USZ Universitäts Spital Zürich

Clinical Study Protocol

EFFECTS OF PHOTODYNAMIC THERAPY ON THE HUMAN INGUINAL SKIN MICROBIOME TO IMPROVE ANTISEPTIC EFFECT – PILOT 2

SHORT TITLE: Effect of photodynamic therapy on skin microbiome (PHOMIC-II)
Single center study

Study Type:	Health-related intervention
Study Categorization:	Other Clinical Trial Category *A*
Study Registration:	*Bundesamtes für Gesundheit: www.kofam.ch.* Fill out after ethical approval *International trial registry ClinicalTrials.gov (clinicaltrials.gov)* NCT04618276
Study Identifier:	*To fill out after ethical approval* *Sponsor study Identifier: PHOMIC-II*
Sponsor-Investigator and Principal Investigator:	*PD Dr. med. Yvonne Achermann* University Zurich *Division of Infectious Diseases and Hospital Hygiene* *Yvonne Achermann, MD* *University Hospital Zurich* *Rämistrasse 100, 8091 Zürich* *Switzerland* Phone: *044 255 34 02* E-Mail: yvonne.achermann@usz.ch
Study Intervention:	*Effects of photodynamic treatment on skin microbiome*
Protocol Version and Date:	*V04, 27.11.2020*

SIGNATURE PAGE

Study number	*Not yet* *Bundesamtes für Gesundheit: www.kofam.ch.* *International trial registry ClinicalTrials.gov (clinicaltrials.gov)*: *NCT04618276*
Study Title	*Effects of photodynamic therapy on the human inguinal skin microbiome to improve antiseptic effect –Pilot 2*

Sponsor-Investigator (Principal Investigator):

This clinical trial protocol was subject to critical review and has been approved by the Sponsor-Investigator. The information herein is consistent with

- the current risk/benefit evaluation of the intervention,
- the moral, ethical and scientific principles governing clinical research as set out in the current version of the Declaration of Helsinki, Good Clinical Practice.

PD Dr. med. Yvonne Achermann

Zürich, 27.11.2020

Place/Date	Signature

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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	*PD Dr. med. Yvonne Achermann*
Study Title:	***Effects of photodynamic therapy on the human inguinal skin microbiome to improve antiseptic Effect – pilot 2***
Short Title / Study ID:	*Effects of photodynamic therapy on skin microbiome (PHOMIC-II)*
Protocol Version and Date:	*v04, 27.11.2020*
Trial registration:	*Bundesamtes für Gesundheit: www.kofam.ch.* *SNCTP* *International trial registry ClinicalTrials.gov (clinicaltrials.gov)* *NCT04618276*
Study category and Rationale	Other clinical study Category A
Background and Rationale:	Periprosthetic joint infections are a feared complication after orthopedic surgery in particular in our increasing elderly population. These infections are usually difficult to treat, because microorganisms persist in biofilms on the orthopedic implant surface. Therefore, it would be desirable to prevent these infections. It is hypothesized that bacteria from the skin surface or dermis - such as *Staphylococcus aureus*, coagulase-negative staphylococci, or *Cutibacterium* sp. - are transmitted into the periimplant tissue during surgery. In an ongoing interdisciplinary study with the Orthopedic University Hospital Balgrist (data in preparation for publication), we see that common skin antisepsis preparation is not effective to eliminate skin bacteria before surgery because they persist in sebaceous or sweat glands. Photodynamic therapy (PDT) has recently gained attention in the treatment of acne, a disease of the pilosebaceous unit, in which also *Cutibacterium acnes* is implicated. The PDT works here on the one hand through a long-lasting destruction of the sebaceous glands, and on the other hand due to anti-inflammatory and antimicrobial effects.
Objective(s):	The overarching aim of this research project is to prevent orthopedic implant-associated infections. This study aims to investigate if PDT has an effect on bacterial skin colonization in order to improve skin antisepsis strategies for the prevention of surgical site infections. In a previous pilot study, we investigated if skin antisepsis is improved with previous PDT with the photosensitizer-inducing prodrug 5% topical methyl aminolevulinate (MAL) on inguinal skin in 10 participants. The induced photosensitizer was protoporphyrin IX (Pp IX, 635 nm) activated by red light. We showed a complete sterilization of colonizing skin bacteria at the same day after this treatment However, orthopedic surgeons are hesitant to perform an arthroplasty surgery after such a treatment due to skin erythema for a few days. We are entirely convinced about this novel prevention concept but need to identify the photosensitizer with the ideal balance of bactericidal effect versus skin irritation. Building upon the data we gathered, we will explore PDT with the two photosensitizers MAL and Methylene blue with potentially less local side-effects (skin erythema).

Outcome(s):	Primary outcome: **Effect** of photodynamic treatment with the photosensitizers Pp IX **(MAL)** and **Methylene blue** in combination with surgical antisepsis on bacterial skin colonization on the day of application and on day 1, 3, and 5 Secondary outcome: Effect of PDT on the skin microbiome using molecular techniques.
Study design:	Pilot study, open label, single center
Inclusion / Exclusion criteria:	**Inclusion criteria** Healthy male and female participants ≥ 18 years who • volunteer for the pilot study in which a routine photodynamic treatment in the Department of Dermatology will be applied and effect of skin colonization will be analyzed, and • an informed consent is signed by the participant (after information about the project). **Exclusion criteria** • Pregnant and lacting women • Participants with inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc., • Participants taking antibiotics in the 14 days prior to PDT or until follow-up at 21 days • Participants who received oral retinoid therapy within the last 6 months • Participants who received anti-inflammatory agents as NSAR within the 14 days prior and after the PDT • Participants taking any photosensitizing drugs within 4 weeks prior to PDT • Participants who had a history of photosensitivity disorder • Fitzpatrick's skin phototype V-VI
Study Intervention:	• Photosensitizer application, followed by PDT (1x) • Skin swabs on day 0, 1, 3, and 5 Group A: use of MAL induced Pp IX photosensitizer Group B: use of Methylene blue photosensitizer
Reference Intervention:	Skin swabs before and after skin antisepsis in 10 participants without PDT from the contralateral side.
Number of Participants with Rationale:	Aim: 10 volunteers in group A and 10 volunteers in group B There will be only descriptive statistics to see if numbers of colonizing bacteria are decreased with PDT to plan a clinical trial in patients getting a hip joint arthroplasty and previous antisepsis.
Study Duration:	1 year

Study Schedule:	• Project start (FPFV): January 2021
	  ○ First participant: January 2021
	  ○ Last participant: June 2021
	• Project end (LPLV): December 2021

Investigator(s):	Yvonne Achermann, MD Division of Infectious Diseases and Hospital Hygiene University Hospital Zurich Rämistrasse 100, 8091 Zürich Email: yvonne.achermann@usz.ch Tel: 044 255 34 02
Study Centre(s):	Single-center
Statistical Considerations:	Categorical data will be tested for differences using Fisher's exact or chi-squared tests, as appropriate, whereas continuous variables will be tested using Wilcoxon rank sum tests.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

LIST OF ABBREVIATIONS

AE	Adverse Event
ClinO	Clinical Trial Ordinance (KlinV)
CRF	Case Report Form
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Council on Harmonization
ISF	Investigator Site File
PI	Principal Investigator
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trial Portal
SOP	Standard Operating Procedure
TMF	Trial Master File
PJI	Periprosthetic Joint Infection
C. avidum	*Cutibacterium avidum*
CNS	Cogulase-negative staphylococci
Sp.	Species
CEC	Competent Ethics Committee
PDT	Photodynamic therapy
MAL	Methyl aminolevulinate
NSAR	Non-steroidal anti-inflammatory drugs
Pp IX	Protoporphyrin IX

