pharmacokinetic parameters of interest for this study will be C_{max}, AUC_{0-T} and $AUC_{0-\infty}$. Other parameters such as T_{max}, $AUC_{0-T/\infty}$, λ_Z and T_{half} will be provided for information purposes only.

The main absorption and disposition parameters will be estimated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule will be used to estimate the area under the curve (linear trapezoidal linear interpolation) and the terminal phase will be estimated by maximizing the coefficient of determination estimated from the log-linear regression model. However, $AUC_{0-\infty}$, $AUC_{0-T/\infty}$, λ_Z and T_{half} parameters will be estimated for individual concentration-time profiles only when the terminal log-linear phase can be reliably characterized using the following criteria:

- Phoenix® WinNonlin® Best fit range selection
- R^2 of at least 80%
- The corresponding terminal half-life value must be lower than or equal to 2 times the time interval over which λ_Z was estimated (i.e. $T_{half} \leq$ twice the time interval difference between T_{LQC} and T_{LIN}).

Descriptive statistics will be calculated for plasma concentrations at each individual time point and for all pharmacokinetic parameters. The individual plasma concentration/time profiles will be presented using the actual sampling times whereas the mean plasma concentration/time profiles will be presented using the theoretical sampling times.

Pharmacokinetic analyses will be generated using validated pharmacokinetic software (i.e. Phoenix® WinNonlin® version 6.3 or higher, Phoenix® Connect™ version 1.3.1 or higher).

9.3. STATISTICAL ANALYSIS

No statistical analysis will be performed.

9.4. SAMPLE SIZE JUSTIFICATION

The objective of this study is to demonstrate that no or negligible systemic exposure occurs after a single topical application of ReadyPrep® CHG. Based on the sponsor's data, it is estimated that 12 subjects should be sufficient to meet this objective.

10.REGULATORY REQUIREMENTS

10.1. LIABILITIES

It is the sponsor's responsibility to guarantee sufficient insurance coverage should any serious events or deaths result directly or not from the execution of the present protocol.

The present article is not to be interpreted as engaging the sponsor's responsibility in the event of fault or negligence of the subjects, investigators, or any persons or employees under the control of the clinical site.

10.2. STATEMENT OF INVESTIGATOR

The FDA 1572 form, Statement of Investigator [Title 21, CFR Part 312], will be signed by the Principal Investigator, and will be kept on file and will remain available upon request.

10.3. DELEGATION OF INVESTIGATOR DUTIES

The Principal Investigator will ensure all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Principal Investigator will maintain a list of sub-investigator(s) and other appropriately-qualified persons to whom he delegates significant trial-related duties.

Should the Principal Investigator delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical legal qualifications. The Principal Investigator should also ensure key staff personnel have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

10.4. INSTITUTIONAL REVIEW BOARD (IRB)

This protocol and the ICF will be submitted to an IRB (or IEC) prior to initiation of the study and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the final report.

This study will be conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the ICH Guideline E6

for GCP, the FDA GCP Code of Federal Regulations (CFR) Title 21 (part 56), and the European regulation EU 536/2014.

10.5. INFORMED CONSENT FORM (ICF)

Before screening activities can commence, each volunteer will be given a copy of the consent to read, and a full explanation of the purpose of the study, the procedures to be carried out, and the potential adverse event(s). Once this essential information is provided to the volunteer and the medical investigator or designee has the conviction the volunteer understands the implications of participating in the study, if the volunteer(s) chooses to continue screening, they will be requested to sign and date a properly executed written informed consent document in compliance with the U.S. Code of Federal Regulations (Title 21, Part 50). Subjects will be assured they may withdraw from the study at any time without jeopardizing their medical care or future study participation (for which they qualify). They will be given a signed copy of the informed consent.

If an amended or revised ICF is introduced during the study, each subject's further consent should be obtained.

10.6. CASE REPORT FORM

Data required by the protocol will be accurately reported on the CRF for each subject included (i.e., who received an Investigational Product treatment) in a clinical trial. The complete CRF will be approved and signed by the Principal Investigator or designee, who will receive a signature delegation from the investigator.

A copy of the CRFs will be provided to the sponsor with the final report.

10.7. RECORD RETENTION

All essential documents and records will be maintained by the clinical site in accordance with, and for the period specified in the applicable regulatory requirement(s) (FDA CFR 312.57 (C)).

10.8. QUALITY ASSURANCE/QUALITY CONTROL

Designated personnel from Algorithme Pharma will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH Guideline E6 for Good Clinical Practices, applicable requirements as outlined in the FDA and OECD Principles of GLP, and the *Reflection paper for*

laboratories that perform the analysis or evaluation of clinical trial samples (EMA/INS/GCP/532137/2010).

10.9. MONITORING OF THE STUDY

The sponsor or its representative may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. The clinical site will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

10.10. DATA MANAGEMENT AND PROCESSING

Data management activities will be performed using either Clintrial™ or the Medrio electronic data capture software in accordance with Algorithme Pharma's standard operating procedures.

Data entered will be checked at the point of entry and through validations for accuracy. When the database is declared to be complete and accurate, it will be locked.

