Clinical Investigational Plan

Study Title: A Prospective, Non-Randomized, Multicenter Pivotal Study of Nano-Pulse Stimulation™ (NPS™) Treatment of Cutaneous Non-Genital Warts

Short Title: *NPS™ Treatment of Cutaneous Non-Genital Warts*

Protocol No: NP-WP-010

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Study Sponsor:

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PROPRIETARY AND CONFIDENTIAL

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1.0 INTRODUCTION AND BACKGROUND

1.1 Common and Flat Warts of Hand and Fingers

Non-genital warts (verruca vulgaris) are an extremely common, benign, and usually a self-limited skin disease. Infection of epidermal cells with the human papillomavirus (HPV) results in cell proliferation and a thickened, round, raised papule on the skin ranging in size from a pinhead to 10 mm. The appearance of warts is determined by the type of virus and the location of the infection. There are several reasons why some individuals are affected by warts, and other remain trouble free. These include: the type and strength of the viral strain, the health of the exposed person, and the strength of an individual's immune response. Any area of skin can be infected, but the most common sites are the hands and feet. **Common warts** are most often seen on the hands and present as skin-colored papules with a rough 'verrucous' surface. **Flat warts** are most often seen on the backs of the hands and on the legs. They appear as slightly elevated, small plaques that are skin-colored or light brown. **Plantar warts** occur on the soles of the feet and look like very thick callouses.

Current Care

Current treatments for common and flat warts involve destruction of the infected cells either chemically or physically and treatment depends on the size, location, number, type, age of the patient, risk of scarring and patients' commitment to the therapy. The clinical management of these warts is challenging, and no current treatment is singularly effective, especially against warts that are recalcitrant. These include non-surgical, pharmacologic and surgical treatment modalities: topical peeling methods like salicylic acid; immune modulators using contact immunotherapies; intralesional candida antigen or bleomycin and; cryotherapy; duct tape occlusion; photodynamic treatment; pulsed dye laser; and general surgical procedures.

1.2 Non-Surgical Approach

Chemical Destruction:

Salicylic Acid

The use of salicylic acid is one of the two most commonly used treatments for warts. Dermatologists prescribe chemical destruction treatments where patients apply an over-the-counter preparation, usually less than 17% salicylic acid or prescription salicylic acid containing up to 70% salicylic acid at home every day. Treatment response rates of 40-84% with an average of 61% have been reported as an effective therapy for non-genital cutaneous warts.[1] Minor skin irritation was reported occasionally in some of the other trials, but generally there were no major harmful effects of topical salicylic acid.[2] A systematic review of local treatments of cutaneous warts by Mitsuishi et al., found evidence that topical treatments with salicylic acid have a therapeutic effect, with a cure rate of 75 percent compared with 34-48 percent in placebo controls.[1,3] Other agents used for chemical destruction are monochloracetic acid, dichloracetic acid, trichloroacetic acid, silver nitrate, glycolic acid and 80% phenol in solution. Complications associated with using chemicals include pain, hyperpigmentation, hypopigmentation, burning sensation and erythema.[4]

Cantharidin

Cantharidin is used as an agent in the clinic by "painting" the wart causing oxidative stress by inhibiting phosphatases 1 and 2A that damages both DNA single- and double-strand breaks and triggers p53 dependent apoptosis.[4] Cantharidin causes a blister to form under the wart. In a week or so, the patient returns to the office and the dermatologist clips away the dead wart.

Immune Modulators

This treatment uses the patient's own immune system to fight the warts. Forms of immune modulators include imiquimod, intralesional immune modulators using Candida antigen or anti-cancer such as Bleomycin; contact immunotherapy, cimetidine, zinc, and retinoids. Because wart proliferation is controlled by the immune system, various methods have been used to stimulate the immunologic response to HPV. This treatment is used when the warts remain despite using other treatments and the ability to treat many lesions simultaneously. One type of immunotherapy involves applying a chemical diphenylcyclopropenone (DPCP). Among these are topically applied inorganic molecules capable of eliciting contact hypersensitivity, such as imiquimod and intralesional interferons[5] to the warts. A mild allergic reaction occurs around the treated warts which stimulates the body's innate response to fight the virus.

Physical Destruction*:*

Cryotherapy

For common warts in adults and older children, cryotherapy is a standard treatment and can be done in the physician's office. Cryotherapy involves freezing a wart using a very cold substance (usually liquid nitrogen). The liquid nitrogen application usually takes less than a minute and most warts require 1 to 4 treatments, with 1 to 3 weeks between each treatment. Pain from cryotherapy can last up to 3 days. Healing is generally quick (7 to 14 days) with little or no scarring[6]. It can cause dark spots in people who have dark skin. With cryotherapy, it is common for repeat treatments.

Laser

Laser treatment is an option, mainly for warts that have not responded to other therapies. Before laser treatment, the dermatologist may numb the wart with an anesthetic injection.

1.3 Surgical Approach

Electrosurgery and Curettage:

Electrosurgery (burning) is an available treatment for common warts, filiform warts, and foot warts. Curettage involves scraping off (curetting) the wart with a sharp knife or small, spoon-shaped tool. These two procedures often are used together. The dermatologist may remove the wart by scraping it off before or after electrosurgery.

