An Open-Label Dose Escalation Trial to Evaluate Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD), Safety, and Tolerability of Microneedle Arrays containing Doxorubicin (D-MNA) in Participants with Basal Cell Carcinoma (BCC)

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.3	Updated the schedule of activities .	To be consistent with the information in the table footers.
8.3.3.1	Updated the language to reference the appropriate scale for pain related adverse events as recorded on the Numerical Rating Scale (NRS).	Adverse event severity terms are required for capturing of the AE in the case report forms.
12.2	NRS scale with adverse event severity added to the appendix.	A reference tool for consistent recorded of adverse events.
ALL	Grammatical and formatting revisions.	Appropriate corrections.

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR).

The Principal Investigator will assure that no deviation from or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) sponsor, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	An Open-Label Dose Escalation Trial to Evaluate Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD), Safety, and Tolerability of Microneedle Arrays containing Doxorubicin (D-MNA) in Participants with Basal Cell Carcinoma (BCC)
Study Description:	This study is designed as an open-label dose escalation trial of D-MNA in Participants with BCC (subtype: superficial or nodular). The goal of the dose escalation is to determine the maximum tolerated dose and assess lesion responses in the different dose groups to inform a decision on the doses to be tested in a subsequent Phase II study. Escalation will follow a traditional 3+3 design with a sentinel patient dosing approach for each cohort as documented in the Data Monitoring Committee (DMC) charter. Specifically, in each dose group N=3 participants will be treated. If no dose-limiting toxicities (DLTs) are observed, the study will escalate to the next dose level. If DLTs are observed in 2 or more participants, then the maximum tolerated dose (MTD) will have been exceeded. If 1 DLT is observed, an additional 3 participants will be treated at the same dose level. If no DLTs are observed in the additional 3 participants, the study will escalate to the next dose level. If DLTs are observed in 1 or more of the 3 additional participants, the MTD will have been exceeded. The first 2 groups, placebo and 25 µg, may screen and enroll patients concurrently.

A Data Monitoring Committee (DMC) will be in place to monitor participant safety during the study including dose escalation decisions.

Objectives:

Primary Objective:

- To establish the highest safe and tolerable dose of single applications of D-MNA, one application administered weekly, three times over a two week period,in placebo, 25 µg, 50 µg, 100 µg, and 200 µg dose groups in participants with BCC

Secondary Objectives:

- To evaluate the efficacy of single applications of D-MNA, one application administered weekly, three times over a two week period,in participants with BCC
- To evaluate safety and tolerability and to characterize the adverse events profile of the different D-MNA dose groups

Exploratory Objectives:

- To quantify the approximate amount of doxorubicin released after application of the MNA
- To evaluate by photographic assessment the efficacy of single applications of D-MNA, one application administered weekly, three times over a two week, period in participants with BCC

Endpoints:

Primary Endpoint:

- Assessment of Dose limiting toxicity (DLT) and Maximum Tolerated Dose (MTD) as defined in Appendix 1 using the LSR grading scale or any systemic ≥ Grade 3 adverse event according to CTCAE v 5.0 that cannot be attributed to another cause

Secondary Endpoints:

- Lesion response as assessed by a central reader after the 3-week course of treatment will be categorized as either absence or presence of Complete Response (CR) defined as no histologically proven BCC cells in excised tissue.
- Visual evidence of BCC at the treatment site pre and post MNA application by visual and dermatoscopic inspection and of the treatment site
- Local tolerance of the MNA on the skin according to the Local Skin Response (LSR) Grading Scale (Appendix 1)
- Pain assessment using an 11-point numerical rating scale (NRS) (Appendix 2)

Exploratory Endpoint:

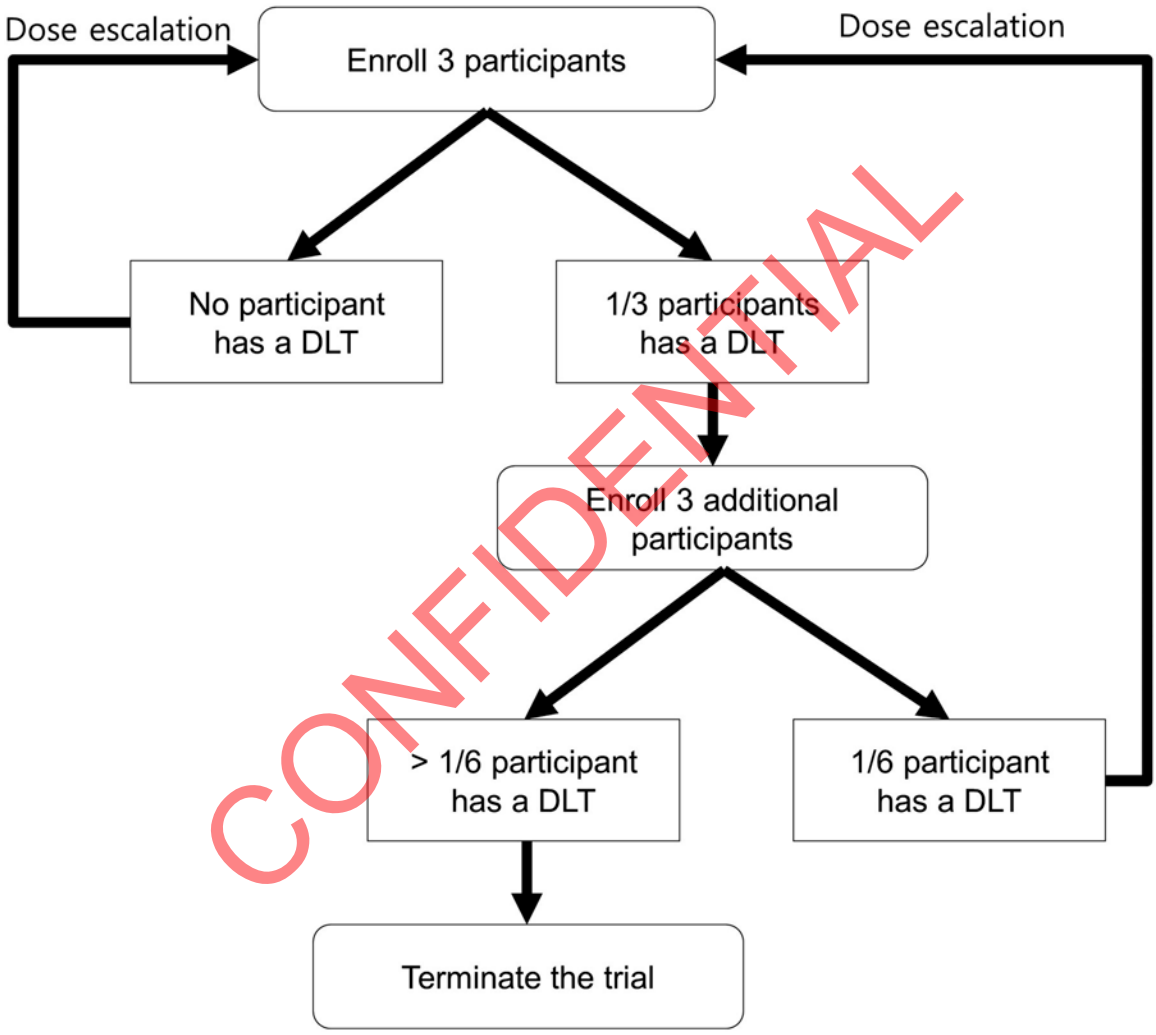
- Compare the listed dosage for each doxorubicin cohort to the amount of doxorubicin remaining in each MNA after use, such amounts being determined by the validated analytical method.

- Visual evidence of BCC at the treatment site pre and post MNA application by photographic assessment of the treatment site

Study Population:	Men and women with BCC (superficial or nodular sub-type) age 18 or older and in general good health. 15 participants (3 in each of the 5 dose groups) are planned. Up to 15 additional participants may be recruited in case of emergence of dose limiting toxicities.
Phase:	Three study treatments are planned I
Description of Sites/Facilities Enrolling Participants:	Clinical trial to be conducted by qualified dermatologists (or other sub-specialty physicians with equivalent qualifications) One study site in the United States will participate in this clinical trial.
Description of Study Intervention:	The participant will be treated with microneedle arrays containing doxorubicin (D-MNA) or microneedle arrays containing placebo. The D-MNA or MNA-placebo is applied to the BCC lesion and secured to the skin with a bandage applying constant pressure. The D-MNA is removed from the skin after 30 minutes. Each participant will receive three (3) weekly applications of the D-MNA unless a dose limiting toxicity (DLT) requires skipping or postponement of an application. The investigational product is chemotherapeutic agent doxorubicin (25 µg, 50 µg, 100 µg, or 200 µg) delivered to specific skin strata by a novel delivery system, MNA *or* placebo delivered to specific skin strata by MNA.
Study Duration:	Recruitment of 15 to 30 participants is expected to complete in approximately 5-7 months
Participant Duration:	Individual participant participation is expected to be approximately up to 11 weeks (4 weeks screening + 7 weeks from the first treatment to the final follow up visit).

