The Cleveland Clinic Foundation
Consent to Participate in a Research Study

Project Title: CASE 4623; **Short contact protocols to reduce pain during treatment of actinic keratoses with 10% ALA gel red-light photodynamic therapy (PDT)**

Sponsor: Biofrontera, Inc.
Principal Investigator: Edward V. Maytin, M.D. Ph.D. [redacted]
Study Coordinator: Beverly Doyle, [redacted]

Cancer research studies are coordinated by physicians and scientists from Cleveland Clinic, University Hospitals and Case Western Reserve University (CWRU) through the NIH National Cancer Institute (NCI) designated Case Comprehensive Cancer Center (Case CCC). The goal of this collaboration is to enhance cancer treatment and research in Northeast Ohio. This study is being offered at Cleveland Clinic (CC).

Key Information: The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Why am I being invited to take part in a research study?
We invite you to take part in a research study because you have been diagnosed with a type of pre-cancer, Actinic Keratosis (AK), on your face.

What should I know about a research study?
- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

Why is this research being done?
The purpose of this study is to determine if shortening the incubation time (the amount of time the medicine sits on your skin prior to being activated by the red light) can lower pain levels during Photodynamic Therapy (PDT) while still effectively treating your AKs. In previous studies on PDT with a short incubation time, patients reported lower pain levels and were found to have similar results to patients treated with a standard PDT regimen. Your participation in this study will help us to design effective PDT regimens that cause less pain to patients.

Photodynamic Therapy (PDT) is a light-based therapy in which a medication gel is applied to the skin and activated with a red light. The activated medication then kills the AK cells. PDT is approved by the Food and Drug Administration (FDA) for the treatment of AKs. The topical medication gel (Ameluz) being used in this study to treat AKs is also approved by the FDA. The amount of time it sits on your skin is different from the treatment times approved by the FDA.

How long will the research last and what will I need to do?
There are 4 visits during the study. Visits 1 and 3 are PDT treatments, and the other 2 are follow up visits to assess the progress of your AKs. You will also have photos taken of your AKs, answer questions about your pain levels and satisfaction with the treatment, and fill out a questionnaire about any side-effects you have from the treatment.

Your participation in the research will last about 4 months.

More detailed information about the study procedures can be found under "What extra tests and procedures will I have if I take part in this study?"

Is there any way being in this study could be bad for me?
You may not want to participate in this study if you want to have a conventional PDT treatment or if you want your AKs to be treated without PDT.

More detailed information about the risks of this study can be found under "What possible risks can I expect from taking part in this study?"

What possible benefits can I expect from taking part in this study?
We cannot know if you will have any benefit as a result of your participation in the study; it is possible the study treatment may improve your condition, which may give you relief from some symptoms or improve your quality of life. However, it is possible that your condition could worsen. Your participation in this study will help us obtain information about treating patients with actinic keratosis (AKs).

What is the usual approach to my Actinic keratosis?
If you choose not to participate, your actinic keratosis will still be treated using PDT or other standard treatment modalities, such as cryosurgery or 5FU cream.

What are my other choices if I do not take part in this study?
If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available
- or you may choose not to be treated. For example: comfort/palliative care

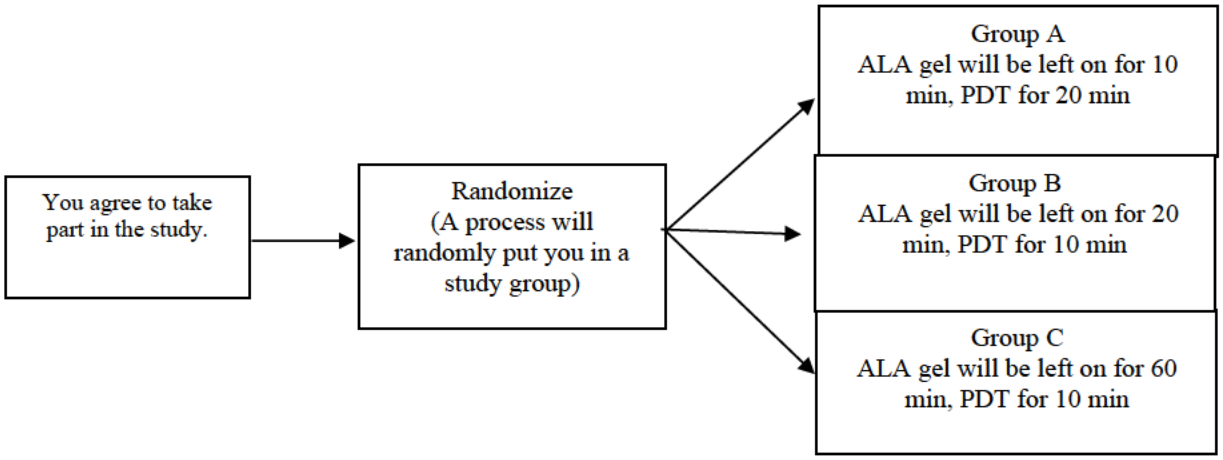
Detailed Information: The following is more detailed information about this study in addition to the information listed above.

What are the study groups?
This study has three study groups (Groups A, B, or C). The group you are placed in will determine the amount of time the medicine will sit on your skin before the PDT and how long the PDT will last. The table below shows the study treatment groups:

Study Group	Medication Treatment Time	Light Treatment Time
Group A	10 Minutes	20 Minutes
Group B	20 Minutes	10 Minutes
Group C	60 Minutes	10 Minutes

You have an equal (1 out of 3) chance of being assigned to each study group. A process will be used to assign you, by chance, to one of the study groups. Neither you nor your doctor can choose which group you are in. This is done by chance because no one knows if one study group is better or worse than the other.

To find out what will happen to you during this study read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



*SEE PAGE 11 FOR COMPLETE STUDY CALENDAR

What extra tests and procedures will I have if I take part in this study?
In order to evaluate the effectiveness of this new method for treating your AKs, there may be extra procedures that you will need to have if you take part in this study.

Photodynamic Therapy (PDT)
PDT is a noninvasive treatment FDA approved for AKs in which a topical agent (called Ameluz or ALA) is applied to the skin and then exposed to a particular type of light, in our case Red Light (BF-RhodoLED). The topical agent, Ameluz, is a preparation containing aminolevulinic acid (ALA) as its active ingredient. It is applied to the skin as a gel. Exposure to the light targets and kills the AKs.

Photographs
Photographs of your face including the AK lesions will be taken during the study. These photos

will be used to determine the clinical response of your AKs to treatment. Safeguards are in place to protect from any inappropriate access to your photos including the use of codes (instead of names), encrypted and/or password protected computers and phones, and limiting data access to the research team exclusively.

Before you begin the study:
You will need to have the following extra exam to find out if you can be in the study:

- Physical exam and documentation of at least 10 AKs on the face.

If the exams shows that you can take part in the study, and you choose to take part, then you will need the following extra study procedures. They are not part of the usual approach for AKs.

During the study the following will be additional research procedures:

- Skin exam and lesion count (at 3 visits)
- Photography of AK lesions (at 4 visits)

What possible risks can I expect from taking part in this study?
If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual.
- You may be asked sensitive or private questions which you normally do not discuss.
- The study drug(s)/study approach may not be better, and could possibly be worse, than the usual approach for your condition.

You will also be receiving topical Ameluz and activation with light (PDT). Side effects of PDT, are described in more detail below. As with all treatments, there is always some risk that you could have side effects from the study drug(s)/study approach

Here are important points about side effects in general:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study treatment to try to reduce side effects.

Potential Risk or Discomfort from Research Procedures

Photodynamic Therapy Risks

PDT causes photosensitivity of the treated area for 48 hours. Photosensitivity means the area of your skin where PDT was performed is more sensitive to sunburn. It is important to avoid sun exposure to the treated area for 48 hours after PDT.

ALA, the active ingredient in Ameluz, is a natural component found in all cells in the human body. ALA may have the following side effects when applied to the skin:

- Allergic reaction (Hypersensitivity)
- Sensitivity of skin to sunlight
- Irritation or swelling of the lips or eyes.