10.11. PREMATURE TERMINATION OR SUSPENSION OF A STUDY

The sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, the clinical site or the Principal Investigator (or designee) should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority(ies) when required.

10.12. ADHERENCE TO PROTOCOL

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and FDA guidelines. Any deviation from the protocol will be recorded and explained.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB for approval.

11.REFERENCES

1. Nicolay, A. et al., Rapid HPLC Method for Determination of Parachloroaniline in Chlorhexidine Antiseptic Agent in Mouthrinses, Ophthalmic and Skin Solution, American Journal of Analytical Chemistry, 2011, 2, 422-428
2. 2% Chlorhexidine gluconate cloth [Label] (06/24/2014). NDA 021669, Drugs@FDA, FDA Web site. http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed 2017/05/17.
3. Center for Drug Evaluation and Research, Application Number 21-669, Pharmacology Review

Table 1. Study Design and Schedule of Assessments

	Pre-Trial	Period 1			Wash-Out	Period 2			Wash-Out	Period 3			End of Study
Days [a]	-28 to -1	-1	1	2	1-7	7	8	9	8-14	14	15	16	16
Informed Consent Form Signed [b]	X												
Admission to Unit		X				X				X			
Medical History	X												
Physical Examination	X												X
Laboratory Tests	X	X[c]				X[c]				X[c]			X
HIV Ag/Ab Combo, HBsAg (B) and HCV (C) Tests	X												
Alcohol and Drugs of Abuse Screening	X	X				X				X			
Pregnancy Test	X	X				X				X			X
Vital Signs	X		X	X			X	X			X	X	
Visual Skin Evaluation	X		X	X			X	X			X	X	
Drug Application			X				X				X		
Blood Sampling		X	X	X		X	X	X		X	X	X	
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X

a The days assigned to each period may change according to the exact wash-out determined between the drug administrations
b The last version must be signed prior to subject's inclusion (first drug administration)
c General biochemistry only

Table 2. Blood Sampling Schedule

Sample No	Sampling Time (hours)	Clock time*
01	-10.00**	21:00
02	-2.00**	05:00
03	-0.50**	06:30
04	1.00	08:00
05	2.00	09:00
06	3.00	10:00
07	4.00	11:00
08	5.00	12:00
09	6.00	13:00
10	8.00	15:00
11	12:00	19:00
12	24:00	07:00

* Clock time may change according to the exact time of drug administration. Study medications will be applied to each subject consecutively for the purpose of accurate sampling time.

** Before treatment

Table 3. Pharmacokinetic Parameters

C_{max}	Maximum observed plasma concentration
T_{max}	Time of maximum observed plasma concentration; if it occurs at more than one time point, T_{max} is defined as the first time point with this value
T_{LQC}	Time of last observed quantifiable plasma concentration
AUC_{0-T}	Cumulative area under the plasma concentration time curve calculated from 0 to T_{LQC} using the linear trapezoidal method
$AUC_{0-\infty}$	Area under the plasma concentration time curve extrapolated to infinity, calculated as $AUC_{0-T} + C_{LQC}/\lambda_Z$, where C_{LQC} is the measured concentration at time T_{LQC}
$AUC_{0-T/\infty}$	Relative percentage of AUC_{0-T} with respect to $AUC_{0-\infty}$
T_{LIN}	Time point where the log-linear elimination phase begins
λ_Z	Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration *versus* time curve
T_{half}	Terminal elimination half-life, calculated as $\ln(2)/\lambda_Z$

APPENDIX 1: AMENDMENT 01

RATIONALE:

Reason for amendment:

1) The study design was updated to control for the presence of chlorhexidine in the environment.
2) To exclude the use of oral acetylsalicylic (and salicylic acid) at screening and on-study as these compounds may interact with the bioanalytical assay of chlorhexidine.
3) To correct a discrepancy in Table 1

Requested by:

1) Algorithme Pharma and Medline
2-3) Algorithme Pharma

TEXT OF AMENDMENT:

Amendment 01:

1) A control treatment with no topical application of ReadyPrep® CHG or placebo was added to the study. The study design is now a single center, randomized, single dose, laboratory-blinded, 3-period, 3-sequence, crossover design. The protocol and ICF were updated accordingly.

2) Baseline levels, consisting of 3 blood samples, will be assessed before each treatment. In the event that chlorhexidine levels are measurable, the pharmacokinetic parameters will be estimated with and without baseline adjustment. The protocol and ICF were updated accordingly.

3) 'Drug application' was changed to 'treatment' throughout the protocol and ICF.

4) Protocol and ICF were updated to exclude the use of oral acetylsalicylic acid (ASA) and salicylic acid or any oral product containing ASA or salicylic acid, in the previous 7 days before study day 1 and during the study

5) The line for Drug Removal was deleted from Table 1 as this is not applicable

AUTHORED BY:

_____ _____

Julie Basque, M.Sc., Date (yyyy/mm/dd)
Senior Clinical Research Scientist
Altasciences Company Inc. (doing business as Algorithme Pharma)