Clinical Investigational Plan

Study Title: A Multicenter, Prospective, Treat and Resect IDE Feasibility Study of the CellFX® System for the Treatment of Basal Cell Carcinoma (BCC) Lesions

Short Title: CellFX Treat & Resect BCC Feasibility Study

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1.0 INTRODUCTION AND BACKGROUND

1.1 Basal Cell Carcinoma Lesions

Basal cell carcinoma (BCC) arises from the basal cell layer of the epidermis and is the most common cancer among Caucasians globally.[1] The lesions usually occur on sun-exposed skin in adults, and locations are stratified by risk. Medium- and high-risk locations are the head, neck, genitals, hands, feet, and pretibial while low risk areas are the trunk and extremities (aside from the ankles and other areas included in the medium- and high-risk locations).[2] BCC lesions are rarely life threatening and the primary goal of treatment is complete removal of the tumor with maximum preservation of function and cosmesis.[2]

1.2 Current Care

The current care of BCC lesions includes topicals such as imiquimod cream, radiotherapy, curettage and electrodesiccation, cryosurgery, photodynamic therapy, MOHs surgery and surgical excision depending on multiple factors such as sub-type of the BCC, risk status, lesion size, anatomic location, patient age, etc. The currently recommended treatments of electrodessication and curettage, surgical excision/MOHs surgery or other modalities are often dependent upon the technique of the health care professional for adequate results and often leave scars and require down time for healing.[3]

1.3 Non-Surgical Approach

Topical Treatments

Topical Imiquimod 5% Cream

Topical 5% Imiquimod Cream is indicated for use on primary superficial BCC lesions. It requires doses 5 times per week for 6 weeks and is applied by the patient. Imiquimod is a toll-like receptor (TLR)-7 agonist and is thought to exert its anti-tumor effect via modification of the immune response and stimulation of apoptosis in BCC cells.[4] Intense local inflammatory reactions can occur with side effects including itching, pain and tenderness at the target site, burning, erythema, scabbing, excoriation/flaking, induration, edema, ulceration and vesicles.[5] The cosmetic outcome for topical imiquimod cream is superior to surgical excision but inferior in cure rate. 5% Imiquimod cream may also be used as pretreatment to Mohs in order to decrease tumor size and furthermore reduce surgical defect size or as an adjuvant therapy.[6]

Topical 5-fluorouracil

5-fluorouracil is a pyrimidine analogue which induces apoptosis due to cytotoxic metabolite incorporation into DNA and RNA.[7] This treatment modality is approved for use for superficial BCCs and involves topical application two times per day for a minimum of two weeks. This method has similar efficacy, safety, and cosmetic outcomes as imiquimod.[2] The most common skin effects include erythema, pruritus, dermatitis, burning sensation and photosensitivity.[7]

Oral Medications/Systemic Therapies

Hedgehog Pathway Inhibitors

Current FDA approved hedgehog pathway inhibitors, such as vismodegib and sonidegib, are used for locally advanced BCCs in which curative radiotherapy and surgery are not feasible. Vismodegib is FDA approved for treatment in adults with metastatic BCC or locally advanced BCC

that has recurred following surgery or who are not candidates for surgery or radiotherapy. Drawbacks for hedgehog pathway inhibitors are that resistance can be developed in advanced BCCs and AEs were seen in almost all subjects in clinical trials conducted. The most common AEs seen included muscle spasms, alopecia, nausea, weight loss and fatigue.[2]

Intralesional Interferon

Intralesional injection of interferon alpha-2b can be effective in treating low risk BCC lesions but it does not offer much patient convenience as it requires injections 3 times a week for 3 weeks and can be expensive. Side effects include erythema and flu-like symptoms.[1,8]

Physical Destruction

Radiotherapy (RT)/Radiation Therapy

Radiotherapy, along with surgical excision and Mohs surgery have the lowest failure rates among treatment options for BCC with overall 5-year cure rates ranging from 79%-100%.[9] This treatment modality is often utilized for lesions in areas that are difficult to resect, where patients are not good candidates for surgery and is recommended for patients over the age of 60. The length of the treatment regimens may vary, as the total dose and dose per fraction of radiotherapy used differ. The main concerns with this therapy are acute toxicity to normal cells, late radiation toxicity and long-term side-effects due to radiotherapy. Most published studies have concluded cosmetic outcomes to be satisfactory where evaluated. A visible scar is common based on the dose regimen. Other cosmesis related effects include alopecia, pigmentation change, telangiectasia, fibrosis/scar, atrophy, contraction and epiphora; and rarely soft tissue necrosis, bone necrosis, cataracts, dry eye, conjunctival scarring, and eyelid deformity in published studies.[9]

Cryosurgery

This treatment method involves the application of extreme cold to the lesion area with liquid nitrogen. The direct cooling applied to the BCC lesion disrupts the cellular architecture, membrane integrity, and enzymatic activity. Malignant cells are particularly sensitive to cryo therapy due to their nature of high-water content, high metabolism and microcirculation.[7] Once the growth freezes, it tends to fall off within days. Treatment results may vary with this procedure; past research has shown that pigmentary changes such as hypopigmentation are common, as well as erythema, edema, blistering, hypertrophic scarring, alopecia, tissue distortion and milia or pyogenic granuloma formation. [7] The cosmetic outcome is lower for cryotherapy compared to other treatment modalities. The pigmentary changes that arise due to treatment is shown to be dependent on the patient's Fitzpatrick Scale ranking.

Lasers & Photodynamic Therapy (PDT)

Photodynamic therapy is a light emitting therapy where low risk BCC lesions are treated with combined use of visible light and a photosensitizing agent, commonly 5-aminolevulinic acid (ALA), methyl aminolevulinate (MAL) or porfimer sodium. The skin is pre-treated using a photosensitizing, prescription gel that reacts with the light source, either IPL (Intense pulsed light) or a 405-420 nanometer blue light laser.[10] Generally, this mode of treatment will require several treatment visits, such as 4 sessions at 4-week interval when using the 405-420nm blue light laser.[10] Debulking prior to PDT has shown to be more efficacious and has become standard practice with this treatment method.[7] This method has greater cosmesis when compared to surgical excision, with effects seen including ulcerations but is reserved for superficial BCC lesions less than 1-2mm thick due to insufficient penetration of the photosensitizer and light source. [7]

PDT has similar efficacy as cryo, imiquimod and 5-FU but higher recurrence rates compared to imiquimod and higher patient pain reported compared to other modalities.[1]

Treatment of BCC with lasers include treatments with long pulsed 1064nm NDYAG Lasers and 595 pulsed dye lasers. Lasers work to treat BCCs by specifically targeting the vasculature that supplies the tumor to reduce tumor burden or eliminate the BCC.[11] Multiple treatments are often required. Post laser treatment a crust appears and tends to fall off after a week. Treatments may lead to transient side-effects including infection, erythema, edema, crusting and discoloration. The pigmentary changes that arise post-treatment may be dependent on Fitzpatrick Scale ratings.

Curettage and Electrodesiccation (C&E)

This treatment modality is a recommended treatment option for low-risk basal cell carcinomas in non-hair-bearing areas that do not involve tissue past the subcutaneous layer. [1]

The electrocautery procedure uses a pencil-shaped metal instrument or needle to destroy or heat the growth via a high-frequency electric current that is applied within the lesion.

Curettage involves scraping off the BCC lesion with a sharp knife or small, spoon-shaped tool down to a firm layer of normal epidermis.[1] Curettage may be combined with electrocautery to prevent regrowth of the lesion and it can also be used in conjunction with liquid nitrogen to produce better results than just using liquid nitrogen alone.

When the two procedures are combined, first, a curette is used to scrape off undesirable cells down to the level of uninvolved tissue. This is then followed by electrosurgery to widen the region of cell destruction and removal, and to cauterize the wound in order to limit bleeding. The healing process for such procedures can take a few weeks or longer, depending on the size of the wound and other factors. A scab forms and will generally fall off in a few days. The procedure can cause post-inflammatory hyperpigmentation in the treated area and although electrocauterization provides complete removal, there is no guarantee that another lesion will not develop nearby. Risk factors include reopening of wounds, scarring, temporary or permanent nerve damage (in regions with extensive nerves), subcutaneous bleeding and/or infections.

1.4 Surgical Approach

Standard Surgical Excision

This treatment modality is the standard of care for off-face BCC lesions, as it is the most effective and efficient for eliminating the BCC Lesion. This therapeutic method will be utilized in this study 60 days post-NPS treatment (Visit 6). It involves a standard excision with 4-mm clinical margins and post-operative margin assessment with second intention healing, linear repair or skin graft.[2] This treatment modality often leaves a scar and some areas are difficult to excise rendering this method infeasible.

Mohs Micrographic Surgery (MMS)

Mohs Micrographic Surgery with margin assessment is also a standard of care and has the lowest 5-year recurrence rate (1% and 6% of primary and recurrent BCC lesions, respectively). It allows intraoperative analysis of 100% of the excision margin. [1]

1.5 Alternative Approach

CellFX® System

The CellFX System is intended to be used for dermatological procedures in adult patients (greater than or equal to 22 years old) for the reduction, removal, and/or clearance of cellular-based benign lesions and low-risk basal cell carcinoma (BCC), as an alternative to surgery and other more destructive methods for removing skin lesions. The CellFX System utilizes localized delivery of a timed series of low energy, nanosecond electrical pulses that can trigger regulated cell death. The effect on tissue takes place in a very shallow depth of skin directly below the sterile treatment tip. Histology of skin treated with CellFX has demonstrated selective effects on cellular structures, including melanocytes, epidermal cells, and adnexal structures, including sebaceous glands and eccrine glands, with no apparent damage to the adjacent acellular dermis. The device delivers less energy to tissue, and does not emit thermal energy like laser, electro-surgery, or electro-cautery equipment.

Prior Clinical Studies Summary

Thirteen (13) clinical studies have been or are currently being conducted using IRB approved non-significant risk protocols and consent with the Nano-Pulse Stimulation (NPS) device. Two approved IDE pivotal studies are currently being conducted. A combined total of approximately 3,600 NPS application cycles have been delivered to about 700 adult Subjects. Anatomic locations where NPS has been used include the face, trunk, neck, arms, legs, hands, and feet. Discomfort in all protocols was managed with localized injected buffered Lidocaine, often with epinephrine. Side effects consisted of relatively minor reactions consistent with routine wound healing. No device or procedure complications and no serious related adverse events were reported. Only minor expected adverse skin effects were observed that are expected to resolve.

A Non-Significant Risk (NSR) Acne Feasibility study (NP-AF-009) was conducted using the Nano-Pulse Stimulation (NPS) device on back acne. The study involved the treatment of acne lesions in a 7cmx7cm area of the back with 49 cycles of energy delivered via the 10.0mm x 10.0mm treatment tip across a range of energy settings. The entire treatment area healed as expected with some residual hyperpigmentation, which is expected to resolve over time.

An initial NSR BCC feasibility study (NP-BC-005) demonstrated that the NPS Device was successful in treating basal cell carcinoma lesions without safety concerns. A portion of 1-2 biopsy confirmed BCC lesions were treated in the 48 Subjects enrolled. 48 NPS treated areas were evaluated by a board certified dermatopathologist. There was no presence of BCC located within the NPS treated area in all samples analyzed for superficial and nodular low risk BCC lesions. The treated areas showed favorable healing clinically.

1.6 Study Rationale

The rationale for this treat-and-resect BCC IDE feasibility study is to collect data on the safety and effectiveness of the CellFX System for the treatment of low-risk BCC lesions in adult subjects. The data derived from this feasibility study will additionally be utilized to determine an optimal treatment for basal cell carcinoma and design a pivotal study to support FDA approval for such intended use.

2.0 STUDY DEVICE DESCRIPTION

The study device being evaluated is the Pulse Bioscience CellFX® System.

2.1 Pulse Bioscience CellFX® System

The CellFX System is manufactured by Pulse Biosciences, Inc. and consists of an electrical pulse console (similar to devices used to electro-coagulate tissue) combined with a handpiece which is held by the clinician during application of pulses to the skin surface. The handpiece is coupled to a sterile, single patient-use treatment tip.

Once the electrical pulse console is turned on and a predetermined treatment energy setting is selected, a sequence of pre-programmed electrical pulses is administered to an area of skin directly beneath the treatment tip. A common commercially available sterile contact gel may be applied to the skin or treatment tip surface to ensure good electrical contact to the tissue. The three system components are as follows, shown in **Figures 1-3**.

1. CellFX Console including a built-in touch screen for setting selection.
2. CellFX Handpiece (re-usable)
3. Sterile Single Patient-Use CellFX Tip (multiple different tip sizes available)