- A very rare side effect of Ameluz in combination with PDT, when applied directly to the entire face or forehead, is temporary memory loss for up to 24 hours after treatment. Only a few cases have ever been observed and no long term memory impairment linked to PDT treatment has been recorded.

When ALA is activated by PDT, the following signs and symptoms may occur:

- Stinging and/or burning sensation
- Localized redness
- Swelling
- Peeling
- Blisters (rare)

It is necessary to wear eye protection during PDT. Protective eyewear will be provided for you.

Reproductive Risks

Although very little reproductive risk is thought to be associated with topical photodynamic therapy, it is not known for sure if ALA has any effect on fertility or reproductive function. If you are pregnant or nursing at the time of study participation, you cannot be in this study.

Confidentiality Risks

There is a potential risk of loss of confidentiality of your data. Every effort will be made to keep your information (data) confidential through the use of the following safeguards: You will be assigned a study code and all clinical data required by the protocol will be identified using that code. All data is stored using a unique subject assigned number and no personal identifying data will be entered. Approved members of the Cleveland Clinic and Case Comprehensive Cancer Center will have access to your data.

What happens to the information collected for the research?

If identifiers are removed from your identifiable private information, that information could be used for future research studies or distributed to another investigator for future research studies without your additional informed consent. Some of your data, primarily your AK treatment results and pain scores, may be sent outside of the Cleveland Clinic to the sponsoring company (Biofrontera). Be assured that any personal information that might identify you will be removed before any data are shared.

Can I stop taking part in this study?
Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study requirements
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA.

What are my rights in this study?
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

What are the costs of taking part in this study?
The following research study activities are being done only because you are participating in this research study and will be paid for by the study sponsor and will not be billed to you or your health insurance plan. These "research only" activities include: Topical treatment with Ameluz and Red Light PDT, office visits with the study doctor, skin exams, photography, and aftercare supplies provided at study visits.

Some of the services you may receive during this research study are considered to be conventional routine clinical services that you would have received even if you were not participating in the research study and will be billed to you or your health insurance plan. Examples of these routine services include: Treatment of any AK's outside of the facial area, treatment of any AKs remaining after the study, or treatment of any non-AK lesions. You are responsible for paying any deductibles, copayments or co-insurance that are a normal part of your health insurance plan.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://www.cancer.gov/clinicaltrials/learningabout.

Are there any payments to you if you participate in this study?
You will receive a free parking voucher on the day of each of your study visits. In addition, you will receive a $100 stipend at the completion of the final visit.

The IRS requires CCF to report payments to an individual of $600 or greater (in a calendar year) on a Form 1099-MISC. Your name, address and social security number will be collected to track the payments made to you and, if you receive $600 or greater, will be used to process a Form 1099-MISC.

What happens if I am injured or hurt because I took part in this study?
If you believe that you are injured as a result of the research procedures being performed, please immediately contact the study doctor.

In the event you suffer a research related injury as a result of being in this study, Cleveland Clinic will provide appropriate medical treatment for such injury in a timely manner. Provision of such medical treatment does not imply any negligence or other wrongdoing on the part of Cleveland Clinic or any of the physicians or other personnel involved in the study. If you believe that you have been injured as a result of participating in the study, please immediately contact your Cleveland Clinic study doctor even if you may have already been seen or treated by another doctor. If you are seen or treated by a doctor other than the study doctor, you should inform such doctor that you are in this study and, if possible, take this document with you as it may help such doctor treat you.

If injury occurs as a result of your involvement in this research, medical treatment is available from Cleveland Clinic or another medical facility but you/your medical insurance will be responsible for the cost of this treatment. A research injury is an injury that happens as a result of taking part in this research study. If you are injured by a medical treatment or procedure that you would have received even if you weren't in the study, that is not considered a "research injury". There are no plans for payment of medical expenses or other payments, including lost wages, for any research related injury. To help avoid injury, it is very important to follow all study directions.

Further information about research-related injuries is available by contacting the Cleveland Clinic Institutional Review Board at ([redacted].

What else do I need to know?
Your information may be used to create products or to deliver services, including some that may be sold and/or make money for others. If this happens, there are no plans to tell you, or to pay you, or to give any compensation to you or your family.

