Statistical Analysis Plan

Study Title

A phase 1, dose blocked-randomized, double-blind, placebo controlled, single dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous(IV) administration in healthy male subjects

Protocol No.	IM_hzVSF_v13-0001
Principal Investigator	In Jin Jang MD, PhD
Sponsor	ImmuneMed, Inc.
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Revision History

Version No.	Effective Date (YYYY/MM/DD)	Description of Changes	Revised by
1.0	2019/11/29	Initial version	N.A.

Table of Contents

1. Introduction

This statistical analysis plan (statistical analysis plan) presents details on the clinical characteristic analysis method of the pharmacokinetic and safety/tolerability data described in the hzVSF-v13 protocol of ImmuneMed, Inc., for describe the method and procedure to evaluate the purpose of the clinical trials.

2. Study Objectives

2.1. Primary Objective

The safety and tolerability were evaluated after intravenous(IV) administration of a single dose of the study drug hzVSF-v13 in healthy male subjects.

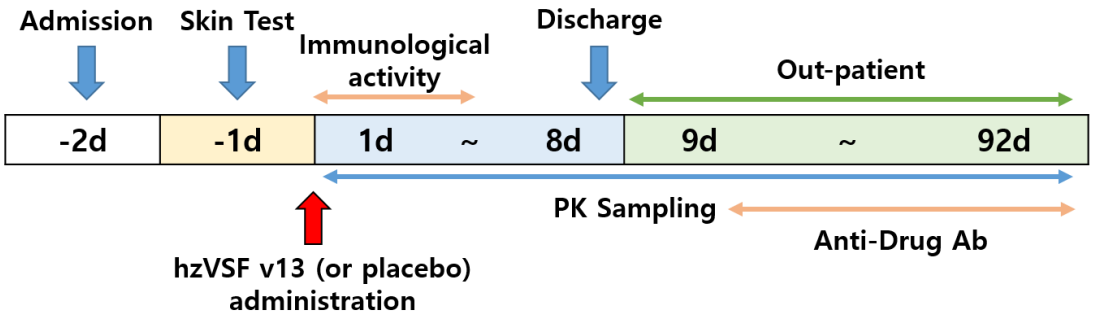
2.2. Secondary Objective

The pharmacokinetic characteristics were evaluated after intravenous(IV) administration of a single dose of the study drug hzVSF-v13 in healthy male subjects.

3. Investigational Plan

3.1. Overall Study Design

This is a Phase 1, dose blocked-randomized, double-blind, placebo controlled, single dosing, dose-escalation study to investigate the safety, tolerability, pharmacokinetic characteristics of hzVSF-v13 after intravenous(IV) administration in healthy male subjects.



3.2. Drug Administration

Dose Group	The number of subjects
Group 1 (10 mg IV)	hzVSF-v13: 3 Placebo: 1
Group 2 (20 mg IV)	hzVSF-v13: 3 Placebo: 1
Group 3 (50 mg IV)	hzVSF-v13: 6 Placebo: 2
Group 4 (100 mg IV)	hzVSF-v13: 6 Placebo: 2
Group 5 (200 mg IV)	hzVSF-v13: 6 Placebo: 2
Group 6 (400 mg IV)	hzVSF-v13: 6 Placebo: 2
Group 7 (800 mg IV)	hzVSF-v13: 6 Placebo: 2
Group 8 (1200 mg IV)	hzVSF-v13: 6 Placebo: 2

3.3. Schedule of Study

◆ Flow Chart

Schedule	Screening	Hospitalization Period					Outpatient Period
Day (d) / Item	-28 ~ -2	-2	-1	1	2 ~ 7	8	9 ~ 92
Obtaining an informed consent form	●						
Checking demographic information/medical history	●						
Serology[1]	●						
Urine drug test[2]	●						
Checking the inclusion/exclusion criteria	●						
Assigning the randomization/subject numbers[3]			●				
Admission[4]		●					
Discharge[5]						●	
Skin test[6]			●				
Administration of the investigational product[7]				●			
Physical examination[8]	●			●		●	●
Vital signs[9]	●			●	●	●	●
Electrocardiography (12-lead ECG)[10]	●			●		●	●
Clinical laboratory tests[11]	●			●	●	●	●
Blood collection for pharmacokinetics[12]				●	●	●	●
Immunogenicity test[13]	●					●	●
Monitoring of adverse events		●	●	●	●	●	●
Checking on the concomitant medications	●	●	●	●	●	●	●
Tolerability/safety assessments[14]							●

[1] Serology: Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) tests shall be performed only at the screening.

