

Urtica comp. gel for prevention and therapy of radiation dermatitis

An interdisciplinary, interprofessional Phase II randomized controlled trial in patients with breast cancer

Urtica comp. zur Vorbeugung und Behandlung von Strahlenerthem
[Short title: Urtica comp for radiation dermatitis / Urtica comp. gel für Strahlenerthem]

Clinical Study Protocol

Study Type:	Clinical trial with Investigational Medicinal Product (IMP)
Study Categorisation:	Risk category according to LHR : A
Study Registration:	Name of study registry: clintrial.gov [NCT ID not yet assigned] Unique Protocol ID: 211820931
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Investigational Product:	Urtica comp. (swissmedic listed as “Anthroposophic Medication without Indication”)
Protocol Version and Date:	Version number 1.8 and validity date: 01.Feb.2018

CONFIDENTIAL

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Urtica comp. gel for prevention and therapy of radiation dermatitis
[version 1.8, 01. Feb. 2018, Study ID 211820931]

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STUDY SYNOPSIS

Sponsor and Principal Investigator	Dr. Nikola Cihoric
Applicant (and Investigator)	Prof. Dr. Ursula Wolf
Study Coordinator (/Project Leader)	Dr. Gisa A. Gerstenberg
Study Title:	Urtica comp. gel for prevention and therapy of radiation dermatitis
Short Title / Study ID:	Urtica comp for radiation dermatitis Study ID 211820931 IRDIS DB 1151
Protocol Version and Date:	Version 1.8 (date: 01.Feb. 2018)
Trial registration:	Provide the name of the study registry and the registration number and date (if not registered then indicate the anticipated registry) We will register the study on https://clinicaltrials.gov/
Study category and Rationale	Clinical drug trial category A Urtica comp. gel is a swissmedic listed medication and is traditionally used for any kind of burns and skin lesions. This study explores the use for radiation dermatitis, for which there is currently only good clinical evidence, however so far no studies have been published. Thus, a registered drug is used in patients in regular dosing in line with medical standards.
Clinical Phase:	Phase II Urtica comp. is according to Swissmedic listed as: „Zur Zulassung nach Artikel 17 Absatz 1 oder 2 KPAV vor dem 1. Oktober 2008 angemeldete homöopathische und anthroposophische Präparate ohne Indikation“
Background and Rationale:	Radiation dermatitis is one of the most common side effects of radiotherapy for cancer and affects around 95 % of patients receiving radiotherapy [1, 3]. Patients with breast cancer as well as patients with head and neck cancer are most frequently affected, due to the higher radiation dose to the skin, as compared to other cancer types. Radiation dermatitis has a profound impact on the quality of a patient's life, due to pain and discomfort. Skin lesions bear a marked risk of infection. In addition, all these issues may be the cause of interruption of radiation therapy, resulting in inadequate disease treatment [9]. Despite a plentitude of studies researching local and systemic therapeutic approaches, currently no treatment (aside from local steroids which bear substantial side-effects [16]) can be explicitly recommended [2, 3, 4]. Thus, further research, especially in therapeutic options with a positive side-effect spectrum would be highly beneficial. Urtica comp. gel is a Swissmedic registered medication. It is e.g. applied in first and second-degree burn and scalding as well as sunburn and has been used in over 80 years with an excellent safety profile [5]. Positive clinical experience in treating radiation dermatitis with Urtica comp. gel suggest studying this therapeutic option in a pilot trial.

Objective(s):	Examining the effect of Urtica comp. in prevention and treatment of RD in breast cancer patients.
Outcome(s):	<p>Primary Endpoints Incidence and severity of radiation dermatitis (RD)</p> <p>Secondary Endpoints Percentage requiring no additional therapy for RD (e.g. Flammazine or Ialugen plus) Percentage of patients RD free at end of therapy Percentage of patients with secondary skin infection / need of topical and systemic antibiotics Patients quality of life / patients evaluation of the treatment</p>
Study design:	<p>Prospective pilot study in Breast Cancer patients. This randomized pilot study will have an active control group receiving the institutional standard skin care "Excipial-Hydro lotion", and will be conducted open label.</p>
Inclusion / Exclusion criteria:	<p>Inclusion:</p> <ul style="list-style-type: none"> • Radiation therapy for Breast Cancer • Age >= 18 years • Written informed consent <p>Exclusion:</p> <ul style="list-style-type: none"> • Ulcerated cancer at beginning of radiation therapy • Skin lesions in the radiation area before start of radiation therapy • Known allergies, hypersensitivity or reactions against one of the constituents of the investigational product [5] • Any neurological or psychiatric conditions that, in the evaluation of the treating physician, deem the patient incapable to participate in the study • Other clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.) as judged by the PI <p>The following criteria are exclusion criteria for the conduct of the radiation therapy, which is prerequisite for inclusion into the study. Thus, such patients will anyway not meet the inclusion criteria and are explicitly excluded from participation:</p> <ul style="list-style-type: none"> • Women who are pregnant or breast feeding • Lack of safe contraception, defined as: Female participants of childbearing potential, not using and not willing to continue using a medically reliable method of contraception for the entire study duration, such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices, or who are not using any other method considered sufficiently reliable by the investigator in individual cases. • Please note that female participants who are surgically sterilised / hysterectomised or post-menopausal for longer than 2 years are not considered as being of child bearing potential.

Measurements and procedures:	<p>Population: All eligible patients of the Department of Radiation Oncology. Patients will undergo all regularly assigned therapy at the Department of Radio- Oncology Inselspital, including the standard skin care “Excipial-Hydro lotion”. Additionally the patients of the test group will receive the study medication Urtica comp. gel.</p> <p>Assessment is done at baseline, during the radiation therapy on a weekly base, at end-of-therapy and follow-up. The assessment consists of the regular clinical assessment conducted as usual during radiation therapy, plus</p> <ul style="list-style-type: none"> • the Common Toxicity Criteria for Adverse Events (CTCAE) of the National Cancer Institute • a visual analog scale (VAS) where the patient self-assesses the skin condition • the Skindex16, a clinical outcome assessment for skin (16 Items) • the FACIT-TS-G assessing the patients treatment satisfaction at the end of therapy
Study Product / Intervention:	<p>The skin care of the study patients will be conducted in line with the guidelines of the Department of Radiation Oncology Inselspital: „Pflege bei PatientInnen, die bestrahlt werden“ Section 3.2 „Hautpflege bei einer Strahlenreaktion“ [4].</p> <p>For the patients of the test-group Urtica comp gel is applied three times per day locally on the skin as soon as the patient senses “itching, tingling” and/or reddening. Otherwise the skincare is exactly as the control group in line with the departments general guidelines.</p> <p>In case of marked worsening, e.g. epitheliolysis, the patient may receive “Flammazine and lalugen plus” as rescue-care.</p> <p>Rescue care: according to the departments therapeutic guidelines patients will receive “Flammazine and/or lalugen plus” as clinically indicated at the discretion of the treating physician (usually in cases of marked worsening of the skin condition like e.g. epitheliolysis).</p> <p>Skin condition is regularly checked before each radiation therapy session.</p> <p>The study will be conducted, and the study therapy will be administered until the radiation treatment, including follow-up, has finished. If the radiation dermatitis has ceased and the skin recovered before end of study, the patient will finish the study receiving no further cream or lotion past the point of recovery.</p>
Control Intervention (if applicable):	<p>Control group receiving the institutional standard skin care “Excipial-Hydro lotion” – all other therapeutic interventions, assessments and rescue-care will be the same in both groups.</p>
Number of Participants with Rationale:	<p>As this is a first pilot study 30 patients with breast cancer will participate. (This pilot data will be utilized to test feasibility and calculate the power and sample size of a following larger randomized controlled trial).</p>
Study Duration:	<p>11 to 15 weeks per patient. 5 Month enrollment time. Total study duration: 9 month. Screening / Planning CT etc.: one week before therapy start treatment duration: generally a radiation course of 6 weeks follow-up: 6 weeks after EOT</p>

