Project**: SEAWave**

SEAWave Clinical study initiation package

Work Package:	WP7
Deliverable:	D7.2
Deliverable No.:	D24

Abstract

The skin is the largest organ of the body. It acts as a physical and immunological barrier against many physical and microbial dangers. These include electromagnetic waves (EMW) such as radiowaves, ultraviolet (UV) and X rays, as well as a long list of pathogens (bacteria, viruses, fungi, and parasites). 5G New Radio Frequency Range 2 (5G NR FR2) is a novel technology that will soon be deployed in Europe. The effect on human tissue is surmised to be small, based on previous studies performed at lower frequencies. The SEAWave-Clin study will provide essential data on the effect of 5G NR FR2 on normal human skin, thanks to healthy volunteers. It will also study the effects on skin that may be much more susceptible. Patients with dermatoporosis, skin tumour syndromes or atopic dermatitis are among the most sensitive individuals. In these patients, the data collected will be more likely to detect potential 5G-induced changes. Indeed, these patients are the ones who will likely benefit most from a better understanding of the effects of 5G NR FR2 on the skin.

Project Details

Project name	SEAWave
Grant number	101057622
Start Date	01 Jun 2022
Duration	36 moinths
Scientific coordinator	Prof. Th. Samaras, Aristotle University of Thessaloniki (AUTH)

Deliverable Details

Deliverable related number	D7.2
Deliverable No.	D24
Deliverable name	SEAWave Clinical study initiation package
Work Package number	WP7
Work Package name	Health Risk Studies: Biological Effects of FR2 Exposure on Human Skin
Editors	Professor Oliver Gaide, Dr Christine Pich-Bavastro
Distribution	Public
Version	H.0
Draft/final	Final
Keywords	5G, skin, cancer, dermatoporosis, genetic disease, atopic dermatitis

Double-blind randomized controlled study of the effects of 5G radiation on skin

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category B according to ClinO, Art. 61
Study Registration:	1. NCT05933954 2. SNCTP000005651
Sponsor:	Prof. O. Gaide CHUV-Dpt Dermatologie et Vénéréologie Hôpital de Beaumont Avenue de Beaumont 29 1011 Lausanne [redacted]
Principal Investigator :	Prof. O. Gaide CHUV-Dpt Dermatologie et Vénéréologie Hôpital de Beaumont Avenue de Beaumont 29 1011 Lausanne [redacted]
Investigated Intervention:	5G radiation Ondes 5G
Protocol ID	Protocol number
Version and Date:	Version 2.1 (dated 21/08/2023)

CONFIDENTIALITY STATEMENT

PROTOCOL SIGNATURE FORM

Study Title	Effects of 5G radiation on skin (SEAWave-Clin) Effets des ondes 5G sur la peau (SEAWave-Clin)
Study ID	2023-00884

The Sponsor has approved the protocol version 2.1 (dated 21/08/2023) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor-Investigator:

Name: Olivier Gaide

Date: _____ Signature: _____

TABLE OF CONTENTS

TABLE OF CONTENTS 2
GLOSSARY OF ABBREVATIONS 3
1 STUDY SYNOPSIS 3
2 BACKGROUND AND RATIONALE 4
3 STUDY OBJECTIVES AND DESIGN 7
3.1 Hypothesis and primary objective 7
3.2 Primary and secondary endpoints 7
3.3 Study design 8
3.4. Study intervention 8
4 STUDY POPULATION AND STUDY PROCEDURES 8
4.1 Inclusion and exclusion criteria, justification of study population 9
4.2 Recruitment, screening and informed consent procedure 11
4.3 Study procedures 11
4.4 Withdrawal and discontinuation 13
5 STATISTICS AND METHODOLOGY 14
5.1. Statistical analysis plan and sample size calculation 14
5.2. Handling of missing data and drop-outs 15
6 REGULATORY ASPECTS AND SAFETY 15
6.1 Local regulations / Declaration of Helsinki 15
6.2 (Serious) Adverse Events and notification of safety and protective measures 15
6.3 (Periodic) safety reporting 17
6.4 Radiation 17
6.5 Pregnancy 17
6.6 Amendments 17
6.7 Notification and reporting upon completion, discontinuation or interruption of the study 18
6.8 Insurance 18
7 FURTHER ASPECTS 18
7.1 Overall ethical considerations 18
7.2 Risk-benefit assessment 19
8 QUALITY CONTROL AND DATA PROTECTION 19
8.1 Quality measures 19
8.2 Data recording and source data 20
8.3 Confidentiality and coding 20
8.4 Retention and destruction of study data and biological material 21
9 MONITORING AND REGISTRATION 21
10. FUNDING / PUBLICATION / DECLARATION OF INTEREST 22
11. REFERENCES 22
Appendix 1: Schedule of assessments 24

GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ASR	*Annual Safety Report*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case Report Form*
eCRF	*electronic Case Report Form*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
SAE	*Serious Adverse Event*
5G FR2	*5G New Radio Frequency Range 2*
AD	*Atopic Dermatitis*
BCC	*Basal Cell Carcinoma*
CTU	*Clinical Trial Unit*
DP	*Dermatoporosis*
EMW	*ElectroMagnetic Waves*
FOEN	*Federal Office for the Environment*
GTF	*Genomic Technology Facility*
GG	*Gorlin-Goltz Syndrome*
ICNIRP	*International Comission on Non-Ionizing Radiation Protection*
ORNI	*Ordinance on Protection against Non-Ionizing Radiation*
OCT	*Optical Coherence Tomography (non-invasive skin imaging)*
SB	*Spiegler Brook Syndrome*
SCC	*Squamous Cell Carcinoma*
scRNAseq	*single cell RNA sequencing*
SECO	*State Secretariat for Economic Affairs*
SIB	*Swiss Institute for Bioinformatics*
SPEAG	*Schmid & Partner Engineering AG*
STS	*Skin Tumour Syndrome*
UV	*UltraViolet*
XPV	*Xeroderma Pigmentosum Variants*

1 STUDY SYNOPSIS

Study synopsis not filled as the protocol is less than 25 pages.

2 BACKGROUND AND RATIONALE

The skin is the largest organ of the body. It acts as a physical and immunological barrier against many physical and microbial dangers. These include electromagnetic waves (EMW) such as radio waves, ultraviolet (UV) and X rays as well as a long list of pathogens (bacteria, viruses, fungi and parasites)[1]. To cope with these insults, the skin needs a high cellular turnover. This is correlated with an increased risk of DNA mutations that, coupled with those due to UV light, drives cellular transformation leading to cancer[2]. As a result, skin cancer accounts for close to 50% of all human cancer, affecting both sexes in similar numbers and making it a central health issue in Caucasian populations. The barrier function of the skin is also linked to a strong immune appartus aimed at fighting against microbial pathogens. Dysregulation of this system is the basis for many frequent skin diseases such as psoriasis and atopic dermatitis[1]. Regarding cutaneous tumours, the skin immune system plays a counteracting role (tumour-editing) as evidenced by the >20-fold increase in skin cancer in immuno-suppressed patients[3].

5G New Radio Frequency Range 2 (5G FR2) is a novel technology that will soon be deployed in Europe. The effect on human tissue is surmised to be small, based on previous studies on the impact of EMW of the 3-4G range[4]. However, this has not fully quieted the questions and worries of the public, prompting the most extreme anti-5G partisans to set fire to 4G/5G antennas. It is easy to condemn those worries and call it obscurantism. However, the increase of data transfer from human mobile phone activity and device to device communication (internet of things), coupled to the fact that 5G FR2 has higher average/peak exposures (in comparison to 2G-5G FR1 communication systems), does raise the question of a potential tissue damage. Hence, despite the converging evidence of their innocuity, the effect of 5G exposure remains to be assessed in a definite manner. In this context, it is essential to provide clear and non-biased studies on the effect of 5G frequency ranges to the scientific community, decision makers and the public. And this has to be done on the skin, since it is the main if not the only target of these waves.