[2] Urine drug test: It shall be performed only at the screening (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates).

[3] Assigning the randomization/subject numbers: The randomization and subject numbers shall be assigned after the skin test at −1 d.

[4] Admission: Subjects shall be admitted in the afternoon at −2 d.

[5] Discharge: Subjects shall be discharged after completing all scheduled tasks in the morning at 8 d.

[6] Skin test: The skin test shall be performed at 9 a.m. at −1 d.

[7] Administration of the investigational product: HzVSF-v13 (or the placebo) shall be administered intravenously at 9 a.m. at 1 d.

[8] Physical examination: It shall be performed at the screening, 1 d 0 h (pre-dose), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22d 0h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose).

[9] Vital signs: It shall be performed at the screening, 1 d 0 h (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24 (2 d 0 h), 36 (2 d 12 h), 48 (3 d 0 h), 60 (3 d 12 h), 72 (4 d 0 h), 96 (5 d 0 h), 120 (6 d 0 h), 144 (7 d 0 h), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose) (systolic blood pressure, diastolic blood pressure, pulse rate, and temperature).

[10] Electrocardiography (12-lead ECG): It shall be performed at the screening, 1 d 0 h (pre-dose), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose).

[11] Clinical laboratory tests: It shall be performed at the screening, 1 d 0 h (pre-dose), 24 (2 d 0 h), 72 (4 d 0 h), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose) (hematology, blood chemistry, and urinalysis).

[12] Blood collection for pharmacokinetics: It shall be performed at 1 d 0 h (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24 (2 d 0 h), 36 (2 d 12 h), 48 (3 d 0 h), 60 (3 d 12 h), 72 (4 d 0 h), 96 (5 d 0 h), 120 (6 d 0 h), 144 (7 d 0 h), 168 (8 d 0 h), 336 (15 d 0 h), 504 (22 d 0 h), 672 (29 d 0 h), 840 (36 d 0 h), 1,176 (50 d 0 h), 1,512 (64 d 0 h), 1,848 (78 d 0 h) and 2,184 h (92 d 0 h; post-dose).

[13] Immunogenicity test: It shall be performed at the screening, 168 (8 d 0 h), 336 (15 d 0 h), 672 (29 d 0 h), 1,344 (57 d 0 h) and 2,184 h (92 d 0 h; post-dose).

[14] Tolerability/safety assessments: The tolerance and safety of the relevant dose group were evaluated after completing all scheduled tests up to 15 d in order to determine whether to proceed to the next dose group.

3.4. Determination of the Sample Size

The purpose of the study was exploratory which was not to verify statistical hypotheses, and in the case of clinical studies conducted using new drugs for which safety is not established, it is ethically desirable to conduct the study in the minimum number of subjects while satisfying the study objectives. In addition, dose groups had a certain ratio of subjects who received the placebo to enable double-blind for an objective safety and tolerability review. In this study, for the low dose groups (Groups 1 and 2), the sentinel dose groups, the target number of subjects per dose group had been set to 4 subjects per dose group, and the target number of subjects for other dose groups had been set to 8 subjects per dose group.

4. Documentation of Variables

4.1. Safety Variables

4.1.1. Adverse Events

4.1.1.1. Adverse Events (AE)

It refers to undesirable and unintended symptoms (including signs, abnormalities in laboratory test results, etc.), symptoms, or diseases that occurred to a subject after administration of an investigational product and not necessarily have a causal relationship with the investigational product.

4.1.1.2. Adverse Drug Reaction (ADR)

It refers to any hazardous and unintended reaction that occurs at any dose of an investigational product, where the causal relationship with the investigational product cannot be excluded.