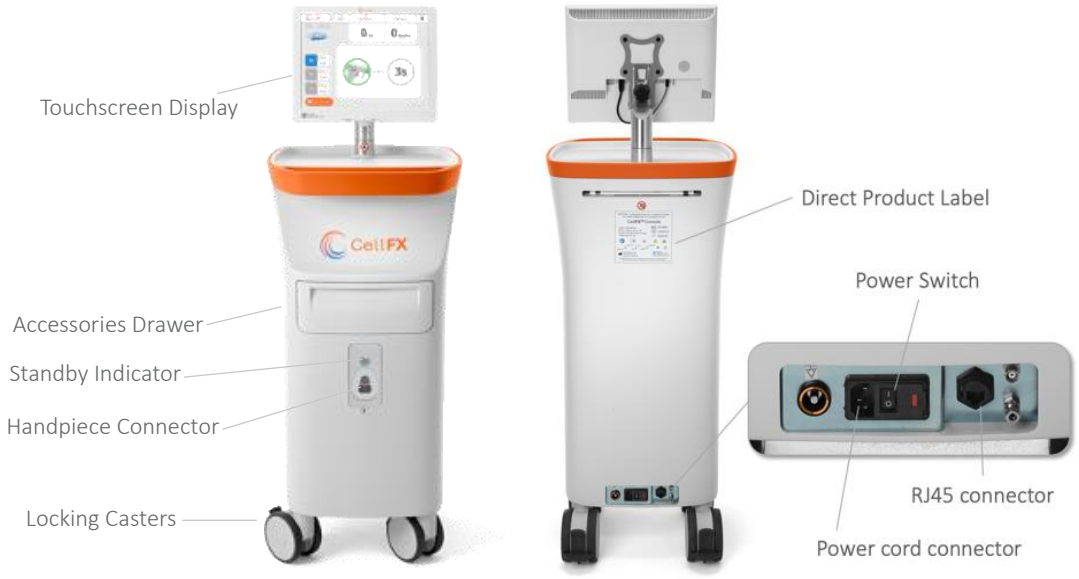


Figure 1: CellFX Console

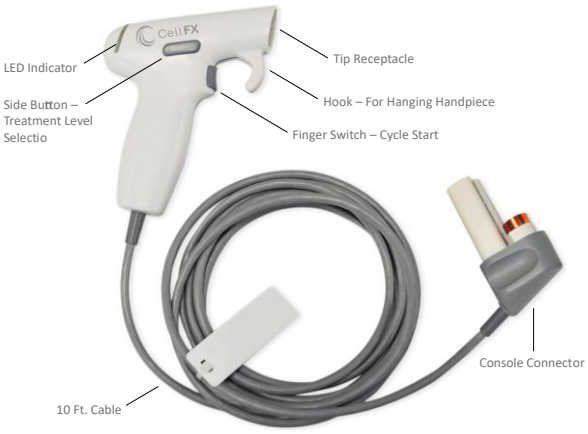


Figure 2: CellFX Handpiece

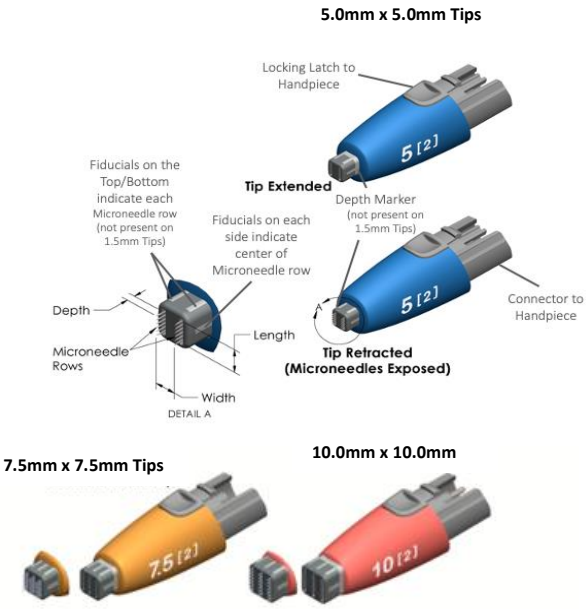


Figure 3: CellFX Tips

2.2 Proposed Indication for Use

The Pulse Biosciences' CellFX System is investigational in the U.S. and the system is indicated for dermatologic procedures requiring ablation and resurfacing of the skin including the treatment of benign and non-malignant lesions.

3.0 PROTOCOL

3.1 Study Objectives

The primary objectives of this study are to evaluate the safety and effectiveness of the CellFX System in adults with low-risk basal cell carcinoma. Table 1 below reflects the study endpoints associated with the two objectives.

Table 1. Study Objectives and Endpoints

Objectives	Endpoints
Safety To evaluate the safety of the CellFX System in adults with low-risk basal cell carcinoma	Primary: • No serious adverse events related to CellFX Treatment or Procedure
	Secondary: • Local Skin Reactions (Investigator) • Procedural pain assessment (Subject)
Effectiveness To evaluate the effectiveness of the CellFX System in adults with low-risk basal cell carcinoma	Primary: • Complete histological clearance of the target lesion on microscopic evaluation of hematoxylin and eosin stains
	Secondary: • Visible/clinical clearance of the target lesion by clinical/dermatoscopic evaluation • Partial response of the study lesion as assessed by WHO criteria (≥ 50% decrease in the product of the longest perpendicular diameters of each target lesion) • SCAR-Q Appearance Scale (Subject) • Manchester Scar Scale (Investigator) • Healing assessment questions (Investigator)

3.2 Study Design

This study is designed as a prospective, multicenter IDE feasibility study in up to 30 adult participants with low-risk basal cell carcinoma utilizing the CellFX System at up to 6 sites within the United States. The study will consist of a single treatment session with the CellFX System followed by surgical tumor excision (with 5 mm margins) 60 days post-treatment.

Eligible subjects with 1-2 histologically confirmed, primary BCC lesion(s) who meet the inclusion and exclusion criteria will be enrolled. The BCC lesion(s) may be present anywhere on the body except neck, axilla, hands, feet, or genitals. In cases where the subject has more than 1-2 BCC lesions that meet the study criteria, the PI will select the lesion(s) to include in the study.

The subject will receive treatment of their confirmed BCC lesion(s) with the CellFX system. The treatment area will be evaluated at 3-days, 7-days, 14-days, 30-days and 60-days post-NPS treatment. At the 60-day follow-up visit, participants will undergo complete surgical excision of the tumor plus 5 mm margins. The subject will return for 3 more follow-up visits post-excision at 14 days (suture removal), 30 days and 60 days (typical skin check post-surgical excision) for a total of 9 study visits. The 3-day, 7-day, and 30-day post-NPS treatment follow-up visits as well as the 30-day post-surgical excision visit may be performed as telemedicine visits.

The excised tissue at the 60-day post-treatment visit will be shipped for histological analysis. Preparation and analysis of the excised tissue will be performed by Pinkus Dermatopathology Laboratory and a board certified dermatopathologist who has extensive experience in interpreting cutaneous neoplasms. Details of the preparation, shipment and analysis of the excised tissue are provided in the Tissue Handling and Analysis Procedure.

Photography of the study lesion(s) will be captured along with the investigator's assessments at all in-office visits. Detailed instructions for photography of the lesion area are provided in the photography instruction manual.

3.3 CellFX Procedure

The intended CellFX treatment device is described as the CellFX® System using the skin contacting component referred to as the "tip". The three available tip sizes for this study are the 5.0mm x 5.0mm, 7.5mm x 7.5mm, and 10.0mm x 10.0mm tips defined in length and width, which may range from 2.0mm to 3.0mm in depth. When a treatment tip is attached, the CellFX Handpiece delivers a timed series of energy pulses, referred to as a "Cycle". The subject will be treated with appropriate tip sizes according to the size of the BCC lesion. The tip depth will be selected according to the guidelines defined in **Table 2a** below. The BCC lesion(s) will be treated with a pre-determined treatment energy level per tip size within the range provided in **Table 2b.**

Table 2a: Treatment Tip Depth Selection Guidance

Tip Depth (mm)	Criteria
2.0	Standard recommended treatment depth tip
3.0	Lesions with BCC located in the deeper dermis in the diagnostic biopsy sample. Diagnosed nodular/non-superficial BCC lesion located on the back or shoulder where skin is thicker and where the 2mm depth tip may not be sufficient.

Table 2b: Treatment Level Range per Tip

Tip Size (L x W, mm)	Minimum Treatment Level per Cycle (mJ/mm^3)	Maximum Treatment Level per Cycle (mJ/mm^3)
5.0 x 5.0	45	155
7.5 x 7.5	40	85
10.0 x 10.0	20	85

For this device, the term treatment level (TL) refers to the energy density value (mJ/mm^3) delivered to the tissue by the treatment tip per cycle. These treatment levels do not exceed the maximum safe ranges of settings previously tested in clinical studies. Multiple cycles of energy may be delivered with one or more tip sizes in order to treat the entire BCC lesion(s) along with a defined 5 mm margin during a single CellFX treatment session.

A tattoo will be applied prior to the CellFX treatment to identify the treatment area for evaluation. Four tattoo marks will be placed to identify the margin of the treatment zone within the tissue area of the eventual ellipse of the excision. The tattoo may be "touched up" or re-applied at future visits as needed. The tattoo will be applied to the area of the skin designated to be removed during the surgical excision of the BCC lesion on Day 60 (Visit 6). An analgesic will be used to manage potential treatment discomfort during the CellFX treatment.

3.4 Site Selection

The study will be conducted at up to 6 clinical research sites. The sites will be selected based on the appropriate patient population, board certified dermatologist, and sufficient resources to

support this IDE study.

3.5 Number of Subjects

Up to 30 subjects at up to 6 sites will be enrolled.

3.6 Clinical Study Duration

It is anticipated that the enrollment of subjects in this study will take approximately 2-3 months in duration. All subjects included in this IDE feasibility study will return for follow-up visits at 3-days, 7-days, 14-days, 30-days, and 60-days post-NPS treatment. At the 60-day follow-up visit, participants will undergo complete surgical excision of the tumor plus 5 mm margins. The subject will return for 3 more follow-up visits at 14-days, 30-days, and 60-days post-excision for a total of 9 study visits. The total study duration will be 7 months.