1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator (Principal Investigator)

Division of Infectious Diseases and Hospital Hygiene
PD Dr. med. Yvonne Achermann
University Hospital Zurich
Rämistrasse 100, 8091 Zürich
Tel: 044 255 34 02
Email: yvonne.achermann@usz.ch

1.2 Study Nurse

To be determined

1.3 Laboratory

Microbiological cultures:
Institute of Medical Microbiology
Prof. Dr. med. Reinhard Zbinden
University Zurich
Gloriastrasse 30/32, 8006 Zürich
Tel. +41 44 634 27 00
Email: rzbinden@imm.uzh.ch

Research fellow:
Julia Prinz
University Hospital Zurich
Rämistrasse 100, 8091 Zürich
Julia.prinz@usz.ch

1.4 Collaboration

Dr. med. Laurence Imhof, Klinik für Dermatologie and Prof. Heinrich Walt (emeritus Professor of the University of Zurich, group leader of oral oncology).

1.5 Monitoring Institution

Since we only measure microbiological data from skin samples, we think, that intern monitoring would be adequate. See chapter 12.3.

ETHICAL AND REGULATOR ASPECTS

Before this study will be conducted, the protocol, the proposed participant information and consent form as well as other study-specific documents will be submitted to a properly constituted Competent Ethics Committee (CEC) in agreement with local legal requirements, for formal approval.

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from the CEC has been received.

1.6 Study Registration

The study will be registered at the Swiss National Clinical Trials Portal (SNCTP) and in the international trial registry ClinicalTrials.gov (clinicaltrials.gov).

1.7 Categorization of the Study

Category A: The health-related study intervention (PDT) entails only minimal risks and burdens.

1.8 Competent Ethics Committee (CEC)

Approval from the appropriate constituted Competent Ethics Committee is sought for the clinical trial. The reporting duties and allowed time frame are respected. No substantial amendments are made to the protocol without prior CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.9.

1.9 Ethical Conduct of the Study

The study will be carried out in accordance with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, and Swiss competent authority's requirements.

CEC will receive annual safety and interim reports and be informed about non-substantial amendments, the course of the study, and the study stop/ end in agreement with local requirements.

1.10 Declaration of Interest

No conflict of interest

1.11 Participant Information and Informed Consent

The investigator must explain to each Participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment.

The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All participants for this study will be provided a participant information sheet and a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study.

The participant information sheet and the consent form will be submitted with the protocol for review and approval for the study by the CEC. The formal consent of a participant, using the approved consent form, must be obtained before that participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

1.12 Participant Privacy and Confidentiality

The investigators are liable to treat the entire information related to the study and the compiled data strictly confidentially. Any passing-on of information to persons that are not directly involved in the study must be approved by the owner of the information.

Data generation, transmission, archiving and analysis of personal data within this study, strictly follows the current Swiss legal requirements for data protection. Prerequisite is the voluntary

approval of the Participant given by signing the informed consent prior start of participation of the clinical trial.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Participant's confidentiality will be further ensured by utilizing participant identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's personal physician or to other appropriate medical personnel responsible for the participant's welfare, if the patient has given his/her written consent to do so.

Data generated as a result of this study are to be available for inspection on request by the monitors and by the CEC.

1.13 Early Termination of the Study

The Sponsor-Investigator may discontinue the study prematurely according to certain circumstances:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

1.14 Protocol Amendments

Substantial amendments (significant changes) are only implemented after approval of the CEC.

Significant changes to be authorized by the CEC are the following:

- changes affecting the participants' safety and health, or their rights and obligations;
- changes to the protocol, and in particular changes based on new scientific knowledge which concern the trial design, the method of investigation, the endpoints or the form of statistical analysis;
- a change of trial site, or conducting the clinical trial at an additional site; or
- a change of sponsor, coordinating investigator or investigator responsible at a trial site.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human participants may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.
All Non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

2 INTRODUCTION

2.1 Background and Rationale

The use of orthopedic implants has been steadily increasing over the last 50 years. Despite considerable technical progress, including perioperative skin disinfection and antibiotic prophylaxis, implant-associated infections remain a feared complication. Infection rates up to 2% after primary joint arthroplasties (Tande and Patel 2014) have been described. National data published by Swissnoso – the National Center for Infection Prevention –reported an infection rate of 1.2% in hip arthroplasties (Vergleichsbericht 2015/2016). Considering an infection rate of up to 1.2%, 400 surgeries with primary hip arthroplasty implantation at the Orthopedic Department of the Balgrist University Hospital (data of 2015) would result in five periprosthetic joint infections

(PJI) per year, which is medically highly relevant regarding morbidity, mortality and estimated costs of 225'000 CHF in total.

Because bacteria grow and persist in biofilms on the implant surface such infections are difficult to eradicate. Definite cure of biofilm infections requires adequate surgical debridement and prolonged treatment with an antimicrobial agent resulting in high health-care costs (Tande and Patel 2014). Most commonly isolated microorganisms in implant-associated infections are staphylococci, streptococci, enterococci, Gram-negative bacteria, and anaerobic bacteria such as *Cutibacterium acnes/avidum* (formerly *Propionibacterium acnes/avidum*) (Tande and Patel 2014).

The majority of implant-associated infections are acquired during surgery. It is hypothesized that the same bacteria that colonize the skin surface contaminate the orthopedic implant and cause acute or chronic infections (Pulido, Ghanem et al. 2008). Prevention of implant-associated infections is key to avoid re-operations and prolonged antibiotic treatment. Current preoperative prevention strategies are multifaceted with the focus on skin antisepsis and single shot of an antibiotic within 30-60 minutes before surgery (Bratzler, Dellinger et al. 2013, Dumville, McFarlane et al. 2015). Preoperative skin antisepsis is performed with alcoholic povidone-iodine (PVI) or chlorhexidine gluconate (CHG) prior to implantation as a standard skin preparation (Dumville, McFarlane et al. 2013, Berrios-Torres, Umscheid et al. 2017). Povidone iodine oxidizes cell constituents and inactivates proteins by iodinating them. Regarding the skin commensal *Cutibacterium acnes*, it could be shown that despite administration of standard preoperative prophylaxis before shoulder arthroplasty surgeries, *C. acnes* could be detected in different sample types (in dermis, fascia, synovium, and glenoid tissue of shoulder) of 3 out of 10 patients without any signs of infection (Matsen, Russ et al. 2015). There is an increasing number of studies reporting the presence of bacteria in deep tissue, which is commonly considered as sterile. A recent study by Lee et al. found viable *C. acnes* in the dermal tissue in seven out of 10 male volunteers after surface skin antisepsis (Lee, Pottinger et al. 2014). All these study results have led to the assumption that not only the superficial skin bacteria but also bacteria in the dermis may find the way to deeper structures and infect an implant.

We hypothesize that local PDT is able to reduce persistent skin colonizing bacteria through the destruction of the sebaceous and sweat glands as well through bactericidal effects and thus improve skin antisepsis before surgical incision and implantation of foreign material leading to a lower rate of surgical site infections.

In a previous pilot study, we investigated if skin antisepsis is improved with previous PDT with the photosensitizer- inducing prodrug 5% topical methyl aminolevulinate (MAL) on inguinal skin in 10 participants. The induced photosensitizer was protoporphyrin IX (inducing a photodynamic effect with 635 nm light source) and we showed a complete sterilization of colonizing skin bacteria after this treatment (Waldmann, Schmid et al. 2020). However, due to skin erythema for a few days after PDT, orthopedic surgeons would be hesitant to perform an arthroplasty surgery after this treatment. Therefore, we aim to have a PDT with less local side-effects (skin erythema).

Ondine's methylene blue based photosensitizer NF-031 is mainly formulated in a primarily hydrophilic carrier, and therefore does not penetrate the stratum corneum over short periods of time, providing potent surface disinfection. According to the company Ondine, we can expect less side effects as with Pp IX. We will also repeat the MAL PDT with day light as a promising light source with expected less side effects such as pain and redness (Wiegell, Haedersdal et al. 2008, Rubel, Spelman et al. 2014).

The aim of this pilot study is to evaluate the effect of PDT with the photosensitizer MAL with and the photosensitizer Methylene blue on colonizing bacteria immediately before surgical skin antisepsis and after it. If we see promising results in this pilot study, we will plan a prospective clinical trial in patients undergoing hip arthroplasty surgery.

2.2 Study Intervention and Indication

Study intervention	Indication
PDT - **Photosensitizer in group A: MAL** - **photosensitizer in group B: methylene blue**	- Bactericidal effect on skin bacteria (skin sterility)
Skin swabs	- Skin scraping method - Measurement of bacterial growth of colonizing bacteria and quantitative bacterial changes using molecular methods

2.3 Clinical Evidence to Date

PDT has recently gained attention in the treatment of acne, a disease of the pilosebaceous unit, in which also *C. acnes* is implicated. The PDT works here on the one hand through a long lasting destruction of the sebaceous glands, and on the other hand due to anti-inflammatory and antimicrobial effects (Sakamoto, Lopes et al. 2010). In following studies, photodynamic therapy not only validated its efficient activity against bacteria involved in acne such as *C. acnes*, it showed also activity against various other classes of microorganisms (Awad, Tovmasyan et al. 2016). The mechanism of action of PDT is a photochemical reaction through the generation of reactive oxygen species in the presence of oxygen, mainly excited singlet oxygen, by a non-toxic photosensitizer reacting with visible light. PDT is routinely performed among others for non-melanoma skin cancer and therapy-refractory inflammatory dermatoses at the Department of Dermatology at the University Hospital Zurich. The treatment enjoys great popularity as it is well tolerated, can be repeated arbitrarily often, and gives excellent cosmetic results.

In a previous pilot study, we investigated if skin antisepsis is improved with previous PDT with the photosensitizer- inducing prodrug 5% topical methyl aminolevulinate (MAL) on inguinal skin in 10 participants. The induced photosensitizer was protoporphyrin IX (inducing a photodynamic effect with 635 nm light source) and we showed a complete sterilization of colonizing skin bacteria after this treatment (Waldmann, Schmid et al. 2020). However, due to skin erythema for a few days after PDT, orthopedic surgeons would be hesitant to perform an arthroplasty surgery after this treatment. Therefore, we aim to have a PDT with less local side-effects (skin erythema).

2.4 Justification of Study Intervention

PDT enjoys great popularity as it is well tolerated. Therefore, we select this promising treatment to investigate an innovative strategy to improve skin antisepsis in a pilot study. If we see that we have sterile cultures after PDT and skin antisepsis without side effects, we will plan a larger prospective study based on these data.

2.5 *Explanation for Choice of Comparator Intervention*

We will use for our control group without PDT the contralateral groin of the same participants (no further participants needed).

2.6 Risk / Benefits

In the following, we describe benefits, weakness, opportunities, and risks of this study.

Benefits
- Important topic in our society of more elderly patients with the increasing need of orthopedic implants
- PDT is a promising method for improving skin anti-sepsis
- established network with infectious diseases specialists (Lead), microbiologists, dermatologists, and orthopedic surgeons

Weakness
- not applicable

Opportunities
- Improved skin antisepsis by PDT would change routine praxis in orthopedic surgery as well as overall in surgery with the consequent reduction in morbidity, mortality, and health-care costs

Risks
- Minimal risk (transient erythema and pain) using PDT (no long-term sequelae). No inflammation seen on histopathology in previous trial

Possible side effects of the PDT are pain in the area of treatment, erythema and edema during and after light treatment (Borgia, Giuffrida et al. 2018). These side effects are self-limiting. We expect less erythema with day-light PDT and with the photosensitizer Methylene blue than with the previously tested MAL induced Pp IX photosensitizer (Waldmann, Schmid et al. 2020).

Since our study interventions (see above) have minimal risks for participants, it is reasonable to conduct this pilot study before starting a larger clinical trial with patients undergoing hip arthroplasty surgery.

2.7 Study Population

Twenty healthy male and female volunteers' ≥ 18 years will be recruited for this clinical study. The first ten enrolled participants will be allocated to receive MAL (group A), the other ten participants will receive Methylene blue (group B). The type of PDT (group A and B) is not blinded to both participant and study investigator. The study will be approved by the local ethical committee and conducted with a study nurse and a doctoral thesis student (to be determined) in collaboration with the Clinic for Dermatology at the University Hospital Zurich, and with the Institute of Medical Microbiology at the University of Zurich. An informed consent will be obtained from each participant. We will exclude pregnant and lactating women, participants taking antibiotics in the 14 days prior to the PDT or until follow-up at 21 days, participants who received oral retinoid therapy within the last 6 months, participants who received anti-inflammatory agents within the 14 days prior and after the photodynamic treatment, participants taking any photosensitizing drugs within 4 weeks prior to the photodynamic treatment, participants who had a history of photosensitivity disorder or having a fitzpatrick's skin phototype V-V (16).

We will not include vulnerable participants. There will be a financial compensation (value CHF 50.00) to the participants as in the previous trial (PHOMIC) was asked by the ethical committee.

3 STUDY OBJECTIVES

3.1 Overall Objective

The overarching aim of this research project is to prevent orthopedic implant-associated infections.

3.2 Primary Objective

In this study we aim to investigate if PDT with MAL or methylene blue has an effect on bacterial skin colonization and decreases number of colonizing bacteria to improve skin antisepsis strategies for the prevention of surgical site infections.
In a previous pilot study, we investigated if skin antisepsis can be improved with previous PDT with MAL-induced Pp IX on inguinal skin in 10 participants. We showed a complete sterilization of colonizing skin bacteria at the same day after this treatment. However, orthopedic surgeons are hesitant to perform an arthroplastic surgery after such a treatment due to skin erythema for a few days.
We are entirely convinced about this novel prevention concept but need to identify the optimal irradiation source and the photosensitizer with the ideal balance of antibacterial effect versus skin irritation.

3.3 Secondary Objectives

Effect of PDT on the skin microbiome using molecular techniques.

3.4 Safety Objectives

Evaluation of adverse events

4 STUDY OUTCOMES

4.1 Primary Outcome

Effect of PDT with the MAL-induced Pp IX (group A) and Methylene blue (Ondine NF-031) (group B) in combination with skin antisepsis on bacterial skin colonization on the day of application and on day 0, 1, 3 and 5

1.1. To quantitatively evaluate bacterial density and species before and after PDT and skin antisepsis using culture techniques

4.2 Secondary Outcomes

Effect of PDT on the skin microbiome using molecular techniques.