1.2 SCHEMA

Refer to Section 1.3 for the Schedule of Activities



1.3 SCHEDULE OF ACTIVITIES (SOA)

	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
PROCEDURE	Screening Visit	Treat-ment #1	Treat-ment #2	Treat-ment #3	End of Treatment	Follow-up #1	Follow-up #2	Final Follow-up
	Day -28 (+/- 2 days)	Day 1	Day 7 (+/- 2 days)	Day 14 (+/- 2 days)	Day 21 (+/- 2 days)	Day 22 (1 day post excision)	Day 35 (+/- 2 days)	Day 50 (+/- 2 days)
Study Assessments								
Informed Consent	X							
Review of inclusion/exclusion criteria	X							
Medical history including prior & concomitant medication	X							
Concomitant medication review		X	X	X	X	X	X	X
Initial Full Physical exam (including height and weight)[1]	X							
Adverse Event(s), assessment		X	X	X	X	X	X	X
Follow-up Visit w/ Physical Exam (including weight)					X			
Vital signs	X	X	X	X	X	X	X	X
Administer IP to BCC lesion for 30 minutes (+/- 3 minutes)		X	X	X				
Local Skin Response (LSR) of MNA[4]		X	X	X				
Dermatological inspection of the lesion pre-MNA application		X	X	X				
Dermatological inspection of the lesion post-MNA application		X	X	X	X[5]			
Dermatoscopic evaluation of the lesion pre-MNA application		X	X	X				
Dermatoscopic evaluation of the lesion post-MNA application[3]		X	X	X	X[5]			
Photography of lesion site pre-MNA application		X	X	X				
Photography of lesion site post-MNA application		X	X	X	X[5]			
Shave biopsy of the BCC lesion w/ interpretation	X[2]							
Excision of the BCC lesion / treatment site					X			

Preparation and shipment of excision					X			
Suture Removal							X	
Wound Healing						X	X	X
Hematology (Sample collection only)	X				X			
Serum chemistry (Sample collection only)	X				X			
Urinalysis (Sample collection only)	X				X			
Urine pregnancy test	X				X			
ECG	X				X			
Dermpath biopsy analysis					X			
Administration of Pain Assessment Scale		X	X	X	X[6]			
Investigational Product Dispensing		X	X	X				

[1] Height collected at Visit 0 only
[2] Diagnostic shave biopsies will be performed at least 7 days before the 1st MNA application if patient not previously diagnosed with an eligible lesion.
[3] Dermatoscopic evaluation is to be conducted ≤5 minutes after removal of the MNA.
[4] Assess treatment area at removal of the MNA at V1; pre-application and post removal of MNA at V2, V3 and V4. To be obtained ≤15 minutes after removal of MNA for V1 – V3.
[5] Final dermatology, dermatoscopic and photography evaluation of treatment area prior to excision of the lesion
[6] Pain assessment to be completed prior to standard of care excision

2 INTRODUCTION

2.1 STUDY RATIONALE

This is a Phase I study in participants with superficial or nodular Basal Cell Carcinoma (BCC), designed to assess dose limiting toxicities and maximum tolerated dose, efficacy, safety, and tolerability of dissolvable, tip-loaded, microneedle arrays containing doxorubicin (D-MNA). Doxorubicin is a cytotoxic anthracycline antibiotic and is currently approved for the treatment of a broad range of cancers, including but not limited to: breast, bladder, gastric, and ovarian cancers; small cell lung cancer; acute lymphoblastic leukemia; and acute myelo blastic leukemia. SkinJect, Inc. has developed a novel delivery system in the form of a dissolvable microneedle array (MNA) which is intended to allow topical delivery of doxorubicin directly to the lesion at concentrations that are far below standard systemic dosing, thereby reducing the adverse events associated with systemic delivery.

The primary objective of this investigation is to establish the highest safe and tolerable dose of single applications of D-MNA, one application administered weekly, three times over a two week period in placebo, 25 µg, 50 µg, 100 µg, and 200 µg dose groups in participants with BCC.

Safety, efficacy and tolerability of the different doses will be evaluated, and additionally, quantification of the doxorubicin delivered to the BCC lesion and doxorubicin remaining in the microneedle array after use will be performed.

Doxorubicin's mechanism of action has not been fully elucidated, but it is generally accepted to be largely due to its ability to intercalate with DNA base pairs, resulting in inhibition of topoisomerase II, and subsequent DNA breakage[1,2]. Additional antineoplastic effects are thought to be attributable to a P-450-mediated one-electron reduction resulting in the formation of an unstable and reactive radical species[3]. It is anticipated that the mechanism of action of locally administered doxorubicin is comparable to systemic administration. Enhanced local anti-tumor effects are a result of direct tumor lysis, acute phase inflammation, and local recruitment of innate and tumor specific immune effectors. Basal cell carcinoma is the most common cancer in humans, with an estimated annual global incidence of 2.75 million cases[4]. Basal cell carcinoma arises from the basal cells in the epidermis and are associated with both chronic and intermittent acute UV exposure. The development of basal cell carcinoma is thought to be attributable, in part, to a deregulation of the Hedgehog (Hh) signaling pathway. The Hedgehog pathway is involved in stem cell maintenance, regulation of cell proliferation and differentiation, and carcinogenesis, and dysfunctional activation has been implicated in the

[1]Yang F, Teves SS, Kemp CJ, Henikoff S. Doxorubicin, DNA torsion, and chromatin dynamics. Biochim Biophys Acta . 2014;1845(1):84-89. .
[2]. Fornari FA, Randolph JK, Yalowich JC, Ritke MK, Gewirtz DA. Interference by doxorubicin with DNA unwinding in MCF-7 breast tumor cells. Mol Pharmacol. 1994;45(4):649-56.
[3]. Sinha BK. Is Metabolic Activation of Topoisomerase II Poisons Important In The Mechanism Of Cytotoxicity? Journal of Drug Metabolism & Toxicology. 2015;06(03):186-186.
[4] Verkouteren JAC, Ramdas KHR, Wakkee M, Nijsten T. Epidemiology of basal cell carcinoma: scholarly review. Br J Dermatol. 2017;177(2):359-372.

development of multiple cancers, including BCC[5]. Chemotherapeutic inhibition of Hedgehog signaling has been demonstrated to be effective against advanced BCC[6].

While BCC is highly-curable and only rarely metastasizes, it can result in significant morbidity in terms of cosmetic and functional loss. Current standard of care for localized BCC is typically surgical, either via standard excision or Mohs micrographic surgery. While surgical excision remains the standard-of-care for the treatment of BCC, it carries risks typically associated with surgical procedures, including bleeding, scarring, and infection. Surgical treatment may not be desirable or indicated for all participants, resulting in a demand for non-surgical treatment options. Commonly used topical treatments for BCC include: imiquimod; 5-fluorouracil; and tazarotene.

Imiquimod primarily acts as an agonist of toll-like receptors (TLR) 7 and 8, leading to activation of nuclear factor-kappa B (NF-kappaB). This activation results in the induction of pro-inflammatory cytokines and chemokines, ultimately resulting in a T-cell-mediated anti-tumor immune response.[7] Imiquimod has demonstrated efficacy in the treatment of both superficial and nodular BCC; however, imiquimod's efficacy is significantly inferior to surgery, with 84% of imiquimod-treated patients remaining tumor-free after 3-years, compared to 98% of surgically-treated patients[8].

5-Fluorouracil is an antimetabolite and blocks DNA replication by inhibiting thymidylate synthase[9]. Three-year tumor-free status following treatment with 5-Fluorouracil is inferior to that of imiquimod, with 68% of patients remaining tumor-free after 3-years[10].

Tazarotene's mechanism-of-action as an anti-neoplastic agent is not fully understood, but it is believed to be related to its ability to cause caspase-dependent apoptosis[11]. Tazarotene is a less-promising surgical alternative, with only 30.5% of patients remaining tumor-free at 3 years[12]

[5] Gupta S, Takebe N, Lorusso P. Targeting the Hedgehog pathway in cancer. Ther Adv Med Oncol. 2010;2(4):237-50.
[6] Soura E, Chasapi V, Stratigos AJ. Pharmacologic treatment options for advanced epithelial skin cancer. Expert Opin Pharmacother. 2015;16(10):1479-93..
[7] Schön MP, Schön M. Imiquimod: mode of action. Br J Dermatol. 2007;157 Suppl 2:8-13.
[8] Bath-hextall F, Ozolins M, Armstrong SJ, et al. Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial. Lancet Oncol. 2014;15(1):96-105.
[9] Nakamura A, Nakajima G, Okuyama R, et al. Enhancement of 5-fluorouracil-induced cytotoxicity by leucovorin in 5-fluorouracil-resistant gastric cancer cells with upregulated expression of thymidylate synthase. Gastric Cancer. 2014;17(1):188-95.
[10] Roozeboom MH, Arits AH, Mosterd K, et al. Three-Year Follow-Up Results of Photodynamic Therapy vs. Imiquimod vs. Fluorouracil for Treatment of Superficial Basal Cell Carcinoma: A Single-Blind, Noninferiority, Randomized Controlled Trial. J Invest Dermatol. 2016;136(8):1568-74.
[11] Wu CS, Chen GS, Lin PY, et al. Tazarotene induces apoptosis in human basal cell carcinoma via activation of caspase-8/t-Bid and the reactive oxygen species-dependent mitochondrial pathway. DNA Cell Biol. 2014;33(10):652-66.
[12] Bianchi L, Orlandi A, Campione E, et al. Topical treatment of basal cell carcinoma with tazarotene: a clinicopathological study on a large series of cases. Br J Dermatol. 2004;151(1):148-56.

The goal of the present study is to determine the maximum tolerated dose and to assess whether D-MNA represents an alternative to the currently available non-surgical, and in some cases, surgical treatments for BCC.

Treatment of BCC with D-MNA is intended to treat local visible tumor. Based on the potential for D-MNA to induce immunogenic effects, future clinical trials will assess the potential of the D-MNA to prevent recurrence at the treated site, the growth of additional primary tumors, or both.

The proposed approach relies on localized delivery of doxorubicin to the accessible tumor microenvironment. In the mouse melanoma model, doxorubicin delivered by the MNAs caused local, acute tumor cell death at low doses (e.g., 25 µg). Such a dose delivered systemically would be sub-therapeutic and non-toxic.

