CLINICAL STUDY PROTOCOL

Phase 1b clinical study to investigate the safety and immunogenicity of the Bris10 (A/Brisbane/10/2007) M2SR and Sing2016 (A/Singapore/INFIMH-16-0019/2016) M2SR H3N2 monovalent influenza vaccines

Products	Bris10 M2SR Vaccine and Sing2016 M2SR Vaccine
Protocol Number	FLUGEN-H3N2-V003
IND Number	016968
Clinical Phase	1b
Clinical Indication	Not applicable (Healthy Volunteers)

Initial Protocol Version 1.0, 30-Apr-2019
Amendment 1 Version 2.0, 14-May-2019
Amendment 2 Version 3.0, 17-May-2019
Amendment 3 Version 4.0, 08-August-2019
Amendment 4 Version 5.0, 21-August-2019
Amendment 5 Version 6.0, 26-September-2019
Amendment 6 Version 7.0, 28-October-2019
Amendment 7 Version 8.0, 18-May-2020

This study will be conducted in compliance with this protocol, the ICH Note for Guidance on Good Clinical Practice (CMPM/ICH/135/95) and with the applicable regulatory requirement(s)

Sponsor	FluGen Corporation
Sponsor Representative	Pamuk Bilsel
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SIGNATURES

Signature of FluGen, Inc. Representative

Study Title: Phase 1b clinical study to investigate the safety and immunogenicity of the Bris10 (A/Brisbane/10/2007) M2SR and Sing2016 (A/Singapore/INFIMH-16-0019/2016) M2SR H3N2 monovalent influenza vaccines

Protocol Date: 30APR2019

Name: Pamuk Bilsel, PhD

Affiliation: FluGen, Inc.

Address: 597 Science Drive, Madison, WI USA 53711

This Clinical Study Protocol has been reviewed and approved by the Sponsor in order to ensure compliance with Good Clinical Practice.

Signature:

Date:

Signature of FluGen, Inc. Statistician

Study Title: Phase 1b clinical study to investigate the safety and immunogenicity of the Bris10 (A/Brisbane/10/2007) M2SR and Sing2016 (A/Singapore/INFIMH-16-0019/2016) M2SR H3N2 monovalent influenza vaccines

Protocol Date: 30APR2019

Name: Roger Aitchison

Affiliation: North Rim Consulting

Address: 814 Plateau Road, Longmont, Colorado USA 80504

This Clinical Study Protocol has been reviewed and approved by the study statistician in order to ensure that the protocol and any amendments cover all relevant statistical matters clearly and accurately, using technical terminology as appropriate.

Signature:

Date:

PROTOCOL HISTORY

FluGen, Inc. – FLUGEN-H3N2-V003

Document	Issue Date	Amendment Type	Comments
Initial Clinical Study Protocol	30APR2019	Not applicable	
Protocol V2.0	14MAY2019	Non-substantial amendment	1. Statement that study is funded by US Department of Defense 2. New exclusion: Active military personnel not allowed to participate in the study 3. Subjects are not allowed to use a Legally Authorized Representative 4. ICF must be administered individually to each subject and in a private setting 5. Clarified duties and responsibilities of Medical Monitor 6. Minor corrections and clarifications including word modification and administrative changes
Protocol V3.0	17May2019	Non-substantial amendment	1. Updated to reflect what information will be collected if pregnancy occurs during the study 2. Expanded and added clarity on the roles and responsibilities of the Medical Monitor 3. Added details on how subjects will be identified and recruited for this study
Protocol V4.0	08August2019	Non-substantial amendment	1. Updated to clarify pregnancy occurring during trial. 2. Added further details on identifying and recruiting subjects.
Protocol V5.0	21August2019	Non-substantial amendment	1. Updated to change the Lead Principal Investigator and site PI credentials 2. Clarified that a site-specific Informed Consent Form, not a separate protocol ICF, may be used for consent to assess a subject's microneutralization titer to Sing2016 3. Clarified inclusion and exclusion criteria 4. Added a ± 1-day window to Day 4 after each dose and 90-day window for pre-screen 5. Clarified study event details 6. Minor corrections and clarifications including word modification and administrative changes

Protocol V6.0	26September2019	Non-substantial amendment	1. Corrected 60-day to 90-day for MN titers consistent with other sections of protocol 2. Updated exclusion 3 to clarify that subjects with clinically significant abnormal screening lab values should be excluded
Protocol V7.0	28October2019	Non-substantial amendment	1. Clarified that concomitant medications are to be recorded from time of signing ICF to Day 57. 2. Clarified that subjects are to be observed approximately 5 and 30 minutes after dosing. 3. Clarified that subjects are to be at rest for approximately 5 minutes prior to measurements of vital signs. 4. Inserted text at 6.1.3 to instruct sites in regions of increased influenza activity to ask subjects to report any influenza symptoms and to collect a nasal swab if needed for lab confirmation of influenza infection.
Protocol V8.0	18May2020	Non-substantial amendment	1. Section 9.8 was revised in protocol v4.0 08AUG2019 but the original language was inadvertently re-instated in v5.0 21AUG2019 and remained in later versions. The language from section 9.8 of protocol v4.0 is the intended language. 2. Section 6.1.2.8, exclusions 6 and 15, and Table 3 were revised to allow for a safety phone call on Day 209 due to prevalence of COVID-19. 3. Addition of vendors to Study Administrative Structure and Investigators. 4. Minor corrections and clarifications including word modifications.

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PROTOCOL SYNOPSIS

Study Title	Phase 1b clinical study to investigate the safety and immunogenicity of the Bris10 (A/Brisbane/10/2007) M2SR and Sing2016 (A/Singapore/INFIMH-16-0019/2016) M2SR H3N2 monovalent influenza vaccines		
Product	Bris10 M2SR Vaccine (Lot#10250) Sing2016 M2SR Vaccine (Lot# 19097)	**Clinical Phase**	1b
Protocol Number	FLUGEN-H3N2-V003	**Indication**	Prophylactic H3N2 monovalent influenza vaccines, Bris10 (A/Brisbane10/2007) M2SR and Sing2016 (A/Singapore/INFIMH-16-0019/2016) M2SR, for protection against influenza disease caused by seasonal influenza A viruses.
IND Number	IND# 016968		

Sponsor	FluGen Corporation 597 Science Drive Madison, WI USA 53711 Funded by: United States Department of Defense (DoD)
Sponsor Representative	Pamuk Bilsel, PhD
Principal Investigator(s) (*Lead PI)	1. Carlos Fierro, MD* 2. Howard Schwartz, MD 3. Mark Adams, MD 4. Kimberly J. Ellis, DO
Clinical Center(s)	1. Johnson County Clin-Trials 2. Research Centers of America 3. Alliance for Multispecialty Research, Lexington 4. Alliance for Multispecialty Research, Norfolk
Study Period	**Initiation:** August 2019 **Completion:** April 2020
Number of Subjects	Approximately 250 evaluable subjects

Introduction:

FluGen, Inc., a biotech company based in Madison WI, USA, is developing a novel M2-deficient single replication live influenza vaccine platform M2SR to provide safe, effective protection against seasonal influenza strains. The vaccine virus does not express an essential viral protein (influenza M2), restricting it to a single replication cycle in the host. The initial (prototypical) product, designated as Bris10 M2SR vaccine, was intended to elicit an immune response to the vaccine virus, A/Brisbane/10/2007 (H3N2). Available data from Phase 1 and 2a studies have shown that a single intranasal dose of Bris10 M2SR vaccine is safe, immunogenic, and provided protection against a highly drifted H3N2 influenza challenge agent among adult subjects who demonstrated a serum immune response following vaccination. Ultimately the vaccine development program aims to evaluate a quadrivalent M2SR vaccine containing two influenza A subtypes (H1N1-like and H3N2-like viruses) and two influenza B types.

Previous clinical experience with the M2SR vaccine platform includes a First Time in Human (FTIH) Phase 1 dose escalation study in healthy adults, an on-going Phase 1 safety and immunogenicity study in adolescents and a Phase 2a challenge study in healthy adults using the H3N2 vaccine Bris10 M2SR.

Between the FTIH Phase 1 and the Phase 2a challenge studies, a total of 72 adult subjects have been exposed to the highest dose of Bris10 M2SR tested (10^8 $TCID_{50}$) with no SAEs or AEs of clinical significance or observations that would halt these studies. In addition, in the challenge study, 48 subjects who received the live, single-replication M2SR virus were subsequently challenged with a live, replicating influenza virus. A portion of those individuals experienced infection and symptoms consistent with influenza (e.g., nasal congestion, runny nose, sore throat, cough, tiredness, headache), but at frequency less than observed among individuals in the same study who did not receive vaccine prior to challenge. Of the 19 adolescents enrolled in the ongoing second Phase 1 study, while the randomization was set at 1:1 active to placebo, it is not known exactly how many received active investigational vaccine (M2SR), but in blinded review no safety concerns related to the M2SR vaccine have been reported. Combined, these findings indicate that the vaccine is safe and generally well tolerated as a single 10^8 $TCID_{50}$ dose.

The purpose of this Phase 1b dose escalation clinical study is to assess the safety, tolerability/reactogenicity, and immunogenicity of M2SR vaccines when delivered at higher dosages or in two doses to increase the proportion of subjects responding serologically to the vaccine. For this study, an updated vaccine, Sing2016 M2SR, has been prepared that will provide the HA and NA components from A/Singapore/INFIMH-16-0019/2016, the H3N2 strain recommended for the 2018-2019 influenza season.

Due to the COVID-19 pandemic, local governments may issue stay-at-home orders which prevent centers from conducting on-site Day 209 visits. This protocol allows for Day 209 visit to be a safety follow-up phone call.

Objectives:

Primary Objectives:

The primary objectives are:

1. To assess the safety and tolerability of one and two administrations of the Bris10 M2SR influenza vaccine each at 10^8 $TCID_{50}$ delivered intranasally to healthy adult subjects.

2. To assess the safety and tolerability of one and two administrations of the Sing2016 M2SR influenza vaccine each at 10^8, $10^{8.5}$ and 10^9 $TCID_{50}$ delivered intranasally to healthy adult subjects

Secondary Objectives:

The secondary objectives are:

1. To assess the immunogenicity (serum antibody, mucosal antibody and cellular immune responses) of one and two administrations of Bris10 M2SR vaccine at 10^8 $TCID_{50}$.
2. To assess the immunogenicity (serum antibody, mucosal antibody and cellular immune responses) of one and two administrations of Sing2016 M2SR vaccine at 10^8, $10^{8.5}$ and 10^9 $TCID_{50}$.
3. To evaluate vaccine virus shedding after intranasal delivery.

Exploratory Objectives:

The exploratory objectives are:

1. To evaluate cell mediated immunity for up to 2 months after the last vaccination.
2. To evaluate additional vaccine-related immune responses during the period of study participation.

Criteria for Evaluation:

Primary endpoints:

The primary endpoints are:

1. The number and percentage of study participants who experience any vaccine-associated adverse events (AEs) or serious adverse events (SAEs) after Bris10 M2SR or placebo administration.
2. The number and percentage of study participants who experience any vaccine-associated AEs or SAEs after Sing2016 M2SR or placebo administration.

Secondary endpoints:

The secondary endpoints are:

1. The number and percentage of study participants who after one or two doses of Bris10 M2SR or placebo demonstrate:
    i. Influenza-specific serum antibody responses measured at specified time points;
    ii. Influenza-specific mucosal IgA antibody responses measured at specified time points;
    iii. Influenza-specific cellular immune responses measured by cytokine enzyme-linked immunospot (ELISPOT) at specified time points.
2. The number and percentage of study participants who after one or two doses of Sing2016 M2SR or placebo demonstrate:
    - Influenza-specific serum antibody responses measured at specified time points;
    - Influenza-specific mucosal IgA antibody responses measured at specified time points;
    - Influenza-specific cellular immune responses measured by ELISPOT at specified sampling time points.

3. Vaccine virus shedding evaluated by influenza A-specific qPCR on day 7 post IP administration.

Exploratory endpoints:

The exploratory endpoints are:

1. Cell-mediated immunity (CMI) assessed by frequencies and fold increases of antigen-specific T-lymphocytes.
2. Additional influenza-specific immunological assays may be performed.

Overview of Study Design:

This is a randomized, double-blind, placebo-controlled Phase 1 study evaluating the safety and immunogenicity of the Bris10 M2SR and Sing2016 M2SR H3N2 influenza vaccines delivered intranasally to healthy adults.

Eligible subjects will be screened and randomized to receive two administrations 28 days apart of Sing2016 at three dose levels, Bris10 at one dose level, or placebo in a 1:1:1:1:1 ratio. An overview of the planned dose cohorts is presented in (Table 1).

Table 1: Dose Cohorts

Dose Cohort	Number of Subjects	Number in Sentinel Group	Number in Expansion Group
1. 10^8 $TCID_{50}$ Sing2016 M2SR	50	9	41
2. $10^{8.5}$ $TCID_{50}$ Sing2016 M2SR	50	9	41
3. 10^9 $TCID_{50}$ Sing2016 M2SR	50	9	41
4. 10^8 $TCID_{50}$ Bris10 M2SR	50	9	41
5. Placebo	50	9	41
Total	250	45	205

As shown in Table 2, three sentinel groups will be vaccinated first, each containing 15 subjects (9 subjects receiving escalating doses of Sing2016 M2SR, 3 subjects receiving Bris10 M2SR, and 3 subjects receiving placebo), followed by the remainder of the subjects in an expansion group. Cohorts are split into multiple groups to alleviate PBMC processing issues of large numbers of samples. Dosing will be staggered to allow for review of AEs through Day 3 post-administration for each sentinel group prior to dose escalation. A Safety Review Committee (SRC) will review available safety data from all sentinel subjects after subjects have completed 7 days after vaccination, prior to dosing of the expansion group. A comprehensive list of safety parameters collected during the study are described in Table 3.

Table 2: Dosing and Safety Reviews

	Dose Cohort *	N	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15
Sentinel Group 1	1	9	Dose 1	Safety			Dose 2	Safety									
	4	3	Dose 1	Safety			Dose 2	Safety									
	5	3	Dose 1	Safety			Dose 2	Safety									
Sentinel Group 2	2	9			Dose 1	Safety			Dose 2	Safety							
	4	3			Dose 1	Safety			Dose 2	Safety							
	5	3			Dose 1	Safety			Dose 2	Safety							
Sentinel Group 3	3	9					Dose 1	Safety			Dose 2	Safety					
	4	3					Dose 1	Safety			Dose 2	Safety					
	5	3					Dose 1	Safety	SRC		Dose 2	Safety	SRC				
Expansion Group	1	21								Dose 1	Safety			Dose 2	Safety		
	2	21								Dose 1	Safety			Dose 2	Safety		
	3	21								Dose 1	Safety			Dose 2	Safety		
	4	21								Dose 1	Safety			Dose 2	Safety		
	5	21								Dose 1	Safety			Dose 2	Safety		
	1	20										Dose 1	Safety			Dose 2	Safety
	2	20										Dose 1	Safety			Dose 2	Safety
	3	20										Dose 1	Safety			Dose 2	Safety
	4	20										Dose 1	Safety			Dose 2	Safety
	5	20										Dose 1	Safety			Dose 2	Safety

*Dose Cohort 1 = Sing2016 M2SR 10^8, Dose Cohort 2 = Sing2016 M2SR $10^{8.5}$, Dose Cohort 3 = Sing2016 M2SR 10^9, Dose Cohort 4 = Bris10 M2SR10^8, Dose Cohort 5 = saline placebo
Notes: Safety indicates a review by the Lead PI and/or Medical Monitor as detailed below in Study Conduct. SRC indicates a review by the SRC as detailed below in Study Conduct. The Expansion Group schedule may be extended based on speed of enrollment.

Using one nasal sprayer per nare, up to 0.5 mL of the Sing2016 M2SR vaccine or placebo (a total of up to 1.0 mL) and up to 0.2 mL of the Bris10 M2SR vaccine (a total of up to 0.4 mL), will be delivered per subject per administration. The study will administer escalating doses of Sing2016 M2SR vaccine, with a starting dose of 10^8 $TCID_{50}$ increasing in half log (3-fold) increments to a maximum dose of 10^9 $TCID_{50}$. Controls will be saline placebo and a 10^8 $TCID_{50}$ dosage of Bris10 M2SR.

Five (5) dose cohorts of 50 subjects each will be enrolled, for a total of approximately 250 subjects randomized 1:1:1:1:1 to receive either Sing2016 M2SR 10^8, Sing2016 M2SR $10^{8.5}$, Sing2016 M2SR 10^9, Bris10 M2SR or saline placebo. A sentinel group of 9 subjects (~18% of each escalating dose cohort) will be vaccinated first, followed by the remainder of the dose cohort in an expansion group. Subjects in each sentinel group will be actively followed for 3 days and if the Medical Monitor and/or Lead PI determine that no halting rules have been met, the next sentinel group will be enrolled. After all sentinel subjects have completed 7 days following vaccination, a Safety Review Committee (SRC) will review available safety data prior to enrollment and vaccination of the expansion groups. All dosed subjects will receive a second dose of the assigned investigational product (IP) approximately 28 days after receiving the first dose. The SRC review of sentinel data prior to enrollment of expansion subjects may occur concurrently with or following the administration of second doses of vaccine to sentinel subjects.

SAEs occurring at any time during the study will be recorded. Administration site and solicited AEs will be recorded through 7 days after each vaccination (Days 8 and 29) and unsolicited AEs will be recorded through 28 days after the last vaccination (Day 57). An SRC, comprised at a minimum of two independent physicians experienced in vaccine

research and a biostatistician, will be available to review safety data at specified time points and as needed.

Based on the safety reviews, an intermediate or lower dose may be chosen to replace the planned dose for a dose cohort. If a lower or intermediate dose is chosen that dose will be used for an entire dose cohort. Should dosing be delayed for safety review or enrollment issues, subjects may receive their second dose at a time later than defined in the proposed dosing window.

While safety and tolerability are the primary objectives, this clinical study is also designed to assess the immune response to one and two doses of each of the investigational vaccines at each of the designated dose levels. Immunogenicity will be assessed by measuring serum antibody responses by hemagglutination inhibition (HAI) and/or microneutralization (MN) assay. Additional immune parameters will be assessed including mucosal antibody titers and cell-mediated immunity. Subjects will be pre-screened, under a site-specific Informed Consent Form (ICF), to avoid enrollment of individuals with high MN titers (> 1:20) against the target component (A/Singapore/INFIMH-16-0019/2016 [H3N2]).

Study Conduct

After subjects have signed an informed consent and have met the inclusion /exclusion criteria, healthy adults will receive a single administration of the IP (active M2SR or placebo) delivered intranasally as a liquid formulation. The Phase 1 and Phase 2a trials in adults and the ongoing Phase 1 trial in adolescents have demonstrated that a single dose of Bris10 M2SR at 10^8 $TCID_{50}$ with and without a subsequent administration of a live, replicating influenza virus is generally safe and well tolerated with no shedding of infectious vaccine virus. Hence, the study will be conducted in an outpatient setting and with safety reviews as shown in Table 2 and summarized here:

1. Deliver first dose to sentinel group 1 on Day 1. Lead PI reviews AEs through 3 days post-administration of first dose (Day 4), confirms that no halting rules have been met, and communicates this to the Sponsor.
2. If no safety concerns in sentinel group 1, deliver first dose to sentinel group 2. Lead PI reviews AEs for sentinel group 2 through Day 4, and cumulative AEs for sentinel group 1, confirms that no halting rules have been met, and communicates this to the Sponsor.
3. If no safety concerns in sentinel groups 1 and 2, deliver first dose to sentinel group 3. Lead PI reviews AEs for sentinel group 3 through Day 4 and cumulative AEs for sentinel groups 1 and 2, confirms that no halting rules have been met, and communicates this to the Sponsor.
4. If no halting rules are met, second doses are administered to sentinel subjects in all groups at Day 29 according to the study schedule.
5. Safety reviews through 3 days post administration of the second dose (Day 32) are conducted in the same manner as outlined above for second doses of sentinel groups.

6. After sentinel subjects have completed 7 days following first vaccination (Day 8), SRC reviews available safety data for sentinel groups 1-3. If no safety concerns are identified, deliver first dose to expansion group subjects.
7. After all sentinel subjects have completed 7 days following second vaccination (Day 36), SRC reviews cumulative safety data. If no safety concerns are identified, deliver second dose to expansion group subjects.
8. During enrollment of the expansion cohorts, the occurrence of events which could prompt a study halt will be reviewed weekly by the Medical Monitor, until all subjects have completed 7 days following second vaccination (Day 36).

Each subject will undergo the following testing (also depicted in Table 3): [Note that a Pre-screen with blood draw to assess the subject's microneutralization (MN) titer to Sing2016 may be conducted under a site-specific ICF in the period spanning 90 calendar days before enrollment in this study.] Subjects who meet eligibility criteria will be enrolled in the proposed Phase 1b study, have a baseline blood draw, be randomized to a dose cohort and administered IP of either active M2SR vaccine or placebo on Days 1 (Visit 01) and 29 (Visit 04). For 7 days following each dose the subjects will record symptoms in a Symptom Memory Aid (Appendix 5) and after 3 days (Days 4 and 32) will be contacted via phone call by the site staff representative to report symptoms and AEs. Subjects will attend the investigational site for follow-up on Days 8, 29, 36, 57 and 209 (Visits 03, 04, 06, 07 and 08, respectively) for a limited physical exam, safety evaluation, nasal swabs and blood draws. Day 209 will also be the end of study visit for each subject in the study. Serum samples for analysis of anti-HA antibody titers for the H3N2 antigen in Sing2016 and Bris10 will be collected at baseline and on Days 8, 29, 36, 57 and 209. PBMC samples for analysis of cell-mediated immunity and/or innate transcriptome gene expression will be collected at baseline and on Days 4 (optional), 8, 29, 32 (optional), 36 and 57 from select sites. Nasal swabs will be collected on Days 1, 8, 29, 36, 57 and 209 for analysis of IgA-specific anti-HA antibody titers. Nasal swabs will be collected at Days 1, 8, 29, and 36 to evaluate shedding of vaccine virus. A nasal swab collected at Day 1 may be evaluated for presence of respiratory pathogens. Safety clinical laboratory testing will be performed at screening, and on Days 1, 8, 29, and 36. During the treatment period (Day 1 – Day 57), subjects will be asked to notify the site immediately if symptoms of influenza (fever, chills, sore throat, rhinorrhea, cough, muscle/body aches) occur. When increased influenza infections are being reported in the geographic region of the investigational site, subjects will additionally be contacted at Days 15±2, 21±2, 43±2, and 50±2 by phone or messaging. If influenza is suspected the subject will be asked to return to the site for laboratory confirmation of influenza using nasal swabs.

Halting Rules

Vaccination of subjects will be suspended until after review of safety data by the SRC if any of the following halting rules are met:

1. One or more subjects experience a Grade 4 AE, vital sign or laboratory AE that cannot be clearly attributed to another cause.
2. Three or more subjects within a single sentinel group or ten or more subjects within the expansion group experience the same Grade 3 AE, vital sign or laboratory AE that cannot be clearly attributed to another cause.
3. One or more subjects experiences a SAE assessed as related to IP.

4. One or more subjects has laryngospasm, bronchospasm, or anaphylaxis associated with the study product within 72 hours of product administration.

Any AE or SAE that falls into the above criteria for suspending or terminating the study (including the occurrence of ***any*** Grade 3 AE, vital sign or laboratory AE that cannot be clearly attributed to another cause) must be reported by the investigator to the Sponsor ***immediately (within 24 hours).***

In the case of halting rules being met, the SRC will be convened as quickly as possible. After review of the safety data the SRC will make a recommendation to the Sponsor whether to resume, suspend or terminate the study. The Sponsor will communicate a decision to suspend or terminate the study to the Investigators.

Subsequent review of serious, unexpected, and related AEs by the Medical Monitor, SRC, IRB, the Sponsor(s), or the FDA or relevant local regulatory authorities may also result in suspension of further trial interventions/administration of study product at a site. The FDA and study Sponsor(s) retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

Safety Parameters

Visual assessment of the nose on the day of IP administration (pre-dose, 5 minutes post-dose and at 30 minutes post-dose) and at follow-up assessments along with exam of throat and lungs on Patient Days 8, 29, 36, 57 and 209 will be part of a limited physical exam. Note: Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine.

Clinical pathology will be evaluated at screen, Day 1 pre-dose, Day 8, Day 29 pre-dose and Day 36 and at additional time points as judged by the Investigator for safety evaluation.

Unsolicited local and systemic adverse events for 28 days post-dose.

Solicited AEs using a symptom memory aid for 7 days post-dose.

SAEs from vaccination until Day 209.

Changes in physical examination, vital signs, laboratory safety tests, lung function and pregnancy tests over the course of the study.

Study Population:

Healthy male and non-pregnant/lactating female subjects ages 18-49 years old.

The study plans to enroll approximately 250 subjects who will receive two doses of experimental Bris10 or Sing2016 M2SR vaccine or placebo (physiological saline) on Study Days 1 and 29. Subjects will be randomized 1:1:1:1:1 (Sing2016 M2SR 10^8, Sing2016 M2SR $10^{8.5}$, Sing2016 M2SR 10^9, Bris10 M2SR or Saline placebo).

Inclusion Criteria:

1. Give written informed consent to participate; a legally authorized representative (LAR) may not be used.
2. Age 18 – 49 years old, inclusive.
3. Judged suitable by the PI, as determined by medical history, physical examination, vital signs, and clinical safety laboratory examinations.

4. Negative test for pregnancy at screening visit and on Day 1. A positive test on Patient Day 29 will exclude subject from a second dose.
5. Negative test (urine) for drugs of abuse at screening. Patients who are on stable (6 months or longer) medications prescribed by their physician which result in a positive screen for that substance are allowed at the discretion of the investigator.
6. Female subjects should fulfill one of the following criteria:
    a. Post-menopausal status defined as no menses for 12 consecutive months without an alternative medical cause.
    b. Surgically sterile.
    c. Willing to use oral, implantable, transdermal or injectable contraceptives, or sexual abstinence as outlined in inclusion criteria 7, from screening and until 28 days after second vaccine dose (Patient Day 57).
7. Female subjects of childbearing potential must agree to sexual abstinence, use a reliable form of contraception approved by the Investigator (e.g., oral, implantable, transdermal, or injectable contraception, combined oral, intrauterine device [IUD], or a sterile sexual partner) from screening and until 28 days after the second vaccine dose (Patient Day 57). Non-surgically sterile male subjects who are sexually active with a female partner(s) of childbearing potential (i.e. males who have not been sterilized by vasectomy for at least 6 months prior to screening) must be willing to use condoms from screening and until 28 days after the second vaccine dose (Patient Day 57).
8. Willing to adhere to the requirements of the study and willing and able to communicate with the Investigator and understand the requirements of the study.
9. Non-smoker (defined as no use of tobacco products and no use of inhaled non-tobacco products in the past 30 days prior to Study Day 1; nicotine patches and gum are allowed). Subject must also agree to restrict the use of these products until 7 days after last vaccine administration.
10. H3N2 Sing2016 MN titers ≤1:20 (determination within 90 calendar days of study enrollment is acceptable and does not need to be repeated for entry to this study).

Exclusion Criteria:

1. Any subject who is a family member of a) study site personnel and other personnel directly involved in conduct or monitoring of study, or b) the Sponsor.
2. Any condition that would limit the subject's ability to complete the study based on the opinion of the Investigator (for example, a recent surgical procedure).
3. Clinically significant abnormal screening hematology or chemistry value, as assessed by the investigator.
4. Pulse rate or blood pressure outside the reference range for this study population and considered as clinically significant by the Investigator.
5. Has an acute or chronic medical condition or history of a medical condition that, in the opinion of the Investigator, would render the study procedures unsafe or would interfere with the evaluation of the responses, including but not limited to, respiratory, autoimmune, or immune suppression conditions, neuroinflammatory conditions, mental illness (including depression), active hematological, renal, hepatic, pulmonary, central nervous, neurological, cardiovascular, endocrine (including diabetes mellitus) or gastrointestinal disorders.

6. Has been vaccinated against influenza within the last 6 months or plans to be inoculated with an influenza vaccine (other than study vaccine) until one month after completion of follow up on Patient Day 209.
7. Had a flu-like illness (i.e., fever, chills and myalgia), influenza treatment (i.e., commercial drug such as Oseltamivir, etc.), or prophylactic influenza viral drug administered in the previous 6 months before screening.
8. Positive screening test or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).
9. History of cancer within 5 years prior to screening (except basal cell carcinoma and cervical carcinoma in situ).
10. Presence or clinically significant history of lung disease, asthma, chronic obstructive pulmonary disease (COPD), or otherwise poor lung function. Childhood asthma that resolved by age 12 years is not criteria for exclusion.
11. Any significant abnormality altering the anatomy of the nose or nasopharynx. A test swabbing by mock swab may be performed at screening at the Investigator's discretion.
12. Any confirmed or suspected immunosuppressive or immunodeficient state including: asplenia, recurrent severe infections and chronic (more than 14 days) immunosuppressant medication (such as systemic corticosteroids at a dose of $\geq$ 0.5 mg/kg/day for longer than 1 week, or immunosuppressants such as cytotoxic drugs) within the last 6 months (topical steroids are permitted). Use of immunosuppressive medications, such as allergy shots, immune globulin, interferon, or immunomodulators in the past 6 months or planned to be used during the course of the trial. Use of intranasal corticosteroids within the last 7 days before screening.
13. Significant adulthood history of seasonal hay fever, a seasonal allergic rhinitis, perennial allergic rhinitis, chronic nasal or sinus condition such as sinusitis, at the discretion of the investigator.
14. Received any licensed vaccine within 1 month before screening and during the course of the study.
15. Received or planned administration of another investigational vaccine or drug during the period from 90 days prior to Day 1 to one month after completion of Day 209 follow up
16. History of allergy/hypersensitivity to any vaccine component (sucrose, sodium chloride, phosphate, glutamate), or material in nasal delivery device (polycarbonate, polypropylene, synthetic rubber).
17. Experienced a life-threatening reaction(s) after a previous administration of any vaccine or experienced an allergic reaction after a previous administration of any influenza vaccine or component.
18. A history or prior diagnosis of Guillain-Barré Syndrome.
19. Living in the same household with any person with a non-functional or suppressed immune system, or with a confirmed influenza infection or febrile illness within the previous two weeks.
20. History of drug or alcohol abuse in the 6 months before the study.

21. Current use of any new prescription or new over-the-counter (OTC) medications starting within 1 month of vaccination, except for contraceptive pills, implants, transdermal or injections in female subjects, which may have been started within the previous 1 month. Herbal medications and supplements other than vitamins are prohibited.
22. Receipt of blood products or immunoglobulin within 6 months before study entry or planned for within 180 days after the last vaccination.
23. Donation of blood or blood products within 30 days before study entry or planned donation at any time during the 30 days post last vaccination.
24. Females who are pregnant or lactating (i.e., a nursing mother).
25. Acute febrile illness within 72 hours prior to vaccination, defined as the presence of a moderate or severe illness with or without fever (as determined by the Investigator through medical history and physical examination), or presence of a fever >38ºC orally. Vaccination (or administration of the second dose of vaccine) should be delayed until the subject has recovered. Persons with a minor illness, such as diarrhea, or mild upper respiratory tract infection with or without low-grade fever, may be enrolled after resolution of the illness.
26. Any condition, in the opinion of the Investigator, (such as subjects who have medically high-risk conditions) that might interfere with the primary study objectives for safety of the study subject.
27. Previous exposure to M2SR investigational vaccine.
28. Any active military personnel/member.

Exclusions at Day 29:

Pregnancy, receipt of a prohibited medication, or new prohibited diagnosis, including laboratory confirmed influenza and or treatment for influenza, or high-risk condition are exclusions for second vaccination.

Note: At the discretion of the investigator, subjects may be rescreened; out-of-range clinical laboratory tests may be repeated twice, and vital signs may be repeated three times. Results of any retest must be available prior to enrollment.

Test Product, Dose, Mode of Administration:

Bris10 M2SR Vaccine: One IP is termed Bris10 M2SR and is a recombinant, monovalent influenza A virus that encodes the viral antigens, hemagglutinin (HA) and neuraminidase (NA) from Influenza A/Uruguay/716/2007, an A/Brisbane/10/2007-like H3N2 virus strain. Bris10 M2SR has been initially tested in the Phase 1, first-time-in-humans (FTIH) study FluGen-H3N2-V001 under US IND 016968 (also see ClinicalTrials.gov identifier NCT02822105), in a Phase 1 adolescent study in the US (BB-IND 18170) and in a Phase 2a virus challenge study in Belgium (EudraCT 2017-004971-30). The vaccine (Lot# 15100251) for these three studies was manufactured using a master virus stock and working cell bank at Meridian Life Sciences (Memphis, Tennessee, USA) under current Good Manufacturing Practice (cGMP) in a liquid formulation.

Sing2016 M2SR Vaccine: The second IP is termed Sing2016 M2SR and is a recombinant, monovalent influenza A virus that provides the HA and NA components

from A/Singapore/INFIMH-16-0019/2016 that were recommended for the 2018-2019 influenza season.

The Bris10 M2SR vaccine (Lot# 10250) and the Sing2016 M2SR (Lot# 19097) for this Phase 1b study were manufactured at Ology Bioservices (Alachua, Florida, USA) under current Good Manufacturing Practice (cGMP) in a liquid formulation. The Bris10 M2SR vaccine and the Sing2016 M2SR vaccine will be provided frozen and in single-use. A pharmacist or designee will thaw the vial contents to room temperature just prior to dose administration. The contents will be diluted to the target dosing concentration with provided SPG diluent for each subject. The final diluted product will be drawn into two 1 mL disposable polypropylene syringes each fitted with a mucosal atomization device (MAD301; Teleflex, Salt Lake City, Utah, USA) for intranasal delivery.

For delivery, on each of Days 1 and 29, subjects will receive a single intranasal dose of vaccine (or placebo) via two nasal spray devices. Subjects will be in a semi-recumbent position and receive approximately two administrations of ~50% volume per nasal cavity by employing two spray devices. Devices will be weighed pre- and post-dose to allow calculation of dose eliminated from the devices. Subjects will remain semi-recumbent and under observation for thirty (30) minutes and will not be allowed to blow their noses, eat or drink during this time.

Reference Product, Dose, Mode of Administration:

The reference product (placebo) is a physiological saline suitable for intranasal delivery. The placebo will be provided as a liquid and in single-use vials. The placebo will be drawn into two 1 mL disposable syringes that are fitted with a Teleflex MAD301 sprayer for intranasal delivery. Administration will be as described for the M2SR vaccines.

The placebo is a clear solution whereas the M2SR vaccines are a light yellowish color. The unblinded pharmacy staff will prepare the vaccine and placebo doses, fill delivery devices and apply an opaque label to the device barrel to obscure any coloration of the contents or volume differences and maintain the blind.

Study/Treatment Duration:

All subjects will receive either active vaccine or placebo on Days 1 and 29.

Eligible subjects will be enrolled and receive a first dose on Day 1, be contacted by the site on Day 4 for report of symptoms/AEs (or optionally may attend the clinic if consenting to PBMC collection at select sites) and will attend the clinic on Day 8 for safety follow-up. Subjects will return to the site for a second dose administration on Day 29, be contacted by the site on Day 32 for report of symptoms/AEs and will attend the clinic on Day 36 for safety follow-up. Subjects return to the clinic on Day 57 and then on Day 209 (180 days after the last dose) for the final study follow-up visit. If Day 209 visit cannot be conducted in person, a safety follow-up call will be conducted. Duration of participation for each subject is anticipated to be 7 months.

Sentinel subjects will be treated in three staggered groups of approximately 15. After subjects in all sentinel groups have completed 7 days following first vaccination (Day 8), SRC will review available safety data for sentinel groups 1-3 and the expansion subjects may be enrolled. It is anticipated that a total study length of 8-9 months will be required.

The study will be subject, investigator and sponsor blinded. However, after all sentinel subjects have completed study visits through day 28 after the second dose (Day 57) and/or after all study subjects have completed study visits through 28 days after the second dose administration (Day 57), the study sponsor may be unblinded. Study subjects, blinded investigational site personnel and blinded study monitors will remain blinded until all subjects have completed the study.

For vaccine program planning purposes, an early review of partial data may occur prior to all subjects completing the day 57 visit. In such case, to maintain the overall study blind, minimize operational bias, and protect trial integrity, the majority of operational team members will remain fully blinded to individual subject treatment. Specified team members (as defined in a Blinding Plan) will receive the datasets unblinded by treatment group only with no subject identifiers. This will allow for summary tables to be generated by placebo versus active yet will not unblind individual subject treatment. The data will not be used to make decisions about the dis/continuation of or alterations to the trial.

Statistical Methods:

The Statistical Analysis Plan (SAP), including table shells will be finalized prior to database lock.

The final analysis will be done after the last subject has had the day 57 visit and the data base has been locked. The day 209 data will be included as a supplemental analysis.

Analyses will be done using SAS software version 9.4 or higher.

<u>Safety Analyses</u>

Safety and tolerability of the Bris10 M2SR and Sing2016 M2SR influenza vaccines will be assessed using subject diaries, solicited and unsolicited AEs, vaccine -associated AEs, SAEs, safety labs, vital signs, and physical examinations.

Exposure

Vaccine exposure will be summarized by actual dose, % of expected dose, and % of subjects receiving the expected dose.

Adverse Events

Treatment-emergent AEs (local and systemic) will be summarized as N (%) with AEs, with related AEs, and by worst severity.

Incidence of TEAEs will be reported by Medical Dictionary for Regulatory Activities (MedDRA)-coded System Organ Class (SOC), Preferred Term (PT) and maximum severity.

Incidence of most frequent TEAEs and most frequent treatment-related TEAEs will be reported by SOC and PT

Listings of subjects who died, discontinued the study due to an AE, or experienced an SAE will be provided.

Dose-site reactions will be presented by reaction and severity.

Post-administration symptoms (memory aid) will be summarized by timepoint, worst occurrence, and days with symptoms.

Clinical Laboratory Tests

Biochemistry and hematology laboratory results and change from baseline results will be summarized by timepoint using descriptive statistics.

Shift tables of maximum grade compared to baseline tabulated according to the FDA guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, or in accordance with the normal ranges of the clinical laboratory (below, within, or above normal range) for parameters for which no toxicity grades are defined.

A listing of clinical laboratory test results outside the reference ranges will be provided.

Vital Signs

Vital sign results and change from baseline results will be summarized by timepoint using descriptive statistics.

Limited Physical Examination

Abnormal findings in physical examination will be listed.

Pregnancy

A listing of pregnant subjects will be displayed.

Additional Analyses (descriptive only; p-values are descriptive and not corrected for multiple testing)

Immunogenicity

Serum antibody, mucosal antibody and cellular immune response will be summarized using descriptive statistics by sampling timepoint for all subjects and by baseline values.

Seroconversion rates will be presented by timepoint and by baseline starting values.

Vaccine virus detection

Viral shedding will be summarized using descriptive statistics.

Additional (exploratory) endpoints may be analyzed.

Sample size

The sample size of 50 subjects per group was chosen based on reports of studies of other vaccines in early stage development. This study is not powered for any formal comparisons.

Subject Characteristics Data Set

Demographics will include by-treatment summaries of age, height, weight, BMI, race, and gender.

Other baseline characteristics may be summarized.

Analysis Datasets

The Safety set will include any subject who receives at least one administration of IP.

The full analysis set (FAS) will include all subjects randomized, received IP and had at least one post baseline assessment.

If necessary, a per protocol set (PPS) will include all subjects in the FAS with no major protocol violations or deviations.

Issue Date (Version) 18May2020 (v8.0)

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

List of Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	adverse event
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	confidence interval
CMI	cell-mediated immunity
CoA	certificate of analysis
COPD	chronic obstructive pulmonary disease
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunoSpot
eTMF	electronic Trial Master File
FACS	fluorescence-activated cell sorting
FDA	Food and Drug Administration
FTIH	first time in human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HA	hemagglutinin
HAI	hemagglutination inhibition
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRPO	Human Research Protection Office
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICS	intracellular cytokine staining
IEC	Independent or Institutional Ethics Committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IN	intranasal(ly)
IND	Investigational New Drug Application
IP	investigational product
IRB	Institutional Review Board

IUD	intrauterine device
LAR	Legal Authorized Representative
M2SR	**M2**-deficient **S**ingle **R**eplication vaccine
MAD	mucosal atomization device
MedDRA®	Medical Dictionary for Regulatory Activities
mL	milliliter
mM	millimolar
MMWR	Morbidity and Mortality Weekly Report
MN	microneutralization
MNT	microneutralization test
N	number (typically refers to subjects)
NA	neuraminidase
NAI	neuraminidase inhibition assay
NSAID	nonsteroidal anti-inflammatory drug
OTC	over the counter
PBMC	peripheral blood mononuclear cell
PE	physical exam
PCR	polymerase chain reaction
PI	Principal Investigator
PP	Per-protocol Set
PT	Preferred Term
QIV	quadrivalent influenza vaccine
qRT-PCR	real-time quantitative reverse transcription PCR
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	standard error
SRC	Safety Review Committee
SPG-NaCl	sucrose phosphate glutamate with sodium chloride
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
SUSAR	suspected unexpected serious adverse reaction
TCID	50% tissue culture infective dose
TEAE	treatment-emergent adverse event
TIV	trivalent influenza vaccine
US DoD	United States Department of Defense
US	United States
VE	vaccine effectiveness

Definitions of Terms

Baseline	Day of vaccine/placebo administration; typically last measurement taken prior to initiating treatment, determined at the record, not the visit level.
BMI	Weight in kilogram divided by the square of height in meters

STUDY ADMINISTRATIVE STRUCTURE AND INVESTIGATORS

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1. INTRODUCTION

1.1. Overview

FluGen, Inc. is developing Bris10 M2SR and Sing2016 M2SR, two novel M2-deficient single replication live influenza vaccines, to provide safe, effective protection against seasonal influenza strains. The vaccine virus does not express an essential viral protein (influenza M2), restricting it to a single replication cycle in the host. Bris10 M2SR has been tested in a Phase 1, first-time-in-humans (FTIH) study FluGen-H3N2-V001 (ClinicalTrials.gov identifier NCT02822105) under United States (US) Investigational New Drug (IND) Application 016968, and in a Phase 2a Challenge Study FluGen-H3N2-V002 under EudraCT 2017-004971-30. A Phase 1 study in adolescents (BB-IND 18170; sponsored by DMID and NIAID; NCT03553940) is also underway. The proposed study will be a FTIH study for Sing2016 M2SR.

This Phase 1b dose escalation study is to assess the safety, tolerability/reactogenicity, and immunogenicity of M2SR vaccines when delivered at higher dosages or in two doses to increase the proportion of subjects responding serologically to the vaccine. For this study, an updated vaccine, Sing2016 M2SR, has been prepared that will provide the hemagglutinin (HA) and neuraminidase (NA) components from A/Singapore/INFIMH-16-0019/2016, the H3N2 strain recommended for the 2018-2019 influenza season.

1.2. Background Information

1.2.1. Influenza

Influenza viruses typically circulate widely in the US annually from the late fall through early spring. Although most persons who become infected will recover without sequelae, influenza can cause serious illness and death, particularly among persons age ≥ 65 years, children < 2 years, and individuals with underlying medical conditions that confer an increased risk of influenza-related complications (Centers for Disease Control and Prevention [CDC] 2013). Over the past 40 years, estimated influenza-associated deaths have ranged from 3,000 to 49,000 annually, with approximately 200,000 hospitalizations in the US annually (CDC 2015).

Annual influenza vaccination has long remained the primary means of preventing influenza infection and its complications, and has been consistently recommended by various advisory bodies over the past 60 years. Although routine vaccination was initially recommended only for high-risk populations in the US, the CDC and the Advisory Committee on Immunization Practices (ACIP) have recommended since 2010 that all persons aged ≥ 6 months who do not have contraindications should be vaccinated (CDC 2015). Recent evaluations conducted by a US government-supported network of large clinics (US Flu-VE Network; Treanor 2012), have demonstrated an overall vaccine effectiveness (VE) of at most 60% (95% confidence interval [CI], 53-66) for prevention of laboratory-confirmed, medically attended influenza illness due to any influenza virus, even in years in which there was a good match between vaccine and circulating strains (Treanor 2012). VE estimates in the US among individuals

age ≥ 65 years have been consistently lower than in younger age groups, which is consistent with the well-documented reduction in immunogenicity of influenza vaccine in older adults (Osterholm 2012). Given the substantial and further increasing resource allocations to the US influenza vaccination programs, the continued search for more effective vaccines to further improve the population-level impact of the program – and particularly among older adults and others at high risk of serious influenza complications – remains a critically important public health challenge.

1.2.2. Current Influenza Vaccines

Currently available inactivated and recombinant influenza vaccines primarily aim to induce neutralizing antibodies that recognize the virus envelope protein HA. These antibodies can provide effective immunity, but they depend on a close match between the vaccine immunogen and circulating viruses. Such vaccines are therefore relatively ineffective against newly emerging viruses or viruses that have drifted away from the vaccine strain. Conventional egg-derived inactivated vaccines, which currently comprise approximately 90% of the US market, generally provide limited or no broadly cross-reactive (heterosubtypic) immunity needed to protect against divergent strains. Currently available trivalent (TIV) or quadrivalent (QIV) preparations provide only the HA antigen and either none or limited and non-standardized amounts NA antigen. Moreover, at least one HA component of these vaccines must often be updated due to accumulated point mutations in the HA protein that allow the viruses to evade the human immune response. In addition, while a strong relationship has been established between pre-existing T cell immunity and illness severity in subjects seronegative for influenza virus-specific antibody (Wilkinson 2012), no or minimal cellular immune responses have been shown to be elicited following vaccination with these conventional preparations.

1.2.3. Live attenuated vaccines

In contrast to conventional inactivated and recombinant vaccines, live influenza virus vaccines are generally believed to offer broad-spectrum immune responses because they induce diverse types of adaptive responses, including serum antibodies, mucosal immunity, and induction of cytotoxic T lymphocytes, which target conserved virus epitopes (Clements 1986, Tamura 2005, Zhu 2010; Lanthier 2011, Ambrose 2012, Jin 2015). Only one such live vaccine, (FluMist®), which has been attenuated empirically by cold-adaptation, has been approved in the US, and is presently indicated only for persons 2-49 years of age. However, immune mechanisms conferring protection against influenza following receipt of FluMist vaccine are not fully understood; serum antibodies, mucosal antibodies, and influenza-specific T cells may play a role but there is no established surrogate of efficacy. Accumulating data also indicate that pre-existing cross-reactive immunity present in most adults limits vaccine virus replication, which in turn reduces a consistently effective immune response (Eick 2009, Ohmit 2006, Wang 2009, Monto 2009). This in part explains the observation that young, seronegative children are the population in which FluMist vaccination is typically most effective.

1.2.4. FluGen's H3N2 (A/Brisbane/10/2007) M2SR vaccine

FluGen is developing a novel live virus vaccine platform known as "M2SR" to address the need for more effective influenza vaccines that will provide more consistent and broad-spectrum immunity for adults, and especially the elderly. The product is a live virus vaccine for intranasal administration that has been shown to provide protection against multiple influenza A subtypes in animal models (see below). The vaccine is a replication-defective recombinant influenza virus that does not express the essential M2 protein (and hence, the derivation of the "M2SR" naming convention [**S**ingle **R**eplication phenotype due to lack of **M2**]). The M2SR vaccine virus backbone is comprised of (1) five of the six internal proteins of the donor virus Influenza A/Puerto Rico/8/34 (PR8), a strain that has been used for decades in traditional inactivated influenza vaccine manufacturing; (2) the sixth internal protein, M2, which is acquired from the cell substrate used to grow the vaccine virus, M2 Vero cells, which stably express and supply M2 protein for vaccine virus growth; and (3) the two influenza virus surface protein antigens, HA and neuraminidase (NA), which can be derived from any selected Type A influenza strain. The resulting vaccine virus can infect normal cells in the respiratory epithelium of the vaccine recipient and then uncoat and initiate infection similar to a wild-type influenza virus, thereby evoking an immune response. However, because the M2SR genome does not encode for M2 protein, no viral progeny are subsequently produced after the initial (single round) infection, such that no cell-to-cell spread or subsequent shedding of virus occurs. The HA and NA of an A/Brisbane/10/2007-like H3N2 virus was chosen as the prototype monovalent vaccine to be initially tested in humans and is further referred to here as "Bris10 M2SR".

Like FluMist, Bris 10 M2SR is administered intranasally and is intended to mimic a naturally acquired, wild-type infection and to induce broad-spectrum immunity, including mucosal and cell-mediated responses. However, unlike FluMist, Bris 10 M2SR can still infect respiratory epithelial cells and induce immune responses in preclinical animal models in the presence of pre-existing antibody. In addition to eliciting neutralizing antibody responses to HA, M2SR induces antibody responses against the highly conserved stem region of the HA, as well as the NA surface protein in animal studies. Moreover, M2SR-based vaccines have induced strong cross-reactive T cell responses against the highly conserved internal viral antigens that have been recalled after heterosubtypic challenge. Flow cytometric analyses of CD8+ T cells in bronchoalveolar lavage studies in animals have also revealed that the majority of these cells have an effector/memory or effector phenotype, the presence of which has been shown in humans to reduce influenza related symptoms upon exposure to wild-type influenza (Wilkinson 2012). By contrast, cell-mediated responses (either effector or memory) are generally not elicited by current split or subunit vaccines (Hoft 2017, He 2006). These properties suggest that vaccines based on this approach may potentially confer additional advantages over currently available influenza vaccines, including FluMist, and are intended to model natural (wild-type) infection, while at the same time incorporate the critical safety feature of only precipitating a single round of virus replication.

1.2.5. FluGen's H3N2 (A/Singapore/INFIMH-16-0019/2016) M2SR vaccine

Sing2016 M2SR and is a recombinant, monovalent influenza A virus that was generated as described above for Bris10 M2SR. It contains a similar PR8 backbone but with nine amino

acid changes distributed over five genes (PB1, PB2, PA, NP and NS1) that facilitate growth in the production cell line, M2VeroA. The mechanism of attenuation (deletion of the M2 gene) is not affected. The Sing2016 M2SR also provides the HA and NA components from A/Singapore/INFIMH-16-0019/2016 that were recommended for the 2018-2019 influenza season. The current study is the FTIH study for Sing2016 M2SR.

1.3. Non-Clinical Studies of M2SR

In addition to the features described above, and as further summarized in the Investigator's Brochure (IB) accompanying this protocol, data obtained in animal models provide a strong basis for proceeding with clinical testing of the Bris 10 M2SR prototype vaccine in humans based on the following features:

1.3.1. Non-Clinical Safety

The safety of Bris10 M2SR monovalent vaccine was evaluated in a Good Laboratory Practice (GLP)-compliant, repeat-dose toxicity study in ferrets. In that study (Battelle Study Number 37234E), male and female ferrets were intranasally administered Bris10 M2SR once on Days 1 and 28 at dosages of 1.1×10^7 or 1.1×10^8 50% tissue culture infective dose ($TCID_{50}$) using the clinical spray device (Teleflex VaxINator). Overall, there were no observed toxicities from the two administrations of vaccine. The M2SR H3N2 vaccine was considered well tolerated, with only a transient reduction in physical activity being observed after the initial administration of 1.1×10^8 $TCID_{50}$. No redness or swelling of the nares and no gross or microscopic lesions of tissues surrounding the administration site were notable after intranasal administration of Bris10 M2SR with either dose level. No vaccine-related effects were observed in either dose group in the physical examinations or on body weights, body temperature, food consumption, eye exams, clinical chemistry, hematology, urinalysis, or coagulation parameters, organ weights or gross pathology. The only vaccine-related finding was mild to moderate inflammation of the distal bronchioles and adjacent alveoli and the perivascular tissue, observed 2 days after the first and second administration of Bris10 M2SR (on Days 3 and 30), particularly in the high dose group. The inflammation was not associated with any adverse clinical signs, clinical pathology, gross pathology or organ weight changes and was transient in nature, completely resolving by the end of the 21-day recovery period.

In multiple non-GLP studies of M2SR-based constructs (including H1N1, H3N2, and H5N1), there was (a) no evidence of weight loss or clinical symptoms in ferrets after intranasal administration; (b) no adverse histopathologic findings in any of the respiratory organs or brains of ferrets; and (c) no transmission of vaccine virus in any ferrets (3 donors and 6 contacts).

There is no evidence of M2SR vaccine virus replication when organs and nasal washes were analyzed for presence of virus. Moreover, the M2SR construct deletion prevents reversion, as confirmed by >10 serial passages in permissive cells and blind passage in non-permissive cells and in mice.

1.3.2. Non-Clinical Efficacy

Non-clinical studies of the M2SR platform confirm:

- M2SR-based constructs (including H1N1, H3N2, and H5N1) stimulate potent systemic and mucosal immune responses and confer protective immunity to animals against lethal homo-, hetero-, and intra-subtypic influenza virus challenge;
- Protection following vaccination is superior to that conferred by inactivated (split) or live attenuated vaccines (FluMist); and
- Robust immune responses are elicited in vaccinated animals, even in the presence of pre-existing anti-influenza antibody.

These characteristics illustrate the potential for the M2SR platform to become a potentially safe and effective alternative to existing influenza vaccines.

Please see the IB for a more complete description of the product and additional details of the pre-clinical studies.

1.4. Clinical Studies

Previous clinical experience with the M2SR vaccine platform includes a FTIH Phase 1 dose escalation study in healthy adults, an on-going Phase 1 safety and immunogenicity study in adolescents, and a Phase 2a challenge study in healthy adults using the H3N2 vaccine Bris10 M2SR. Sing2016 M2SR has not been previously studied in humans.

1.4.1. Phase 1 Dose Escalation Study

For the FTIH Phase 1 study, 96 healthy adult male and non-pregnant female subjects ages 18-49 years, were stratified by baseline hemagglutination-inhibition (HAI) antibody titers (<10 to 80) against influenza A/Brisbane/10/2007 (Bris10) and enrolled under US IND 016968 (also see ClinicalTrials.gov identifier NCT02822105). First subject first visit occurred in July 2016 and last subject last visit (Day 180) was in April 2017. Subjects were randomly assigned to receive either a single administration of Bris10 M2SR at dose levels of 10^6, 10^7 or 10^8 $TCID_{50}$ (24 subjects per dose level) or saline placebo (N=24; 8 for each Bris10 M2SR dose group). Each subject received ~ 0.1 mL of vaccine or placebo intranasally (IN) in each nostril – except for the 10^8 group, who received 0.15 mL per nostril – using a mucosal atomization device (MAD) from the Teleflex VaxINator kit including a MAD301 sprayer. The vaccine was safe and well tolerated at all dose levels, generated a dose-response effect for humoral (hemagglutination-inhibition antibody) and mucosal antibodies against both homologous and heterologous influenza variants, and elicited robust T-cell responses. No infectious virus was detected in nasal swabs collected on Days 1, 2, 3 and 7 post-dose in any vaccinated subject. One subject in the 10^7 dose cohort and one subject in the placebo cohort self-reported fevers as high as 38.2°C (day 7 post-dose) and 38.4°C (day 3 post-dose), respectively. Subjects were followed through Day 180 post-dose. There were no severe local or systemic reactions recorded on subject 7-day diaries, no reported serious adverse events (SAEs) or adverse events (AEs) of significance (attributed to the treatment) and none of the pre-specified halting rules (including laryngospasm, bronchospasm or anaphylaxis) were met.

1.4.2. Phase 1 Study in Adolescents

In a Phase 1 study in adolescents (BB-IND 18170; sponsored by DMID and NIAID) 50 males and non-pregnant females ages 9 to 17 years old, inclusive are being enrolled. Subjects are randomized 1:1 to receive one 10^8 $TCID_{50}$ dose of Bris10 M2SR vaccine or placebo administered intranasally (IN) followed by one dose of licensed quadrivalent influenza vaccine (QIV) administered intramuscularly 3 months later. As of February 2019, 19 subjects have been enrolled (first subject first visit was in August 2018) and have received both dose treatments. These subjects have been followed through at least the Day 113 visit (21 days after administration of the QIV) with no reported SAEs, AEs of significance or halting rules met.

1.4.3. Phase 2a Challenge Study

The Phase 2a challenge study included 108 healthy male and non-pregnant female subjects ages 18-55 years old who had microneutralization titers (MNT) of ≤ 20 to H3N2 A/Belgium/4217/2015. Subjects were randomized 1:1 into two cohorts (Bris10 M2SR or Placebo) each receiving investigational product (IP) of either a 10^8 $TCID_{50}$ dose of Bris10 M2SR vaccine (N=48) or a saline control (N=51) under EudraCT 2017-004971-30. Approximately 28 days later, 99 of these subjects were challenged via intranasal inoculation with approximately 10^6 $TCID_{50}$ dose of an antigenically distinct H3N2 A/Belgium/4217/2015. The first subject first dose was in May 2018 and the last subject completed the Day 180 post-IP follow-up visit in March 2019. In the period following IP treatment (Day -28) until Day 1, there were no severe AEs or severe local or systemic complaints and there were no reported fevers (≥38°C). The active phase of this Phase 2a challenge study has been completed and there were no SAEs, AEs of significance or observations that would halt the study. All subject samples (including serum, PBMC and nasal swabs for humoral, cellular and mucosal immunity, respectively) have been collected and are undergoing analytical testing. Nasal swabs collected for detection of influenza virus have been analyzed. The finalization and locking of the clinical database and final analyses are in process.

Preliminary results from the Phase 2a challenge study suggest that the vaccine was effective against challenge in subjects for whom a detectable serum immune response was measured after vaccination. Subjects who demonstrated any increase from baseline in serum antibody response (~50% of the M2SR cohort) by MNT to the intranasal M2SR vaccine had lower viral load and influenza-like symptoms than placebo subjects. These preliminary results suggest that M2SR could potentially provide higher efficacy levels if a greater proportion of M2SR recipients can demonstrate an appropriate serological response. In an effort to increase the number of sero-responders to H3N2 M2SR, the Phase 1b study described in this protocol is planned to further optimize the dose and schedule for M2SR vaccinations. Subjects in the proposed Phase 1b study must have a MNT ≤ 20 to A/Singapore/INFIMH-16-0019/2016 in order to be enrolled.

Between the FTIH Phase 1 and the Phase 2a challenge studies, a total of 72 adult subjects have been exposed to the highest dose of Bris10 M2SR tested (10^8) with no SAEs or AEs of significance or observations that would halt these studies. In addition, in the challenge study, 48 subjects who received the live, single-replication M2SR virus were subsequently challenged with a live, replicating influenza virus. A portion of those individuals experienced

infection and symptoms consistent with influenza (e.g., nasal congestion, runny nose, sore throat, cough, tiredness, headache), but at frequency less than observed among individuals in the same study who did not receive vaccine prior to challenge. Of the 19 adolescents enrolled in the ongoing second Phase 1 study, while the randomization was set at 1:1 active to placebo, it is not known exactly how many received active investigational vaccine (M2SR), but in blinded review no safety concerns related to the M2SR vaccine have been reported. Combined, these findings indicate that the vaccine is safe and generally well tolerated as a single 10^8 $TCID_{50}$ dose.

1.5. Overall Rationale for the Study

Currently available inactivated and recombinant influenza vaccines primarily aim to induce neutralizing antibodies that recognize only the HA and depend on a close match between the vaccine and circulating viruses, rendering them much less effective against drift viruses. In addition, while a strong relationship has been established between pre-existing T cell immunity and illness severity, inactivated vaccines do not elicit cellular immune responses and therefore generally do not provide broadly cross-reactive (heterosubtypic) immunity needed to protect against divergent strains. For example, the severity of the 2014-15 influenza season was due, at least in part, to mismatch between the circulating epidemic strain and the inactivated vaccine, resulting in VE of just 13% (Paules 2018). Similarly, during the 2017 influenza season in Australia, the inactivated vaccines displayed a preliminary VE estimate of only 10%, again related to mismatch between the vaccine strain and the circulating seasonal H3N2 virus that had accumulated antigenic changes (i.e., “drifted”) (Paules 2018). These recent examples indicate the need for an influenza vaccine that can protect against seasonal influenza drift variants.

In contrast to currently available influenza vaccines, pre-clinical testing of M2SR vaccine has shown induction of broadly reactive immune responses against multiple influenza subtypes and heterosubtypic protection in animal models, including demonstration of robust systemic, cellular and mucosal immunogenicity (Sarawar 2016, Hatta 2017), even in the presence of pre-existing anti-influenza immunity. In a pre-clinical proof-of-concept study, Bris10 M2SR (one of the vaccines to be used in the current study) provided protection to ferrets against a drifted H3N2 challenge virus, A/Alaska/140/2015, a virus belonging to clade 3c.2a1. In addition, adult subjects who received Bris10 M2SR (10^8 $TCID_{50}$ dose) in the Phase 1a FTIH and Phase 2a studies demonstrated broad-spectrum immune responses. In the FTIH study, vaccine induced serum and mucosal antibody responses were cross-reactive against multiple antigenically different H3N2 viruses including recent strains that belong to the same clade (3c.3b) as the challenge virus used in the Phase 2a study (FluGen IB). In the Phase 2a study, early data suggest that the vaccine was effective against challenge with an antigenically drifted virus in subjects for whom a serum response to the vaccine was detected (data on file).

This Phase 2a dose escalation clinical study is designed to assess the safety, tolerability/reactogenicity, and immunogenicity of M2SR vaccines when delivered at higher dosages or in two doses to increase the proportion of subjects responding serologically to the vaccine. For this study, an updated vaccine, Sing2016 M2SR, has been prepared that will provide the HA and NA components from A/Singapore/INFIMH-16-0019/2016, the H3N2 strain recommended for the 2018-2019 influenza season.

1.6. Risk/Benefit Analysis

1.6.1. Potential Risks

In previously conducted trials, 72 adult subjects and 19 adolescents have been treated with Bris10 M2SR (or placebo in adolescents as the ongoing study is still blinded). No SAEs or AEs of significance have been reported. In the challenge study, 48 subjects who received the live, single-replication M2SR virus were subsequently challenged with a live, replicating influenza virus. A portion of those individuals experienced infection and symptoms consistent with influenza (e.g., nasal congestion, runny nose, sore throat, cough, tiredness, headache), but at frequency less than observed among individuals in the same study who did not receive vaccine prior to challenge. Combined, these findings indicate that the vaccine is safe and generally well tolerated as a single 10^8 $TCID_{50}$ dose.

As outlined in greater detail in the accompanying IB, the potential risks of vaccine administration are expected to be similar to those associated with other live attenuated influenza vaccines (such as FluMist). Subjects with contraindications to live vaccines, such as severe allergic reactions (e.g., anaphylaxis) after a previous dose of any influenza vaccine, and immunocompromised persons, are excluded from study participation. Severe risks known to be associated with vaccine administration include anaphylaxis. As with any experimental product, there may be unknown risks.

1.6.2. Potential Benefits

There are no expected benefits to individual subjects participating in this study. There is a need for an influenza vaccine that can protect against seasonal influenza drift variants. Bris10 M2SR administration has shown induction of broadly reactive immune responses against multiple influenza subtypes and heterosubtypic protection in animal models, including demonstration of robust systemic, cellular and mucosal immune, even in the presence of pre-existing anti-influenza immunity. This study is expected to provide important additional information to guide continued development of M2SR vaccine in a quadrivalent formulation with the aim of improving efficacy relative to currently licensed influenza vaccines.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives are:

1. To assess the safety and tolerability of one and two administrations of the Bris10 M2SR influenza vaccine each at 10^8 $TCID_{50}$ delivered intranasally to healthy adult subjects.
2. To assess the safety and tolerability of one and two administrations of the Sing2016 M2SR influenza vaccine each at 10^8, $10^{8.5}$ and 10^9 $TCID_{50}$ delivered intranasally to healthy adult subjects

2.1.2. Secondary Objectives

The secondary objectives are:

1. To assess the immunogenicity (serum antibody, mucosal antibody and cellular immune responses) of one and two administrations of Bris10 M2SR vaccine at 10^8 $TCID_{50}$.
2. To assess the immunogenicity (serum antibody, mucosal antibody and cellular immune responses) of one and two administrations of Sing2016 M2SR vaccine at 10^8, $10^{8.5}$ and 10^9 $TCID_{50}$.
3. To evaluate vaccine virus shedding after intranasal delivery.

2.1.3. Exploratory Objectives

The exploratory objectives are:

1. To evaluate cell mediated immunity for up to 2 months after the last vaccination.
2. To evaluate additional vaccine-related immune responses during the period of study participation.

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints are:

1. The number and percentage of study participants who experience any vaccine-associated AEs or SAEs after Bris10 M2SR or placebo administration.
2. The number and percentage of study participants who experience any vaccine-associated AEs or SAEs after Sing2016 M2SR or placebo administration.

2.2.2. Secondary Endpoints

The secondary endpoints are:

1. The number and percentage of study participants who after one or two doses of Bris10 M2SR or placebo demonstrate:
    i. Influenza-specific serum antibody responses measured at specified time points;
    ii. Influenza-specific mucosal immunoglobulin A (IgA) antibody responses measured at specified time points;
    iii. Influenza-specific cellular immune responses measured by cytokine enzyme-linked immunospot (ELISPOT) at specified time points.
2. The number and percentage of study participants who after one or two doses of Sing2016 M2SR or placebo demonstrate:
    i. Influenza-specific serum antibody responses measured at specified time points;
    ii. Influenza-specific mucosal IgA antibody responses measured at specified time points;
    iii. Influenza-specific cellular immune responses measured by ELISPOT at specified sampling time points.
3. Vaccine virus shedding evaluated by influenza A-specific qPCR on day 7 post IP administration.

2.2.3. Exploratory Endpoints

The exploratory endpoints are:

1. Cell-mediated immunity (CMI) assessed by frequencies and fold increases of antigen-specific T-lymphocytes.
2. Additional influenza-specific immunological assays may be performed.

3. STUDY DESIGN

3.1. Overview of Study Design

This is a randomized, double-blind, placebo-controlled Phase 1 study evaluating the safety and immunogenicity of the Bris10 M2SR and Sing2016 M2SR H3N2 influenza vaccines delivered intranasally to healthy adults.

Eligible subjects will be screened and randomized to receive two administrations 28 days apart of Sing2016 at three dose levels, Bris10 at one dose level, or placebo in a 1:1:1:1:1 ratio. An overview of the planned dose cohorts is presented in Table 1.

Table 1: Dose Cohorts

Dose Cohort	Number of Subjects	Number in Sentinel Group	Number in Expansion Group
1. 10^8 $TCID_{50}$ Sing2016 M2SR	50	9	41
2. $10^{8.5}$ $TCID_{50}$ Sing2016 M2SR	50	9	41
3. 10^9 $TCID_{50}$ Sing2016 M2SR	50	9	41
4. 10^8 $TCID_{50}$ Bris10 M2SR	50	9	41
5. Placebo	50	9	41
Total	250	45	205

Abbreviations: $TCID_{50}$=50% tissue culture infective dose.

As shown in Table 2, three sentinel groups will be vaccinated first, containing 15 subjects (9 subjects receiving escalating doses of Sing2016 M2SR, 3 subjects receiving Bris10 M2SR, and 3 subjects receiving placebo), followed by the remainder of the subjects in an expansion group. Cohorts are split into two groups to alleviate PBMC processing issues of large numbers of samples. Dosing will be staggered to allow for review of AEs through day 3 post-administration for each sentinel group prior to dose escalation. A Safety Review Committee (SRC) will review available safety data from all sentinel subjects, after subjects have completed 7 days after vaccination, prior to dosing of the expansion group. A comprehensive list of safety parameters collected during the study are described in Table 3.

Table 2: Dosing and Safety Reviews

	Dose Cohort *	N	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 13	Week 14	Week 15
Sentinel Group 1	1	9	Dose 1	Safety			Dose 2	Safety									
	4	3	Dose 1	Safety			Dose 2	Safety									
	5	3	Dose 1	Safety			Dose 2	Safety									
Sentinel Group 2	2	9			Dose 1	Safety			Dose 2	Safety							
	4	3			Dose 1	Safety			Dose 2	Safety							
	5	3			Dose 1	Safety			Dose 2	Safety							
Sentinel Group 3	3	9					Dose 1	Safety			Dose 2	Safety					
	4	3					Dose 1	Safety			Dose 2	Safety					
	5	3					Dose 1	Safety	SRC		Dose 2	Safety	SRC				
Expansion Group	1	21								Dose 1	Safety			Dose 2	Safety		
	2	21								Dose 1	Safety			Dose 2	Safety		
	3	21								Dose 1	Safety			Dose 2	Safety		
	4	21								Dose 1	Safety			Dose 2	Safety		
	5	21								Dose 1	Safety			Dose 2	Safety		
	1	20										Dose 1	Safety			Dose 2	Safety
	2	20										Dose 1	Safety			Dose 2	Safety
	3	20										Dose 1	Safety			Dose 2	Safety
	4	20										Dose 1	Safety			Dose 2	Safety
	5	20										Dose 1	Safety			Dose 2	Safety

*Dose Cohort 1 = Sing2016 M2SR 10^8, Dose Cohort 2 = Sing2016 M2SR $10^{8.5}$, Dose Cohort 3 = Sing2016 M2SR 10^9, Dose Cohort 4 = Bris10 M2SR10^8, Dose Cohort 5 = saline placebo
Note: Safety indicates a review by the Lead PI and/or Medical Monitor as detailed below in Study Conduct.
Note: SRC indicates a review by the SRC as detailed below in Study Conduct. The Expansion Group schedule may be extended based on speed of enrollment.

Using one nasal sprayer per nare the IP, up to 0.5 mL of the Sing2016 M2SR vaccine or placebo (a total of up to 1.0 mL) and up to 0.2 mL of the Bris10 M2SR vaccine (a total of up to 0.4 mL), will be delivered per subject per administration. The study will administer escalating doses of Sing2016 M2SR vaccine, with a starting dose of 10^8 $TCID_{50}$ increasing in half log (3-fold) increments to a maximum dose of 10^9 $TCID_{50}$. Controls will be saline placebo and a 10^8 $TCID_{50}$ dosage of Bris10 M2SR.

Five (5) dose cohorts of 50 subjects each will be enrolled, for a total of approximately 250 subjects randomized 1:1:1:1:1 to receive either Sing2016 M2SR 10^8, Sing2016 M2SR $10^{8.5}$, Sing2016 M2SR 10^9, Bris10 M2SR or saline placebo. A sentinel group of 9 subjects (~18% of each escalating dose cohort) will be vaccinated first, followed by the remainder of the dose cohort in an expansion group. Subjects in each sentinel group will be actively followed for 3 days and if the Medical Monitor and/or Lead PI determine that no halting rules have been met, the next sentinel group will be enrolled. After all sentinel subjects have completed 7 days following vaccination, a Safety Review Committee (SRC) will review safety data prior to enrollment and vaccination of the expansion groups. Note that the expansion subjects will be dosed in rolling waves in order to accommodate time-consuming study procedures, i.e., PBMC isolation, and not due to safety concerns. All dosed subjects will receive a second dose of the assigned IP approximately 28 days after receiving the first dose. The SRC review of sentinel data prior to enrollment of expansion subjects may occur concurrently with or following the administration of second doses of vaccine to sentinel subjects.

SAEs occurring at any time during the study will be recorded. Administration site and solicited AEs will be recorded through 7 days after each vaccination (Days 8 and 29) and unsolicited AEs will be recorded through 28 days after the last vaccination (Day 57). An SRC, comprised at a minimum of two independent physicians experienced in vaccine research and a biostatistician, will be available to review safety data at specified time points and as needed.

Based on the safety reviews, an intermediate or lower dose may be chosen to replace the planned dose for a dose cohort. If a lower or intermediate dose is chosen that dose will be used for an entire dose cohort. Should dosing be delayed for safety review or enrollment issues, subjects may receive their second dose at a time later than defined in the proposed dosing window.

While safety and tolerability are the primary objectives, this clinical study is also designed to assess the immune response to one and two doses of each of the investigational vaccines at each of the designated dose levels. Immunogenicity will be assessed by measuring serum antibody responses by HAI and/or microneutralization (MN) assay. Additional immune parameters will be assessed including mucosal antibody titers and cell-mediated immunity. Subjects will be pre-screened, under a site-specific Informed Consent Form (ICF), to avoid enrollment of individuals with high MN titers (> 1:20) against the target component (A/Singapore/INFIMH-16-0019/2016 [H3N2]).

3.2. Study Conduct and Safety Reviews

After subjects have signed an informed consent and have met the inclusion /exclusion criteria, healthy adults will receive a single administration of the IP (active M2SR or placebo) delivered intranasally as a liquid formulation. The Phase 1 and Phase 2a trials in adults and the ongoing Phase 1 trial in adolescents have demonstrated that a single dose of Bris10 M2SR at 10^8 $TCID_{50}$ with and without a subsequent administration of a live, replicating influenza virus is generally safe and well-tolerated with no shedding of infectious vaccine virus. Hence, the study will be conducted in an outpatient setting and with safety reviews as shown in Table 2 and summarized here:

1. Deliver first dose to sentinel group 1 on Day 1. Lead PI reviews AEs through 3 days post-administration of first dose (Day 4), confirms that no halting rules have been met, and communicates this to the Sponsor.
2. If no safety concerns in sentinel group 1, deliver first dose to sentinel group 2. Lead PI reviews AEs for sentinel group 2 through Day 4, and cumulative AEs for sentinel group 1, confirms that no halting rules have been met, and communicates this to the Sponsor.
3. If no safety concerns in sentinel groups 1 and 2, deliver first dose to sentinel group 3. Lead PI reviews AEs for sentinel group 3 through Day 4 and cumulative AEs for group 1 and 2, confirms that no halting rules have been met, and communicates this to the Sponsor.
4. If no halting rules are met, second doses are administered to sentinel subjects in all groups at Day 29 according to the study schedule.
5. Safety reviews through 3 days post administration of the second dose (Day 32) are conducted in the same manner as outlined above for second doses of sentinel groups.
6. After sentinel subjects have completed 7 days following first vaccination (Day 8), SRC reviews available safety data for sentinel groups 1-3. If no safety concerns are identified, deliver first dose to expansion group subjects.

7. After all sentinel subjects have completed 7 days following second vaccination (Day 36), SRC reviews cumulative safety data. If no safety concerns are identified, deliver second dose to expansion group subjects.
8. During enrollment of the expansion cohorts, the occurrence of events which could prompt a study halt will be reviewed weekly by the Medical Monitor, until all subjects have completed 7 days following second vaccination (Day 36).

Each subject will undergo the following testing (also depicted in Table 3): [Note that a Pre-screen with blood draw to assess the subject's microneutralization (MN) titer to Sing2016 may be conducted under a site-specific ICF in the period spanning 90 calendar days before enrollment in this study.] Subjects who meet eligibility criteria will be enrolled in the proposed Phase 1b study, have a baseline blood draw, be randomized to a dose cohort and administered IP of either active M2SR vaccine or placebo on Days 1 (Visit 01) and 29 (Visit 04). For 7 days following each dose the subjects will record symptoms in a Symptom Memory Aid (Appendix 5) and after 3 days (Days 4 and 32) will be contacted via a phone call by the site staff representative to report symptoms and AEs. Subjects will attend the investigational site for follow-up on Days 8, 29, 36, 57 and 209 (Visits 03, 04, 06, 07 and 08, respectively) for a limited physical exam, safety evaluation, nasal swabs and blood draws. Day 209 will also be the end of study visit for each subject in the study. Serum samples for analysis of anti-HA antibody titers for the H3N2 antigen in Sing2016 and Bris10 will be collected at baseline and on Days 8, 29, 36, 57 and 209. PBMC samples for analysis of cell-mediated immunity and/or innate transcriptome gene expression will be collected at baseline and on Days 4 (optional), 8, 29, 32 (optional), 36 and 57 from select sites for ~160 subjects. Nasal swabs will be collected on Days 1, 8, 29, 36, 57 and 209 for analysis of IgA-specific anti-HA antibody titers. Nasal swabs will be collected at Days 1, 8, 29, and 36 to evaluate shedding of vaccine virus. A nasal swab collected at Day 1 may be evaluated for presence of respiratory pathogens. Safety clinical laboratory testing will be performed at screening, and on Days 1, 8, 29, and 36. During the treatment period (Day 1 – Day 57), subjects will be asked to notify the site immediately if symptoms of influenza (fever, chills, sore throat, rhinorrhea, cough, muscle/body aches) occur. When increased influenza infections are being reported in the geographic region of the investigational site, subjects will additionally be contacted at Days 15±2, 21±2, 43±2, and 50±2 by phone or messaging. If influenza is suspected the subject will be asked to return to the site for laboratory confirmation of influenza using nasal swabs.

A Safety Review Committee (SRC) will review blinded safety data, as needed. The SRC includes 3 members, 2 independent infectious disease clinicians and a statistician. The SRC will be convened if halting rules are met (Section 7.3) or at the request of the Sponsor, Medical Monitor, Investigator, or any SRC member if they have cause for concern regarding subject safety in relation to the vaccine where no other cause could be attributed (Section 9.11).

3.3. Expected Duration of a Subject's Participation in the Entire Study

Subjects are expected to participate in person for a duration of up to approximately 7 months. This includes up to 30 days for screening pre-vaccination and 209 days post-initial IP treatment. Study entry is defined as the moment that the subject signs consent.

3.4. Total Study Duration

It is anticipated that the total study length will be 8 to 9 months.

3.5. Discussion of Study Design

3.5.1. Rationale for Use of Bris10 M2SR (H3N2) Vaccine and Route of Administration

The Bris10 M2SR (H3N2) and Sing2016 M2SR vaccines contain live, single-replication viruses. Intranasal administration of the vaccines, as proposed for this trial, mimics the natural route of infection of a wild-type influenza virus in which the virus adsorbs onto cells in the upper respiratory tract, enters the cell and uses host cell processes to generate viral RNA and proteins and stimulate mucosal and systemic immune responses by the host.

3.5.2. Rationale for Dose Selection

FluGen has conducted 3 clinical trials with Bris10 M2SR (a FTIH Phase 1 study, an ongoing Phase 1 study in adolescents, and a Phase 2a challenge study). See Sections 1.4.1, 1.4.2, and 1.4.3, respectively, for summaries of these studies.

Combined, the findings of these 3 clinical trials indicate that (1) the vaccine is safe and generally well tolerated as a single 10^8 $TCID_{50}$ dose; and (2) did not lead to exacerbated symptoms when followed by administration of a live, replicating wild-type influenza virus. Thus, there are no signals indicating that a safety concern might exist for studies that will increase either the dose level or exposure to more than one consecutive administration of M2SR as proposed in the current protocol.

3.5.3. Rationale for Placebo Control

Placebo control will be used to establish the frequency and magnitude of changes in laboratory and clinical endpoints that may occur in the absence of active vaccination.

3.5.4. Rationale for Randomization and Blinding

Randomization will be used to avoid bias in the assignment of subjects to, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Only the pharmacist or their designee preparing the treatment, the unblinded monitor and the unblinded statistician who prepares the randomization list are unblinded with respect to treatment.

4. SELECTION OF STUDY POPULATION

Sites will undergo a rigorous site qualification vetting to ensure they have an existing site database that can support the study requirements. Once the sites are allowed to screen, they will be instructed to search within the site database for candidates based generally on the inclusion/exclusion criteria (Section 4.1 and Section 4.2, respectively). Candidates who have indicated an interest in future study participation will be contacted by email using an IRB approved "email blast". FluGen will also provide the sites with IRB-approved advertising (emails, posters, flyers). Sites may request to use their own advertising (including radio, print, social media) and these requests will be considered on a case-by-case basis and must be IRB-approved. Potential candidates may also contact the site via a provided phone number in the email blast or advertising. As a follow-up, trained interviewers from the site will make phone calls to responsive candidates.

Screening for eligible subjects, healthy male and non-pregnant/lactating female subjects ages 18 49 years old, will be performed within approximately 4 weeks prior to randomization. Candidates who respond to outreach will be assessed by phone for interest in the study, have the opportunity to ask questions, and will be queried to confirm general eligibility (e.g. pregnancy status, age). Eligible and willing candidates will then be scheduled to attend the on-site screening visit. At this visit, the site staff will discuss study details with potential candidates. If the candidate agrees to be screened to determine eligibility for participation in the study, he/she will be asked to review and sign the informed consent prior to any study procedures. Activities conducted at the screening visit (e.g., collecting subject health information and biological samples, and a physical exam) are listed in Section 6.1.1 and further described in Section 6.2. Candidates who screen fail will be added to the site database if they agree to participate in future studies. Recruitment and enrollment metrics will be provided by each site to the Sponsor for tracking purposes.

The study will enroll approximately 250 subjects who will receive two doses of experimental Bris10 or Sing2016 M2SR vaccine or placebo (physiological saline) on Study Days 1 and 29. Subjects will be randomized 1:1:1:1:1 (Sing2016 M2SR 10^8, Sing2016 M2SR $10^{8.5}$, Sing2016 M2SR 10^9, Bris10 M2SR or Saline placebo).

For details on the sample size calculation, please refer to Section 8.3.1.

Because this is a Department of Defense funded study and subjects are expected to attend all study related visits, active military personnel are excluded from participating in this study.

4.1. Inclusion Criteria

Subjects meeting all the following criteria are eligible to participate in this study:

1. Give written informed consent to participate; a legally authorized representative (LAR) may not be used.
2. Age 18 – 49 years old, inclusive.
3. Judged suitable by the PI, as determined by medical history, physical examination, vital signs, and clinical safety laboratory examinations.
4. Negative test for pregnancy at screening visit and on Day 1. A positive test on Patient Day 29 will exclude subject from a second dose.

5. Negative test (urine) for drugs of abuse at screening. Patients who are on stable (6 months or longer) medications prescribed by their physician which result in a positive screen for that substance are allowed at the discretion of the investigator.
6. Female subjects should fulfill one of the following criteria:
    a. Post-menopausal status defined as no menses for 12 consecutive months without an alternative medical cause.
    b. Surgically sterile.
    c. Willing to use oral, implantable, transdermal or injectable contraceptives, or sexual abstinence as outlined in inclusion criteria 7, from screening and until 28 days after second vaccine dose (Patient Day 57).
7. Female subjects of childbearing potential must agree to sexual abstinence, use a reliable form of contraception approved by the Investigator (e.g., oral, implantable, transdermal, or injectable contraception, combined oral, intrauterine device [IUD], or a sterile sexual partner) from screening and until 28 days after the second vaccine dose (Patient Day 57). Non-surgically sterile male subjects who are sexually active with a female partner(s) of childbearing potential (i.e. males who have not been sterilized by vasectomy for at least 6 months prior to screening) must be willing to use condoms from screening and until 28 days after the second vaccine dose (Patient Day 57).
8. Willing to adhere to the requirements of the study and willing and able to communicate with the Investigator and understand the requirements of the study.
9. Non-smoker (defined as no use of tobacco products and no use of inhaled non-tobacco products in the past 30 days prior to Study Day 1; nicotine patches and gum are allowed). Subject must also agree to restrict the use of these products until 7 days after last vaccine administration.
10. H3N2 Sing2016 MN titers ≤1:20 (determination within 90 calendar days of study enrollment is acceptable and does not need to be repeated for entry to this study).

4.2. Exclusion Criteria

Subjects meeting any of the following criteria are excluded from participation in this study:

1. Any subject who is a family member of a) study site personnel and other personnel directly involved in conduct or monitoring of study, or b) the Sponsor.
2. Any condition that would limit the subject's ability to complete the study based on the opinion of the Investigator (for example, a recent surgical procedure).
3. Clinically significant abnormal screening hematology or chemistry value, as assessed by the investigator.
4. Pulse rate or blood pressure outside the reference range for this study population and considered as clinically significant by the Investigator.
5. Has an acute or chronic medical condition or history of a medical condition that, in the opinion of the Investigator, would render the study procedures unsafe or would interfere with the evaluation of the responses, including but not limited to, respiratory, autoimmune, or immune suppression conditions, neuroinflammatory conditions, mental illness

(including depression), active hematological, renal, hepatic, pulmonary, central nervous, neurological, cardiovascular, endocrine (including diabetes mellitus) or gastrointestinal disorders.

6. Has been vaccinated against influenza within the last 6 months or plans to be inoculated with an influenza vaccine (other than study vaccine) until one month after completion of follow up on Patient Day 209.
7. Had a flu-like illness (i.e., fever, chills and myalgia), influenza treatment (i.e., commercial drug such as Oseltamivir, etc.), or prophylactic influenza viral drug administered in the previous 6 months before screening.
8. Positive screening test or known infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).
9. History of cancer within 5 years prior to screening (except basal cell carcinoma and cervical carcinoma in situ).
10. Presence or clinically significant history of lung disease, asthma, chronic obstructive pulmonary disease (COPD), or otherwise poor lung function. Childhood asthma that resolved by age 12 years is not criteria for exclusion.
11. Any significant abnormality altering the anatomy of the nose or nasopharynx. A test swabbing by mock swab may be performed at screening at the Investigator's discretion.
12. Any confirmed or suspected immunosuppressive or immunodeficient state including: asplenia, recurrent severe infections and chronic (more than 14 days) immunosuppressant medication (such as systemic corticosteroids at a dose of $\geq$ 0.5 mg/kg/day for longer than 1 week, or immunosuppressants such as cytotoxic drugs) within the last 6 months (topical steroids are permitted). Use of immunosuppressive medications, such as allergy shots, immune globulin, interferon, or immunomodulators in the past 6 months or planned to be used during the course of the trial. Use of intranasal corticosteroids within the last 7 days before screening.
13. Significant adulthood history of seasonal hay fever, a seasonal allergic rhinitis, perennial allergic rhinitis, chronic nasal or sinus condition such as sinusitis, at the discretion of the investigator.
14. Received any licensed vaccine within 1 month before screening and during the course of the study.
15. Received or planned administration of another investigational vaccine or drug during the period from 90 days prior to Day 1 to one month after completion of Day 209 follow up.
16. History of allergy/hypersensitivity to any vaccine component (sucrose, sodium chloride, phosphate, glutamate), or material in nasal delivery device (polycarbonate, polypropylene, synthetic rubber).
17. Experienced a life-threatening reaction(s) after a previous administration of any vaccine or experienced an allergic reaction after a previous administration of any influenza vaccine or component.
18. A history or prior diagnosis of Guillain-Barré Syndrome.

19. Living in the same household with any person with a non-functional or suppressed immune system, or with a confirmed influenza infection or febrile illness within the previous two weeks.
20. History of drug or alcohol abuse in the 6 months before the study.
21. Current use of any new prescription or new over-the-counter (OTC) medications starting within 1 month of vaccination, except for contraceptive pills, implants, transdermal or injections in female subjects, which may have been started within the previous 1 month. Herbal medications and supplements other than vitamins are prohibited.
22. Receipt of blood products or immunoglobulin within 6 months before study entry or planned for within 180 days after the last vaccination.
23. Donation of blood or blood products within 30 days before study entry or planned donation at any time during the 30 days post last vaccination.
24. Females who are pregnant or lactating (i.e., a nursing mother).
25. Acute febrile illness within 72 hours prior to vaccination, defined as the presence of a moderate or severe illness with or without fever (as determined by the Investigator through medical history and physical examination), or presence of a fever >38ºC orally. Vaccination (or administration of the second dose of vaccine) should be delayed until the subject has recovered. Persons with a minor illness, such as diarrhea, or mild upper respiratory tract infection with or without low-grade fever, may be enrolled after resolution of the illness.
26. Any condition, in the opinion of the Investigator, (such as subjects who have medically high-risk conditions) that might interfere with the primary study objectives for safety of the study subject.
27. Previous exposure to M2SR investigational vaccine.
28. Any active military personnel/member.

Exclusions at Day 29:

Pregnancy, receipt of a prohibited medication, or new prohibited diagnosis, including laboratory confirmed influenza and/or treatment for influenza, or high-risk condition are exclusions for second vaccination.

Note: At the discretion of the investigator, subjects may be rescreened; out-of-range clinical laboratory tests may be repeated twice, and vital signs may be repeated three times. Results of any retest must be available prior to enrollment.

4.3. Lifestyle Guidelines

No blood donation will be allowed until 30 days after the second vaccination.

Information on prohibited therapies can be found in Section 5.9.2.

4.3.1. Contraception

Female subjects are either postmenopausal (defined as without menses for at least 12 consecutive months without an alternative medical), are surgically sterile, or if of childbearing potential, must agree to sexual abstinence or the use of a reliable method of contraception as noted in Section 4.1.

Non-surgically sterile male subjects who are sexually active with a female partner(s) of childbearing potential must also agree to use a reliable method of contraception as noted in Section 4.1.

5. TREATMENTS

5.1. Study Vaccines

Bris10 M2SR Vaccine: One IP, Bris10 M2SR, is a recombinant, monovalent influenza A virus that was initially generated by use of a plasmid rescue system. The virus does not express an essential viral protein (influenza M2), restricting it to a single replication cycle in the host. Therefore, for production it is grown in an M2-complementing cell line, M2VeroA. The Bris10 M2SR also provides the HA and NA components from A/Brisbane/10/2007.

Sing2016 M2SR Vaccine: The second IP is termed Sing2016 M2SR and is a recombinant, monovalent influenza A virus that was generated as described above for Bris10 M2SR. It contains a similar PR8 backbone but with nine amino acid changes distributed over five genes (PB1, PB2, PA, NP and NS1) that facilitate growth in the production cell line, M2VeroA. The mechanism of attenuation (deletion of the M2 gene) is not affected. The Sing2016 M2SR also provides the HA and NA components from A/Singapore/INFIMH-16-0019/2016 that were recommended for the 2018-2019 influenza season.

The Bris10 M2SR vaccine (Lot# 10250) and the Sing2016 M2SR (Lot# 19097) for this Phase 1b study were manufactured using master virus stocks and working cell bank at Ology Bioservices (Alachua, Florida, USA) under current Good Manufacturing Practice (cGMP) in a liquid formulation. The Bris10 M2SR vaccine will be provided frozen and in single-use cryovials. The Sing2016 M2SR vaccine will be provided frozen and in single-use cryovials. Details for IP titer and dilutions will be provided in the study-specific Pharmacy Manual.

Copies of the certificates of analysis (CoAs) of the Bris10 M2SR and Sing2016 M2SR vaccines will be provided upon request.

A pharmacist or designee will thaw the vial contents to room temperature just prior to dose administration. The contents will be diluted to the target dosing concentration with provided SPG diluent for each subject. The final diluted product will be drawn into two 1 mL disposable polypropylene syringes each fitted with a mucosal atomization device (MAD301; Teleflex, Salt Lake City, Utah, US) for intranasal delivery.

5.2. Placebo Administered in the Study

The reference product (placebo) is a physiological saline suitable for intranasal delivery. The placebo will be provided as a liquid and in single-use vials. The placebo will be drawn into two 1 mL disposable syringes (~50% volume each) that are fitted with a Teleflex MAD301 sprayer for intranasal delivery. Administration and post-dose restrictions will be as described for the M2SR vaccines.

The placebo is a clear solution whereas the M2SR vaccines are a light yellowish color. The unblinded pharmacy staff will prepare the vaccine and placebo doses, fill delivery devices and apply an opaque label to the device barrel to obscure any coloration of the contents and maintain the blind.

Commercially available supplies of the placebo will be used and will be supplied by the site following approval from the Sponsor.

5.3. Packaging and Labeling

5.3.1. Vaccines

Manufacturing, packaging, and labeling of the M2SR vaccines is under the responsibility of the Sponsor.

The Bris10 M2SR vaccine will be provided frozen and in single-use cryovials. The Sing2016 M2SR vaccine will be provided frozen and in single-use cryovials. The viruses are suspended in SPG-NaCl buffer comprised of 303 mM sucrose, 5 mM glutamic acid, 136.9 mM sodium chloride, 2.67 mM potassium chloride, 1.47 mM potassium dihydride phosphate and 8.1 mM disodium phosphate, at pH 7.2. Each vial will be diluted in SPG-NaCl buffer based on the intended dose and is considered to be a single-use vial.

The primary package for both the vaccine products and for the SPG-NaCl buffer is a 2 mL cryovial with a threaded cap closure. The vaccine and buffer will be labeled according to local law and regulatory requirements. Each vial label will include the following information: product name, item and lot numbers, date of manufacture, storage condition, volume, vial number, manufacturer, and “Caution: New Drug – Limited by Federal law to Investigational Use.” The vial label for the vaccine is a light-blue label with black text and for the SPG-NaCl buffer is a white label with black text. Sample vial labels are shown in Figure 1.

The vaccine and buffer vials will be packed into separate multi-vial boxes. Each box will be labeled with the following information: product name, item and lot numbers, storage condition, vial number range and volume, manufacturer and “Caution: New Drug – Limited by Federal law to Investigational Use.” The box label for the vaccine will be a light-blue label with black text and for the buffer will be a white label with black text.

Figure 1: Sample labels for drug product and SPG-NaCl buffer.

Bris10 M2SR Drug Product
Item #.: 10-0002305 Lot #.: XXXXXXX
DOM: DDMMMYYYY Store at ≤ -65°C
Volume: 0.5 mL Vial # XYZ
Manufactured by Ology Bioservices, Inc.
Caution: New Drug-Limited by Federal
Law to Investigational Use

Sing2016 M2SR Drug Product
Item #.: 10-0004082 Lot #.: XXXXXXX
DOM: DDMMMYYYY Store at ≤ -65°C
Volume: 0.5 mL Vial # XYZ
Manufactured by Ology Bioservices, Inc.
Caution: New Drug-Limited by Federal
Law to Investigational Use

SPG-NaCl Diluent
I/N: 10-0001613 L/N: XXXXXXX
DOM: DDMMMYYY Store at ≤ -65°C
Vial# XYZ Volume: 0.5 mL
Manufactured by Ology Bioservices, Inc.
Caution: New Drug- Limited by Federal
Law to Investigational Use

5.3.2. Placebo

The placebo is a commercially available physiological saline that will be supplied in single-use containers. The 0.9% sodium chloride for injection, USP, is a sterile, nonpyrogenic, isotonic solution of sodium chloride and water for injection. It is preservative-free and supplied in a single-dose container. The pharmacist or designee will aseptically fill placebo into the delivery devices on an as needed basis. A CoA will be provided for the placebo.

5.4. Storage and Drug Accountability

The Investigator (or designee) is responsible for the safe storage of all study drugs assigned to the clinical site, in a locked, secure storage facility with access limited to those individuals authorized to dispense the study drugs and maintained within the appropriate ranges of temperature. All study drugs must be stored as specified at delivery and in the original packaging. Instructions for the storage and handling of the study drugs will also be provided to the clinical site.

5.4.1. Vaccines

The M2SR vaccine products and the SPG-NaCl buffer will be delivered frozen and must be stored frozen at < -65°C in the provided multi-vial boxes. Each vaccine vial is a single-use vial. Once the vial contents have been thawed, the vial must be stored at 2-8°C prior to use in vaccine administration. The thawed vial contents will remain stable in the Sponsor-identified cryovials, neat or diluted with SPG-NaCl buffer, for up to 8 hours. Any vaccine product that has been

thawed and held at 2-8°C for longer than 8 hours is no longer suitable for use in the study and must be accounted for. Such product will be labeled as damaged and will be quarantined at room temperature until the study monitor conducts on-site drug accountability. After that, this product should be destroyed per clinic Standard Operating Procedures (SOPs) and a certificate of destruction, or equivalent should be filed on site and provided to the Sponsor for internal filing.

Each SPG-NaCl buffer vial is a single-use vial. Once the vial contents have been thawed, the vial must be stored at 2-8°C prior to use in treatment administration. The thawed vial contents will remain stable in the Sponsor-identified cryovials for up to 8 hours. Any buffer product that has been thawed and held at 2-8°C for longer than 8 hours is no longer suitable for use in the study and must be accounted for and then destroyed per clinic SOPs.

Investigational product must be stored under temperature-controlled and monitored conditions. The site will also maintain a temperature log record of the relevant equipment for IP storage. Should an excursion in storage conditions occur, the clinical site must not further dispense the affected study vaccine until after notification and consultation with the Sponsor.

The Investigator is responsible throughout the study for ensuring inventory and account record of all study drugs received at the clinical site. All drug accountability records must be stored in the site file and must be readily available for inspection by the study monitor and/or auditor, and open to regulatory inspections at any time.

As misallocations of study drugs may have a detrimental effect on subjects' safety and/or the study drugs' efficacy and are a potential source of bias, utmost care should be taken to correctly dispense the study drugs as assigned by the randomization code.

The vaccine and placebo should be dispensed under the supervision of the Investigator, a qualified member of the clinical staff, or by a hospital/clinic pharmacist or designee. The pharmacist or designee must maintain accurate records demonstrating date and amount of vaccine and the placebo supplied to whom and by who. The investigational vaccine and placebo will be supplied only to subjects participating in the study.

The Sponsor's designated study monitor will periodically check the supplies of vaccine and the placebo held by the Investigator or pharmacist/designee to ensure accountability and appropriate storage conditions of all vaccine and placebo used.

Unused vaccine and placebo must be available for verification by the study monitor during on-site monitoring visits. Any discrepancies between returned and expected returned vaccine and placebo should be explained and documented.

After the database has been locked and all on-site drug accountability has been completed by the monitor, any unused vaccine (including neat and diluted remnants) may be returned to the Sponsor or destroyed at the clinical site with the Sponsor's written permission (in this case a certificate of destruction or equivalent will be provided and filed in the electronic Trial Master File [eTMF]).

Hazardous materials such as used ampoules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

5.4.2. Placebo

Each placebo cartridge is a single-use container. The solution will be stored at USP controlled room temperature (20 – 25°C) prior to use in treatment administration. The contents may be used up to the date of expiry as stated by the manufacturer.

Procedures for handling and storage of the commercially available placebo are detailed on the product-specific labels.

5.5. Randomization

Subjects will be assigned to IP (M2SR vaccines or saline) using a permuted block design. The randomization list will be prepared prior to study start by Sponsor's statistician and shared with the unblinded pharmacist or designee. This treatment assignment list is to be treated as a controlled document and is not to be shared with other blinded personnel. Eligible subjects will be randomized to receive two administrations 28 days apart of Sing2016 at three dose levels, Bris10 at one dose level, or placebo in a 1:1:1:1:1 ratio. Approximately 15 subjects will be vaccinated at a time in up to 3 sentinel groups, and approximately 41 subjects will be vaccinated in expansion groups.

5.6. Blinding

The blind will be maintained during this trial, including use of the following measures:

(1) All subjects, whether receiving a M2SR vaccine or placebo, will undergo the same procedures, i.e., administration, AE assessment, blood collections, nasal swabs, etc.

(2) The unblinded pharmacist or designee will prepare doses (active and placebo), fill delivery devices and apply an opaque label to the device barrel to obscure any coloration of the contents.

(3) The unblinded site staff and unblinded study monitor will agree to maintain the blind by not providing details of the dose (active or placebo) to any blinded clinic staff including the Investigator and to study subjects. Furthermore, the unblinded individuals will be restricted from participating in other study procedures the interpretation of which could be impacted by their unblinded status, such as evaluation of AEs.

(4) If any blinded investigational site staff learn of treatment assignments, a record of the event will be maintained, and the investigator will be informed. The investigator will consult with FluGen on how to preserve the blind.

With the exception of the unblinded statistician who generates the randomization list, the unblinded pharmacist(s) or their designee(s) who prepare the study product for administration and the unblinded study monitor who may observe the study product preparation and performs IP accountability, all subjects, the Investigator, statistical programmers and all clinical site staff will be blinded to IP treatment (vaccine or placebo). All clinic staff who may be involved in making assessments of safety (including local reactions) will be blinded to treatment. Should a blinded monitor observe study product preparation, precautions must be taken to maintain the blind.

Masking of the IP (vaccine or placebo) will be described in the Pharmacy Manual.

The randomization schedule will be inaccessible to the Investigator or to the blinded study team (monitors and/or FluGen team) during the study. After the Day 209 is complete for all subjects, after database lock, and after reconciliation with pharmacy and site records, the randomization code will be provided to the Study Statistician to enable data analysis by the Sponsor. Data collected at the Day 209 visit will be maintained in a separate follow-up database, and will be unblinded after cleaning and reconciliation, as for the primary database.

The unblinded Statistician provides the randomization list to the unblinded pharmacist or their designee. This list will be used to prepare study product dosages and in the event of an emergency code break (see below).

In the event of a medical emergency wherein knowledge of the IP treatment assignment will influence the subject's care, the Principal Investigator (PI) may be provided with the IP treatment assignment for that subject, at the discretion of the PI. The unblinded pharmacist or their designee will use the IP treatment assignment code to break the blind for the PI only in case of emergency. The PI will contact the FluGen Medical Monitor and document the event with the information regarding the reasons for unblinding as soon as possible, and no later than 24 hours after such unblinding. In the event the IP treatment code is broken, it will be broken ONLY for the subject in question. The reason for unblinding will be documented in the subject's paper source. Subjects who are unblinded for any reason during their participation in the study will not be replaced and will be withdrawn immediately from the study; however, all attempts will be made to collect safety data through 28 days post-dose of the vaccine/placebo. In the event of a request to break a treatment code, the study monitor will be notified within 24 hours and the rationale for breaking the code will be documented.

5.7. Dose and Administration

5.7.1. Vaccine

A rationale for the doses of vaccine selected in this study is provided in Section 3.5.2.

Subjects will be randomly and sequentially assigned, according to the randomization schedule and in a blinded fashion, to one of 3 IP treatments: i.e., vaccine or placebo.

Each vaccine and placebo dose will be filled into a sterile 1 mL polypropylene syringe that is fitted with a Teleflex MAD301 sprayer for intranasal delivery (Figure 2) by the unblinded pharmacist or designee.

Figure 2: Image of the MAD301 Sprayer Device Fitted to a Syringe

To fill the syringe, the contents are drawn into the syringe barrel via an 18-gauge needle. The needle is removed and replaced with the MAD301 sprayer via a Luer lock fitting. The spray device

is then primed. Further details for filling and actuating the spray device are provided in the Pharmacy Manual. The pharmacist or designee will wrap an opaque label completely around the circumference of the syringe barrel to conceal any color of the liquid contents and will use an indelible marker to record the subject's ID on the label. The clinical staff credentialed to administer vaccines will then use the masked, filled spray device to administer the dose (active or placebo) intranasally to the subject.

For delivery, on each of Days 1 and 29, subjects will receive a single intranasal dose of vaccine (or placebo) via a MAD301 spray device. Subjects will be in a semi-recumbent position and receive approximately two administrations of ~50% volume per nasal cavity by employing 2 spray devices. Devices will be weighed pre- and post-dose to allow calculation of dose eliminated from the devices. Subjects will remain semi-recumbent and under observation for thirty (30) minutes and will not be allowed to blow their noses, eat, or drink during this time; any deviations are captured in the source documents and reported to the study monitor/Clinical Project Manager.

Any deviation from the dose defined in the protocol must be documented on source and in the eCRF system.

5.8. Treatment Compliance

Monitoring treatment compliance is not applicable because treatment will be administered per protocol in the clinic by study personnel.

5.9. PRIOR AND CONCOMITANT THERAPY

The use of concomitant therapies should be kept to a minimum throughout the study. All therapies administered (prescriptions and over-the-counter medications), other than the vaccine, from informed consent until the day 57 study visit, must be recorded in the source documents and in the concomitant therapy section of the Electronic Case Report Form (eCRF) (name of the drug, dosage, route and dates of administration).

In the event that medical conditions after study treatment dictate use of medications, subjects are encouraged to obtain adequate care, comply with the course of therapy as prescribed by their physician, and inform the Investigator as soon as practical.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered to a study subject.

Female subjects of childbearing potential and non-vasectomized male subjects having a female partner of childbearing potential must agree to the use of an effective method of contraception throughout the study, as outlined in Section 4.1. The use of oral, injectable, and implantable hormonal contraceptives is to be recorded in the source documents and in the concomitant therapy section of the eCRF.

5.9.1. Permitted Concomitant Therapies

The following medications and treatment are permitted in this study after Day 1:

- Non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, or antihistamines may be used after dosing if the subject has a fever ≥ 38.0°C (100.4°F)

or if the subject has significant nasal pain, myalgia, or headache. NSAIDs or acetaminophen should only be taken after documentation of symptoms or fevers on the Symptom Memory Aid and should not be taken prophylactically.

- Low-dose aspirin

5.9.2. Prohibited Concomitant Therapies

The following medications are not permitted in the study 7 days prior to each vaccination and continuing until 7 days after each vaccination:

- Concomitant use of any new prescription or over-the-counter (OTC) medications (except for contraceptive pills, implants, transdermal or injections)

Any medication that is not covered by the permitted and non-permitted medication sections can be allowed at the discretion of the Investigator and documented on eCRF.

6. ASSESSMENTS

6.1. Timing of Assessments

An overview of the timing of treatment(s) and assessments is given in the Schedule of Events (Table 3). Details of safety and efficacy assessments are provided in Section 6.2.1 through Section 6.2.3, and Section 6.2.4, respectively.

When visit assessments are planned at the same time point in the study, the order of assessments should be in order of less invasive to more invasive. For example, during the randomization visit, vitals, medical history, pregnancy testing and drug testing should be conducted before blood work and subsequent nasal swab.

Table 3: Schedule of Events

Study Visit Number	V00	V01	V02	V03	V04	V05	V06	V07	V08	Early Term[7]
Study Day Post-First Dose	Days -30 to -1	Day 1	Day 4 ±1	Day 8 ±1	Day 29 +/- 7	Day 32	Day 36	Day 57	[20]Day 209	
Study Day Post-Second Dose					D1	Day 4 ±1	Day 8 -1/+7	Day 29 +/-7	D181 +/-14	
Informed Consent	X									
Inclusion/Exclusion	X	X[2]			X[2]					
Demography	X									
Physical exam	X[1]									X[8]
Limited physical exam[10]		X[2,4]		X	X[2,4]		X	X	X	X[9]
Medical/medication history	X	X[2]			X[2]					
Vital signs (height, weight, BP, HR, temp)[16]	X	X[2, 4]		X	X[2, 4]		X	X	X	X[8]
Pregnancy testing (urine)	X	X[3]			X[3]					
Hematology[6]	X	X[2,5]		X	X		X			X[13]
Chemistry[6]	X	X[2,5]		X	X		X			X[13]
Urinalysis (dipstick)	X	X[2, 5]		X			X			X[13]
Urine Drug Screen	X									
Serology for HIV, Hep B & C	X									
Symptom Memory Aid [11]		X		X	X		X			X
Scripted phone call with site to report symptoms			X			X				
Assessment for influenza[19]		X	X	X	X	X	X	X		
Serum collection (HAI, MN, NAI and ELISA)	X	X[2]		X	X[2]		X	X	X	X
PBMC collection (CMI) & plasma[18]		X[2, 15]	X[17]	X[15]	X[2, 15]	X[17]	X[15]	X		X
Nasal swab for secretory IgA immune response and/or vaccine virus detection	X[12]	X[2, 9, 12,14]		X[9, 12]	X[2, 9, 12]		X[9, 12]	X[12]	X[12]	X[9, 12]
Dose administration		X			X					
Device Weights		X			X					
AEs		X[4]	X	X	X[2,4]	X	X	X		X
Conmeds	X	X[2]	X	X	X[2]	X	X	X		X
SAEs and medically attended AEs	X	X	X	X	X	X	X	X	X	X

[1]Complete Physical is required; neurological, rectal and gynecological exams do not need to be performed unless clinically indicated

[2]Prior to dosing
[3] Pregnancy test by urine dipstick on days 1 and 29 must be negative and reviewed prior to dosing
[4]At 5 (+/- 1) and 30 (+/- 3) min after dosing
[5] Lab values at Day 1 are considered baseline
[6]Laboratory tests as indicated in Appendix 2.
[7]Early Term visit is only applicable if a subject does not complete the study within 28 days after dose administration
[8]Limited physical exam and vital sign evaluations will be completed if early termination occurs within 28 days after dose administration
[9]Sample aliquoted for vaccine virus detection (qPCR & infectivity)
[10] Specifically includes the nares (including edema), throat, and lungs (including evaluation for wheezing). A targeted physical examination may be performed on other body systems if indicated based on review of interim medical history or subject symptoms as observed by site or by PI.
[11] Dispense/Review/Collect for 7 days following each dose administration including day of dosing
[12] Sample aliquoted for secretory IgA immune response
[13] Sample collected if subject presents with AE
[14] Sample may be tested for respiratory pathogens
[15] Collected from PBMC processed blood
[16] Blood pressure will be measured from the subject's arm after the subject has been at rest (seated or semi-recumbent) for approximately 5 minutes with the arm supported at the level of the heart. Blood pressure will be recorded to the nearest mmHg. Height and weight will be measured only at the screening visit.
[17] Optional PBMC collection (Days 4 and 32) at select sites based on subject consenting on Day 4 and/or Day 32
[18] PBMC and plasma collected at select sites for ~160 subjects
[19] During the treatment period (Day 1 – Day 57), subjects will be asked to notify the site immediately if symptoms of influenza (fever, chills, sore throat, rhinorrhea, cough, muscle/body aches) occur. Subjects will be reminded at every scheduled visit and phone call, and in addition to visits and calls scheduled above (when increased influenza infections are being reported in the geographic region of the investigational site) will be contacted at Days 15±2, 21±2, 43±2, and 50±2 by phone or messaging. If influenza is suspected the subject will be asked to return to the site for laboratory confirmation of influenza using nasal swabs.
[20] Due to the COVID-19 pandemic, local governments may issue stay-at-home orders which prevent centers from conducting on-site Day 209 visits. This protocol allows for Day 209 visit to be a safety follow-up phone call.

6.1.1. Screening Period 1 (Days -30 to Dosing)

In a private, individual setting, subjects will be given a full explanation of the nature of the study and written informed consent (IRB approval will be obtained before any study-related assessment) will be carried out. Group consenting will not be permitted and subjects requiring a Legally Authorized Representative may not participate in this study.

Screening for eligible and consenting subjects will be performed within approximately 30 days prior to randomization/IP administration.

Subjects may be consented and screened for serosusceptibility under a site-specific IRB-approved ICF.

At screening, subjects will be asked to attend the clinical site to have assessments performed as indicated in the Schedule of Events (Table 3).

All results from the screening procedure needed to evaluate eligibility, including the clinical laboratory results, must be available prior to study vaccination on Day 1. Any abnormal assessment at the screening visit will be assessed according to its clinical relevance, and if found clinically significant, the subject will not be included in the study.

During the screening period, the following procedures and assessments will be carried out for each subject to determine their eligibility for participation in the study:

- Obtain informed consent prior to any procedures being performed
- Record demographics
- Confirm eligibility criteria for enrollment and vaccination
- Obtain medical history
- Record concomitant medications
- Perform complete physical examination (neurological, rectal and gynecological exams do not need to be performed unless clinically indicated)
- Vital signs (height, weight, blood pressure, heart rate, and temperature)
- Collect urine for drug screen
- Collect urine for pregnancy test (applicable females only)
- Collect blood for serology for HIV, Hepatitis B & HCV
- Collect blood for serum chemistry and hematology
- Collect blood for immunogenicity assays
- Urinalysis (dipstick)
- Perform nasal swab
- Record any concomitant therapy/medically attended AEs/SAEs after signing of consent

Unscheduled visits may be planned to assess, confirm, and follow-up on out-of-range clinical laboratory test, or vital sign values that determine a subject's eligibility, or in case of a positive

urine drug screen. The result of the retest will be considered for subject eligibility. Findings made during unscheduled visits should be reported in the eCRF system.

A record of the number of screening failures and the reasons for screening failure will be captured in eCRF, but subjects who fail screening and are not enrolled will not otherwise be included in the database. The failure details will be documented in the subjects' study file.

6.1.2. Treatment Period (Day 1 to Day 57)

Assessments will be performed as indicated in the Schedule of Events (Table 3).

6.1.2.1. Day 1

- Update medical history
- Vital signs (blood pressure, heart rate, and temperature)
- Collect urine for pregnancy test (applicable females only)
- Collect blood for serum chemistry and hematology
- Urinalysis (dipstick)
- Review of inclusion and exclusion criteria
- Collect pre-dose blood sample for humoral immunogenicity assays (baseline MNT and other serum assays)
- Collect pre-dose blood sample (PBMC) for cellular immunogenicity assays (ELISpot) and/or innate transcriptome gene expression – select sites only
- Collect pre-dose blood sample (plasma) for cytokine expression – only if PBMC collected by site
- Perform limited physical examination
- Nasal swab into buffer for mucosal IgA and virus shedding
- Symptom Memory Aid (distribute and provide instructions, fill out form pre-dose to train subject on execution)
- Randomization
- Device weights (pre- and post-IP administration)
- IP administration
- Record concomitant therapy prior to dosing
- Record AEs/SAEs at 5 (+/- 1) and 30 (+/- 3) min after dosing

6.1.2.2. Day 4 ± 1 day

- Optional on-site visit for collection of blood sample (PBMC and plasma) for innate transcriptome gene expression – select sites only
- If subject does not attend on-site visit, scripted phone call with site to report symptoms (if unable to reach subject then email or SMS is acceptable)

- Record concomitant therapy/AEs/SAEs

6.1.2.3. Day 8 ± 1 day

- Perform limited physical examination
- Vital signs (blood pressure, heart rate, and temperature)
- Collect blood for serum chemistry and hematology
- Urinalysis (dipstick)
- Symptom Memory Aid reviewed
- Nasal swab into buffer for mucosal IgA and virus shedding
- Collect blood sample for humoral immunogenicity assays (MNT and other serum assays)
- Collect blood sample (PBMC) for cellular immunogenicity assays (ELISpot) and/or innate transcriptome gene expression – select sites only
- Collect blood sample (plasma) for cytokine expression – only if PBMC collected by site
- Record concomitant therapy/AEs/SAEs

6.1.2.4. Day 29 ± 7 days

- Confirm eligibility for second vaccination
- Update medical history
- Vital signs (blood pressure, heart rate, and temperature)
- Collect urine pre-dose for pregnancy test (applicable females only)
- Collect blood for serum chemistry and hematology
- Perform limited physical examination
- Nasal swab into buffer for mucosal IgA and virus shedding
- Collect pre-dose blood sample for humoral immunogenicity assays (MNT and other serum assays)
- Collect pre-dose blood sample (PBMC) for cellular immunogenicity assays (ELISpot) – only by select sites
- Collect pre-dose blood sample (plasma) for cytokine expression – only if PBMC collected by site
- Symptom Memory Aid (distribute and provide instructions)
- IP administration
- Device weights (pre- and post-IP administration)
- Record concomitant therapy/AEs/SAEs prior to dosing and at 5 (+/- 1) and 30 (+/- 3) min after dosing

6.1.2.5. Day 32 (3 days ± 1 day after second dose)

- Optional on-site visit for collection of blood sample (PBMC and plasma) for innate transcriptome gene expression – select sites only
- If subject does not attend on-site visit, scripted phone call with site to report symptoms (if unable to reach subject then email or SMS is acceptable)
- Record concomitant therapy/AEs/SAEs

6.1.2.6. Day 36 (7 days -1/+7 day after second dose)

- Perform limited physical examination
- Vital signs (blood pressure, heart rate, and temperature)
- Collect blood for serum chemistry and hematology
- Urinalysis (dipstick)
- Symptom Memory Aid reviewed
- Nasal swab into buffer for mucosal IgA and virus shedding
- Collect blood sample for humoral immunogenicity assays (MNT and other serum assays)
- Collect blood sample (PBMC) for cellular immunogenicity assays (ELISpot) – only by select sites
- Collect blood sample (plasma) for cytokine expression – only if PBMC collected by site
- Record concomitant therapy/AEs/SAEs

6.1.2.7. Day 57 (28 days ± 7 days after second dose)

- Perform limited physical examination
- Vital signs (blood pressure, heart rate, and temperature)
- Nasal swab into buffer for mucosal IgA and virus shedding
- Collect blood sample for humoral immunogenicity assays (MNT and other serum assays)
- Collect blood sample (PBMC) for cellular immunogenicity assays (ELISpot) – only by select sites
- Record concomitant therapy/AEs/SAEs

6.1.2.8. Day 209 (180 days ± 14 days after second dose)- on-site visit

- Perform limited physical examination
- Vital signs (blood pressure, heart rate, and temperature)
- Nasal swab into buffer for mucosal IgA and virus shedding
- Collect blood sample for humoral immunogenicity assays (MNT and other serum assays)
- Record SAEs

Due to the COVID-19 pandemic, local governments may issue stay-at-home orders which prevent centers from conducting on-site Day 209 visits. This protocol allows for the Day 209 visit to be a follow-up phone call focusing on the following safety points:

- Has the subject received any licensed vaccines since Day 1 of the trial?
- Has the subject received any investigational product (other than study IMP/placebo) since Day 1?
- Has the subject had any SAEs or medically attended AEs since the last contact with the site?

6.1.3. Testing for Influenza

During the treatment period (Day 1 – Day 57), when increased influenza infections are being reported in the geographic region of the investigational site, subjects will be asked to notify the site immediately if they experience symptoms of influenza (fever, chills, sore throat, rhinorrhea, cough, muscle/body aches). If influenza is suspected the subject will be asked to return to the site and will have nasal swabs collected for laboratory confirmation of influenza. Subjects will be reminded at every scheduled visit and phone call, and in addition to visits and calls scheduled above, will be contacted at Days 15±2, 21±2, 43±2, and 50±2 by phone or messaging. Subjects may also have a rapid diagnostic test performed and may be treated for influenza at the investigator's discretion.

6.1.4. Early Termination Visit

Subjects who withdraw consent will be asked to attend the clinic for safety evaluation as described in Early Termination assessments.

Early Termination assessments should be completed within 7 (± 3) days of discontinuation for subjects who discontinue from the study. The following assessments are to be performed:

- Complete physical examination (neurological, rectal and gynecological exams do not need to be performed unless clinically indicated); a limited physical exam will be completed if early termination occurs within 28 days after dose administration
- Vital signs (height, weight, blood pressure, heart rate, and temperature)
- Collect blood for serum chemistry and hematology
- Urinalysis (dipstick)
- Symptom Memory Aid
- Nasal swab into buffer for mucosal IgA and virus shedding
- Collect blood sample for humoral immunogenicity assays (MNT and other serum assays)
- Collect blood sample for cellular immunogenicity assays (PBMC, ELISpot) – only for select sites
- Collect blood for gene expression (PBMC, plasma) – only for select sites
- Record concomitant therapy/AEs/SAEs

6.1.5. Unscheduled Visits

Unscheduled visits can be planned:

- To obtain additional information to ensure safety to the subject. Additional blood and urine samples may be taken at the discretion of the Investigator.
- To obtain a nasal swab for assessment of potential influenza infection.
- To assess, confirm, and follow-up on out-of-range clinical laboratory test, or vital sign values that will determine a subject's eligibility, or in case of a positive drug screen.
- The result of the retest will be considered for subject eligibility.

Findings made during unscheduled visits should be reported in the eCRF.

6.2. Study Assessments

6.2.1. Clinical Evaluations

6.2.1.1. Medical History

A complete medical history will include a review of all major body systems. Significant past and present medical history will be obtained by interview during the screening visit.

6.2.1.2. Concomitant Medications

Details of prescription and over-the-counter medications (including vitamins) currently used will be recorded during the screening visit. Concomitant medications will be reviewed at each visit and any new medications will be documented on the eCRF.

6.2.1.3. Demographics

Demographics will be obtained during screening only. Demographics will include the age and race as described by the subject.

6.2.1.4. Physical Examination

6.2.1.4.1. Complete Physical Examination

A complete physical examination will be performed for each subject at the time points specified in the Schedule of Events (Table 3). The examination will consist of assessment of the following organs/systems:

- Head
- Eyes
- Ears, nose, throat
- Neck
- Cardiovascular
- Chest

- Respiratory
- Abdomen
- Genitourinary – only if clinically indicated
- Extremities
- Musculoskeletal
- Nervous system – only if clinically indicated
- Dermatological
- Other conditions of note

6.2.1.4.2. Limited Physical Examination

A limited physical exam will be performed for each subject at the time points specified in the Schedule of Events (Table 3). The examination will include the nares (including edema), throat, and lungs (including evaluation for wheezing). A targeted physical examination may be performed on other body systems if indicated based on review of interim medical history or subject symptoms as observed by site or by PI.

6.2.1.5. Vital Signs

Vital signs include height, weight, oral temperature (°C), blood pressure (mmHg), pulse rate (beats per minute). Vital signs will be obtained at the time points specified in the Schedule of Events (Table 3). Subjects should have weight and height measured while wearing light street clothing and with shoes off. Blood pressure will be measured from the subject's arm after the subject has been seated or semi-recumbent for approximately 5 minutes with the arm supported at the level of the heart. Blood pressure will be recorded to the nearest mmHg.

6.2.1.6. Symptom Memory Aids

Subjects will be asked to record post-treatment symptoms in a Symptom Memory Aid (Appendix 5) at the time points specified in the Schedule of Events (Table 3) for reactogenicity. At time of first dose, the first entries will be in concert with study staff as a training session at pre-dose, the second entry will be the evening of vaccination and subsequent 6 entries will be made each evening following the IP delivery. Since visit Day 36 may occur ±1 day, the subject may not complete all days listed on the memory aid prior to the first post-dose visit. For subjects who attend the clinic at Day 35, a stamped and pre-addressed envelope will be provided so that the diary may be completed and mailed to the Site. Symptoms recorded on diaries returned by mail will be reviewed with the subject by telephone, if needed. Subject diaries will be retained as source documents.

Events that are reported in the Symptom Memory Aid will be reviewed by the study staff and assessed and recorded as AEs according to the appropriate toxicity scale (Appendix 1 for vital signs and systemic AEs and Appendix 3 for reactogenicity assessments). During this time, subjects are asked to take their oral temperature (at approximately the same time each evening using the thermometer provided to them by the site) and record it in the Symptom Memory Aid. Any medications taken by the subjects will also be recorded in the Symptom Memory Aid. In addition,

subjects will be asked to record symptoms they may be experiencing during this time period, including:

- Feverish
- Nasal irritation
- Nasal bleeding
- Runny nose
- Stuffy nose/Congestion
- Sore/scratchy/itchy or painful throat
- Body/muscle aches
- Joint pain
- Headache
- Cough
- Body rash
- Tiredness
- Nausea
- Vomiting
- Other symptoms

6.2.1.7. Urine Samples

Urine samples for the determination of pregnancy for women of childbearing potential, drug screening, and urinalysis will be collected at the time points specified in the Schedule of Events (Table 3).

A midstream urine sample will be collected for urinalysis by dipstick for specific gravity, pH, glucose, protein, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase, and occult blood. If dipstick urinalysis is abnormal, microscopic examination for WBC, RBC, and epithelial cells will be performed. Crystals, casts, and bacteria will only be reported if present.

A urine drug of abuse screen will be performed.

6.2.2. Bioanalysis

Blood and urine samples for determination of the concentration of analytes specified in Appendix 2 will be analyzed by a qualified vendor under the responsibility of the Sponsor, using validated analytical methods.

The Investigator must review the laboratory report, document this review, and record any change occurring during the study he considers to be clinically relevant in the AE section in the EDC system. Laboratory values outside the normal range will be flagged and their clinical relevance as

an AE will be assessed by the Investigator. Laboratory values which are Grade 3 or higher based on the grading scales in Appendix 2 will be reported to the Sponsor **within 24 hours** of investigator awareness, and assessment of clinical relevance will be reviewed by the Medical Monitor.

The laboratory analysis will be carried out following the principles of Good Laboratory Practice (GLP) regulations.

6.2.3. Adverse Events

Adverse events will be monitored continuously from first administration of IP treatment until study Day 57. At regular intervals during the study, subjects will be asked non-leading questions to determine the occurrence of any AEs. All AEs reported spontaneously during the course of the study will be recorded as well. Solicited and unsolicited signs and symptoms will be reported as AEs after review by the Investigator or designee, either separately using the corresponding Medical Dictionary for Regulatory Activities (MedDRA) terminology of the sign or symptom or combined using the appropriate term. For example, a subject who experiences dysuria with blood, WBCs, and bacteria in the urine would be recorded as having a urinary tract infection.

For detailed definitions and reporting procedures of AEs, see Section 9.

6.2.4. Efficacy Evaluations

6.2.4.1. Nasal Swabs

Nasal swabs will be collected from subjects for the following purposes:

1. To determine mucosal immunity
2. To test for the presence of shedding influenza virus
3. To test for the presence of respiratory viruses and bacteria (Optional)

Nasal swabs will be collected at the time points specified in the Schedule of Events (Table 3) from all subjects. Individual swabs will be collected from each nostril and combined into a single vial of media. Samples will be aliquoted to use in various tests.

To evaluate mucosal immunity, an ELISA-based test will be used to measure 1) mucosal IgA antibody titer to HA and 2) total IgA concentration

To detect shedding influenza virus, a quantitative H3N2 RT-PCR assay will be used. Only swabs that have a positive qRT-PCR test result will be subjected to quantitative infectious culture assay.

Possible infection with respiratory viruses and bacteria may be evaluated by use of a qualitative PCR test. This multiplexed assay will be performed by use of a commercial, qualitative viral and bacterial upper respiratory tract infection panel PCR device (adventitious agent screening).

If a subject presents within 7 days of vaccination with symptoms of fever, upper respiratory illness, nephritis/cystitis, conjunctivitis or diarrhea, regardless of the severity of the symptoms, an additional nasal swab(s) should be collected and/or analyzed outside of the defined time points.

6.2.4.2. Delivery Device Weights

The weight of each IP-filled device will be collected prior to dose administration and the weight recorded in the eCRF at the time point specified in the Schedule of Events (Table 3). Following administration of the dose (active and placebo) the actuated device will again be weighed, and the weight recorded in the eCRF. A calculation of the filled device weight minus the emptied device weight will indicate the weight of dose that was delivered from the device and will be used to determine volume dispensed.

6.2.4.3. Blood Collection for Influenza Antibody Testing

Blood samples will be collected and used for serum antibody titers against influenza using microneutralization (MN) and research assays. Samples will be collected as indicated in the Schedule of Events (Table 3).

The MNT will measure all serum antibodies that neutralize the virus and prevent infection of cells and will be analyzed as directed in the Laboratory Manual.

Research testing will be performed by the Sponsor or a vendor under supervision of the Sponsor. The research assays include enzyme-linked immunosorbent assays (ELISAs) or similar methods that may be used to detect anti-influenza immunoglobulin G (IgG) and/or IgA antibodies against influenza HA, HA stalk or NA. Additional assays may be conducted for detection of antibody response to influenza or other respiratory virus, for example neuraminidase inhibition assays (NAI).

Further details regarding sample collection, processing and shipping can be found in the Laboratory Manual.

6.2.4.4. PBMCs for Cell-mediated Immunity Testing

Blood samples will be collected from all subjects at select sites and peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved to be tested for CMI. Samples are taken as indicated in the Schedule of Events (Table 3) for ~160 subjects.

PBMCs will be used to evaluate T cell responses by ELISPOT assays measuring cytokine secretion upon stimulation with influenza specific peptides. PBMCs may also be evaluated using flow cytometric (FACS) methods and intracellular cytokine staining (ICS) to characterize the duration of the responses, and whether memory phenotypes are generated. PBMCs may also be used in a direct ex-vivo ELISPOT assay for evaluation of plasma B cell responses or for detection of memory B cell responses after stimulation.

Further details regarding sample collection, processing and shipping can be found in the Laboratory Manual. PBMC preparation will be the responsibility of each site.

6.2.4.5. Plasma for Gene Expression and Cytokine Testing

The plasma fraction will be collected from all subjects at select sites from blood samples processed for PBMC isolation. The plasma will be isolated, at select sites, and cryopreserved for later use for innate transcriptome gene expression and cytokine profile analysis. Samples are taken as indicated in the Schedule of Events (Table 3). These exploratory samples are being collected for research purposes only.

Further details regarding sample collection, processing and shipping can be found in the Laboratory Manual.

Serum, plasma, PBMC and nasal swab samples that remain after protocol-specific assessments have been performed may be used for further exploratory work on pharmacokinetics, metabolites, plasma protein binding, protein analysis, and biochemistry. No human deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) analysis will be performed, except cytokine expression as specified in the protocol or study manual.

7. STUDY TERMINATION/COMPLETION

7.1. Study Completion and End of Study Definition

A subject will be considered to have completed the study if he or she received the last study vaccination and attended the last protocol-defined follow-up visit.

End of study will be defined as the point when all patients have completed follow up. The Sponsor will notify all applicable regulatory agencies in accordance with local requirements when the study has ended.

7.2. Termination of the Study by the Sponsor

This study may be discontinued at any time due to safety concerns, failure to meet expected enrollment goals, administrative reasons, or at the discretion of the Sponsor. Should the study be terminated prematurely, the Sponsor will provide written notification to all Investigators and regulatory authorities and will specify the reason(s) for early termination. The Lead PI must inform the IRB promptly and provide the reason(s) for the termination.

7.3. Study Halting Rules

Vaccination of subjects will be suspended until after review of safety data by the SRC if any of the following halting rules are met:

1. One or more subjects experience a Grade 4 AE, vital sign or laboratory AE that cannot be clearly attributed to another cause.
2. Three or more subjects within a single sentinel group or ten or more subjects within the expansion group experience the same Grade 3 AE, vital sign or laboratory AE that cannot be clearly attributed to another cause.
3. One or more subjects experiences a SAE assessed as related to IP.
4. One or more subjects has laryngospasm, bronchospasm, or anaphylaxis associated with the study product within 72 hours of product administration.

Any AE or SAE that falls into the above criteria for suspending or terminating the study (including the occurrence of ***any*** Grade 3 AE, vital sign or laboratory AE that cannot be clearly attributed to another cause) must be reported by the investigator to the Sponsor ***immediately (within 24 hours).***

In the case of halting rules being met, the SRC will be convened as quickly as possible. After review of the safety data the SRC will make a recommendation to the Sponsor whether to resume, suspend or terminate the study. The Sponsor will communicate a decision to suspend or terminate the study to the Investigators.

Subsequent review of serious, unexpected, and related AEs by the Medical Monitor, SRC, IRB, the Sponsor(s), or the FDA or relevant local regulatory authorities may also result in suspension of further trial interventions/administration of study product at a site. The FDA and study Sponsor(s) retain the authority to suspend additional enrollment and study interventions/administration of study product for the entire study, as applicable.

7.4. Removal of Subjects from the Study

Subjects have the right to withdraw from the study at any time for any reason, including personal reasons. A subject can withdraw without giving a reason. The Investigator should however try to determine why a subject withdraws from the study and document the reason for withdrawal in the source documents and in the EDC system.

Subjects **may** be withdrawn from the study in the event of:

- Meeting any of the halting rules in Section 7.3
- A severe AE or serious AE (SAE);
- Difficulties in obtaining blood or other samples;
- Failure of the subject to comply with the protocol requirements or to cooperate with the Investigator.

Subjects **must** be withdrawn from the study in the event of:

- Withdrawal of consent
- Lost to follow-up
- Death
- Termination of the study by the Sponsor (described in Section 7.2)
- For safety reasons, it being in the best interest of the subject that he/she be withdrawn, in the Investigator's opinion;
- A positive pregnancy test (the subject or, if reported by a male subject, his female partner), or if the subject/partner is non-compliant with the contraception requirements (see Section 4.1);
- Development of a medical condition that requires concomitant treatment with a prohibited therapy (see Section 5.9.2);
- Breaking of the randomization code during administration of the study drugs. If the code is broken for safety reporting purposes, the subject may remain in the study; however, in such case subject and site staff will remain blinded to IP treatment.

The monitor and Sponsor will be informed in the event of a subject being withdrawn from the study. In case of withdrawal due to an SAE (for details on AE reporting see Section 9.7), the Sponsor should be notified within 24 hours; in case of withdrawal for other reasons; the Sponsor should be notified within 2 days from the event.

Subjects who are withdrawn from the study prior to completion of the scheduled study procedures for any reason (AE, withdrawal of consent, etc.) should be invited to complete the assessments as much as possible: as long as the subject consents, all relevant assessments of the day on which the subject withdrew from the study should be completed, at least those related to safety, and the subject should come for a safety follow-up visit 4 weeks after vaccination. In case of an AE, the appropriate follow-up will be done.

Subjects who are withdrawn from the study will not be replaced.

8. STATISTICAL METHODS AND CONSIDERATIONS

8.1. General Considerations

Prior to the analysis of the study data, statistical methods and table shells will be detailed in a Statistical Analysis Plan (SAP) and finalized before database lock.

The final analysis will be done after the last subject has had the day 57 visit and the data base has been locked. The day 209 data will be included as a supplemental analysis.

Statistical analysis will be the responsibility of Northrim Consulting, Inc, using SAS® (SAS Institute Inc., Cary, NC, USA; version 9.4 or higher).

There are primary, secondary and exploratory objectives, endpoints and analyses. Depending upon the result of the primary and secondary analyses, not all exploratory analyses may be done.

Safety and subject disposition analyses will be conducted on the safety analysis set.

Summarization of primary and secondary efficacy endpoints will be done using FAS. These summaries may be repeated using the PP analysis set.

There are no formal tests of hypotheses in this study. Efficacy outcomes are descriptive only.

The data will be summarized in tables listing the number, mean, standard deviation, median, minimum, maximum, standard error (SE) and a 95% CI of subjects for continuous data, or in tables listing count and percentage for categorical data where appropriate. Tables will be presented by IP treatment and overall. Data listing by subject will be provided.

8.2. Analysis Sets

The following populations are defined for this study:

- Safety Set (SS) – consists of any subject who receives at least one administration of IP;
- Full Analysis Set (FAS) – consists of all subjects randomized, received IP and had at least one post baseline assessment.
- (If necessary) Per-protocol Set (PP) - consists of all subjects in FAS with no major protocol violations or deviations.

Unless otherwise specified the FAS population will be used for analysis.

8.3. Subject Disposition and Baseline Comparability

Subject disposition will be tabulated; the number of enrolled, randomized, prematurely terminated and completed subjects will be summarized by IP treatment group and overall. A list of dropouts will be prepared including reason and (study) time of discontinuation.

Subject IP treatment groups will be characterized using tables, figures and descriptive statistics for demographic and baseline variables. Observed differences between the groups, should there be any, will be interpreted for clinical significance and their potential use as covariates in the analysis of efficacy endpoints

8.3.1. Sample Size

The sample size of 50 subjects per group was chosen based on reports of studies of other vaccines in early stage development. This study is not powered for any formal comparisons.

8.3.2. Subject Characteristics Data Set

Demographics will include by-treatment summaries of age, height, weight, BMI, race, and gender.

BMI will be calculated in metric units using the formula provided below:

$$\text{BMI} = \text{weight (kg)}/\text{height (m)}^2$$

Other baseline characteristics may be summarized.

8.3.3. Safety Analyses

Safety and tolerability of the Bris10 M2SR and Sing2016 M2SR influenza vaccines as assessed by subject diaries, solicited and unsolicited AEs, vaccine -associated AEs, SAEs, safety labs, vital signs, and physical examinations.

Exposure

Vaccine exposure will be summarized by actual dose, % of expected dose, and % of subjects receiving the expected dose.

Adverse Events

Treatment-emergent AEs (local and systemic) will be summarized as N (%) with AEs, with related-AEs, and by worst severity.

Incidence of TEAEs will be reported by MedDRA-coded SOC, PT and maximum severity.

Incidence of most frequent TEAEs and most frequent treatment-related TEAEs will be reported by SOC and PT

Listings of subjects who died, discontinued the study due to an AE, or experienced an SAE will be provided.

Dose-site reactions will be presented by reaction and severity.

Post-administration of symptoms (memory aid) will be summarized by time point, worst occurrence, and days with symptoms.

Clinical Laboratory Tests

Biochemistry and hematology laboratory results and change from baseline results will be summarized by timepoint using descriptive statistics.

Shift tables of maximum grade compared to baseline tabulated according to the FDA guidance: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, or in accordance with the normal ranges of the clinical laboratory (below, within, or above normal range) for parameters for which no toxicity grades are defined.

A listing of clinical laboratory test results outside the reference ranges will be provided.

Vital Signs

Vital sign results and change from baseline results will be summarized by timepoint using descriptive statistics.

Limited Physical Examination

Abnormal findings in physical examination will be listed.

Pregnancy

A listing of pregnant subjects will be displayed.

8.3.4. Additional Analyses

Additional analyses will be descriptive only; p-values are descriptive and not corrected for multiple testing.

Immunogenicity

Serum antibody, mucosal antibody and cellular immune response will be summarized using descriptive statistics by sampling timepoint for all subjects and by baseline values.

Seroconversion rates will be presented by timepoint and by baseline starting values.

Viral shedding will be summarized using descriptive statistics.

Additional (exploratory) endpoints may be analyzed.

8.4. Appropriateness of Measurements

The assessments which will be made in this study are standard, and are generally recognized as reliable, accurate, and relevant.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal result of diagnostic procedures, including clinical laboratory test abnormalities.

AEs will be monitored continuously from the first administration of IP treatment until Day 57. SAEs or medically attended events will be documented until Day 209. Events recorded at the follow-up phone call will be assessed and followed up as appropriate.

Serious Adverse Event

An SAE is any untoward medical occurrence that meets any of the following conditions:

- results in death;
- is life-threatening, i.e., the subject was at risk of death at the time of the event (e.g., ventricular fibrillation and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.
- requires inpatient hospitalization or prolongation of existing inpatient hospitalization:
    - Hospitalization refers to an overnight admission into hospital for the purpose of investigating and/or treating the AE. Hospitalization for an elective procedure, or routinely scheduled treatment for a pre-existing condition that has not worsened, is not an SAE.
- results in persistent or significant disability/incapacity, i.e., causing substantial disruption of the subject's ability to conduct normal life;
- is a congenital anomaly/birth defect;
- is medically significant, i.e., may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject's health or may require intervention to prevent one of the above outcomes. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

Unlisted (Unexpected) Adverse Event

An AE is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information (FluGen IB).

Suspected Unexpected Serious Adverse Reactions (SUSARs)

A SUSAR is an unexpected serious adverse reaction to the IP.

The Sponsor is to determine if the event is unexpected or not and if unexpected and to report the SUSAR to the Lead PI and FDA. The Lead PI will report any SUSAR(s) to the central IRB. For death and life-threatening cases, reporting should be done within 7 days and follow-up information with details provided within an additional 8 days. All other SUSARs have to be reported within 15 days.

9.2. Intensity of Adverse Events

All AEs will be assessed by the clinician using the grading system from FDA vaccine toxicity criteria (Appendix 1 for vital signs and systemic AE assessment; Appendix 2 for laboratory AE assessment, and as described in Section 6.2.2). For assessment of reactogenicity in this study, see Appendix 3. For events not included in the protocol-defined grading system, then the following guidelines will be used to quantify intensity.

Mild: events require minimal or no treatment and do not interfere with the patient's daily activities.

Moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

Severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Life threatening: any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

9.3. Causality Assessment

The clinician's assessment of an AE's relationship to test article (vaccine or placebo) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study product assessed using the terms related or not related. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

Related – There is a reasonable possibility that the study product caused the AE. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the AE.

Not Related – The AE is not related to the study product if there is evidence that clearly indicates an alternative explanation. If the subject has not received the study product, the timing of the exposure to the study product and the onset of the AE are not reasonably related in time, or other facts, evidence or arguments exist that strongly suggest an alternative explanation, then the AE is not related.

9.4. Reactogenicity

Reactogenicity events may be common and are known to occur for the vaccine being studied and will be collected as solicited AEs in a standard, systematic format using a grading scale based on functional assessment or magnitude of reaction. In this study, the following reactogenicity events will be collected for the first 7 days after each dose of IP:

- Feverish
- Nasal irritation
- Nasal bleeding
- Runny nose
- Stuffy nose/Congestion
- Sore/scratchy/itchy or painful throat
- Body/muscle aches
- Joint pain
- Headache
- Cough
- Body rash
- Tiredness
- Nausea
- Vomiting
- Other symptoms

These will be evaluated and graded daily based on the functional scale specified within the Symptom Memory Aid (Appendix 5).

Should a subject experience a severe reaction (graded as a 3) and/or measure a body temperature equal to or greater than 39°C, he/she should immediately contact the site.

9.5. Outcome

The outcome of each AE must be rated as follows:

- Recovered/resolved;
- Recovering/resolving;
- Not recovered/not resolved;
- Recovered with sequelae/resolved with sequelae;
- Fatal;
- Unknown.

9.6. Recording of Adverse Events

All (S)AEs occurring during the clinical investigation must be documented in the source documents and eCRF.

Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record their opinion concerning the relationship of the (S)AE to the study drugs in the EDC System. All measures required for (S)AE management must be recorded in the source documents and reported according to Sponsor's instructions.

All AEs occurring at any time during the study (including the in-person follow-up period) will be followed by the Investigator until satisfactory resolution (e.g., value back to baseline value) or stabilization or until final database lock. If necessary, in order to obtain additional information to ensure safety of the subject, additional blood and urine samples may be taken at the discretion of the Investigator. Certain long-term AEs related to therapy cannot be followed until resolution within the setting of this study. In these cases, follow-up will be the responsibility of the treating physician.

9.7. Reporting of Serious Adverse Events to the Sponsor for Pharmacovigilance

All SAEs, independent of the circumstances or suspected cause, must be recorded on a Serious Adverse Event Form by the Investigator and reported to the Sponsor within 24 hours of knowledge of the event. The SAE may be initially reported by phone (Dr Ruth Ellis; 703-401-8189), with the completed SAE Form sent to FluGen by email (Safety@flugen.com) or fax (608-260-7704) within 24 hours of knowledge of the event.

The Sponsor will immediately notify the Medical Monitor, who will evaluate the SAE report(s) within 1 working day of receipt to determine the regulatory reporting priority or, if necessary, request additional information from the site to make an evaluation.

The SAE form should include a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae, in order to allow a complete medical assessment of the case and independent determination of the possible causality.

Follow-up and outcomes should be reported for all subjects who experience an SAE.

It is critical that the information provided on the Serious Adverse Event Form matches the information recorded in the source documents and in the EDC system for the same event.

Copies of additional laboratory tests, consultation reports, postmortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. Follow-up reports relative to the subject's subsequent course must be submitted to FluGen and IRB (as applicable) until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

9.8. Pregnancy

All initial reports of pregnancy in subjects or in partners of male subjects must be reported to the Sponsor by the Investigator within 24 hours of his/her knowledge of the event. This is done by contacting FluGen via email (Safety@flugen.com) or fax (608-260-7704). Any subject who becomes pregnant during the study must be promptly withdrawn from the study (Code of Federal Regulations [CFR] Section 8).

The Investigator will contact the subject at the expected time of delivery for follow-up and will provide the pregnancy outcome to the Sponsor. Abnormal pregnancy outcomes (e.g., spontaneous or induced abortion, stillbirth, neonatal death, congenital abnormality, birth defect) are considered SAEs and must be reported using the Serious Adverse Event Form.

9.9. Reporting of Serious Adverse Events to Competent Authorities/Ethics Committees

Adverse events reporting, including suspected unexpected serious adverse reactions (SUSARs), will be carried out in accordance with applicable local regulations.

All SUSARs will be the subject of expedited reporting. The Sponsor and Investigator shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IEC/IRB within 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information is communicated within an additional 8 days, or according to the IEC/IRB's required time frame. All other SUSARs will be reported to the relevant competent authorities and IEC/IRB within 15 days after knowledge by the Sponsor of such a case. FluGen will provide investigators with all details of all SAEs reported to regulatory authorities.

9.10. Medical Monitor

The Medical Monitor is an independent clinician (i.e. not directly employed by the Sponsor or the site) responsible for safety oversight of the study. He/she should have no apparent conflict of interest and cannot be under the supervision of the PI or other investigators or research staff. The Medical Monitor will oversee interventions, interactions, data matching, data collection and data analysis, review the clinical monitoring plan, review SAE and SUSAR reports (Section 9.7), review AEs which may prompt a study halt (Section 7.3), participate in the Safety Review Committee (Section 9.11), participate in decisions regarding emergency unblinding (Section 5.6), participate in review of Grade 3 laboratory abnormalities, and review summary AE data prior to final database lock. The Medical Monitor is responsible to promptly report his/her observations to the IRB or other designated official and to the HRPO. The Medical Monitor has the authority to stop the study, remove individual human subjects from a research protocol if needed and take any steps necessary to protect the safety and well-being of the subjects until the IRB can assess the monitor's report. The Medical Monitor will also participate via phone in site training and will be available to answer questions related to study eligibility and safety for the duration of the study and may discuss the research protocol with investigators.

9.11. Safety Review Committee

Safety oversight will be under the direction of an SRC which is composed of an independent group of experts including two clinicians and a statistician who will be available to review blinded safety data, as needed. The SRC will monitor subject safety and advise the Sponsor. SRC members will be separate and independent of study personnel participating in this study and should not have scientific, financial or other conflict of interest related to the study.

The SRC will operate under the rules and procedures of a Sponsor-approved charter. The SRC will review applicable data including, but not limited to, enrollment, demographic, dosing, laboratory and safety data if study halting rules are met, as defined in the protocol and the SRC charter. The SRC may receive data in aggregate and presented by treatment group, but without the treatment group identified. The SRC may review aggregate safety data for increased rate of occurrence of serious suspected adverse reactions. The SRC may be unblinded to study treatment, as needed, to assess safety issues. As an outcome of each review/meeting, the SRC will advise the Sponsor of its findings and make recommendations with respect to continuation of the study.

Throughout the study, the SRC will be convened if halting rules are met. The SRC also may be convened at the request of the Investigator, Medical Monitor, Sponsor or any SRC member, if they have cause for concern regarding subject safety. The SRC can recommend study enrollment and vaccinations be stopped if AEs that meet the halting criteria are reported or for any overriding safety concern. Further details regarding composition and operation of the SRC are provided in the SRC Charter.

10. ETHICAL ASPECTS

10.1. Study-Specific Design Considerations

Potential subjects will be fully informed of the nature of the study and of the risks and requirements of the study before any study-related assessment will be carried out. During the study, subjects will be given any new information that may affect their decision to continue participation. They will be informed that their participation in the study is voluntary and that they may withdraw from the study at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential AEs of the study, and who provide their consent voluntarily will be enrolled in the study.

10.2. Regulatory Ethics Compliance

10.2.1. Investigator Responsibilities

The Investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirements, and should provide evidence of such qualifications through up-to-date curriculum vitae or other relevant documentation requested by the Sponsor, the IRB/IEC, or the regulatory authorities.

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current International Council for Harmonisation (ICH) guidelines on GCP, and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles originating from the Declaration of Helsinki (1964 and revisions), and that the clinical study data are credible.

10.2.2. Independent Ethics Committee or Institutional Review Board (IEC/IRB)

An IRB/IEC should safeguard the rights, safety, and well-being of all study subjects. Special attention should be paid to studies that may include vulnerable subjects.

Before the start of the study, the Sponsor (or Investigator where required) will provide the IEC/IRB with current and complete copies of the following documents:

- final protocol and, if applicable, amendments;
- Sponsor-approved ICF (and any updates or any other written materials to be provided to the subjects);
- Subject recruiting materials;
- IB (or equivalent information) and addenda;
- available safety information;
- information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable;

- Investigator's current curriculum vitae or other documentation evidencing qualifications (unless not required, as documented by the IEC/IRB);
- Clinical trial agreement;
- any other documents that the IEC/IRB may require to fulfill its obligation.

This study will be undertaken only after the IEC/IRB has given full written approval of the final protocol and amendments (if any), the ICF(s) and updates (if any), applicable recruiting materials, and any other written information to be provided to the subjects, and the Sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study, the Sponsor (or Investigator where required) will send the following documents and updates to the IEC/IRB for its review and approval, where appropriate:

- protocol amendments;
- revision(s) to the ICF and any other written materials to be provided to the subjects;
- new or revised subject recruiting materials approved by the Sponsor;
- revisions to compensation for study-related injuries or payment to subjects for participation in the study;
- IB addenda or new edition(s);
- summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually);
- reports of AEs that are serious, unlisted, and associated with the IMP;
- new information that may adversely affect the safety of the subjects or the conduct of the study;
- deviations from or changes to the protocol to eliminate immediate hazards to the subjects;
- report of death of any subjects under the Investigator's care;
- notification if a new Investigator is responsible for the study at the clinical site;
- any other requirements of the IEC/IRB.

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s), except when necessary to eliminate immediate hazard to the study subjects. If a deviation from or a change to the protocol was implemented to eliminate an immediate hazard to study subjects, then the implemented deviation or change, the reasons for it, and, if appropriate, the protocol amendment should be submitted to the IEC/IRB as soon as possible.

The Sponsor (or Investigator will notify the IEC/IRB about the study completion within 90 days after the end of the study (defined as LPLV).

10.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor and the reviewing IEC/IRB. The informed consent should be in accordance with the principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before enrollment in the study, the Investigator or an authorized member of the clinical staff must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may refuse to participate or withdraw consent to participate at any time, without penalty or loss of benefits to which the subject was entitled. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities, US DoD representative as part of its human subject protection oversight activities and authorized Sponsor staff without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject is authorizing such access and agrees to allow his or her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

The language about the study used in the oral and written information, including the ICF, should be non-technical and practical and should be understandable to the subject. The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained consent, a copy of the ICF must be given to the subject.

The collection and processing of personal data from subjects enrolled in the study will be limited to those data that are necessary to investigate the safety, quality, and utility of the IMP used in the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data need to agree to keep the identity of the study subjects confidential.

The informed consent obtained from the subjects includes explicit consent for the processing of personal data and for the Investigator to allow direct access to subjects' original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

11. ADMINISTRATIVE REQUIREMENTS

11.1. Protocol Amendments

Neither the Investigator nor the Sponsor will modify this protocol without a formal amendment. All protocol amendments must be issued by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IEC/IRB approval nor when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazard to the subjects, in which case an amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the Investigator and IEC/IRB must be provided to the Sponsor or his designee. When the change(s) involves only logistic or administrative aspects of the study, the IRB (and IEC where required) only needs to be notified.

11.2. Subject Identification, Enrollment, and Screening Logs

The Investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the Sponsor site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the Investigator in the study file. To ensure subject confidentiality, no copies will be made. All reports and communications related to the study will identify subjects by initials and/or assigned number only.

The Investigator must also complete a subject screening log which reports on all subjects who were seen to determine eligibility for inclusion in the study.

11.3. Source Documentation

The investigator will maintain a list of qualified staff to whom study responsibilities have been delegated. These individuals authorized to fulfill these responsibilities should be outlined and included in the Delegation of Authority Form.

Source documents are original documents, data, and records for which the study data are collected and verified. Example of such source documents may include, but are not limited to, subject hospital/medical records, laboratory reports, physicians' and nurses' notes, subject diaries and correspondence. At a minimum, source documentation must be available for the following: subject identification, eligibility, and study identification; date of subject consent, dates of visits, results of safety and efficacy parameters as required by the protocol, record of all AEs, follow-up of AEs, concomitant medication, drug receipt/dispensing/return records, study drug administration information, laboratory printouts (if not available digitally), date of study completion, and reason for early discontinuation of study drugs or withdrawal from the study, if applicable.

The Investigator and study staff are responsible for maintaining a comprehensive filing system of all subject records that are readily available to support monitoring activities in compliance with ICH-GCP guidelines and regulatory and institutional requirements for the protection of confidentiality of subjects. The Investigator shall supply the Sponsor or designee, on request, with any required background data from the study documentation or clinic records. Such requests may occur, for example, when documents are illegible or when errors in data transcription are

suspected. In case of requests for audit inspections and/or queries from National Authorities/Regulatory Agency, it will be necessary to have access to the complete study records, provided that subject confidentiality is maintained.

No study documents should be discarded without prior written agreement between the Sponsor and the Investigator. Should storage no longer be available to archive source documents or must be moved to an alternative location, the site should notify the key sponsor contact prior to the shipping of documents.

11.4. Case Report Form Completion

Authorized study site personnel will complete eCRFs designed specifically for this study and completion guidelines will be provided. An eCRF is required and must be completed for each subject enrolled into the study and will be available for all data required to be entered into the clinical database and must match the data contained in the study specific source documentation. The Investigator will ensure that the eCRFs are accurate, complete and legible. The Investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed. As required by the protocol, eCRFs should also be completed for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF and thorough efforts should be made to clearly document outcome.

The eCRFs will be maintained in an electronic data collection system for this study. After the Investigator or designees have been appropriately trained, they will be given access to the EDC system and will be able to enter the data required by the protocol. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

11.5. Study Monitoring

The Sponsor is responsible for assuring the proper conduct of the study with regard to protocol adherence and validity of the data recorded on the eCRFs. Subject confidentiality will be maintained.

In addition, monitors designated by the Sponsor will periodically contact the site, including conducting on-site and remote monitoring visits. The on-site and remote monitoring visits will be conducted as frequently as necessary to ensure that all aspects of the study are carefully monitored for compliance with applicable government regulations with respect to current GCP practice and the current SOPs. The visits will be conducted in accordance with the Sponsor's SOP and Clinical Monitoring Plan.

The unblinded study monitor will be limited to observation (in real-time or via review of documentation) of IP preparation and delivery device filling and weighing, adherence to randomization to treatment group, storage of IP and IP accountability and to review of consent and eligibility documents. They will not participate in activities related to subject assessments.

In general, the Investigator agrees to fully cooperate with the monitor, allow the monitor direct access to all relevant documents, to allocate his time and the time of his staff to the monitors to discuss any findings and any relevant issues as needed.

11.6. Data Management

Electronic data collection will be used to enter study data. During the data collection process, automated quality assurance programs will be used to identify missing data, incorrect data and other data discrepancies. Requests for data clarification or correction will be queried to the investigative study site for resolution via the EDC system.

Quality assurance and quality control systems will be implemented and maintained to ensure that the data are generated, recorded and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Data collection and storage will provide an audit trail, security mechanisms and electronic signature capabilities that meet the requirements of FDA Title 21 of CFR Part 11 regarding electronic records and electronic signatures.

Data security will be controlled through appropriate and specific restriction of access to only data and systems required by individual users to accomplish their roles in the data management process. Individual login and password protections will be employed. The database will exist on physically secured servers. Data backups will be done regularly and will be stored in a separate facility.

11.7. Data Quality Assurance

The accuracy and reliability of the study data will be assured by the selection of qualified Investigators and appropriate study sites, review of protocol procedures with the Investigator and associated personnel prior to the study, and by periodic monitoring visits by the Sponsor or designee.

Written instructions will be provided for the collection, preparation, and shipment of biological test samples.

The Sponsor or designee will review the paper source and eCRF entries for accuracy and completeness during (on-site) monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. After upload of the data into the clinical study database, their accuracy will be verified using appropriate validation programs.

In accordance with Good Clinical Research Practice Guidelines and Recommendations, the Sponsor will be entitled to audit the facilities used in the clinical and laboratory parts of the study, as well as to access all the data files pertaining to the study. Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

11.8. On-Site Audits

Representatives of the Sponsor’s clinical quality assurance department may visit the clinical site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRF system. Subject privacy must, however, be respected. The Investigator and clinical staff are to be present

and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or his designee.

Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

11.9. Study Termination

The Sponsor has the right to terminate the study at any time. In case of an early termination of the study for safety reasons, or temporary halt by the Sponsor, the IEC/IRB should be notified within 15 calendar days and should be provided with a detailed written explanation for the termination/halt.

An end-of-study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete study has ended. This notification will be submitted within 90 days after the end of the study.

11.10. Record Retention

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all paper source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents will be retained for a longer period if required according to the applicable regulatory requirements or per agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

If the responsible Investigator retires, relocates, or for any other reasons withdraws from his responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents without having obtained written approval from the Sponsor.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation related to the study, the Investigator must permit access to such reports.

11.11. Use of Information and Publication

All information, including but not limited to, information regarding the Bris10 or Sing2016 M2SR vaccines or the Sponsor’s operations (e.g., patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the Sponsor to the

Investigator and not previously published, and any data generated as a result of this study are considered confidential and remain the sole property of the Sponsor. The Investigator agrees to maintain this information in confidence, to use this information only to accomplish this study, and not to use it for other purposes without the Sponsor's prior written consent.

The Investigator understands that the information generated in this clinical study will be used by the Sponsor in connection with the continued development of the study drug, and thus may be disclosed as required to other clinical Investigators or regulatory agencies. To permit information derived from the clinical studies to be used, the Investigator is obliged to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated under the responsibility of the Sponsor and will contain EDC system data from all clinical sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating Investigator.

Clinical narratives may be written for the following events (for example):

- All deaths (irrespective of drug relationship)
- All other SAEs during treatment with the study drugs
- All discontinuations of the study drugs due to AEs (irrespective of drug relationship)
- Any events of special interest explicitly requested by the regulatory agencies
- At the discretion of the team and after statistical analysis of the data, certain discontinuations not related to AEs or treatment failure, i.e., related to lost to follow-up or withdrawal of consent (irrespective of treatment group).

The Sponsor and Medical Monitor will sign off the final version of the Clinical Study Report. A summary of this final version will be provided to the Investigators, the applicable regulatory authorities, and the IECs/IRBs, if required by the applicable regulatory requirements, within 1 year after the end of the study (LPLV).

The Sponsor shall have the right to publish study data and information without approval from the Investigator. If an Investigator wishes to publish information from the study, the Investigator must first request to do so in writing to the Sponsor at least 60 days before submission or presentation of the study data. A copy of the manuscript or presentation must also be provided to the Sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials to the best of the Sponsor's ability and only if Sponsor agrees to allow Investigator to submit such materials to an outside party. The Investigator will withhold such publication for up to an additional 60 days or until the Sponsor provides its express written consent for Investigator to move forward with publication or presentation of any study data. In the event that issues arise regarding scientific integrity or regulatory compliance, the Sponsor will review these issues with the Investigator. The Sponsor will not mandate modifications to scientific content but in no case, will Investigator have the right to publish, present or share with any outside party study data and/or information without the express written consent of the Sponsor. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have

made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

11.12. Results

The Sponsor will register the existence of a clinical study and disclose its results as required by law.

11.13. Investigator Indemnity

The Sponsor holds and will maintain an adequate insurance policy covering damages arising out of Sponsor-sponsored clinical research studies.

The Sponsor will indemnify the Investigator and hold him/her harmless for claims related to damages arising from the investigation, provided that the study drugs were administered under the Sponsor's or deputy's supervision and in strict accordance with accepted medical practice and the study protocol.

The Investigator must notify the Sponsor immediately upon notice of any claims or lawsuits.

11.14. Confidentiality

Subject confidentiality is strictly held by the participating Investigators, their staff, and the Sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study monitor or other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. Throughout this study, all data will be linked to the eCRF via a unique identification number. The data will be blinded correspondingly in all data analyses. The Investigator should keep a subject enrollment log showing codes, names and addresses. The Investigator should maintain documents that are not for submission to the Sponsor (such as written consent forms) in strict confidence.

However, in compliance with the ICH Guidelines and in fulfillment of its obligations to FluGen to verify compliance with this protocol, FluGen Inc. or its designee requires that the Investigator permit FluGen designated monitors, representatives from any Regulatory Authority, FluGen designated auditors, or the appropriate Independent Ethics Committee, to review the subject's primary medical records (source data or documents) including, but not limited to, laboratory test result reports, admission and discharge summaries, and SAEs occurring during the study. Should access to such medical records require a waiver or authorization separate from the statement of informed consent, the Investigator will obtain such permission in writing from the subject before the subject is entered into the study.

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APPENDICES

APPENDIX 1: VITAL SIGN AND SYSTEMIC TOXICITY ASSESSMENTS

Please see next page.

Vital signs

Please score items based on the following guidance (from FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials):

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic Symptoms
Please score items based on the following guidance (from FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials):

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2–3 loose stools or < 400 g/24 hours	4–5 stools or 400-800 g/24 hours	6 or more watery stools or > 800g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

APPENDIX 2: LABORATORY ASSESSMENTS

- Urine drug screen[a]
- Serology[a]: HIV, HCV, HbsAg
- Urinalysis: Dipstick: specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase

  In case of positive dipstick results, the sediment will be examined microscopically for red blood cells, white blood cells, and epithelial cells. Crystals, casts, and bacteria will only be reported if they are present.
- Hematology: Hemoglobin, white blood cells with differential (including neutrophils, lymphocytes, and eosinophils), platelets
- Biochemistry: Albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate (or carbon dioxide), calcium, chloride, potassium, sodium, lipid panel[a] (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides), total bilirubin, direct bilirubin[b], total protein, creatinine, C-reactive protein, creatine kinase, blood urea nitrogen (or urea)
- At screening, a urine pregnancy test will be performed for women of childbearing potential
- At the indicated time points, a urine pregnancy test will be performed for women of childbearing potential

a. At screening only.
b. To be assessed if total bilirubin is elevated above normal range.

Grading Scale for Laboratory AEs

Please score items based on the following guidance (from FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials):

Serum*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)****
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.4	2.5 – 2.7	< 2.5	--

Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in liver function test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when liver function test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example. a low sodium value that falls within a Grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***"ULN" is the upper limit of the normal range.

Hematology*	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Grading Scale for Urinalysis AEs

Please score items based on the following guidance (from FDA Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials):

Urine *	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

APPENDIX 3: REACTOGENICITY ASSESSMENTS

Please see next page.

Local Reactions (intranasal administration)

Please score reactions as follows:

Local reaction	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Nasal pain / irritation	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Nasal congestion/ rhinorrhea	Does not interfere with activity	Use of saline or other decongestant > 24 hours or interferes with activity	Repeated use of decongestants or significantly interferes with daily activity	Emergency room (ER) visit or hospitalization
Bleeding/ Epistaxis	Does not interfere with activity	Requires intervention (e.g., squeezing of nose to reduce bleeding) > 24 hours or interferes with activity	Required repeated or near continuous intervention or significantly interferes with daily activity	Emergency room (ER) visit or hospitalization

APPENDIX 4: INVESTIGATOR SIGNATURE PAGE

Signature of Investigator **Site Number:**

Study Title: Phase 1b clinical study to investigate the safety and immunogenicity of the Bris10 (A/Brisbane/10/2007) M2SR and Sing2016 (A/Singapore/INFIMH-16-0019/2016) M2SR H3N2 monovalent influenza vaccines

Name:

Affiliation:

Address:

I have read this Clinical Study Protocol and agree that it contains all information necessary for proper conduct of the study. I will carry out the study as outlined herein and will complete the study within the designated time and in accordance with the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) after approval by an Institutional Review Board.

Signature:

Date:

APPENDIX 5: SYMPTOM MEMORY AID FOR VACCINATION PERIOD

Please see next page for sample document showing Day 1 – Day 7. A similar document will be provided for Day 29 – Day 35.

Symptom Memory Aid

Day 1 – Day 7

FIRST DOSE

Phase 1b clinical study to investigate the safety and immunogenicity of the Bris10 (A/Brisbane/10/2007) M2SR and Sing2016 (A/Singapore/INFIMH-16-0019/2016) M2SR H3N2 monovalent influenza vaccines

Protocol Number:
FLUGEN-H3N2-V003

Subject Number:				-			

In the event of a medical emergency, call 911 then call the Study Doctor as soon as possible at the following telephone number [Site Emergency Number].

For medical problems which are not emergencies, call the Study Doctor at the following telephone number [Site Emergency Number].

SYMPTOM MEMORY AID INSTRUCTIONS

1. **PLEASE BRING THIS MEMORY AID WITH YOU TO EVERY VISIT.**
2. This Memory Aid is used to help you remember any symptoms you might have after each of your vaccinations. The first entry to the memory aid will be done before your vaccine dose. The clinic staff will train you on how to use this document by having you complete the "Training Entry" column. The second entry will be on the evening of the vaccination and the remaining 6 entries will be made each evening in the week following vaccination.
3. Starting on the day of your vaccine dose, complete the Memory Aid at about the same time each day.
4. You have been given a thermometer to measure your oral temperature and the site staff will teach you how to use this thermometer. Take your temperature at about the same time each day with the provided thermometer. Record your temperature daily, in degrees Celsius (°C) (Example: 38.2° C), as shown on the thermometer.
5. If you think you may have a fever at any time, take your temperature and record it as shown on the thermometer.
6. Refer to the intensity levels from the guidelines on page 3 if you experience any symptoms.
7. Enter a 0, 1, 2 or 3 intensity level for each symptom listed on each day of your Symptom Memory Aid.
8. Record any other symptoms that you may have experienced under each day that you experienced the symptom on page 5. Then record the intensity level according to the table on page 5.
9. The completed Memory Aid will be collected by the study staff during your Day 8 visit, however if you have any visits prior to Day 8, please bring this with you to the site.

PLEASE REMEMBER TO BRING THIS MEMORY AID WITH YOU TO YOUR NEXT VISIT.

HOW TO TAKE YOUR TEMPERATURE

- Measure your temperature at approximately the same time each day. If multiple temperatures are measured in one day, record the highest temperature. Do not eat, drink, or smoke for 10 minutes prior to taking your temperature.
- Push the power button on the thermometer and place it under your tongue toward the back of your mouth. The tip of the thermometer should rest in the "correct area" as shown in the diagram to the right.
- Keep your mouth closed and the thermometer still until the thermometer beeps rapidly, indicating completion. If you do not hear the beep, leave the thermometer in your mouth for 2 minutes.
- Record the temperature displayed on the screen. Press the button to turn the thermometer off.

√= Correct Area
X=Incorrect areas

For all symptoms, record the intensity level (0, 1, 2, or 3) using the guidelines below.

SYMPTOM	INTENSITY LEVEL	DESCRIPTION
Feverish Tiredness Body/Muscle aches Joint Pain Body Rash	0	No symptoms
	1	Mild - No interference with activity
	2	Moderate - Some interference with activity
	3	Severe - Significant interference, prevents daily activity
Stuffy Nose/Nasal Congestion	0	No symptoms
	1	Mild - Noticeable but does not interfere with daily activity
	2	Moderate - Moderate discomfort/interferes with breathing from nose
	3	Severe - Not being able to breath from nose, or prevents daily activity or seeks medical encounter
Runny Nose	0	No symptoms
	1	Mild - Noticeable but does not interfere with daily activity
	2	Moderate - Moderate discomfort/interferes with daily activity
	3	Severe - Significant discomfort/prevents daily activity or seeks medical encounter
Nasal Pain/Irritation/Dryness	0	No symptoms
	1	Mild - Noticeable but does not interfere with daily activity
	2	Moderate - Moderate discomfort/interferes with daily activity
	3	Severe - Significant discomfort/prevents daily activity or seeks medical encounter
Nasal Bleeding	0	No symptoms
	1	Mild - Total duration of all episodes in a 24-hour period <30 minutes
	2	Moderate - Total duration of all episodes in a 24-hour period ≥ 30 minutes
	3	Severe - Any bleeding that required visit for medical encounter
Sore/Scratchy/Itchy or Painful Throat	0	No symptoms
	1	Mild - Noticeable but does not interfere with eating and/or drinking
	2	Moderate - Moderate discomfort. