Protocol SKNJCT-001

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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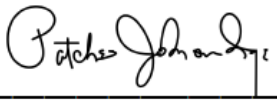
Patches Johnson Inge, PhD Project Statistician Instat Consulting, Inc.	Signature:  Date: 04May2021
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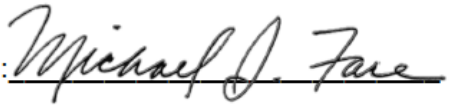
Michael Fare Chief Operating Officer SkinJect, Inc.	Signature:  Date: 4 May 2021

1 Glossary and Abbreviations

Abbreviation	Definition
AE	Adverse Event
ALL	All Subjects Population
BCC	Basal Cell Carcinoma
CI	Confidence Interval
CRF	Case Record Form
CTCL	Cutaneous T-cell lymphoma
DLT	Dose Limiting Toxicity
DLTP	Dose Limiting Toxicity population
DMC	Data Monitoring Committee
DOX	Doxorubicin
D-MNA	Doxorubicin microneedle array
EFF	Efficacy population
ICH	International Council for Harmonisation
LSR	Local skin reaction
MedDRA	Medical Dictionary for Regulatory Activities
MNA	Microneedle array
MTD	Maximum Tolerated Dose
NRS	Numerical Rating Scale
PT	Preferred Term
SAE	Serious Adverse Events
SAF	Safety Population
TEAE	Treatment Emergent Adverse Event
TL	Tables and Listings

2 Introduction

This study is a Phase I study designed as an open-label dose escalation trial of D-MNA in subjects with BCC (subtype: superficial or nodular). The goal of the dose escalation is to determine the maximum tolerated dose (MTD) 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.

The statistical methods to be implemented during the analyses of data collected within the scope of this study will be outlined in this document. The purpose of this plan is to provide specific guidelines from which the statistical analysis will proceed. Any deviations from this plan will be documented in the clinical study report.

3 Study Rationale, Background and Objectives

3.1 Study Rationale

This is a Phase I study in subjects with superficial or nodular Basal Cell Carcinoma (BCC), designed to assess dose limiting toxicities (DLTs) and MTD, efficacy, safety, and tolerability of dissolvable, tip-loaded, microneedle arrays containing doxorubicin (D-MNA). Doxorubicin (DOX) 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 myeloblastic leukemia. SkinJect, Inc. has developed a novel delivery system in the form of a dissolvable microneedle array (MNA) which is intended to allow subepidermal 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 DOX dose groups in subjects with BCC.

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

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.

3.2 Background

BCC is the most common skin cancer, with more than 4-million cases diagnosed each year in the US[1]. Despite its relatively low mortality rate, BCC is responsible for approximately 3000 deaths annually[2], and, along with SCC, results in $4.8 billion/year in healthcare spending in the US[3]. 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.

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[4]). The primary objective of the study is to evaluate the safety of escalating, low doses (25-200 µg) of DOX delivered directly into CTCL lesions using a MNA system. Secondary objectives include evaluations of the pharmacokinetics and pharmacodynamics of DOX 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. The initial Phase 1 clinical trial by Prof. Falo incorporates a single-arm, placebo- controlled (within subjects), open-label, accelerated dose escalation study design to determine the MTD (or effective dose) of DOX. This is followed by an extended evaluation of safety and effectiveness at the determined MTD or effective dose.

In Prof. Falo's trial, the first cohort of three subjects was treated with 25 µg of DOX via MNA. Subjects were treated once/week for four weeks, followed by a one-week break. No toxicities were observed at the 25-µg dose, and the original cohort, plus a new three-subject cohort were escalated to the 50-µg dose. DLT, a cutaneous reaction, was observed in one subject at the 50-µg dose and the cohort was expanded to two additional subjects, with no additional DLT reported. One subject in the 50-µg cohort exhibited a complete resolution of mycosis fungoides in response to D-MNA[5].

SkinJect's trial uses a 3+3 design, enrolling five dosing cohorts, namely, placebo MNAs, 25 µg D-MNA, 50 µg D-MNA, 100 µg D-MNA, and a 200 µg D-MNA.

3.3 Data Monitoring Committee (DMC)

A DMC has been chartered for this study. Membership in this committee includes qualified physicians who are dermatologists with expertise in treating skin cancer and sponsor's medical monitor, as well as individuals with DMC expertise. The DMC will review the safety data at the end of each cohort during the dose escalation phase of the study. After the last end-of-treatment (i.e., Day 21) visit for the last subject in the trial has occurred, the DMC will review the safety data for all of the subjects for DLTs and determine when a MTD has been reached. Details of the safety review as well as recommended dose selection for future clinical trials will be defined by the DMC.

4 Study Objectives

4.1 Primary Objective

The primary objective 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 (Time 0, Week 1 and Week 2 timepoints), in placebo, 25 µg, 50 µg, 100 µg and 200 µg DOX dose groups in subjects with BCC.

4.2 Secondary and Exploratory Objectives

Secondary objectives are:

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

Exploratory objectives are:

- To quantify the approximate amount of DOX 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 subjects with BCC.

5 Study Design

5.1 Overall Study Design

This is a Phase I open-label dose-escalation trial to evaluate DLT, MTD, safety, and tolerability of MNAs containing DOX in subjects with BCC.

One study site in the US will enroll all subjects in the study.

5.2 Dose Justification

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 DLT.

The study design also includes a placebo-MNA (P-MNA) group. Inclusion of P-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 DOX 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 DOX delivered by the D-MNA.

As each subject completes his or her treatment course in any given dosing cohort, the BCC lesion is excised. All BCC cells will be removed regardless of the dose group to which the subjects were assigned.

5.3 Subjects

Qualified subjects are men and women with BCC (superficial or nodular sub-type) age 18 or older and in general good health. Fifteen subjects (three in each of the five dose groups) are planned. Up to 15 additional subjects may be recruited in case of emergence of DLTs.

5.4 Study Design Summary

One study site in the United States is participating in this clinical trial. The trial is being conducted by qualified dermatologists (or other sub-specialty physicians with equivalent qualifications).

The participating subjects are treated with MNAs containing DOX or MNAs containing placebo. The D-MNA or P-MNA is applied to the BCC lesion and secured to the skin with a bandage. The D-MNA and P-MNA are removed from the skin after 30 minutes. Each subject will receive three (3) weekly applications of the D-MNA unless a DLT requires skipping or postponement of an application.

The investigational product is chemotherapeutic agent DOX (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.

Individual subject 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).

6 Determination of Sample Size

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 of the study protocol. Based on this design, between 15 and 30 subjects will be required to be evaluable for the primary DLT endpoint.

7 Randomization

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 P-MNA 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 subject;
- 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 identification information 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 identification number with the second unique identifier.

8 Analysis Populations

Three subject populations will be defined for this study.

- DLTP evaluable population (DLT): All subjects who complete the study through the Day-21 visit (End of Treatment) without experiencing a DLT or subjects who experience a DLT regardless of discontinuation. Subjects who discontinue the study prior to Visit 4 without experiencing a DLT will not be considered evaluable for the primary DLT endpoint;

- Safety population (SAF): All enrolled subjects who receive at least one treatment. The SAF population will be included in all safety analyses and summaries;

- All subjects population (ALL): All randomized subjects;

- Efficacy population (EFF): All subjects in the safety population with at least one dose of study medication (active or placebo). Efficacy analyses will be conducted on the efficacy population.

9 Statistical Analysis

9.1 General Considerations

The statistical analyses will be reported using summary tables and listings (TLs). Numbering for TLs will be based on the recommended numbering convention provided by the International Council for Harmonisation (ICH). All summary tables will be presented by treatment group.

Select baseline tables may also include a total column summary. Tables and listings will be presented in PDF format.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum and maximum. Categorical (qualitative) variables will be summarized by frequencies and percentages of subjects in corresponding categories. The denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group with non-missing data for the variable of interest.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to one degree of precision more than the observed data and measures of spread (standard deviation) will be reported to two degrees of precision more than the observed data.

Percentages will be presented to one decimal place unless otherwise specified. Assessments done on unscheduled visits will not be summarized but will be listed.

No hypothesis testing is planned, so no P-values will be reported.

For analysis purposes, repeat laboratory rest results will not be used unless the original laboratory value is missing or indicated as invalid, in which case the first non-missing repeat laboratory value will be used for data analysis.

All collected data will be presented in listings and will be sorted by subject. CDISC-compliant datasets (STDM and ADAM) will also be provided to the sponsor.

All analyses and tabulations will be performed using SAS® version 9.3 or higher. Upon completion, all SAS programs will be validated by an independent programmer. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency with tables, and consistency between tables and corresponding data listings.

9.2 Baseline Values

Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the administration of the first study treatment. When applicable, unscheduled visits will be used in the determination of baseline values.

9.3 Maximum Tolerated Dose (MTD)

The MTD is defined as the highest dose with a DLT rate below 33%.

9.4 Handling of Missing Data

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.

In general, with the exception of the clinical response data at Visit 4, missing values are not considered for percentage calculations, unless stated otherwise. In these cases, footnotes will specify the percentage denominator definition.

10 Background Characteristics

10.1 Subject Disposition

Study completion and reasons for discontinuation for all subjects in the study will be summarized for each treatment group. Discontinuations by reason will be tabulated for each treatment group. All subjects and study completion status will be presented in a listing.

10.2 Demographic and Baseline Characteristics

Continuous demographic variables (e.g., age, height, weight) will be summarized by descriptive statistics for each treatment group. Qualitative demographic characteristics (e.g., gender, race, ethnicity) will be summarized by counts and percentages for each treatment group. Demographics will also be presented in a subject listing.

10.3 Prior and Concomitant Medications

All medications taken during the course of the study with a start date or an end date on or after the date of the first study treatment administration or marked as ongoing will be considered concomitant. Medications stopped prior to the date of the first study treatment administration will be considered prior medications.

If start and/or end dates for medications are missing, the dates will be imputed as described below.

Imputing partial or missing start dates:

- If the year is unknown, the start date will not be imputed. The data will remain missing.
- If the month is unknown, and the year is the same as the first treatment date of the study, and the corresponding stop date is not prior to the first treatment date of the study, then impute the month and day of the date to be equal to the first dose month and day. Otherwise, impute the month as January.
- If the day is unknown and the month and year are the same as the first treatment date of the study, and the corresponding stop date is not prior to the first treatment date of the study, then impute the day to be equal to the day of the first treatment. Otherwise, impute the day as '01'.

Imputing partial or missing end dates:

- If the year is unknown, the end date will not be imputed. The data will remain missing.
- If the month is unknown, impute the month as December.
- If the day is unknown, impute the day to be the last day of the month.

If an imputed stop date is greater than the last medication date or study completion/discontinuation date of the study, then the imputed stop date will be set equal to the maximum of these two dates (last medication date or completion/discontinuation date).

The number and percentage of subjects using each concomitant medication will be summarized for each dose group according to the World Health Organization Drug Dictionary (WHODRUG) (Version March 1, 2019) Anatomical Therapeutic Chemical (ATC) Classification preferred term (PT). Subjects with multiple use of a concomitant medication during a treatment period will be counted only once for a given drug class or PT for the treatment period. Medication summaries will be based on the SAF and presented in summary tables and a subject listing.

10.4 Medical History

Medical history (past and ongoing medical illness) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 22.0) coding dictionary. Medical history is defined as any

illness documented at the screening visit that the subject may have had prior to first application of the study treatment.

Prior (conditions ending prior to the first application of the study treatment) and ongoing (conditions present while receiving study treatment) medical conditions will be summarized by presenting for each group the number and percentage of subjects having any condition. Prior and ongoing conditions will be presented in separate Medical History tables.

Subject data listing of all medical history will also be presented.

11 Study Treatment

A summary table will be provided detailing counts of subjects and dispensation of investigational product as well as dose levels and treatment exposure.

12 Primary and Secondary Endpoint Analysis

12.1 Primary Endpoint Analysis: Assessment of DLT

The primary efficacy endpoint is the assessment of DLT through Visit 4 (21 days) as defined in Appendix 1 of the Protocol using the LSR grading scale. or any systemic ≥ Grade 3 adverse event according to Common Terminology Criteria for Adverse Events v 5.0 that cannot be attributed to another cause All DLTs will be summarized by dose group, including placebo. A subject-level listing of DLT assessment will also be presented.

12.2 Secondary Endpoint Analysis

12.2.1 Lesion Response

The proportion of subjects achieving a histological complete response (CR) at Visit 4 (21 days) will be summarized with the associated 95% exact lower, 1-sided confidence interval (CI) for each dose group including placebo. Lesion Response results will also be presented in a subject-level listing.

12.2.2 Additional Endpoints

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

- Evidence of BCC at the treatment site pre and post MNA application by 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).

13 Safety Analysis

All enrolled subjects who receive at least one treatment will be included in the safety analysis and summaries. Adverse events will be coded using MedDRA and summarized by dose group. Summaries by the number of subjects reporting the adverse event and the number of adverse events reported will be presented. 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 and reported in a subject-level listing.

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.

13.1 Adverse Events

Adverse events (AEs) will be recorded throughout the study and at early discontinuation. AEs and medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 22.0) and summarized by dose group. Summaries by the number of subjects reported the AE and the number of AEs reported will be presented. A by-subject AE listing including verbatim term, PT, dose group, severity and relationship to study n will be provided.

Adverse events will further be categorized by severity and relationship to study medication. Serious adverse events will also be summarized. Other information collected will be listed, as appropriate.

Treatment-emergent adverse events (TEAEs) will be defined as any event not present prior to the initiation of treatment or any event already present that worsens in either intensity or frequency following exposure to treatment. TEAEs will be summarized by dose group, presenting the number and percentage of subjects having any treatment-emergent AE, having an AE in each

body system and having an individual AE. (Note: In any given category [e.g., body system], a subject will only be counted once.)

13.2 Laboratory Data

The summary statistics of raw data (hematology, chemistry and applicable urinalysis) and change from baseline values (means, medians, standard deviations, min, and max) will be presented. For urinalysis parameters that are categorical, the number and percentage of subjects falling under each category of the test will be presented. Clinical laboratory tests to be performed are:

Category	Parameters
Hematology	hemoglobin, hematocrit, platelets, and white blood cell (WBC) count
Chemistry	blood urea/blood urea nitrogen (BUN), creatinine, glucose, potassium, chloride, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, amylase, lipase, total bilirubin, potassium, calcium, phosphate, lactate dehydrogenase
Urinalysis	macroscopic, microscopic, specific gravity, pH, protein, glucose, ketones, hemoglobin.

13.3 Vital Signs and Body Measurements

Data from vital signs and body measurements (see below) will be listed and any other information collected will be listed. Data will be summarized by treatment group using mean change from baseline. Variables to be summarized are:

Measurement
Heart Rate
Diastolic Blood Pressure
Systolic Blood Pressure
Respiratory Rate
Body Temperature
Weight

14 Exploratory Analyses

Quantification of the DOX remaining in the used MNA will be summarized by dose group using descriptive statistics. Additional exploratory analyses may be defined at a later date.

15 Interim Summaries and Data Monitoring

There is no planned statistical output for DMC review.

16 References

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17 Planned Tables and Listings

17.1 Planned Tables

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14.3.4.4	Urinalysis Summary (Categorical Variables – SAF)
14.3.4.5	Summary of Abnormal Laboratory Values (SAF)
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17.2 Planned Listings

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