This investigation's therapeutic approach is intended to eradicate basal cell carcinoma cells locally; the potential of inducing long-lasting systemic, anti-tumor immunity will be evaluated in future studies. Enhanced local anti-tumor effects are believed to be the result of direct tumor lysis, acute phase inflammation, and local recruitment of innate and tumor specific immune effectors. It is thought that adaptive immunity may result from the immunogenic tumor cell death, which will stimulate the activation of innate immune mechanisms capable of overcoming local immunosuppression to induce antigen-specific effector and memory cellular immune responses.[1] Doxorubicin is a particularly well-suited chemotherapeutic drug for this purpose as it creates an immunogenic "good death" for tumor cells[13]. Doxorubicin chemotherapy has been shown to result in innate immune activation, including the attraction and activation of antigen presenting cells. The simultaneous cell death process facilitates the activation of these antigen presenting cells and their internalization and processing of dying tumor cell derivatives through underlying mechanisms that include ATP and HMGB1 release, and calreticulin exposure.

Microneedle Arrays (MNAs) are intended to enable *in situ* alteration of the tumor microenvironment. Drug delivery is a major barrier for skin cancer therapy. User variability and irregular diffusion kinetics make traditional intradermal injection an inefficient and highly variable method for localized drug delivery to specific skin strata. On the other hand, the potential for skin penetration for an active drug delivered topically is quite variable and largely dependent on its physiochemical properties. Reproducibility is dependent on several factors, from variability in stratum corneum penetration/retention to user variability. Very few chemotherapeutics or adjuvants have been successfully formulated for topical use.

Based on pre-clinical and clinical studies (see Pharmacology and Toxicology, section 2.3.1 and 2.3.2), it appears that the D-MNA, at doxorubicin doses of 25-200 µg per MNA, will be well-tolerated and will demonstrate certain local tumoricidal activity.

[13] Galluzzi L, Senovilla L, Zitvogel L, Kroemer G. The secret ally: immunostimulation by anticancer drugs. Nat Rev Drug Discov. 2012;11(3):215-33.

2.2 BACKGROUND

Basal cell carcinoma is the most common skin cancer, with more than 4-million cases diagnosed each year in the US [14]. Despite its relatively low mortality rate, BCC is responsible for approximately 3000 deaths annually[15], and, along with SCC, results in $4.8-billion/year in healthcare spending in the US[16]. The development of a successful chemo-immunotherapy for the treatment of BCC represents an alternative, non-invasive treatment of this disease, particularly for individuals for whom surgical resection is contra-indicated or is done with elevated risk. The introduction of a safe, locally-administered, effective non-surgical treatment has the potential to reduce morbidity, mortality, and healthcare expenditures.

PRECLINICAL STUDIES

Basal Cell Carcinoma

The development of a viable and replicable animal model of BCC has presented a challenge to researchers; there are currently no models appropriate for assessing an immune-modulating treatment for BCC[17]. Until such time that a viable animal model of BCC is developed, it is necessary to rely on data from other dermatological malignances to support BCC research. Data regarding the use of D-MNA in murine models of squamous cell carcinoma and melanoma are presented below.

Squamous Cell Carcinoma

Dr. Louis Falo at the University of Pittsburgh has developed both a murine model and a human *ex-vivo* model for Squamous Cell Carcinoma (SCC) and has used these models to demonstrate the efficacy of D-MNA at 25 µg in the treatment of SCC lesions. In the murine model, mice inoculated with SCC cells were treated with either D-MNA (n=5) or MNA-Blank (n=5); 20-days post-inoculation, 100% of the D-MNA-treated mice survived, compared with 0% of the MNA-Blank-treated mice. Additionally, D-MNA-treated mice demonstrated increased levels of pro-inflammatory cytokine gene expression, increased cell death, and decreased tumor growth. Similarly, D-MNA treated ex-vivo human SCCs showed increased levels of cell death. These results suggest that D-MNA is capable of inducing tumor cell death and increasing survival in an animal model[18].

A subsequent study conducted by Dr. Falo attempted to further elucidate the mechanisms by which D-MNA at 25 µg exerted its anti-tumor effects, specifically by examining the expression of genes

[14] Cancer Facts and Figures 2018. American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed May 15, 2018.
[15] . Gould A, Missailidis S. Targeting the hedgehog pathway: the development of cyclopamine and the development of anti-cancer drugs targeting the hedgehog pathway. Mini Rev Med Chem. 2011;11(3):200-13.
[16] Guy GP, Machlin SR, Ekwueme DU, Yabroff KR. Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. Am J Prev Med. 2015;48(2):183-7.
[17] Hochberg M. Experimental Models for BCC. Journal of Dermatology and Clinical Research. 2013;1(1):1002.
[18] Friedman B, Donahue C, Erdos G, Falo LD. A topical chemo-immunotherapy for squamous cell carcinoma. The Journal of Immunology. 2016;196(1):213.9.

associated with pro- and anti-tumor environments in both normal human tissue and in ex-vivo human cutaneous SCCs, both untreated (n=5) and D-MNA-treated (n=5). They found that relative to untreated cutaneous SCCs, D-MNA-treated cutaneous SCCs demonstrated a significant decrease in pro-tumorigenic genes (IDO, ARG2, S100A7 and VEGF-A) and a significant increase in anti-tumorigenic genes (CXCL14, HMGB1, and Caspase-8). D-MNA-treated cutaneous SCCs phenotypically resembled normal human tissue, suggesting that D-MNA was able to induce a reversion of cutaneous SCCs to normal, healthy tissue[19].

Melanoma

Early research[20] into the efficacy of D-MNA on a murine model of melanoma also demonstrates activity. Prof. Louis Filo's laboratory at the University of Pittsburgh used a subcutaneous model of B16 melanoma which results in visible tumors 14 – 21 days following injection. As shown in Figure A (below), treatment with D-MNA at 25 µg resulted in a reduction in tumor area. Figure B (below) compares survival percentages over time of animals that received no treatment (n=10), D- MNAs (n=10), Poly(I:C) via MNAs (n=10), and both doxorubicin and Poly(I:C) incorporated into the array matrix (n=10).

In summary, the preclinical D-MNA data reported for both cutaneous SCC and melanoma provides hypothetical justification for the investigation of its use as a potential treatment for BCC.

[19] Friedman B, Carey C, Edros G, Falo LD. Topical chemo-immunotherapy converts a pro-tumorigenic tumor microenvironment to a pro-inflammatory phenotype in human cutaneous squamous cell carcinoma. The Journal of Immunology. 2017;198(1):66.21

[20] Falo LD, Erdos G, Ozdoganlar B. Microneedle Arrays for Cancer Therapy Applications. May 2016.

FIGURE A

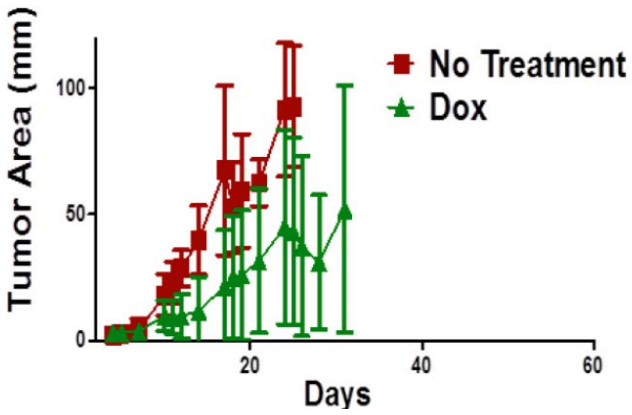
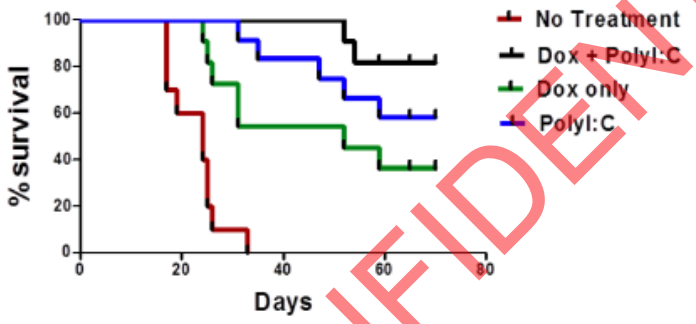


FIGURE B



CLINICAL STUDIES

Early clinical data demonstrates the potential efficacy of D-MNA in treatment of mycosis fungoides, a common subtype of cutaneous T-Cell lymphoma (CTCL). An early clinical study is currently being conducted by Professor Louis Falo at University of Pittsburgh (IND #1224482[21]). The primary objective of the study is to evaluate the safety of escalating, low doses (25-200 µg) of doxorubicin delivered directly into CTCL lesions using a MNA system. Secondary objectives include evaluations of the pharmacokinetics and pharmacodynamics (PK/PD) of doxorubicin when delivered using the D-MNA system; and evaluations of local, locoregional, and distant responses, biologic responses, and effects of treatment on the tumor microenvironment. This initial Phase 1 clinical trial incorporates a single-arm, placebo-controlled (within patient), open-label, accelerated dose escalation study design to determine the maximum tolerated dose (MTD) (or effective dose) of doxorubicin; followed by an extended evaluation of safety and effectiveness at the determined MTD (or Effective Dose).

The first cohort of 3 patients was treated with 25 µg of doxorubicin via MNA. Patients were treated once/week for 4-weeks, followed by a one-week break. No toxicities were observed at the 25-µg dose, and the original cohort, plus a new 3-patient cohort was escalated to the 50-µg dose. Dose-limiting toxicity (DLT), a cutaneous reaction, was observed in one patient at the 50-µg dose and the cohort was expanded to 2 additional patients, with no additional DLT reported. One patient in the 50-µg cohort exhibited a complete resolution of mycosis fungoides in response to D-MNA[22]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Known Risks Specific to D-MNA

Doxorubicin hydrochloride and the excipients used in D-MNA were formulated to specific requirements and studied in model systems of sensitization (the murine local lymph node assay), pyrogenicity, and irritation (the New Zealand rabbit model). The test articles in the mouse and rabbit study generated no remarkable findings at any of the doses studied in either model.