The CHUV is part of a large research consortium, which just received an important Horizon Grant and additional funding by the Federal Office for the Environment (FOEN). The project is entitled SEAWave, which stands for Scientific-based Exposure and risk Assessment of radiofrequency and mm-Wave systems from children to the elderly (5G and Beyond). The SEAWave project represents a unique opportunity to generate the data so long awaited in this field.

Preliminary data suggest that, like other EMW, 5G FR2 transfer energy to human cells and may thus change the biology of their proteins or DNA. Previous studies revealed that both 4G and 5G exposure of the human body concerns foremost the superficial tissues such as the eye and skin[5,6]. Importantly: i) skin is the main tissue exposed to 5G, ii) skin damage by some EMW favours cancer development and iii) skin cancer is exceedingly frequent[7]. For these reasons, the study of the impact of 5G on skin/skin cancer, at the core of this project, is a number one priority.

The goal of the SEAWave consortium biological studies is to assess the effects of 5G FR2 at 27.5 GHz. We chose this specific frequency as it will be used both in Europe and the US. The International Comission on Non-Ionizing Radiation Protection (ICNIRP) published in March 2020 guidelines regarding the exposure to EMF between 100 KHz and 300 GHz[8]. The exposure dose used will be below the basic restriction for occupational exposure as determined by the ICNIRP. It is stated that this exposure level was obtained by dividing by 2 the exposure level that induced biological effects, to take account of scientific uncertainty, as well as differences in thermal physiology within the population and variability in environmental conditions and physical activity levels. According to ICNIRP, "occupationally exposed persons are defined as adults who are

exposed under controlled conditions associated with their occupational tasks, trained to be aware of the potential risks associated with radiofrequency EMFs", and "occupationally exposed persons are not considered to be more exposed than the general public, provided that appropriate screening and training are provided to take account of all known risks". Thus, the use of the basic occupational restriction can be justified, as i) the likelihood of a participant being occupationally exposed cannot be ruled out; ii) those exposed at this level "are not deemed to be at greater risk" than those exposed at lower levels; iii) exposure will be well controlled, and subjects will be informed of potential risks and monitored; iiii) the maximum permissible exposure is necessary to maximize the effect of the physical exposure agent (in order to identify hazards other than those that have been established).

In South Korea, the average time spend on a smartphone is 4h[9]. A Swiss study showed that using a phone for more than 4h per day is detrimental for health[10]. The regulation of 5G FR2 phones allows an emission up to 20 W/m^2 in 6 min[8]. This short duration is characterized by a temperature increase (more than 1°C) which does not allow a blind exposure. We set the exposure time to 20 min to ensure that it was shorter than the harmful duration of use, convenient for the participant and limited the temperature rise. The system will emit 27.5 GHz waves at 20W/m^2, requiring a power of 1.5 W, for 20 min limiting the temperature rise to 1°C which is below the tissue operational adverse health effect threshold of 5°C[8]. Our 5G FR2 system is being built by our partners of the IT'IS Foundation (Foundation for Research on Information Technologies in Society) and will be calibrated by Schmid & Partner Engineering AG (SPEAG), a company that is certified by the State Secretariat for Economic Affairs (SECO) to perform this type of analysis and routinely certifies smartphones of the major brands (such as Apple and Samsung).

It is important to note that single exposures to EMW have been known to elicit measurable biological effects without increasing significantly the risk of skin cancer. A perfect example are UVBs. A single exposure sufficient to induce a sunburn (with measurable impact on skin biology), does not raise significantly the risk of carcinoma or melanoma. For this study, we have chosen a setting in which we major the chance of measuring a biological effect, yet does not raise pause a significant threat, according to all available data on EMW of 2G-5GFR1.

The skin is a very complex organ, composed of a high number of different cell types, that all influence its state. Studying it requires a profound knowledge of its function. The skin is divided in an outer part, the epidermis, an intermediate part, the dermis, and an inner fat part, the hypodermis. Each layer has specific roles and components. The epidermis keeps water in and UV and microbes out. It also plays other important roles such as touch, vitamin D synthesis and immune surveillance. It is composed of keratinocytes, as well as melanocytes, Merkel and Langerhans cells. Dermis is composed of fibroblasts, and a variety of immune cells including dermal dendritic cells, mast cells, CD4+ and CD8+ T cells, dermal γδ T cells, macrophages, natural killer cells, and innate lymphoid cells. It has a supportive role for the epidermis, provides elasticity and plays an important immunological role. Hypodermis is mainly composed of adipocytes, which have a cushioning and metabolic role[1].

The high complexity of the skin has prompted teams around the world to invest time and resources in novel techniques that use high throughput DNA or RNA sequencing to provide comprehensive and unbiased studies of skin modifications. In our team, we have used these techniques to delineate immune cell trafficking in the skin[11]. And more recently, we used single cell RNA (scRNAseq) analysis to study the biology of the most frequent human cancer, basal cell carcinoma (BCC)[12–15]. To the best of our knowledge, these techniques have not yet been used to study the effect of EMW on human cells and human tissues. It is important to stress here that, because unbiased and powerful studies like the one proposed herein do not exist, debate still

rages about the negative impact of 5G. And although there is a stream of evidence for the safety of these new EMW type, scientist and politician do not have the clear-cut results they need. Indeed, previous studies have taken educated guess on the best read-outs for the effect of EMW. As a result, the data generated is incomplete and, importantly, biased. For example, there is a clear lack of studies on the impact of 1-5G on the immune system, despite its essential role it plays in tumour editing (the capacity to recognize budding cancer cells and eliminate them). Hence, the SEAWave project represents the most ambitious and comprehensive research program ever attempted in this field. There are no similar programs elsewhere in the world.

The SEAWave Project will provide essential data on the effect of EMW on normal human skin, thanks to healthy volunteers. We also intend to study its effect on skin that may be much more susceptible to these types of exposures. Patients with dermatoporosis (DP), skin tumour syndromes or atopic dermatitis are among the most sensitive individuals. In these patients, the data collected will be more likely to detect potential 5G-induced changes. And these patients are the ones who will likely benefit most from a better understanding of the effect of 5G on the skin. DP is a disease caused by chronological aging, long-term and unprotected sun exposure, and probably undefined genetic factors[16]. The hallmark of DP skin is that it is significantly thinner than healthy skin, thus letting more 5G waves in. Skin tumour syndromes (STS; eg Familial Basal Cell Cancer or Gorlin-Goltz (GG) Syndrome (OMIM 109400)[17], Familial Cylindromatosis or Spiegler Brook (SB) Syndrome (OMIM 132700/605041)[17], Xeroderma Pigmentosum variants (XPV) (OMIM 278750)[17] are diseases leading to early tumour development. XPV is a disease due to an impaired DNA repair machinery, leading to premature skin cancer and aging[18]. These type of skin contain pre-malignant cells that may be more susceptible to 5G waves. Atopic dermatitis (AD) is a frequent disease displaying both a damaged skin barrier and increased inflammation/immunity[19]. This skin is in a state of perpetual sub-clinical inflammation that may make cells more sensitive to EMW exposure. We chose to expose 2.5 cm of the inner arm skin. The inner arm is a body part with little exposure to the sun. This surface size will able us to collect 2 biospies of 7.5 mm (5 mm + 2.5 mm punchs) without affecting each other, in particular via the inflammation produced by the biopsy. Studies showed that nascent RNAs are already detectable 10 min[20] and 30 min[21] after UV irradiation, that transcription slows down after 40 min[20] and that normal RNA level is reached 24h after[20,21]. Moreover, it has been shown by RNAseq that skin injuries induce different trancription modifications 1 hour and 24 hours after injury[22,23]. Hence, the 1st biopsy will be taken 1h after the beginning of the exposure (and thus 40 min after the end of the exposure), to measure the immediate cellular response[22,23]. A shorter time would give the cell little time to set up its protein expression machinery and might not be enough to detect transcription changes above the background. The 2nd biopsy will be taken 24h after exposure, to measure the delayed cellular response and, importantly, any changes in the cell population, such as entry into the cell cycle or the migration of immune/inflammatory cells[20–24]. It is also convenient for participants, who do not have to come at night. Later time points would be interesting, but would require too many trips and biopsies for participants. What's more, the results could be distorted by exposure to the 4G/5G waves that are part and parcel of everyday life.

The risks are minor or negligible. At the level of the skin, the delivered dose is very low (lower than the exposure dose tolerated during standard use of a cell phone, as defined by the ICNIRP[8] and the Ordinance on Protection against Non-Ionizing Radiation (ORNI), last revised on 01.01.2022, and its long-term effects can be considered as negligible according to the current scientific knowledge (in particular compared to the daily radiation of 4G and 5G). It has been shown that two 4h-exposures in two days induces no major changes in culture cell and reconstituted skin model[25]. As 5G waves do not go beyond the skin, the risk of adverse side

effects on another part of the body is negligible. Thus, we do not expect any adverse events (AE) related to 5G radiation. Biopsies under local anaesthesia induce small scars. There is a small risk (less than 1/1000) of a local infection that can be treated with antibiotics or of bleeding. Therefore, we consider this study to be a Category B.

In conclusion, the project adresses an important biological question, essential to the well-being of the community, in an ubiased way and with a neglible risk.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

We are aiming to determine whether 5G radiations have an effect on the skin homoeostasis and may affect the volunteer's wellbeing.

The primary objective of the study is to evaluate the effects of 5G radiation on normal and at-risk skin: DP, STS, and AD, comparing exposed and unexposed skin.

The second objective of the clinical study is to compare the effects of 5G on the skin of women and men.

The third objective is to determine if an at-risk skin is more sensible than normal skin to 5G.

3.2 Primary and secondary endpoints

Patients with DP, STS or AD are among the most sensitive individuals. Therefore, the data collected is more likely to detect potential 5G-induced changes, if they exist. As a read-out, exposed vs non-exposed (double-blinded) skin samples will be subjected to scRNAseq, an up-to-date and very sensitive tool, to maximize the chance of observing even minute modification of cell behaviour, and do so in the many cell types composing the skin. This extremely powerful and unbiased analysis will highlight any and all modifications in the transcriptome provoked by 5G radiation. We will compare exposed and non-exposed skins 1h and 24h after exposure. Each participant is his/her own control (unexposed vs exposed arm) for two time-points. We will compare exposed and non-exposed skins, pooling women and men, in each group. We will also perform this comparison separating the genders in each group. In addition, we will be able to compare our results to published lists of genes (signatures) known to be modified in BCC, squamous cell carcinoma (SCC), melanoma and atopic dermatitis, in the stromal and non-stromal cells [13–15,26–29]. This is based on educated guesses and is slightly biased but maximizes the chances of finding if 5G EMW have a measurable impact on skin tissue or not (Figure 1).

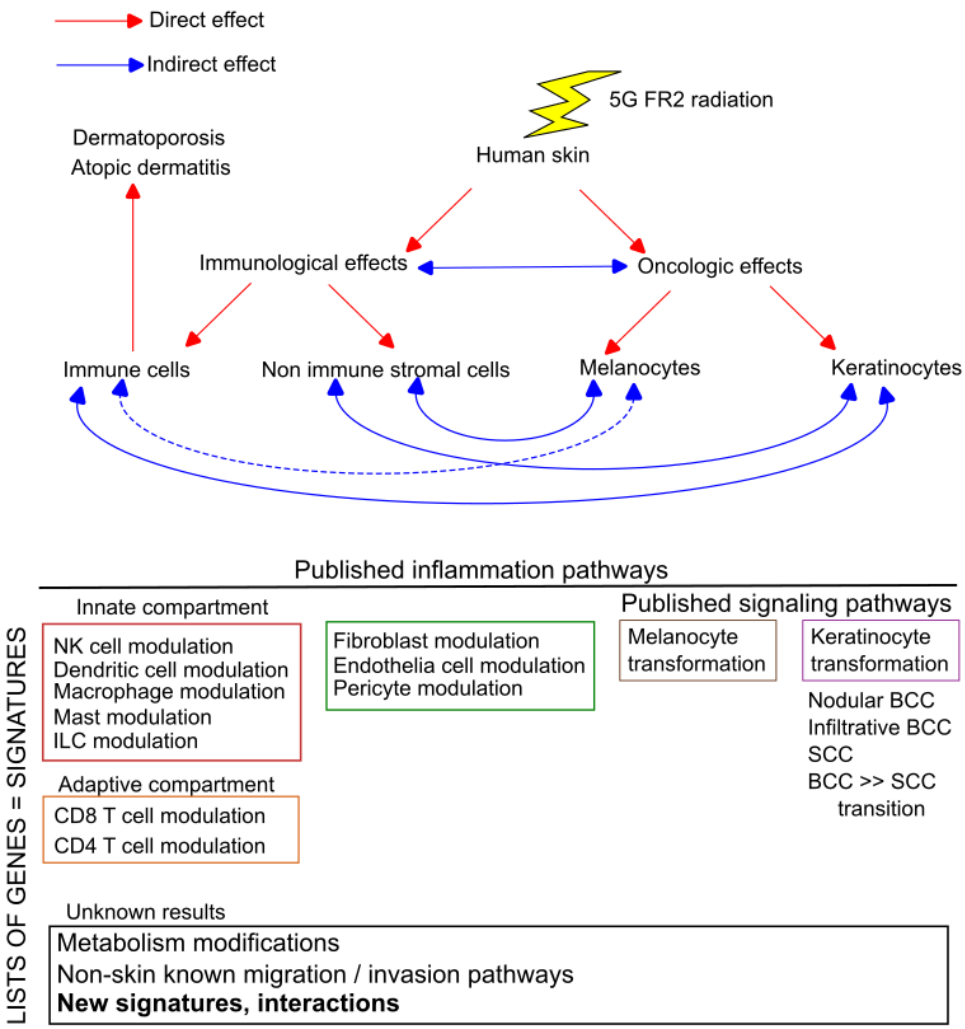

Figure 1. Potential results of the scRNAseq. Schematic of direct and indirect effects of 5G FR2 radiation of the human skin. Modulations can be activation (pro-inflammation), inhibition (immunosuppression), changes in cell proportion and/or recruitment, known skin cell migration and / or invasion pathways. We may obtain unknown results (in particular new signatures and new interactions) and we will be able to do comparisons with published signatures, including our own [13–15,26–29]. BCC: Basal Cell Carcinoma, ILC: Innate Lymphoid Cells, NK: Natural killer, SCC: Squamous Cell Carcinoma.

3.3 Study design

To understand the effects of 5G waves on skin, we will perform a clinical trial. In this study, participants will be first examined by optical coherence tomography to determine the skin thickness, then exposed to carefully chosen 5G parameters and skin will be analysed by state-of-the-art scRNAseq analysis (an unbiased and very sensitive technique ideal for studying cell behaviour changes).