4.3 Safety Outcomes

Every PDT is documented as in routine clinics on a standardized protocol in the KISIM database (see appendix 1).

Clinical signs and symptoms after PDT as adverse events. We will distinguish between:

- Mild redness and pain as to be expected (yes/no)
- Advanced redness and pain more than expected (yes/no): adverse event.
    - “More than expected” is defined, if patients needs to take more than 1 painkiller/day
- Other signs and symptoms not expected (yes/no)

5 STUDY DESIGN AND COURSE OF STUDY

5.1 General Study Design and Justification of the Design

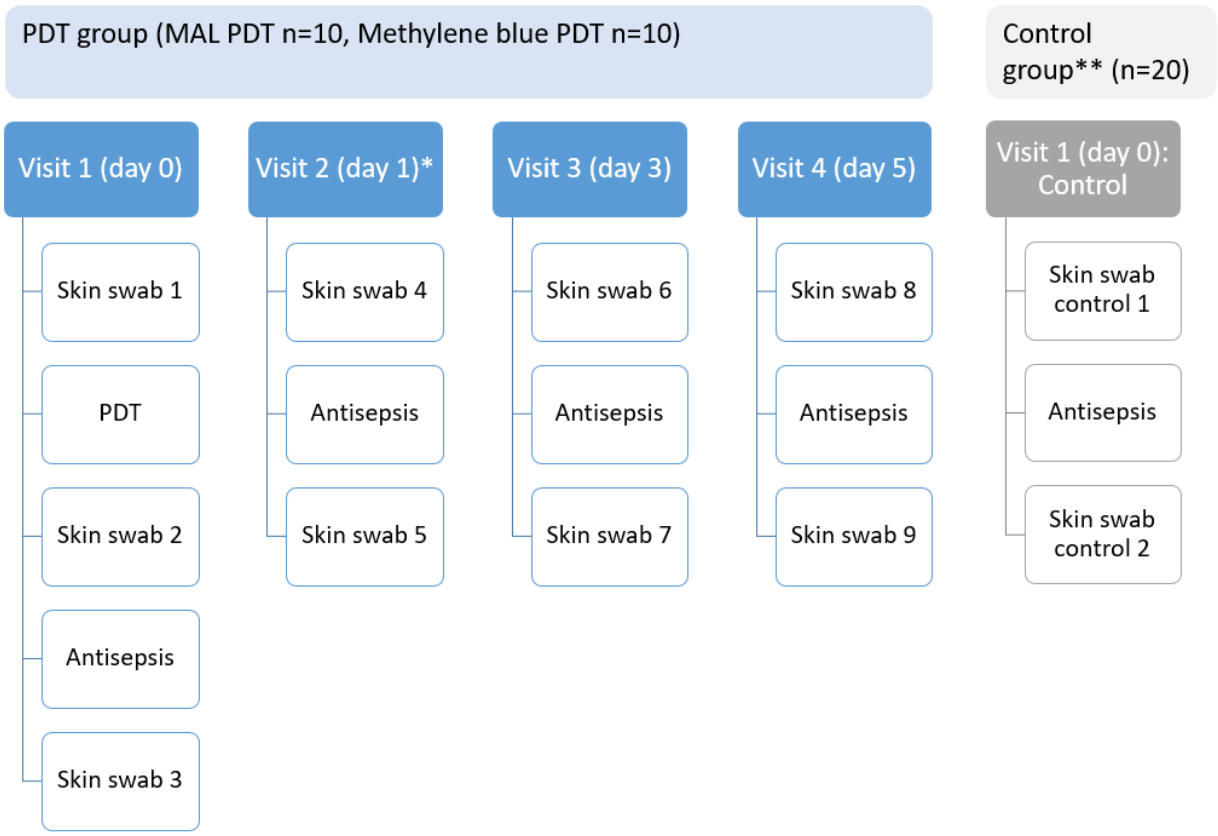
This is a pilot study of healthy volunteers, open label, and single center. We will use a parallel assignment of Arm A and B without masking (open label). Allocation is non-randomized, we will start with group A, followed by group B.

If we see promising results, we will plan a prospective clinical trial in patients undergoing hip arthroplasty surgery.
The intended procedures are PDT on the first day followed by skin swabbing for control of skin microbiome of treated area immediately after PDT (day 0) and after 1, 3 and 5 days of PDT to analyze how long the effect lasts.
We think that this study design with healthy volunteers is adequate before starting a clinical trial.

5.2 Study Duration and Study Schedule

The expected duration of participant's participation is 6 days from first study visit to the last follow-up time to report side effects of photodynamic treatment. The screening visit can be any time before but at least 1 week before the first study visit. The study schedule is indicated below.

Figure 1. Flow chart of the study*



*Visit 2 must be within 24 hours after photodynamic treatment
** same participants as in the PDT group but swabs and skin antisepsis on the contralateral leg site

At the screening visit, the voluntary participant will be informed and asked for signing the informed consent by Dr. Yvonne Achermann. This visit and the last visit will be at the outpatient clinic for Infectious Diseases at the University Hospital Zurich. Demographic data (age, sex, current medications, and underlying diseases) will be noted.

Appointments for the photodynamic treatment (day 0) and the control visits (day 1, 3 and 5) will be made.

Study schedule:

Group A (MAL group):

On day 0, a skin scraping of the groin will be performed and sent for microbiological culture. Then, 5% topical methyl aminolevulinate (MAL) as the prodrug for the photosensitizer Pp IX will be applied (5 x 10cm in the right groin) and the photodynamic process will be started by irradiation of the area with day light source.

Group B (Methylene blue group)

On day 0, a skin scraping of the groin will be performed and sent for microbiological culture. Then, 5ml of the 0.01% methylene blue based photosensitizer (NF-031) will be applied for an area of 5 x 10cm in the right groin of the patient. Immediately after application, the photodynamic process will be started by irradiation of the area with 40J/cm2 red light from a 635nm (absorption peak 670nm) emitting LED during 4 minutes.

Immediately after the PDT, skin antisepsis will be performed. Antisepsis of the skin is performed with a povidone-iodine/alcohol solution (Betaseptic®, Mundipharma, Limburg, Germany) and repeated three times for a total duration of 3 minutes to imitate standard surgical antisepsis before a hip arthroplasty surgery. Skin scraping will be repeated after the antisepsis and after 1, 3 and 5 days for bacterial cultures.

As a control group, we will take skin swabs before and after skin antisepsis without PDT on the contralateral site of all participants.

On day 5 of the study, volunteers will be seen for the last study visit to document any adverse effects.

5.3 Methods of Minimizing Bias

Excluded bias in our collective

- No selected participants
- Both sexes can be included
- Any age

Potential bias in our collective:

- Since we will search for healthy volunteers, the microbiome analysis might be slightly different to the population undergoing a hip arthroplasty surgery in an orthopedic hospital.

6 STUDY POPULATION

Ten healthy male and female volunteers' ≥ 18 years in each arm will be recruited for this clinical study.

6.1 Eligibility Criteria

6.1.1 Inclusion Criteria

Patients fulfilling all of the following inclusion criteria may be enrolled in the study

Inclusion criteria:

Healthy male and female participants ≥ 18 years who

- volunteer for the pilot study in which PDT will be applied and effect of skin colonization will be analyzed, and
- an informed consent is signed by the participant (after information about the project).

