STATISTICAL ANALYSIS PLAN

PROTOCOL FRV-002

A randomized multicenter Phase II trial to evaluate the safety and immunogenicity of two doses of vaccination with Folate Receptor Alpha peptides with GM-CSF in patients with Triple Negative Breast Cancer defined as primary tumor that is Her2-neu negative and low (≤10%) ER/PR nuclear staining

Protocol Number: **Protocol Version and Date:**	FRV-002 Original Protocol: 07 October 2015 Protocol Amendment 1 (Edition 02): 30 November 2015 Protocol Amendment 2 (Edition 03): 16 June 2016 Protocol Amendment 3: 30 November 2016 Protocol Amendment 4 (Edition 04): 05 December 2016 Protocol Amendment 5 (Edition 05): 24 April 2017 Protocol Amendment 6 (Edition 06): 04 February 2019
Name of Test Drug:	TPIV200 (hu-FRα peptide vaccine with GM-CSF adjuvant)
Phase:	Phase II
Methodology:	Open-label, Randomized, Parallel groups trial
Sponsor:	Marker Therapeutics, Inc. 3200 Southwest Freeway, Suite 2240 Houston, TX 77027
Sponsor Representative:	Richard T. Kenney, MD, FACP Marker Therapeutics Medical Monitor
Analysis Plan Date:	31 October 2019
Analysis Plan Version:	Version 1.0

APPROVAL SIGNATURE PAGE

Protocol Title: A randomized multicenter Phase II trial to evaluate the safety and immunogenicity of two doses of vaccination with Folate Receptor Alpha peptides with GM-CSF in patients with Triple Negative Breast Cancer defined as primary tumor that is Her2-neu negative and low (≤ 10%) ER/PR nuclear staining

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Protocol Number: FRV-002

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Date: 13 FEB 2020

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidances and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report.

Sponsor Signatory:

Richard T. Kenney, MD, FACP
Medical Monitor

Signature: _____

Date: 5 Feb 2020

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
AST	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
FRα	Folate receptor alpha
GM-CSF	Granulocyte-macrophage colony-stimulating factor
huFR	Humane folate receptor
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IRB	Institutional Review Board

Abbreviation	Definition
ITT	Intent-to-treat
IV	Intravenous
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
NCI	National Cancer Institute
OS	Overall survival
PD	Progressive disease
PR	Progesterone receptor
PT	Preferred term
RFS	Relapse-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SI	International System of Units
SOC	System organ class
TEAE	Treatment-emergent adverse event
TNBC	Triple-negative breast cancer
Treg	Regulatory T-cell
TSH	Thyroid-stimulating hormone
WHO	World Health Organization

1. INFORMATION FROM THE STUDY PROTOCOL

1.1 Introduction and Objectives

1.1.1 Introduction

This document is the statistical analysis plan (SAP) for study FRV-002, a randomized, multicenter Phase II trial evaluating the safety and immunogenicity of 2 doses of vaccination with Folate Receptor Alpha (FRα) peptides with granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with triple negative breast cancer (TNBC) defined as primary tumor that is Her2-neu negative and low (≤ 10%) estrogen receptor (ER)/progesterone receptor (PR) nuclear staining. This document is based on Protocol FRV-002, Edition 6, dated 04 February 2019.

1.1.2 Study Objectives

The primary study objectives are:

- To evaluate high- and low-dose hu-FRα peptide vaccine with GM-CSF administered every month for 6 months (the vaccination phase) to elicit a FRα-specific T cell response.
- To evaluate cyclophosphamide priming prior to vaccinations to elicit a FRα-specific T cell response.
- To evaluate the safety and tolerability of high- and low-dose hu-FRα peptide vaccine with GM-CSF.
- To evaluate the long-term safety and tolerability of booster vaccination of hu-FRα peptide vaccine with GM-CSF.

The secondary study objectives are:

- To determine FRα expression status of primary tumors when available as a formalin-fixed, paraffin-embedded material and whether expression correlates with the emergence of a FRα-specific T cell response.
- To determine the relapse-free survival (RFS) of patients with TNBC after treatment with hu-FRα peptide vaccine with GM-CSF.

This SAP is designed to outline the methods to be used in the analysis of study data in order to answer the study objectives. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the clinical study report (CSR) for this trial.

This SAP will also outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2 Study Design

1.2.1 Summary of Study Design

This is an open-label, randomized, parallel groups Phase II trial conducted at up to 20 clinical sites in the United States in 80 eligible female patients with TNBC who are ≥ 18 years of age.

Patients will be randomized to 1 of 4 treatment groups in a 2×2 design: low-dose versus high-dose FRα peptide vaccine and cyclophosphamide priming versus none. A total of 20 patients will be enrolled in each treatment group.

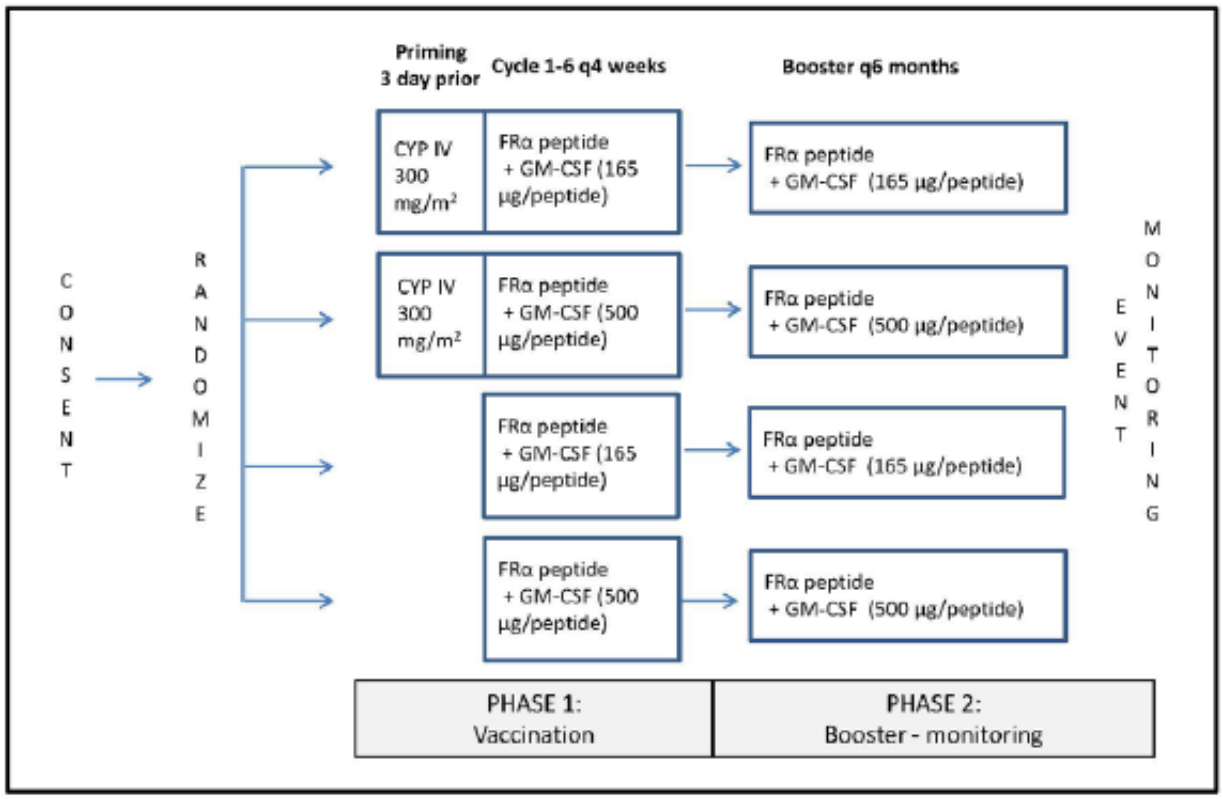
The vaccine will be administered in 2 phases: a vaccination phase and a booster phase. The vaccination phase will include 6 administrations of the vaccine at 4-week intervals. The booster phase will include administration of the vaccine every 6 months (defined as approximately 180 days) during a 3-year follow-up or until cancer recurrence.

The total duration of the study will be 3.5 years. Assessment for disease recurrence will be conducted every 6 months from the end of treatment until documented disease progression.

The vaccination will be administered intradermally with a low dose of 165 µg/peptide and a high dose of 500 µg/peptide. Cyclophosphamide will be administered intravenously (IV) at a dose of 300mg/m^2.

The study design is summarized in Figure 1:

Figure 1: Study Schema



1.2.2 Randomization Methodology

This study will use an automated central randomization procedure to allocate patients in a 1/1/1/1 ratio to each of the treatment groups. The randomization will be stratified based on the disease stage (ie, pretreatment clinical Stage I, II, or III), treatment (ie, neoadjuvant or just adjuvant), and outcome to last cycle of chemotherapy prior to randomization (ie, pathologic complete response: yes or no).

1.2.3 Stopping Rules

The Medical Monitor and the study statistician will review the study periodically, after every 6 months, to identify accrual, toxicity, and endpoint problems that might be developing. The study statistician will prepare a report containing accrual, adverse event (AE), and efficacy data that will be submitted to an independent data safety monitoring board (DSMB) every 3 months until all patients are off study Phase 1 (vaccination phase) and every 6 months thereafter. The DSMB will include no less than 3 members (2 physicians and a statistician).

At any point in the vaccination phase, after 5 or more patients have been enrolled in each treatment group, if more than 20% of the enrolled patients develop a Grade 2 allergic reaction, Grade 2 autoimmune reaction, Grade 3 injection site reaction, Grade 2 neurologic problem, Grade 2 Proteinuria, Grade 3+ Hematologic AE, Grade 3+ Non-hematologic (excluding

alopecia), or any other Grade 3+ toxicity, then enrollment to the trial will be suspended. All safety data will be reviewed; a trial recommendation will be formulated by the study team and presented to the independent DSMB and institutional review board (IRB) for approval.

For example, assuming 22 patients have been treated in the study, using this stopping rule the probability of suspending enrollment for various hypothetical toxicity rates is as follows:

Hypothetical toxicity rate (%)	0	5	10	15	20	25	30
Probability (%) of suspending enrollment	0	0.4	6.2	22.6	45.7	67.7	83.5

The frequency of toxicities will be tabulated. If toxicities are observed, the DSMB may estimate an upper bound on the underlying toxicity rate using standard statistical methods. For example, assuming 22 patients have been enrolled, the upper bound of the 90% confidence interval (CI) based on an exact binomial test is as follows:

Number of patients observed with toxicity	0 (0%)	1 (4.5%)	2 (9.1%)	3 (13.6%)	4 (18.2%)
Upper bound of 90% CI for the underlying toxicity rate	12.7%	19.8%	26.0%	31.6%	36.9%

1.2.4 Study Procedures

The schedule of assessments, as outlined in the study protocol, is provided in Table 1-1.

Table 1-1 Schedule of Assessments

Tests and Procedures	Prior Protocol Activity	≤ 28 Days before Cycle 1	CYP IV [2]	PHASE 1 – Vaccination [1]							PHASE 2
				Cycle 1	Cycle 2 ± 4 days	Cycle 3 ± 4 days	Cycle 4 ± 4 days	Cycle 5 ± 4 days	Cycle 6 ± 4 days	28 ± 4 Days after Cycle 6	Booster and Follow-up for 3 years (q 6 months)[1]
Screening	X										
Administer informed consent	X										
Inclusion Exclusion Criteria		X									
Submission of primary tumor specimen for FRα antigen [6]	X										At recurrence X
Demographics, Medical history, Disease staging, Breast cancer treatment history		X									
Urine or Serum pregnancy test [5]		X	X	X	X	X	X	X	X		X
Height & weight		X									
Clinical examination, vitals		X [9]	X [10]	X	X	X	X	X	X	X [4]	X [4]
CYP IV			X								
HuFR vaccination				X	X	X	X	X	X		X [11]
Injection site tolerance					X	X	X	X	X	X	
Adverse events[12]		X		X	X	X	X	X	X	X	X [12]
Concomitant medications[13]		X			X	X	X	X	X	X	X [13]
TSH and ANA		X			X		X			X	

