Phase 1 Trial of IFx-Hu2.0 to Evaluate Safety in Patients with Skin Cancer

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The terms "outcome measures" and "endpoints" are used interchangeably in this document.

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
Various pertinent sections	• Removed cutaneous melanoma from the list of indications to be studied under this protocol	• This was done in response to the FDA review team's feedback from 25 May 2021 • This was done to mitigate the risk of enrolling patients with brain metastases
1.3 Schedule of Activities	• Added testing for HIV/AIDS and hepatitis B/C	• This was done in response to the FDA review team's feedback from 25 May 2021
5.2 Exclusion Criteria	• An exclusion criterion was added to not inject lesions on scalp with bone erosions	• This was done in response to the FDA review team's feedback from 25 May 2021
5.2 Exclusion Criteria	• An exclusion criterion was added to not enroll patients with active HIV/AIDS or hepatitis B/C	• This was done in response to the FDA review team's feedback from 25 May 2021
9.2 Sample Size Determination	• The DLT definition was revised to include all AEs at least "possibly" related to the IP	• This was done in response to the FDA review team's feedback from 25 May 2021

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TRIAL COMPLIANCE

The trial will be carried out in accordance with the United States (US) Code of Federal Regulations (CFR) applicable to clinical trials (i.e. 45 C.F.R. § 46, 21 C.F.R. § 11, § 50, § 56, and § 312 (2020)) and applicable state and local research requirements. Investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of the trial have completed Institutional Review Board (IRB)-approved Good Clinical Practice training (i.e. on US Food and Drug Administration (FDA) Regulations and ICH GCP E6(R2)).

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 patient is enrolled. Any amendment to the protocol will require IRB review and approval before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR AGREEMENT

I will conduct the trial in compliance with the protocol agreed to by the sponsor, and if required, by the regulatory authority(ies), and which was given IRB-approval/favorable opinion.

I will not implement any deviation from, or changes to, the protocol without sponsor agreement and prior IRB review and approval/favorable opinion of an amendment, except where necessary to eliminate an immediate hazard(s) to patients, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of contact information such as phone number(s)).

I will document and explain any deviation from the IRB-approved protocol.

I may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to patients without prior IRB approval/favorable opinion. As soon as possible, I will submit the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s):

a) To the IRB for review and approval/favorable opinion.
b) To the sponsor for agreement and, if required.
c) To the regulatory authority(ies).

_____ _____

Investigator Name and Signature Date (DD Mon YYYY)

SPONSOR AGREEMENT

I agree to the conduct of the trial in accordance with this protocol.

_____ _____

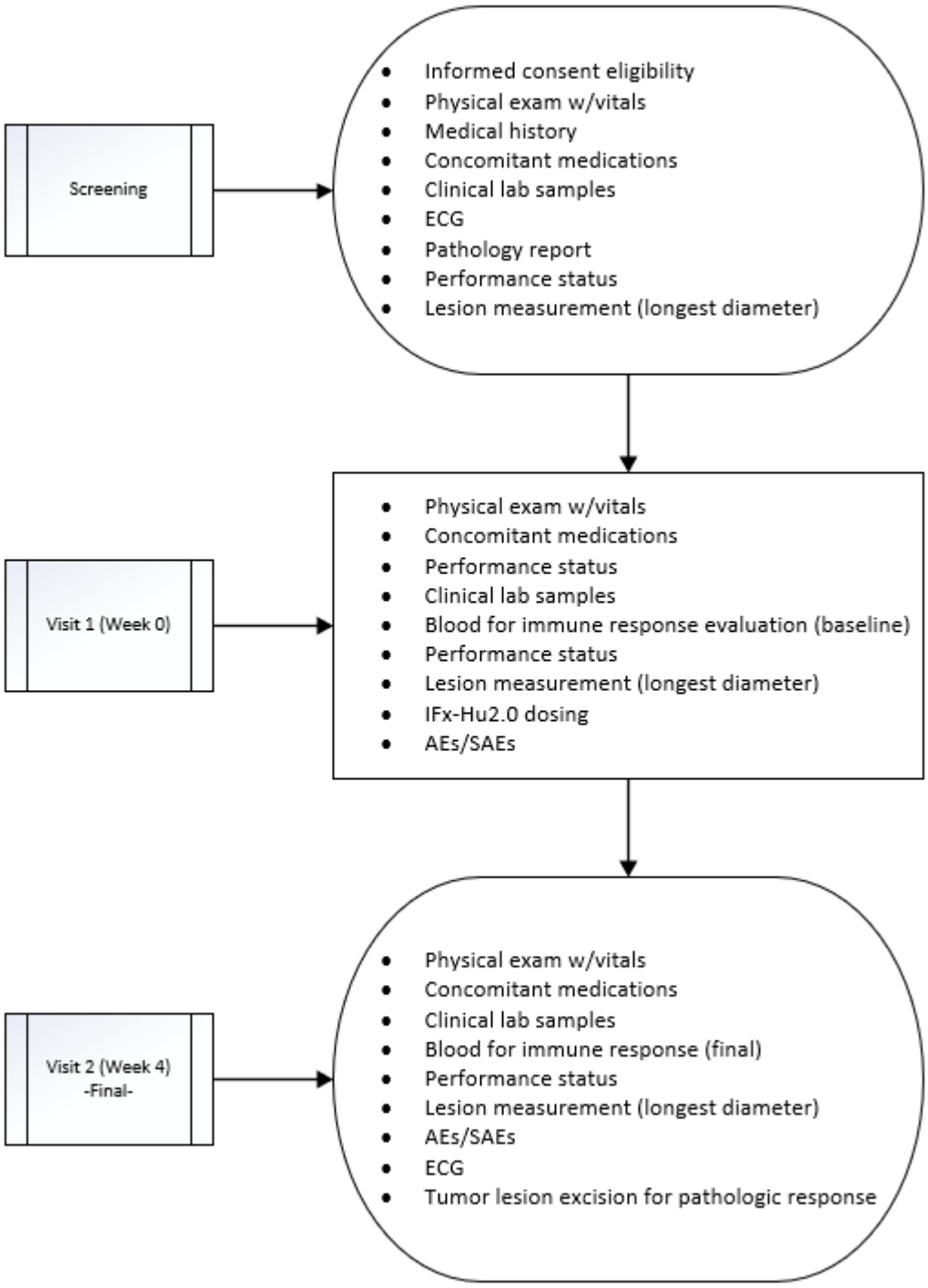
Sponsor Representative Name and Signature Date (DD Mon YYYY)

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**Phase 1 Trial of IFx-Hu2.0 to Evaluate Safety in Patients with Skin Cancer**
Study Description:	One hundred patients will receive IFx-Hu2.0 on an outpatient basis at a single time point in a single lesion. These patients will be assessed for any immediate adverse reactions and at Week 4 (Day 28+/-5 days) for any delayed adverse events.
Objectives:	Primary Objective: To assess safety and feasibility Secondary Objective: To assess post-therapeutic pathological response Tertiary/Exploratory Objective: To assess anti-tumor immunity post-treatment.
Endpoints:	Primary Endpoint: The primary endpoints of this trial will be the safety and feasibility of the treatment regimen. Safety will be reported using the most current version of the Common Terminology Criteria for Adverse Events (CTCAE). Feasibility will be defined as the ability to treat at least 85 of the approximate 100 patients enrolled without investigational product (IP) related dose-limiting toxicity (DLT). Secondary Endpoints: The secondary endpoint is Pathological Response defined as a response assessment to IFx-Hu2.0 in tumor lesions excised by evaluating percent Residual Vial Tumor (%RVT), at four weeks as: • pathological complete response (pCR), • major pathological response (mPR), • partial pathological response (pPR), or • pathological non-response (pNR) Tertiary/Exploratory Endpoints: Patient samples (plasma and/or serum) will be assayed to detect tumor antigen specific antibody generation in addition to a protein biomarker discovery assay specific to immuno-oncology therapy assessments. IHC will be performed on pre- and post-treatment tissue samples to contrast the cell sub-types across time points.
Study Population:	Adult male or female subjects with confirmed cutaneous squamous cell carcinoma, or basal cell carcinoma with lesions accessible for intralesional injection.
Phase:	Phase 1
Description of Sites/Facilities Enrolling Participants:	Approximately 5 NCI-designated cancer centers, academic medical centers, clinics, and doctor's offices within the United States, qualified to perform clinical studies under GCP.
Description of Study Intervention:	Plasmid DNA encoding a Streptococcal antigen in a cationic polymer-based solution in doses of 100 µg delivered intralesionally at a single time point "Week 0".
Study Duration:	12 Months
Participant Duration:	Up to six weeks

1.2 SCHEMA


Screening
Informed consent eligibility
Physical exam w/vitals
Medical history
Concomitant medications
Clinical lab samples
ECG
Pathology report
Performance status
Lesion measurement (longest diameter)
Visit 1 (Week 0)
Physical exam w/vitals
Concomitant medications
Performance status
Clinical lab samples
Blood for immune response evaluation (baseline)
Performance status
Lesion measurement (longest diameter)
IFx-Hu2.0 dosing
AEs/SAEs
Visit 2 (Week 4)
-Final-
Physical exam w/vitals
Concomitant medications
Clinical lab samples
Blood for immune response (final)
Performance status
Lesion measurement (longest diameter)
AEs/SAEs
ECG
Tumor lesion excision for pathologic response

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening Visit Day -14 to -1	Baseline Visit Week 0/Day 0	DLT Follow up Week 4/Day 28 +/-5 days	Unscheduled Visit	Early Termination Visit
Informed consent	X				
Demographics	X				
Medical History	X				
Physical exam w/vitals	X	X	X	X	X
Performance Status	X	X	X	X	X
Tumor Burden (lesion measurements)	X	X	X	X	X
Concomitant medications review	X	X	X	X	X
Electrocardiogram (ECG)	X		X	X	X
Pathology Report Confirming Diagnosis (specific to lesion marked for injection)	X				
Clinical laboratory samples (safety)[a]	X	X	X	X	X
Pregnancy test	X[b]	X[c]	X[b]	X[b]	X[b]
Blood for Immune Response Evaluation		X	X	X	X
IFx-Hu2.0 dosing		X			
Adverse event review and evaluation		X	X	X	X
Tumor excision for pathological response (final)			X		X

[a] **Clinical laboratory samples (safety);** samples will include blood and urine for the following tests:

- Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT) and activated partial thromboplastin time (aPTT)
- Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Thyroid tests (TSH and FT4)
- Serology: Hepatitis B Core Antibody (IgM), Hepatitis C Antibody (Anti-HCV), HIV-1/2 Antigen and Antibodies
- Urinalysis: UA with microscopic evaluation
- Anti-double-stranded DNA (anti-dsDNA) antibody test
- Anti-DNase B Titer, Serum

[b] **Serum pregnancy test** – indicated only in women of childbearing potential

[c] **Urine pregnancy test** done within 24 hours prior to IFx-Hu2.0 administration and results must be available prior to IFx-Hu2.0 administration, – only in women of childbearing potential

2 INTRODUCTION

2.1 STUDY RATIONALE

M proteins, the cell surface antigens responsible for the M serospecificities of *S. pyogenes*, are encoded by *emm* genes. Emm55 is one of hundreds of M proteins. Anchored in the *S. pyogenes* cell wall, M proteins mediate adhesion to host cells and connective tissues as well as bacterial cell invasion. M proteins act as antiphagocytic factors which are crucial for defense against human innate immunity(1). Due to high variability at the N-terminal region of M proteins, there have been more than 200 distinct types recorded in public databases. M proteins have been considered as vaccine candidates against group A Streptococcal-mediated strep throat and suppurative skin diseases(2). However, some M proteins bind collagen and may cause side effects such as acute rheumatic fever in humans through molecular mimicry of collagen(3). Emm55, though, has been shown not to bind collagen due to the conformational influences of flanking sequences(4). In the IFx-Hu2.0 immunotherapeutic, the Emm55 protein acts as an immunologic priming antigen aimed at attracting the patient's immune system to tumor cells.

The product being tested in this clinical study, IFx-Hu2.0, is designed to exploit the inherent vulnerability of specific differences from patient to patient, lesion to lesion, and cell to cell. Regardless of the degree of complexity of an individual's antigenic signature, this truly patient-specific approach capitalizes on the antigenic differences to create the broadest immune response possible. By introducing the *emm55* gene from *S. pyogenes* into a patient's tumors by intralesional injection, the highly immunogenic Emm55 protein is expressed on tumor cells and initiates an immune cascade leading to the activation of multiple immune cells, including cytotoxic T cells. The goal of this study is to determine the safety and feasibility of injecting IFx-Hu2.0 into cutaneous tumor lesions in patients with early-stage disease and to also evaluate each patient's pathological response at four weeks post-treatment.

2.2 BACKGROUND

IFx-Hu2.0, a plasmid DNA construct (pAc/*emm55*) formulated with *in vivo*-jetPEI®, a cationic polymer that aids in cellular uptake of DNA, and dextrose, will be administered by intralesional injection. IFx-Hu2.0 is a cancer immunotherapy that stimulates the immune system to fight cancer. When introduced into tumor cells, pAc/*emm55* drives expression of the highly immunogenic Emm55 protein in the cytoplasm and on the surface of the tumor cells. IFx-Hu2.0 provides a stimulus for a targeted immune response against tumor cells in patients with skin cancer. In this protocol, IFx-Hu2.0 will be utilized as a monotherapy in a safety and feasibility study design that also evaluates each patient's specific pathological response post-treatment.

Cancer immune evasion transpires when two events occur: 1) immune surveillance fails to recognize the alterations and abnormalities of tumors and 2) tumors take advantage of inhibitory pathways which are hardwired into the immune system for avoiding autoimmunity(5) IFx-Hu2.0 is designed to exploit the inherent vulnerability of specific differences from patient to patient, lesion to lesion, and cell to cell. Regardless of the degree of complexity of an individual's antigenic signature, this truly patient-specific approach capitalizes on the antigenic differences to create the broadest immune response possible. By introducing the *emm55* gene from *Streptococcus pyogenes* (*S. pyogenes*) into a patient's tumors via intralesional injection, the highly immunogenic Emm55 protein is expressed on tumor cells and initiates an immune cascade leading to the activation of multiple immune cells, including cytotoxic T cells. However, optimal T cell responses may be abrogated by tightly regulated immune checkpoints whose function is to avoid collateral damage and autoimmunity. The interplay between antigen presentation/T

cell activation and T cell suppression is critically important in determining the outcome of immunotherapeutic interventions.

Epidemiology Data

More than 5 million new cases of nonmelanoma skin cancer (NMSC) occur annually in the United States, including 80% basal cell carcinomas (BCCs), 20% squamous cell carcinomas (SCCs), and a few rarer types. Annual incidence is increasing by 4% for SCC and 1% for BCC in the United States. Of solid organ transplant recipients, 15% to 43% will develop NMSC within 10 years(6).

Ultraviolet radiation from sun exposure is a major risk factor, causes mutations in key genes, and explains the predilection of NMSC for sun-exposed skin. Hedgehog signaling pathway mutations are involved in BCC pathogenesis. p53 Mutations are involved in both SCC and BCC pathogenesis, and in the development of actinic keratoses, which are the precursors of SCCs. There are several histopathologic subtypes of each NMSC. The more infiltrative or poorly differentiated variants are more clinically aggressive (e.g., morpheaform BCC and spindle cell SCC)(6).

TNM staging classifications exist for most types of NMSC and depend on clinical characteristics, pathologic features, and radiologic evaluation of the primary tumor, adjacent structures, lymph nodes, and viscera. BCCs that are large, deep, or infiltrative may be locally aggressive and recurrent, but metastasize only rarely (0.003% to 0.55%). SCCs have a greater metastatic rate, especially those that are large, deep, or poorly differentiated; have perineural invasion; or are located on the lip, ear, temple, cheek, or sites of chronic infection, ulceration, or radiation(6).

Primary treatment for both BCCs and SCCs is surgical. Mohs micrographic surgery is preferred for ill-defined or aggressive lesions because it allows microscopic control of tumor margins. The 5-year local recurrence rate for primary BCC is 1% for Mohs surgery compared with 5% for other types of surgical excision. The 5-year local recurrence rate for primary cutaneous SCC is 3.1% for Mohs surgery compared with 7.9% for non-Mohs modalities. Alternative primary therapies include various forms of physical destruction and radiation therapy. Interferons and inducers of interferons (e.g., imiquimod) are useful in selected cases. Hedgehog pathway agents, retinoids, vitamin D3, and inhibitors of PD-1/PD-L1 and epidermal growth factor receptor (EGFR) are other promising adjunctive and chemopreventive modalities(6).

Unmet Medical Need

The application of IFx-Hu2.0 in a neoadjuvant setting may support an improvement in current recurrence rates for these cancers. This could materialize based on the mechanism of action of IFx-Hu2.0 and its ability to elicit therapeutically relevant cellular and humoral tumor-specific immune responses. Findings from prior human use of IFx-Hu2.0 in patients with stage III to IV cutaneous melanoma supports this biological outcome.

Preclinical Pharmacology

Study # 20151023 – Murine Melanoma Study

In the preclinical murine melanoma model, no adverse events were reported for single or repeat dosing of the drug product. For monotherapy, a statistically significant reduction in tumor weight and tumor area as well as a statistically significant increase in percent survival were observed (treatment vs. control). For combination therapy, a statistically significant reduction in tumor area was observed (combination therapy vs. monotherapy). In conjunction with T cell infiltration and IFN-γ data for these mice, the immune responses observed were logically consistent with the hypothesized mechanism of action of IFx-Hu2.0.

Table 1 Snapshot of Study # 20151023

Animal Model – Cutaneous Melanoma	Treatment Regimen	Safety Profile	Efficacy Signal
Mus musculus (C57BL/6NCrl); B16-F10 syngeneic melanoma cell line (n=257)	Monotherapy: 0.02 mg of IFx-Hu2.0 intralesional injection in three indexed cutaneous lesions once weekly for three doses (n=81) Combination Therapy: 0.02 mg of IFx-Hu2.0 intralesional injection in three indexed cutaneous lesions once weekly starting on day zero for three doses + 0.25 mg of PD-1 antagonist antibody (RMP1-14) intraperitoneal injection twice weekly starting on day eight for three doses (n=24) Other Therapies: IFx-Hu2.0 + immune response modifier (n=20) Controls: pAc/empty ± immune response modifier (n=132) Note: IFx-Hu2.0 intralesional dose was limited by the physical size of palpable, cutaneous tumors in mice	No Adverse Events: No secondary tumor growth, other injuries or signs of pain and no significant coat condition, disposition, and fecal or urine output findings (n=257)	Monotherapy: Treatment vs. Control: Statistically significant increase in overall survival (OS) and decrease in tumor burden (tumor mass and area) Combination Therapy: Combination Therapy vs. Monotherapy: Statistically significant reduction in tumor burden (tumor area)

In a series of experiments, mice transplanted with B16-F10 murine melanoma cells were treated with IFx-Hu2.0 vaccine to measure the safety and antitumor effect of Emm55 protein-expressing tumor cells alone or in combination with immune response modifiers. The study encompassed a pilot proof-of-concept

experiment, nine exploratory experiments and a biodistribution experiment. In general, B16-F10 melanoma cells ($1x10^5$ cells/100 mcL/mouse) were injected subcutaneously in syngeneic C57BL/6NCrl mice to establish tumors. The day of B16-F10 cell injection was designated Day 0. Approximately seven to ten days post injection, animals with palpable tumors (approximately 25 mm^2) were randomly divided into experimental treatment cohorts. In some experiments, mice were subcutaneously injected with $3x10^5$ MO5 tumor cells, an OVA-expressing B16 cell line. Vaccination consisted of IFx-Hu2.0 or negative vector controls; pAc/empty or pAc/GFP-N1 plasmid DNA similarly complexed with in vivo-jetPEI® transfection reagent. A vaccine dose consisted of 20 mcg plasmid DNA in a total volume of 50 mcL. Three weekly vaccine doses were administered intralesionally. Studies were also carried out combining IFx-Hu2.0 vaccine with antibodies targeting the immune response modifiers PD-1, CTLA-4 and 4-1BB. Throughout these studies, tumor growth was measured and monitored 2-3 times per week.

All the experiments incorporated safety assessments of the mice as part of the continued safety monitoring and final safety evaluation. Mice were monitored twice per day by animal care technicians for adverse effects. This consisted of monitoring for presence of lesions other than at the site of B16-F10 injection, adverse changes to the B16-F10 injection site, other injuries, coat condition, disposition, signs of pain, as well as fecal and urine output, according to the approved IACUC protocol for rodent husbandry (University of South Florida Division of Comparative Medicine SOP#400.14 issued 12/03 updated 7/16). No adverse findings were reported.

The pilot experiment evaluated the feasibility of IFx-Hu2.0 administration and assessed potential bioactivity. Six of the exploratory experiments assessed bioactivity of IFx-Hu2.0 as a monotherapy and in combination with antibodies targeting immune response modifiers. Preliminary mechanism of action assays were also performed in multiple experiments. For the biodistribution study, mice received one dose of IFx-Hu2.0 or similarly complexed pAc/empty.

Bioactivity experiments focused on the effect of IFx-Hu2.0 on animal survival, tumor mass and tumor area. In the pilot study, survival of animals vaccinated with IFx-Hu2.0 was compared to animals vaccinated with pAc/empty, or pAc/GFP-N1. There was a significant difference between treatment groups as assessed by Log rank Mantel-Cox survival test ($p=0.017$), with median survival times of 26 days for pAc/empty and pAc/GFP-N1 controls, and 40 days for IFx-Hu2.0 vaccine recipients. In a second survival test, there were significantly more IFx-Hu2.0 recipient mice alive than pAc/empty control mice ($p=0.032$) on Day 29, the median survival time for the pAc/empty group. For IFx-Hu2.0 recipients, median survival time had not yet been reached by Day 29, i.e. more than 50% of vaccinated mice were still alive. This difference in survival translated into a Hazard ratio (Mantel-Haenszel) of 5.7, which translates to a survival rate 5.7 times higher than that of pAc/empty recipients.

Two experiments focused on the effect of IFx-Hu2.0 on tumor mass. In the first experiment, the mean ± standard deviation (SD) tumor mass of mice vaccinated with IFx-Hu2.0 was 315 mg ± 87 mg, while the mean ± SD tumor mass of mice treated with pAc/empty was 997 mg ± 335 mg. This approximately 3-fold decrease in tumor mass over 27 days was significant using a heteroscedastic Student's T-test ($p=0.0083$). In the second experiment evaluating cotreatment with PD-1 antagonist, the mean tumor mass of mice receiving IFx-Hu2.0 was less than pAc/empty vaccinated animals after 25 days, irrespective of antibody cotreatment.

The impact of IFx-Hu2.0 vaccination on tumor area over time was assessed in several experiments. In all experiments, mean tumor area from mice vaccinated with IFx-Hu2.0 was less than negative controls.

Another experiment investigated the effects of IFx-Hu2.0 in combination with antibodies targeting the immune response modifiers PD-1, 4-1BB, and CTLA-4. The mean tumor area in mice given IFx-Hu2.0 was significantly less than the mean tumor area in mice receiving pAc/empty at Days 18, 21 and 25. Also,

pAc/empty combined with any of the three checkpoint Antagonists yielded significantly smaller mean tumor areas on Days 18, 21 and 25 than pAc/empty alone. The same or greater significance was observed at the same timepoints for IFx-Hu2.0 with checkpoint inhibition compared to pAc/empty, depending on the Antagonist. At Day 25, the mean tumor area in mice treated with IFx-Hu2.0 in combination with PD-1 antagonist was smaller than IFx-Hu2.0 or PD-1 antagonist alone, significantly so for IFx-Hu2.0.

Two experiments were designed to further investigate the effect of IFx-Hu2.0 in combination with PD-1 antagonist on tumor area. In the first experiment, statistically significant differences in mean tumor area were detected at Day 22 between mice receiving pAc/empty compared to mice receiving IFx-Hu2.0 and IFx-Hu2.0 in combination with PD-1 antagonist. Furthermore, on Day 25, statistically significant differences in mean tumor area were again observed between mice receiving pAc/empty and mice receiving IFx-Hu2.0 in combination with PD-1 antagonist. On Day 27, statistically significant differences in mean tumor area were detected between mice receiving IFx-Hu2.0 versus mice receiving IFx-Hu2.0 in combination with PD-1 antagonist. These data suggest an additive effect of IFx-Hu2.0 in combination with PD-1 antagonist as suggested by previous data.

Correlative pilot studies were performed to investigate IFx-Hu2.0 mechanism of action. Quantitative reverse transcriptase PCR showed expression of emm55 mRNA following injection of IFx-Hu2.0.

Immune cell subsets in the spleen and tumors were characterized to determine if the antitumor effect of IFx-Hu2.0 was immune-mediated. TIL isolated from mice were analyzed for CD8 expression using flow cytometry. There was an approximately 5- to 6-fold increase in the number of infiltrating $CD8^+$ T cells/mg tumor tissue in IFx-Hu2.0 injected mice compared to PBS and pAc/empty injected controls, suggesting the anti-tumor activity of IFx-Hu2.0 is T cell-mediated. This was further supported by immunohistochemical staining of tumors isolated from mice, which showed increased staining of CD3, CD4 and CD8 in the three treatment groups compared to the control group.

Flow cytometric analyses of TIL isolated from mice resulted in a mean ± SD of 30.6% ± 5.8% $CD8^+$ $PD\text{-}1^+$ T cells in IFx-Hu2.0 injected mice. Expression of PD-1 suggests that the anti-tumor activity of IFx-Hu2.0 could be further enhanced using a combination therapy with PD-1 targeting antibodies.

Cytotoxic T cell function was assessed using intracellular staining of TIL for IFN-γ and CD107a, a marker of $CD8^+$ T cell degranulation, upon activation. The level of $CD8^+$ IFN-γ^+ $CD107a^+$ T cells increased in IFx-Hu2.0 treated mice compared to the control group.

Splenocytes isolated from animals vaccinated with IFx-Hu2.0 as a monotherapy or in conjunction with PD-1 antagonist, were evaluated for IFN-γ production using an ELISA. The level of IFN-γ was significantly higher ($p=0.047$) in the IFx-Hu2.0 + PD-1 antagonist treatment group compared to pAc/empty treated controls.

To gain insight into tumor infiltration of immune cells following vaccination, an indirect analysis of antigen specific infiltration of tumors was carried out using the OT1-MO5 experimental model. The B16 subline, MO5, expresses an ovalbumin peptide in the context of $H2K^b$. OT-1 T cells express a T cell receptor (TCR) that recognizes the ovalbumin peptide. This results in MHC class I-restricted, ovalbumin-specific, $CD8^+$ T cells (OT-1 cells), which primarily recognize the ovalbumin peptide when presented by MHC I. The level of OVA TCR-expressing cells in tumors of IFx-Hu2.0 recipient mice was significantly higher than that of control mice ($p=0.0018$), suggesting a vaccine-induced increase in antigen-specific T cell infiltration. Another experiment investigated infiltration of T cells by analyzing endogenous T cells in the spleen and tumor. In tumors, there was a significant reduction in $CD8^+$ $PD\text{-}1^+$ cells from IFx-Hu2.0 treated mice compared to pAc/empty control mice ($p=0.035$), which may be due to a vaccine-induced reduction in the number of exhausted T cells.

Taken together, these bioactivity and mechanistic studies highlight important points concerning the efficacy and mode of action of IFx-Hu2.0 in the selected melanoma model system. IFx-Hu2.0 significantly increased animal survival and decreased tumor burden. This effect was enhanced when used in combination with PD-1 antagonist.

The B16-F10/C57BL/6NCrl murine melanoma study demonstrated that:

a) pAc/*emm55* (i.e. the drug substance) delays tumor growth and improves survival
b) Intralesional injection of pAc/*emm55* enhances T cell infiltration in tumors
c) Systemic immune responses elicited by the pAc/*emm55* are T cell-dependent
d) Systemic immune responses elicited by pAc/emm55 are antigen specific

Recently, Bunch et al. published the murine melanoma study (# 20151023) on 18 June 2020 in the Springer Cancer Immunology, Immunotherapy journal (7). The study was modeled after the murine melanoma study conducted by Liu et al (8, 9). Here, additional key efficacy insights will be summarized and presented from the Bunch et al. manuscript.

Bunch et al. conclude that treatment with the pAc/emm55 vector drug substance increases T cell tumor infiltration and delays tumor growth, while the anti-tumor efficacy of the dug substance is T cell dependent and that **this anti-tumor efficacy is improved with drug substance + PD-1 antagonist combination therapy**. These conclusions are echoed in the study report and summary found in the IND.

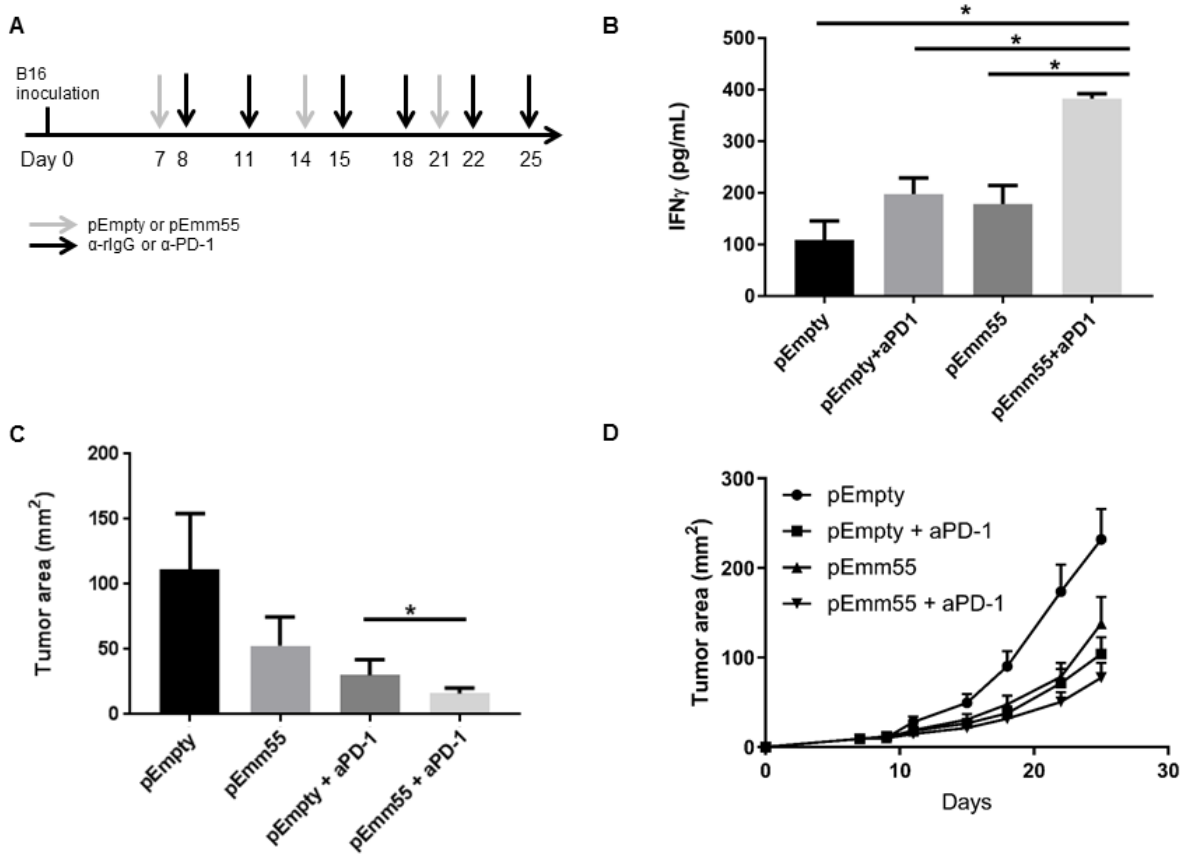


Figure **1** illustrates the anti-tumor efficacy of drug substance monotherapy and drug substance/PD-1 antagonist combination therapy.

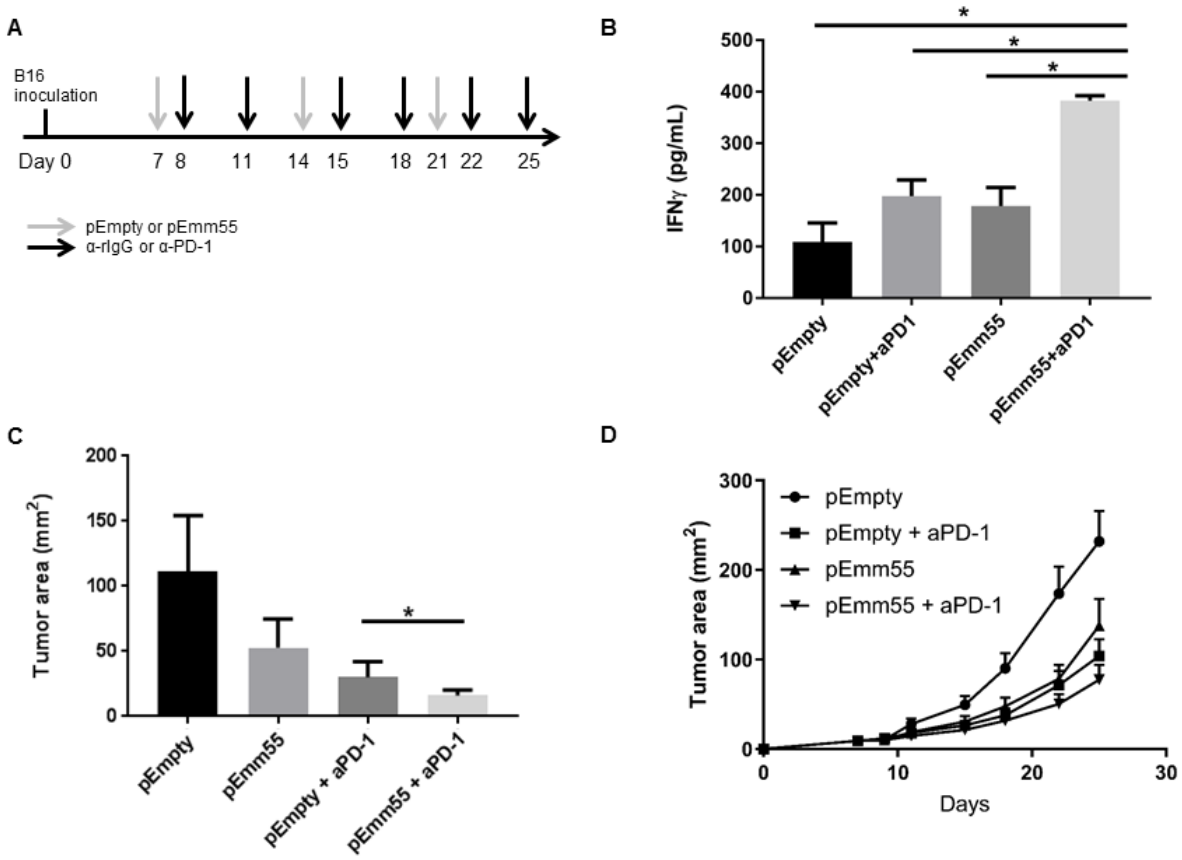


Figure 1. IFNγ production increases upon the addition of pAc/*emm55* and PD-1 antagonist therapy. Murine melanoma B16-F10 cells were injected subcutaneously on Day 0.

pEmpty vector (control) or pEmm55 vector was injected on days 7, 14, and 21. Starting on day 8, mice received intraperitoneal injection of either isotype control antibody or PD-1 antagonist (250 µg/200µL/IP) twice weekly (A). (B) Splenocytes collected from mice treated with emm55 vector ± PD-1 antagonist therapy were co-cultured with B16-F10 melanoma cells and culture supernatants were collected after 24 hours. Levels of IFNγ were measured ($p < 0.01$ utilizing unpaired T test with Bonferroni correction). (C) Tumor sizes for these B16-F10 tumors at day 25 were also measured and demonstrated an increased response with pEmm55/PD-1 antagonist compared to PD-1 antagonist therapy alone ($p < 0.01$; unpaired T test). (D) Tumor growth curves from each treatment group ($p<0.02$; unpaired T test with Bonferroni correction). (N=12 for treatment groups, N=9 for control pEmpty group).

Study # 20170516 – Murine Melanoma Biodistribution Study

A separate biodistribution murine melanoma study showed that IFx-Hu2.0 injections resulted in high levels of pAc/*emm55* expression vector presence and emm55 mRNA expression in injected tumors. It also showed substantially lower levels thereof in all non-target (i.e. non-skin) organs tested. No adverse events were reported.

The biodistribution and pharmacokinetic properties of IFx-Hu2.0 were evaluated in the B16-F10/C57BL/6NCrl melanoma model. Mice initially received an injection of the syngeneic B16-F10 melanoma cell line. After tumors were palpable, mice were randomly selected into treatment cohorts to receive a single vaccine injection of IFx-Hu2.0 or a similarly complexed negative control vector (pAc/empty), which lacks the emm55 coding region (20 mcg in 50 mcL). Animals were sacrificed and tissues were harvested one day post vaccination, which was the expected time of peak detection, and at seven and 14 days post-injection, to evaluate clearance of the emm55 transgene from tissues. Genomic DNA (gDNA), RNA and cDNA were prepared from the injected tumor and eight organs at each time point. A quantitative PCR assay meeting the sensitivity recommendation of ≤50 copies of vector/1 mcg DNA was used to measure the absolute level of pAc/emm55 transgene and relative levels of emm55 mRNA expression normalized to the endogenous control gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

To determine the biodistribution pAc/*emm55*, absolute levels of emm55 were measured in injected tumors and organs over time and are reported in copy numbers per µg gDNA. As expected, transgene levels were highest in tumor samples one day post vaccination, with a maximum level of $1.16x10^{10}$ copies. This represents ~7.3% of the copies injected. Although the transgene was detected in gDNA prepared from all organs, the absolute level was approximately 4 orders of magnitude higher in tumor gDNA than in the next highest tissue one day post injection, and was 4-7 orders of magnitude higher than in all other tissues at this timepoint. At seven days post injection, the transgene was detected at 3-6 orders of magnitude lower in other tissues than in tumor. At 14 days post injection, the transgene was detected at 2-4 orders of magnitude lower than in tumor.

To determine the kinetics of transgene expression, normalization was used to compare relative levels over time in each tissue. Normalized levels of emm55 mRNA in tumor (9.8910^{-01}), kidney ($9.01x10^{-05}$) and lung ($5.82x10^{-04}$) peaked at one day post injection. In lymph node and spleen, peak levels were similar at days one and seven post injection relative to the SD of these samples. In liver, peak levels were detected at seven days post injection. In heart, peak levels were detected and 14 days post injection. Expression in brain and ovaries was uniform over time relative to SD. In addition to transgene biodistribution and expression kinetics, all animals involved in this study were monitored for vaccine-related adverse reactions.

In conclusion, this study demonstrates that intralesional injection of IFx-Hu2.0 resulted in high levels of emm55 transgene uptake and mRNA expression in tumors with substantially lower levels in other organs in which it was detected. These residual levels did not result in any adverse events in the study animals.

<u>Previous Human Experience</u>

Phase 1 Study CM 2017-01 (NCT03655756)

Morphogenesis has completed a Phase 1, non-randomized, open-label, uncontrolled, interventional, single-center trial of IFx-Hu2.0 monotherapy in six adult patients (≥ 18 years of age) with unresectable stage III or distant metastatic (stage IV) cutaneous melanoma refractory to prior therapy (chemotherapy and/or PD-1 antagonist +/- CTLA-4 antagonist therapies). Patients received a fixed dose of 0.1 mg of IFx-

Hu2.0 per lesion in up to three lesions at a single time point. Subjects were observed for any acute adverse events post injection and for any delayed adverse events at Day 28 ± 7 days.

The primary outcome was safety. The primary outcome measure was the number of Grade 3 to 5, treatment-related adverse events per CTCAE 5.0. This study accrued 6/6 evaluable patients. At the conclusion of the trial, no patient experienced any grade 3 to 5 treatment-related adverse events. One patient received injections at multiple time points. More than one patient had more than one lesion injected at a given timepoint.

Clinical data available to date (i.e., tumor tissue biopsies and blood sample analysis) is presented below from 3 of the 6 evaluable patients (P1, P3, and P4). Tumor biopsies were analyzed via fluorescent multi-color immunohistochemistry (mIHC) staining.

This interim cellular analysis indicates that:

1. all patients (3/3 patients) experienced a significant decrease in SOX10+ melanoma cells indicating melanoma cell death within the target lesion, and
2. all patients (3/3 patients) experienced a decrease in FOXP3/CD8+ regulatory T cells mediating immunosuppression correlating with an improved overall prognosis (i.e., an increased likelihood of a clinical immune response), and
3. P1 and P4 (2/3 patients) experienced hypocellularity indicating cell death within the target lesion.

Clinically, P1 went on to receive nivolumab monotherapy (PFS of 19 months and SD), P3 went on to receive talimogene laherparepvec monotherapy (PFS of 12 months and SD), and P4 went on to receive nivolumab/ipilimumab combination therapy (PFS of 12 months and PR). The study intervention exhibited a strong safety profile with no Grade 3 to 5 treatment-related adverse events per CTCAE v5.0.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

IFx-Hu2.0 primes the immune system to a broad array of patient-specific tumor antigens. When breaking tolerance to tumor-associated antigens, which are ‘self’ antigens, there is a possibility of inducing some form of autoimmunity. Since efficacy and adverse events of immunotherapies are in general mediated by the same underlying pathways and mechanisms, there may be an increased risk of autoimmunity with immunotherapies such as IFx-Hu2.0. Patients receiving immunotherapies have been reported to experience mild pyrexia, cutaneous reactions, diaphoresis, rigor, tachypnea and hypotension.

In the IFx-Hu2.0 monotherapy phase I trial (NCT03655756), eight patients were screened, seven patients were enrolled and treated, and six patients were evaluable for the primary endpoint. There was one screen failure and one death unlikely related to the study drug as determined by the principal investigator. The primary outcome measure of this trial was the rate of DLTs defined as the rate of grade 3 to 5 treatment-related adverse events (AEs) that were deemed unacceptable toxicities by the principal investigator. No grade 3 to 5 treatment-related adverse events (AE) per CTCAE v5.0 were reported (Grade 1 – mild; Grade 2 – moderate). Table 2 and Table 3 reflect all AEs observed in this trial.

Table 2 Treatment-Related AEs based on preliminary data from the IFx-Hu2.0 monotherapy phase I trial (NCT03655756)

All Treatment-Related Adverse Events (Attribution: possible to definite), n=6	Number of Patients (%)	Severity
Injection site reaction	4 (67%)	Mild to Moderate
Tumor hemorrhage	2 (33%)	Mild to Moderate
Tumor pain	1 (17%)	Moderate
Erythema	1 (17%)	Mild
Paresthesia	1 (17%)	Mild
Back pain	1 (17%)	Mild
Lymphocyte count decreased	1 (17%)	Mild
Muscle cramp	1 (17%)	Mild
Pruritus	1 (17%)	Mild
Total	6 (100%)	

Table 3 All AEs based on preliminary data from the IFx-Hu2.0 monotherapy phase I trial (NCT03655756)

All Adverse Events, n=7	Number of Patients (%)	Severity
Injection site reaction	4 (67%)	Mild to Moderate
Tumor hemorrhage	2 (33%)	Mild to Moderate
Hypertension	2 (33%)	Mild to Severe
Erythema	1 (17%)	Mild
Paresthesia	1 (17%)	Mild
Back pain	1 (17%)	Mild
Lymphocyte count decreased	1 (17%)	Mild
Muscle cramp	1 (17%)	Mild
Pruritus	1 (17%)	Mild
Anorexia	1 (17%)	Mild
Dry mouth	1 (17%)	Mild
Insomnia	1 (17%)	Mild
Flatulence	1 (17%)	Mild
Lymphedema	1 (17%)	Mild
Constipation	1 (17%)	Moderate
Tumor pain	1 (17%)	Moderate
Gastric pneumatosis	1 (17%)	Severe
Clostridial sepsis	1 (17%)	Death
Multiple organ dysfunction syndrome	1 (17%)	Death
Total	7 (100%)	

Note: Clostridial sepsis and multi organ failure was experienced by the same patient leading to death. These AEs were deemed unlikely related to the study drug based on the assessment of the principal investigator.

2.3.2 KNOWN POTENTIAL BENEFITS

Mechanism of Action

IFx-Hu2.0 is an immunomodulator and belongs to the class of noncellular, therapeutic cancer vaccines. Injection of IFx-Hu2.0 into the target lesion facilitates the localized expression of the highly immunogenic Emm55 protein by the tumor cells on their surface. This expression is readily and prominently recognized by the immune system. This initial recognition primes an immune cascade that exposes tumor-specific and tumor-associated antigens to the effector mechanisms of the immune system. The immune response becomes systemic as epitope spreading activates subsequent neoantigen recognition which in turn induces reactive T cells. Hereby injected and non-injected lesions experience a treatment effect.

Resensitizing the tumor immune microenvironment through immunomodulation with IFx-Hu2.0 could lead to an increase in tumor lymphocyte infiltration. This approach could overcome T cell exhaustion to achieve durable antitumor T cell responses for long-term tumor control (10-14).

Equine Melanoma Model

pAc/*emm55* (drug substance) monotherapy showed 73% stable disease (SD) and 27% partial response (PR) per RECIST v1.1 (n=24). Additional details regarding this study can be found in section 4.2.2.1 of the Investigator's Brochure.

B16-F10/C57BL/6NCrl Murine Melanoma Model

IFx-Hu2.0 monotherapy showed a statistically significant increase in overall survival (OS) and a decrease in tumor burden (treatment vs. control). Combination therapy with a PD-1 Antagonist showed a statistically significant reduction in tumor burden (combination therapy vs. monotherapy). Additional details regarding these studies can be found in section 4.2.1 of the Investigator's Brochure.

Phase 1 First-In-Human Trial of IFx-Hu2.0 in Stage III to IV Cutaneous Melanoma

Correlative study findings for the first three evaluable patients indicate that all patients experienced a significant decrease in SOX10+ melanoma cells indicating cell death within the target lesion, all patients experienced a decrease in FOXP3/CD8+ regulatory T cells mediating immunosuppression correlating with an improved overall prognosis (i.e. an increased likelihood of a clinical immune response), and that 2 out of 3 patients experienced hypocellularity indicating cell death within the target lesion. This preliminary efficacy signal will be further evaluated in this trial.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
Safety; i.e., to assess the safety, tolerability, and feasibility of treatment with IFx-Hu2.0 as a monotherapy in patients with skin cancer.	The primary endpoints of this trial will be the safety and feasibility of the treatment regimen. Safety will be reported using the most current version of Common Terminology Criteria for Adverse Events (CTCAE). Feasibility will be defined as the ability to treat at least 80 of the approximately 100 patients enrolled without dose-limiting toxicity (DLT).
Secondary	
To assess post-therapeutic pathological response at four weeks post-treatment.	The secondary endpoint is Pathological Response defined as a response assessment to IFx-Hu2.0 in tumor lesions excised by evaluating percent Residual Vial Tumor (%RVT), at four weeks as: • pathological complete response (pCR), • major pathological response (mPR), • partial pathological response (pPR), or • pathological non-response (pNR)
Tertiary/Exploratory	
To assess anti-tumor immunity post-treatment.	Patient samples (plasma and/or serum) will be assayed to detect tumor antigen specific antibody generation in addition to a protein biomarker discovery assay specific to immuno-oncology therapy assessments. IHC will be performed on pre- and post-treatment tissue samples to contrast the cell sub-types across time points.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multi-site, -open label, interventional, prospective, phase 1 trial to assess safety and tolerability of IFx-Hu2.0 in patients with basal cell carcinoma, or squamous cell carcinoma.

A total of approximately one hundred (100) male and/or female adult patients (greater than or equal to 18 years old), of any ethnicity and race, with at least one cutaneous squamous cell carcinoma, or basal cell carcinoma lesion accessible for direct injection, who meet all inclusion and no exclusion criteria, will be eligible for enrollment and treatment with IFx-Hu2.0.

Enrollees will receive IFx-Hu2.0 as a single intralesional injection at a single time point. The target dose will be 100 µg of plasmid DNA per lesion injected at a final dose volume of 200 µL per lesion. The injected lesion will be completely excised at the follow-up visit four weeks later, and will be biopsied for confirmation of diagnosis and for the establishment of a pathological response baseline Peripheral blood will be collected from these patients prior to treatment administration and at the follow-up visit four weeks later. These samples will be used to perform complete blood counts (CBC) and clinical chemistry tests. A urine sample will be obtained for urinalysis for protein and blood at the same frequency. Blood samples will be drawn for immune response evaluation as well.

4.2 JUSTIFICATION FOR DOSE

IFx-Hu2.0 is composed of pAc/*emm55* (plasmid DNA (pDNA)) complexed with *in vivo*-jetPEI® (linear polyethylenimine), a transfection reagent, and dextrose, a complex stabilizer. The ionic balance within the *in vivo*-jetPEI®/pDNA complexes is crucial. For effective cell entry, the complexes should be cationic. The N/P ratio is a measure of the ionic balance within the complexes and is defined as the number of Nitrogen residues of *in vivo*-jetPEI® per nucleic acid Phosphate. Approximately one in three nitrogen atoms within the *in vivo*-jetPEI® molecule is cationic. Therefore, electroneutrality of *in vivo*-jetPEI®/pDNA complexes is reached at an N/P ratio > 2 to 3. in vivo-jetPEI® is provided as a 150 mM solution (expressed as nitrogen residues). Given that 1 mcg of nucleic acid contains 3 nmoles of anionic phosphate, the amount of *in vivo*-jetPEI® to be mixed with pDNA in order to obtain a specific N/P ratio is calculated using the following formula:

$$mcL\ of\ in\ vivo - \text{jetPEI®}\ \text{to be used} = \frac{(mcg\ of\ pDNA\ x\ 3\ nmol) \times {}^{N}/_{P}\ ratio}{150\ mM}$$

The N/P ratio of 6 has been optimized for *in vitro* delivery of IFx-Hu2.0. This is the N/P ratio used for the preparation of clinical doses of IFx-Hu2.0.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Ability to receive intralesional injections
4. Male or female, aged ≥ 18 years
5. Histologically confirmed cutaneous squamous cell carcinoma, or basal cell carcinoma with accessible lesions (based on archival tissue or new tissue biopsy for histological confirmation)
6. Life expectancy of at least 24 weeks at the time of screening
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
8. Must have measurable disease greater than 3 mm
9. At least one injectable lesion
10. Adequate organ function as defined below (Note: these screening laboratory tests must be obtained within two weeks prior to the baseline visit, Day 0):
    - 10.1. Hemoglobin (Hb) >10 g/dL
    - 10.2. Absolute Neutrophil Count (ANC) >1,500 cells/mcL
    - 10.3. Platelet Count (PLT) >75,000/mcL
    - 10.4. Prothrombin Time (PT) or International Normalized Ratio (INR) ≤1.5 times the institutional ULN unless patient is receiving anticoagulant therapy as long as PT or INR is within therapeutic range of the intended use of anticoagulants.
    - 10.5. Activated Partial Thromboplastin Time (aPTT) ≤1.5 times the institutional ULN unless patient is receiving anticoagulant therapy as long as aPTT is within therapeutic range of the intended use of anticoagulants.
    - 10.6. Serum Creatinine (SCr) ≤1.5 times the institutional ULN
    - 10.7. Total Bilirubin ≤1.5 times the institutional ULN
    - 10.8. Aspartate Aminotransferase (AST) ≤3 times the institutional ULN
    - 10.9. Alanine Aminotransferase (ALT) ≤3 times the institutional ULN
    - 10.10. Lactate Dehydrogenase (LDH) ≤2 times the institutional ULN
    - 10.11. Alkaline Phosphatase (ALP) ≤2.5 times the institutional ULN
    - 10.12. Gamma GT (GGT) ≤2.5 times the institutional ULN
11. Lymphocyte count ≥500,000 cells/mL
12. For females of reproductive potential: must have a negative urine or serum pregnancy test result within 24 hours prior to receiving IFx-Hu2.0; must use highly effective contraception (e.g.,licensed hormonal or barrier methods) for at least one month prior to screening and agreement to use such a method during study participation and for an additional 26 weeks after the end of study treatment
13. For males of reproductive potential: use of barrier method or other methods to ensure effective contraception with partner

5.2 EXCLUSION CRITERIA

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

1. Concurrent participation in any other clinical trial
2. Inability to consent for self
3. Lesions on scalp with bone erosions must not be selected as injection sites for IFx-Hu2.0

4. Life expectancy of fewer than 24 weeks at the time of screening
5. Prior systemic anti-cancer treatment within three weeks from start of treatment (Day 0)
6. Treatment with any investigational product within the three weeks preceding injection
7. Concurrent chemotherapy or biological therapy. Concurrent radiotherapy is allowed as long as it is not the same site as the injected lesion.
8. Current treatment with systemic immunosuppressive corticosteroid (greater than 10 mg of daily prednisone) doses or other immunosuppressants such as those needed for solid organ transplants. Medications needed to treat conditions such as reactive airway disease are not excluded.
9. Is pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 26 weeks after the last dose of trial treatment
10. Immunizations for encapsulated bacteria were not given for patients who have undergone a splenectomy
11. Serious underlying medical or psychiatric conditions, active infections requiring the use of antimicrobial drugs, or active bleeding that would make the subject unsuitable or unable to participate in the study
12. Active Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) or Hepatitis B/C. Patients with treated HIV/AIDS or Hepatitis B/C with no evidence of active infection may be enrolled
13. History of organ allograft transplantation
14. Presence of any uncontrolled and significant medical or psychiatric condition which would interfere with trial safety assessments

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

1. Refrain from altering (i.e., initiating, modifying, or discontinuing) dietary habits (incl. diets) other than those expressly mentioned below without consulting the treating physician.
2. Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate for 6 hours before receiving IFx-Hu2.0
3. Abstain from alcohol for 24 hours before receiving IFx-Hu2.0
4. Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.
5. Abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during participation in the study (e.g., watching television, reading).
6. Minimize interactions with household contacts who may be immunocompromised.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

This study will have a goal of 100 evaluable patients. It is the intent of the study team to recruit additional patients to be screened and enrolled if any of the existing patients are lost to follow-up or withdraw consent.

Potential participants will be identified by sites through physician referrals, available recruitment databases, and other methods available to participating sites to identify potential participants. Specific recruitment materials may be developed by the sponsor. In addition, if any site decides to utilize participant-focused materials for recruitment, such materials and a usage plan will be submitted for IRB review and approval prior to implementation. A clinical enrollment manager (CEM) or sponsor designee(s) may locally support the research team and facilitate patient recruitment at the study site in addition to all other measures/efforts. Under no circumstance will referral fees, incentives, or bonuses to physicians for recruitment be allowed.

There is no specific plan to target participants based on race, gender, or age. All eligible potential participants will be approached for inclusion.

It is anticipated that recruitment will take up to 12 months to complete at approximately five research sites. Sites will be NCI-designated cancer centers, academic medical centers, clinics, and doctor's offices within the United States. Sites can include community facilities as a primary site or a satellite site of a participating center as long as they meet the requirements regarding the proper handling and administration of the investigational agent.

Due to the size and short duration of the study, there is no planned retention or compensation plan for participants. Throughout the study, participants will be reminded about upcoming visits and the procedures to be performed at the visit. New information that surfaces during the study will be communicated to participants through IRB-approved mechanisms.

In alignment with the Internal Revenue Service (IRS) 2020 Standard Mileage Rate (Notice 2020-05), participants can be reimbursed at a rate of 17 cents per mile driven in an automobile for traveling for study-related medical purposes. This will be done approximately one month after travel receipts are submitted by study staff to the sponsor.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

pAc/*emm55*, the drug substance (also known as the active pharmaceutical ingredient), is a recombinant plasmid expression vector containing the *Streptococcus pyogenes* serotype M55 (Isolate A928171) modified cell surface M virulence protein as an antigen. The plasmid backbone is derived from the Takara Bio stable, constitutive, nonviral, mammalian expression vector pAcGFP1-N1. pAc/*emm55* is expressed in *Escherichia coli* (Thermo Fischer Scientific Invitrogen™ One Shot™ Stbl3™ (derived from HB101)).

6.1.2 DOSING AND ADMINISTRATION

The amount of drug administered to the participant is 0.1mg injected into a single lesion. IFx-Hu2.0 must be administered within 4 hours of constitution (see Investigator's Brochure section 3.3).

IFx-Hu2.0 is intended for intralesional (i.e. cutaneous, subcutaneous, or lymph nodal) injection. All participants will be monitored for 30 minutes after injection for any immediate adverse events. Participants must abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 6 hours and abstain from alcohol for 24 hours before the administration of IFx-Hu2.0.

Administration

1. Avoid placing fingers near the lesion being injected to prevent needlesticks.
2. Use a single insertion point for each lesion.
3. Inject evenly throughout the lesion on multiple tracks, pulling the needle back after injecting a portion of the drug without withdrawing it from the lesion, then rotating it radially on another track until the entire lesion is treated. If the lesion is resistant to drug injection, apply slow, steady pressure, moving the needle slightly as needed. Local anesthetic should not be injected into the lesion or the surrounding tissue, since it may alter pH and therefore drug stability.
4. Withdraw the needle slowly to reduce the risk of drug leakage.
5. Clean the injection site and surrounding area with an alcohol pad.

A single dose (0.1mg) will be used in this trial and at a single timepoint, therefore no dose escalation or reduction is proposed.

6.1.3 STUDY PROCEDURES AND SCHEDULE

Participant engagement will involve a screening period, baseline visit, and follow-up/final study visit for a total of three visits. The total duration of participation for each individual participant is expected to be approximately six weeks. A snapshot of the study schedule of events can be found in section 1.3.

Screening (Day -14 to Day -1)

1. Obtained signed, informed consent (if not obtained prior to this visit)

2. Demographic information
3. Medical history
4. Concomitant medications
5. Physical exam, including vital signs, height, weight
6. ECOG performance status
7. Electrocardiogram (ECG)
8. Tumor lesion measurement
9. Tumor biopsy for histologic confirmation of carcinoma diagnosis
   9.1. If a diagnostic biopsy has previously been performed, the report of the biopsy resultsof the tissue block would be acceptable to confirm diagnosis
10. Electrocardiogram (ECG)
11. Laboratory tests
    11.1. Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT) and activated partial thromboplastin time (aPTT)
    11.2. Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Thyroid tests (TSH and FT4)
    11.3. Urinalysis: UA with microscopic evaluation
    11.4. Anti-double-stranded DNA (anti-dsDNA) antibody test
    11.5. Anti-DNase B Titer, Serum
12. Serum pregnancy tests for females of reproductive potential

Baseline (Visit 1; Day 0)

1. Concomitant medications
2. ECOG performance status
3. Physical exam, including vital signs, weight
4. Laboratory tests
   4.1. Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT) and activated partial thromboplastin time (aPTT)
   4.2. Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Thyroid tests (TSH and FT4)
   4.3. Urinalysis: UA with microscopic evaluation
   4.4. Anti-double-stranded DNA (anti-dsDNA) antibody test
   4.5. Anti-DNase B Titer, Serum
5. Adverse event recording per CTCAE v5.0
6. Tumor lesion measurement (longest diameter)
7. Urine pregnancy tests for females of reproductive potential; done within 24 hours prior to IFx-Hu2.0 administration, and results must be available prior to IFx-Hu2.0 administration

8. 40 mL of blood for exploratory analysis
9. IFx-Hu2.0 administration

Final Visit (Day 28 ± 5 days) or Early Termination Visit

1. Concomitant medications
2. ECOG performance status
3. Physical exam, including vital signs, weight
4. Electrocardiogram (ECG)
5. Laboratory tests
   5.1. Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT) and activated partial thromboplastin time (aPTT)
   5.2. Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Thyroid tests (TSH and FT4)
   5.3. Urinalysis: UA with microscopic evaluation
   5.4. Anti-double-stranded DNA (anti-dsDNA) antibody test
   5.5. Anti-DNase B Titer, Serum
6. Adverse event recording per CTCAE v5.0
7. Tumor lesion measurement (longest diameter)
8. Serum pregnancy tests for females of reproductive potential
9. 40 mL of blood for immune response evaluation
10. Tumor excision (wide local excision) for pathological response (final)

Unscheduled Visit

If participants require a visit between the baseline and final study visits, then the following procedures may be performed, as indicated (per investigator discretion):

1. Concomitant medications
2. ECOG performance status
3. Physical exam, including vital signs, weight
4. Electrocardiogram (ECG)
5. Laboratory tests
   5.1. Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT) and activated partial thromboplastin time (aPTT)
   5.2. Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Thyroid tests (TSH and FT4)
   5.3. Urinalysis: UA with microscopic evaluation
   5.4. Anti-double-stranded DNA (anti-dsDNA) antibody test
   5.5. Anti-DNase B Titer, Serum
6. Adverse event recording per CTCAE v5.0

7. Tumor lesion measurement (longest diameter)
8. Serum or urine pregnancy tests for females of reproductive potential

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

IFx-Hu2.0, the drug product, is composed of pAc/*emm55*, an immunomodulator, complexed with Polyplus in vivo-jetPEI® (linear polyethylenimine), a transfection reagent, and dextrose, a complex stabilizer. After compounding IFx-Hu2.0 per the Pharmacy Manual at the Investigational Drug Services (IDS) pharmacy, each vial contains 0.2 mg of pAc/*emm55* in 0.4 mL of solution.

The sponsor provides IFx-Hu2.0 as a vaccine kit with finished drug product preparation instructions and consumables (except for the final clinical site-supplied syringe for direct patient care).

To request vaccine kits delivered to the site, the site personnel should complete the investigational product (IP) requisition form (Appendix A) and email it to IP-Requisition@Morphogenesis-Inc.com. Whenever the sponsor distributes IP to a site, a sponsor-initiated IP distribution form will accompany the order and require the dated signature of the receiving site personnel.

Any unused IFx-Hu2.0 vaccine kits will be reverse-distributed by the site to the sponsor under the following conditions:

a) A vaccine kit has met its retest date,
b) The participation of the primary investigator at the clinical site has been discontinued,
c) The participation of the clinical site has been discontinued, or
d) The trial has been completed.

To reverse distribute the unused vaccine kits from the site to the sponsor, site personnel should complete the IP reverse distribution form (Appendix B of the Pharmacy Manual), schedule delivery with the carrier noted on this form, copy the completed form for his or her own records and include the original, completed form in the delivery to the sponsor.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The sponsor provides the investigational product (IP) as a vaccine kit with drug product preparation instructions and consumables (except for the final clinical site-supplied syringe for direct patient care).

Up-to-date information regarding the IP formulation, appearance, packaging, and labeling can be found in the Pharmacy Manual.

6.2.3 PRODUCT STORAGE AND STABILITY

Store the IFx-Hu2.0 vaccine kits and their contents refrigerated at 2 – 8°C.

The prepared drug product must be administered intralesionally within 4 hours from the time of complexing and final incubation.

6.2.4 PREPARATION

Store all IFx-Hu2.0 vaccine kits and their contents refrigerated at 2 – 8°C. Remove vaccine kits from the refrigerator as needed when ready to prepare drug product. One vaccine kit makes a fixed dose for one intralesional injection. Perform each step aseptically in a primary engineering control (PEC) (i.e., a vertical laminar airflow workbench in an International Organization for Standardization [ISO] 5 environment) whenever feasible. Follow the current official United States Pharmacopeia (USP) <797> chapter as well as the instructions in the Pharmacy Manual to prepare one single-dose vial of IFx-Hu2.0.

6.3 STUDY INTERVENTION COMPLIANCE

To document study drug administration, vial identification information, time of administration, and any notes regarding the injection(s) will be documented by the administering investigator on the drug administration case report form. Study drug compliance will be reviewed by the study monitors and the principal investigator.

6.4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications, and supplements taken during participation and over 90 days prior to enrollment.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE). Subjects with treatment-related toxicity will be followed for the ongoing drug-related adverse events until resolved, return to baseline, deemed irreversible by the treating physician, the subject has been properly referred to an appropriately licensed practitioner for further evaluation and treatment, or until the subject is lost to follow up, withdrawal of study consent, removal of the subject from the trial by the treating physician, or start of a subsequent anti-cancer therapy.

The data to be collected at the time of study intervention discontinuation will include the following:

1. Concomitant medications
2. ECOG performance status
3. Physical exam, including vital signs, height, weight
4. Laboratory tests
   - 4.1. Hematology: CBC - hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count; blood clotting tests: prothrombin time (PT) and activated partial thromboplastin time (aPTT)
   - 4.2. Biochemistry: CMP - glucose, calcium, albumin, total protein, sodium, potassium, CO2, chloride, BUN, creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), Thyroid tests (TSH and FT4)
   - 4.3. Urinalysis: UA with microscopic evaluation
   - 4.4.
   - 4.5. Anti-double-stranded DNA (anti-dsDNA) antibody test
   - 4.6. Anti-DNase B Titer, Serum
5. Adverse event recording per CTCAE v5.0
6. Tumor lesion measurement (longest diameter)
7. Serum pregnancy tests for females of reproductive potential
8. 40 mL of blood for immune response evaluation
   - 8.1. Tumor biopsy for pathological response (final)

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

1. Pregnancy

2. Significant study intervention non-compliance
3. If any clinical adverse event (AE), 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
4. Disease progression
5. If the participant meets an exclusion criterion or fails to meet an inclusion criteria (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the case report form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for scheduled visit(s) 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:

1. The site will attempt to contact the participant and reschedule the missed visit 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.
2. 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 or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
3. 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 SAFETY AND OTHER ASSESSMENTS

This study will comply with all applicable regulations on IND safety reporting requirements to the FDA in accordance with 21 CFR 312.32. This study will utilize CTCAE v5.0 for toxicity and AE reporting. All appropriate treatment areas at the clinical sites will have access to a copy of the CTCAE v5.0. Careful evaluation to determine the toxicity IFx-Hu2.0 as a monotherapy will be performed. Adverse events will be documented beginning at initiation of treatment (Day 0) as well as at the follow-up visit whether that be end of study as planned or early termination.

Subjects with treatment-related toxicity will be followed for the ongoing drug-related adverse events until resolved, return to baseline, deemed irreversible by the treating physician, the subject has been properly referred to an appropriately licensed practitioner for further evaluation and treatment, or until the subject is lost to follow up, withdrawal of study consent, removal of the subject from the trial by the treating physician, or start of a subsequent anti-cancer therapy.

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE) (21 CFR 312.32(A))

An AE is defined as any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

An ongoing or intermittent adverse event should be recorded only once, with the highest/worst grade reported for the event. This study will utilize the Common Terminology Criteria for Adverse Events version 5 (CTCAE v5) for toxicity and adverse event reporting.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE) (21 CFR 312.32(A))

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, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect in the offspring of a participant. 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.3.1 SEVERITY OF EVENT

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity:

1. **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
2. **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
3. **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator 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.

1. **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 (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive., with use of a satisfactory rechallenge procedure if necessary.
2. **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.
3. **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.
4. **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).

5. **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.

8.2.3.3 EXPECTEDNESS

The medical monitor will be responsible for determining whether an 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 described in the current Investigator Brochure for IFx-Hu 2.0.

8.2.4 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.

All AEs including local and systemic reactions 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.

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 a pre-existing condition deteriorates at any time during the study, it will be recorded as an AE, with use of descriptors in the AE term to designate that it is a pre-existing condition (e.g., worsening of or exacerbation of)

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.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. 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.

8.2.5 ADVERSE EVENT REPORTING

Adverse events will be documented. The principal investigator at the site is responsible for notifying the sponsor of any adverse event as soon as possible. The medical monitor will review all adverse event reports and ensure that participants are receiving appropriate clinical care and identify any potential safety concerns. The medical monitor will assess the information provided to determine the relatedness of the event to the study intervention as well as propose any changes to the protocol and/or consent form based on the event. All adverse events will be documented and reported to the FDA in the annual report. Adverse events that meet the requirements for reporting to the IRB will be reported within the guidelines required by the IRB of record, along with necessary supporting information and revised trial documentation, as necessary.

8.2.6 SERIOUS ADVERSE EVENT REPORTING

Serious events will be documented on the current OMB approved FDA Form 3500A following the current instructions for reporting. The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure. The report must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis).

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

The medical monitor will review all adverse event reports and ensure that participants are receiving appropriate clinical care and identify any potential safety concerns. The medical monitor will assess the information provided to determine the relatedness of the event to the study intervention as well as propose any changes to the protocol and/or consent form based on the event. 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.

8.2.7 REPORTING OF EVENTS TO PARTICIPANTS

Changes in the risk profile and/or risk/benefit ratio from observed adverse and/or serious adverse events will be communicated to participants through an IRB-approved revised consent form or addendum, as deemed appropriate given the information to be provided. If re-consent of the participants is required for continued participation, it must be obtained prior to continuing study related procedures.

8.2.7 REPORTING OF PREGNANCY

All females of reproductive potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

All investigators are required to report any pregnancy that occurs during the study within 24 hours of learning of the pregnancy. The site shall complete the Pregnancy Report Form and forward to the Sponsor’s safety vendor Drug Safety Navigator (DSN).

The investigator is not obligated to actively seek pregnancy information in former study participants, but if the investigator learns of a pregnancy through spontaneous reporting, a Pregnancy Report Form must be completed and faxed to DSN.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The null hypothesis is that IFx-Hu2.0 may not be given safely as a neoadjuvant to patients with cutaneous squamous cell carcinoma, or basal cell carcinoma.

The alternative hypothesis is that IFx-Hu2.0 may be given safely as a neoadjuvant to patients with cutaneous squamous cell carcinoma, or basal cell carcinoma.

9.2 SAMPLE SIZE DETERMINATION

The intent of this study is to enroll approximately 100 evaluable patients to assess the safety of IFx-Hu2.0 as a monotherapy. A sample size of 100 has the following precision for estimation of DLT rates ranging from 0.1 to 0.5. A DLT is defined as an adverse event equal to or greater than grade 3, at least possibly related to the investigational agent, occurring within a 4-week period following IP administration, and deemed as having unacceptable toxicity by the principal investigator and/or medical monitor. Precision is measured by 1-sided 95% upper confidence limit on the estimated DLT rate via exact binomial distribution. For example, if no DLT is observed in patients on IFX-Hu 2.0, then the true underlying DLT rate is lower than 0.099 with 95% confidence.

9.3 POPULATIONS FOR ANALYSES

Safety Analysis Dataset: the subset of participants who received at least one dose of study intervention.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

This is a safety and feasibility study that is designed to evaluate the safety and feasibility of IFx-Hu2.0 use as monotherapy. Safety will be assessed and reported based upon CTCAE v5.0 criteria. Feasibility will be defined as the ability to treat at least 80 of the 100 patients enrolled without dose-limiting toxicity.

The secondary endpoint is Pathological Response defined as a response assessment to IFx-Hu2.0 in tumor lesions excised at four weeks as; pathological complete response (pCR), major pathological response (mPR), partial pathological response (pPR), or pathological non-response (pNR) by evaluating percent Residual Vial Tumor (%RVT)(15).

9.4.2 SAFETY ANALYSES

Maximum planned sample size	100
The event probability (ϑ)	0.2
Desired probability of early stopping	0.05

The trial will be stopped if the number of Dose Limiting Toxicities (DLTs) is equal to or exceeds b_n out of n patients with completed follow-up.

Number of Patients, *n*	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Boundary, b_n	-	-	3	4	4	5	5	6	6	6	7	7	7	8	8	8	9	9	9	10
Number of Patients, *n*	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**
Boundary, b_n	10	10	11	11	11	11	12	12	12	13	13	13	13	14	14	14	15	15	15	15
Number of Patients, *n*	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**53**	**54**	**55**	**56**	**57**	**58**	**59**	**60**
Boundary, b_n	16	16	16	17	17	17	17	18	18	18	18	19	19	19	20	20	20	20	21	21
Number of Patients, *n*	**61**	**62**	**63**	**64**	**65**	**66**	**67**	**68**	**69**	**70**	**71**	**72**	**73**	**74**	**75**	**76**	**77**	**78**	**79**	**80**
Boundary, b_n	21	21	22	22	22	22	23	23	23	23	24	24	24	24	25	25	25	25	26	26
Number of Patients, *n*	**81**	**82**	**83**	**84**	**85**	**86**	**87**	**88**	**89**	**90**	**91**	**92**	**93**	**94**	**95**	**96**	**97**	**98**	**99**	**100**
Boundary, b_n	26	26	27	27	27	27	28	28	28	28	29	29	29	29	30	30	30	30	31	31

This boundary is equivalent to testing the null hypothesis, after each patient, that the event rate is equal to 0.2, using a one-sided level 0.008340 test.

Sequential boundaries will be used to monitor dose-limiting toxicity rate. The accrual will be halted if excessive numbers of DLTs are seen, that is, if the number of DLTs is equal to or exceeds b_n out of n patients with full follow-up. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most [probability of early stopping] when the rate of DLTs is equal to the acceptable rate [event probability θ] (16).

θ	**ϕ***	**E[Y]**	**SD[Y]**	**E[N]**	**SD[N]**	**E[Y/N]**	**SD[Y/N]**
0.20	0.0497	19.31	4.40	96.58	16.21	0.21	0.10
0.30	0.6116	20.12	7.86	67.08	34.29	0.37	0.16
0.40	0.9883	11.85	6.31	29.65	22.10	0.50	0.18
0.50	1.0000	7.61	3.56	15.22	10.91	0.61	0.19
0.60	1.0000	5.71	2.31	9.52	6.29	0.71	0.19
0.70	1.0000	4.62	1.63	6.60	3.96	0.79	0.17
0.80	1.0000	3.89	1.14	4.86	2.51	0.87	0.14
0.90	1.0000	3.37	0.69	3.74	1.41	0.94	0.11
1.00	1.0000	3.00	0.00	3.00	0.00	1.00	0.00

Definitions:
Y = the number of events, random, between 0 and N
N = the number of patients, random, between 1 and K
ϕ* = the actual probability of early stopping (hitting the boundary)
E[ ] denotes the expected value (mean)
SD[ ] denotes the standard deviation

Resource: http://cancer.unc.edu/biostatistics/program/ivanova/ContinuosMonitoringForToxicity.aspx

The medical monitor will provide recommendations for proceeding with the study to the clinical team and study sponsor. The study sponsor will inform the FDA of the temporary halt and the disposition of the study.

9.4.3 BASELINE DESCRIPTIVE STATISTICS

Study cohorts and groups will be compared on baseline characteristics, including demographics and laboratory measurements, using descriptive statistics.

9.4.4 EXPLORATORY ANALYSES

The tumor-specific immune response elicited by the investigational therapy will be assessed based on laboratory correlative studies performed on liquid biopsies and tumor biopsies pre- and post-treatment.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Written documentation of informed consent, including detailed description of the study agent, study procedures, and risks, is required prior to performing any study related procedures.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their 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 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 signed 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. If additional new information surfaces throughout the study that may affect the participant's willingness or ability to continue, it will be provided to them.

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 the 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

- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of the utility pathologic response assessment
- 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 is strictly held in trust by the participating investigators, their staff, and the sponsor and their agents. 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 the prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies (including the Food and Drug Administration [FDA]) or pharmaceutical company supplying study product 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 2 years after the completion of an BLA filing or determination not to pursue, or as long a period as dictated by the reviewing IRB, Institutional policies, if longer.

Data will be captured in a 21 C.F.R. § 11-compliant electronic data capture (EDC) system. The EDC system will be reviewed periodically by sponsor-designated monitors throughout the conduct of the trial per the clinical trial agreement and the monitoring plan. This review will include source data verification utilizing patients' medical records.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored by the sponsor. After the study is completed, the de-identified, archived data will be stored by the sponsor.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored by the sponsor. These samples would be used to research the response to IFx-Hu2.0 by evaluating tumor-specific immune responses post-treatment.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent regarding biosample storage may not be possible after the study is completed.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Study leadership will be the responsibility of the PI and the clinical coordinator in collaboration with the study sponsor and/or its representative. Study leadership will meet periodically as needed.

This trial will be monitored continuously by the PI, who will be assisted by the assigned clinical trial coordinator.

Study Sponsor	Patricia D. Lawman, PhD Chief Executive Officer Morphogenesis, Inc. 10500 University Center Dr, Ste 110 Tampa, FL 33612-6419 813-875-6600 ext. 102 *plawman@morphogenesis-inc.com*
Medical Monitor	Georgia Latham, MD Peachtree Bioresearch Solutions, Inc. 4985 Lower Roswell Rd, #100 Marietta GA 30068-4337 336-707-2170 *georgia.latham@peachtreebrs.com*
Institutional Review Board	Advarra 6940 Columbia Gateway Dr, Ste 110 Columbia, MD 21046-2878 410-884-2900
Contract Research Organization	Peachtree Bioresearch Solutions, Inc. 4985 Lower Roswell Rd, #100 Marietta GA 30068-4337 678-373-4660

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the medical monitor and the Sponsor's designated Drug Safety Unit. The medical monitor reviews and evaluates safety and/or efficacy data on an ongoing basis to ensure the safety of patients and the validity and integrity of data. The medical monitor reviews SAEs, deviations, Interim analysis and final report forms, and can make the following determinations, Accepted, Acceptable with Corrective Action, or Tabled. The PI shall provide a report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study, as often as is applicable.

10.1.7 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects 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 good clinical practice (GCP), and with applicable regulatory requirements.

The site PIs and the Clinical Research Coordinator assigned to the case will be responsible for collecting all study data and maintaining all study-related documents, including the Investigator's Study File (ISF) and patient Case Report Forms (CRFs). All CRF entries will be made by the study site into the sponsor-provided EDC. eCRFs will be verified by the sponsor-contracted monitor against both paper source documentation and electronic medical records (EMR). The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

Regulatory documents will be reviewed and CRFs will be monitored by the CRA according to Standard Operating Procedures (SOPs). Monitoring will be performed regularly for accuracy, completeness, and 100% source data verification, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and all applicable regulatory requirements.

To ensure adherence to the protocol, monitoring reports will be submitted to the sponsor according to the timelines specified in the Clinical Monitoring Plan (CMP).

10.1.8 COMPENSATION FOR RESEARCH-RELATED INJURY

Participants will be asked to notify study staff immediately if they become ill or are injured during study participation. The sponsor will pay for those medical expenses necessary to treat a participant's research-related injury that is not covered by medical insurance or any other third-party coverage. Participants are notified in the informed consent form that they will not lose any legal rights or release any research personnel of liability by signing the informed consent form. Participants will also be notified that insurance and Medicare information (if applicable) will be collected for treatment and reporting purposes.

10.1.9 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality Control (QC) procedures will be implemented beginning with the Data Management provider 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 for clarification/resolution.

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 clinical site(s) will provide direct access to all trial-related sites, source data/documents, and reports, for the purpose of monitoring and auditing by the sponsor and the sponsor's designee and for inspection by local and regulatory authorities.

10.1.10 DATA HANDLING AND RECORD KEEPING

10.1.10.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

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

Hardcopies of the study visit worksheets will be provided for use as 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 AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by the sponsor. 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.

10.1.10.2 STUDY RECORDS RETENTION

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.

10.1.11 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or current clinical practice requirements at the clinical site. 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, and 4.5.3
- 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 to use continuous vigilance to identify and report deviations within seven working days of identification of the protocol deviation or within seven working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff are responsible for knowing and adhering to IRB requirements.

10.1.12 PUBLICATION AND DATA SHARING POLICY

This study will adhere with the details set forth in the clinical trial agreements between Morphogenesis, Inc. (sponsor) and the clinical site(s) as it pertains to the sharing and publication of clinical research data.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy and the Section 801 of the Food and Drug Administration Amendments Act of 2007 requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine.

10.1.13 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 trial.

10.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure

ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.1	27 Oct 2020	Original version	n/a
2.0	11 May 2021	Updates and revisions prior to patient enrollment: • Eliminated the pre-treatment tissue requirement • Week 0 pregnancy test requirement changed from serum to urine	Clarification, feasibility, current investigational product safety information, and relevance to patient population

		• Updated required laboratory tests • Amended post-injection observation time from four hours to 30 minutes • Revised the consenting policy	
3.0	02 Jun 2021	• Removed cutaneous melanoma from the list of indications to be studied under this protocol • An exclusion criterion was added to not inject lesions on scalp with bone erosions • An exclusion criterion was added to not enroll patients with active HIV/AIDS or hepatitis B/C • The DLT definition was revised to include all AEs at least "possibly" related to the IP • Added testing for HIV/AIDS and hepatitis B/C	This was done in response to the FDA review team's feedback from 25 May 2021

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