# Phase IIb Study of the Efficacy of FLU-v, a Broad Spectrum Influenza Vaccine in an H1N1 Influenza Healthy Human Challenge Model

## Statistical Analysis Plan

**NCT Number:** NCT03180801

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# Statistical Analysis Plan

FLU-v-004: Phase IIb Study of the Efficacy of FLU-v, a Broad Spectrum Influenza Vaccine in an H1N1 Influenza Healthy Human Challenge Model

Version 2.0 17 January 2018

Prepared by: National Institute of Allergy and Infectious Diseases,
PepTcell t/a SEEK and hVIVO

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**Approvals:**

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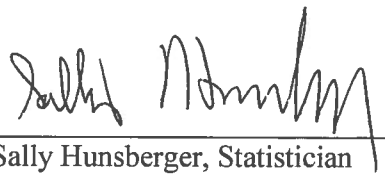
|  | |
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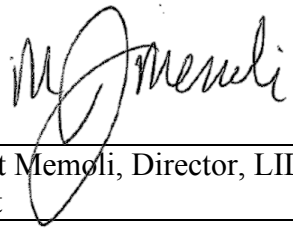
| |  |
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| 17/01/2018 | 17 JAN 2018 |
| Michael Ghebre, Statistician | John Efthimiou, Executive Vice President, Translational Medicine |

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## 1 Study Design

A randomized, double-blind, placebo-controlled efficacy and safety trial of FLU-v administered as 2 vaccinations or 1 vaccination vs placebo prior to intranasal challenge with the Influenza A 2009 H1N1 human virus.

In this study, the main efficacy comparisons are for each of the FLU-v groups to placebo. The study will not compare the two FLU-v dosing arms as the study may not have enough power to detect a significant difference in the primary efficacy endpoint of mild to moderate influenza induced disease (MMID) rates between the FLU-v groups.

## 2 Current Approved Study Protocol

The current approved study protocol is version 3.0 dated 18APR2017.

## 3 Study Hypothesis

The hypothesis is that vaccination with one dose or two doses of FLU-v + adjuvant will significantly reduce MMID when compared to individuals vaccinated with placebo.

## 4 Sample Size Justification and Analysis Plan

Sample size was calculated for 3 groups, a placebo group and 2 Investigational Medicinal Product (IMP) (i.e. one dose and two doses of FLU-v) groups. Each FLU-v arm will be compared to the placebo arm. Groups are randomized 1:1:1. All comparisons are at the 0.05 one-sided alpha level, and any p-value less than 0.05 would be considered as significant. This may increase the type-I error rate of potentially moving forward with an inactive treatment, but is appropriate for an early phase II trial of this type. Sample sizes assuming two different placebo MMID rates and for 80% power are given in Table 1 below.

**Table 1.**

| **Probability (rate) of MMID** | | **Sample size per arm** | **Total sample size** | **Power** | **One-sided alpha** |
|---|---|---|---|---|---|
| Placebo | Vaccine | | | | |
| 0.7 | 0.4 | 40 | 120 | 80% | 0.05 |
| 0.8 | 0.5 | 37 | 111 | 80% | 0.05 |

Table 1 shows that a sample size of 120 (40 per group) provides good power (80%) for a placebo MMID rate of 0.7 and an absolute reduction of 30%. The difference is clinically meaningful and the assumptions of a placebo MMID rate of 0.70 is reasonable and based on past experience.[1]

## 5 Analysis Plan and Reports

The primary analysis population will be the Intent to Treat (ITT) population and will be used for the analysis of all primary and secondary endpoints. The ITT will include those participants who received both vaccination and challenge with an influenza virus.

The Per Protocol (PP) analysis population is defined as a subset of the ITT population who have no major protocol deviations (complied with the protocol appropriately in order to ensure that these data would be likely to reveal the effect of treatment). At a Blinded Data Review Meeting (BDRM), which will take place prior to database lock, ITT analysis set subjects will be reviewed for their inclusion/exclusion to the PP population.