4.0 STUDY PROCEDURES

4.1 Screening

Recruitment will be conducted via direct communication by the investigator and/or his/her designated staff, advertisement and/or office ads. The Informed Consent discussion and signature process will be conducted by the investigator and/or designated staff. No study-specific assessments will be performed prior to obtaining consent.

A Screen Failure will be defined as a subject who did not meet one or more of the following criteria:

- Did not meet all inclusion and/or exclusion criteria
- Did not sign informed consent
- Signed the informed consent but did not subsequently undergo a treatment with the CellFX system

A screen failure will not be assigned a subject ID and information on this subject will not be entered in the electronic database. Information will be transcribed on the enrollment/screen failure log.

4.2 Subject Selection

The study population includes Adults with low-risk basal cell carcinoma.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.2.1 Inclusion Criteria

Candidates for this study must meet **ALL** the following criteria:

1. Subject is at least 22 and no older than 85 years of age.
2. Subject has 1-2 primary, non-recurrent, superficial, or nodular visible basal cell carcinoma lesion up to 1.5 cm in size with well-defined borders that has been verified by biopsy.
3. Lesion(s) is appropriate for full linear excision with 5 mm margins.
4. Subject is capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5. Subject gives voluntary, written informed consent to participate in this clinical investigation and from whom consent has been obtained.
6. Subject is willing to have BCC lesion(s) treated in a single treatment session and must comply with all study procedures including follow-up visits.
7. Subject consents to have photographs taken of the BCC lesion(s).
8. Subject agrees to refrain from using all other lesion removal products or treatments (topical medication including over-the-counter medications or treatments from PI or another physician) during the study period.
9. Subject agrees to refrain from prolonged sun exposure of the treatment area during the study period.

4.2.2 Exclusion Criteria

Candidates will be excluded from the study if **ANY** of the following apply:

1. Subject has an implantable electronic medical device (i.e., pacemaker, implantable cardioverter defibrillator).
2. Subject has an active infection or history of infection in designated test area within four weeks prior to treatment.
3. Subject is not willing or able to sign the Informed Consent.
4. Subject is known to be immune compromised/has a history of immunosuppression (e.g., organ transplant, long-term use of psoralen) or genetic disease (e.g., nevoid basal cell carcinoma syndrome [Gorlin syndrome], xeroderma pigmentosum).
5. The basal cell carcinoma lesion intended for treatment with the CellFX System is on the face, neck, scalp, axilla, hands, feet, or genitals.
6. The basal cell carcinoma intended for treatment with the CellFX System is a high-risk BCC subtype including perineurial, infiltrative, sclerosing, morpheaform, desmoplastic, micronodular, basosquamous or exhibiting aggressive growth patterns.
7. Subject is known to be a keloid producer.
8. Subject has allergies to Lidocaine or Lidocaine-like products.
9. Subject has a history of radiation to the area intended for treatment.
10. Subject has current or prior metastatic BCC.
11. Subject is currently being treated or has been previously treated with Sonidegib or Vismodegib.
12. Subject has recurrent BCC lesions.
13. Subject has a systemic infection.
14. Subject has a history of epilepsy.
15. Subject has a history of cardiac arrhythmia, myocardial infarction or structural heart disease.
16. Subject is employed by the sponsor, clinic site, or entity associated with the conduct of the study.
17. Subject has any condition or situation which, in the Investigator's opinion, puts the subject at significant risk, could confound the study results, or may interfere significantly with the subject's participation in the study.
18. Subject has a history of use of any other investigational drug, therapy, or device within the past 30 days of enrollment or concurrent participation in another research study, with the exception of participation in a COVID vaccination related clinical trial.

4.3 Process for Obtaining 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 from to be eligible for study participation. The informed consent must contain all elements required by 21 CFR Part 50 and ISO 14155:2011/AC:2011 and comply with the ethical principles of the Declaration of Helsinki.

4.3.1 Process for Obtaining Informed Consent

The patients will be informed by the Investigator or Investigator's designee that they are free to refuse participation in this research study. If they elect to participate, it will be made clear that they may withdraw from the study at any time without prejudicing further care.

The Investigator or the Investigator's designee will inform patients that their medical records will be subject to review by the sponsor or appropriate regulatory bodies. This information will be used during the analysis of the results of the clinical study, but the patients' identities will be treated as confidential. Patients will be assigned a unique study subject code that will not reveal the patients' identity, and this code will be used on all data and data collection forms during the study period. The Investigator will explain the conditions of the study, giving the patient sufficient time to ask questions and to consider whether to participate. Eligible patients who agree to participate will be asked to sign and date an IRB approved informed consent. If the patient agrees, an IRB approved consent form will be provided to the patient for signature and date. One copy shall be returned to the Investigator and filed in the patient's case history; the other copy is for the patient to keep.

4.3.2 Addition of New Information

Pulse Biosciences, Inc. will revise the written informed consent form whenever new information becomes available that may be relevant to the subject's confirmed participation in the study. The revised information will be sent to the Investigator for approval by the IRB. After approval of the IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to the repeated. Please follow the central IRB guidelines on the process of re-consenting subjects.

4.4 Schedule of Events and Evaluations

Schedule of events and evaluations required for this study are provided in **Table 3**.

Table 3. Schedule of Events

Study Activity/ Procedure	**Visit 1** Screening/ Enrollment & Tx	**Visits 2-4** 3, 7, 14-days Post-Tx	**Visits 5** 30-days Post-Tx	**Visit 6** Excision (60-days Post-Tx)	**Visit 7** 14-days Post Excision	**Visit 8** 30-days Post Excision	**Visit 9** 60-days Post Excision
Study Day	0	3/7/14	30	60	74	90	120
Visit Window	Day 0	±2 days	±5 days	±5 days	±3 days	±5 days	±5 days
Type of Visit ***OV*** *– In-Office Visit Required* ***OV/TM*** *– In-Office Visit or Telemedicine Visit*	OV	**Visit 2 & 3:** OV/TM **Visit 4:** OV	OV/TM	OV	OV	OV/TM	OV
Inclusion/Exclusion Informed Consent	✓						
Demographics, Medical HX, Fitzpatrick Skin Type, etc.	✓						
Lesion History	✓						
History of Pigmentary Changes	✓						
Photographs	✓[a]	✓*	✓*	✓[a]	✓[a]	✓*	✓
Lesion Assessment (Investigator)	✓[a]	✓*	✓*	✓[a]	✓	✓*	✓
Tattoo Treatment Area	✓						
CellFX Treatment	✓						
Procedural Pain Assessment (Subject)	✓			✓			
Surgical Excision				✓			
Suture Removal (as applicable)					✓		
SCAR-Q Appearance Scale (Subject)				✓[b]			✓
Manchester Scar Scale (Investigator)				✓[b]			✓
Healing Assessment Questions (Investigator)				✓[b]			✓
Lesion Measurement	✓			✓[b]			
Clinical Clearance Assessment				✓[b]			
Adverse Events	✓	✓	✓	✓	✓	✓	✓
Study Exit							✓

[a] Pre- and post-procedure / Surgical Excision / Suture Removal
[b] Pre-procedure / Surgical Excision
* Required for in-office visits only

4.5 Screening / Enrollment Procedures (Visit 1)

The following activities are required at the time of the subject screening/enrollment visit. The order of the activities may vary within reason as long as all activities are performed after consent is obtained. The Screening Visit and Treatment Visit (subject enrollment visit) may occur on different days.

4.5.1 Activities prior to or on same day as study enrollment

- Evaluation for Inclusion/Exclusion criteria.
- Collect Demographic information and medical history including but not limited to age, gender, race, ethnicity, dermatologic conditions, and Fitzpatrick skin type.
- Sign the consent form prior to any study activities.
- Receive a copy of the signed consent form.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria.