The clinical study will be monocentric, as the CHUV is the only contributing site.

The exposure will be double-blind and randomized (computer-controlled), performed only once, short (20 min), localized (2.5 cm circular area), painless, and safe.

3.4. Study intervention

The day of the exposure, participants will be taken care of by Prof. Gaide and placed in a closed room. An examination of the skin with optical coherence tomography will be first performed to

determine the skin thickness. This non-invasive procedure provides a picture of the first 2 mm of the skin ressembling an ultrasound. It is painless and perfectyl safe.

The participants will be installed confortably on a hospital bed for the 20 minutes.

The certified 5G sources will be placed on each arm of the participants, but only one will be active. Our clinical trial requires precise and consistent 5G FR2 waves emission, which cannot be obtained by applying a commercial 5G phone on the skin. Our partners of the IT'IS Foundation are building a specifically designed 5G antenna that alleviates this problem, and will thus allow us to safely expose human skin to 5G FR2 waves: a 27.5 GHz exposure system for well-controlled double-blinded exposure of a 2.5 cm circular area on both upper arms of the volunteers (Figure 2, provided by IT'IS). These devices will be calibrated by SPEAG, a company that is certified by the SECO to perform this type of analysis and routinely certifies smartphones of the major brands (such as Apple and Samsung). IT'IS will be responsible for the installation and quality assurance during the execution of the experiment.

These sources will emit 5G waves in a very localized way (Figure 2) and thus expose only a small area of the arms. Only one of the two sources will emit waves (controlled and randomized by a computer), but in order not to distort the study, neither the participants nor Prof. Gaide will know which one.

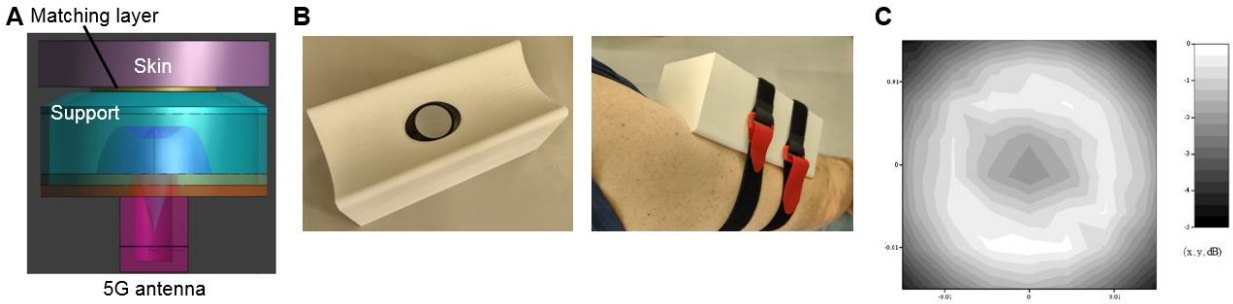

Figure 2. 5G FR2 exposure system. A) Schematic of the 5G FR2 antenna. The matching layer prevents the skin reflection, and the support extends the exposure surface. B) Pictures of the 5G FR2 patient exposure system. C) Measurement of the radiation at the surface of the 5G antenna.

This exposure will be lower than the exposure dose tolerated during standard use of a cell phone, as defined by the ICNIRP[8] and the ORNI.

This exposure will not be painful.

After the exposure, the participants will wait 1h and we will perform, under local anaesthesia, a biopsy sample on each arm and we will proceed to the closure of the wound by a simple suture. Immediately after collection, the biopsies will be put in culture medium or snap-frozen. We will take a second set of samples 24h after the exposure with the same procedure. We will monitor the healing and plan/execute the removal of suture material. The four biopsies will be processed at the same time for scRNAseq and for later validation.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Our clinical trial will involve healthy participants, patients with DP or whose skin is prone to develop cancer or who suffer from AD. These patients are among the most sensitive individuals. As a result, the collected data is more likely to detect potential 5G-induced changes when

compared to young, healthy skin not recently exposed to the sun. Healthy young adults should be close to their 18th birthday (limit if the adulthood) in order to have skin as close as posible to their best state of health and thickness. After the age of 25, the progressive skin changes linked to sun exposure or disease can lead to great variability in skin anatomy and physiology.

We will recruit 42 volunteers divided in 4 groups:

- Healthy volunteers, from 18 to 25 yo, without skin disease, 6 females, 6 males,

or

- Dermatoporosis patients, 60yo and more, with active disease, 6 females, 6 males,

or

- Skin tumour syndromes, 18yo and more, with active disease, 3 females, 3 males,

or

- Atopic dermatitis, 18yo and more, with active disease, 6 females, 6 males

STS are rare diseases, so there are few patients. The STS group was therefore reduced to a reasonable number.

List the study inclusion criteria:

- Patients will be recruited in accordance with European and Swiss standards for the targeted diseases:

Dermatoporosis defined as a chronic skin fragility syndrome[30,31]

or

GG Syndrome defined as OMIM 109400[17],

or

Familial Cylindromatosis or SB Syndrome defined as OMIM 132700/605041[17],

or

XPV defined as OMIM 278750[17]

or

Atopic dermatitis defined as a chronic inflammatory skin disease characterised by eczematous skin lesions and intense pruritus[32,33]

- Able to give informed consent as documented by signature,
- Adults, 18 yo and more, according to groups.

List the study exclusion criteria:

- Recent intense exposure to sun (defined as causing a sunburn, within the last 7 days)
- Pregnant (excluded with a pregnancy test) or lactating women,
- Patients taking anti-coagulants
- Clinically significant concomitant diseases (cutaneous exam by the specialist),
- Active enrolment in another clinical trial,
- Participants incapable of judgment or participants under tutelage.

4.2 Recruitment, screening and informed consent procedure

The department of dermatology-venereology of the CHUV is the reference centre in the French speaking part of Switzerland for patients suffering from STS, DP, and AD. As such, it is fully suitable to recruit the study population. Prof. Gaide is the principal investigator (PI) of several clinical studies on oncological conditions (lymphoma, Merkel cell carcinoma patients, Flash radiotherapy) and he is co-investigator on more than 50 other studies. These include investigator-initiated studies. Thus, Prof. Gaide has shown capacity to recruit patients for more difficult studies. The onco-dermatology unit lead by Prof. Gaide is the de facto local reference centre for patients suffering from STS and DP. Prof. Gaide thus follows 10 patients with STS at the CHUV, 5 males and 5 females (3XP, 5GG, 2BS). He also follows hundreds of DP and AD patients. Hence, we know that recruitment is well within the capacity of the centre.

Participant recruitment will occur through the study coordinator in his daily clinical practice, as well as the placement of flyers for the recruitment of healthy volunteers.

The investigator 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 or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating physician (for study monitoring purposes).

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.

The formal consent of a participant, using the approved consent form, will be obtained at least 24 hours before the participant is submitted to any study procedure.

The consent form will be signed and dated by the investigator or his designee. A copy of the signed informed consent will be given to the study participant. The consent form will be retained as part of the study records and the patient's electronic file of the CHUV.

Participants will receive the following compensation for their contribution to this study: a lump sum of CHF 500.- for their time and payment of actual travel expenses (train, gasoline, parking accordingly).

Their participation will have no financial consequences for them or their health insurance.

4.3 Study procedures

The clinical study will last for 18 months, beginning with the recruitment of volunteers in September 2023 and ending with the delivery of the last reports in January 2025. The recruitment will start after the authorities give the authorization.

The recruitment should last for a few month (September 2023 – January 2024).