A placebo- controlled, 14-day toxicity and toxicokinetic study[23] of Yucatan minipigs was conducted to assess cutaneous reactions to placebo-MNA, 3 doses of D-MNA (25 µg, 50 µg, and 200 µg), and parenteral doxorubicin hydrochloride at 2 mg/kg. All D-MNA dose groups exhibited some macroscopic findings at the dose site; the placebo-treated minipigs exhibited findings that were similar to, though milder than, the D-MNA-treated minipigs. Red discoloration of the epidermis of the dose site was

[21] Clinicaltrials.gov. (2018). Micro Needle Array-Doxorubicin (MNA-D) in Patients With Cutaneous T-cell Lymphoma (CTCL) - Full Text View - ClinicalTrials.gov. [online] Available at: https://clinicaltrials.gov/ct2/show/NCT02192021?term=doxorubicin+dermal&draw=2&rank=1 [Accessed 14 Jun. 2018].

[22] Akilov O, Mccann S, Chao E, Cullison SJ, Erdos G, Falo L. 581 Phase 1, single-arm, open-label, dose escalation trial of microneedle array-doxorubicin in patients with mycosis fungoides. Journal of Investigative Dermatology. 2018;138(5

[23] SRC Study No.: S15055: A 14-Day Toxicity and Toxicokinetic Study of Doxorubicin Delivered Topically by Microneedle Array (MNA) to Yucatan Minipigs

identified in four animals, in the 50 µg and 200 µg groups. In two of the 200 µg group female animals, the red discoloration correlated microscopically with serocellular crust, and additionally with dermis congestion in one of those animals. The other two animals (males) did not have a microscopic correlate. Abnormal surface (scabbing) of the epidermis of the dose site was observed in a 200-µg group male animal and correlated microscopically with serocellular crust. One minipig receiving parenteral doxorubicin exhibited hemorrhage of the right axillary region, which corresponded to microscopic hemorrhage. This finding was believed to be related to either blood collection or injection procedures. Hemorrhage of the right axillary region was observed in a single animal in Group 5 (intravenous Doxorubicin) and correlated microscopically to hemorrhage. It was believed to be related to blood collection or injection procedures.

Other macroscopic findings represented incidental background findings typical for this species, or else did not have a microscopic correlate.

Known Risks Specific to Parenteral Doxorubicin

The foregoing information from a standard package insert for doxorubicin hydrochloride assumes a parenteral use of the compound at doses designed for systemic distribution and utility against solid tumors. The D-MNA, it must be emphasized, is introducing microgram quantities of doxorubicin into the epidermal space, limiting systemic exposure to the compound and the associated systemic and regional side effects. Studies in both mice and minipigs demonstrate that treatment with D-MNA did not result in any measurable blood levels of doxorubicin. In the murine model, mice were 100 µg or 200 µg of doxorubicin (iv), or 200 µg D-MNA. Blood samples were collected 5, 20, and 60 minutes post-dose. Blood levels of doxorubicin were measured by spectrofluorimetry and quantitated against a calibration curve, with a lower limit of quantitation (LLOQ) of 0.1 µg/ml. No detectable quantities of doxorubicin were observed in the mice receiving the 200 µg D-MNA, while doxorubicin levels were detectable in the intravenously injected mice. In the minipig, all D-MNA-treated groups (25, 50, and 200 µg) showed doxorubicin plasma levels below the LLOQ) which for this LC-MS/MS method was 0.25 ng/ml. In contrast, doxorubicin was detectable in the plasma following parenteral administration. The Sponsor concludes that there was no measurable systemic exposure to doxorubicin when administered by D-MNA[23].

In standard chemotherapeutic regimens, doxorubicin hydrochloride can cause myocardial damage, including acute left ventricular failure. The risk of cardiomyopathy is generally proportional to the cumulative exposure. The clinician should include prior doses of other anthracyclines or anthracenediones in calculations of total cumulative dosage for doxorubicin hydrochloride. Cardiomyopathy may develop during treatment or up to several years after completion of treatment and can include decrease in left ventricular ejection fraction (LVEF) and signs and symptoms of congestive heart failure (CHF). The probability of developing cardiomyopathy is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m^2 of doxorubicin hydrochloride, 3 to 5% at a dose of 400 mg/m^2, 5 to 8% at a dose of 450 mg/m^2, and 6 to 20% at a dose of 500 mg/m^2, when doxorubicin hydrochloride is administered every 3 weeks. There is an additive or potentially synergistic increase in the risk of cardiomyopathy in patients who have received radiotherapy to the mediastinum or concomitant therapy with other known cardiotoxic agents such as cyclophosphamide and trastuzumab. Pericarditis and myocarditis have also been reported during or following doxorubicin hydrochloride treatment.

The clinician should assess left ventricular cardiac function (e.g., multigated acquisition scan or echocardiogram) prior to initiation of doxorubicin hydrochloride, during treatment to detect acute changes, and after treatment to detect delayed cardiotoxicity. Increase the frequency of assessments as

the cumulative dose exceeds 300 mg/m^2 . The same method of assessment of LVEF should be used at all time points.

Other known risks of parenteral doxorubicin hydrochloride therapy include arrhythmias, secondary malignancies, and extravasation from the i.v. needle and tissue necrosis.

2.3.2 KNOWN POTENTIAL BENEFITS

The cytotoxic effect of doxorubicin HCl on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin HCl cytocidal activity[24] . Based on preclinical data in SCC and melanoma, the Sponsor concludes that doxorubicin in the microgram amounts being delivered by the microneedles is causing an environment hostile to basal cell carcinoma and inducing tumor lysis.

Based on the animal studies performed to date, the D-MNA system may offer an effective alternative to the current standard of care. Excisionalstandard of care surgery can be painful and time-consuming, while the time and expense of Mohs micrographic surgery can be quite high if multiple procedures are required. Other topical dosage forms, such as 5-fluorouracil and imiquimod, can produce unpleasant topical side effects and may not be particularly effective.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

An independent Data Monitoring Committee (DMC) will be set up prior to the start of this study. Membership to this committee will include qualified clinicians- dermatologists with expertise in treating skin cancer and a statistician. The DMC will review data for each dose escalation for dose limiting toxicities and determine when maximum tolerated dose has been exceeded. Details of the safety review as well as recommended dose selection for future clinical trials will be defined by the DMC.

The IRB(s) will be kept informed of the DMC decisions during the study.

[24] Doxorubicin Package Insert: Accessdata.fda.gov. (2018). [online] Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/050629s022lbl.pdf [Accessed 8 Jun. 2018].

3 OBJECTIVES AND ENDPOINTS

Primary Objective

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary Objective		
• To establish the highest safe and tolerable dose of single applications of D-MNA, one application administered weekly, three times over a two week period, in placebo, 25 µg, 50 µg, 100 µg, and 200 µg dose groups in participants with BCC	• Escalation will follow a traditional 3+3 design. Specifically, in each dose group n=3 participants will be treated. If no DLTs are observed, the study will escalate to the next dose level. If DLTs are observed in 2 or more participants, then the maximum tolerated dose (MTD) will have been exceeded. If 1 DLT is observed, an additional 3 participants will be treated at the same dose level. If no DLTs are observed in the additional 3 participants, the study will escalate to the next dose level. If DLTs are observed in 1 or more of the 3 additional participants, the MTD will have been exceeded. The first 2 groups, placebo and 25 µg, may screen and enroll patients concurrently in the study.	• Dose escalation follows a traditional 3+3 design to evaluate DLTs and identify the MTD.

Secondary and Exploratory Objectives

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Secondary		
• To evaluate the efficacy of single applications of D-MNA, one administered weekly, three times over a two week period, in participants with BCC • To evaluate safety and tolerability and to characterize	• Clinical response as assessed by a central reader after the 3-week course of treatment will be categorized as either absence or presence of Complete Response (CR) defined as no histologically proven BCC cells in excised tissue. • Visual evidence of BCC at the treatment site pre and post MNA application by visual and dermatoscopic inspection of the treatment site	• Reporting of complete histological response to treatment is standard per literature review and consistent with the clinical trial evaluation of Imiquimod indicated for treatment of superficial BCC[25]. • Clinical response will be assessed by independent central reader as detailed in the Central Reader Manual.

[25] Geisse J, Rich P, Pandya A et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: A double-blind, randomized, vehicle-controlled study*. J Am Acad Dermatol. 2002;47(3):390-398.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
the adverse events profile of the different D-MNA dose groups	• Local tolerance of the MNA on the skin according to the Local Skin Response (LSR) Grading Scale • Pain assessment using an 11-point numerical rating scale (NRS)	• Dermatologic inspection, dermatoscopic evaluation photography of the lesion are routine evaluations for BCC lesions
Exploratory		
• To quantify the approximate amount of doxorubicin released after application of the MNA • To evaluate by photographic assessment, the efficacy of single applications of D-MNA, one application administered weekly, three times over a two week period, in participants with BCC	• Compare the listed dosage for each doxorubicin dosing cohort to the amount of doxorubicin remaining in each MNA after use as determined by the validated analytical method. • Visual evidence of BCC at the treatment site pre and post MNA application by photographic assessment of the treatment site	• To gain additional information on the microneedle array delivery system • Photography of the lesion is a routine evaluation for BCC lesions

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase I open-label dose escalation trial to evaluate dose limiting toxicity, maximum tolerated dose, safety, and tolerability of Microneedle Arrays containing Doxorubicin (D-MNA) in participants with Basal Cell Carcinoma (BCC).

It is expected that one study site in the US will enroll all participants in the study.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We hypothesize that treatment with D-MNA will result in tumor destruction and the induction of potent, immunogenic anti-tumor responses. Because MNAs enable this agent to be delivered at very low doses to a confined tumor microenvironment we expect only minimal, if any, systemic drug toxicity; thus, facilitating optimal local dose levels and durable clinical responses.