ADDITIONAL STUDIES SECTION: This section is about optional studies you can choose to take part in

1. **Use of Photographs in Publication (Optional):**

You may choose to allow the research team to use the photos taken of your AKs in medical publications or public presentations that result from the research. No personal information from you will be associated with these photos, although it may not be possible to alter the photos to hide your identity since lesions are on the face. You do not need to agree to have your photos used for publication to participate in the study. Agreeing to allow your photos to be used in this way does not require you to complete any additional study activities. You can indicate your photo preference by checking the appropriate box at the end of this document. If you decline to

participate in the option below it will have no effect on your eligibility to participate in the overall study and will not interfere with the benefits to which you are entitled.

	YES	NO
I give the study staff permission to use the photograph(s) taken of the affected area(s) of my skin for medical publications or presentations.		

Initial and Date: _____

HIPAA AUTHORIZATION
Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you volunteer to participate in this research, your protected health information (PHI) that identifies you will be used or disclosed to Dr. Edward Maytin MD, PhD, and the research study staff at Cleveland Clinic or the purposes of this research and to Case Western Reserve University for administration.

The PHI that we may use or disclose (release) for this research may include your name, address, phone number, date of birth, Social Security number, information from your medical record, lab tests, or certain information relating to your health or condition..

Some of the tests and procedures done solely for this research study may also be placed in your medical record so other doctors know you are in this study. Upon completion of the study, you may have access to the research information that is contained in your medical record.

In addition to the investigators and research staff listed above, your PHI may be looked at by other groups involved with the study such as the Cleveland Clinic Institutional Review Board, and the Case Comprehensive Cancer Center Protocol Review and Monitoring Committee. Your PHI may also be used by and/or disclosed (released) to:

- Biofrontera, and its representatives
- Biofrontera's collaborators and licensees
- Case Comprehensive Cancer Center members and collaborators
- The Food and Drug Administration;
- The Department of Health and Human Services;
- The National Cancer Institute (NCI);
- Other Institutional Review Boards;
- Data Safety and Monitoring Boards;

Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

Your research information may be used and disclosed indefinitely, but you may stop these uses

and disclosures at any time by writing to:

Dr. Edward Maytin, MD
Case Comprehensive Cancer Center
Cleveland Clinic
9500 Euclid Ave.
Cleveland, OH 44195

Your participation in the research will stop, but any information previously recorded about you cannot be removed from the records and will continue to be used as part of this research. Also, information already disclosed outside the Cleveland Clinic cannot be retrieved. This will not affect your rights to treatment or benefits outside the research study.

The Cleveland Clinic will not use your information collected in this study for another research purpose without your written permission; unless the Cleveland Clinic Institutional Review Board (IRB) assures your privacy and confidentiality is protected. The IRB is a committee whose job it is to protect the safety and welfare of research subjects.

By signing this informed consent form, you are authorizing such access to your research and medical record information. If you choose not to sign this consent form, you will not be able to participate in this research study. This Authorization does not have an expiration date.

Voluntary Participation
Your participation in this research study is voluntary. Choosing not to participate will not alter your usual health care or involve any penalty or loss of benefits to which you are otherwise entitled. If you decide to join the study, you may withdraw at any time and for any reason without penalty or loss of benefits. If information generated from this study is published or presented, your identity will not be revealed.

In the event new information becomes available that may affect the risks or benefits associated with this study or your willingness to participate in it, you will be notified so that you can decide whether or not to continue participating.

Questions about the Research
If you have any questions, concerns or complaints about the research, or develop a research-related problem, contact Dr. Edward Maytin, Department of Dermatology at [redacted].

After hours, you should contact the page operator at [redacted] or toll free at [redacted] and ask for the dermatologist on call.

Where Can I Get More Information?
If the researchers cannot be reached, or if you would like to talk to someone other than the researcher(s) about: concerns regarding the study, research participant's rights; research-related injury; or other human subjects issues, you may contact the Institutional Review Board (IRB) at Cleveland Clinic IRB [redacted].