Tests and Procedures	Prior Protocol Activity	≤ 28 Days before Cycle 1	CYP IV [2]	PHASE 1 – Vaccination [1]							PHASE 2
				Cycle 1	Cycle 2 ± 4 days	Cycle 3 ± 4 days	Cycle 4 ± 4 days	Cycle 5 ± 4 days	Cycle 6 ± 4 days	28 ± 4 Days after Cycle 6	Booster and Follow-up for 3 years (q 6 months)[1]
CBC with differential		X			X		X		X	X	X [4]
Metabolic panel		X			X		X		X	X	X [4]
Urinalysis for proteinuria [3]		X			X	X	X	X	X	X	
Primary tumor genotyping [6]		X									
Recurrence / RFS evaluation [4]		X								X	X
Research Blood Samples [7]		X		X	X		X			X	X [8]

Abbreviations: ANA = antinuclear antibody; CBC = complete blood count; CYP IV = cyclophosphamide infusion; FRα = folate receptor alpha; huFR = human folate receptor; RFS = relapse-free survival; NCCN = National Comprehensive Cancer Network; q = every; TSH = thyroid-stimulating hormone

1. Each vaccination cycle will be 28 days ± 4 days in length. Booster doses start at 12 months ± 14 days after Cycle 1 dose.
2. Cyclophosphamide IV - 300 mg/m^2 – Done 3 days prior to Cycle 1 vaccine injection.
3. All patients must have a urinalysis. If ≥ 2+ proteinuria, a 24-hour urine should be collected for protein quantification.
4. Disease evaluation will occur during a meeting with a physician at each visit throughout the study. At a minimum, this will include per standard practice a history, physical examination, and hematology and chemistry group, per standard of care. Mammogram or breast ultrasound will be performed annually per standard of care. If there is suspicion of disease recurrence, further testing (e.g. imaging, etc.) should be performed per standard of care (NCCN guidelines) for women who have a history of breast cancer as part of their disease follow-up.
5. Required for women of child-bearing potential only. Must be done ≤7 days prior to registration.
6. Test does not need to be completed prior to enrollment.
7. Refer to Table in Protocol Section 6.
8. Samples taken at the 6-, 12-, 18-, and 24-months post vaccination phase visits.
9. Complete Physical Examination at Baseline (≤ 28 days prior to cycle 1) only, as noted in Section 3.5 of the protocol.
10. Symptom Directed Examination – Whenever the patient meets with the physician, per standard of care as noted in Protocol Section 5.4.4. Patients will have these at Cycles 2, 4, 6, and 28 days after cycle 6, as well as at all Booster and Follow-up visits.
11. No booster vaccination at last visit.

12. After completion of cycle 6, TEAEs are capture during th e28-day time period following Booster Vaccinations. NOTE: All serious adverse events (SAEs) as defined in Protocol Section 10.1 of the protocol, Events of Special Interest (Protocol Section 10.2.1), Secondary Malignancies (Protocol Section 10.2.2) or Pregnancies (Protocol Section 10.2.3) are reported when they occur, regardless of the timing of last vaccine administration.
13. After completion of cycle 6, new concomitant medications are capture from date of booster vaccination until 28 days post vaccination. New concomitant medications administered after the 28-day time point but prior to the next Booster vaccination do not need to be capture unless they are still ongoing at the time of the next Booster vaccination.

1.2.5 Efficacy and Safety Parameters

1.2.5.1 Efficacy Parameters

The primary efficacy endpoint of this study is maximum observed FRα-specific T cell response. A vaccine-induced increase in FRα-specific T cell responses will be defined as (1) a ≥ 3-fold increase in FRα-specific T cells at any point during treatment if there were detectable pretreatment levels of FRα-specific T cells or (2) levels of FRα-specific T cells above the threshold of the assay at any point in the vaccination phase if pre-treatment levels of FRα-specific T cells are non-detectable.

Other efficacy parameters include:

- Immune response
    - Change from baseline in T cell response, using maximum observed FRα-specific T cell response.
    - Time to maximum observed FRα-specific T cell responses.
    - Slope of the FRα-specific T cell responses after the vaccination phase of the trial, determined from the terminal log-linear portion of the T cell response curve (as a measure of the persistence FRα-specific T cell immune response during the booster phase).
    - Immune response status per patient.
- FRα tumor expression
    - Tumor membrane staining intensity, as scored by a pathologist (0 = negative, 1+ = weak, 2+ = moderate, 3+ = strong).
    - Percent of cells within each tissue core stained at each intensity will be recorded to calculate an H-score. The H-score is a weighted score that captures both the proportion of positive staining and intensity for each tumor.
- Duration of RFS, defined as the time from registration to any local, regional, or distant recurrence of breast cancer; the development of a contralateral breast cancer or secondary primary other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or lobular carcinoma in situ of the breast; or death from any cause without the documentation of 1 of these AEs.
- Exploratory correlative research
    - Tumor infiltration from immune-cell subsets such as TIL, CD4+ regulatory T-cell (Treg), myeloid cells by immunofluorescence and expression of T cell activations such as 4-1BB (CD137), OX40, GITR, CD40, and ICOS, as well as known pathway inhibitors such as PD-1/PD-L1, IDO, B7, LAG3, TIM-3, CTLA-4.
    - Tumor cell markers such as Ki and epidermal growth factor receptor (EGFR).
    - Circulating inhibitory T cells such as Tregs and myeloid derived suppressor cells (MDSC).

- Tumor genotyping to identify TNBC subtypes.

1.2.5.2 Safety Parameters

Safety evaluations performed during the study include physical examinations, measurement of vital signs; monitoring of injection site tolerance; clinical laboratory evaluations including hematology, chemistry, urinalysis, and measurement of thyroid-stimulating hormone (TSH) and antinuclear antibody (ANAs) values; and monitoring of AEs and concomitant medications.

Adverse events are graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 grading scheme. If the CTCAE grading does not exist for an AE, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an AE (5) will be used.

The primary safety endpoint of this study is incidence of treatment-emergent AEs (TEAEs). Other safety endpoints include incidence of serious AEs, incidence of TEAEs leading to study withdrawal, and overall survival (OS).

2. PATIENT POPULATION

2.1 Population Definitions

The following patient populations will be evaluated and used for presentation and analysis of the data:

- Safety Population (SP): All patients who are enrolled, are randomized to treatment, and receive at least one dose of treatment (cyclophosphamide or study vaccine).
- Modified Intent-to-Treat Population (mITT): All patients who are randomized to treatment, received at least 1 dose of study vaccine, and have a result for the baseline and at least 1 post-baseline immune response evaluation.

The SP will be the primary population for analyses of safety and tolerability. The mITT is the primary population for the analysis of all efficacy endpoints, and for the analysis of the T cell immune response. It is expected that the SP and the mITT will not differ.

All safety analyses and all efficacy analyses will be conducted according to the study treatment regimen received. Should a patient's randomized study treatment regimen differ from their received study treatment, this will be evaluated on a case-by-case basis in the CSR.

2.2 Protocol Violations

A protocol violation is any departure from procedures and requirements outlined in the protocol. Protocol violations and departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored at each site for (1) significance, (2) frequency, and (3) effects on the study objects, to ensure that site performance does not compromise the integrity of the trial.

All protocol violations will be recorded in the Protocol Violations electronic case report form (eCRF). Additionally, each site is responsible for tracking and reporting protocol violations to their IRB as required by IRB regulations. The Marker Therapeutics Clinical Monitor must be contacted immediately if an unqualified/ineligible participant is randomized to treatment in the study.

All protocol violations will be listed by patient.

3. GENERAL STATISTICAL METHODS

3.1 Sample Size Justification

The emphasis of this Phase II study is estimation of immune response effect size and incidence of AEs, rather than confirmatory hypothesis testing of clinical endpoints such as RFS. In study MC1015, patients treated with hu-FRα and GM-CSF had a mean (±standard deviation [SD]) increase from baseline in the T cell responses targeting the hu-FRα antigen of 175 (±200) T cells. Assuming the same mean (175) and SD (200) for the 2 low-dose groups in this study, a sample size of 20 patients per group, a doubling of the T cell response in the high-dose groups at the end of the vaccination phase, a drop-out rate of no more than 10%, and statistical testing using the Mann-Whitney test stratified by level of cyclophosphamide priming, the power to detect a difference between the combined low-dose groups versus the combined high-dose groups depends on the variability of the T cell response in the high-dose groups, as follows:

Standard Deviation in High-Dose Groups of the Change from Baseline in T Cell Count at End of Vaccination Phase	**Statistical Power (%)**
200	92
225	89
250	86
275	82
300	78
325	73
350	69
375	64
400	60

3.2 General Methods

All data listings that contain an evaluation date will contain a relative vaccine start day. Pretreatment and on-treatment study days are numbered relative to the day of the first dose of study vaccine, which is designated as Day 0. The preceding day is Day -1, the day before that is Day -2, etc. Each data listing presenting an evaluation date will present the Rel Day variable, eg "Off Treatment Date (Rel Day)."

All output will be incorporated into Microsoft Word files, sorted and labeled according to the International Conference on Harmonisation (ICH) recommendations, and formatted to the appropriate page size(s).

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters as described in Section 4. For categorical variables, summary tabulations of the number and percentage of patients within each category (with a category for missing data) of the parameter will be presented. Two-sided 90% CIs using the Clopper-Pearson exact method will be calculated for the proportion of patients achieving a T cell immune response in each of the 4 treatment groups. For continuous variables, the number of patients, mean, median, SD, minimum, and maximum values will be presented along with the 90% CI of the mean where

appropriate. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 90% CIs, as well as percentage of censored observations.

The following tests will be used for formal statistical hypothesis testing on the specified parameters:

- Primary efficacy analysis: Mann-Whitney test comparing distributions of maximum T cell response between low and high vaccine dose groups, stratified by level of cyclophosphamide priming
- Exploratory efficacy analysis: Mann-Whitney test comparing distributions of maximum T cell response between cyclophosphamide priming groups, stratified by level of vaccine dose received
- Exploratory efficacy analysis: Wilcoxon signed rank test comparing change from baseline in maximum T cell response within each of the 4 treatment groups

All tests will be conducted at the 1-sided, 0.10 level of significance. Summary statistics will be presented, as well as CIs on selected parameters, as described in the sections below.

3.3 Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software, version 9.4, unless otherwise noted. Medical history and TEAEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA, version 19.0 or higher). Concomitant medications will be coded using World Health Organization (WHO) Drug Dictionary (March 2016 or later). The National Cancer Institute (NCI) CTCAE, version 4.03 will be used to determine TEAE severity grades where applicable.

3.4 Baseline Definitions

For non-efficacy analyses, baseline will be defined as the most recent measurement before the first administration of study vaccine.

For the efficacy analyses of FRα-specific T cell response and analyses stratified by immune response status, efficacy baseline value definition will be the same for all treatment groups. For any FRα parameter, the efficacy baseline value is the minimum pre-vaccination result. The minimum pre-vaccination result is calculated by first averaging Media results per date per patient for Media results prior to first vaccine dose; followed by averaging FRα parameter results per parameter per date per patient. Minimum pre-vaccination result is the difference between FRα parameter average and Media average; if the initial difference is a negative value, the result is set to 0. If there are multiple pre-vaccination dates for any parameter, the minimum difference of averages is used as the minimum pre-vaccination result for that FRα parameter and will be used as the baseline value.

3.5 Methods of Pooling Data

All analyses will primarily be conducted separately for each of the 4 treatment groups, unless otherwise specified.

To evaluate the safety and tolerability of hu-FRα peptide vaccine with GM-CSF, data will be pooled by high dose and low dose vaccine groups.

To evaluate the ability of the hu-FRα peptide vaccine with GM-CSF to elicit a FRα-specific T cell response, data will be pooled by high dose and low dose vaccine groups and compared via the Mann-Whitney test after aligning ranks within each cyclophosphamide level. An exploratory analysis to evaluate cyclophosphamide priming prior to hu-FRα peptide vaccinations to elicit a FRα-specific T cell response will pool data by cyclophosphamide use and no cyclophosphamide use and will compare these two groups via the Mann-Whitney test after aligning ranks within each vaccine dose level.

3.6 Adjustments for Covariates

No formal statistical analyses that adjust for possible covariate effects are planned for tests of clinical efficacy.

Exploratory correlative research will be conducted to determine whether an immune measurement or tissue marker may be a predictor of a robust FRα-specific T cell response after vaccination. Such a predictor of immune response may be used clinically to rapidly assess whether or not immune protection against recurrence will be established. Surrogate markers could be used to assess the need for booster immunizations that may be required if immunity wanes.

3.7 Multiple Comparisons/Multiplicity

The primary analysis of this study is the comparison of high and low dose vaccine groups to elicit a FRα-specific T cell response, and thus multiplicity is not of concern for this study with a single primary efficacy analysis. All other analyses will be considered exploratory and/or hypothesis generating.

3.8 Subpopulations

The SP will be the primary population for analyses of safety and tolerability. The mITT is the primary population for the analysis of all efficacy endpoints, and for the analysis of the T cell immune response.

3.9 Withdrawals, Dropouts, and Loss to Follow-up

If a patient is withdrawn before completing the study, the reason for withdrawal will be entered on the End-of-Study Form and other appropriate eCRF pages will be completed. If the patient is not deceased, final physical examinations and clinical laboratory assays will be performed, if possible. All patient data collected before discontinuation will be made available to Marker Therapeutics, Inc. Patients who are withdrawn or discontinue from the study will not be replaced.

3.10 Missing, Unused, and Spurious Data

Patients in the mITT population who discontinue prior to the end of the vaccination phase will be considered non-immune responders, if immune response status cannot be determined by the end of the vaccination phase.

In general, there will be no substitutions made to accommodate missing data points. All data recorded on the eCRF will be included in data listings that will accompany the CSR. No imputation will be performed for missing data elements and data will be analyzed as recorded in the eCRF. For the time-to-event distributions, patients will be censored at the time of the last known evaluation, should they have missing information regarding event endpoints, eg missing outcome data.

When tabulating AE data, partial onset dates will be handled as follows. If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as study treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the date of treatment. If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the study treatment. In this case, the event onset will be coded to the day of treatment in order to conservatively report the event as treatment-emergent. A missing onset date will be coded as the day of treatment initiation.

3.11 Visit Windows

It is expected that all visits should occur according to the protocol schedule. All data will be tabulated per the evaluation visit as recorded on the eCRF even if the assessment is outside of the visit window. If the evaluation visit is missing in the database but there is data from an unscheduled or additional visit that is inside the visit window, the data from the unscheduled or additional visit will be used in data summaries. In data listings, the relative day to first study vaccine dose will be presented for all dates.

If a patient presents with an acute illness (eg, cold, influenza), the vaccination will be withheld until the illness has resolved. Subsequent cycles will commence 24 to 32 days after the next cycle is initiated rather than according to the schedule established before the illness-induced delay.

There will be no modifications to the planned vaccine dose. There may be allowances for the timing of the administration of vaccine to accommodate patient schedules or special circumstances. Such variations in the timing of vaccinations will be decided in advance on a case-by-case basis by the study Medical Monitor (see Protocol Section 5.4.1).

Table 3-1 Evaluation Intervals for Efficacy Analysis

Phase	Evaluation	Protocol-Specified Interval	Interval for Analysis
	Prior Protocol Activity (Screening)	Prior to Cycle 1 Day -28	Prior to Cycle 1 Day -28
	≤ 28 days Prior to Cycle 1 (Baseline)	Cycle 1 Day -28 to Day -1	Cycle 1 Day -28 to Day -1
	CYP IV	Cycle 1 Day -3 (72±10 hours)	Cycle 1 Day -3 (72±10 hours)
Phase 1 – Vaccination	Cycles 1–6	28 days ± 4 days	28 days ± 4 days
	28±14 days after Cycle 6	28 days ± 14 days after Cycle 6	28 days ± 14 days after Cycle 6
Phase 2 – Booster and Follow-up Over 3 years (q6 months)	12 months after Cycle 1 injection (±14 days) and every 6 months ±14 days for 3 years	12 months after Cycle 1 injection (±14 days) and every 6 months ±14 days for 3 years	12 months after Cycle 1 injection (±14 days) and every 6 months ±14 days for 3 years

Abbreviation: CVP IV = cyclophosphamide infusion; q = every.

3.12 Interim Analyses

There are no interim analyses planned for investigating primary endpoints.

An informal analysis investigating FRα-specific T cell responses (secondary study objective) was performed by the Sponsor after n=24 patients had concluded Phase I (Vaccination Phase) of the trial. No formal statistical tests were conducted on the interim data.

4. STUDY ANALYSES

4.1 Patient Disposition

Patient disposition will be tabulated and include the number of patients who:

- Were enrolled
- Were randomized to study treatment
- Received at least 1 dose of cyclophosphamide or study vaccine
- Received low-dose and high-dose FRα peptide vaccine alone
- Received low-dose and high-dose FRα peptide vaccine after cyclophosphamide priming
- Were in each patient population for analysis
- Withdrew before completing the study; reason(s) for withdrawal will be tabulated
- Completed Phase 1 (all 6 cycles of FRα peptide vaccine)
- Completed Phase 2 (booster and 3 years of follow-up every 6 months)

Study completion information, including dosing dates, dates of disease progression, treatment group, date of discontinuation/completion, and the reason for premature study withdrawal, if applicable, will be listed by patient. This listing will be presented for the overall study as well as by investigational site.

4.2 Demographics and Baseline Characteristics

Demographics, baseline characteristics, and medical history (including disease staging and breast cancer treatment history) information will be summarized overall and stratified by treatment group and immune FRα-specific T cell responder status for the SP and mITT populations. No formal statistical comparisons will be performed.

Demographic and baseline data, including medical history and physical examinations, will be listed by patient. In addition, results of screening evaluations and final weight measurements will be listed by patient. Age at informed consent will be listed with demographic data, and will be calculated as the integer part of (date of informed consent – date of birth + 1).

The following evaluations will be performed before cyclophosphamide priming or first vaccination and collected data/results will be tabulated and listed:

- Recent medical and surgical history (preceding 5 years or chronic conditions), including underlying breast cancer status and history.
- Body weight (kg).
- Vital sign measurements, including temperature and blood pressure.
- Physical examination findings.
- Clinical laboratory testing:

  - Complete blood count (CBC) with differential and platelet count.
  - Serum chemistry (electrolytes, glucose, blood urea nitrogen [BUN], calcium, phosphorus, albumin, creatinine, bilirubin (total and direct), aspartate aminotransferase (AST)/alanine aminotransferase (ALT), alkaline phosphatase).
  - Urinalysis with proteinuria.
  - TSH and ANA.
  - Pregnancy test, if applicable.
    Note: for the purpose of this protocol the following criteria are used to determine reproductive potential: postmenopausal by history, defined as > 60-years-old and no menses for > 12 months naturally or secondary to radiation/chemotherapy; or serum follicle-stimulating hormone, luteinizing hormone, and estradiol levels in the postmenopausal range; or history of hysterectomy, history of bilateral tubal ligation; or of bilateral oophorectomy.

- Collection of blood for exploratory correlative immune monitoring research, as detailed in Protocol Section 6.

In addition, immunohistochemistry (IHC) findings based on review of the primary tumor specimen submitted to the IHC central laboratory (Protocol Section 16) for FRα antigen-expression testing will be listed.

4.3 Efficacy Evaluation

4.3.1 Primary Efficacy Endpoint – Immune Response

Patients will have FRα-specific T cell response measurements to the following FRα parameters: FR30, FR56, FR56, FR76, FR113, FR238, and FRα protein. These parameters will also accompany a Media parameter as a control measurement. Each patient will have 3 measurements per evaluation date per parameter. The 3 measurements will be averaged per date per parameter and will have the Media date-average subtracted: for each date, T cell response = (FRα parameter average – Media average); if the initial difference is a negative value, the T cell response value will be set to 0. The maximum on-study result for each patient will be the maximum difference of averages between any FRα parameter and Media average, following the first vaccination dose; each patient will have only one maximum on-study result. The distribution of maximum observed FRα-specific T cell response in the high dose group will be compared to the distribution of maximum observed FRα-specific T cell response low dose group (anticipated n=40 for each group) via a Mann-Whitney test using a one-sided alpha of 0.10, stratified by level of cyclophosphamide priming.

An exploratory analysis will be performed, comparing the distributions of maximum observed FRα-specific T cell response between cyclophosphamide priming groups (anticipated n=40 for each group) via a Mann-Whitney test using a one-sided alpha of 0.10, stratified by level of vaccine dose received.

The mean (90% CI) and change from baseline in FRα-specific T cell responses will be computed at the end of the vaccination phase using the maximum T cell response per patient to

any FRα parameter; hypothesis testing will be done at the end of the vaccination phase using the maximum T cell response per patient to any FRα parameter.

4.3.2 Additional Efficacy Endpoints

4.3.2.1 Immune Response

To evaluate each treatment arm with respect to change from baseline in FRα-specific T cell response, descriptive statistics of maximum T cell response per patient will be provided and statistical analysis will be performed using the Wilcoxon signed-rank test.

The following parameters will be computed for each patient: change from baseline in T cell response, using maximum observed FRα-specific T cell response; time to maximum observed FRα-specific T cell response, defined as the time in days from date of first dose of FRα peptide vaccination to date of observed maximum FRα-specific T cell response; and slope of the FRα-specific T cell response after the vaccination phase of the trial (determined from the terminal log-linear portion of the T cell response curve as a measure of the persistence FRα-specific T cell immune response during the booster phase); immune response status. These parameters will be summarized for each treatment group.

The emergence of a FRα-specific T cell response (ie, immune responder) will be defined as:

1. A 3-fold or greater increase in FRα-specific T cells at any point during treatment if there were detectable pretreatment levels of FRα-specific T cells, or
2. Levels of FRα-specific T cells above the threshold of the assay at any point in the vaccination phase if pre-treatment levels of FRα-specific T cells are non-detectable.

Immunologic data are currently represented in spots/2.5×10^5 cells. The immunologic data will be multiplied by 4 for figures in order to be presented in spots/million cells.

Immune response will be a categorical variable based on the following processes:

- Immunologic and media measurements will be averaged by date per patient.
- A difference of averages will be calculated by subtracting the media average from the immunologic parameter average per date. If the value is less than 0, the difference of averages will be set to 0.
- If there are multiple pre-treatment dates, the baseline difference of averages will be the minimum difference of averages before treatment initiation per patient.
- If there are multiple evaluation dates after vaccine start date, the on-study difference of averages will be the maximum of difference of averages after the vaccine start date per patient.
- If the baseline value is detectable ($\geq$ 12.5 spots/2.5×10^5 cells) and the on-study difference of averages is at least three times as great as the baseline difference of averages for any FRα parameter, the patient is a responder.

- If the baseline value is not detectable (< 12.5 spots/2.5 × 10^5 cells) and the on-study difference of averages is greater than 12.5 spots/2.5 × 10^5 cells for any FRα parameter, the patient is a responder.
- If the baseline value is detectable (≥ 12.5 spots/2.5 × 10^5 cells) and all of the on-study difference of averages are less than three times the value of the baseline difference of averages for all FRα parameters, the patient is not a responder.
- If the baseline value is not detectable (< 12.5 spots/2.5 × 10^5 cells) and all of the on-study difference of averages are less than or equal to 12.5 spots/2.5 × 10^5 cells for any FRα parameter, the patient is not a responder.

Calculation:

$$If\ PRE < 12.5\ then\ Responder = \begin{Bmatrix} Y, & if\ ONSTDY > 12.5 \\ N, & if\ ONSTDY \leq 12.5, \end{Bmatrix},$$

$$If\ PRE \geq 12.5\ then\ Responder = \begin{Bmatrix} Y, & if\ \dfrac{ONSTDY}{PRE} \geq 3 \\ N, & if\ \dfrac{ONSTDY}{PRE} < 3, \end{Bmatrix},$$

$$where\ ONSTDY = MAX(DIFFAVGS_{POSTV1}), PRE\ = MIN(DIFFAVGS_{PRETRT}),$$
$$and\ DIFFAVGS = AVG(PARAM) - AVG(MEDIA)$$

A 90% binomial CI will be constructed for percentage of patients who develop an immune response among those patients in each treatment group.

4.3.2.2 FRα Tumor Expression

Tumor membrane staining intensity will be scored by a pathologist as negative (0), weak (1+), moderate (2+), and strong (3+). The percent of cells within each tissue core stained at each intensity will be recorded to calculate an H-score on the pre-baseline tumor sample. The H-score is a weighted score that captures both the proportion of positive staining and intensity for each tumor. H-score values can range from zero (no membrane staining) to a maximum of 300 (100% membrane staining at 3+). The staining intensity, percent of cells, and H-score will be listed by patient. Mean H-scores will be presented in a table by treatment group.

4.3.2.3 Duration of RFS

The RFS distributions will be estimated using the Kaplan-Meier method for each treatment group using the mITT population. Time-to-event data will be summarized using Kaplan-Meier methodology using 25th, 50th (median), and 75th percentiles with associated 2-sided 90% CIs, as well as percentage of censored observations.

4.3.2.4 Exploratory Correlative Research

Correlative data analyses are included to determine whether an immune measurement or tissue marker may be a predictor of a robust FRα-specific T cell response after vaccination. Such a

predictor of immune response may be used clinically to rapidly assess whether or not immune protection against recurrence will be established. Surrogate markers could be used to assess the need for booster immunizations that may be required if immunity wanes.

The following markers may be evaluated as baseline predictors if the data is available:

1. Tumor infiltration from immune-cell subsets such as TIL, CD4+ Treg, myeloid cells by immunofluorescence and expression of markers of T cell activations such as 4-1BB (CD137), OX40, GITR, CD40, and ICOS, as well as known pathway inhibitors such as PD-1/PD-L1, IDO, B7, LAG3, TIM-3, CTLA-4
2. Tumor cell markers such as Ki and EGFR [1]
3. Circulating inhibitory T cells such as Tregs and MDSC
4. Tumor genotyping to identify TNBC subtypes [2]

4.4 Safety Analyses

Safety analyses will be performed using the SP population.

4.4.1 Primary Safety Endpoint

The primary safety endpoint is incidence of TEAEs by severity and attribution, as described in Section 1.2.5.2. The incidence of TEAEs will be summarized for each treatment group and tabulated by severity and attribution.

4.4.2 Additional Safety Endpoints

4.4.2.1 Study Drug Exposure

Study drug exposure will be calculated as the number of days patients were administered study drug, as determined by (date of last FRα peptide vaccination – date of first FRα peptide vaccination), and will be summarized using descriptive statistics, including the number and percentage of patients completing each study vaccine cycle. Additionally, overall study duration from dose of cyclophosphamide to last follow-up visit will be provided using descriptive statistics.

Duration of study drug exposure and number of study drug vaccinations received will be listed by patient.

4.4.3 Adverse Events

All TEAEs will be coded using MedDRA and displayed in tables and data listings using system organ class (SOC) and preferred term (PT). Treatment-emergent AEs in the eCRF reported as having a severity of Grade 0 or those missing a severity will not be tabulated or listed.

Treatment-emergent AEs will be summarized overall and by treatment group, severity, and causality (unrelated, related to cyclophosphamide, or related to study vaccine). All TEAEs considered to be possibly, probably, or definitely related to study drug and occurring after

initiating cyclophosphamide but before the first treatment with study vaccine (Cycle 1) will be considered treatment-related due to cyclophosphamide. Related TEAEs occurring after the first treatment vaccination are considered to be due to the vaccine (Cycle 1 through Phase 2 Booster Phase), unless clearly consistent with a known delayed reaction to cyclophosphamide. Symptoms collected on the baseline eCRF (such as fatigue, fever, erythema multiforme) will not be considered as TEAEs, as these were collected before the first dose of cyclophosphamide and will be summarized with the medical history.

Adverse events will be summarized by patient incidence rates; therefore, in any tabulation, a patient will contribute only once to the count for a given SOC/PT.

The following TEAE summaries will be provided overall and by treatment group. In these tabulations, each patient will contribute only once (ie, the most related occurrence or the most intense occurrence) to each of the incidence rates in the descriptive analysis, regardless of the number of episodes

- All TEAEs
- All Grade 3 or higher TEAEs
- All serious TEAEs
- All study drug-related TEAEs (possibly, probably, and definitely related)
- All TEAEs leading to study withdrawal
- Deaths (Grade 5 TEAEs)

All AEs occurring on-study will be listed by patient.

All TEAEs will be listed by patient; serious TEAEs and TEAEs leading to study withdrawal will be flagged.

Additionally, TEAEs of injection site reaction will be listed by patient and tabulated by CTCAE grade.

4.4.4 Clinical Laboratory Evaluations

Clinical laboratory values will be expressed using the International System of Units (SI). Values will be summarized for each clinical laboratory parameter, including hematology (CBC with differential and platelet count), serum chemistry (electrolytes, glucose, BUN, calcium, phosphorus, albumin, creatinine, bilirubin [total and direct], AST, ALT, and alkaline phosphate), urinalysis, TSH, and ANA.

Local laboratory ranges are utilized, and will be converted to standard units for analysis. Age-specific (age at informed consent/assent as applicable) and gender specific ranges (ie, adult or pediatric, male or female) will be used to flag out-of-range values and to categorize by CTCAE grade where applicable.

All laboratory data will be listed by patient and compared with their corresponding normal ranges. Data outside the normal range and/or data noted by the Investigator or Medical Monitor

as clinically significant will be flagged. Normal ranges will be obtained from the Mayo Clinic Medical Laboratories website.

The actual value and change from baseline (most recent result before Day 0) to each on-study evaluation will be summarized for each clinical laboratory parameter. In the event of repeat values, the last non-missing value per study day/time will be used. Laboratory data obtained at any time after the vaccination will not be used as baseline data.

Shifts in toxicity grade from values collected at baseline to timepoints on study vaccine (see Table 1-1, Schedule of Assessments, for the timepoints at which each laboratory parameter is collected) and to the worst value on study will be summarized using CTCAE grading.

4.4.5 Vital Sign Measurements and Physical Examinations

The actual value and change from baseline to each on-study evaluation will be summarized for clinical examinations, vital signs, and weight.

Vital sign measurements will be listed by patient.

Physical examination results at each timepoint will be summarized using shift tables to indicate change in status (normal/abnormal) from baseline to each post-baseline assessment.

All physical examination findings will be listed by patient.

Baseline and final weight measurements will be listed by patient.

4.4.6 Concomitant Medications

Patients should receive full supportive care while in this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications given from the day of the first vaccine administration until 28 days after the Cycle 6 administration, and within 28 days after each Booster vaccination, will be collected for Adverse Events and recorded in the eCRFs. Medications given for planned procedures that are related to the patient's history of breast cancer, such as breast reconstruction, or for planned procedures related to conditions recorded in Medical History, such as a knee replacement, do not need to be captured as TEAEs. Every effort should be made to collect and capture key concomitant medications given for the treatment of SAEs. However, as patients may be treated at outside facilities, it is understood that this information may be limited and not fully available.

Concomitant medications will be coded using the latest version of the WHO Drug Dictionary. Results will be tabulated by Anatomic Therapeutic Chemical (ATC) class and PT.

Medications recorded on the baseline concomitant medication eCRF will be considered both prior and concomitant. All other medications will be considered concomitant as identified by cycle, and tabulated by interval, including time between each vaccination cycle and during the observation phase, where any medications that did not end before the first dose of

cyclophosphamide or first dose of vaccine (depending on treatment assignment) will be included.

Concomitant medications will be listed by patient.

4.4.7 Overall Survival

Overall survival is defined as time from date of first FRα peptide vaccination (Rel Day 0) to date of death or censorship. Overall survival will be censored at the date of last follow-up if subject is alive. The OS rate at Cycle 6, Booster and follow-up 12 months, Booster and follow-up 24 months, and Booster and follow-up 36 months will be reported.

5. CHANGES TO PLANNED ANALYSES

In Protocol FRV-002 v06 Section 8, the document reads:
"The Medical Monitor and the study statistician will review the study periodically (after every 5 patients have completed the first vaccination cycle) to identify accrual, toxicity, and endpoint problems that might be developing. The study statistician will prepare a report containing accrual, adverse event, and efficacy data which will be submitted to an independent DSMB every 3 months until all patients are off study Phase 1 (vaccination phase) and every 6 months thereafter. The DSMB will include no less than 3 members (2 physicians and a statistician)."
The periodical review by the study statistician after every 5 patients have completed the first vaccination cycle to identify accrual, toxicity, and endpoint problems was not followed per protocol. However, the reports for DSMB meetings every 3 months until all patients are off study Phase 1 and every 6 months thereafter were and are being completed per protocol.

In Protocol FRV-002 v06 Section 9.4, the document reads:
"All subjects who received one dose of vaccine will be included in the analysis of safety and tolerability."
The Safety Population for this study will include any patient who receives at least one dose of treatment, either cyclophosphamide or study vaccine. See Section 2.1.

In Protocol FRV-002 v06 Section 9.4.3, the document reads:
"The mean H-scores for each treatment group and the percentage of 0+, 1+, 2+ and 3+ staining will [be] compared by a Mann-Whitney test."
The comparison of mean H-scores through the Mann-Whitney test will not be included in the statistical analyses of this study. Mean H-scores will be presented for descriptive purposes.

In Protocol FRV-002 v06 Section 9.4.4, the document reads:
"To evaluate each treatment arm with respect to change from baseline in T-cell response, descriptive statistics will be provided and statistical inference will be performed using the Wilcoxon signed rank test. The primary efficacy endpoint is highest T-cell response in high dose group versus low dose group (anticipated n=40 for each group) using a two-sided alpha of 0.10."
Prior to finalization of Protocol v6.0, discussion with Marker Therapeutics concluded with the decision to use one-sided alpha of 0.10 for this analysis. This decision is reflected in Section 1.2.5.1, Section 3.2, Section 3.8, and Section 4.3.2.3

In Protocol FRV-002 v06 Section 9.4.6, the document reads:
"The clinical efficacy endpoint is the duration of disease-free survival (DFS). DFS is the time from registration to any local, regional, or distant recurrence of breast cancer; the development of a contralateral breast cancer or second primary other than squamous or basal cell carcinoma of the skin, carcinoma in situ of the cervix, or lobular carcinoma in situ of the breast; or death from any cause without the documentation of one of these adverse events.
"The distribution of disease-free survival times will be estimated using the method of Kaplan-Meier for each treatment group."
As RFS and DFS are both used throughout the protocol, it is not clear which of the two should be evaluated per protocol. After discussion with Marker Therapeutics, it was decided that RFS would be the clinical efficacy endpoint as discussed in Section 1.1.2, Section 1.2.5.1, Section

3.2, Section 3.8, and Section 4.3.1.

6. REFERENCES

1. de Mascarel, I., et al., *Comprehensive prognostic analysis in breast cancer integrating clinical, tumoral, micro-environmental and immunohistochemical criteria.* Springerplus, 2015. **4**: p. 528.

2. Lehmann, B.D., et al., *Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies.* J Clin Invest, 2011. **121**(7): p. 2750-67.

7. REVISION HISTORY

7.1 Statistical Analysis Plan Version 0.1: 20 November 2018

Rationale of Revisions

SAP v0.1 written.

7.2 Statistical Analysis Plan Version 0.2: 12 February 2019

Rationale of Revisions

SAP v0.2 updated to incorporate following protocol changes:

- Reflected the company name change from TapImmune, Inc. to Marker Therapeutics, Inc, and updated the company address and contacts
- Clarified TEAE and concomitant medications collection and reporting during the Booster Phase
- Clarifies statistical analysis plan and primary efficacy endpoint
    - Removed H-score analyses and analyses stratified by H-score quartile
    - Updated efficacy parameters
    - Removed analyses comparing cyclophosphamide priming groups

7.3 Statistical Analysis Plan Version 1.0: 31 October 2019

Rationale of Revisions

SAP v1.0 included the following changes:

- Added Mann-Whitney test comparing cyclophosphamide groups as an exploratory analysis
- Removed all references to cyclophosphamide relative day; only vaccine relative day will be used
- Clarified methods for primary and exploratory analyses
- Revised baseline definitions for non-efficacy analyses. Baseline will be defined the same for all four treatment groups
- Clarified methods of pooling data for primary and exploratory analyses
- Revised immune response categorical variable derivation based on updated minimum number of spots detectable.
- Lab scatterplots removed, as primary and shift values presented in tables are informative enough

8. APPENDIX 1: RANDOMIZATION PLAN

The Randomization Plan is saved as "TAP FRV-002_Randomization Plan final v2.0" in P:\Tapimmune\FRV002\Biostats\Random\Randomization Plan\Final on Veristat's network drive.