4.5.2 Definition of Enrollment

Once the subject has been consented and has received a CellFX treatment, the subject will be considered enrolled and each enrolled subject will be assigned a unique Study Identification Number.

4.5.3 CellFX Treatment Procedure

- 1-2 clinically diagnosed BCC lesion(s) that meet the study criteria will be selected by the treating investigator. The identified lesion(s) will be labeled.
- Baseline photographs will be taken (prior to use of analgesic for pain management and prior to tattooing).
- Baseline clinical measurements of the BCC lesion(s) shall be taken
- The site investigator will perform a baseline lesion(s) assessment.
- A template will be applied to the skin and used to map out the treatment application.
- A tattoo (4 marks) will be applied within the area designated for excision to mark the treatment zones for the purpose of identifying the treatment area during evaluation.
- An analgesic for pain management, such as local injection of lidocaine, will be administered to the selected study lesion area(s).
- Each study lesion will be treated with the CellFX system per Table 2 according to the treatment tips utilized.
- The total number of treatment cycles with the CellFX system will be recorded.
- The subject will be asked to rate his/her pain immediately after the treatment session for each lesion treated with the CellFX system by using a numerical rating score, depicted in Figure 4.
- Post-procedure lesion assessment will be performed by the investigator.
- Post-procedure photographic images of each selected lesion will be taken.
- A light bandage and/or any physician recommended dressing may be applied before the subject leaves.
- Any adverse events will be identified and documented.

4.6 3-Day Follow-up Visit (Visit 2)

- This visit may be performed in-office or as a telemedicine visit.
- Photographic images of each study lesion will be taken. Photographs are not required if the visit is not performed in-office.
- All lesions will be examined and clinically assessed by the site investigator. If the visit is not performed in-office, clinical assessment is not required.
- A light bandage and/or any physician recommended dressing may be applied post-evaluation.
- Any adverse events will be identified and documented. If the visit is not performed in office, the clinical site must inquire regarding any adverse events either by phone call, text, e-mail or video conference.

4.7 7-Day Follow-up Visit (Visit 3)

- This visit may be performed in-office or as a telemedicine visit.
- Photographic images of each study lesion will be taken. Photographs are not required if the visit is not performed in-office.
- All lesions will be examined and clinically assessed by the site investigator. If the visit is not performed in-office, clinical assessment is not required.
- A light bandage and/or any physician recommended dressing may be applied post-evaluation.
- Any adverse events will be identified and documented. If the visit is not performed in office, the clinical site must inquire regarding any adverse events either by phone call, text, e-mail or video conference.

4.8 14-Day Follow-up Visit (Visit 4)

- Photographic images of each study lesion will be taken.
- All lesions will be clinically assessed by the investigator.
- A light bandage and/or any physician recommended dressing may be applied post-evaluation.
- Any adverse events will be identified and documented.

4.9 30-Day Follow-up Visit (Visit 5)

- This visit may be performed in-office or as a telemedicine visit.
- Photographic images of each study lesion will be taken. Photographs are not required if the visit is not performed in-office.
- All lesions will be examined and clinically assessed by the site investigator. If the visit is not performed in-office, clinical assessment is not required.
- Any adverse events will be identified and documented. If the visit is not performed in office, the clinical site must inquire regarding any adverse events either by phone call, text, e-mail or video conference.

4.10 60-Day Follow-up Visit (BCC Surgical Excision Day – Visit 6)

- Photographic images of each study lesion will be taken.
- All lesions will be clinically assessed by the investigator.
- The site investigator shall assess each treatment area based on the Manchester Scar Scale

prior to excision.
- The site investigator shall complete the healing assessment questions for each treatment area prior to excision.
- Clinical measurements of the BCC lesion(s) shall be taken
- The site investigator shall complete the clinical lesion clearance assessment for each treatment area prior to excision.
- The subject shall assess each treatment area based on the SCAR-Q Appearance Scale prior to excision.
- A complete surgical tumor excision will be performed by the investigator with at least 5mm margins for each study lesion.
- The subject will be asked to rate his/her pain immediately after surgical excision by using a numerical rating score.
- All tissue shall be handled and shipped to the dermatopathology laboratory per the Tissue Handling and Analysis Procedure.
- Any adverse events will be identified and documented.

4.11 14-Day Post-Excision Follow-up Visit (Visit 7)

- Photographic images of each study area will be taken.
- Each study area will be clinically assessed by the investigator.
- Sutures shall be removed, as applicable.
- Photographic images of each study area will be taken post-suture removal.
- Any adverse events will be identified and documented.

4.12 30-Day Post-Excision Follow-up Visit (Visit 8)

- This visit may be performed in-office or may be performed as a telemedicine visit.
- Photographic images of each study area will be taken. Photographs are not required if the visit is not performed in-office.
- Each study area will be examined and clinically assessed by the site investigator. If the visit is not performed in-office, clinical assessment is not required.
- Any adverse events will be identified and documented. If the visit is not performed in office, the clinical site must inquire regarding any adverse events either by phone call, text, e-mail or video conference.

4.13 60-Day Post-Excision Follow-up Visit (Visit 9)

- Photographic images of each study area will be taken.
- Each study area will be clinically assessed by the site investigator.
- The site investigator shall assess each treatment area based on the Manchester Scar Scale.
- The site investigator shall complete the healing assessment questions for each treatment area.
- The subject shall assess each treatment area based on the SCAR-Q Appearance Scale.
- Any adverse events will be identified and documented.

4.14 Subject Withdrawal

A study subject has the right to discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitles or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. A withdrawn subject will be treated according to standard of medical care and will not be replaced.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

4.15 Discontinuation of CellFX Treatment Session

A participant may be discontinued from treatment with the CellFX System prior to completion of the entire treatment session in the event of intolerable pain or system failure of the CellFX System. If the study subject elects not to complete the treatment session, a study exit form shall be completed and documented as early termination. System failure of the CellFX System or component failure shall be documented on the Device Malfunction Form.

4.16 Lost to Follow-Up

A study subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or will continue in the study.
- For the surgical excision visit (Visit 6), the sites must confirm the surgical excision date with the participant 1-2 times, 1 week to 1 day prior to the visit day and reiterate the importance of completing the surgical excision visit in order to ensure the cancer does not return or spread. If the subject does not confirm and/or does not come in on their schedule excision date, the site must attempt to contact the participant with at least three phone calls. If the site cannot reach the participant, the site is to send a certified letter to the participant's last known mailing address or local equivalent methods.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts are to be documented in the participant's medical record.
- If the participant continues to be unreachable, he/she will be considered to have withdrawn from the study.

5.0 BENEFITS AND RISKS

5.1 Benefits

There are no guaranteed benefits from participation in this study. Participation in the study offers another dermatological approach to accomplish the same clinical effect as the typical topicals, surgical devices or surgical excision currently used to treat patients with BCC lesions. The information learned from this study may contribute to the ultimate use of a safer and more effective device and the availability of the device to treat benign and non-benign lesions as an alternative for use in future patients.

5.2 Risks

For detailed information on the risks of the devices used in the study procedure, including a complete list of warnings, precautions, and potential adverse events, please refer to the Instructions for Use (IFU) for the Pulse Bioscience CellFX® System.

An additional risk for study participants is the delay in performing surgical excision of the tumor; however, basal cell carcinomas are slow-growing, so a delay of 60 days is considered a minimal risk. The wait times for standard surgical excisions are often longer than 60 days in some areas and practices. Because biopsy and surgical excision are standard of care for basal cell carcinoma and will also be occurring in this study, risks of these procedures are not considered in the benefit/risk assessment.

5.3 Mitigation of Risks

As with any dermatological procedure, appropriate safety precautions will be followed. Risks observed or theoretical adverse events have been mitigated through the Instructions for Use, physician training, and patient selection in the study protocol. The subject will receive full care of their BCC lesion(s).

All efforts will be made to minimize these risks by:

- Site Selection
- Patient Population that represents the demographics of the U.S
- Ensuring compliance to the protocol and IFU
- Study monitoring
- Safety processes-protocol adverse events reporting requirements

The following plan is set in place in order to mitigate the risk of the study participant treated with the CellFX system not returning for their surgical excision visit to receive full care of their BCC lesion(s):

- Prominent language is added to the Informed Consent Form to emphasize that the CellFX treatment has not yet been shown to remove all cells from a skin tumor, and therefore surgical removal is of the utmost importance to ensure that the cancer does not return or spread.
- Training of the PI and their clinical study staff will emphasize the importance of subject selection in selecting subjects who will commit to all study visits, an explanation of the importance for all subjects to complete their surgical excision of the diagnosed BCC lesion, training to remind and confirm the study visits with the subjects at each visit, with emphasis on the surgical excision visit.
- Subject compensation is structured to motivate the subject to complete the surgical excision, and safety follow up visits with the highest compensation assigned to the surgical excision visit (Visit 6), higher monetary values assigned to the later follow-up visits (visits 7-9), as well as an all-visit bonus offered for subjects who complete all study visits.

- Site compensation includes an all-visit bonus to motivate the site to closely follow-up with the study subjects to ensure all visits are completed.
- Remote and on-site monitoring of subject visits at all participating sites to ensure compliance of subject attending scheduled study visits.

6.0 STATISTICAL CONSIDERATIONS

6.1 General Approach

For descriptive statistics, counts and percentages will be calculated for categorical variables. Continuous variables will be summarized using the mean, standard deviation, median, minimum and maximum. No inferential tests are planned for this study, but 2-sided confidence intervals will be produced where appropriate. Where 2-sided p-values are calculated, they should be interpreted as descriptive only.

6.2 Analysis of the Primary Effectiveness Endpoint

The count and proportion with the primary endpoint of histological clearance will be calculated along with a 95% confidence interval (CI). The primary population for this analysis will be the Per-Protocol population, though estimates will be produced for the modified intent-to-treat/ safety population (patients who begin treatment) and Complete Treatment population (subjects who complete all required cycles of treatment).

6.3 Analysis of Secondary Endpoints

No formal hypothesis testing is planned for secondary endpoints. Any p-values comparing groups should be considered descriptive. The secondary endpoints will be evaluated using the modified intent-to-treat/ safety population, but these analyses may be repeated for complete treatment and per-protocol populations as well.

6.3.1 Change in Lesion Size

Lesion size (as measured by the productof the longest perpendicular diameters) will be calculated at baseline and at follow-up day 60 post-NPS treatment. The two longest diameters (longest length and longest perpendicular width) of each study lesion will be measured and the product will be calculated for each individual study lesion at baseline and at 60 days-post NPS treatment study visits. Calipers will be provided to each study site to perform the measurements per standardized procedures. A standard adhesive ruler will also be included in photographs taken of each study lesion. Within-lesion change in lesion size from baseline to the 60-Day follow-up time-point will be calculated. A mixed model for repeated measures will be used to estimate the mean reduction and its 95% confidence interval. Baseline lesion size will be included as a fixed effect.

6.3.2 Lesion Reduction Category

The visible/clinical clearance of the target lesions will be rated according to the lesion reduction categories listed in Table 4. The lesion reduction category will be derived from the lesion size measurements at baseline and follow-up day 60 Post-NPS treatment described in **Section 6.3.1**. The % reduction will be calculated as the change in lesion size divided by the baseline value. This percentage will be categorized according to the table 4 below:

Table 4. BCC Lesion Reduction Categories

BCC Lesion Reduction Categories			
CLEAR	MOSTLY CLEAR	PARTIALLY CLEAR	NOT CLEAR
0mm/100% reduction	99-51% reduction	50-25% reduction	<25% reduction

6.3.3 Partial response of target (study) lesion as assessed by WHO criteria

Partial response will be assessed using the WHO criteria. Partial response is defined as a ≥ 50% decrease in the product of the perpendicular diameters of each target/study BCC lesion compared to baseline. The 50% reduction will be determined through the product of the longest perpendicular bidimensional diameters (longest length and longest perpendicular width) of each study lesion treated. Calipers will be provided to each study site to perform the measurements per standardized procedures. A standard adhesive ruler will also be included in photographs taken of each study lesion. Partial response will be assessed for in-clinic measurements at follow-up day 60 Post-NPS treatment. The number and proportion of lesions meeting the definition of partial response and confidence interval for the proportion will be calculated.

6.3.4 SCAR-Q Appearance Scale (Subject)

The SCAR-Q is a patient-reported outcome instrument designed to measure outcomes specific to any type of scar. This instrument has subscales for scar appearance, psychosocial impact and scar symptoms. Least-square means and confidence intervals will be calculated for each scale and subscale using generalized linear models with lesion size included as a fixed effect.

6.3.5 Manchester Scar Scale (Investigator)

The Manchester Scar Scale evaluates the following five characteristics of scar: color (score: 1–4), distortion (score: 1–4), contour (score: 1–4), texture (score: 1–4), and transparency (score: 1–2). The distribution of responses will be summarized for each characteristic. Least-square means and confidence intervals will be calculated for the total score using generalized linear models with treatment lesion size included as a fixed effect.

6.3.6 Healing assessment questions (Investigator)

The following assessment questions will be asked on the Day 60 post-NPS treatment visit prior to surgical excision as well as on the Day 60 post-surgical excision visit:

a. Is the healing pattern cosmetically acceptable? (yes, no)
b. How likely is a scar? (1 = unlikely, 2 = possible, 3 = probable)
c. Once healed, how do you anticipate the treated area will look compared to curettage and desiccation? (1 = better, 2 = the same, 3 = worse)
d. Once healed, how do you anticipate the treated area will look compared to surgical

excision? (1 = better, 2 = the same, 3 = worse)

The distribution of responses will be summarized for each question.

6.4 Safety Endpoints

Unless otherwise noted, the safety population will be used to assess safety endpoints.

6.4.1 Primary Safety Endpoint

The primary safety endpoint is the incidence of any serious AEs or complications associated with the application of NPS (procedure and treatment). Information about AEs and complications will be solicited by site investigators at scheduled follow-up visits. The count and proportion with the primary safety endpoint will be calculated along with a 95% confidence interval. Adverse events and complications will also be summarized by MedDRA preferred term.

6.4.2 Investigator Local Skin Reaction Assessment

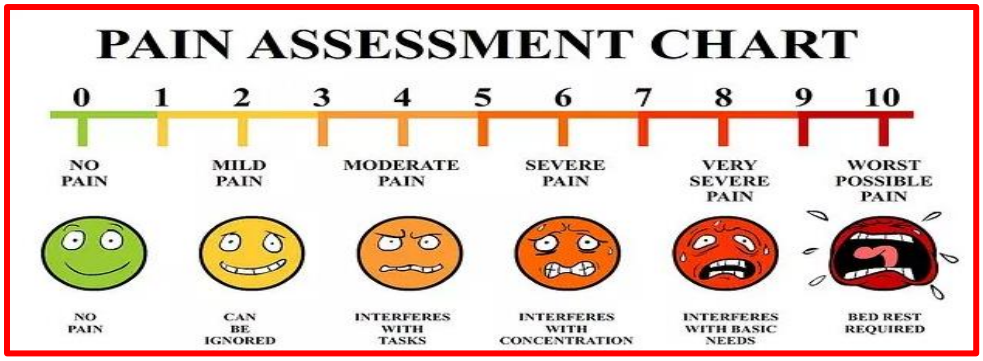
The Investigator will perform clinical assessments on the local skin reaction of the treatment area based on the following characteristics: presence and severity of erythema, edema, exudate, eschar, peeling scaling, bleeding, ulceration, scarring, and pigmentary changes. Assessment will be based on a validated 5-point scale: None, Mild, Moderate, Moderate to Severe, Severe. The wound healing characteristics will be assessed by the investigator at the 14-Day and 60-Days Post-NPS visits. The 3-Day, 7-Day, and 30-Days Post-NPS visits are optional in-office and will be summarized separately and included as a descriptive analysis. The rate of each event individually and a composite of any of these events will be calculated for each treated lesion area. The number and proportion of lesions with any reporting of any erythema, edema, exudate, eschar, peeling scaling, bleeding, ulceration, scarring, or pigmentary changes (regardless of severity) will be summarized by time-point.

6.4.3 Participant Assessment of Procedural Pain

The participant will give an assessment of procedural pain on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable). The Pain Assessment Chart with an assigned numerical rating between 0 (smiling) and 10 (crying) will be used to assess pain at Day 0, as reference in Figure 4. The pain scale will be assessed immediately after each lesion treatment session.

Pain levels will be grouped into four categories: No Pain (Score of 0), Mild Pain (Scores of 1-3), Moderate Pain (Scores of 4-6) and Moderate-to-Severe Pain (Scores of 7-10). The number and percentage will be tabulated for each category of pain, averaged for overall pain and may be analyzed against other parameters.

Figure 4: Pain Assessment Chart



6.5 Sample Size Determination

No formal hypothesis tests will be performed for this study, so the sample size was selected to produce a representative sample of BCC lesions to determine whether treatment effects are consistent across study participants. A maximum of 30 participants will be treated to allow for assessment of the endpoints outlined in this protocol.

6.6 Populations for Analyses

The following populations are defined in Table 5.

Table 5. Population Descriptions for Analysis

Population	Description
Modified Intent-to-treat / Safety Population	All enrolled participants who began treatment with the CellFX system, irrespective of completed study treatment session, subsequent withdrawal, or deviation from the protocol.
Complete Treatment	This population consists of mITT participants who completed the entire CellFX treatment session.
Per-Protocol	Participants who received treatment, completed the CellFX treatment session, excision surgery and all required study visits.

6.7 Sub-Group Analyses

Subgroup analyses will be performed for the following subgroups:

- Lesion Size Tertiles
- Fitzpatrick skin type

6.8 Interim Analyses

No interim analysis is planned for this study.

6.9 Missing Data

All possible efforts will be made to minimize missing data in this study. However, based on previous studies, any missing data that does occur is likely due to missed follow-up visits. However, the sensitivity of the final results to missing data will be examined by comparing the primary outcomes to the results using a longitudinal model with the 60-day post treatment results, and a tipping-point analysis will be performed for the endpoints at 60 days to determine whether the missing data could change the inference compared to the primary models.

6.10 Exploratory Analysis

Exploratory analysis may be performed to compare the different BCC subtypes. Wound healing characteristics for the post-excision area will also be assessed and compared to the wound healing characteristics post-NPS.

Exploratory analysis may be performed for dermatologic similarities of skin type based on anatomic subcategories:

- Sun-exposed limbs
- Non-sun exposed limbs
- Torso

7.0 CLINICAL PHOTOGRAPHY

The Sponsor will use standardized photographic capture methods described in the photography instruction manual. Photographs will be taken at each in-office study visit. In order to ensure consistent serial clinical photography is achieved during the study, all subject photographs will be reviewed (monitored) on an ongoing basis. Digital images will be transferred/stored in a secure, password protected portal.

8.0 ADVERSE EVENTS

Pulse Biosciences will classify each reported Adverse Event according to ISO 14155:2011. All protocol specific AEs, whether device-related or not, will be recorded on the AE case report form and reported. 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. All AEs related to the lesion site(s) should be reported and classified by the site Investigator and be followed by the Investigator to determine the relationship of the AE to the device or the study procedure.

All AE information will be collected from enrollment through the last study visit at 60 days following the surgical excision of the BCC lesion(s) (120 Days after the CellFX treatment session). All AEs will be followed until the event has resolved (in the case of permanent impairment, the event will be followed until it stabilizes, and the overall clinical outcome has been ascertained). Medical occurrences that begin before receiving a CellFX treatment but after obtaining informed consent will be recorded on the Medical History section of the CRF rather than the AE section.

When reporting AEs/SAEs, the Investigator should include the following information:

- Description of event
- Onset of event
- Duration of event (including resolution dates or whether the AE is ongoing)
- Severity
- Relationship to device or procedure
- Action taken
- Subject outcome

Severity describes the intensity of an event and will be assessed as:

- **Mild**: The AE does not interfere in a significant manner with the subject's normal functioning level.
- **Moderate**: The AE produces some impairment of function but not hazardous to health.
- **Severe**: The AE produces significant impairment of function or incapacities and/or it is a hazard to the subject.

Relationship to device or procedure will be assessed as:

- **Unlikely**: There is no indication that the AE was caused by the investigational or standard of care device.
- **Possibly**: It cannot be excluded that the AE was caused by the investigational or standard of care device.
- **Likely**: A causal relationship between the investigational or standard of care device and the AE is at least a reasonable possibility, i.e. there is evidence or argument suggesting a causal relationship.

8.1 Adverse Event Definitions

8.1.1 Adverse Event (AE): (*ISO 14155:2011 3.2*)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device.

NOTE 2: This definition includes events related to the procedures involved.

***For the purposes of this protocol, only dermatologic AEs will be reported to the Sponsor**.

8.1.2 Adverse Device Effect (ADE): (*ISO 14155:2011 3.1*)

Adverse event related to the use of an investigational medical device

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

8.1.3 Serious Adverse Event (SAE) (ISO 14155:2011 3.37)

Adverse event that

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

8.1.4 Serious Adverse Device Effect (SADE): (ISO 14155:2011 3.36)

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

8.1.5 Unanticipated Adverse Device Effect (UADE): *(21CFR812.3)*
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

8.2 Device Deficiencies (*ISO 14155:2011 3.15*)

8.2.1 Definitions

Device Deficiency is an Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance.

NOTE*:* Device deficiencies include malfunctions, use errors, and inadequate labelling.

Device Malfunction is a failure of the study device to perform in accordance with its intended purpose when used in accordance with the instructions for use or study protocol.

8.3 Safety Reporting Requirements

Table 6 summarizes the time sensitive requirements for adverse events and device deficiencies. The Sponsor is the contact person for these reporting requirements.

Table 6. Investigator Responsibilities for Submitting Adverse Events to the Sponsor

Type of Adverse Event	Reporting Timeframe
*Serious Adverse Device Effects (SADE), including Unanticipated Serious Adverse Device Effect (USADE)	As soon as possible, but in no case later than 3 calendar days after the clinical site first learns of the event or of new information in relation with an already reported event
**Serious Adverse Events (SAE)	As soon as possible, but in no case later than 3 calendar days after the clinical site first learns of the event or of new information in relation with an already reported event
Adverse Device Effects (ADE)	As soon as possible, but in no case later than 3 calendar days after the clinical site study team first learns of the event or of new information in relation with an already reported event
All other AEs (dermatologic only)	Submit in a timely manner after the clinical site first learns of the event
**Device Deficiency with SADE potential	As soon as possible, but in no case later than 3 calendar days after the clinical site study team first learns of the deficiency or of new information in relation with an already reported deficiency
All other Device Deficiencies	Submit in a timely manner after the clinical site first learns of the deficiency

*The Sponsor will report the results of an evaluation of an unanticipated serious or serious adverse device effect to the FDA and all reviewing IRBs and investigators within 10 working days after the Sponsor first received notice of the adverse effect per 21 CFR 812.150.

**It is the responsibility of the investigator to inform their IRB of serious adverse events and device deficiencies as required by their IRB guidelines.

9.0 STUDY MANAGEMENT (SPONSOR RESPONSIBILITIES)

9.1 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 the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312). The study sponsor will adhere to sponsor general duties as described in ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice, and CFR Part 812, 50, 56, 54 and the World Medical Association Declaration of Helsinki.

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, secure area 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).

General Duties

Pulse Biosciences will ensure that the application is submitted to the appropriate regulatory authorities, obtaining copies of IRB approvals and ensuring documentation of IRB approvals prior to the shipping of devices, ensuring proper clinical site monitoring, ensuring patient informed consent is obtained, providing quality data that satisfies regulations and informing the Investigators and IRBs of unanticipated adverse device effects, events, and deviations from the protocol as appropriate.

9.2 Selection of Clinical Sites

The primary requirements of site and Investigator selection and continued participation in the Trial include adequate experience, commitment to safety, consistency in adherence to the protocol, and patient volume. 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.

9.3 Site Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor. 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 will present a formal training session to study site personnel which will review the Instructions for Use of the device, the Investigational Plan, instructions on data collection, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the Sponsor through the regular site monitoring.

9.4 Investigator Training

The Sponsor will provide appropriate Investigator training on the use of the CellFX System, Handpiece, and Treatment Tips. 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. Photography training as well as training on the electronic data capture system and photo management system will also be conducted.

9.5 Monitoring of Study Sites

9.5.1 Monitoring Methods

Monitoring functions for this study will be conducted by Pulse Biosciences. The study will be monitored to ensure that the protocol, applicable regulations, and Good Clinical Practice Guidelines are followed. The study monitor will ensure that the rights and well-being of subjects are protected, and the clinical trial data are accurate, complete, and verifiable. Specific monitoring requirements are detailed in the study specific Monitoring Plan.

Prior to subject enrollment, the Sponsor will obtain the essential regulatory documents required to initiate the study. The Sponsor will be responsible for the review and approval of the following essential documents:

- Current Protocol Revision
- Investigator Agreement
- IRB approval letter for the protocol and consent form
- IRB approved consent form
- IRB membership roster or assurance number

Copies of file documents will be maintained by the Sponsor.

9.5.2 Periodic Monitoring Visits (Onsite and Remote)

Periodic monitoring visits will be made at the investigational site throughout enrollment of the clinical study to assure that the Investigator obligations are fulfilled, and all applicable regulations and guidelines are being followed. These visits will assure that the facilities are still acceptable; the protocol and investigational plan are being followed, the IRB/HREC has been notified of approved protocol changes as required, complete records are being maintained, appropriate and timely reports have been made to the Sponsor and the IRB, device and device inventory are controlled and the Investigator is carrying out all agreed activities. The monitor will verify accuracy of CRF or EDC completion against source documents maintained at the site.

During monitoring visits, the Monitor will perform a review of study eligibility, Inclusion/Exclusion criteria, informed consent, all reports of device malfunction, all events meeting criteria for serious adverse event reporting as well as safety and efficacy endpoints.

Additional review will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits.

The monitor will ensure that Investigators are aware of the regulatory requirement to maintain information in the study subject's medical records which corroborate data collected on the CRF or EDC system. To comply with these regulatory requirements, the following information will be maintained and made available as required by the sponsor and/or regulatory inspectors:

The monitor will compare key variables (demographics, inclusion/exclusion criteria, and safety) on the CRFs or EDC database with each subject's source documents. Any discrepancies will be noted and resolved.

9.5.3 Site Close-out Visit

Upon completion of the clinical study (when all subjects enrolled have completed the follow-up visits and the CRFs or EDC and queries have been completed), the Sponsor will notify the site of closeout and a study closeout visit will be performed. All CRFs, unused study devices, and any unused study materials will be collected and returned to the Sponsor. The Monitor will ensure that the Investigator's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

9.6 Protocol Deviations

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

Deviations shall be reported to the Sponsor regardless of whether medically justifiable, pre-approved, or taken to protect the subject in an emergency. Subject specific deviations will be reported on the provided protocol deviation form. Non-subject specific deviations will be reported to the sponsor in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

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

9.7 Study Completion

The study is considered completed after all subjects have undergone all of their protocol required follow-up visits, all eCRFs have been submitted, all queries have been resolved, and all action items have been closed. All unused study materials and study devices will be collected and returned to Pulse Biosciences or appropriately discarded as per instruction. After study closure, a final report will be completed.

9.8 Audits / Inspections

Pulse Biosciences, national/international regulatory authorities and IRBs may conduct initiated

audits or inspections at the study sites during the course of, or after completion of the study. The Investigator shall allow access to the original medical records and provide all requested information.

9.9 Publication Policies

Publications based on the results of the study will follow the process outlined in the Investigator Agreement. The study will be registered on www.clinicaltrials.gov.

9.10 Data Management

Pulse Biosciences will be responsible for database creation and validation. Prior to finalizing and locking the database, all decisions concerning the inclusion or exclusion of data from the analysis for each subject will be determined by appropriate clinical and statistical personnel. All exclusions related to either safety or efficacy will be documented in subject listings. Data management will follow department SOPs during the conduct of this feasibility study.

9.11 Case Report Forms /Transmission of Data

All required data for this study will be collected via web-based electronic data capture (EDC) system and entered in electronic Case Report Forms (eCRFs). A unique study identifier will be assigned to each study subject. The database will contain only the study identifier to identify the subject.

Required data will be recorded on the appropriate electronic Case Report Forms at the time of or as soon as possible after the subject visit. This will enable timely monitoring visits.

Any data discrepancies identified during data review or a monitoring visit will be queried by Pulse Biosciences and must be resolved by the site staff and Investigator in a timely manner.

9.12 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 study. 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 staff of 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.).

10.0 INVESTIGATOR RESPONSIBILITIES

The role of the Principal Investigator is to implement and manage the conduct of the clinical study at their site, as well as ensure data integrity and the rights, safety, and well-being of the participating subjects.

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 summary to the IRB. The summary should be submitted to the Sponsor within three (3) months of study completion or termination. The Investigator will provide the Sponsor with copies of all IRB/HREC actions regarding the study.

10.1 IRB Approval and Informed Consent

The clinical study must be reviewed and approved by the IRB before subject enrollment may begin. All proposed changes to the investigational plan 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 the 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 site along with the other investigational case report forms or source documents. A signed copy of the consent form must be given to each subject enrolled in the study.

10.2 Data Collection and Reporting

Case report forms or source documents will be used to record demographic, procedural, and follow-up data, as well as any adverse events 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.

The Investigator must comply with the safety reporting requirements specified in **Section 8.3**.

Qualified study staff at each clinical site will perform primary data collection drawn from source-

document (hospital or clinic chart) reviews. The Monitor will perform clinical monitoring, including review of CRFs, source documents and/or Electronic Data Capture (EDC) system with verification of study eligibility, informed consent process, scheduled follow-up visits and AEs to the source documentation.

10.3 Source Documents / Records 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, progress notes of the physician, the individual's hospital or clinic chart(s), and the nurses' notes. 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.

10.4 Device Accountability

The Investigator shall maintain adequate records of the receipt and disposition of all study devices. When the enrollment is complete, the Investigator shall return any unused devices to the Sponsor. 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 lot number.
2. The names of all persons who received, used, or disposed of each device.
3. Why and how many device(s) were returned to the Sponsor, or otherwise disposed of.

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12.0 APPENDICES

12.1 Appendix A: Patient Informed Consent

12.2 Appendix B: Case Report Forms

APPENDIX A: Patient Informed Consent

Patient Informed Consent will be provided as a separate attachment.

APPENDIX B: Case Report Forms

Case Report Forms will be provided as a separate attachment.