STATISTICAL ANALYSIS PLAN

Final v1.0

Protocol SC 2020-01 (Version 3.0, 02JUN2021)

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

Date: October 26, 2021

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LIST OF ABBREVIATIONS

%RVT	***Percent Residual Vial Tumor***
AE	***Adverse Events***
ANCOVA	***Analysis of Covariance***
CI	***Confidence Interval***
CTCAE	***Common Terminology Criteria for Adverse Events***
DLT	***Dose Limiting Toxicity***
DPS	***Data Presentation Specification***
DSMB	***Data Safety Monitoring Board***
ITT	***Intend-to-Treat***
ICH	***International Committee for Harmonization***
IP	***Investigational Product***
LSMEANS	***Least-squares Means***
MedDRA	***Medical Dictionary for Drug Regulatory Affairs***
PBRS	***Peachtree BioResearch Solution***
PT	***Preferred Term***
SAE	***Serious Adverse Events***
SAP	***Statistical Analysis Plan***
SAS	***Statistical Analysis System***
SD	***Standard Deviation***
SOC	***System Organ Class***
TEAE	***Treatment emergent adverse events***
US	***United States***

1. INTRODUCTION

1.1 Objectives

Primary Objective:

- To assess safety and feasibility

Secondary Objectives:

- To assess post-therapeutic pathological response

Exploratory Objectives:

- To assess anti-tumor immunity post-treatment.

1.2 Design

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.

2. ELABORATION OF STUDY PROTOCOL

2.1 Study Populations

- Safety Analysis Dataset: the subset of participants who received at least one dose of study intervention (IFx-Hu2.0). All safety analyses will be conducted on Safety Analysis Set.

2.2 Study Endpoints

2.2.1 *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).

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.

2.2.2 *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))

2.2.3 *Exploratory Endpoint*

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.

2.3 Sample Size

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.

3. STATISTICAL METHODS

3.1 General

All data will be analyzed using the Statistical Analysis System (SAS®; Version 9.2 or higher). Continuous variables will be summarized using descriptive statistics, including sample size, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number and percent of subjects for each outcome.

All statistical tests will be two sided, and statistical significance level is 0.05.

3.2 Subject Disposition, Demographics and Baseline Characters

- Reasons for withdrawal will be summarized.
- Demographics and baseline characters will be summarized on safety analysis set using descriptive statistics.
- Medical history will be summarized with MedDRA system organ class (SOC) and preferred term (PT) for Safety analysis set.
- Prior and concomitant medications will be summarized with WHO Drug Class 3 name for Analysis of Study Endpoints

3.2.1 *Safety Analysis*

The safety analysis will be conducted on safety analysis set that includes all treated subjects.

Safety endpoints will be analyzed as summary statistics during treatment and/or as change scores from baselines such as shift tables. Treatment emergent adverse events (TEAEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). TEAE severity and relationship to study treatment will be presented by dose cohort, MedDRA system organ class (SOC) and preferred term (PT).

The information reported about each AE will be the start date, stop date, severity, relationship, outcome, and duration). AEs leading to premature discontinuation from the study and serious treatment emergent AEs will be presented with either a summary table or a data listing.

- **Adverse Events**

TEAEs are defined as signs or symptoms that emerge during treatment or within 28 days of the last dose of Investigational Product, including those signs and symptoms that have been absent pre-treatment or that have worsened relative to the pre-treatment assessment. Any adverse event considered related to treatment will also be considered a TEAE, regardless of the elapsed time since the last dose of Investigational Product.

Number and percentage of subject with any DLT will be reported by dose cohort, MedDRA SOC and PT. Overall DLT rate for safety analysis set will be provided with 95%CI.

Number and percentage of subject with any TEAEs will be summarized by MedDRA SOC, PT, intensity, and relationship to the study treatment.

Number and percentage of subject with serious TEAE will also be summarized and listed.

- **Vital Signs**

The observed vital signs at each visit and the change from baseline to each post-baseline visit will be summarized by cohort using descriptive statistics.

- **Physical Examination**

Abnormal findings in the physical examination will be summarized by dose cohort using descriptive statistics.

- **Clinical Laboratory Tests**

Clinical laboratory test values outside the normal range and clinically significant abnormal range will be flagged in the data listing. Laboratory data will be summarized by cohort using shift tables (baseline to notable post-baseline visit). The change from baseline will be summarized using descriptive statistics.

- **ECOG**

The data observed from ECOG performance status will be summarized appropriately.

- **ECG**

The results of ECGs will be summarized appropriately.

3.3.2. Exploratory Analyses

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.

3.3.3. Subgroup Analyses

No subgroup analyses of safety endpoints will be planned.

3.4. Handling of Missing Data

Missing data will not be imputed for safety analyses.

3.5. Protocol Deviations

Listing for all protocol deviations will be provided.

3.6. Interim Analyses

Interim analysis will not be planned.

3.7. Key Data Items

Study Analysis Population Definition:

- Safety analysis set: All enrolled patients who have received at least 1 dose of IFx-Hu2.0.

Important Derived Variables:

- Age = (Screening Date – Date of Birth +1)/365.25.
- Prior Medications and Treatments: the medications and treatments started before enrolled to the study.
- Concomitant Medication and Treatments: the medications and treatments started after being enrolled to the study.
- Baseline: Day 0 (Baseline Visit). All clinical measurements collected at Day 0 or before the dose of IFx-Hu2.0 on Day 0 will be analyzed as baseline.
- Post Baseline (post dose): All clinical measurements collected after the dose of IFx-Hu2.0 on Day 0 will be analyzed as post baseline.
- Dose-Limiting Toxicity (DLT): Treatment emergent adverse event (TEAE) equal to or greater than grade 3, at least possibly related to the investigational agent, occurring within a 4-week period following IFx-Hu2.0 administration

3.8. Change to Planned Protocol Analysis

Not applicable.

4. OUTPUT PLANNED FOR THE STUDY REPORT

4.3. Tables to be Included in Study Report

In the following sections, the different results are presented in the order in which it is planned to make them appear in the study report.

The table templates are available in the Appendix of the SAP. The content shown in the templates is only meant as an example. It is not based on real study data or details concerning design.

4.3.2. Summary of Subject Information

Table 14.1.1.1 Subject Disposition – Safety Analysis Set

4.3.3. Demographic and Other Baseline Characteristics

Table 14.1.2.1 Summary of Demographics – Safety analysis set

Table 14.1.2.2 Number (%) of Subjects with Medical History by MedDRA System Organ Class and Preferred Term - Safety Analysis Set

Table 14.1.2.3 Number (%) of Subjects with Current Medical Conditions by MedDRA System Organ Class and Preferred Term - Safety Analysis Set

Table 14.1.2.4 Number (%) of Subjects with Prior Medications by WHO Drug Class 3 Name and Preferred Term - Safety Analysis Set

Table 14.1.2.5 Number (%) of Subjects with Concomitant Medications by WHO Drug Class 3 Name and Preferred Term - Safety Analysis Set

4.3.4. Summary of Safety Endpoints

Table 14.3.1.1 Overall Summary of Adverse Events - Safety Analysis Set

Table 14.3.1.2 Number (%) of Subjects with TEAEs by SOC and PT - Safety Analysis Set

Table 14.3.1.3 Number (%) of Subjects with DLT by MedDRA SOC and PT – Safety Analysis Set

Table 14.3.1.4 Number (%) of Subjects with Serious TEAE by MedDRA SOC and PT – Safety Analysis Set

Table 14.3.1.5 Number (%) of Subjects with Study Treatment Related TEAE by MedDRA SOC and PT – Safety Analysis Set

Table 14.3.1.6 Number (%) of Subjects with Immune Response Treatment Emergent Adverse Events – Safety Analysis Set

Table 14.3.1.7 Number (%) of Subjects with TEAE by MedDRA Preferred Term and Overall Frequency – Safety Analysis Set

Table 14.3.2.1Summary of Chemistry Laboratory Tests by Visit - Safety Analysis Set

Table 14.3.2.2 Summary of Hematology Laboratory Tests by Visit - Safety Analysis Set

Table 14.3.2.3 Summary of Urinalysis Laboratory Tests by Visit - Safety Analysis Set

Table 14.3.2.4 Summary of Qualitative Urinalysis Laboratory Tests by Visit - Safety Analysis Set

Table 14.3.2.5 Shift Tables of Laboratory Results from Baseline to the Worst Post-Baseline Visit (Chemistry) - Safety Analysis Set

Table 14.3.2.6 Shift Tables of Laboratory Results from Baseline to the End of Study (Chemistry) - Safety Analysis Set

Table 14.3.2.7 Shift Tables of Laboratory Results from Baseline to the Worst Post-Baseline Visit (Hematology) - Safety Analysis Set

Table 14.3.2.8 Shift Tables of Laboratory Results from Baseline to the End of Study (Hematology) - Safety Analysis Set

Table 14.3.2.9 Shift Tables of Laboratory Results from Baseline to the Worst Post-Baseline Visit (Urinalysis) - Safety Analysis Set

Table 14.3.2.10 Shift Tables of Laboratory Results from Baseline to the End of Study (Urinalysis) - Safety Analysis Set

Table 14.3.3.1 Summary of Vital Signs and Change from Baseline - Safety Analysis Set

Table 14.3.4.1 Number (%) of Subject with Abnormal Physical Examinations - Safety Analysis Set

Table 14.3.5.1 Number (%) of Subject with ECOG Performance Status - Safety Analysis Set

Table 14.3.6.1 Number (%) of Subject with Abnormal ECG - Safety Analysis Set

Table 14.3.7.1 Summary of Pathological Response - Safety Analysis Set

4.4. Figures to be Included in the Clinical Study Report

No figures are planned for this study.

4.5. Listings to be Included in the Clinical Study Report

4.5.2. Listings of subject information

Listing 16.2.1.1 Subject Disposition - Safety Analysis Set

Listing 16.2.2.1 Protocol Deviations - Safety Analysis Set

4.5.3. Demographics and Baseline Characters

Listing 16.2.4.1 Demographic and Baseline Characteristics - Safety Analysis Set

Listing 16.2.4.2 Subjects with Past and Current Medical Conditions - Safety Analysis Set

Listing 16.2.4.3 Subjects with Prior Medications - Safety Analysis Set

Listing 16.2.4.4 Subjects with Concomitant Medications - Safety Analysis Set

Listing 16.2.4.5 Subjects with Disease Characteristics for Primary Tumor Type – Safety Analysis Set

4.5.4. Study Drug Exposure

Listing 16.2.5.1 Study Drug Exposure – Safety Analysis Set

4.5.5. Lesion Evaluation

Listing 16.2.6.1 Injected Lesion Evaluation – Safety Analysis Set

4.5.6. Listings of safety data

Listing 16.2.7.1 Treatment Emergent Adverse Events - Safety Analysis Set

Listing 16.2.7.2 Serious Treatment Emergent Adverse Events - Safety Analysis Set

Listing 16.2.7.3 Treatment Emergent Adverse Events of DLT – Safety Analysis Set

Listing 16.2.7.4 Study Treatment Related Adverse Events – Safety Analysis Set

5. REFERENCES

Protocol: Phase 1 Trial of IFx-Hu2.0 to Evaluate Safety in Patients with Skin Cancer, Version 3.0, 02 Jun 2021, Morphogenesis, Inc.

6. ATTACHMENT: THE SHELLS OF TABLES, FIGURES AND LISTINGS PLANNED FOR CLINICAL STUDY REPORT

Approval for Statistical Analysis Plan

Title:	**Phase 1 Trial of IFx-Hu2.0 to Evaluate Safety in Patients with Skin Cancer**
Reference:	**SC 2020-01/SAP**
Version:	**1.0**
Date effective:	
Author:	**Dion Chen PhD., Peachtree BRS**

Author's signature: Dion Chen Date: 10/27/2021

The above Statistical Analysis Plan has been reviewed and approved by the Sponsor:

Name of Reviewer/Approver	**Ashraf Dehlawi**
Position:	**Sr. Director of Development Operations, Morphogenesis, Inc.**

Signature for sponsor: Ashraf Dehlawi Date: 10/28/2021

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