6.1.2 Exclusion Criteria

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

Exclusion criteria:

- Pregnant and lacting women
- Participants inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc.,
- Participants taking antibiotics in the 14 days prior to PDT or until follow-up at 14 days
- Participants who received oral retinoid therapy within the last 6 months
- Participants who received anti-inflammatory agents as NSAR within the 14 days prior and after the PDT
- Photodermatoses Participants taking any photosensitizing drugs within 4 weeks prior to PDT
- Fitzpatrick's skin phototype V-VI

6.2 Recruitment and Screening

Volunteers for this pilot study will be recruited by the Division of Infectious Diseases of the University Hospital Zurich with a flyer (appendix 2) as a recruitment tool (on pinboard at the University Hospital Zurich and the University Hospital Balgrist). Written informed consent will be taken under supervision of PD Dr. Y. Achermann.
The participants will be informed in writing and verbal on:

- The nature, purpose and duration of, and procedure for the research project;
- Their right to withhold or to revoke their consent at any time without giving reasons;
- Their right to receive information at any time in response to further questions relating to the research project;
- Their right to be informed of results concerning their health, and their right for such information or to designate a person who is to take this decision for them;
- Measures to protect the biological material and the personal data

All participants will have enough time to decide whether to participate or not (at least 1 week).
The formal consent of a participant will be obtained before the participant is submitted to any study procedure. The consent form will be signed and dated by the investigator or his designee at the same time as the participant sign. A copy of the signed informed consent will be given to the study participant. The form will be retained as part of the study records in the patient file.

There will be a financial compensation (value CHF 50.00) to the participants.

6.3 Criteria for Withdrawal/ Discontinuation of Participants

A participant must be withdrawn from the study if

- safety reasons of PDT (other side effects than expected, or more intense known side effects).
- Withdrawal of participant informed consent

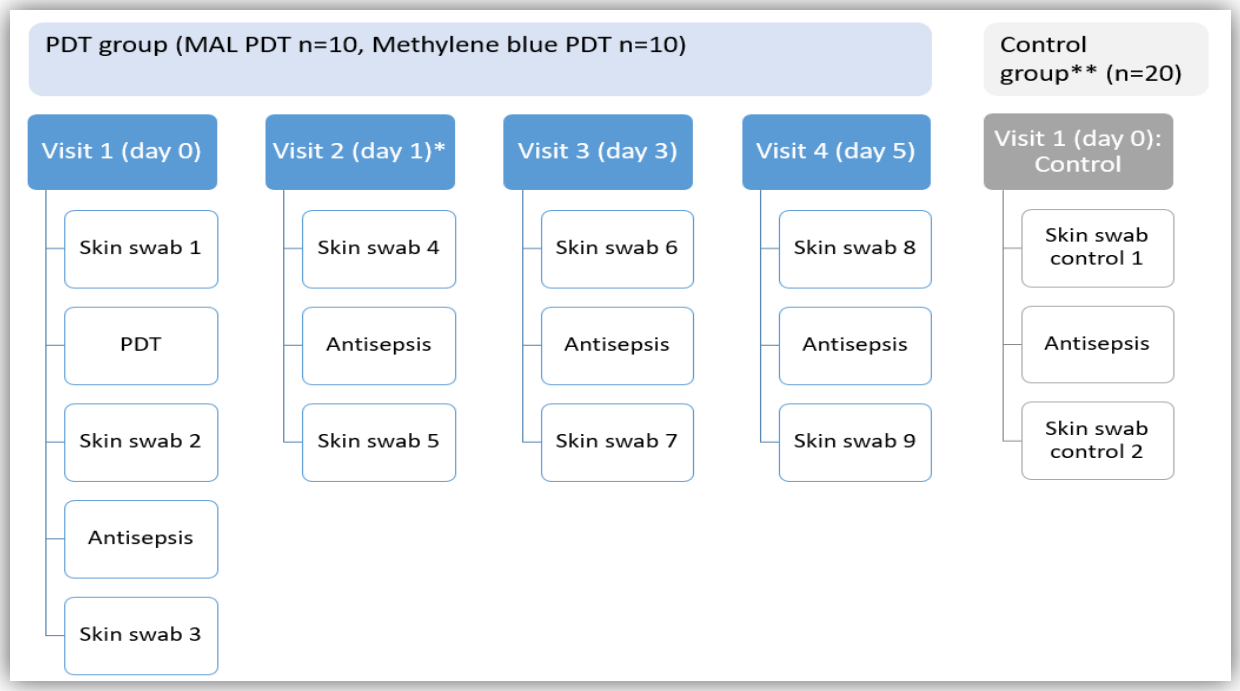
Participants who discontinued the study (premature withdrawal) will be follow-up at least once after PDT treatment (1 week) to ask for side effects. If no intervention was done, no follow-up is needed.

After withdrawal of consent, the encoded patient samples and data will be analyzed. After analysis, the samples and data will be completely anonymised (according to Art. 9 KlinV), except if the participant has consented to further use of the samples and data and not withdrawn his consent. In this case, the samples and data will be stored as mentioned in chapter 12.6."

7 STUDY INTERVENTION

7.1 General Information

The following flowchart shows all steps described in the study plan:



7.1.1 Study Intervention

Study Intervention(s) (group A and B)

Who	List of interventions
PD Dr. med. Yvonne Achermann	Skin antisepsis, taking swabs, PDT with MAL (group A) or Methylene blue (group B)

* In collaboration with Dr. med. Laurence Imhof from the Department of dermatology and Prof. Heinrich Walt (emeritus Professor of the University of Zurich, group leader of oral oncology).

7.1.2 Control Intervention

Skin antisepsis without PDT on the contralateral site of the first 10 participants

7.2 Administration of Study Intervention

7.2.1 Study Intervention

Since the clinic of dermatology is located in the circle and not anymore in the main campus of the University Hospital of Zurich, the study intervention on day 0 is at the circle.
The following visits can be done at the main campus at the department of Infectious Diseases.

Details of study Intervention	Justification
1. Inguinal skin scraping before PDT	Baseline microbiome data
2. Photosensitizer application, followed by PDT (1x)	Treatment to reduce colonization bacteria
3. Skin scraping, skin antisepsis in the groin, skin scraping after antisepsis	To measure bacterial colonization after PDT – before and after skin antisepsis

7.2.2 Modification of Interventions

Trial is not modifiable

7.3 Compliance with Intervention

There will be no compliance problem of the study participant since the intervention takes place at the visits. No intervention by the participant is needed except reporting of adverse effects.

7.4 Data Collection and Follow-up for Withdrawn Participants

Not applicable

7.5 Concomitant Intervention(s)

Since we only include participants for our analysis who do not take antibiotics or NSAR in the 14 days prior to the photodynamic treatment or until follow-up at 14 days, we will inform on that issue at the screening and at each study visit. We will record it in our eCRF.

8 STUDY PROCEDURES

8.1 Table of Study Procedures and Assessments

Study plan: Effects of PDT on the human inguinal skin microbiome to improve antiseptic effect

Study tasks	**Screening**	**Intervention Period Visit**			
Visits	**0**	**1**	**2**	**3**	**4**
	at least -7 days before visit 1	0	1 (within 24 hours)	3	5
1. Participant information and informed consent	√				
2. Inclusion- and exclusion criteria	√				
3. Demographic data	√				
4. Inguinal skin scraping before photodynamic treatment		√			
5. **Study intervention**: PDT		√			
6. Skin antisepsis in the groin, skin scraping before and after antisepsis		√	√	√	√
7. (serious) adverse events		√	√	√	√
8. End of study information of study results					√

Skin scrapping

For all skin swabs, we will apply the scratching method using a scalpel as described previously (Boni, Kuster et al. 2018) and illustrated below in Figure 2. The swabs will be analyzed for bacterial growth. The remaining sample will be immediately frozen at -80C° for later molecular analysis such as metagenomics.

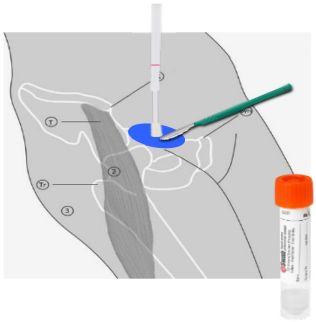


Figure 2. Specimen collection in the groin of the hip before disinfection. Skin scrapings will be removed with sterile blades and transferred to ESwab culture swabs (Copan).
T, musculus tensor fascia latae; Tr, trochanter

Photodynamic treatment

Group A (MAL group):

On day 0, a skin scraping of the groin will be performed and sent for microbiological culture. Then, 5% topical methyl aminolevulinate (MAL) as the prodrug for the photosensitizer Pp IX will be applied under occlusion in the right groin of the patient. After the incubation, the PDT will be started by irradiation of the area with day-light.

Group B (Methylene blue)

On day 0, a skin scraping of the groin will be performed and sent for microbiological culture. Then, 5ml of the 0.01% methylene blue based photosensitizer (NF-031) will be applied for an area of 5 x 10cm in the right groin of the patient. Immediately after application, the PDT will be started by irradiation of the area with 40J/cm2 red light from a 635 emitting LED during 4 minutes.

Skin antisepsis

After PDT, we will perform skin antisepsis as routinely done in clinics three times with a povidone-iodine/alcohol solution (Betaseptic®, Mundipharma, Limburg, Germany) for a total duration of 3 minutes to imitate standard surgical antisepsis before a hip arthroplasty surgery.

8.2 Assessments of Outcomes

8.2.1 Assessment of Primary Outcome

What	***When***	***How***
Bacterial density and species of skin swabs	Visit 1, 2, 3 and 4	Skin swab, microbiological diagnostic methods (see below)

Microbiology

In short, the patient's sample swabs will be streaked out onto Columbia sheep blood agar plate without antibiotics (bioMérieux, Mary-l'Etoile, France), colistin-nalidixic acid (CNA) blood agar (bioMérieux) plate for aerobic cultivation and a Brucella plate (in-house sheep blood agar plates with hemin and vitamin K1) for anaerobic cultivation using GENbag (bioMérieux). Final identification will be done by matrix-assisted laser desorption ionization-time of flight mass spectrometry spectrometry (MALDI-TOF MS) using a Bruker MALDI Biotyper. The amount of bacteria will be semiquantitiative described as +, ++, +++ based on growth on agar plates. All cultured microorganisms will be stored in skim milk at -80C° for potential subsequent analysis by whole genome sequencing for analyzing the secondary outcome.

8.2.2 Assessment of Secondary Outcomes

To evaluate the bacterial dynamics on the skin after PDT and skin antisepsis within one week

using PCR technique in collaboration with PD Dr. sc. nat. Philipp Bosshard, Laborleiter FAMH at the clinic for dermatology at the University Hospital of Zurich.

What	*When*	*How*
Bacterial dynamics	After termination of all study participants	Real-Time PCR

8.2.3 Assessment of Safety Outcomes

8.2.3.1 Serious Adverse Events

Recording of serious adverse event (SAE) information time of onset, duration, resolution, action to be taken, assessment of intensity, and relationship with study intervention.

8.2.4 Assessments in Participants who prematurely Stop the Study

Participants who are withdrawn from the study prematurely due to adverse event, will be followed-up until adverse-effects disappeared. Follow up may include but is not limited to physical examination, laboratory tests, vital signs, telephone calls. Outcomes and resolution of events will be recorded in the Case Report Forms. In case of lost to follow up, efforts will be made to contact the patient or to ascertain the vital status of the participant.

8.3 Procedures at Each Visit

8.3.1 Screening Visit

Screening visit,– at least -7 days before the study start

- Information of the study and all necessary study visits
- Check for In- and Exclusion criteria
- Enrollment if agree to participate in study
- Enter basic demographic parameters in electronic CRF (age, sex, current medications, and underlying diseases)
- Scheduling of all study visits

Duration: ca. 30 minutes
Location: Division of Infectious Diseases, University Hospital Zurich

8.3.2 Visit 1 = Day 0 of the study

Group A (MAL group):

On day 0 with Dr. Achermann, a skin scraping of the groin will be performed and sent for microbiological culture. Then, 5% topical methyl aminolevulinate (MAL) as the as the prodrug for the photosensitizer Pp IX will be applied (5 x 10cm in the right groin) and followed by irradiation of the area with day light.

Group B (Methylene blue group)

On day 0 with Dr. Achermann, a skin scraping of the groin will be performed and sent for microbiological culture. Then, 5ml of the 0.01% methylene blue based photosensitizer (NF-031) will be applied for an area of 5 x 10cm in the right groin of the patient. Immediately after application, the photodynamic process will be started by irradiation of the area with 40J/cm2 red light from a 635 emitting LED during 4 minutes.

Immediately after the PDT, skin antisepsis will be performed. Antisepsis of the skin is performed with a povidone-iodine/alcohol solution (Betaseptic®, Mundipharma, Limburg, Germany) and

repeated three times for a total duration of 3 minutes to imitate standard surgical antisepsis before a hip arthroplasty surgery.

For all inguinal swabs, we will use the scratching method using a scalpel as already applied in a previous study (ethical approval BASEC-Nr 2016-01017). The swabs will be sent to the microbiology laboratory of the University of Zurich for bacterial analysis (analysis under supervision of Prof. R. Zbinden).

Duration: 1-2 hours
Location: Clinic for Dermatology (located in the Circle since October 2020), University Hospital Zurich

8.3.3 Visit 2, 3, 4 (day 1, 3, 5)

Skin scraping after skin antisepsis will be repeated 1, 3, and 7 days later and analyzed for bacterial cultures.

In short:

- Inguinal skin scraping
- Skin antisepsis
- Inguinal skin scraping
- Documentation of adverse effects

Duration: 30 - 60 minutes
Location: Division of Infectious Diseases, University Hospital Zurich

9 SAFETY

During the entire duration of the study, all serious adverse events (SAEs) that may be causally related to the study intervention are collected and documented in source documents. Reportable events are recorded in the case report form (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

In order to guarantee participants' safety and health, further adverse events which must be documented or reported are to be designated in the protocol or at the request of the responsible CEC.

9.1 Definitions

Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation participant after the intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any favorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the intervention, whether or not related to the intervention. An AE may also consist of a new disease, an exacerbation of a pre-existing illness or condition, a recurrence of an intermittent illness or condition, a set of related signs or symptoms, or a single sign or symptom.

Serious Adverse Event

A serious adverse event is defined as any event which:

- requires inpatient treatment not envisaged in the protocol or extends a current
- hospital stay;
- results in permanent or significant incapacity or disability;
- is life-threatening or results in death; or
- causes a congenital anomaly or birth defect.