Study Schedule:	<p>Month Year of First-Participant-In (planned): December 2017 Month Year of Last-Participant-Out (planned): August 2018 Data entry. Data clean and analysis completed: January 2019 Publication: March 2019</p>
Investigator(s):	<p>Prof. Dr. med. Ursula Wolf (Investigator) Dr. med. Gisa Gerstenberg Universität Bern, Institut für Komplementärmedizin Fabrikstrasse 8, 3012 Bern</p> <p>Dr. med. Nikola Cihoric, Stv. Oberarzt / senior physician, Inselspital, Universitätsklinik für Radio-Onkologie (Primary Investigator) Susanne Sester, Pflegeexpertin Onkologie, Department DOLS Timo Nannen, Study Nurse, Inselspital, Universitätsklinik für Radio- Onkologie Freiburgstr. 4 , Inselspital, Universitätsklinik , 3010 Bern</p>
Study Centre(s):	single-centre: Inselspital, Universitätsklinik für Radio-Onkologie
Statistical Considerations:	<p>Since this is a pilot study no power analysis will be carried out, but the data of the pilot study are utilized for feasibility-assessment and will serve as the base for planning an adequately powered RCT.) (“Machbarkeitsstudie”)</p> <p>Calculations will include: Incidence and severity of radiation dermatitis Percentage of patients developing RD Percentage requiring no additional Tx for RD (e.g. Ialugen +) Percentage of patients RD free at end of therapy / follow-up</p> <p>The courses of therapy will be compared with an active control group receiving the institutional standard skin care “Excipial-Hydro lotion” (as well as with historic standard-courses and the Incidence and percentages described in literature.)</p>
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
CTU	Clinical Trial Unit
ClinO	Ordinance on Clinical Trials in Human Research (<i>in German: KlinV</i>)
CTCAE	Common terminology criteria for adverse events
DofH	Declaration of Helsinki [22]
DSUR	Development safety update report
eCRF	Electronic Case Report Form
EOT	End of Therapy
FACIT-TS-G	Functional Assessment of Chronic Illness Therapy treatment satisfaction general
GCP	Good Clinical Practice
IB	Investigator's Brochure
Ho	Null hypothesis
H1	Alternative hypothesis
HFG	Humanforschungsgesetz (Law on human research) [24]
HMG	Heilmittelgesetz [26]
HRA	Federal Act on Research involving Human Beings
ICH	International Conference on Harmonization [23]
IMP	Investigational Medicinal Product
IIT	Investigator-initiated Trial
ISO	International Organisation for Standardisation [27]
ITT	Intention to treat
KlinV	Verordnung über klinische Versuche in der Humanforschung (<i>English: ClinO</i>)[25]
PI	Principal Investigator
RD	Radiation Dermatitis
RTx	Radiotherapy
sAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
VAS	Visual analog scale
wks	weeks

STUDY SCHEDULE

Visit Form or action	Screening / Planning of RTx*	Baseline (at first treatment Visit) *	Visits during intervention (Treatment duration generally 6 wks * / **)	EOT / close- out visit *	Follow- up (EOT + 6wks*)
Therapeutic intervention	-	-	Radiotherapy (all) Group A: Urtica comp. Group B: standard care	-	-
Radomisation		x			
Assessment					
Eligibility	x				
Informed consent		x			
Med History		x			
Primary Endpoints					
Extended CTCAE (physician)	-	x	At each weekly assessment x x x x x x	x	x
Extended CTCAE (nurse)	-	x	If Dr's score is >= 1.5	x	x
Secondary Endpoints					
Clinical assessment (physician)	x	x	At each weekly assessment x x x x x x	x	x
Skindex 16 Items (patient)	-	x	One measurement point at mid of therapy - - - x - -	x	x
VAS (patient)	-	x	At each weekly assessment x x x x x x	x	x
FACIT-TS-G (patient)	-	-	-	x	-
End of Study form					x***

*allowed time frames for each visit: the dates and time frames are aligned with the radiation-therapy schedule clinically assigned for the patient. The regular schedule for radiation therapy of breast cancer starts with a planning CT and therapy is beginning a week later consisting of a course of six weeks, 5 weeks of total mamma irradiation and one week of "boost / volume reduction" resulting in a total of 25 fractions à 2 Gy. Follow-up is conducted 6 weeks (+/- one week) after end of therapy. In clinical experience this timeframe is strictly adhered to in 99% of patients, however should a patient require deviation from the schedule, e.g. due to tolerability-issues of the radiation therapy, the deviation as well as the reason for it will be recorded in the CRF.

** 6 intervention visits, including the baseline and EOT visit. In detail: BL, BL+1wk, BL+2wks, BL+3wks, BL+4wks, BL+5wks=EOT

***at follow-up or whenever the patient ends his/her participation in the study (e.g. in case of drop-out at the time of drop-out or as soon as possible after it.)

1. STUDY ADMINISTRATIVE STRUCTURE

Applicant (and Investigator):

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Fabrikstrasse 8, 3012 Bern
Phone: +41 (0)31 631 81 40
Email: ursula.wolf@ikom.unibe.ch

Initiation and Responsibility of the study; Overseeing and final responsibility for the conduct of the study, the data-interpretation and writing of the report. Medical expertise and responsibility for the study drug Urtica comp. and related study decisions.

Sponsor and Principal Investigator:

Dr. Nicola Cihoric, Inselspital, Universitätsklinik für Radio-Onkologie
Freiburgstr. 4 , Inselspital, Universitätsklinik, 3010 Bern
Phone: 031/632 29 32
Email: Nikola.cihoric@insel.ch

Responsibility of the study; Overseeing and final responsibility for the conduct of the study, the data-interpretation and writing of the report. Leading study-physician and researcher at the project site, responsible for trial-site related medicinal decisions related to radiation oncology.

Project Leader and Coordinating researcher:

Dr. med. Gisa Gerstenberg , Universität Bern, Institut für Komplementärmedizin
Fabrikstrasse 8, 3012 Bern
Phone: +41 (0)31 631 81 43
Email: gisa.gerstenberg@ikom.unibe.ch

Initiation and responsibility of the study, designing the study, organizing collection, management, analysis, and interpretation of data. Responsible for writing of the report.

Study Nurse:

Timo Nannen, Study Nurse, Inselspital, Universitätsklinik für Radio-Onkologie
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1.1 Sponsor

Dr. med. Nicola Cihoric, Inselspital, Universitätsklinik für Radio-Onkologie
(Please find Details above in section 1)

1.2 Principal Investigator

Dr. med. Nicola Cihoric, Inselspital, Universitätsklinik für Radio-Onkologie
(Please find Details above in section 1)

1.3 Statistician ("Biostatistician")

Dr. med. Gisa Gerstenberg (Project Leader and Coordinating researcher)
and
Dr. Andreas Limacher, PhD, Head of Statistics & Methodology University of Bern, CTU Bern
(Please find Details above in section 1)

1.4 Laboratory

Not applicable.

1.5 Monitoring institution

Sponsor in combination with the Clinical Trial Unit (CTU)

The CTU will set up the database REDCap. Otherwise no specific monitoring is required, as the study is considered to have a low risk level: application of the clinically recommended dosage of a Swissmedic registered cream, which is already marketed for over 80 years with a very favourable side effect profile (see section 3.4). Furthermore no invasive tests or therapy is part of the study. However a quality-visit of the CTU ("Qualitätsvisite") will be considered.

CTU University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland
Yves Bochud, Clinical Data Manager
Tel +41 31 631 56 73; yves.bochud@ctu.unibe.ch
www.ctu.unibe.ch

1.6 Data Safety Monitoring Committee

Not applicable.

1.7 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

2. ETHICAL AND REGULATORY ASPECTS

Before the study will be conducted, the protocol, the proposed patient information and consent form as well as other study-specific documents shall be submitted to the KEK.

Swissmedic approval will not be applicable as the study is expected to fall into Category A. Any amendment to the protocol will be as well be approved (if legally required) by these institutions.

The decision of the CEC and Swissmedic competent authority 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 all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

The research project will be carried out in accordance with the research plan and with principles enunciated in the current version of the Declaration of Helsinki (DoH) [22]

2.1 Study registration

The study should be registered in a registry listed in the WHO International Clinical Trials Registry Platform (ICTRP, <http://www.who.int/ictcp/en/>). In addition, registration in a national language in the Swiss Federal Complementary Database (Portal) is required.

The study is in the process of registration at clinicaltrials.gov
[NCT ID not yet assigned] Unique Protocol ID: 211820931

2.2 Categorisation of study

Klinischer Versuch
Unterart und Kategorie
Klinischer Versuch mit Arzneimitteln
Kategorie A

Clinical drug trial category A

The Swissmedic listed medication Urtica comp. gel falls into the category of “Anthroposophic Medication without Indication”. Urtica comp. gel is traditionally used for any kind of burns and skin lesions. This study explores the use for radiation dermatitis, for which there is currently only good clinical evidence, however so far no studies have been published.

Thus, a registered drug is used in patients in accordance with the prescribing information and in regular dosing in line with medical standards.

2.3 Competent Ethics Committee (CEC)

The investigator ensures that approval from an appropriately constituted Competent Ethics Committee (CEC), in this case the KEK, is sought for the clinical study.

The reporting within this research project will follow the regular allowed time frame in line with the DoH [6] (all changes in the research activity and all unanticipated problems involving risks to humans; including in case of planned or premature study end and the final report). No changes are made to the protocol without prior Sponsor and 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

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after study end. Amendments are reported according to chapter 2.10.

2.4 Competent Authorities (CA)

No Swissmedic approval is required for this category A study.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki [22], the guidelines of Good Clinical Practice (GCP) issued by ICH, [23] the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

The following statement applies for Prof U. Wolf (Applicant), Dr. N. Cihoric (PI and Sponsor) and Dr. G. Gerstenberg (Study Coordinator / Project leader):

"I have no pecuniary or other personal interest, direct or indirect, in any matter that raises or may raise a conflict with my duties in this clinical study.

In particular not any of the following relevant financial links with the company of the drug Urtica comp. or a relevant competitor:

Employment, Ownership of stocks and shares, Travel and accommodation expenses, Paid consultancy or directorship, Paid membership of speakers panels/bureaus and advisory board or acting as an expert witness, Being in receipt of a fellowship, equipment, writing, or administrative support."

2.7 Patient Information and Informed Consent

The investigators will 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 will 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 assistance and treatment.

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

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

At the Planning meeting for radiation therapy the patient is informed about the study and will be given time to consider participation until the baseline assessment when therapy starts (generally about 7 days).

The patient information sheet and the consent form will be submitted to the CEC and to the competent authority (as applicable) to be reviewed and approved. The formal consent of a participant, using the approved consent form, will be obtained before the 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.

2.8 Participant privacy and confidentiality

The investigator will and uphold the principle of the participant's right to privacy and comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting

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the data at scientific meetings or publishing them in scientific journals.

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

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- 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

2.10 Protocol amendments

The Project Leader in conjunction with the Sponsor-Investigator is allowed to amend the protocol or to provide suggestions for a protocol amendment. Important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) will be firstly discussed within this group and then communicated to the study-team and relevant parties (e.g., investigators, CEC, competent authorities, trial participants, trial registries, journals, regulators).

Substantial amendments are only implemented after approval of the CEC and CA respectively.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC/CA. Such deviations shall be documented and reported to the sponsor and the CEC/CA as soon as possible.

All Non-substantial amendments are communicated to the CA as soon as possible if applicable and to the CEC within the Annual Safety Report (ASR).

Sponsor, Principal Investigator, Applicant and Study Coordinator / Project Lead together will consider to potentially amend the study after the pilot phase in order to increase patient numbers and / or investigate this therapeutic approach in further patient groups.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Radiation dermatitis is one of the most common side effects of radiotherapy for cancer and affects around 95 % of patients receiving radiotherapy [1, 3]. Patients with breast cancer are most frequently affected, due to the higher radiation dose to the skin, as compared to other cancer types.

Radiation dermatitis has a profound impact on the quality of a patient's life, due to pain and discomfort. In addition, it may be the cause of interruption of radiation therapy, resulting in inadequate disease treatment [9].

Despite a plentitude of studies researching local and systemic therapeutic approaches, currently no treatment (aside from local steroids) can be explicitly recommended [2, 3, 4].

However, topical corticosteroid use may have substantial adverse effects. The most frequent adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpura. Those that occur with lower frequency include hypertrichosis, pigmentation alterations, delayed wound healing, exacerbation of skin infections, cutaneous tinea and contact sensitization against corticosteroids [14].

Thus, further research, especially in therapeutic options with a positive side-effect spectrum would be highly beneficial.

Positive clinical experience in treating radiation dermatitis with *Urtica comp. gel* suggest studying this therapeutic option in a pilot trial.

Urtica comp. gel is a Swissmedic registered medication.

The scope of application of *Urtica comp.* is an imbalanced, affected process of skin-regeneration, in particular when stemming from an overdose of heat or light.

It is applied in first and second-degree burn and scalding, sunburn, allergic and hyperergic (excessive) skin conditions (dermatoses), insect bites, abrasions and ulcers.

Urtica comp. has been used for over 80 years with an excellent safety profile. The only known side effects are allergies and overreactions against ingredients, namely *Arnica*, *Thuja* or *Urtica* [5].

Also its separate ingredients have been traditionally used in complementary and herbal medicine: *Urtica*, has anti-inflammatory properties [6,7], helps with itching [7] and allergies [8]. *Arnica montana* has a decongestant effect and is soothing to inflammations of the skin by its effect on the capillary of the terminal vessels and the interstitial fluids. *Calendula officinalis* is assumed to support angiogenesis, namely the sprouting of arterial capillaries and furthermore the buildup of granulation tissue. *Thuja* is used to prevent keloid, scar proliferation and contractures. *Symphytum officinale* may regulate the body's fluid processes and has centrally analgesic properties. *Argentum colloidae* is supposed to facilitate the equilibrium between assembly and degradation processes of the skin. *Cantharis ex animale* is used for burns [8].

So far, no clinical studies with *Urtica comp. gel* have been published yet.

Taking all these findings into account, it appears that *Urtica comp. gel*, based on its composition as well as on clinical experience, may well be suited to complement the prevention and therapy of radiation dermatitis. Given the fact that no satisfactory standard treatment option exists yet for radiation dermatitis along with the excellent safety profile and favorable acceptance of complementary therapeutics among patients in oncologic therapy, a pilot trial with *Urtica comp.* for the prevention and treatment of radiation dermatitis appears promising.

3.2 Investigational Product (treatment, device) and Indication

Urtica comp. is according to Swissmedic listed as: „Zur Zulassung nach Artikel 17 Absatz 1 oder 2 KPAV vor dem 1. Oktober 2008 angemeldete homöopathische und anthroposophische Präparate ohne Indikation“

For details please refer to the separately uploaded attachments BASEC documents section 16 for product characteristics:

16a nonclinical overview and 16b clinical overview, 16c Commission C Monograph, 16d Packet Insert (Fachinformation) and 16e Swissmedic “Zulassungsbescheinigung”.

3.3 Preclinical Evidence

Urtica comp. gelatum in its commercial formulation is used. The colorless gel is also called “Wound and Burn Gel” and contains seven active substances: Argentum colloidal Dil. D5, Arnica montana e floribus LA 20%, Calendula officinalis e floribus LA 20%, Cantharis ex animale toto GI Dil. D5, Symphytum officinale ex herba LA 20%, Thuja occidentalis e summitatibus LA 20%, Urtica urens ex herba LA 20%.

All of them were manufactured based on to the methods as described in the German Homeopathic Pharmacopoeia (GHP, also known as HAB).

Most of Wound and Burn Gel's active substances are homeopathic dilutions and/or aqueous extracts, so there are no pharmacological effects related to dosage or blood concentration.

For this reason, no further studies, e. g., on bioavailability have been conducted.

For medicinal products containing potentised substances pharmacologic, pharmacodynamics and pharmacokinetic data do not add value for an appropriate use within the anthroposophical therapy. Thus, such studies are not being performed.

A review of relevant bibliographic information on the toxicological action of the starting materials of the active substances does not reveal evidence for acute or chronic toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, antigenicity, immunotoxicity or local intolerance of Wound and Burn Gel if used according to the recommended route of administration and the given dosage regime. Indications of serious drug-associated risks for Wound and Burn Gel have not become apparent.

The conducted bacterial reverse mutation assay (AMES-test) with Arnica montana e planta tota and Thuja occidentalis e summitatibus ferm 33e provide no evidence for genotoxic potential (refer to section 2.6.6.4 of the preclinical dossier).

Moreover, all the highest calculated daily maximum doses of the relevant toxic compounds in Wound and Burn Gel, Gel, e.g. cantharidin, thujone or pyrrolizidine alkaloids are below mentioned toxicological thresholds and recommended average daily dose limits for the intended patient groups.

The good efficacy, good tolerance and safe use of Wound and Burn Gel, Gel in adults, children and infants was confirmed in written surveys (refer to section 2.5.4 and 2.5.5 of the preclinical dossier).

Wound and Burn Gel, Gel is therefore a safe medication, even for especially sensitive patient groups such as children, pregnant women or nursing mothers. However, as a general precaution Wound and Burn Gel, Gel, as all medicinal products, should only be used during pregnancy and lactation following a consultation with a doctor.

Furthermore, this medicinal product should not be used in case of hypersensitivity to thuja, arnica and/or to any other plant of the Compositae family.

The following side effects are listed in the package leaflet: After using the medicinal product, redness and itching at the application site as well as allergic skin reactions may occur which require that the use of this medicinal product be discontinued.

To sum up all, Wound and Burn Gel is a safe medication, even for especially sensitive patient groups such as infants, children, pregnant women and nursing mothers when administered according to the current package leaflet.

3.4 Clinical Evidence to Date

Urtica comp. Gel has been marketed since 1969. It was officially announced in 1978 in Germany and registered in Switzerland in 2014.

During the last three years, an average of 86,121 maximal daily doses of Wound and Burn Gel had been sold per year. Since its international birth date, 10 individual case safety reports on adverse effects have been reported spontaneously to WALA Heilmittel GmbH.

Analysis of adverse effects:

The only SE that has occurred with Urtica comp. in over 80 years of clinical practice is allergic reaction.

In average 4.6 adverse events per 100.000 sold packs* have been recorded by Wala GmbH.

None of them was serious. (No death, no hospitalization, no life-threatening events, no prolongation of hospitalization no congenital abnormalities, no resulting disabilities.)

Pharmacovigilance data of Urtica comp. by the WALA Heilmittel GmbH:

All adverse events ever recorded **	TOTAL NUMBERS (Up to September 2016)
Application site eczema	1
Application site erythema	5
Application site hypersensitivity	1
Application site pain	3
Application site pruritus	3
Application site pustules	1
Blister	1
Burning sensation	2
Encapsulation reaction	1
Erythema	1
Expired product administered	1
Hypersensitivity	1
Pruritus	2
Skin discolouration	1
Skin reaction	3

* Sum of all pack sizes in all countries

** Partially more than one symptom per reported side effect has been recorded

Established international databases (e.g., PubMed, Vigilit), have been thoroughly searched for literature data on clinical research (such as human studies, meta-analyses or reviews).

The evaluation of the data retrieved has revealed no risks to human health as far as Wound and Burn Gel and/or its active substances are concerned. No relevant individual case reports have been found,

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either. As a result, no risk of acute or chronic toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, antigenicity, immunotoxicity or local incompatibility can be derived from the bibliographic data assessed (see clinical overview 2.6.6).

The medicinal product should, however, not be used in case of hypersensitivity to thuja and/or arnica or other plants of the Compositae family.

Clinical efficacy, safety and compatibility of Wound and Burn Gel even for infants and children have been confirmed by several surveys (see clinical overview 2.5.4, 2.5.5).

The recommendations in the package leaflet concerning Wound and Burn Gel's dosage and method of administration are based on therapeutic experience in anthroposophical and homeopathic medicine.

After using this medicinal product, redness and itching at the site of application and allergy related skin reactions may occur which require that the use of this medicinal product be discontinued.

Comprehensively, Wound and Burn Gel is a very compatible medicinal product, if it is used according to the recommendations of the package leaflet. The data presented confirm its favourable benefit-risk-profile.

3.5 Dose Rationale

The dosing is in line with the general use of this swissmedic listed medication.

3.6 Explanation for choice of comparator (or placebo)

Prospective pilot study with n=15 Breast Cancer patients per study arm.

This randomized pilot study will have a control group receiving the institutional standard skin care "Excipial-Hydro lotion", and will be conducted open label. (Rescue-care of Ialugen and Flammazine is the same for both groups.)

As currently Excipial-Hydro lotion is the standard skin care in the Department of Radiation Oncology [4] this treatment is chosen as the comparator.

Local steroids, although recommended in some international guidelines [2, 3], are not chosen as comparator, as due to their side-effect profile the treatment guideline of the Department of Radiation Oncology [4] clearly favors Excipial-Hydro lotion followed by Ialugen and Flammazine for rescue-care as required.

Owing to the fact that this is a pilot-study it is considered suitable to run this pilot open-label for ease of conduct.

3.7 Risks / Benefits

Risks

In section 3.4 the so far reported adverse events of Urtica comp. are listed and discussed.

In order to minimize such rare adverse events further, which have been reported as allergic reactions, all patients with a known history of allergies against any of the constituents of Urtica comp. will be excluded from participation in the study.

Patients are, for the whole duration of application of the study drug, regularly checked for adverse events. As no adverse events markedly after the application have been reported during the 80 years of Urtica comp. history, no post-trial care aside of the regular follow-up is considered necessary.

Individual Benefits

All patients receive the standard skin care “Excipial-Hydro lotion”. Additionally the patients of the test-group will receive the study medication Urtica comp. gel. It is entirely possible that these patients will have no additional benefit due to this therapy. Although the base assumption for the conduct of this study is the clinical observation, that patients benefit from the use of Urtica comp. and it may prevent or alleviate the symptoms of radiation dermatitis.

General Benefits

This pilot study will provide a first indication, helping to assess which benefit Urtica comp. may offer in the prevention and treatment of radiation dermatitis. Depending on the results of this study, as well as potentially following further studies, the future therapy of patients receiving radiation therapy may be improved.

Potential threats to the study

Currently there are no competing trials planned or ongoing. As the study is with 6 month enrolment time relatively short, it is considered unlikely that competing studies will be initiated during this time.

3.8 Justification of choice of study population

No vulnerable participants will be included.

Study population are patients with breast cancer undergoing radiation therapy.

- Radiation dermatitis is one of the most common side effects of radiotherapy for cancer and affects around 95 % of patients receiving radiotherapy [1, 3].
- Patients with breast cancer are most frequently affected by radiation dermatitis, due to the higher radiation dose to the skin, as compared to other cancer types. Furthermore patients with breast cancer are traditionally very open towards complementary approaches and highly interested in alleviating radiation dermatitis.

4. STUDY OBJECTIVES

4.1 Overall Objective

To assess, whether Urtica comp. is a viable treatment modality for radiation dermatitis (RD).
Examining the effect of Urtica comp. in prevention and treatment of RD in breast cancer patients.

4.2 Primary Objective

Incidence and severity of radiation dermatitis (RD)
As compared to the control group.

4.3 Secondary Objectives

Percentage requiring no additional therapy for RD (e.g. Flammazine or lalugen plus)
Percentage of patients RD free at end of therapy and at follow-up
Percentage of patients with secondary skin infection / need of topical and systemic antibiotics
Patient's assessment of the skin condition / quality of life / patient's evaluation of the treatment
As compared to the control group.

4.4 Safety Objectives

The following two secondary Objectives are assessing directly the safety of the study drug in comparison to the standard skin-care:

Percentage requiring no additional therapy for RD (e.g. Flammazine or lalugen plus)
Percentage of patients with secondary skin infection / need of topical and systemic antibiotics

Furthermore the primary Objective, the occurrence of radiation dermatitis itself could be considered a safety-objective, as the study aims to assess also whether prevention of radiation-dermatitis is possible by administration of Urtica comp.

These Objectives will be dealt with in their respective section.

5. STUDY OUTCOMES

5.1 Primary Outcome

Primary outcome of the study is the skin condition in the radiation area as measured by the extended CTCAE.

A precise assessment of the skin condition with respect to erythema, scalding etc. as it is done with the extended CTCAE (described in section 9.2.1).

Comparing this assessment between the treatment groups may reveal the effect of Urtica comp. in prevention as well as in treatment of RD in breast cancer patients.

5.2 Secondary Outcomes

Percentage of patients requiring no additional therapy for RD (e.g. Flammazine or lalugen plus)

A patient would require the rescue-care of Flammazine or lalugen plus when, despite the regular skincare or study medication, the condition of the skin is worsening. Thus the physicians' decision to utilize the rescue-care marks a point of seriousness of the radiation dermatitis.

The use of this rescue-care is compared between the two treatment arms.

“Percentage of patients RD free at end of therapy and at follow-up” is assessed by the Physician scoring the extended CTCAE (primary outcome measure). Although it is common, that RD is still persisting at EOT, it is nevertheless meaningful to know the proportion of patients being free of RD treated by study drug versus comparator, and furthermore follow-up the course 6 weeks after EOT.

For safety reasons the “Percentage of patients with secondary skin infection / need of topical and systemic antibiotics” (which is routinely assessed by the treating physician) shall be compared between the two groups.

The Patients perspective is captured

- by the Skindex 16 , which is a questionnaire commonly used for the self-assessment of skin conditions. The 16 items are rated on an ordinal scale ranging 0-6.
- by visual analog scales (VAS) are used to assess pain, itching, burning, skin irritation, appearance and general quality of life (related to radiation dermatitis).
- By a final evaluation of treatment utilizing a short version of the FACIT-TS-G

5.3 Other Outcomes of Interest

As this is a pilot study further outcomes might be analysed post-hoc.

5.4 Safety Outcomes

Safety outcomes are addressed in primary as well as secondary outcomes, please see above in the respective section (extended CTCAE, rescue care and need of antibiotics).

6. STUDY DESIGN

6.1 General study design and justification of design

Study design

The studied treatment, Urtica comp. is compared to the current gold-standard skin care “Excipial-Hydro lotion” in parallel design. As this is still a comparatively small pilot study with 30 patients in order to assess the feasibility of a potential larger trial, we conduct this study pragmatically in an open fashion. Generally the framework aimed at would be superiority, however given, that this is a pilot it is at this point still of exploratory nature.

Population, Duration and Procedures

All eligible patients with breast cancer of the Department of Radiation Oncology will be offered participation in the study. 1:1 Randomization of the consented patients takes place after the planning CT for radiotherapy.

The radiation therapy is conducted as clinically assigned for the patient, which is generally a course of six weeks, 5 weeks of total mamma irradiation and one week of “boost / volume reduction” resulting in a total of 25 fractions à 2 Gy. Follow-up assessment takes place at the regular follow-up assignment conducted for the radiation therapy 6 weeks after EOT. Thus, all study assessments take place during the regular clinical assessments conducted in the Department of Radiation Oncology.

Patients will undergo all regularly assigned therapy at the Department of Radio- Oncology Inselspital, including the standard skin care “Excipial-Hydro lotion”. Additionally the patients of the test-group will receive the study medication Urtica comp. gel. The gel is applied as soon as the patient senses “sunburn-like” itching or tingling in the radiation area, even, if the area is not reddened yet. In line with the general recommendation, no application is conducted during at least 6 hours before radiation therapy. In case of marked worsening, e.g. epitheliolysis, the patient may receive “Flammazine and lalugen plus” as rescue-care.

Skin condition is regularly checked before each radiation therapy session. In addition to the Baseline and end-of-therapy check, a weekly assessment is conducted by the treating physician using the Common Toxicity Criteria / Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute.

Questionnaires are attached under BASEC Document Number 11.

The study will be conducted, and the study therapy will be administered until the radiation treatment has finished and/or until the radiation dermatitis has ceased and the skin recovered or the latest until follow-up. If a patient wishes to continue to use the cream it can afterwards be obtained during regular clinical case outside of the study.

The reporting of Serious Adverse Events (sAEs) will be conducted in line with the therapeutic standards of the Department of Radiation Oncology.

6.2 Methods of minimising bias

6.2.1 Randomisation

Randomization is conducted according to the standard scientific methods as used at the Clinical Trial Unit of the University of Bern.

Allocation will be done via a dedicated website within the clinical trial management system REDCap, also containing the electronic case report forms.

Patients will be stratified by their bodyweight, as the bodyweight is a strong predictive factor for the development of radiation dermatitis.

Only system administrators who are otherwise not involved in the trial will have access to the algorithm and stored lists during the recruitment period. Investigators receive the allocation only after registration

of a patient. The underlying randomization lists and details of the algorithm will not be disclosed but kept securely at CTU Bern. All these measures will help to ensure concealment of allocation.

6.2.2 Blinding procedures

Not applicable.

6.2.3 Other methods of minimising bias

As the German Version of the CTCAE is not yet fully validated, the English validated Version [16] is used alongside the German Translation of "Deutsche Krebsliga" [17] in order to minimise bias.

For the patients self-assessment a well validated questionnaire, the Skindex16, is used in parallel to the not validated, however standardized visual analog scales. (As so far, no suitable standardized self-assessment specific to Radiation Dermatitis seem to exist).

6.3 Unblinding Procedures (Code break)

Not applicable.

7. STUDY POPULATION

Anticipated study population: adult patients attending the department of radiation therapy for Breast Cancer and set to start radiation therapy, which is conducted in an outpatient setting. In this pilot study no further centers are involved.

7.1 Eligibility criteria

Participants fulfilling all of the following inclusion criteria are eligible for the study:

- Radiation therapy for Breast Cancer
- Age \geq 18 years
- Informed Consent as documented by signature (Appendix Informed Consent Form)

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

- Ulcerated cancer at beginning of radiation therapy
- Skin lesions in the radiation area before start of radiation therapy
- Known allergies, hypersensitivity or reactions against one of the constituents of the investigational product [5]
- Any neurological or psychiatric conditions that, in the evaluation of the treating physician, deem the patient incapable to participate in the study
- Other clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.) as judged by the PI

The following criteria are exclusion criteria for the conduct of the radiation therapy, which is

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prerequisite for inclusion into the study. Thus, such patients will anyway not meet the inclusion criteria and are explicitly excluded from participation:

- Women who are pregnant or breast feeding
- Lack of safe contraception, defined as: Female participants of childbearing potential, not using and not willing to continue using a medically reliable method of contraception for the entire study duration, such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices, or who are not using any other method considered sufficiently reliable by the investigator in individual cases.
- Please note that female participants who are surgically sterilised / hysterectomised or post-menopausal for longer than 2 years are not considered as being of child bearing potential.

7.2 Recruitment and screening

All eligible patients of the Department of Radiation Oncology will be offered participation in the study.

At the planning CT for radiation therapy the patient is informed about the study by his/her treating physician and offered participation. During this time eligibility is assessed by the physician. Until the time of baseline-assessment, which is conducted when the radiation therapy starts, the patient has time to consider and sign the informed consent. This duration is generally one week.

No compensation is offered, as any assessment takes place during the regularly scheduled visits for radiation therapy and thus patients invest no extra time.

7.3 Assignment to study groups

Patient registration/randomization will only be accepted from authorized investigators.

Prior to registration, the following steps have to be taken:

- Fill in the patient screening, enrollment and identification list
- Check the eligibility criteria
- Obtain signed and dated written informed consent from the patient prior to any protocol-specific procedure according to ICH/GCP and local guidelines.
- The CRFs must be completed at the time of registration

Registration is done via Internet www.REDCap (<https://www.project-redcap.org/>). For technical difficulties, investigators are recommended to contact data management of CTU Bern

7.4 Criteria for withdrawal / discontinuation of participants

Patients can anytime withdraw from the study should they wish to do so, their data will be analysed up to that timepoint, as laid out in the informed consent document.

The treating physician can decide at any time to exclude the patient from the study, e.g. in case of concerns due to disease progression, change or premature end of the radiation therapy or any kind of safety concern. In such case the patient will be followed-up as deemed necessary by the treating physician in line with the treatment protocols of the department of radiation therapy.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products (treatment / medical device)

Patients will undergo all regularly assigned therapy at the Department of Radio- Oncology Inselspital, including the standard skin care "Excipial-Hydro lotion". This is the treatment of the comparator group.

The test group (=study drug group) receives Urtica comp. in addition to the regular treatment.

Urtica comp is applied as soon as the patients senses itching, tingling or "sunburn-like" sensations or if reddening of the skin is discovered, and the use is limited to the affected area. Non affected area is continuously cared for with Excipial-Hydro lotion.

8.1.1 Experimental Intervention (treatment)

Urtica comp. gelatum in its commercial formulation and packaging is used. The colorless Gel is also called "Wound and Burn Gel" and contains seven active substances: Argentum colloidal Dil. D5, Arnica montana e floribus LA 20%, Calendula officinalis e floribus LA 20%, Cantharis ex animale toto GI Dil. D5, Symphytum officinale ex herba LA 20%, Thuja occidentalis e summitatibus LA 20%, Urtica urens ex herba LA 20%.

All of them were manufactured based on to the methods as described in the German Homeopathic Pharmacopoeia (GHP, also known as HAB).

Wound and Burn Gel is the only dosage form of Argentum/Urtica comp.

Urtica comp is applied as soon as the patients senses itching, tingling or "sunburn-like" sensations or if reddening of the skin is discovered, and the use is limited to the affected area. Non affected area is continuously cared for with Excipial-Hydro lotion.

8.1.2 Control Intervention (standard/routine/comparator treatment / medical device)

Standard therapy for prevention and treatment of radiation dermatitis is the commercially available Excipial Hydro lotion by Galderma Schweiz AG. The lotion is applied directly onto the skin, like a cream.

1 ml of the lotion contains 20 mg urea. Polihexanid is used for conservation [21].

8.1.3 Packaging, Labelling and Supply (re-supply)

Regular commercial packaging is used.

8.1.4 Storage Conditions

Regular storage in the medication cabinet of the department.

8.2 Administration of experimental and control interventions

8.2.1 Experimental Intervention

The interventional product, Urtica comp, is applied directly onto the skin, like a cream. It is used as soon as the patient senses an itching, tingling or sunburn-like sensation or if reddening of the skin is discovered, and is applied onto the affected Area. The application is recommended 2 to 3 times per day, in line with the recommended use of the product. It can be used during the six weeks of radiation therapy as well as during the follow-up period (six weeks) if required. Patients are however instructed not to use it within 6 hours before radiation therapy, which is the guideline recommendation in the Department of Radiation Oncology.

8.2.2 Control Intervention

Excipial Hydro lotion is used as recommended in the patient leaflet [21] and can be used anytime freely during the six weeks of radiation therapy as well as during the follow-up period if required. Patients are however instructed not to use it within 6 hours before radiation therapy, which is the guideline recommendation in the Department of Radiation Oncology.

8.3 Dose modifications

Not applicable.

8.4 Compliance with study intervention

Clinical practice in the Department has shown that patients with breast cancer are eagerly using the recommended cream or lotion in order to prevent and alleviate the symptoms of radiation dermatitis.

Nevertheless is the use of the study cream and control lotion encouraged and checked at each visit.

Furthermore is the use check at the end of study, when the left-over products are returned.

8.5 Data Collection and Follow-up for withdrawn participants

If a patient withdraws from study an attempt should be made to collect the End-of-Study form. Follow-up is conducted as regularly scheduled for the radiation-therapy follow-up, in case the patient continues his/her radiation therapy. Patients who stop in total the therapy at the Department of Radiation Oncology will be contacted in order to assess the reason behind the withdrawal and a potential relatedness to study procedures.

Patients dropping out of the trial will be replaced.

8.6 Trial specific preventive measures

In case of marked worsening of the radiation dermatitis, e.g. epitheliolysis, the patient may receive "Flammazine and Ialugen plus" [19, 20] as rescue-care. The use of this medications is recorded in the CRF.

Non-trial specific, however important and specific for the radiation therapy is a pregnancy test at baseline and exclusion of pregnant women, women without safe contraception or breastfeeding mothers.

8.7 Concomitant Interventions (treatments)

Concomitant antihormonal therapy is permitted and will be recorded in the CRF as it may increase the occurrence of radiation dermatitis. Also smoking under therapy (although discouraged) will be recorded in the CRF for the same reasons.

8.8 Study Drug Accountability

The study medication and comparator are marketed and regularly used products.

According to recommended indication and dosage in this patient group, the comparator cream is ordered via the regular ordering. The Company WALA will provide the study drug for free. Both drugs are kept at the Department of Radiation Oncology in the regular medication cupboard.

8.9 Return or Destruction of Study Drug / Medical Device

The patients are requested to return unused study drug at the end of therapy.

9. STUDY ASSESSMENTS

9.1 Study flow chart / table of study procedures and assessments

Visit Form or action	Screening / Planning of RTx*	Baseline (at first treatment Visit) *	Visits during intervention (Treatment duration generally 6 wks * / **)	EOT / close- out visit *	Follow- up (EOT + 6wks*)
Therapeutic intervention	-	-	Radiotherapy (all) Group A: Urtica comp. Group B: standard care	-	-
Radomisation		x			
Assessment					
Eligibility	x				
Informed consent		x			
Med History		x			
Primary Endpoints					
Extended CTCAE (physician)	-	x	At each weekly assessment x x x x x x	x	x
Extended CTCAE (nurse)	-	x	If Dr's score is >= 1.5	x	x
Secondary Endpoints					
Clinical assessment (physician)	x	x	At each weekly assessment x x x x x x	x	x
Skindex 16 Items (patient)	-	x	One measurement point at mid of therapy - - - x - -	x	x
VAS (patient)	-	x	At each weekly assessment x x x x x x	x	x
FACIT-TS-G (patient)	-	-	-	x	-
End of Study form					x***

*allowed time frames for each visit: the dates and time frames are aligned with the radiation-therapy schedule clinically assigned for the patient. The regular schedule for radiation therapy of breast cancer starts with a planning CT and therapy is beginning a week later consisting of a course of six weeks, 5 weeks of total mamma irradiation and one week of "boost / volume reduction" resulting in a total of 25 fractions à 2 Gy. Follow-up is conducted 6 weeks (+/- one week) after end of therapy. In clinical experience this timeframe is strictly adhered to in 99% of patients, however should a patient require deviation from the schedule, e.g. due to tolerability-issues of the radiation therapy, the deviation as well as the reason for it will be recorded in the CRF.

** 6 intervention visits, including the baseline and EOT visit. In detail: BL, BL+1wk, BL+2wks, BL+3wks, BL+4wks, BL+5wks=EOT

***at follow-up or whenever the patient ends his/her participation in the study (e.g. in case of drop-out at the time of drop-out or as soon as possible after it.)

9.2 Assessments of outcomes

9.2.1 Assessment of primary outcome

Primary Outcome, the skin condition, is measured by the extended CTCAE scoring system (uploaded under BASEC section 11) assessing the skin condition with respect to radiation dermatitis. This assessment is made by the treating physician and nurse at baseline, at each weekly visit for radiation therapy during the treatment course of 6 weeks, at end of therapy and then at follow-up 6 weeks later.

The physician scores the skin condition on the “extended CTCAE”.

This scoring system was adapted from the Radiation Treatment Oncology Group (RTOG) and NIH Common Toxicity Criteria-Adverse Event (CTCAE) scales for acute radiation skin toxicity, which appears to be the most widely used measurement for radiation dermatitis [16].

The occurrence and severity of radiation dermatitis is measured using this scoring system, ranging 0.0 to 5.0 at increments of 0.5. Half step increments like this have been used in the past e.g. by Ryan et al. [15] to capture more precisely the severity of the radiation dermatitis. The score incorporates changes in redness, pigment, texture and integrity of the skin. Digital images of portraying the appearance of various RDS scores have also been incorporated to complement the verbal descriptions, which are containing the text of the standard CTC criteria, version 4.0 [16] as well as the German Translation of the CTC Criteria by „Deutsche Krebsliga“ [17].

A second rating is conducted by the nurse, in all cases where the physicians score is higher or equal to 1.5. The scores are combined in a joint score for additional precision.

9.2.2 Assessment of secondary outcomes

Percentage requiring no additional therapy for RD (e.g. Flammazine or Ialugen plus)

Percentage of patients RD free at end of therapy and at follow-up

Percentage of patients with secondary skin infection / need of topical and systemic antibiotics

Patient's assessment of the skin condition / quality of life / patient's evaluation of the treatment

As compared to the control group.

Secondary Outcomes are measured

1. by assessing at each visit whether the skin condition requires an additional treatment beyond the regular skincare or study medication with Flammazine or Ialugen plus.
The percentage of the patients requiring such treatment during their radiation therapy is compared between the two groups.
2. by calculating, based on the CTCAE, the Percentage of patients RD free at end of therapy and at follow-up and comparison between the two groups.
3. by assessing secondary skin infection in the radiation field and the need of topical and systemic antibiotics. The percentage of the patients requiring such treatment during their radiation therapy is compared between the two groups.
4. The Patients perspective is captured
 - by the Skindex 16 , which is a questionnaire commonly used for the self-assessment of skin conditions. The 16 items are rated on an ordinal scale ranging 0-6.
 - by visual analog scales (VAS) are used to assess pain, itching, burning, skin irritation, appearance and general quality of life (related to radiation dermatitis).
 - By a final evaluation of treatment utilizing a short version of the FACIT-TS-G (Functional Assessment of Chronic Illness Therapy - treatment satisfaction - general). A functional assessment of chronic illness therapy (FACIT) measure of satisfaction with treatment for chronic illnesses such as cancer and HIV/AIDS.

The patients' perspective is compared as well between both treatment groups.

9.2.3 Assessment of other outcomes of interest

No further assessments are planned.

9.2.4 Assessment of safety outcomes

9.2.4.1 Adverse events

Not applicable for Category A trial.

9.2.4.2 Laboratory parameters

Not applicable.

9.2.4.3 Vital signs

Not applicable.

9.2.5 Assessments in participants who prematurely stop the study

Please refer to section 10 for details

9.3 Procedures at each visit

9.3.1 Screening visit (BL -1wk*)

The screening visit takes place when the patient comes into the clinic for the planning of his/her radiation therapy. At screening visit the patient's eligibility, medical history and clinical details are assessed. (please find a list of all variables per visit as BASEC attachment Nr 05). The patient receives full information about the study. The informed consent document is handed to the patient and he/she can consider participation for a week, when the radiation therapy is starting.

9.3.2 Baseline visit*

The baseline visit takes place at the start of radiation therapy. Assessment "A" is conducted.

"Assessment A": A clinical assessment is conducted including the assessment of sAEs (please find a list of all variables per visit as BASEC attachment Nr 05). The Physician scores the Extended CTCAE. If the physician's score is equal or above 1.5, the Extended CTCAE is also scored by the nurse, who is otherwise blind to the scoring content of the physician. The patient fills in the VAS (visual analog scale) on his/her skin condition in the radiation area.

Additionally the patient fills in the Skindex 16.

Dispense of trial medication.

9.3.3 Visits during intervention

(weekly: BL, BL+1wk, BL+2wks, BL+3wks, BL+4wks, BL+5wks=EOT*)

The visits take place at the regularly scheduled visits for radiation therapy, which generally take place on a weekly base for the duration of six weeks (= 6 times, including the baseline and EOT visit).

"Assessment A" is conducted (see above).

Additionally the Skindex 16 is filled in by the patient at visit 4.

9.3.4 Close-out visit / EOT*

Close-out is conducted at the End Of Therapy, the last and sixth scheduled visit of radiation therapy.

Urtica comp. gel for prevention and therapy of radiation dermatitis
[version 1.8, 01. Feb. 2018, Study ID 211820931]

“Assessment A” is conducted (see above).

Additionally the Skindex 16 and the FACIT-TS-G is filled in by the patient.

9.3.5 Follow-up visit (EOT + 6wks*)

Follow-up is conducted at the regular follow-up visit of radiation therapy, which is six month after End Of Therapy.

“Assessment A” is conducted (see above).

Additionally the Skindex 16 is filled in by the patient.

The End of Study form is completed.

* noted timeframes are for general orientation only, the visit schedule will follow exactly the assigned visits for radiation therapy.

10. SAFETY

10.1 Drug studies

In line with the new law on clinical research (ordinance ClinO) the documentation of AEs for Category A drug trials is not required and will not be conducted beyond the AEs gathered as outlined in the objectives and safety-objectives.

All serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF) in line with the standards of the Department of Radiation Oncology during the entire duration of the study.

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.

10.1.1 Definition and assessment of (serious) adverse events and other safety related events

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. [ICH E6 1.2]

A **Serious Adverse Event (SAE)** is classified as any untoward medical occurrence that:

- results in death,
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

Assessment of Causality

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely(gesichert)	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably (wahrscheinlich)	Temporal relationship Improvement after dechallenge No other cause evident
Possibly (möglich)	Temporal relationship

	Other cause possible
Unlikely (unwahrscheinlich)	Any assessable reaction that does not fulfil the above conditions
Not related (ohne Beziehung)	Causal relationship can be ruled out
Can not be assessed (Nicht zu beurteilen)	Impossible to assess or to judge.
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Unexpected Adverse Drug Reaction

An “unexpected” adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. [ICH E2A]

Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

Assessment of Severity

The grades for severity described in the “Common Terminology Criteria for Adverse Events CTCAE Version 4.0” terminology are used.

10.1.2 Reporting of serious adverse events (SAE) and other safety related events

Reporting of SAEs

All SAEs must be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study, Dr. Nikola Cihoric and must be faxed to the safety desk (++41-(0)31 632 82 63) using the SAE reporting form provided by the sponsor-investigator. The Sponsor-Investigator will re-evaluate the SAE and return the form to the site.

SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) within 7 days.

Exemptions from expedited reporting may be possible if the SAE is a clear result of the underlying disease.

Reporting of SAEs or other safety relevant events to the Marketing Approval Holder (MAH) of the drug(s) will be conducted in line with the regular guidelines of Inselspital.

Reporting of SUSARs

A SUSAR needs to be reported to the local Ethics Committee (local event via local Investigator) within 7 days, if the event is fatal, or within 15 days (all other events).

Reporting of Safety Signals

All suspected new risks and relevant new aspects of known adverse reactions that require safety-related measures, i.e. so called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the local Ethics Committee (local event via local Investigator).

Reporting and Handling of Pregnancies

Pregnancy is an exclusion criterion from the study. However if a pregnancy is diagnosed after the accrual (during the treatment or in the follow-up phase), the continuation and discontinuation of the pregnancy and the treatment will be discussed with the patient.

Any pregnancy during the treatment phase of the study and within 30 days after discontinuation of study intervention will be reported to the Sponsor-Investigator within 24 hours. The course and outcome of the pregnancy should be followed up carefully, and any abnormal outcome regarding the mother or the child should be documented and reported.

Periodic reporting of safety

Not applicable.

10.1.3 Follow up of Serious Adverse Events

Patients with any reported ongoing serious Adverse Events at study end will be followed until resolution of the event or a stabilized condition of the participant has been achieved.

11. STATISTICAL METHODS

The statistical design is mainly based on the randomized part of the study.

11.1 Hypothesis

If a Null Hypothesis is tested, state explicitly both Null and Alternative Hypotheses in terms of the primary endpoint and justify them in regard of the participant population and dose. The stated hypotheses have to be used in the determination of Sample Size. Relate these hypotheses to the study objectives.

Descriptive analysis of demographics, disease and treatment features for the whole cohort and each treatment arm. Hypothesis testing:

- o H0: There is no difference between the test arm and the control arm in the incidence and severity of radiation dermatitis
- o H1: There is a difference between the treatment arm and the control arm in the incidence and severity of radiation dermatitis (favoring the test arm)

Both, the incidence as well as the severity of radiation dermatitis is highly meaningful to compare between the treatment arms in order to examine the effect of Urtica comp. in prevention and treatment of RD in breast cancer patients.

Given, that this is a pilot study to assess feasibility, sample size determination was conducted based on practical reasoning and not related to hypothesis testing.

11.2 Determination of Sample Size

As this is a first pilot study 30 patients with breast cancer will participate.

Since this is a pilot study no power analysis has been carried out, but the data of this pilot study are utilized for feasibility-assessment and will serve as the base for planning further larger and adequately powered randomized controlled research (→ "Machbarkeitsstudie").

According to the patient numbers in the department of Radiation Oncology and estimating a 50% participation and a 19% drop-out rate the recruitment can be achieved within six month.

11.3 Statistical criteria of termination of trial

ICH: A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

Describe the criteria for the termination of the trial or the stopping rules.

Not applicable.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

The datapoints at baseline and end of therapy are essential for the analysis. Patients for whom one or both of this points are missing will thus not be included into the analysis. It can be expected, that patients receiving the radiation therapy as scheduled will also follow the process of caring for their skin.

Both groups (test group and comparison group) will be evaluated according to the intention to treat. Patients for whom at least baseline and EOT values are available will be part of the analyse, in line with their respective group and irrespective of the course of study.

As this is a pilot study, explorative subgroup analysis may be conducted.

11.4.2 Primary Analysis

Incidence and severity of radiation dermatitis throughout the treatment course will be analysed. Both groups (test group and comparison group) will be evaluated according to the intention to treat. The statistical comparison between the groups will be carried out by applying a Man-Whitney-U test. Timepoint of comparison is at EOT.

11.4.3 Secondary Analyses

Calculations for secondary analysis will include:

Percentage requiring no additional Tx for RD (e.g. Ialugen +).

Percentage of patients RD free at end of therapy / follow-up.

Again, the statistical comparisons between the groups will be carried out by applying a Man-Whitney-U test.

The course of therapy of the group receiving Urtica comp. gel (=test group) will be compared with an active control group (comparison group) receiving the institutional standard skin care "Excipial-Hydro lotion" (as well as with historic standard-courses and the incidence and percentages described in literature.)

Statistical test will test whether or not the data are normally distributed and dependent on this finding the primary and secondary endpoints are compared with parametric testing (such a t-test) or nonparametric tests (such as Wilcoxon) between the two groups.

Timepoint of comparison for the secondary analyses is at EOT as well as at follow-up.

A p-value ≤ 0.05 will be considered significant.

11.4.4 Interim analyses

Not applicable.

11.4.5 Safety analysis

Safety analysis is integral part of primary and secondary analysis, please see above.

11.4.6 Deviation(s) from the original statistical plan

Any deviation from the planned analyses will be justified and reported if required

11.5 Handling of missing data and drop-outs

There will be a recruitment of patients until 30 Patient fulfil all the inclusion criteria. The data of dropout patients is treated with care and only the already observed data will be used for further analysis.

12. QUALITY ASSURANCE AND CONTROL

REDCap is used as clinical data management system (CDMS).

Data is recorded at the appointment with the physician and the nurse. Data is managed with the same care as it is standardized for every patient consultation. The paper with the data as well as the electronic patient reports and the CRF are locked and only authorized personnel has access to the data. For further use of the data, the paper version will be entered into REDCap by a co-worker. During the process of digitalisation, the data will be coded. The decoded master list is stored save at the principle investigator.

The training of site personnel is conducted in conjunction with the PI, study-coordinator, head nurse and study nurse.

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

An electronic database, REDCap is utilized and set up by the Clinical Trial Unit.

For each enrolled study participant a CRF is maintained. CRFs must be kept current to reflect subject status at each phase during the course of study. Study-related data of the patient will be collected in a coded manner. The names of the patients will not be disclosed. A code (unique, consecutive numbered) will be attributed to each patient registered.

Only study personnel trained in monitoring is authorized for CRF entries and it must be assured that any authorised person can be identified.

12.1.2 Specification of source documents

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

The source documents comprise the following: demographic data, visit dates, participation in study and Informed Consent Forms, randomisation number, SAEs, AEs of the skin and concomitant medication relevant to the study, results of relevant examinations.

Identification of the data: Data that are recorded in the eCRF in REDCap are uploaded as BASEC document 05: "05 CRF Strahlenerthem Variablenliste_Urtica comp."

Data evaluated by the physician will be entered from the medical history and data which are evaluated by the nurse from the IPDOS system.

12.1.3 Record keeping / archiving

The study database with all archive tables will be securely stored by CTU Bern for at least 15 years. The sponsor also keeps the Trial Master File and interim/final reports for at least 10 years.

12.2 Data management

REDCap is used as clinical data management system (CDMS).

12.2.1 Data Management System

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (REDCap). The EDC system is activated for the trial only after successfully passing a formal test procedure. All data entered in the CRFs are stored on a Linux server in a dedicated MySQL database.

Responsibility for hosting the EDC system and the database lies with CTU Bern.

12.2.2 Data security, access and back-up

Describe who has access to data, how, where and when – and which backup systems are in place (if applicable).

The server hosting the EDC system and the database is kept in a locked server-room. Only the system administrators have direct access to the server and back-up tapes. A role concept with personal passwords (site investigator, statistician, monitor, administrator etc.) regulates permission for each user to use the system and database as he/she requires.

All data entered into the CRFs are transferred to the database using Secure Sockets Layer (SSL) encryption. Each data point has attributes attached to it identifying the user who entered it with the exact time and date. Retrospective alterations of data in the database are recorded in an audit table. Time, table, data field and altered value, and the person are recorded (audit trail).

A multi-level back-up system is implemented. Back-ups of the whole system including the database are run internally several times per day and on external tapes once a day. The back-up tapes are stored in a secure place in a different building.

12.2.3 Analysis and archiving

Describe how data are extracted and where they are stored, database status recording, duration and place of storage (note MD: the archiving period is different for implantable devices).

At final analysis, data files will be extracted from the database into statistical packages to be analyzed. The status of the database at this time is recorded in special archive tables.

12.2.4 Electronic and central data validation

Data is checked by the EDC system for completeness and plausibility. Furthermore, selected data points are cross-checked for plausibility with previously entered data for that participant.

Before database lock the PI will validate the collected data with his signature.

12.3 Monitoring

REDCap is used as clinical data management system and is set up by the CTU. Otherwise no specific monitoring is required, as the study is considered to have a low risk level: application of the clinically recommended dosage of a Swissmedic registered cream, which is already marketed for over 80 years with a very favourable side effect profile (see section 3.4). Furthermore no invasive tests or therapy are part of the study.

However a quality-visit of the CTU (“Qualitätsvisite”) will be considered.

12.4 Audits and Inspections

Not applicable

12.5 Confidentiality, Data Protection

Data generation, transmission, storage and analysis of health related personal data within this project will follow strictly the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5.

Health related personal data captured during this project are strictly confidential and disclosure to third

parties is prohibited; coding will safeguard participants' confidentiality.

Data protection: project data will be handled with utmost discretion and only be accessible to authorised personnel. Direct access to source documents will only be permitted for purposes of audits and inspections.

12.6 Storage of biological material and related health data

Not applicable.

13. PUBLICATION AND DISSEMINATION POLICY

The Trial shall be registered with the ClinicalTrials.gov Database as well as with the Swiss National Clinical Trials Portal (SNCTP).

The study coordinator / project leader shall have the right of first publication in a peer-reviewed journal: Planned is a joint publication with all contributors which is to be organized and prepared by the project leader. Authorship is determined in line with scientific practice by contribution of the individuals and assuming fulfilment of the roles outlined in the protocol and staff list.

(Order of Authors: study coordinator / Project leader, Contributor 1, Contributor 2, Contributor 3 to x, Sponsor, Applicant. Shared first and last authorship may be applied between coordinator / Project leader, Sponsor and Applicant, depending on their contribution to the manuscript.)

All publications and presentations of results of the study shall be in accordance with accepted scientific practice; academic standards and customs.

The study coordinator / project leader will submit all manuscripts to the Sponsor for review at least twenty (20) days prior to the scheduled submission for publication. The sponsor also has the right to provide comments on the manuscript and both parties shall discuss in good faith to incorporate such comments in the publication or disclosure. The sponsor will be co-author of all publications derived from the data and additional co-authorship may be attributed to investigators from the centre.

However in the event that there is no first publication (or reasonable draft publication circulated to all involved co-authors) by the project leader within 24 months after termination of the Trial (LPLV), then notwithstanding the foregoing, the sponsor may individually propose a publication, provided that the proposed publication is first reviewed by the project leader and the applicant of the Department of Complementary Medicine or their respective representative.

14. FUNDING AND SUPPORT

14.1 Funding

The project is supported by the division of Anthroposophically extended Medicine (AEM) at the Institute of Complementary Medicine of the University of Bern (Prof. Dr. U.Wolf) and the Department of Radiation Oncology (Prof. Dr. Aebersold).

Depending on the results and feasibility of the pilot trial funding for the consecutive and larger RTC will be sought.

14.2 Other Support

The study medication Urtica comp. will be provided by WALA Heilmittel GmbH, Bad Boll, Germany.

WALA Heilmittel GmbH has non influence on planning, conduct, data analysis and publishing of the study.

15. INSURANCE

Not applicable (cat. A study).

16. REFERENCES

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- 3 Salvo N et al. Prophylaxis and management of acute radiation-induced skin reactions: a systematic review of the literature. *Curr Oncol.* 2010 Aug;17(4):94-112.
- 4 Nursing Guide of the Radiation Oncology Inselspital: „Pflege bei PatientInnen, die bestrahlt werden“ Section 3.2 „Hautpflege bei einer Strahlenreaktion“.
- 5 packet insert uploade das BASEC document 16d or under:
<https://www.walaarzneimittel.de/de/arzneimittel/wala-wund-und-brandgel.html> <https://www.walaarzneimittel.de/files/walaarzneimittel/medicines/beipackzettel/Wund-und-Brandgel.pdf>
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<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3998827/figure/F1/>
- 16 standard CTC criteria, version 4.0, - https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf
- 17 German Translation of the CTC Criteria by „Deutsche Krebsliga“ (<https://eliph.klinikum.uni-heidelberg.de/pdf/E5.pdf> page 18)
- 18 Flamazine packet insert:
<http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1490937614037.pdf> accessed on 10.08.2017 11:55h

19: Flammazine ® Fachinformation: <https://compendium.ch/mpro/mnr/21971/html/de> accessed on 10.08.2017 11:50h

20: Ialugen plus ® Fachinformation: <https://compendium.ch/mpro/mnr/4022/html/de> accessed on 10.08.2017 11:50h

21 Excipial Patienteninformation / Beipackzettel: <https://compendium.ch/mpub/pnr/23645/html/de>

22 Declaration of Helsinki, Version October 2013, (<http://www.wma.net/en/30publications/10policies/b3/index.html>)

23 International Conference on Harmonization (ICH, 1996) E6 Guideline for Good Clinical Practice. (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4.pdf) and International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf)

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27 ISO 14155:2011 Clinical investigation of medical devices for human subjects -- Good clinical practice www.iso.org

28 WHO, International Clinical Trials Registry Platform (ICTRP) <http://www.who.int/ictrp/en/>

17. APPENDICES

Table of documents as requested in BASEC and where the information is found, either referring to the protocol section or separately provided (uploaded in BASEC under the respective number).

No As in BASEC	Name of document	Info
1	Cover letter	Uploaded in BASEC
2	Synopsis of study plan	Not separately required. see No 4 page 7ff, section "study Synopsis"
3	Participant information sheet and informed consent	German version uploaded in BASEC, French version will be translated after approval of the content of the German version.
4	Study plan (protocol)	<i>This document</i>
4a	Monitoring plan	See No 4, p. 16 section 1.5 "monitoring"
5	CRF	Uploaded in BASEC
6	Investigators / PIs CV	Uploaded in BASEC
7	Investigators / PIs proof of GCP training	Uploaded in BASEC
8	Details on infrastructure suitability	Not applicable: Inselspital Radiation Oncology
9	Agreements	Not applicable
10	Insurance (optional)	Not applicable
11	Other documents handed to study participants	Uploaded Questionnaires : <ul style="list-style-type: none"> • Extended CTCAE (Dr and nurse) • Skindex (patient) • VAS (patient) • FACIT-TS-G (patient)
12	Details on compensation	Not applicable
13	Staff list	Uploaded in BASEC
14	Information on secure handling of biological material and personal data	see No 4: section 12.2, 12.5 and 12.6 for personal data biological material: not applicable
15	Information on review of this proposal by other authorities	Not applicable
16	Product information as approved by Swissmedic	Uploaded documents: 16a nonclinical overview and 16b clinical overview 16c Commission C Monograph 16d Packet Insert (Fachinformation) 16e Swissmedic "Zulassungsbescheinigung"
18	Proof of labelling	See No 4, page 31, section 8.1.1: regular commercial product is used
39	Varia	Not required.