You may call the National Cancer Institute's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

US National Institutes of Health (NIH) Clinical Trial Database:
A description of this clinical trial will be available on http://www.ClinicalTrials.gov, if applicable, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Signature
Signing below indicates that you have been informed about the research study in which you voluntarily agree to participate; that you have asked any questions about the study that you may have; and that the information given to you has permitted you to make a fully informed and free decision about your participation in the study. By signing this consent form, you do not waive any legal rights, and the investigator(s) or sponsor(s) are not relieved of any liability they may have. A copy of this consent form will be provided to you.

Signature of Participant	Date	Printed Name of Participant

Signature of Person Obtaining Consent	Date

Printed Name of Person Obtaining Consent

Timeline and Procedures for Patients Enrolled in the Study

Summary Of Activities	VISIT 1	VISIT 2	VISIT 3	VISIT 4
	PDT treatment #1	Follow-up	PDT treatment #2	Final lesion counts
Scheduled visit: → Procedure: ↓	**Day 1**	**Day 3 ±1 day**	**Week 8 ±1 week**	**Month 3-6**
Informed consent	X			
Skin exam and AK count.	X		X	X
Photos in professional studio.	X	X		
Photos with clinic iPhone.	X		X	X
Apply topical ALA gel	X		X	
PDT treatment	X		X	
Pain level during treatment.	X		X	
Side effects questionnaire.	X		X	
Review aftercare instructions	X		X	
Patient satisfaction questionnaire				X

Visit 1 (Day 1): PDT Treatment #1

The study team will go over the study criteria with you to ensure that you are eligible and fully understand everything, and after that you will sign the Informed Consent form. After this, your AK lesions will be identified, counted, and marked with a pen. Photos of your AKs will be taken by a professional photographer and also in the clinic by study staff using a dedicated iPhone camera. After this, your facial skin will be cleaned with an alcohol wipe and your AKs will be gently rubbed with fine moist sandpaper. A thin layer of the medication gel (called Ameluz or ALA) will be applied to your whole face. The gel will stay on your skin, without being covered, for either 10 minutes, 20 minutes, or 60 minutes, depending on the group you are assigned to. Then you will be positioned under the PDT

lamp (with eye protection) and exposed to the light for either 10 minutes or 20 minutes, depending on the group you are assigned to.

If you are assigned to group A, the ALA gel will be left on for 10 min, and then positioned in front of the red light and exposed for 20 min. If you are assigned to group B, the ALA gel will be left on for 20 min, and then positioned in front of the red light and exposed for 10 min. If you are assigned to group C, the ALA gel will be left on for 60 min, and then positioned in front of the red light and exposed for 10 min.

You will be asked to rate the pain you are experiencing on a scale of 0 to 10 throughout the PDT light treatment. After your treatment, you will be given a set of aftercare instructions, soothing ointment, and a 6-day questionnaire to record your side-effects daily during the coming week. You will also be asked to wear sunscreen and avoid sun exposure for 48 hours.

Visit 2 (Day 3 ± 1 day) Follow-up

For your second visit, you will come back in to see our photographer who will take multiple pictures of your face to record the progress of the treatment.

Visit 3 (Week 8 ± 1 week): PDT Treatment #2

If you have any remaining AKs after your first treatment, they will be identified, counted, and marked with a pen. Photos of your AKs will be taken in clinic by the study staff using the iPhone camera. After this, your skin will be cleaned with an alcohol wipe and gently rubbed with fine moist sandpaper. You will receive the same treatment times for the ALA and PDT light treatment as you did at Visit 1, based on the group you are assigned to.

You will be asked to rate the pain you are experiencing on a scale throughout the PDT light treatment. After your treatment, you will be given a 6-day questionnaire to record your side-effects daily during the coming week. You will be provided with a set of aftercare instructions and soothing ointment. You will also be asked to wear sunscreen and avoid sun exposure for 48 hours.

Visit 4 (Month 3-6) Follow-up

Your final study visit will occur 3-6 months after your first visit. At your final study visit any remaining AKs you might have will be identified and photographed by the study staff using the iPhone camera. You will also be given a satisfaction questionnaire about your experience with the treatment.