9.2 Recording and Assessment of Serious Adverse Events

The investigator has the responsibility for SAE identification, documentation, and assessing the causal relationship study intervention.

All SAEs will be fully documented in the appropriate eCRF. For each SAE, the investigator will provide the onset, duration, treatment required, outcome and action taken with regard to the study intervention.

The assessment by the investigator with regard to the study intervention relation is done according to the following definitions:

Unrelated	• The event started in no temporal relationship to the medical intervention applied and • The event can be definitely explained by underlying diseases or other situations.
Related	• The event started in a plausible temporal relationship to the medical intervention applied and • The event cannot be definitely explained by underlying diseases or other situations.

9.3 Reporting of Serious Adverse Events

If, in the course of a clinical trial, serious adverse events occur in participants in Switzerland, and it cannot be excluded that the events are attributable to the intervention under investigation, the investigator must report these events:

- to the CEC **within 15 days**.

Safety and protective measures

If immediate safety and protective measures have to be taken during the conduct of this clinical trial, the investigator must notify the CEC of these measures, and of the circumstances necessitating them, **within 7 days**.

Annual Safety Report

All SAEs will be summed up in the **annual safety report (ASR)** and submitted to the CEC. ASR shall contain:

- A summary of events including severity and causal relationship to the intervention and on the safety of participants.
- The accompanying letter provided with the Annual Safety Report should contain a short summary of the status of the clinical trial in Switzerland (number of centers open/closed, number of patients recruited/recruitment closed, and number of SAEs).

9.4 Follow up of (Serious) Adverse Events

Participants terminating the study (either regularly or prematurely) with

- reported ongoing SAE, or
- any ongoing AEs of laboratory values or of vital signs being beyond the alert limit

will return for a follow-up investigation. This visit will take place up to 30 days after terminating the treatment period. Follow-up information on the outcome will be recorded on the respective SAE page in the eCRF.

10 STATISTICAL METHODS

Categorical data will be tested for differences using Fisher's exact or chi-squared tests, as appropriate, whereas continuous variables will be tested using Wilcoxon rank sum tests.

10.1 Hypothesis

We hypothesize that PDT improves skin antisepsis by reduction of persistent skin colonizing bacteria by its bactericidal effects.

10.2 Determination of Sample Size

Aim: 20 volunteers to show the effect of PDT in healthy volunteers.

10.3 Planned Analyses

- As a pilot study, we plan to do descriptive statistics only.
- Categorical date will be tested for differences using Fisher's exact or chi-squared tests.
- Continuous variables will be tested using Wilcoxon rank sum tests.
- Data will be analyzed using Stata® version 14.2 (Stata Corporation, College Station, TX). Two-tailed P-values <0.05 are considered statistically significant.

10.3.1 Datasets to be Analyzed, Analysis Populations

All Study participants that terminated the study (n = max 20 volunteers)

10.3.2 Primary Analysis

Descriptive comparisons of microbiological data before and after PDT by Dr. Achermann

10.3.3 Secondary Analyses

Statistical analysis of microbiological data using whole-genome analysis: will be done by Dr. Achermann in collaboration with the Institute of Medical Microbiology and the Clinic for Dermatology.
These analysis will be done after termination of all study participants

10.3.4 Interim Analyses

No interim analyses is needed for this small study design.

10.3.5 Safety Analysis

Analysis of SAE as standard (number of adverse and serious adverse events)

10.3.6 Deviation(s) from the Original Statistical Plan

Not applicable.

10.4 Handling of Missing Data and Drop-Outs

Missing outcome data will be handled as missing. No imputation methods will be used.

11 ELIGIBILITY OF THE PROJECT SITE(S)

PD Dr. med. Yvonne Achermann as the project leader is an Infectious Disease attending physician with a lot of experience in the field of orthopedic infections working at the University Hospital of Zurich. She will be responsible for the study design/protocol, perform skin swabs, PDT in collaboration with the Division of dermatology and with the PDT expert Prof. Heinrich Walt. She will also analyze microbiological cultures in collaboration with the institute for microbiology (IMM,

with Prof. R. Zbinden).

Dr. med. Laurence Imhof is the head of Laser Medicine, Photodermatology and Radiation Therapy. She has a lot of experience in photodynamic treatment and will therefore advice us in any study questions regarding photodynamic treatment as indicated in the study plan.

PD Dr. med. Yvonne Achermann and Dr. med. Laurence Imhof are trained in Good Clinical Practice.

Prof. Dr. med. Reinhard Zbinden provides the infrastructure for examining the skin swabs.

12 DATA QUALITY ASSURANCE AND CONTROL

The Sponsor-Investigator is implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

12.1 DATA HANDLING AND RECORD KEEPING

The study will strictly follow the protocol. If any changes become necessary, they must be laid down in an amendment to the protocol. All amendments of the protocol must be signed by the Sponsor-Investigator and if essential submitted to CEC.

12.1.1 Case Report Forms

The investigators will use electronic case report forms eCRF, one for each enrolled study participant, to be filled in with all relevant data pertaining to the participant during the study. All participants who either entered the study or were considered not-eligible or were eligible but not enrolled into the study additionally have to be documented on a screening log. The investigator will document the participation of each study participant on the Enrolment Log.

For studies with electronic CRF:

For data and query management, monitoring, reporting and coding an internet-based secure data base Redcap® developed in agreement to the Good Clinical Practice (GCP) guidelines will be used for this study. It is the responsibility of the investigator to assure that all data in the course of the study will be entered completely and correctly in the respective data base. Corrections in the eCRF may only be done by the investigator or by other authorized persons. In case of corrections the original data entries will be archived in the system and can be made visible. For all data entries and corrections date, time of day and person who is performing the entries will be generated automatically.

CRFs/eCRFs will be kept current to reflect participant status at each phase during the course of study. Participants must not to be identified in the eCRF by name. Appropriate coded identification (e.g. Participant Number) will be used.

We assure that any authorized person, who may perform data entries and changes in the eCRF, can be identified. A list with signatures and initials of all authorized persons will be filed in the study site file and the trial master file, respectively.

The investigators assure to perform a complete and accurate documentation of the participant data in the eCRF. All data entered into the eCRF must also be available in the individual participant file either as print-outs or as notes taken by either the investigator or another responsible person assigned by the investigator.

Essential documents must be retained for at least 10 years after the regular end or a premature termination of the respective study (KlinV Art. 45).

Any patient files and source data will be archived for the longest possible period of time according to the feasibility of the investigational site, e.g. hospital, institution or private practice.

12.1.2 Specification of Source Documents

The following documents are considered source data, including but not limited to:

- SAE worksheets
- Nurse records, records of clinical coordinators, and

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

The following information (at least but not limited to) should be included in the source documents:

- Demographic data (age, sex)
- Inclusion and Exclusion Criteria details
- Participation in study and signed and dated Informed Consent Forms
- Visit dates
- Microbiological data (identification of bacteria)
- Side effects of PDT (pain, redness)
- SAEs (related) and concomitant medication
- Reason for premature discontinuation

12.1.3 Record Keeping / Archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial (at the Division of Infectious Diseases, University Hospital Zurich).