Excision:

The wart may cut off or surgically excised in combination to using other applications previously mentioned.

1.4 Nano-Pulse Stimulation (NPS) Therapy:

The NPS medical device is intended to clear the skin of benign, undesired skin lesions as an alternative to surgery and other more destructive methods for removing benign lesions. The system is designed to deliver a timed series of very low energy, high amplitude (about the same as the voltage of static electricity) pulses of a time length between 100 and 750 nanoseconds (billionths of a second). The non-thermal effect on tissue takes place in a very shallow depth of skin directly below the sterile treatment tip. The device emits significantly less thermal energy than existing laser, electro-surgery or electro-cautery equipment.

Extensive in vitro research demonstrates stimulation of a form of delayed programmed cell death in a treated area, which is one of the identified mechanisms for observations of clinical and histologic changes to cells in multiple studies of in-vivo treated tissue in both humans and animals. In pre-clinical studies with over 1000 rats and mice, nano-pulsed devices have been demonstrated to reduce or eliminate malignant tumors with a clinically acceptable margin of safety. A pilot clinical trial of common skin cancer lesions was conducted under IRB oversight in 2012 with a similar version of the NPS device, with the findings published in Experimental Dermatology. A total of ten basal cell carcinoma lesions on the skin of three subjects were treated with a range of settings. Seven of the ten lesions were free of basal cells at the conclusion of the study, two partially resolved, and one recurred. No scars were visible at the healed sites of any of the successfully treated lesions. In another pre-clinical study, NPS treatment was applied to a human papillomavirus type 16 (HPV 16)-transformed C3.43 mouse tumor cell model in 15 immuno-competent mice. The results showed that NPS technology is effective in eliminating primary tumors through the induction of immunogenic cell death while subsequently increasing the number of tumor-infiltrating lymphocytes within the tumor microenvironment. The mice were re-challenged and about half of the mice that had cleared established tumors were protected against tumor re-challenge on the opposite flank, indicating that NPS technology has an immune effect that prevents successful tumor re-challenge.[7]

Prior NPS Therapy Clinical Studies:

The NPS device has been successfully deployed in several clinical studies of skin and subcutaneous structures. As of the date of this writing, the following studies have been successfully conducted and concluded: 1) A histological study evaluating use of the device on healthy abdominal human tissue in a dose-response study; 2) A histological study evaluating use of the NPS therapy and comparative devices on healthy abdominal human tissue, 3) histological study following use of the therapy on healthy facial skin tissue in the pre-auricular area; 4) A multi-center study in the treatment of Seborrheic Keratosis lesions Additional detailed summaries of these studies follows.

Abdominal Tissue (Pre-Abdominoplasty) Studies
Study Name: Nano-Pulse Human Tissue Study

A total of 8 subjects participated in this prospective, single site, non-randomized study. All subjects were females representing a wide range of Fitzpatrick Skin Tone Classifications, and ranging in age from the low 40's to middle 60's.

The study was comprised of two sequential segments. The first segment evaluated the serialized use of the test device in demarcated locations on intact abdominal skin predetermined for subsequent resection during a standard abdominoplasty scheduled later. The primary endpoint of the first segment of the study was to establish that the trauma to the

tested skin would be minimal over a range of six progressively increasing energy levels. The appearance of each intact tested tissue location was comparable to that anticipated following any minor surgical excisional procedure. A total of 210 NPS applications were tested and analyzed in this study.

Lidocaine was injected prior to use of the NPS skin exposure. Subjects reported little or no sensation during the treatment session. Subjects further reported little or no discomfort after the Lidocaine effect had diminished. There were no adverse events, no reports of bleeding, and no scarring noted by the Investigator at the end of the 60-day study

The second segment of the study called for the histological analysis of tissue samples prepared from the abdominal section that were resected at the time of the abdominoplasty. Internal technicians and outside expert dermatopathologists evaluated the skin samples using standardized methods of microscopic analysis. This second segment did not impact the participating subject as it occurred after the abdominoplasty procedure. Consequently, Pulse Biosciences, Inc. secured IRB oversight concentrated on the first segment of the study. It should be noted however that the histological analysis to date confirmed that the NPS was successful in achieving its intended effect across the range of tested energy settings.

Abdominal Tissue (Pre-Abdominoplasty) Comparative Studies
Study Name: Nano-Pulse Human Tissue Study

A total of 2 subjects participated in this prospective, single site, non-randomized study. Both subjects were females representing two different Fitzpatrick Skin Tone Classifications and ranging from the high 20's to low 40's in age.

The primary purpose of the study was to collect tissue samples from healthy human resected tissue that had been exposed to various methods of partial tissue ablation prior to a planned abdominoplasty resection date. The skin samples were taken from a section of abdominal skin that was previously exposed to the effect of the NPS therapy during the same time period as two comparator medical devices considered to be the "gold standards" for tissue ablation. Histological analysis of the resected abdominoplasty tissue was performed on samples taken from sites treated with the 2 "gold standard" devices as well as the NPS therapy.

The study is best described as comprised of two sequential segments. The first segment called for the serialized use of the NPS test device and the gold standard "comparatives" in specific locations on intact abdominal skin predetermined to be resected during a standard abdominoplasty. The impact of the study test device, the comparative devices and/or the study process ceased at the time of the abdominoplasty. The primary endpoint of the first segment of the study was to establish that the apparent trauma to the tested skin was minimal for all devices. The appearance of each intact tissue location that was tested with the NPS therapy or the two comparative systems was comparable to that anticipated following any minor surgical excision procedure.

Lidocaine was injected prior to use of the NPS skin exposure, and one of the comparators. Subjects reported little or no sensation during the multiple treatment sessions. Subjects further reported little or no discomfort after the Lidocaine effect had diminished in the days following each treatment. There were no adverse events, no reports of bleeding, and no scarring in the NPS therapy group noted by the Investigator at the end of the 60-day study

The second segment of the study called for the histological analysis of tissue samples prepared

from the abdominal section that was resected at the time of the abdominoplasty. Internal technicians and outside expert dermatopathologists evaluated the skin samples using standardized methods of microscopic analysis.

Pre-Auricular Tissue (Pre-Face Lift) Studies
Study Name: Nano-Pulse Pre-Auricular Tissue Study

A total of 3 subjects participated in this prospective, single site, non-randomized study. Two of the subjects were females and one was a male representing different Fitzpatrick Skin Tone Classifications and all were over the age of 50 years of age.

The study was compromised of two sequential segments. The first segment called for the serialized use of the test device in several locations on intact facial skin pre-determined to be resected during a standard face-lift, which is typically a small section in front of the ear (the pre-auricular area).

The primary endpoint of the first segment of the study was to establish that the visually apparent trauma to the tested skin would be minimal and the appearance of each intact tested tissue location was comparable to the appearance that is anticipated following any minor surgical procedure.

Lidocaine was injected prior to NPS therapy administration to the skin surface. After the first NPS exposure, subjects returned at varying time intervals prior to their scheduled face lift procedure for additional NPS administrations on demarcated areas on each side of their face using varying tip sizes and energy settings. Subjects reported little or no sensation during the NPS administrations. Subjects further reported little or no discomfort after the local anesthetic effect had diminished. There were no adverse events, no reports of bleeding and no scarring noted by the Investigator at the end of the study.

Following the same model as described above, additional studies were performed involving pre-auricular tissue of facial skin in 3 subjects scheduled for eventual face lift procedures. The sole Investigator for this series (NP-PT-003) was Dr. James Newman, MD., Plastic Surgeon, in San Mateo, CA. As noted above for the Pre-Abdominoplasty study, local anesthetic was administered prior to the NPS skin exposure. Subjects reported little or no sensation during the treatment session. Subjects further reported little or no discomfort after the local anesthetic effect had diminished. There were no adverse events, no reports of bleeding, and no scarring noted by the PI at the end of the 60-day study.

Warts Feasibility Study (NP-WF-007)
Study Name: Nano-Pulse Non-genital Warts Feasibility Study

Nineteen (19) treated adult subjects were required to have 2-5 non-genital, off-face cutaneous warts in this multi-center feasibility study. Up to four warts were designated to be treated, while one wart was designated as the sham control. Subjects received an initial NPS-treatment and returned for 3 to 5 follow-up evaluations at 7 days, 30 days, 60 days, 90 days and 120 days after the initial treatment. Each wart was evaluated for size reduction and the condition of the skin. If the reduction in wart size met study criteria, the wart was eligible for an additional treatment and at the discretion of the investigator.

Six (6) of the 19 subjects were male and 13 were female. Ages ranged from 23 to 71, with an average age of 48. Subjects had Fitzpatrick skin types ranging from I to III. A total of 58 warts have been included in the study at the time of this report. 34 warts were identified for treatment and 19 warts as controls. 70% of the study warts had been previously treated with another modality and were not successful at eliminating the wart. 69% of treated warts were located on the hand/fingers and the remaining 31% of treated were located on the feet. Twenty-five (25%) of treated warts received a single treatment, and 75% received two treatments. Of the treated warts, 50% showed 100% reduction in size, 21% showed a 50-90% reduction in size, and 26% showed less than a 50% reduction in size at the last reported visit. Twenty-nine (29%) of the treated warts showed 100% reduction after a single treatment. There were two instances where the control wart showed 100% reduction in size, suggesting that there may be an immune response. Preliminary data analysis indicates that complete coverage of the wart within the treatment zone is required. There is also a trend toward the use of higher settings within the allotted range for better outcomes. There were no instances of hypopigmentation noted, and 3 cases of mild hyperpigmentation at 60 days.

The high rate of wart size reduction suggests the utility of the unique NPS cellular mechanism for the treatment of non-genital, cutaneous warts. Based on these initial results, a larger pivotal study is warranted and will be conducted in the future to further evaluate the use of NPS technology for the treatment of warts.

2.0 STUDY DEVICE DESCRIPTION

2.1 Pulse Bioscience CellFX™ System

The Pulse Bioscience CellFX™ System uses a proprietary platform technology called Nano-Pulse Stimulation™ (NPS™). NPS technology utilizes nanosecond (billionth of a second) pulses of energy that penetrate into the cytoplasm and organelles to induce regulated cell death in a target lesion. The pulses are applied directly to targeted tissue using small microneedles.