We expect to start the study with the first patient soon after receiving the devices at CHUV in September 2023.

For each patient, the study will last for two weeks: 1 day for the exposure and 1st set of biopsies, 1 day after for the 2nd set of biopsies, 12-14 days later for the follow up of the healing and removal of the suture material.

The participants will meet with Prof. Gaide to get the oral and written information on the clinical study. If they accept, an appointment will be schedule for the intervention.

The day of the exposure, participants will be taken care of by Prof. Gaide and placed in a closed room. He will collect the signed informed consent.

The signed informed consent will be uploaded into our Horus Consent account (that we will have access after the approval of this current application from the Ethics Committee) to obtain coded ID for the future samples. The volunteers' information and the coded ID of their samples will be implemented in REDCap® eCRF. Only Prof. Gaide and the authorities will have access to the Horus consent account and eCRF.

An examination of the skin with optical coherence tomography will be first performed to determine the skin thickness.

The participants will lie on a bed for 20 min in order to have a homogeneous exposure. This exposure will not be painful.

A 5G source will be placed on each arm of the participants. These sources will emit 5G waves in a much-localized way and thus expose only a small area of the arms (< 5 cm^2). Only one of the two sources will emit waves (controlled by a computer), but in order not to distort the study, neither the participants nor Prof. Gaide will know which one. The computer will stock the information on which source was active during the exposure. One arm will be exposed to 20W/m^2 (a dose rate inferior to the recommended maximum for EMW exposure in Switzerland), the other not. The exposure time is 20 min. An algorithm will randomly select the arm to be exposed. Measures of the exposures will be performed on both arms (Figure 3A). Only Prof. Gaide, the data analysts and the authorities will have access to this information that will be added to the eCRF.

After the exposure, the participants will wait 1h and Prof. Gaide will perform, under local anaesthesia, one 7.5-mm biopsy by punch (two pieces: one 5-mm punch + half a 5-mm punch; Figures 3B-C) on each arm and he will proceed to the closure of the wound by a simple suture. Immediately after collection, the 5-mm punch will be put in a culture medium and the 2.5-mm punch will be snap-frozen. A second set of samples will be taken 24h after the exposure with the same procedure (Figure 3D). After both skin biopsies, the wounds will be covered with a dressing that will protect the area (from microbes and UV). We will monitor the healing and plan the removal of any suture material.

For each participant, we will use 1 full biopsy per arm and per time-point for the scRNAseq analysis, four in total. The other four half biopsies will be kept frozen for later validation or used as backup if any problem during the scRNAseq process (Figure 3B).

The analyses by scRNAseq will start with the first 4 participants, then every 10 participants, as we can analyze 16 to 40 samples per batch to decrease the variability between the samples. The 1st 16 samples analysis will allow us to ajust the procedure if needed.

The end of the clinical part with the last patient is expected in or before July2024.

The bioinformatics and statistical analyses and validations should end in January 2025.

Reports will be performed at midterm (January 2024) and at the end of the study (January 2025).

If they occur, AE and severe adverse events (SAE) will be regularly reported to the authorities.

A table of the schedule of assessments is available in the Appendix 1.

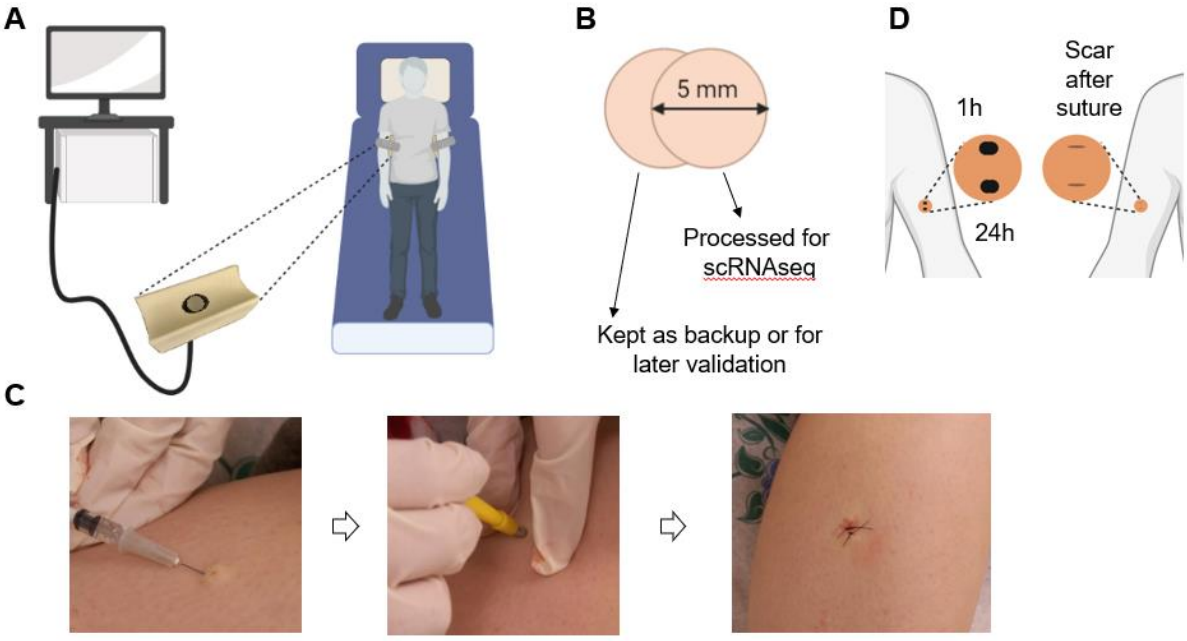

Figure 3. 5G exposure procedure. A) Scheme illustrating the 5G FR2 exposure system connected to the computer and the participant exposure. B) Illustration of the 7.5-mm punch biopsy. C) Picture of a 5-mm punch. D) Illustration of the biopsies on each inner arm (left) and after wounding (right).

The four biopsies will be processed at the same time (to avoid variability between the samples) to obtain intact single cells, which will be stored at -80°C. The protocol for obtaining intact single cells from skin biopsies is derived from a proven protocol used in the dermatology department's research groups. It has been adapted to this large quantity of samples, to optimize consistency between samples. Samples collected every 4 or 10 participants will be analysed by scRNAseq at the Genomic Technology Facility (GTF) of the University of Lausanne. The GTF is the local reference for such analysis in the Canton de Vaud. The scRNAseq analysis will not be based on direct sequencing of the volunteers' RNA, but on sequencing of probes. Thus, we will not obtain genetic data, and it will be impossible to find the identity of the volunteers from the results of this analysis. Sequencing data will be stored on the secured Swiss Institute for Bioinformatics (SIB) servers. The GTF and SIB will provide help for the performance of the quality controls. We will directly start to analyse these first results. This entire process will be repeated for each block of up to 10 participants, until we have collected all samples from all 42 participants.

The leftover biopsies may be used for later validation of the scRNAseq results, and/or for validation of new scientific evidence obtained on the animal and cell studies performed in parallel in the other groups of the SEAWave consortium.

4.4 Withdrawal and discontinuation

If a participant decides to withdraw his/her informed consent, the already collected data and material will be kept coded for the analysis. At the end of the study, we will anonymize the data and destroy the remaining biological material. We will permanently erase the code linking them to the participant, so that no one will know afterwards who the data and samples belonged to. This process is primarily intended to ensure data protection.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

Patients with DP, STS, or AD have a particularly sensitive skin. As a result, the collected data is more likely to detect potential 5G-induced changes when compared to young, healthy skin not recently exposed to the sun. We believe that the effects of 5G will be critical if we detect at least a twofold increase in inflammation: for instance, twice as many inflammatory cells are detected in the exposed area as in the unexposed area, or there is an increase in the inflammatory gene signature in non-immune cells in the exposed area than in the unexposed area. The possible outcomes are described in Figure 1.

We use https://riskcalc.org/samplesize/ to calculate the number of participants: it is a randomized parallel study, equivalence trial. To achieve a 80% power at 5% level of significance with equal allocation (all three are standard), with an allowable difference of 2 (two-fold increase in inflammation), we obtain a result of 5 patients per group per sex. We have therefore selected 6 patients per group, men or women, in case of withdrawal of a participant. For the STS group, patients are scarce, so we decided to select at least 3 men and 3 women. We also relied on the study by Reynolds et al[29]. This study compared non-lesional and lesional skin in 3 patients with AD (two men and one woman), using the same analysis (scRNAseq). This small number enabled them to find significant differences in immune cell populations and activation in lesional skins compared with non-lesional skins, used as control skins, with each participant being his or her own control.

Thus, for our study, we believe that i) an analysis with 6 participants per group, each being their own control, will enable us to detect significant differences induced by 5G, if any; ii) having 6 participants per group per gender instead of 3 will enable us to better include the intra-group heterogeneity and reduce the false-positive responses; iii) the reduction of the STS group to 3 participants per gender should not be detrimental to us.

We have several levels of comparison:

- Each participant is his/her own control (unexposed vs exposed arm) for the two time-points
- In each group (healthy and diseases), we will compare exposed vs unexposed samples at the 1h time point
- In each group (healthy and diseases), we will compare exposed vs unexposed samples at the 24h time point
- We will also compare exposed vs unexposed samples regarding the differences between women and men
- The three disease groups will be compared to the healthy group

Our inputs in the scRNAseq analysis will be from the sequencing and the eCRF, for each sample:

ScRNAseq data from the sample, age, sex, group (healthy, dermatoporosis, atopic dermatitis, genetic syndromes), skin thickness (+/- 10 um), arm of the biopsy, recorded delivered dose on each arm, 1h after exposure (+/- 10 min), 24h after exposure (+/- 1h), concomitant medication, healing process, adverse effects.

The outputs are based on our own analyses and others[13–15,26–29]. We will use Seurat[34] package

to perfom the quality controls of the data on individual samples, then integrate the samples for each patient to analyze their inter-variability. To determine cell types, we will combine unsupervised clustering and differential expression to compare top differentially expressed genes (using Wilcoxon rank sum tests of the FindMarker function of Seurat) with cell type specific expression known from literature. We will also use ProjecTILs package[35] to define more precisely the immune subtypes.

We will then integrate the samples from the same group and sex. At this integration level, we will be able to find the modifications induced by 5G exposure, comparing exposed and non exposed samples, at 1h and at 24h. The next step will be to integrate men and women of the same group and perform the same analyses. The final integration of all the groups will allow us to hightlight the effects of 5G by comparing the 5G-exposed skins from the different groups, keeping only the significant changes found in the previous steps. Relying on the study by Reynolds et al[29], for comparisons of cell proportions between exposed and non exposed skin, the distribution will be modelled as a quasibinomial distribution. The exposure will be provided as a covariate for the proportion of the cell type being assessed. The quasibinomial model will be fit using glm from the MASS R package. The p-value for the significance of the change in proportion between conditions will be assessed using a likelihood-ratio test, computed using the ANOVA function.

5.2. Handling of missing data and drop-outs

We selected one more participants per group per gender than was calculated by riskcalc.org to ensure that we had enough samples at the end of the collection, in case of withdrawal of 1 participant per group or a problem during the procedure.

If during the scRNAseq process one or more samples are lost, we also have the 2nd set of frozen samples that we can process.

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	**Description**
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

The period of AE/SAE will last 30 days after the procedure (as beyond that point a complication due to the biopsy cannot occur anymore).

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

Follow up of (Serious) Adverse Events

The investigator will assess each subject to evaluate for potential AE and SAE within the area of 5G exposure / biopsy site. As specified in section 7.2, we do not expect any detectable side effects due to the exposure and exposure material. Each biopsy site may lead to minimal bleeding or skin infection (skin breach), although these are very rare (less than 1 in 1000). Hence, on a total of 168 biopsies, we can expect less than 1 side effect. If such a side effect occurs, we will monitor it as any bleeding or skin infection following surgery, ie wound dressing and local or systemic antiseptic/antibiotic until complete resolution. We will call the participants 3 months after the exposure/biopsies for a follow-up control asking 1) how they feel, 2) if there is a problem with their biopsies, and 3) if they need to see Prof. Gaide.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics Committee of these measures, and of the circumstances necessitating them, within 7 days.

6.3 (Periodic) safety reporting

An annual safety report (ASR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs 1).

6.4 Radiation

Our clinical trial requires precise and consistent 5G FR2 waves emission, which cannot be obtained by applying a commercial 5G phone on the skin. Our partners of the IT'IS Foundation are building a specifically designed 5G antenna that alleviates this problem and will thus allow us to safely expose human skin to 5G FR2 waves: a 27.5 GHz exposure system for well-controlled double-blinded exposure of a 2.5 cm circular area on both upper arms of the volunteers. Hypoallergenic material is used. These devices will be calibrated by SPEAG, a company that is certified by the SECO to perform this type of analysis and routinely tests smartphones of the major brands (such as Apple and Samsung). The manufacturing of the final system including the control system will be outsourced and purchased by CHUV. IT'IS will be responsible for the installation and quality assurance during execution of the experiment.

At the level of the skin, the delivered dose is very low (lower than the exposure dose tolerated during standard use of a cell phone, as defined by the ICNIRP[8] and the ORNI), and its long-term effects can be considered as negligible according to the current scientific knowledge (in particular compared to the daily radiation of 4G and 5G).

We sent a request to BASEC / CER-VD before completing this application with this information. After examination, the CER-VD considered that the outlined project is to be classified as another clinical trial.

6.5 Pregnancy

A pregnancy test will be performed before the exposure. If a participant discovers that she is pregnant during the study, she should inform the Sponsor-Investigator immediately. In this case, she will be asked to provide information about the progress and outcome of the pregnancy. The Sponsor-Investigator will discuss with her what to do.

However as the delivered dose is very low (lower than the exposure dose tolerated during standard use of a cell phone within the restrictions of the ICNIRP[8] and the ORNI), localized on the upper arm, and its long-term effects can be considered as negligible according to the current scientific knowledge (in particular compared to the daily radiation of 4G and 5G), it is unlikely that the pregnancy will be affected by the study.

6.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. 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 Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

6.7 Notification and reporting upon completion, discontinuation or interruption of the study

Upon regular study completion, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

At the end of the study, the health-related data or remaining biological samples are stored on site and constitute a database or biobank for research purposes, in coded form. These databases do not allow for the identification of the participant in any way.

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

6.8 Insurance

In the event of study-related damage or injuries, the liability of the institution CHUV provides compensation, except for claims that arise from misconduct or gross negligence.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

5G New Radio Frequency Range 2 (5G FR2) is a novel technology that will soon be deployed in Europe. The effect on human tissue is surmised to be small, based on previous studies on the impact of EMW of the 3-4G range. However, this has not fully quieted the questions and worries of the public, prompting the most extreme anti-5G partisans to set fire to some antennas. It is easy to condemn those worries to obscurantism. However, the increase of data transfer from mobile and device to device communication (internet of things), coupled to the fact that 5G FR2 has higher average/peak exposures (in comparison to 2G-5G FR1 communication systems), does raise the question of a potential tissue damage. Hence, despite the converging evidence of their innocuity, the effect of 5G exposure remains to be assessed in a definite manner. In this context, it is essential to provide clear and non-biased studies on the effect of 5G frequency ranges to decision makers.