Any participant who received at least one immunization but did not receive the influenza challenge virus will not be part of the ITT or PP analysis populations, but will be part of the safety population (SAF).

Subject disposition will be presented as a flow chart and will include number of subjects randomised, number of subjects that received one or two doses of FLU-v or placebo, number of vaccinated subjects that received the challenge virus, the number of subjects that withdrew from the study and the number of subjects that completed the study in each arm. Primary, secondary and safety endpoints will be presented in the clinical study report. Analysis and reporting of exploratory endpoints may be separate to the clinical study report.

### 5.1 Primary Objective

To determine the effect of FLU-v in reducing the incidence of Mild to Moderate Influenza Induced Disease (MMID) defined as detectable viral shedding plus at least one symptom of influenza from Day 1 post-inoculation until Day 7. Day 1 post-inoculation evaluations were completed in the evening of Day 1, more than 24 hours post-inoculation.

### 5.2 Primary Endpoint: Incidence of MMID

MMID is defined as positive if a participant has both detectable shedding, as evaluated by RT-qPCR (reverse transcriptase quantitative polymerase chain reaction), and at least one symptom,

as observed on the Physician Assessment of Influenza Symptoms (PAI), at any time during subject quarantine, starting from the evening of Day 1 post-inoculation through the expected end of the quarantine period, Day 7, Discharge. The analysis of this endpoint will be performed by comparing the MMID rates in each of the FLU-v groups to the placebo group. Comparisons will be performed using one-sided Fisher's exact test, and the proportion of subjects with MMID and corresponding p-value will be presented. If a subject has no nasal swab data on two consecutive days, and the available recorded data shows no shedding, the MMID for that subject will be considered as missing. Similarly, if symptom data is not recorded on two consecutive days, and the available recorded data shows no symptoms, the MMID will be considered as missing for that subject. However, if a subject is positive for viral shedding and experiences at least one symptom with the available recorded data, that subject will be included in the MMID analysis. The primary analysis will incorporate missing data as described in section 5.7. The statistical summary data will be presented as tables and figures as described in sections 8-9 of this document.

## 5.3 Secondary Objectives:

To determine the overall effect of FLU-v on influenza disease based on disease severity measures (presence or absence of symptoms or shedding, symptom severity, symptom and shedding duration, total symptoms and shedding, and peak symptom and shedding). Viral shedding was evaluated by RT-qPCR and symptoms were evaluated by PAI, from the evening of Day 1 post-inoculation (more than 24 hours after inoculation) through the expected end of the quarantine period (Day 7, Discharge).

## 5.4 Secondary Endpoints:

- Overview of symptoms (PAI) and of viral shedding (RT-qPCR) from the evening of Day 1 post-inoculation (more than 24 hours after inoculation) through Day 7.
    - If a subject has no nasal swab data on two consecutive days, and the available recorded data shows no shedding, the endpoint will be considered as missing. Similarly, if symptom data is not recorded on two consecutive days, and the available recorded data shows no symptoms, the endpoint will be considered as missing for that subject. However, if a subject is positive for viral shedding with the available recorded data, that subject will be included in the analysis. Similarly, if the subject shows at least one symptom within the recorded data, that subject will be included in the analysis.