12.2 Data Management

All basic demographic data, all microbiological and histopathological results will be manually entered in an automatically secured online processing system (REDCap® electronic data capture system). The PI will check and validate data on a regular basis for consistency.
All study data are encrypted in REDCap®. The principal investigator is responsible for data collection and will keep the screening log, which guarantees the confidentiality of data by the use of participant ID numbers. The participant ID numbers are automatically assigned in consecutive ascending form by the REDCap® system. For the purpose of fulfilling their task, the principal investigator grants the necessary access authorization in the form of user log-in and password to the study staff. Thus, the data cannot be altered in any way by unauthorized persons. In the REDCap® system, all relevant processing operations are documented in a user-specific manner in order to ensure traceability. This is done by means of registration software, which records who has edited which data at which time.

All patients have to give their written consent to the project. These informed consents documents (IC) will be stored according to ethical regulations.

Health related personal data captured during this project from participants are strictly confidential and disclosure to third parties is prohibited; coding will safeguard participants' confidentiality. Confidentiality will be ensured by using coded data. The code will be protected against unauthorized access and will be stored appropriately. Data will be stored for up to 10 years after publishing the study as requested by most journals.

- *Patient's and microbiological data*:

- Yvonne Achermann will be responsible for basic characteristics of the volunteers of this pilot study. After the last study visit, data will be encoded by the PI and safely stored at the Investigator Site File.
- Clinical and microbiological data will be saved in the electronical database Redcap (see above)
- The collected project data may be subject to inspection by the CEC.

- *Handling of isolated bacteria of the scrapped skin samples*:
  The sub-cultivated bacterial samples will be stored and labeled with an encoded name at -80°C at the bacteriology laboratory of the Division of Infectious Diseases and Hospital Epidemiology (responsible Yvonne Achermann). The code for the bacterial strains with correspondence to patient data will be stored at the Investigator Site File.

12.3 Routine Monitoring

Since we only measure microbiological data from skin samples, we think, that an interne monitoring would be adequate. This would include:

- Microbiological study part (cultivation procedures) under supervision of Prof. Zbinden. Regular control of study result by a microbiologist not involved in the study (to be determined)
- Data entry will be done by a doctorand or research associate and by the study nurse by a 4-eyes control. Control of data entry, informed consents, and SAE will be done by the sponsor and by Dominique Braun (attending physician of the Division of Infectious Diseases and Hospital Epidemiology) on a regular base (4-eyes principle).

12.4 Audits and Inspections

A quality assurance audit/inspection of this study may be conducted by the CEC. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections.

12.6 *Storage of Biological Material and Related Health Data*

Encoded data will be stored for up to 10 years after publishing the study as requested by most journals.
The biological material will be labeled with an encoded name and stored at -80°C at the Division of Infectious Diseases and Hospital Epidemiology by the end of the study and destroyed after the end of the study. With the second signature in the study informed consent, further use of data and the biological material for other research projects is possible.

13 PUBLICATION AND DISSEMINATION POLICY

After the statistical analysis of this trial the sponsor will make every endeavor to publish the data in a medical journal.
Data of this study can only be published if Reinhard Zbinden, Laurence Imhof and Yvonne Achermann agree on the data presentation, analysis, and authors list.

☞ ***Commitment for study coordination, ethical protocol, generate microbiological data, data entry, study analysis****: Division of Infectious Diseases and Hospital Epidemiology, USZ (Dr. Achermann)*
☞ ***Commitment for PDT application****: Clinic for Dermatology, University Hospital of Zurich (Dr. Imhof)*
☞ ***Commitment for bacterial culture, bacterial identification, storage****: Institut of Medical Microbiology, UZH (Prof. Zbinden)*
The Principal Investigator will perform the study in accordance with the current protocol version. The Principal Investigator will ensure that any investigators and any other staff comply with the terms of the Protocol and this agreement.

14 FUNDING AND SUPPORT

14.1 Funding

This study is financed by the sponsor and PI (Yvonne Achermann)

External funding is provided by the Vontobel foundation. The company Galderma and Ondine company will provide the photosensitizers.

14.2 Other Support

15 INSURANCE

Insurance is covered by “Versicherung für klinische Versuche und nichtklinische Versuche“ by Zürich Versicherungs-Gesellschaft AG (Policy no.: 14.970.888).

Any damage developed in relation to study participation is covered by this insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the principal investigator (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly, in the event of health problems or other damages during or after the course of study treatment.

The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential.

A copy of the insurance certificate will be placed in the Investigator’s Site File.

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17 APPENDICES

Appendix 1: Documentation of PDT (example for MAL PDT)

Aufklärung über Therapie und Wichtigkeit des UV-Schutzes.

Einzeichnen der Felder und Start PDT am

Felder:

Feld 1-

Heute Feld:

Crème und Einwirkungszeit: Metvix 3h

Maschine:
Aktilite Dosis: 37J/cm2 Abstand: 6 cm

Appendix 2. Flyer

Auswirkungen der Lichttherapie auf Hautbakterien

Probandinnen und Probanden gesucht

Für eine wissenschaftliche Studie suchen wir Frauen und Männer mit Mindestalter 18 Jahre für die Untersuchung der Hautbakterien vor und nach einer Lichttherapie.

Ziel der Studie: Es ist bekannt und natürlich, dass Bakterien die ganze Haut – inklusive Schweiss- und Talgdrüsen - kolonisieren. Vor Operationen wird die Haut desinfiziert um diese Bakterien abzutöten. Leider ist diese Präventionsmassnahme nicht 100% effektiv. Die Gefahr besteht, dass noch vorhandene Bakterien mit dem chirurgischen Schnitt in die Tiefe vorgeschleppt werden und dort eine Infektion verursachen können. Aus diesem Grund müssen die gegenwärtigen Desinfektionsprozesse hinterfragt und verbessert werden. Mit dieser Studie am Universitätsspital Zürich untersuchen wir, ob die Lichttherapie Hautbakterien abtöten. Diese Therapie ist auf der Klinik für Dermatologie etabliert, wird gut vertragen und es entstehen keine Folgeschäden.

Ablauf: Die Studienteilnahme beinhaltet maximal 5 Termine innerhalb von 2 Wochen. Diese finden entweder in der Klinik für Infektionskrankheiten oder der Klinik für Dermatologie statt. Der erste Termin dauert ca. 20 Minuten und dient der Studienaufklärung und Abklärung zur Teilnahme. Der erste Studientermin dauert bis maximal 2 Stunden und beinhaltet die Lichttherapie mit Hautabstrichen vor und nachher. Die zweite, dritte und vierte Studienvisite dauert ca. 30 Minuten zur Kontrolle der Hautbakterien und zum Studienabschluss.

Alle Daten werden vertraulich behandelt. Für die Versuchspersonen ergibt sich kein direkter medizinischer Nutzen. Es gibt eine Entschädigung von CHF 50.00 für die Teilnahme. Alle Untersuchungen sind kostenlos.

Wir würden uns freuen, wenn Sie an einer Studienteilnahme interessiert sind. Sie können gerne per Email oder telefonisch mit PD Dr. Yvonne Achermann Kontakt aufnehmen:

yvonne.achermann@usz.ch;
Tel: +41 44 255 34 02 direkt oder übers Sekretariat (044 255 33 22)

Bitte nehmen Sie zur Kenntnis, dass ihre Daten bei Zustandekommen eines Kontakts registriert werden. Sollten Sie später nicht einer Teilnahme interessiert sein, werden ihre Daten unverzüglich gelöscht.

Dieses Projekt ist organisiert durch:
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