4.3 JUSTIFICATION FOR DOSE

The current dosing regimen is partly based on animal efficacy data performed to date and the toxicology studies performed in mice, rabbits, and minipigs to assess the risk of dermal irritation at dose ranges (25 µg, 50 µg, 100 µg, and 200 µg) These doses are also currently being tested in Prof. Falo's CTCL study, in which these doses have been well tolerated with minimal dose-limiting toxicity.

The study design also includes a placebo group (placebo-MNA). Inclusion of placebo-MNA will allow the evaluation of two questions:

- Tolerability: to assess if there is a cutaneous response to microneedle penetration that is independent of microneedle delivery of doxorubicin to the target tissue
- Efficacy: to assess if a placebo-containing array can stimulate a non-specific immune response in reaction to microneedle penetration of the skin, and compare to the response with the active compound doxorubicin delivered by the D-MNA

The BCC lesion will be excised in all the dose groups at the end of the study. All BCC cells will be removed regardless of the dose group the participants were assigned.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study when (s)he has completed the final study visit including the standard of care excision of the treatment site as shown in the Schedule of Activities (SoA), Section 1.3.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

The participant must meet all the following criteria to be eligible to participate in this study:

1. Adult males and females, 18+ years in general good health as assessed by the investigator.
2. BCC (subtype: superficial or nodular) confirmed histologically by diagnostic shave biopsy at the Screening Visit. If previously confirmed, participants can only have diagnosed BCC via shaved biopsy within 6 months of first study treatment.
3. Primary BCC (i.e., no previous treatment)
4. Lesion size ≥ 64 mm^2 or 8 x 8 mm and ≤ 169 mm^2 or 13 x 13 mm, i.e., the entire lesion must be covered by 13X13 mm area of the array containing the microneedles
5. Clinical laboratory results within the following ranges:
   a. granulocytes ≥2,000/mm^3
   b. platelets >50,000/mm^3
   c. serum creatinine ≤2X the upper limit of normal (ULN)
   d. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase ≤3X the ULN.
6. Participant must have no other "clinically significant" abnormal findings in his/her medical history, physical examination or clinical laboratory test results as assessed by the investigator
7. Female participants must be either postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile upon entry into the study. Female patients of childbearing potential must have a negative pregnancy test upon entry into this study and agree to use a highly effective method of contraception from Screening until the final follow-up visit.
8. Male participants with female partners of child bearing potential must be either surgically sterile or agree to use a double-barrier contraception method (i.e., condom + diaphragm, condom or diaphragm + spermicidal gel or foam) from screening until until the final follow-up visit.
9. Participant must to be willing to adhere to the instructions of the investigator and his or her research team
10. Participant must sign an Informed Consent Form prior to any study specific procedures and entry into the study

5.2 EXCLUSION CRITERIA

A participant who meets any of the following criteria will be excluded from participation in this study:

1. Evidence of clinically significant, unstable medical conditions as assessed by the investigator
2. Excisional biopsy performed on the lesion to be treated in this study
3. Recent therapy(ies) to the BCC treatment area
4. Recurrent BCC (previously treated) at the site presented for treatment
5. BCC lesion to be treated is located in an area where excisional biopsy is undesired or aesthetically unacceptable to the participant
6. Previously demonstrated sensitivity to doxorubicin or carboxymethyl cellulose.

7. Participant with other active malignancies except for non-metastatic prostate cancer and carcinoma in situ of the skin or cervix
8. Participant with evidence of metastatic malignancies
9. Concomitant disease requiring systemic immunosuppressive treatment
10. Genetic skin cancer disorder, e.g., basal cell nevus syndrome
11. Participant is pregnant or breastfeeding
12. Treatment with another investigational drug, device, or other intervention within 3 months prior to the Screening Visit
13. Existing condition or treatment within 3 months prior to the Screening Visit that may have impact on clinical outcome for the treatment of BCC or delay in wound healing from the standard of care excision

5.3 LIFESTYLE CONSIDERATIONS

Female patients of childbearing potential must agree to use a highly effective method of contraception from Screening until the final follow-up visit.

- Highly effective methods of contraception that result in a low failure rate (i.e., <1% per year) when used consistently and correctly include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence;
- True abstinence, when in line with the preferred and usual lifestyle of the patient, is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of study participation (i.e., Screening until the final follow-up visit). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation method) and withdrawal are not acceptable methods of contraception

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not treated at least one time with the investigational product.

Individuals or Screen Failures who do not initially meet the criteria for participation in this trial due to logistic reasons, e.g., planned Treatment Day 1 is more than 28 (+/- 7 days) days after the Screening Visit, may be rescreened.

Rescreened participants should be assigned a different Participant Number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Standard of care excision of the BCC site will be performed on all participants. There are no additional benefits in participating in this study. Participants may be compensated for the additional time, e.g.,

weekly treatment visits and expenses to participate in the study. Compensation for the participant should be reasonable and not excessive. The amount of participant compensation will be reviewed and approved by the IRB prior to the start of the study.

One study site in the United States is planned, and this study site is expected to have an adequate pool of participants available for screening and enrollment into the study.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The investigational product is chemotherapeutic agent, doxorubicin (25 µg, 50 µg, 100 µg, or 200 µg) delivered to the basal layer of skin by a novel delivery system, a MNA.

The delivery system is a square patch 15 x 15 mm in dimension edge to edge. The dissolvable array of 400 microneedles is in a 13 x 13 mm area. The microneedles are 750 microns in length. Each MNA patch delivers 9.6 µL of drug product into the peri-epidermal space.

The microneedles are formed by dissolving an active compound in citric acid, dibasic sodium phosphate, trehalose, and water; by mixing these materials with carboxymethyl cellulose; by plating them on precisely designed molds; and by centrifuging the molds until the arrays have dried and can be extruded from the mold. In this study, doxorubicin is embedded in this matrix at specific doses, tip loaded, so that the needles deliver the doxorubicin sub epidermally to the BCC. A similar process, excluding doxorubicin, is used to make placebo arrays. The dissolvable MNA has the appearance of a “square patch” the size of one’s thumbprint.

6.1.2 DOSING AND ADMINISTRATION

The D-MNA or MNA-placebo is applied to the BCC lesion with the following instructions:

1. Prepare the lesion for the study drug administration by manually rubbing the surface of the lesion and may include a liquid interface.
2. The study personnel must use gloves while handling the MNA.
3. The study personnel will hold the skin taut with one hand while placing the MNA over the lesion with the other hand, ensuring the entire lesion is under the area of the MNA.
4. The time of MNA application is documented.
5. The study personnel push the MNA firmly into the skin with manual pressure for 3 minutes immediately after which the MNA is secured to the skin with a bandage that applies constant pressure over the microneedle array.

The MNA is removed from the skin after 30 minutes (+/- 3 minutes) and the time of removal is recorded in the subject’s source documents. After the array’s removal from skin, the participant should wear a small self-adhesive bandage for the remainder of the day to keep the application site clean and

protected from infection. The participant should be instructed to avoid sun exposure to the treated area for the duration of the study.

Participant will receive up to three (3) weekly (+/- 2 days) applications of the D-MNA or placebo-MNA .

The Sponsor will provide the investigator training on the application of the investigational product prior to the start of the study.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The investigational product will be shipped under controlled temperature conditions (2-8℃).

The Sponsor will supply the different doses of D-MNA and MNA-placebo for use in this study to approved study sites with an authorized investigational pharmacist or delegate as designated by the Investigator. The Investigator or delegate is responsible for the accurate documentation of receipt, inventory, storage, treatment assignment, and dispensing of the investigational product.

After removal from the treatment area, the used MNA is to be stored at refrigerated temperature (2-8°C). These MNAs will be sent to a central laboratory for quantification of doxorubicin remaining in the microneedles.

Detailed information will be provided in the Study Pharmacy Manual.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

D-MNAs are are red in appearance due to the color of liquid doxorubicin. Red dye is not being added to the MNA-placebo in order to eliminate the genotoxicity risk associated with the addition of red dye.

Four (4) MNAs of the same dosage (25 µg, 50 µg, 100 µg, or 200 µg or placebo) are contained in individual foil-sealed“cubes,” and each cube is contained in a 2” x 3” opaque, heat-sealed Uline packet labeled with standard investigational drug text. Four of these packets are stored in a 4” x 6” Ziplock Uline bag packet labeled with standard investigational drug text. This packaging provides 3 MNAs for 3 treatments in a 14-day period, and one additional MNA in case of damage to one of the other 3 arrays.

Each array is contained in individual foil-sealed“cubes,” and each cube is contained in a heat-sealed 2” x 3” opaque Uline packet labeled with standard investigational drug text. Four of these packets are stored in a 4” x 6” Ziplock Uline bag labeled with standard investigational drug text.

An example of the investigational product label below will also include language that corresponds to each dosage (i.e., 25 µg, 50 µg, 100 µg, or 200 µg or placebo).

Protocol No. SKNJCT-001 Lot Number: GA-190306-1
Description: Dissolvable tip-loaded Microneedle Array
Dose: 25ug Doxorubicin Expiry Date: 03-2020 Store at 2-8C
CAUTION: New Drug- Limited by Federal (or United States) law to Investigational Use
Contact info: See Protocol
InClinica, Inc., 701 Lee Road, Suite 210, Wayne, PA 19087

6.2.3 PRODUCT STORAGE AND STABILITY

The unopened D-MNA should be stored under refrigeration (2-8°C) and protected from exposure to light.

Stability of the D-MNA for 3 months at refrigerated temperature (2-8°C) has been established in a non-GLP pilot study.

6.2.4 PREPARATION

The health care provider must follow all standard precautions for handling chemotherapy agents including the use of gloves.

The D-MNAs and MNAs are supplied ready to be applied to the treatment area.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Study treatment is not randomized, and the study design is open-label dose escalation.