- Modified MMID
    - Incidence of at least two symptoms (on PAI) and viral shedding (RT-qPCR) at any time during the quarantine from evening of Day 1 post-inoculation through Day 7. If a subject has no nasal swab data on two consecutive days, and the available recorded data shows no shedding, the Modified MMID will be considered as missing. Similarly, if symptom data is not recorded on two consecutive days and the available recorded data shows no symptoms this endpoint will be considered as missing for that subject. However, if a subject is positive for viral shedding and experiences at least two symptoms with the available recorded data, that subject will be included in the modified MMID analysis.
- Viral shedding duration (days)
    - Measured from the first day with a positive test on RT-qPCR, starting from evening of Day 1 post-inoculation until the last day with a positive test during the expected quarantine period (up to Day 7). Intervening negative or missing test days will be included in the duration. If no positive test occurs, duration is counted as zero.
- Viral shedding quantitation (RT-qPCR)
    - Area under the curve (AUC) will be calculated based on each timepoint tested on RT-qPCR (log copy number/ml) record from evening of Day 1 post-inoculation to the morning of Day 7 (last timepoint before expected quarantine discharge) using Trapezoidal rule, and those samples below lower limit of quantification (LLOQ) will be replaced by half of LLOQ. Linear interpolation will be used for a single missing measurement. If more than one consecutive point is missing, the endpoint is considered as missing. RT-qPCR peak during entire quarantine period (i.e. the highest level of RT-qPCR recorded anytime during the quarantine period, starting from evening of Day 1 post-inoculation up to Day 7. A single maximum RT-qPCR (peak) will be identified for each subject during the quarantine on the assumption that a peak is recorded during the quarantine. Thus, there will not be imputation to predict the peak for subjects who have suspected missing peak data as it is implausible to predict the missing peak from the rest of the existing data.
- Symptom duration in days (PAI)
    - Number of days from first symptom noted, starting the evening of Day 1 post-inoculation until the day of last symptom noted up to Day 7. Intervening days with no symptoms or

missing symptom data will be included in the duration. If no symptoms occur during the entire period, number of days is zero.

- Total number of symptoms experienced (PAI)
  - Mean of total number of symptoms (upper and lower respiratory and systemic symptoms) experienced from the evening of Day 1 post-inoculation until the day of last symptom noted during the expected quarantine period (up to Day 7). Calculated as the total sum of symptoms experienced divided by the number of days in which symptoms were collected.
- Total symptoms score peak (PAI)
  - The highest level of the total sum of all upper and lower respiratory tract and systemic symptoms recorded on any day starting from the evening of Day 1 post-inoculation until the day of last symptom noted during the expected quarantine period (up to Day 7).
- Symptom severity score as measured by FLU-PRO Symptom Questionnaire
  - Mean of daily score over all study quarantine days from Day 1 post-inoculation to Day 7. If a day has missing data, this day will be excluded from the mean calculation (days with 0 as the symptom severity will be included in calculating the average).
- Comparison of each treatment group to placebo of the proportion of asymptomatic infected subjects defined as subjects with symptom score of zero (PAI) from Day 1 post-inoculation time-point through the expected end of quarantine (Day 7) with at least one positive result for viral shedding (RT-qPCR) in any of the quarantine days from the evening of Day 1 post-inoculation.
- Summary of Adverse Events from the Post-Vaccination Diary Card
  - The number of subjects who self-reported at least once any of the adverse events listed in the Post-Vaccination Diary Card during the 21 days following first vaccination and 21 days following second vaccination. Data will be presented for each treatment group by event and according to severity (mild, moderate, severe). The number of subjects in each treatment group with no self-reported events will also be presented.

The statistical software to be used for the analyses will be SAS (version 9.4) and R (version 3.43). The analyses of the secondary binary endpoints will be performed by comparing the rates in each of the FLU-v groups to the placebo group using one-sided Fisher's exact test. For all secondary endpoints, the primary analysis will assume missing data is missing at random so missing data will be ignored.

The analysis of all continuous secondary endpoints will be performed by calculating the median and interquartile range and then performing a one-sided Wilcoxon Rank Sum Test at 0.05 level of significance. These data will be reported as tables and figures as described in sections 8-9 of this document.

Statistical analysis will be performed by a junior statistician at NIAID-NIH and will be reviewed by the senior statistician. In addition, the Senior Clinical and Scientific Leader, will repeat the statistical analysis to validate the results.