Patients with DP, STS or AD are among the most sensitive individuals. Therefore, the data collected is more likely to detect potential 5G-induced changes. These patients are the ones who will benefit most from a better understanding of the effect of 5G on the skin. Although, the research project will not provide any direct benefit to the participants, it will help answer a question of major importance to society.

Participants will be informed of incidental findings if they have an impact on their health. This means that they will be informed if a previously unknown disease is discovered by chance or if a disease can be prevented by preventive measures.

We are certain that our project adresses in an ubiased way an important biological question, essential to the well-being of the whole community, and with a neglible risk.

7.2 Risk-benefit assessment

The risks are minor or negligible. The imaging by optical coherence tomography represents no risk for the participants.

At the level of the skin, the delivered dose of 5G is very low, and its long-term effects can be considered as negligible according to the current scientific knowledge (in particular compared to the daily radiations of 4G and 5G). Compared to UVB radiations, which are known to be carcinogenic, harmful at the minimal erythemal dose (MED; 250J/m^2 for type I and type II skins), and are currently used to test sun screen efficacy, the dose of 20W/m^2 over 20 min represents 0.017J/m^2, 1/15000 MED. As 5G waves do not go beyond the skin, the risk of adverse side effects on another part of the body is negligible. We do not expect any AE related to 5G radiation.

A slight heat could be felt during the exposure, on the zone of exposure to the 5G waves. This heat does not represent any risk to the participant.

Biopsies under local anaesthesia induce small scars. There is a small risk (less than 1/1000) of a local infection that can be treated with antibiotics or of bleeding.

The research project is unlikely to provide any direct benefit to the participants, but it will help answer a question of major importance to society in general. Those that belong to an at-risk category may have higher benefit from the ensuing knowledge. Finally, scRNAseq analysis may lead to incidental finding that may benefit the participants.

Hence, this project will provide an unbiased analysis of the effect of 5G EMW, which is important both to the scientific community and to the Swiss community in general. It does so at a neglible risk for the participants.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

The Clinical Trial Unit (CTU) of the CHUV reviewed this application. It has established a monitoring plan according to the need of this clinical study, and has planned quality visits.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

Source data for the patients will be recorded in their medical files.

Source data for the healthy volunteers will be recorded in a volunteer logbook. In the event of an AE or SAE, a medical record will be opened and the volunteer's source data recorded.

Study data will be recorded in RedCap® eCRF.

Each participant will obtain a coded ID after referencing their informed consent form into Horus Consent software. Their eCRF will be maintained during the study.

The following participants' information will be found in the eCRF:

- Coded ID (obtained after consent collected in Horus Consent)
- Age
- Sex: M / F
- Group:
    - Healthy
    - Dermatoporosis
    - Genetic disease: XP / GG / BS
    - Atopic Dermatitis
- Date of clinical trial information
- Date of consent signed
- List of concomitant medication
- Absence of recent intense exposure to sun (defined as causing a sunburn, within the last 7 days)
- Absence of pregnancy (excluded with a pregnancy test) or breastfeeding
- Absence of anti-coagulants medication
- Absence of clinically significant concomitant diseases (cutaneous exam by the specialist)
- Absence of active enrolment in another clinical trial
- Participants capable of judgment and not under tutelage
- Date of exposure
- Skin thickness (defined by OCT)
- Biopsies:
    - 1h post-exposition, left and right arms, with recorded dose of exposure
    - 24h post-exposition, left and right arms, with recorded dose of exposure
- Control of the healing process:
    - Date of the removal of sutures
    - Control of the healing process
- Adverse effects
- Signature of the Sponsor-Investigator

The scRNAseq results will be published in reports and peer-reviewed journals as required by the Horizon grant.

8.3 Confidentiality and coding

The investigator affirms and upholds the principle of the participant's right to privacy and that the Investigators and all designees and research staff shall comply with applicable privacy laws. Especially, participants coding shall be guaranteed when presenting 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 utilizing subject identification code numbers to correspond to treatment data in the computer files. The subject's data collected in the trial will be stored under this number. Only the Investigator or designee (e.g. CRA) will be able to link the subject's trial data to the subject via an identification list kept at the site.

For data verification purposes, authorized representatives of the Sponsor-Investigator, the authorities may require direct access to parts of the medical records relevant to the study, including participants' medical history.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

Only non-genetic data are used as the sequencing will NOT generate genetic data.

Biological material in this study is not identified by participant name but by a unique participant number. Biological material is appropriately stored in a restricted area only accessible to the authorised personnel.

To prevent unauthorised or accidental disclosure, alteration, destruction and theft of biological material, only the Sponsor-Investigator, the biologist and the PhD student will have access to the material and know their precise location. The coded samples will be directly processed or snap-frozen after collection and stored at -80°C in order to be able to analyse them by batch and thus have a better consistency between samples. Fridges and freezers are under the maintenance of the CHUV, and freezers are connected to alarms to prevent complete thawing.

No biological material will be shipped outside the study site. Personal clinical data will not be shared with anyone.

Coded non-genetic (expression) data will be made available, as requested by the FOEN and the SEFRI, to the SEAWave research consortium and the scientific community. This corresponds to non-genetic health-related data, which can be sent abroad for research as the requirements of Swiss data protection law are met (FADP, Art. 6).

8.4 Retention and destruction of study data and biological material

All study data are archived for 10 years after study termination or premature termination of the study, in the department of dermatology and venereology of the CHUV. At the end of the study, the health-related data or remaining biological samples are stored on site and constitute a database or biobank for research purposes, in coded form. These databases do not allow for the identification of the participant in any way. They can only be used for gene expression comparison studies of cellular populations of the skin (corresponding to the planned use).

9 MONITORING AND REGISTRATION

The monitoring will be performed by the CTU of Lausanne, in accordance with ICH GCP E6(R2). The monitor (independent of the research team) will carry out this activity according to a pre-

established monitoring plan adapted to the risk of the clinical trial. The monitor will verify that the clinical trial is conducted, and that the data are generated, documented and reported in accordance with the requirements of the protocol, the GCP and the applicable regulatory requirements. In concrete terms, an initiation visit, intermediate visits, and a closing visit will be organized on each site by the monitor in accordance with the monitoring plan. At each site, the local PI will ensure that the monitor always has access to the trial data and source documents and will respond to questions and requests for corrections during the monitoring visits.

The study is registered in the Swiss National Clinical Trial Portal (SNCTP via BASEC) and on ClinicalTrials.gov (number NCT05933954).

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

This project is co-funded by Horizon through the SEFRI (HORIZON-HLTH-2021-ENVHLTH-02) and the FOEN (BAFU-320.1-01-60677/2/1/7/7).

As part of the SEAWave project, our partners will have access to our results during the study (under the restrictions described in 8.3), as well as all reports and publications. A data transfer agreement is signed by the CHUV and our partners, detailed in the “Consortium Agreement”. During the study, raw data from the scRNAseq will be stored in the SIB server with restricted access. After publication of the results, this data will be stored in a public repository (e.g. Zenodo). Identification of the participants will not be possible as the sample names will be coded and no genetic data will be analysed (probe sequencing).

If gender effects are observed, they will be published in the final study report. If an analysis is performed but no gender effects are observed, this should also be published.

11. REFERENCES

1. Chambers, E. S. & Vukmanovic-Stejic, M. Skin barrier immunity and ageing. *Immunology* **160**, 116–125 (2020).
2. Degueurce, G. *et al.* Identification of a novel PPAR β/δ/miR-21-3p axis in UV -induced skin inflammation. *EMBO Molecular Medicine* **8**, 919–936 (2016).
3. Jambusaria-Pahlajani, A. *et al.* Predicting skin cancer in organ transplant recipients: development of the SUNTRAC screening tool using data from a multicenter cohort study. *Transplant International* **32**, 1259–1267 (2019).
4. Wu, T., Rappaport, T. S. & Collins, C. M. Safe for Generations to Come: Considerations of Safety for Millimeter Waves in Wireless Communications. *IEEE Microwave Magazine* **16**, 65–84 (2015).
5. Haider, Z. *et al.* High-Resolution Model of Human Skin Appendages for Electromagnetic Dosimetry at Millimeter Waves | IEEE Journals & Magazine | IEEE Xplore. *IEEE Journal of Microwaves* **2**, 214–227 (2022).
6. Christ, A., Samaras, T., Neufeld, E. & Kuster, N. TRANSMISSION COEFFICIENT OF POWER DENSITY INTO SKIN TISSUE BETWEEN 6 AND 300 GHZ. *Radiation Protection Dosimetry* **192**, 113–118 (2020).
7. Stern, R. S. Prevalence of a History of Skin Cancer in 2007: Results of an Incidence-Based Model. *Archives of Dermatology* **146**, 279–282 (2010).
8. Protection (ICNIRP)1, I. C. on N.-I. R. Guidelines for Limiting Exposure to Electromagnetic Fields (100 kHz to 300 GHz). *Health Physics* **118**, 483–524 (2020).
9. Jung, S. I., Lee, N. K., Kang, K. W., Kim, K. & Lee, D. Y. The effect of smartphone usage time on posture and respiratory function. *Journal of Physical Therapy Science* **28**, 186–189 (2016).
10. Berchtold, A., Akre, C., Barrense-Dias, Y., Zimmermann, G. & Surís, J.-C. Daily internet time: towards an evidence-based recommendation? *European Journal of Public Health* **28**, 647–651 (2018).

11. Gaide, O. *et al.* Common clonal origin of central and resident memory T cells following skin immunization. *Nat Med* **21**, 647–653 (2015).
12. Chiang, A. *et al.* Genetic Mutations Underlying Phenotypic Plasticity in Basosquamous Carcinoma. *J Invest Dermatol* **139**, 2263-2271.e5 (2019).
13. Kuonen, F. *et al.* c-FOS drives reversible basal to squamous cell carcinoma transition. *Cell Reports* **37**, 109774 (2021).
14. Yerly, L. *et al.* Integrated multi-omics reveals cellular and molecular interactions governing the invasive niche of basal cell carcinoma. *Nat Commun* **13**, 4897 (2022).
15. Pich-Bavastro, C. *et al.* Activin A-mediated polarization of cancer-associated fibroblasts and macrophages confers resistance to checkpoint immunotherapy in skin cancer. *Clinical Cancer Research* CCR-23-0219 (2023) doi:10.1158/1078-0432.CCR-23-0219.
16. Menzinger, S., Saurat, J.-H. & Kaya, G. Morphological Analysis of Dermatoporosis by in vivo Reflectance Confocal Microscopy and Ultrasonography. *Dermatopathology* 279–287 (2020) doi:10.1159/000505990.
17. Online Mendelian Inheritance in Man.
18. Rizza, E. R. H. *et al.* Xeroderma Pigmentosum: A Model for Human Premature Aging. *Journal of Investigative Dermatology* **141**, 976–984 (2021).
19. Di Lucca-Chrisment, J. & Gilliet, M. Traitements systémiques émergents de la dermatite atopique. *Rev Med Suisse* **600**, 685–689 (2018).
20. Williamson, L. *et al.* UV Irradiation Induces a Non-coding RNA that Functionally Opposes the Protein Encoded by the Same Gene. *Cell* **168**, 843-855.e13 (2017).
21. Liu, J., Wu, Z., He, J. & Wang, Y. Cellular fractionation reveals transcriptome responses of human fibroblasts to UV-C irradiation. *Cell Death Dis* **13**, 1–10 (2022).
22. Ledwon, J. K., Kelsey, L. J., Vaca, E. E. & Gosain, A. K. Transcriptomic analysis reveals dynamic molecular changes in skin induced by mechanical forces secondary to tissue expansion. *Sci Rep* **10**, 15991 (2020).
23. Choudhary, S. *et al.* Genomic analyses of early responses to radiation inglioblastoma reveal new alterations at transcription,splicing, and translation levels. *Sci Rep* **10**, 8979 (2020).
24. Alafiatayo, A. A., Lai, K.-S., Ahmad, S., Mahmood, M. & Shaharuddin, N. A. RNA-Seq analysis revealed genes associated with UV-induced cell necrosis through MAPK/TNF-α pathways in human dermal fibroblast cells as an inducer of premature photoaging. *Genomics* **112**, 484–493 (2020).
25. Kim, K., Lee, Y. S., Kim, N., Choi, H.-D. & Lim, K.-M. 5G Electromagnetic Radiation Attenuates Skin Melanogenesis In Vitro by Suppressing ROS Generation. *Antioxidants* **11**, 1449 (2022).
26. Kuonen, F. *et al.* Loss of Primary Cilia Drives Switching from Hedgehog to Ras/MAPK Pathway in Resistant Basal Cell Carcinoma. *Journal of Investigative Dermatology* **139**, 1439–1448 (2019).
27. Jerby-Arnon, L. *et al.* A Cancer Cell Program Promotes T Cell Exclusion and Resistance to Checkpoint Blockade. *Cell* **175**, 984-997.e24 (2018).
28. Alkon, N. *et al.* Single-cell analysis reveals innate lymphoid cell lineage infidelity in atopic dermatitis. *Journal of Allergy and Clinical Immunology* **149**, 624–639 (2022).
29. Reynolds, G. *et al.* Developmental cell programs are co-opted in inflammatory skin disease. *Science* **371**, eaba6500 (2021).
30. Kaya, G. Dermatoporose : un syndrome émergent. *Rev Med Suisse* **155**, 1078–1082 (2008).
31. Kaya, G. & Saurat, J.-H. Dermatoporosis: A new concept in skin aging. *European Geriatric Medicine* **1**, 216–219 (2010).
32. Piletta-Zanin, A., Hsieh, A., Mühlstädt, M. & Andenmatten-trigona, B. Dermatologie. Dernières avancées des thérapies ciblées dans la dermatite atopique, la pelade et l'urticaire chronique spontanée. *Rev Med Suisse* **767**, 156–160 (2022).
33. Wollenberg, A. *et al.* European guideline (EuroGuiDerm) on atopic eczema: part I – systemic therapy. *Journal of the European Academy of Dermatology and Venereology* **36**, 1409–1431 (2022).
34. Hao, Y. *et al.* Integrated analysis of multimodal single-cell data. *Cell* **184**, 3573-3587.e29 (2021).
35. Andreatta, M. *et al.* Interpretation of T cell states from single-cell transcriptomics data using reference atlases. *Nat Commun* **12**, 2965 (2021).

Appendix 1: Schedule of assessments

Time	**>-1 day**	**D0**	**D+1**	**D+14**
Visit	Information	Intervention/1st visit	2nd visit	3rd visit
Oral and written patient information	+			
Written consent signed at least 24h before		+		
Inclusion-/ exclusion criteria	+	+		
Medical history		+		
Physical examination		+		
Participant characteristics		+		
Skin thickness		+		
Radiation		+		
Sampling		+	+	
Safety		+	+	+