While safety evaluation is the primary objective in this Phase I study, preliminary efficacy evaluations will also be conducted. The placebo (without the addition of red dye) is not a matching placebo to the active investigational product. However, a process to blind the central reader who will assess the clinical response to study treatment will be detailed in the Central Reader Manual. The steps to minimize bias in evaluation of visual and histologic responses include:

- All pre and post treatment biopsies will be centrally read after the end of study excision biopsy is performed in the last study participant.
- Each set of slides/digital images will be randomly assigned a second unique identifier before they are sent to the central reader for assessment.
- The central reader will not have access to the Subject ID or the treatment assignment associated with each set of slides/digital images, i.e., the central reader will not have access to the key linking the Subject ID with the second unique identifier.

6.4 STUDY INTERVENTION COMPLIANCE

The investigational product is dispensed and placed on the treatment area by the investigator or delegated site staff during the clinic visit. Date and time of application and time of removal of the investigational product is to be documented in the participant's file and in the Case Report Form (CRF).

6.5 CONCOMITANT THERAPY

Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and supplements.

Systemic immunosuppressive treatment is prohibited during the study.

6.5.1 RESCUE MEDICINE

Not-applicable

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

A DMC will be established to monitor participant safety and the dose escalation , and an DMC charter including safety stopping rules will be finalized prior to the first participant enrolled into the study. The DMC will be notified of all treatment discontinuationsDMC.

The Investigator may delay/skip a study treatment or prematurely terminate the study treatment according to guideline in Appendix 1.

Additionally, pain at the treatment site will be assessed by the participant using an 11-point numerical response scale (NRS), and the investigator will take into consideration the pain level as assessed by the study participant to determine if treatment should be delayed/skipped or prematurely terminated.

Discontinuation from study treatment does not mean discontinuation from the study. Remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified after enrollment, e.g., change from baseline or anytime during the study, the investigator or qualified designee will determine if any change in medical management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include assessments listed for all follow-up visits.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive study treatment for more than 2 weeks (+/- 2 days) since the last treatment.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). To allow for subjects who discontinue or withdrawal prior to treatment or receiving the 3 planned treatments, additional participants may be enrolled to ensure that each cohort is evaluable. Additional participants will be added according to Section 1.2

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 consecutive scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit within 2 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will 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). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

A visual and dermatoscopic evaluation of the treatment area for visible evidence of BCC will be performed pre and post each application of the D-MNA and at the End-of-Treatment visit prior to excision of the lesion.

An standard of care excision of the treatment site will be performed at Visit 4. The biopsy slide (prepared per standard operation procedures at the site) will be sent to a central reader to assess clinical response to the study treatment. The clinical response will be assessed by a central reader after the 3-week course of treatment and will be categorized as either absence or presence of Complete Response (CR) defined as no histologically proven BCC cells in excised tissue.

Preparation of the biopsy slide and the blinded central reading process are detailed in a Central Reading Procedure Manual.

8.2 SAFETY AND OTHER ASSESSMENTS

Participants will undergo a physical examination including assessment of vital signs at screening and at Visit 4.

Safety laboratory tests (hematology, serum chemistry, urinalysis) will also be performed at the local laboratory at screening and at the Visit 4 follow up visit:

Hematology
- White blood count (WBC)
- Platelet count
- Hematocrit
- Hemoglobin

Serum Chemistry
- Creatinine
- Blood urea nitrogen (BUN)
- Glucose
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Albumin
- Amylase
- Lipase
- Total bilirubin
- Alkaline phosphatase
- Potassium
- Calcium
- Phosphate
- Lactate dehydrogenase

Urinalysis
- Macroscopic
- Microscopic
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Hemoglobin
- Leukocyte esterase
- Nitrite
- Bilirubin

Additionally, ECG will also be performed locally according to standard practice at screening and at the Visit 4 27pEnd-of-Treatment visit.

Pregnancy test will be performed for women of childbearing pontential at Screening and End-of -Treatment visit.

After each application of the MNA, the investigator will visually inspect the skin/treatment area to assess tolerance of the study treatment. Dermatoscopic evaluation and photography of the lesion will be completed pre and post array application. Assessment of dose-limiting toxicity according to the local skin responses grading scale in Appendix 1 of the protocol will be performed. Assessment of wound healing will be performed at all follow-up visits according to standard of care for a typical standard of care excision procedure.

Quantification of the doxorubicin remaining in the used MNA will be performed.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered “serious” if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Except for subject-reported pain AEs via the NRS referenced in Appendix 2, Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be used for severity grading of adverse events (Aes). The CTCAE is not provided as a part of the protocol, but can be accessed and downloaded at the following website:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

For subject-reported pain AEs via the NRS, the numerical rating will be assigned a severity (e.g., mild, moderate, severe) based upon pain intensity-to-severity grading in Appendix 2.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (Aes) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Treatment with D-MNA is expected to elicit local skin reactions which are the most common adverse effects of this non-systemic treatment. Some cutaneous responses (e.g., erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration) to the D-MNA are indicative of drug dispersal.

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Aes characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all adverse events with start dates occurring any time after informed consent is obtained until the Visit 7 Final Follow-up. If a participant discontinues for any reason prior to Vist 7, all Aes ≥ "Potentially Related" (see Section 8.3.3.2) will continue to be followed as defined in Section 8.3.5. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All Aes including local and systemic reactions and abnormal clinically significant laboratory values not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All Aes occurring while on study must be documented appropriately regardless of relationship. All related (i.e., ≥ Potentially Related) Aes will be followed to adequate resolution or stabilization to a grade acceptable to the Investigator and has concurrence by the Sponsor or the subject is lost to follow-up (as defined in Section 7.3).

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The investigator will immediately report to the sponsor any serious adverse event within 24 hours of becoming aware of the event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. All SAEs will be reported to the IRB per local regulatory requirements.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the participant is stable or is lost to follow-up (as defined in Section

7.3). Other supporting documentation of the event may be requested by the Independent Data Monitoring Committee and/or the study sponsor and should be provided as soon as possible.

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

New information gathered during the study that may affect participant's consent to continue participation will be provided to the participants.

8.3.8 EVENTS OF SPECIAL INTEREST

Not Applicable

8.3.9 REPORTING OF PREGNANCY

All female participants of child bearing potential will have negative pregnancy test during the screening process before enrollment into this study. Women with a positive pregnancy test are not eligible to participate in this study.

If a participant becomes pregnant during the study, she will continue to be followed at the scheduled study visit as described in SECTION 7.2, Participant Discontinuation/Withdrawal from the Study.

Male participants with a partner of child-bearing potential should be informed of the reproductive risk per the Product Insert for doxorubicin and to take prophylactic measures to prevent pregnancy.

Pregnancy is not reported as an adverse event, pregnancy will be documented on a specific CRF.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (Ups) to the reviewing Institutional Review Board (IRB) and the sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, Ups will be reported using the following timeline:

- Ups that are serious adverse events (SAEs) will be reported to the IRB and to the study sponsor immediately and within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the study sponsor as soon as possible and within 5 business days of the investigator becoming aware of the problem.
- All Ups should be reported to appropriate institutional officials (as required by an institution's written reporting procedures) and other regulatory agencies according to national and local regulations.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

As applicable, national and local regulations will be followed to inform the trial participants of relevant Ups.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No hypothesis testing or inferential statistical analyses are planned in this Phase I dose escalation study. All statistical analyses will be descriptive. Summary statistics and associated confidence intervals will be calculated for the primary, secondary and safety endpoints for each dose group.

9.2 SAMPLE SIZE DETERMINATION

The study will follow a traditional 3+3 dose escalation design with 4 dose groups plus placebo to define a MTD by evaluating DLTs as described in Section 1.2. Based on this design, between 15 and 30 subjects will be required to be evaluable for the primary DLT endpoint.

9.3 POPULATIONS FOR ANALYSES

- DLT evaluable population:
  Defined as subjects who complete the study without experiencing a DLT or subjects who experience a DLT regardless of discontinuation. Participants who discontinue the study prior to Visit 4 without experiencing a DLT will not be considered evaluable for the primary DLT endpoint.

- Safety Population:
  Defined as all enrolled subjects who receive treatment. The safety population will be included in all safety analyses and summaries.

- Efficacy Population:
  Defined as all subjects in the safety population without major protocol deviations. Efficacy analyses will be conducted on the efficacy population.

9.4 STATISTICAL ANALYSES

A formal Statistical Analysis Plan (SAP) will be a separate document and will be updated as required, in association with any protocol amendments. The plan will provide additional details of the statistical methodology as well as tables, listings, graphs and statistical programming considerations. The SAP will be completed prior to database lock and unblinding of the study data.

9.4.1 GENERAL APPROACH

All statistical analyses will be descriptive. No hypothesis testing is planned. Descriptive statistics will include n, mean, median, standard deviation, minimum and maximum for continuous data and n and percentages for categorical data. All efficacy analyses will be conducted for the efficacy population. Missing clinical response data at Visit 4 (21 days) will be imputed from the clinical response based on biopsy results of standard of care excision at the time of discontinuation, when available. All safety analyses will be conducted on the safety population.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary study endpoint will be the assessment of DLT through Visit 4 (21 days) as defined in Appendix 1 using the LSR grading scale. All DLTs will be summarized for each dose group including placebo. The MTD will be defined as the highest dose with a DLT rate below 33%.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

<u>Lesion Response</u>

The proportion of participants achieving a histological complete response (CR) at Visit 4 (21 days) will be summarized with the associated 95% exact 1-sided confidence interval (CI) for each dose group including placebo.

Additional Endpoints

The following endpoints will be summarized by dose group (including placebo) using descriptive statistics at each study visit:

- Visual evidence of BCC at the treatment site pre and post MNA application by visual and dermatoscopic inspection of the treatment site
- Local tolerance of the MNA on the skin as measured by the LSR grading scale
- Pain assessment using an 11-point numerical rating scale (NRS)

9.4.4 SAFETY ANALYSES

All enrolled participants who receive treatment will be included in the safety analysis and summaries. Adverse events will be coded using MedDRA and summarized by dose group for number of participants reporting the adverse event and the number of adverse events reported. A by-subject adverse event data listing including verbatim term, preferred term, dose group, severity, and relationship to study medication will be provided.