### 5.5 Exploratory Endpoints

- Immunogenicity of FLU-v after vaccination and influenza challenge.
  - The titer of FLU-v specific IgM and IgG antibodies in pre-vaccinated, post-vaccinated and post-challenged sera will be measured. Further isotyping of the response and functional assays may be performed. FLU-v-specific T-cell responses will be measured in PBMCs from pre-vaccination, post-vaccination and post-challenge.
- Broadness of protection of FLU-v
  - PBMCs will be exposed to at least 5 different influenza strains prior to measuring markers of T-cell activation.

The data for the exploratory analysis may be presented separately to the main clinical study report.

### 5.6 Safety Endpoints (pre- and post-inoculation)

- **Adverse Events:** Adverse event (AE) terms will be coded using MedDRA version 19.1. Treatment emergent AEs (TEAE) will be reported within summary presentations, by MedDRA system organ class (SOC) and preferred term (PT), and by treatment group. An AE will be classified as treatment emergent if the onset date of the AE is on or after the first administration of vaccine. In the case of partial dates being recorded, a conservative approach will be adopted for inclusion of such events within these reporting periods. If a subject experiences more than one AE with the same preferred term (within reporting period being considered) that preferred term will be counted only once in summary presentations. It will be assigned the worst observed severity and the strongest relationship to IMP among those events for summaries in which those characteristics are considered. Summary presentations will be produced for the number and percentage of subjects reporting treatment emergent AEs, AEs by severity, and AEs related to vaccine administration (by relationship). In addition, SAEs and AEs directly resulting in withdrawal from study will be summarised. Summaries

will be separated into pre-inoculation (events reported from the time of first vaccination up to Day 0 prior to time of inoculation) and post-inoculation (Day 0 inoculation time through study completion). AE rates, evaluated between groups to placebo, will be performed using Fishers exact test.

- **Laboratory parameters:** Laboratory parameters (haematology, biochemistry, cardiac enzymes, coagulation and urinalysis) will be presented as a comparison of treatment groups and placebo by No abnormality detected, Abnormal Not Clinically Significant (NCS), Abnormal Clinically Significant (CS) and Not Available. Laboratory values outside the normal range will be identified in subject listings.
- **Physical Examination:** Physical examination findings (Complete Physical Exam and Directed Physical Exam) will be included within subject listings.
- **Concomitant medication:** Concomitant medication terms will be coded using the WHO Drug Dictionary Enhanced version 2016:3 (September 1, 2016). Medications will be assigned as being prior to vaccine administration (IMP dosing), or concomitant with IMP dosing based on start and stop dates of the medication and the timing of receiving IMP. If the medication stop date is before the date of IMP (when applicable), the medication will be assigned as being prior to IMP. In all other situations, the medication will be assigned as being concomitant with IMP. Prior and concomitant medications (separately identified) will be included in subject listings.

## 5.7 Handling of Missing Data

This study relies primarily on clinical endpoints, with constant monitoring of the subjects by the quarantine unit clinical staff. The likelihood of missing data for the primary and secondary endpoints is therefore low. However, in the event a significant amount of data is missing, a full investigation will need to be performed to carefully evaluate the study conduct. Participants who did not receive the challenge virus will not be included in any of the analyses, however data will be included in safety listings (i.e. AE, Concomitant Medication, Laboratory, etc.). All participants who received at least one FLU-v vaccination will be included in the SAF population.

For all endpoints where missing data occurs (as defined in section 5) the following sequence of analyses will be performed in order to understand the impact of the missing data on the results.

### 5.7.1 Primary endpoint

- Primary analysis: impute the placebo group's proportion of events for the missing data in each group.
- Sensitivity analysis: ignore missing data.
- Sensitivity analysis: for placebo group impute observed proportion from vaccine group and for vaccine group impute observed proportion from placebo group.

### 5.7.2 Secondary endpoints

For all endpoints where missing data occurs, sensitivity analyses will be performed in order to understand the impact of the missing data on the results.