The CellFX System is intended for the reduction and/or removal of benign and non-benign lesions.

The CellFX System consists of:

- CellFX Console - The Console consists of all the electronics and controls required to generate a nanosecond pulsed electric field. A touchscreen provides the user interface to the system. The power cord electrically connects the Console to the AC mains outlet.

- CellFX Handpiece (re-usable) - When attached to a Single Patient Use Retractable Tip (Treatment Tip), the Handpiece is held by the user to deliver a timed series of energy pulses (referred to as a “Cycle”) from the CellFX Console. The Handpiece has a custom receptacle for attachment to the Treatment Tip, a custom connector that plugs into the Console with a 10-foot cable, a hook for hanging the Handpiece on the Console, a Finger Switch for cycle activation, a LED status indicator, and a pair of side buttons on each side of the Handpiece.

- CellFX Single Patient Use Retractable Tips – A sterile Single Patient Use Tip attaches to the Handpiece. The Tip holds two to three arrays of needles that define the intended treatment area (i.e. lesion zone) where the pulsed electric field is applied. There are fiducial markers on each side of the retractable tip portion, one marker on each side perpendicular to the row of needles and second on each side parallel with the rows of needles that can be used to align to the treatment area.

3.0 PROTOCOL

3.1 Study Purpose and Objectives

The purpose of this study is to evaluate the safety and effectiveness of the CellFX System in patients with cutaneous non-genital warts on all areas of the body, excluding the face.

The study objectives are listed below:

- Evaluate the condition of skin in the treatment areas (erythema, etc.) over the course of 7 to 120 days post-initial NPS treatment
- Evaluate the overall response to NPS treatment by:
    1. Wart clearance (generally accepted as complete clearance of warts from the treated area)
    2. Wart reduction (reduction in the total number of warts)
- Evaluate and assess adverse effects of treatment

3.2 Study Design Overview

The study is designed as a prospective, non-randomized, multicenter pivotal study to evaluate the safety and effectiveness of the CellFX System in patients with non-genital warts, excluding the face. Macrophotography of all treated warts will be captured along with Investigator assessments using a wart measurement scale and tissue response. One of the warts for each subject will be untreated and will serve as the subject's internal control. Please note the Investigator has the option at baseline and at each follow-up visit for curettage of the targeted site prior to NPS treatment. Additionally, at the 30-day, 60-day and 90-day visits the Investigator has the option to retreat any previously treated lesion.

3.3 Site Selection and Number of Subjects

Up to 6 clinical sites will participate in this study. Sites will be selected based on the appropriate patient population, physician experience in the treatment of warts, and adequate resources to support this pivotal study.

Approximately 60 subjects at 6 sites will be enrolled. A site may enroll up to 18 subjects in this study.

3.4. Clinical Study Duration

It is anticipated that the enrollment of subjects in this pivotal study will take approximately 4-months. All subjects included in this clinical investigation will return for follow-up visits at 7, 30, 60, 90 and 120-days post-initial NPS treatment. All lesions will have the possibility of being retreated up to 3 times, with a maximum of 4 total NPS treatments over the course of the study. Total study duration is approximately 8 months.

3.5 Enrollment Definition

For the purposes of enrollment, only those patients who meet all eligibility criteria, sign an IRB

approved consent form and begin treatment with the CellFX device will be considered enrolled in the study. Patients who consent to participate but withdraw prior to the first treatment with CellFX device will be considered a screen failure and this should be documented on the site screening log.

3.6 Study Evaluations

3.6.1 Primary Assessment:

The primary effectiveness evaluation of this study is reduction in wart size and/or clearance using the following wart measurement scale for each treated wart. **(See Table 1)**

Table 1: : Wart Measurement Scale

Rate of Reduction (%)	Scale Value
0-9	4
10-29	3
30-49	2
50-90	1
Clear	0

3.6.2 Secondary Assessment:

The secondary effectiveness evaluation of this study is subject satisfaction.

4.0 STUDY PROCEDURES

4.1 Subject Selection

4.1.1 Inclusion Criteria:

Subjects are required to meet **ALL** inclusion criteria in order to be enrolled in the study.

1. Subjects must be at least 21 and not older than 80 years of age.
2. Subjects must be able to read and speak English or Spanish.
3. Subjects must sign a written informed consent to participate in the study, prior to any study related procedures.
4. Subject must have a minimum of two cutaneous non-genital warts, each not exceeding 10 x 10mm.
5. Subject is willing to undergo all study-mandated procedures.
6. Subject agrees to refrain from using all other wart removal products or treatments (topical medication including over-the-counter medications) during the study period.

4.1.2 Exclusion Criteria:

Subjects who meet **ANY** of the following exclusion criteria will not be enrolled in this study.

1. Subject has an implantable electronic medical device. (pacemaker, implantable cardioverter defibrillator, etc.)
2. Subject has cochlear implants.
3. Subject has an active systemic infection or history of an infection in the designated treatment area within 90 days of enrollment.
4. Subject has a history of and/or current tinnitus.
5. Subject is known to be immune-compromised.
6. Subject is taking a blood thinning medication (Antiplatelet, Anticoagulation, Factor Xa Inhibitor, etc.)
7. Subject has Type 1 Diabetes and is insulin dependent.
8. Subject has a known allergy to Lidocaine or Lidocaine-like products.
9. Subject is a member of a vulnerable population including individuals employed by the Sponsor, clinic site, or entity associated with the conduct of the study.
10. Subject has a comorbidity or condition which may reduce compliance with this protocol, including follow-up visits.
11. Subject is participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device).

4.2 Informed Consent

Prior to undergoing any study-specific tests or procedures, the subject must sign and date the site's current and approved Institutional Review Board (IRB) informed consent form in order to be eligible for study participation. The informed consent will contain all elements required by 21 CFR Part 50 and ISO 14155:2011 and comply with the ethical principles of the Declaration of Helsinki.

4.2.1 Process for Obtaining Informed Consent

The process for obtaining informed consent is outlined below:

- The Investigator or his/her authorized designee conducts the informed consent process
- All aspects of the clinical study that are relevant to the subject's decision to participate will be included in the consent form
- Investigators will avoid any coercion or undue improper influence on, or inducement of, the subject to participate
- The consent process shall not waive or appear to waive the subject's legal rights
- The consent must use native non-technical language that is understandable to the subject
- The Investigator, or designee will provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical trial
- The consent must include personally dated signatures of the subject and the Investigator, or an authorized designee responsible for conducting the informed consent process, and/or all signatures required by the IRB
- The Investigator, or designee, will provide the subject with a copy of the signed and dated informed consent form

4.3 Study Visits

4.3.1 Screening/Baseline Procedures including NPS Treatment – Visit 1 (Day 0)

The following evaluations and procedures are required at the time of subject screening/baseline

- Signed Informed Consent
- Dermatologic Medical History/Demographics
- Wart classification and anatomic location for all study lesions
- Inclusion and Exclusion criteria

<u>Activities on 1st Study Visit Day - NPS Treatment Day</u>

The following assessments and procedures will be performed

- Using a randomization method, the selected wart(s) will be designated to be treated and one will be designated as an untreated control.
- Each selected lesion will be numerically labeled, and photographic images will be taken before the local anesthetic/numbing.
- Local anesthetic/numbing will be administered to all study lesions.
- NPS treatment #1 will be delivered to all lesions.

- Subject will rate the level of pain from a specified pain score.
- Photographic images of all lesions will be taken immediately post-NPS treatment.
- A light bandage and any PI recommended dressing may be applied.
- Adverse event assessment will be performed.

4.3.2 7-Day Follow-up – Visit 2

The following assessments and procedures will be performed

- Photographic images of all study lesions will be taken.
- Each lesion will be clinically assessed, and the appearance will be rated according to specified criteria.
- Adverse event assessment will be performed.

4.3.3 30-Day Follow-Up / Possible NPS Re-Treatment - Visit 3

The following assessments and procedures will be performed

- Photographic images of all study lesions will be taken.
- Wart reduction assessment, including measurement will be performed.
- All lesions will be clinically assessed, and the appearance will be rated according specific criteria.
- All lesions that are rated other than “Clear” are eligible to receive a retreatment with NPS of those lesions.
- In case of an NPS retreatment:
  - Images of each of the selected lesions will be taken before local anesthetic/numbing and after the NPS treatment.
  - Local anesthesia/numbing will be applied to the identified lesions.
  - NPS treatment will be delivered.
  - Subject will rate the level of pain from a specified pain score.
  - A light bandage and any PI recommended dressing may be applied.
- Adverse event assessment will be performed.

4.3.4 60-Day Follow-Up / Possible NPS Re-Treatment - Visit 4

The following assessments and procedures will be performed

- Photographic images of all study lesions will be taken.
- Wart reduction assessment, including measurement will be performed.
- All lesions will be clinically assessed, and the appearance will be rated according specific criteria.
- All lesions that are rated other than “Clear” are eligible to receive an NPS retreatment of those lesions.
- In case of an NPS retreatment:

- Images of each of the selected lesions will be taken before local anesthesia/numbing and after the NPS treatment.
- Local anesthesia/numbing will be applied to the identified lesions.
- NPS treatment will be delivered.
- Subject will rate the level of pain from a specified pain score.
- A light bandage and any PI recommended dressing may be applied.

- Adverse event assessment will be performed.

4.3.5 90-Day Follow-Up / Possible NPS Re-Treatment- Visit 5

The following assessments and procedures will be performed

- Photographic images of all study lesions will be taken.
- Wart reduction assessment, including measurement will be performed.
- All lesions will be clinically assessed, and the appearance will be rated according specific criteria.
- All lesions that are rated other than "Clear" are eligible to receive an NPS retreatment of those lesions.

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- In case of an NPS retreatment:
  - Images of each of the selected lesions will be taken before local anesthetic/numbing and after the NPS treatment.
  - Local anesthesia/numbing will be applied to the identified lesions.
  - NPS treatment will be delivered.
  - Subject will rate the level of pain from a specified pain score.
  - A light bandage and any PI recommended dressing may be applied.

- Adverse event assessment will be performed.

4.3.6 120-Day Follow-Up – Visit 6 (Final Study Visit)

The following assessments and procedures will be performed

- Photographic images of all study lesions will be taken.
- Wart reduction assessment, including measurement will be performed.
- All lesions will be clinically assessed, and the appearance will be rated according specific criteria.
- Adverse event assessment will be performed.
- Subject satisfaction will be evaluated for the appearance of the treated lesions.

Table 2 lists assessments and procedures required at each study visit.

Table 2 : Schedule of Events and Evaluations

Study Visit Interval	#1 0-days Enrollment NPS TX #1	#2 7-days Post-NPS TX #1	#3 30-days Post-NPS TX #1	#4 60-days Post-NPS TX #1	#5 90-days Post-NPS TX #1	#6 120-days Post-NPS TX#1 (Final Visit)
Study Visit Description	Informed Consent All eligibility criteria met TX #1 Photographic images	Lesion(s) evaluation Photographic images	Lesion(s) evaluation TX #2 (if applicable) Photographic images	Lesion(s) evaluation TX #3 (if applicable) Photographic images	Lesion(s) evaluation TX#4 (if applicable) Photographic images	Lesion(s) evaluation Subject Satisfaction Photographic images
Visit Range (# of Days Post-NPS TX #1)		5-9 days	27-37 days	57-67 days	87-97 days	120-130 days

4.4 Subject Compensation

Each subject will be compensated for any inconvenience that study participation may represent. Specifically, each subject will make 6 total visits to the PI's office (approximately 6 hrs. total time). In return for this time commitment, the subject will receive $100 per point of enrollment/1st treatment visit, $50 per follow-up visit at 7-days, $50 per follow-up visit at 30-days, $50 per follow-up visit at 60 days, $50 per follow-up visit at 90 days and $50 per follow-up visit at 120 days. The total amount of compensation will be $350 to those subjects who complete all 6 visits.

5.0 SAFETY REPORTING

All adverse events (AEs) that are device or procedure related will be recorded on the AE case report form. Data to be collected will include the description of the AE, onset and resolution dates (or whether the AE is ongoing), severity, management/treatment, outcome, and determination of the relationship to the device and/or procedure. In general, AEs should be reported and classified by the Investigator. The Investigator will determine the relationship of the AE to the device or the study procedure. The Investigator is required to notify the IRB in accordance with local reporting requirements.

All device deficiencies and malfunctions will be recorded on the case report form. If a deficiency or malfunction meets the definition of a product complaint (any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution), a Pulse Biosciences complaint form will be completed by a Clinical or Quality representative.

The Sponsor will ensure safety reporting for the study is conducted in compliance with all pertinent requirements and regulations for all sites participating in this study.

Table 3 summarizes reportable adverse events.

Table 3: Reportable Adverse Events

Description of Event
Infection which requires medical intervention
Bleeding which requires medical intervention
Pain which requires prescription medication for relief

5.1 Follow-Up and Reporting

All patients enrolled, and devices used in the clinical investigation will be accounted for in the final report. All reasons for exclusion from analysis will be carefully documented. Similarly, for all subjects and devices included in an analysis population, the measurements of all-important variables must be accounted for at all relevant time points. Additional information that is available on patients screened for entry but not enrolled will also be summarized.

6.0 STUDY MANAGEMENT

6.1 Sponsor Ethical and Regulatory Considerations

As the Sponsor of this clinical study, Pulse Biosciences has the overall responsibility for the conduct of the study, including assurance that the study meets US federal and local regulatory requirements appropriate to the conduct of the study and is conducted according to Good Clinical Practices (GCP), 21 CFR 812, 820, 50, 54, and 56, Declaration of Helsinki, applicable IRB requirements, as well as Sponsor general duties as described in ISO 14155:2011/AC: 2011. In this study, Pulse Biosciences will have certain direct responsibilities and may delegate other responsibilities to qualified consultants and/or a Contract Research Organization (CRO).

The protocol and any amendments will be submitted to each site's IRB for formal approval of the study. All subjects considered for this study will be provided a consent form describing this study and providing sufficient information for them to make an informed decision about their participation.

6.2 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study. To maintain confidentiality, all evaluation forms, reports and other records will be identified by a unique subject identification code (ID number). All study records will be kept in a locked file cabinet and clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996).

7.0 SPONSOR RESPONSIBILITIES

7.1 Selection of Clinical Sites

The primary requirements of site and Investigator selection and continued participation in the Trial are: adequate experience, commitment to safety, consistency in adherence to the protocol, and patient volume. Participating sites will be screened to ensure they have adequate numbers of eligible patients who are representative of the target population. The clinical site must have facilities that are capable of processing patients in the manner prescribed by the protocol.

The study Sponsor, Pulse Biosciences, and its designees will select qualified Investigators, ship or deliver devices only to participating Investigators, obtain signed study agreements, and provide Investigators with the information necessary to conduct the study.

7.2 Site Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or designee. The Investigator is responsible for ensuring that his/her staff conduct the study according to the protocol. To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor or designee will present a formal training session to study site personnel which will review the instructions for use of the device, the study protocol, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the Sponsor or designee through the regular site monitoring.

7.3 Investigator Training

The Sponsor will provide appropriate Investigator training on the use of the NPS System. Training will take place prior to the initiation of the clinical investigation. Training will address topics including indications for use of the device, management of complications, and instructions to subjects. Training will be documented for each physician on a training log, signed by both the physician and training representative

7.4 Monitoring of Study Sites

7.4.1 Monitoring Methods

Monitoring functions will be conducted by the Sponsor. Specific monitoring requirements are detailed in the study specific Monitoring Plan maintained in the Pulse Biosciences clinical study project files.

All monitoring activities shall be documented in a written report. Corrective action will be taken to resolve any issues of noncompliance. If Pulse Biosciences finds that an Investigator is not complying with the executed Investigator Agreement, the study protocol, the applicable laws and regulations, or the requirements of the reviewing IRB, prompt action will be taken to secure compliance. Pulse Biosciences will reserve the right to suspend or terminate the participation of the Investigator or the study site.

7.4.2 Monitoring Visits

Scheduled monitoring visits to the clinical study site may occur at the following times: prior to the start of the study, interim visits throughout the clinical study as required per the monitoring plan, and upon completion of the clinical study. Sites that enroll rapidly may be visited more frequently

at Pulse Biosciences discretion. A final Close-Out Visit will be conducted upon completion of the entire clinical study or at the time, a site is terminated.

7.5 Protocol Deviations

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the study protocol or the Investigator Agreement.

Major deviations include those that involve the primary endpoint, the informed consent process and the inclusion/exclusion criteria of the study, or any deviation that involves or leads to a serious adverse event in a study subject.

Deviations shall be reported to the study Sponsor regardless of whether medically justifiable, pre-approved, or taken to protect the patient in an emergency. Patient specific deviations will be reported on the Case Report Form. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures. Deviations from the study protocol will be reviewed and evaluated by the Sponsor on an ongoing basis and, as necessary, appropriate corrective actions put into place.

GCP regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates and reasons for each deviation from the protocol.

7.6 Device Accountability

The Investigator shall maintain adequate records of the receipt and disposition of all study devices according to 21 CFR 812.140 (a)(2). At the completion of the study, all devices shall be returned to the Sponsor. The Investigator's copy of the Device Accountability Log must document devices that have been returned to the Sponsor.

The device accountability log will include records of receipt, use or disposition of a device that relate to:

1. The type and quantity of the device, the dates of its receipt, and the serial or lot number.
2. The names of all persons who received, used, or disposed of each device.
3. Why and how many units of the device have been returned to the Sponsor, or otherwise disposed of.

7.7 Data Management

Pulse Biosciences and Data Management designees will oversee and/or perform all data management functions. Data management functions include database development, system maintenance, user training, data queries, and report generation. The Principal Investigator and /or study staff are responsible for accuracy and completeness of all study data recorded.

7.8 Case Report Forms and Data Collection

All required data for this study will be collected via case report forms or a web-based electronic data capture (EDC) system and entered in electronic Case Report Forms (eCRFs). Case report forms will be used to record dermatologic medical history, demographic, procedural, and follow-up data, as well as adverse clinical events, protocol deviations and premature study withdrawal which may occur

during the study period. The AEs and incidence of morbidity and mortality will be reviewed with Investigators to assess the safety of the device and the procedure.

Qualified study staff at each clinical site will perform primary data collection drawn from source-document (hospital or clinic chart) reviews. The clinical monitor will perform clinical monitoring, including review of CRFs with verification of study eligibility, informed consent process, procedural data, scheduled follow-up visits and AEs to the source documentation.

7.9 Sponsor Data Retention

Pulse Biosciences will maintain copies of correspondence, data, shipment of devices, adverse device effects, Investigator agreements and other records related to the clinical trial. All study records and reports will remain on file at the sites for a minimum of 2 years after completion of the Study and will further be retained in accordance with local guidelines as identified in the clinical study agreement. Study records are to be discarded only upon notification by the study Sponsor. The Investigator must contact the study Sponsor before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, the Sponsor should be contacted if the Investigator plans to leave the investigational site. All required data for this study will be collected on standardized CRFs or an electronic data capture system. All information and data sent to the Sponsor concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. The principal Investigator consents to visits by the Sponsor and its authorized representatives and the U.S. Food and Drug Administration or any other local governmental body to review the study subjects' medical records including any test or laboratory data that might have been recorded on diagnostic tests media (e.g., photographs, etc.).

8.0 INVESTIGATOR RESPONSIBILITIES

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice. The Investigator will provide current copies of the study protocol to all Sub-Investigators or other site personnel responsible for study conduct.

Upon completion or termination of the study, the Investigator will submit a final written report to the study Sponsor and the reviewing IRB. The report should be submitted to the study Sponsor within three (3) months of study completion or termination. The Investigator will provide the study Sponsor or designee with copies of all IRB/HREC actions regarding the study.

8.1 IRB Approval and Informed Consent

The investigation must be reviewed and approved by the appropriate IRB before subject enrollment may begin. All proposed changes to the study protocol must be reviewed and approved by Pulse Biosciences.

Prior to shipment of study devices, a signed copy of the IRB Committee approval letter identifying the clinical study must be submitted to Pulse Biosciences, signifying study approval. Investigators are responsible for obtaining and maintaining approval of the study by the IRB.

Written informed consent is mandatory and must be obtained from all subjects prior to performing any study procedures in this clinical study. Pulse Biosciences will provide each Investigator site with a Sponsor approved consent template. Each site is expected to modify the template, if necessary, to meet their facilities requirements. Modified ICF templates must be reviewed by the Sponsor prior to submission to their IRB.

Informed consent must be obtained and shall inform the subject as to the objective and procedures of the study and possible risks involved. The subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. The clinical study informed consent must be used in addition to any institutional standard consent form for participation in clinical research. The institutional standard subject consent form does not replace the study consent form.

It is the responsibility of the Investigator to obtain both an authorization for patient health information and study consent.

The IRB approved Informed Consent Forms must be retained at the investigational site along with the other investigational case report forms. A signed copy of the consent form must be given to each subject enrolled in the study.

8.2 Protocol Compliance and Delegation of Authority

The Investigator shall conduct the clinical study in compliance with this study protocol and ensure that an adequate study site team and facilities exist and are maintained and documented during the duration of the clinical study. The Investigator must maintain a Delegation of Authority Form of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

8.3 CRF Completion and Submission

Investigators should complete CRFs in a timely fashion, preferably within 5 business days after subject enrollment or follow-up visit. This will enable timely monitoring visits.

Serious adverse events related to the study device or procedure and device malfunctions should be reported to the study Sponsor within 24 hours of first knowledge of the event. Contact information is included on the CRF form.

8.4 Source Documents/Record Retention

The Investigator shall maintain accurate, complete, and current records relating to the investigator's participation in an investigation including records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, H&P, progress notes of the physician, and results of all diagnostic tests as applicable. Such records shall include:

1. Documents evidencing informed consent and, for any use of a device by the Investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each subject shall document that informed consent was obtained prior to participation in the study.

2. All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the investigation, including information about relevant previous medical history and the results of all diagnostic tests.

Investigator files containing all records and reports of the investigation should be retained for a minimum of 5 years after the completion or termination of the investigational study or until two years after they are no longer needed to support product approval. They may be discarded upon notification by Pulse Biosciences. To avoid any error, the Investigator should contact Pulse Biosciences before destroying any records and reports pertaining to the study to ensure they no longer need to be retained.

8.5 Audits/Inspections

If audits are initiated by the Sponsor (or its designate), or national regulatory authorities, the Investigator shall allow access to the original medical records and provide all requested information.

9.0 BENEFITS AND RISK ANALYSIS

9.1 CellFX System Risk

The Investigators for the study are experienced physicians. Use of the CellFX System poses very minimal risk, including scabbing, minor skin pigment changes or scarring and minor discomfort which can be further minimized by covering the spot with a small bandage. Typical wound complications such as infection, bleeding and discomfort which requires prescription medication for relief are not anticipated. If they should occur, they would be considered an unanticipated adverse event and managed as such. If the subject has any questions or concerns about their medical condition or if an unforeseen event should occur the subject will be advised to contact the PIs or their designate.

A volunteer for the proposed study is someone who has elected removal of their wart lesions. Such scars are typically removed via surgical excision, intra-scar steroidal injections or systemic steroids. Participation in the study offers another technique to accomplish the same thing as the typical tools. Experience with the NPS technology to date offers some confidence that the scars may be lessened although no assurances will be offered. The information learned may contribute to the ultimate use of a safer and more effective device available to treat benign and non-benign lesions in future patients.

9.2 NSR Classification of Study

No significant risk is posed by either the use of the NPS technology or the study process. While safety can never be taken lightly, this study is not meant to measure monitor or analyze any significant disease or disorder for which medical treatment is mandatory.

See additional information regarding Non-Significant Risk statement below.

Non-Significant Risk Statement
The proposed study fits the criteria for a non-significant designation for the following reasons:

- Subjects will be recruited to participate in the study on a voluntary basis. Potential subjects will be recruited directly from the Investigator's population of patients who are candidates for removal of their wart lesions.
- Participation in the study takes no more than approximately 1 hour for each of the maximum of 6 study visits.
- Localized anesthesia/numbing will be used to control discomfort at the time of any CellFX System applications.
- After the CellFX device is deployed and the anesthesia/numbing is dissipated, there may be mild, localized discomfort at the site of the treatment. A small scab or crust may develop. This occurrence is transient and should resolve without intervention.
- Prior studies support the proposal that the use of the CellFX System represents minimal risk.
- There is no loss of privacy as no study records will be viewed or retrieved by anyone other than the study team members.
- Protected information will not be captured.
- Subject identity is protected by a coding system to de-identify them.

10. REFERENCES

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11. APPENDICES

11.1 APPENDIX A: Subject Informed Consent

APPENDIX A: Subject Informed Consent

The subject informed consent will be provided as a separate attachment