Wound healing at the surgical standard of care excision site will be assessed during the suture removal visit according to standard of care.

Safety endpoints will include skin evaluations, clinical laboratory tests, urinalysis, physical examination, vital signs, ECG, and adverse events. Descriptive statistics will be used to summarize safety endpoints overall and separately by dose group.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographics and baseline disease characteristics will be summarized by dose group using descriptive statistics.

9.4.6 PLANNED INTERIM ANALYSES

Interim safety summaries will be prepared for review by the DMC prior to each dose escalation.

9.4.7 SUB-GROUP ANALYSES

No subgroup analyses are planned.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

All individual subject data will be reported in data listings by time point.

9.4.9 EXPLORATORY ANALYSES

Quantification of the doxorubicin remaining in the used MNA will be summarized by dose group including placebo using descriptive statistics.

Additional exploratory analyses may be conducted.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to any study specific procedures and administration of study intervention.

An standard of care excision of the BCC lesion will be performed for all subjects. There is no benefit from participation in this study other than contribution to research.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator or designee will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights

and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their representatives. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a database at the Sponsor and/or Clinical Research Organization (CRO)

designated by the sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the CRO research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the CRO designated by the sponsor.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the sponsor and/or designated CRO. After the study is completed, the de-identified, archived data will be transmitted to and stored at the sponsor designated CRO. The data may be used by other researchers including those outside of the study.

Any publication of results obtained from this study will not identify the participant by name.

Absolute participant confidentiality cannot be guaranteed due to the requirements to release information to authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and regulatory agencies. In any event, the sponsor will use reasonable efforts to preserve participant confidentiality.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), images of de-identified biopsy slides, will be stored with the study archive. Tissues collected for the experimental endpoints may also be stored with the participant and IRB approval.

During the conduct of the study, an individual participant can choose to withdraw consent to have biopsy slides stored for future research.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Study Management	**Medical Monitor**
Gregory R Suplick Senior Director, Clinical Operations	Susan Tansey, MD Chief Medical Officer
InClinica	InClinica
Ph: 484.636.9333	Email: *susan.tansey@boydconsultants*.com
Email: gsuplick@inclinica.com	

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of an Data Monitoring Committee (DMC) composed of individuals with the appropriate expertise, including dermatologists, and statistician.DMC The DMC will oversee safety in the study including the dose escalations. The DMC will operate under the rules of an approved charter that will be written prior to enrollment of the first participant.

The IRB(s) and relevant health authority(ies) will be notified of decisions of the DMC in accordance with local regulatory requirements.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP E6 (R2)), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the sponsor's designated CRO, InClinica. Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

The study site staff should be trained in Good Clinical Practice (GCP) and operate under GCP principles for the conduct of the study.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Independent audits may be conducted by Sponsor representative to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted, and data are generated, and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible and indelible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets may be used to supplement other source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (Aes), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into an electronic data capture system which is 21 CFR Part 11-compliant. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harminosation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or study specific manual requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, 4.5.3 and 4.5.4.
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report major deviations, especially those affecting safety of the participants, within one (1) working days of identification of the protocol deviation. All deviations must be addressed in study source documents. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per its policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- All manuscripts, abstracts, or presentations developed from the results of this study must been reviewed and approved in writing by the sponsor in advance of submission or public presentation. The review is intended to protect sponsor proprietary information.
- Investigator may not publish results from his/her study site until after the publication of the primary manuscript describing the full trial results.
- This trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov.

The obligations regarding the publication of any data, material results or other information that is generated or created in relation to the trial will be detailed in the clinical trial agreement between the investigator and sponsor.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

Not-applicable

10.3 ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BCC	Basal Cell Carcinoma
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence Interval
CL	Clearance
Cmax	Maximum Plasma Concentration
CMP	Clinical Monitoring Plan
CR	Complete Response
CRO	Clinical Research Organization
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTLC	Cutaneous T-Cell Lymphoma
DLT	Dose-Limiting Toxicity
D-MNA	Doxorubicin-Microneedle Array
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Forms
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IMP	Investigational Medicical Product
IRB	Institutional Review Board
LVEF	Left Ventricular Ejection Fraction
LSR	Local Skin Responses
MNA	Microneedle Array
MTD	Maximum Tolerated Dose
NCT	National Clinical Trial
NR	No Response
OHRP	Office for Human Research Protections
ORR	Objective Response Rate
PI	Principal Investigator
PD	Pharmacodynamics
PK	Pharmacokinetics
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SCC	Squamous Cell Carcinoma
SOA	Schedule of Activities
SOP	Standard Operating Procedure
Tmax	Time of Maximum Plasma Concentration
t1/2	Half-Life
ULN	Upper Limit of Normal
UP	Unanticipated Problem
US	United States
WBC	White Blood Count

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the pages before the Table of Contents.

Version	Date	Description of Change	Brief Rationale
3.0	11 Feb 2020	Updates to the trial: • Endpoints and objectives (make consistent throughout the document) • Entrance criteria • General update to the document	Clarify and make sections consistent.
3.1	08 Jun 2020	• Update to Schedule of Activities • Revision to inclusion criterion #2	• Clarify and make consistent with the language in the body of the protocol • Clarify and adjust previously diagnosed BCC inclusion criterion
3.2	06 Aug 2020	• Update to the DLT assessment language assocoiated with local skin reactions (LSR).	• Clarify the language and criteria for subjects entering the trial with baseline LSRs.
3.3	28 Dec 2020	• Revision to the study drug administration language	• Clarify the steps that study personnel are to follow for administering the study drug.

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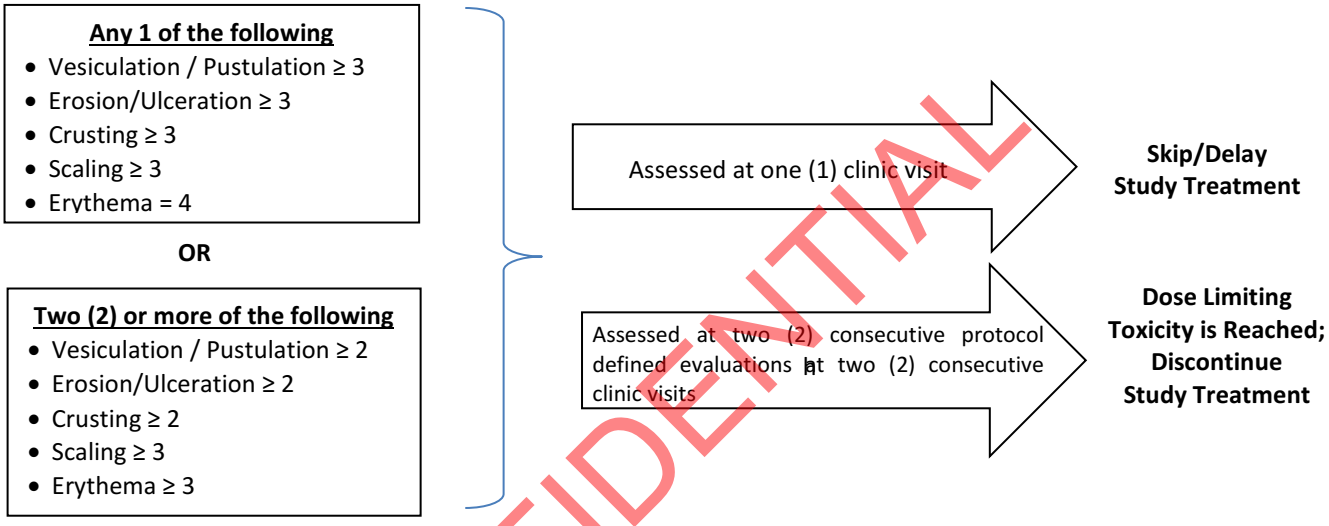
12 APPENDICES

12.1 Appendix 1

Guidelines for skipping/delaying and discontinuation of study treatment and definition of Dose Limiting Toxicity Using the LSR Grading Scale

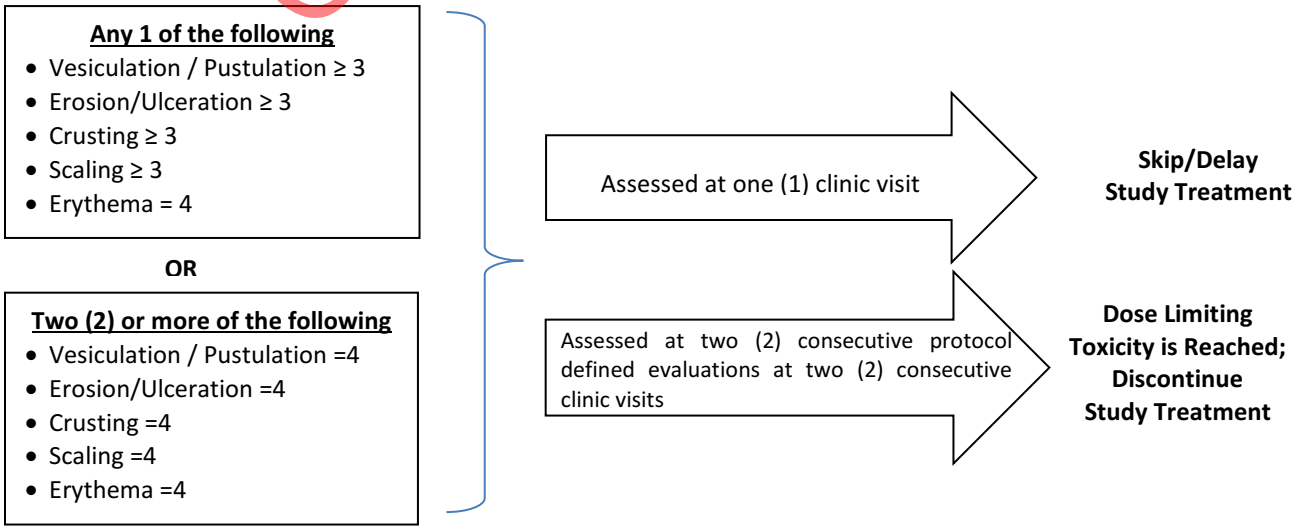
GUIDELINE 1

For subjects who enter the trial with LSR evaluations =Grade 0 and experience an increase in severity during their participation, the guidelines below will be applied:



GUIDELINE 2

For subjects who enter the trial with any LSR evaluation ≥Grade 1 and experience an increase in severity during their participation, the guidelines below will be applied:



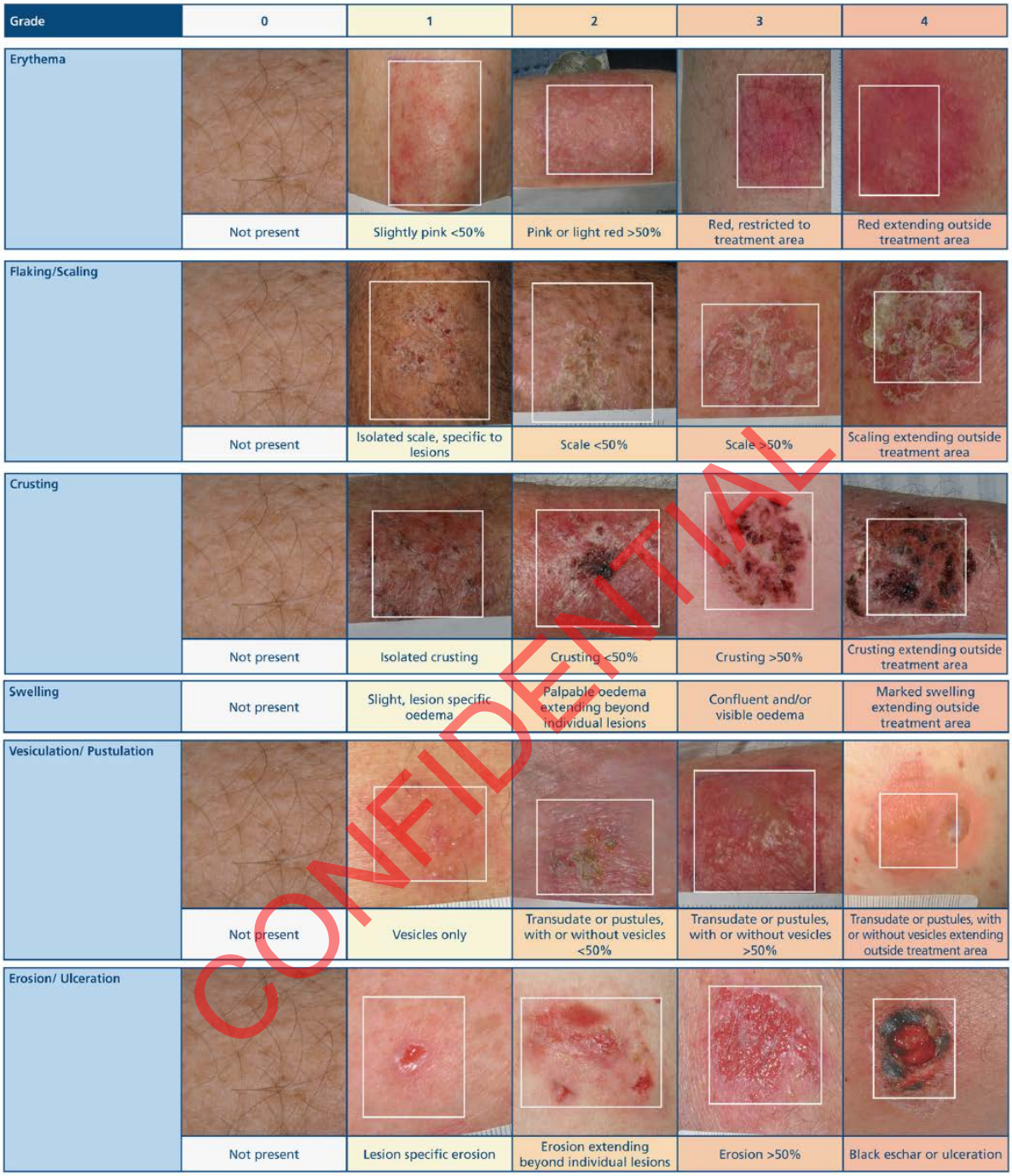
The LSR evaluation and assessment of any potential change in treatment and/or DLT determination is to be conducted on an individual LSR category. For example, a subject may have two (2) grade 0 and three (3) grade 1 LSRs at pre-treatment Visit 1, Day 1. Subsequent evaluations will require use of both guidelines above.

Local Skin Responses (LSR) Grading Scale

Grade

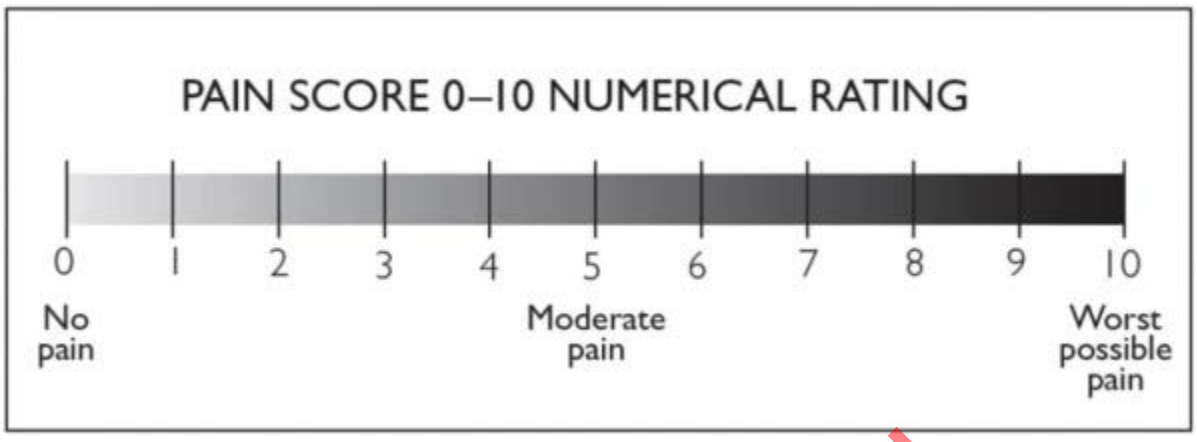
Categories	0	1	2	3	4
Erythema	Not Present	Slightly Pink	Pink or Light Red >50%	Red, Restricted to Treatment Area	Red Extending Outside of Treatment Area
Flaking / Scaling	Not Present	Isolated Scale, Specific to Lesions	Scale < 50%	Scale >50%	Scaling Extending Outside Treatment Area
Crusting	Not Present	Isolated Crusting	Crusting < 50%	Crusting >50%	Crusting Extending Outside Treatment Area
Swelling	Not Present	Slight Lesion Specific Edema	Palpable Edema Extending Beyond Individual Lesions	Confluent and/or Visible Edema	Marked Swelling Extending Outside Treatment Area
Vesiculation / Pustulation	Not Present	Vesicles Only	Transudate or Pustules, With or Without Vesicles < 50%	Transudate or Pustules, With or Without Vesicles >50%	Transudate or Pustules, With or Without Vesicles Extending Outside Treatment Area
Erosion / Ulceration	Not Present	Lesion Specific Erosion	Erosion Extending Beyond Individual Lesions	Erosion >50%	Black Eschar or Ulceration

Appendix 1 (continued next page)



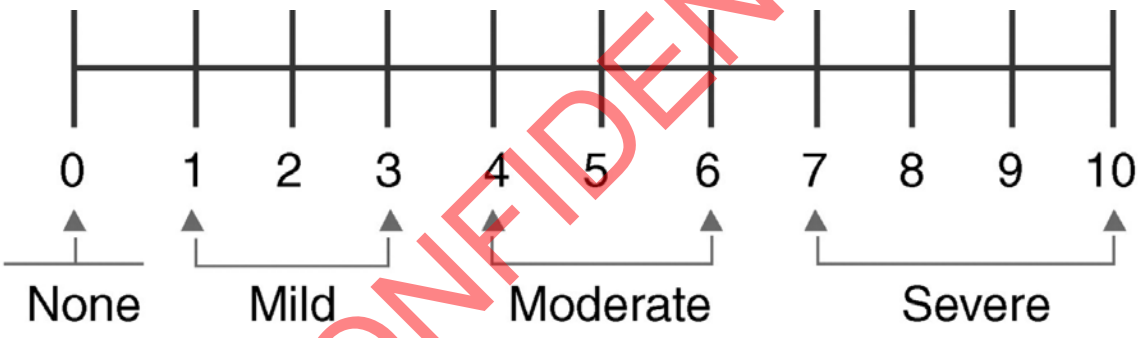
Rosen, Robert, Marmur, Ellen, Anderson, Lawrence, Welburn, Peter, Katsamas, Janelle. A New, Objective, Quantitative Scale for Measuring Local Skin Responses Following Topical Actinic
Keratosis Therapy with Ingenol Mebutate. Dermatol Ther (Heidelb) (2014) 4:207–219 DOI 10.1007/s13555-014-0059-9

12.2 Appendix 2



https://www.physio-pedia.com/Numeric_Pain_Rating_Scale

Pain Intensity-to-Severity Grading



Breivik H, Borchgrevik P, Allen S, Rosseland L, Romundstad L, Breivik Hals E, Kvarstein G, Stubhaug A. Assessment of pain. British Journal of Anaesthesia. 2008; 101(1):17-24