4.1.1.3. Serious Adverse Event (SAE)

It is defined as occurrence that adverse events or adverse drug reaction:

① Results in death or life-threatening.

Life-threatening cases means emergency situations that can lead to death if medical treatment is not performed (eg, hepatic necrosis requiring liver transplantation, anaphylactic shock requiring emergency resuscitation, etc.).

② Requires inpatient hospitalization or prolongation of existing hospitalization

Hospitalization is also considered at the discretion of the investigator if medical treatment is received in an emergency room other than in the hospital room (eg, acute allergic reaction).

Hospitalization for the following is not considered a serious adverse event.

- Examination for the hospitalization or diagnosis during the Pharmacokinetic Sampling period or routine treatment or monitoring that is not related to deterioration of the condition, such as training for test drug administration.

- Hospitalization for pre-scheduled treatment and surgery for a condition that is not related to the indication in clinical trial and does not deteriorated.

③ Results in persistent or significant disability/incapacity

④ Results in a congenital anomaly/birth defect

If pregnancy occurs in a partner of the test subject during the clinical trial, it should be reported immediately to the monitor (or person in charge) of ImmunMed, but this is not a serious adverse events and it should be reported as serious adverse event in case of miscarriage, deformed child, developmental abnormality.

⑤ Results in an important medical event

4.1.2. Vital Signs

Systolic blood pressure, B. Diastolic blood pressure, Pulse Rate, Body temperature

4.1.3. Clinical Laboratory Test

4.1.3.1. Hematology Test

• WBC with differential count (neutrophil(seg.), lymphocyte, monocyte, eosinophil, basophil), RBC, Hemoglobin, Hematocrit, Platelet

4.1.3.2. Blood Chemistry Test

• Sodium, Potassium, Chloride, Calcium, Phosphorus, BUN, Creatinine, Total protein, Albumin, Total bilirubin, Alkaline phosphatase, AST, ALT, γ-GT, LDH, CPK, Glucose, Cholesterol, LDH, Uric acid, Amylase, Lipase, Triglyceride

4.1.3.3. Urine Test

• Color, Specific gravity, pH, WBC(s), Nitrite, Albumin, Glucose, Ketone, Urobilinogen, Bilirubin, Occult blood with Microscopy

4.1.4. 12-Lead Electrocardiogram Test

Ventricular rate, PR interval, QRS, QT, QTc

4.1.5. Physical Examination

During the screening tests, all signs and symptoms of physical examination are recorded in the case report form (CRF), and newly observed abnormalities or any changes to previously observed

abnormalities (deterioration or improvement) in subsequent tests are recorded in the case report form (CRF).

4.1.6. Immunogenicity Test

Immunogenicity was evaluated by confirming the production of antibodies against hzVSF-v13

4.2. Pharmacokinetic Variables

4.2.1. Pharmacokinetic Measurements

Blood samples are collected to assess the pharmacokinetics of hzVSF-v13 until 2,184 hours after administration of the investigational product.

- Blood collection time: 1d 0h (pre-dose), 0.5, 1, 2, 4, 6, 8, 10, 12, 24(2d 0h), 36(2d 12h), 48(3d 0h), 60(3d 12h), 72(4d 0h), 96(5d 0h), 120(6d 0h), 144(7d 0h), 168(8d 0h), 336(15d 0h), 504(22d 0h), 672(29d 0h), 840(36d 0h), 1176(50d 0h), 1512(64d 0h), 1848(78d 0h), 2184h(92d 0h) (post-dose)

4.2.2. Pharmacokinetic Parameters

Parameter	Unit	Definition	Calculation Method
T_{max}	h	Time to reach maximum blood levels after administration	Direct observation in data
C_{max}	mg/L	Maximum blood concentration after administration of a single dose	Direct observation in data
AUC_{last}	mg·h/L	Area under the blood concentration-time curve from administration to the last blood collection point	Linear up/Log down (calculated by applying the linear trapezoidal rule for the increase in blood concentration and the logarithmic trapezoidal rule for the decrease in blood concentration)
AUC_{inf}	mg·h/L	Area under the blood concentration–time curve extrapolated to infinity after administration of a single dose. $AUC_{inf} = AUC_{last} + C_{last} / \lambda_z$	$AUC_{last}+C_{last}/\lambda_z$
$t_{1/2}$	h	Elimination half-life	$\ln(2)/\lambda_z$
CL	L/h	Clearance after administration of a single dose. CL = Dose / $AUC_{last,}$	$Dose/AUC_{inf}$

V_d	L	Volume of distribution after administration of a single dose. $V_d = CL / \lambda_z$	$Dose/(AUC_{inf}*\lambda_z)$

C_{last}: Blood concentration at last quantifiable blood collection time point
λ_z: Loss rate constant obtained by linear regression analysis in the log-linear plot of the part corresponding to the terminal phase of the blood concentration-time curve

5. Definitions of the Analysis Sets

5.1. Screened Set

All subjects who signed on the consent and be given the screening number.

5.2. Randomized Set

All subjects who randomized (Intention-To-Treat, ITT).

5.3. Safety Analysis Set

Subjects who are administered the investigational product at least once were analyzed.

5.4. Pharmacokinetic Analysis Set

It is intended for the subjects (Per Protocol) who have completed a as per the protocol without significant protocol violations that may affect the pharmacokinetic results. However, it can refered to the information of the subject who dropped out during the pharmacokinetic evaluation.

6. General Presentation of Summaries and Analyses

6.1. Summary Statistics

Unless other statement, continuous data (number of subjects, mean, standard deviation, coefficient of variation [%], minimum, median, maximum) is suggested by descriptive statistics. Categorical data suggested by frequency (N) and ratio (%).

6.2. Definition of Subgroups for Analysis

6.2.1. Dose Group

The subjects who are assigned on the dose group (10 mg, 20 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg).

6.2.2. Treatment Group

The subjects who are administered the investigational products indeed (Placebo, 10 mg, 20 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg).

6.3. Baseline

Unless other statement, the baseline is defined as the first value of prior to administration.

6.4. Handling of Missing Data

Unless otherwise stated, missing data (missing values) are not replaced with other values.

6.5. Software for Statistical Analysis

Statistical analysis is performed using SAS® (version 9.4 or most recent version available), etc.

6.6. Significance Level

Unless otherwise stated, statistical analysis is performed under the significance level of 0.05.

7. Methods for Analyses

7.1. Disposition and Protocol Deviations

7.1.1. Subject Disposition

An assessment of clinical study participation status is done for the screened set. The following are summarized and tabulated for each treatment group in each dose group: screened subjects, subjects that failed screening, randomized subjects, subjects that received and did not receive investigational product administration after randomization, subjects dropped out after receiving investigational product administration, and subjects that completed the clinical study.

The clinical study participation status data of each subject will be presented as a listing for all randomized subjects (randomized set).

7.1.2. Summary for Analysis Sets

The subjects included in each analysis group (Randomized Set, Safety Analysis Set, Pharmacokinetic Analysis Set) are summarized by dose group and treatment group.

7.1.3. Protocol Deviations

The evaluation of violation of the protocol is conducted for the Randomized Set. Each violations of protocol are summarized by the number of subjects, percentage (%), and number of occurrences by treatment group, and data of each subject are presented in a listing.

7.2. Demographics and Baseline Characteristics

7.2.1. Demographics

The subjects' demographic characteristics for the following items are summarized by the overall subjects, by dose group, and by treatment group.

- Age, height, weight, BMI
- Alcohol use history, smoking history, caffeine consumption

For the following items, each subject data is presented in a listing.

- Demographics
- Interview
- Urine Drug Screening
- Serology

7.2.2. Medical History

Evaluation of medical history is conducted for the Safety Analysis Set. All medical history are standardized as System Organ Class (SOC) and Preferred Term (PT) by using MedDRA® (version 21.1 or most recent version). For each treatment group and all subjects, each evaluation item is summarized in terms of the number of subjects, ratio (%), and number of occurrence cases. The data of each subject are presented as a listing.

7.2.3. Concomitant Medication

Evaluation of concomitant drug is conducted for the Safety Analysis Set. Concomitant drugs are coded into Anatomical main group (Level 1) and Therapeutic subgroup (Level 2) using WHO-DD (World Health Organization Drug Dictionary) (version 2018 or recent version), and summarize by number of subjects, percentage (%), and number of occurrences. Each subject data is presented as a listing.

7.3. Safety Evaluation

Safety evaluation is carried out for the safety set.

7.3.1. Adverse Events

All reported TEAEs/ADRs are standardized as SOC and PT by using MedDRA® (version 21.1 or most recent version). For each treatment group and all subjects, each evaluation item (severity, seriousness, causal relationship, actions taken, outcomes, treatment) are summarized in terms of the

number of subjects, ratio (%), and number of occurrence cases. If necessary, statistical testing using Fisher's exact test is performed to evaluate the differences in the pattern of adverse event occurrences between the treatment groups. The data of each subject are presented as a listing.

7.3.2. Vital Signs

Vital signs are reviewed comprehensively and were described in the clinical study report if there was clinical significance, and their relationship to the investigational product is determined. For blood pressure, pulse rate, and temperature, the quantity changes compared to the results at each point of testing, as well as compared to the baseline were summarized by treatment group. The data of each subject are presented as a listing.

7.3.3. Clinical Laboratory Test

Clinical laboratory test results are reviewed comprehensively and are described in the clinical study report if there is clinical significance, and their relationship to the investigational product is determined. For hematology and blood chemistry, the quantity changes compared to the results at each point of testing, as well as compared to the baseline are summarized by treatment group. The data of each subject are presented as a listing

7.3.4. 12-Lead Electrocardiogram Test

Electrocardiography results are reviewed comprehensively and are described in the clinical study report if there is clinical significance, and their relationship to the investigational product is determined. The quantity changes compared to the results at each point of electrocardiography, as well as compared to the baseline are summarized by treatment group. The data of each subject are presented as a listing.

7.3.5. Physical Examination

Physical examination results are reviewed comprehensively and were described in the clinical study report if there is clinical significance, and their relationship to the investigational product was determined. The data of each subject are presented as a listing.

7.4. Pharmacokinetics

Pharmacokinetic evaluation is performed on the Pharmacokinetic Analysis Set.

7.4.1. Pharmacokinetic Measurements

The blood concentration of hzVSF-v13 is summarized as the nominal time for each dose group of the test drug. And the blood concentration of each subject is presented as a listing.

7.4.2. Pharmacokinetic Profiles

The average blood concentration-time pattern of hzVSF-v13 is shown in linear and log-linear graphs for each dose group of the investigational product, and the individual blood concentration-time graph of each subject is also shown in the same way.

7.4.3. Pharmacokinetic Parameters

The pharmacokinetic parameters of hzVSF-v13 are summarized by dose group, and the pharmacokinetic parameters of each subject are presented as a listing.

To confirm dose-proportionality of the study drug, the Cmax and AUC parameters of hzVSF-v13 is shown as a graph of each administration dose of the study drug, and a regression analysis is performed using the power model.

7.5. Immunogenecity

7.5.1. Immunogenicity measurements

The immunogenicity test of hzVSF-v13 is summarized according to the nominal time of blood collection for each dose group. The immunogenicity test of each subjects is presented as listing.

7.5.2. Immunogenicity profiles

The average blood immunogenic titer-time pattern of hzVSF-v13 is shown in linear and log-linear graphs for each dose group of test drug. In addition, the individual blood concentration-time graph of each subject is also shown in the same way. If necessary, statistical tests can be performed to confirm differences between dose groups.

8. Sensitivity Analysis

Sensitivity analysis is not performed in this study.

9. Interim Analysis

No interim analysis other than the tolerability and safety evaluation to determine whether to proceed to the next dose group is performed. However, to confirm the safety of the subject, a statistical analysis can be performed by combining the tolerability and safety evaluation.

10. Change from Protocol

N.A.

11. References

N.A.

12. Appendix: List of Tables, Figures, and Listings

12.1. List of Tables

12.2. List of Figures

12.3. List of Listings