### 5.7.3 Binary endpoints

- Primary analysis: Assuming missing data is missing at random: ignore missing data
- Sensitivity analysis: impute the placebo group's proportion of events for the missing data in each group
- Sensitivity analysis: for placebo group impute observed proportion from vaccine group and for vaccine group impute observed proportion from placebo group

### 5.7 4 Continuous endpoints:

- Primary Analysis: ignore missing data
- Sensitivity analysis: In Wilcoxon test give placebo group the best rank and the vaccine group the worst rank

## 5.8 Post-Hoc Analyses

Where possible all analyses will be prospectively planned and carried out according to this SAP. However, in the event of any significantly anomalous data or events which make any data or conclusions unreliable or scientifically questionable, then further relevant post-hoc analyses may be carried out. For example, but not limited to:

- Analysis of primary and secondary endpoints with removal of data from subjects where other respiratory infections have occurred concomitantly with the study challenge influenza virus (including 48 hours pre-inoculation and on day 2 or day 5 post-inoculation);
- Analysis of efficacy data including only subjects with an Haemagglutinin inhibition (HAI) titer for the challenge strain pre-inoculation lower than 40,
- Analysis of efficacy data comparing subjects whose HAI titer to the challenge strain rose from screening to pre-inoculation compared to those whose titer didn't change,

- Analysis with removal of data from subjects with any pre-existing heterotypic T-cell immunity to the study flu challenge virus,
- Due to the recall of atomisers in batch 160728, six subjects were inoculated with Challenge Virus with atomisers from the recalled batch, and 34 subjects were administered Challenge Virus using one atomiser per nostril rather than two atomisers per administration. Post-hoc analyses will be performed on the primary and secondary endpoints to assess whether there was any effect of the atomizer recall or/and from inoculating with one rather than two atomisers.
- Analysis of primary and secondary endpoint data (RT-qPCR and PAI) to include the data for subjects discharged from quarantine after Day 7.
- Analysis of the FLU-PRO secondary endpoint to include data for subjects discharged from quarantine after Day 7. This post-hoc analysis may also include reporting of proportion of symptomatic days and duration of symptoms for quarantine days.

## 6 Changes to the protocol-specified analyses

No changes to the protocol-specified analyses apart from the proposed and pre-defined post-hoc analyses.

There is a discrepancy between the sample size stated in the protocol and the sample size stated in Section 4 of this document. The protocol allowed for one additional subject per treatment group to account for unexpected subjects exclusion in the per protocol population due to a major protocol deviations.

## 7 References

[1]Memoli MJ et al. Validation of the wild-type influenza A human challenge model H1N1pdMIST: an A(H1N1) pdm09 dose-finding investigational new drug study.
Clin Infect Dis. 2015 Mar 1;60(5):693-702. doi: 10.1093/cid/ciu924. Epub 2014 Nov 20

# 8 Tables, Figures and Listings

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| 16.2.4.1 | Demographics |
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| Listing | Title |
|---|---|
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| Table | Title |
|---|---|
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| 14.3.3 | Clinical Laboratory Safety - Overall Summary |

*Per Protocol (PP) population differs from Intent to Treat (ITT) by only 1 subject. The data will be presented for Intent to Treat only in the final analyses, unless analyses of using PP differs significantly. If PP is presented, an additional digit will be added to table numbers with ITT as 14.2.X.X.1 and PP as 14.2.X.X.2.

**Summary of Figures**

**For all figures listed below:**
a) box plots with medians, 25%, 75%tiles by group will be shown ignoring missing data.
b) box plots with medians, 25%, 75%tiles by group will be shown imputing missing as described for the sensitivity analysis.

| Figure | Title |
|---|---|
| 14.1.1 | Subject Disposition – Safety |
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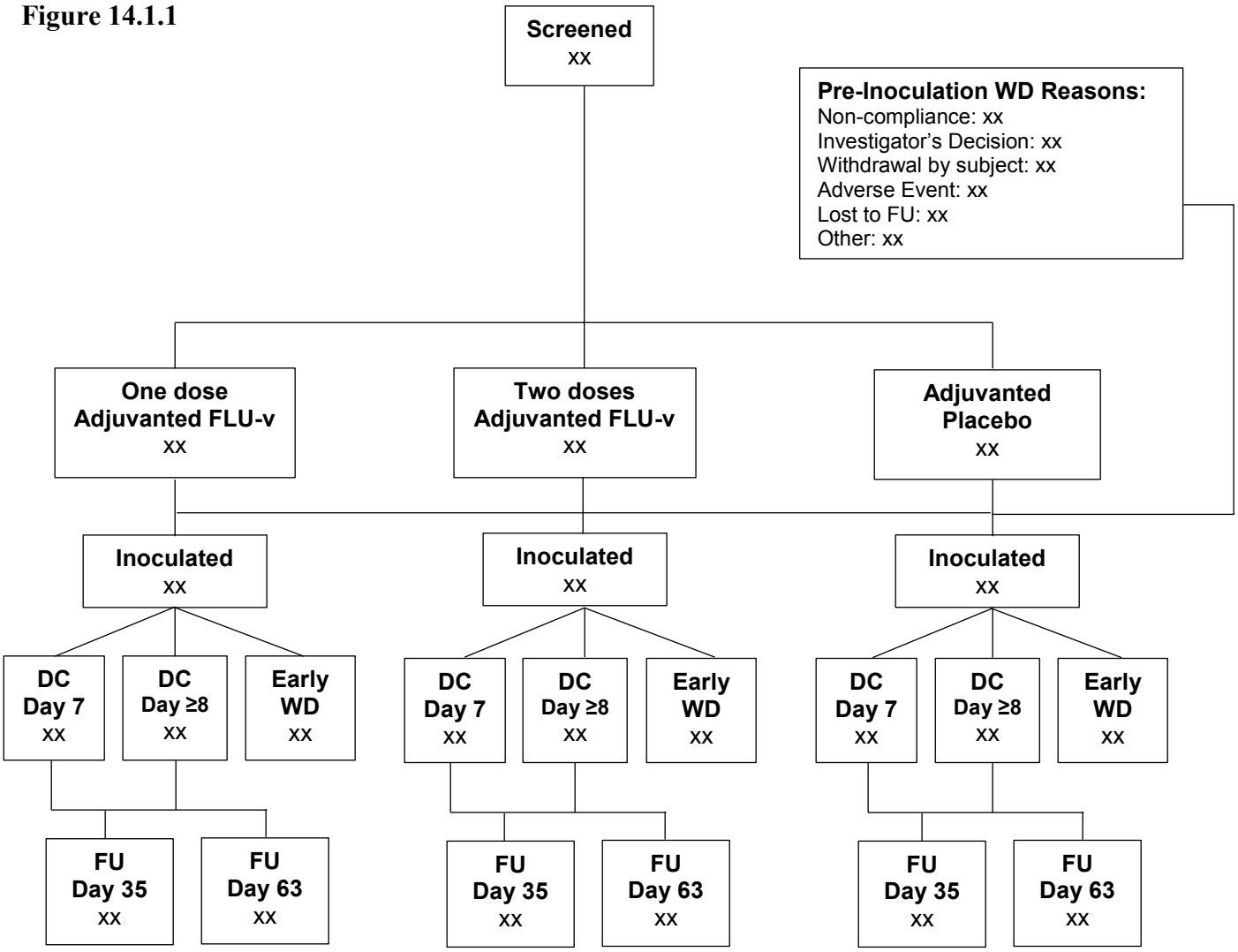
# 9 Appendix – Shell Figure 14.1.1 and Shell Tables

**Shell tables are provided as a separate document**

**Figure 14.1.1**




DC = Discharge; WD = Withdrawal; FU = Follow-up
Source dataset: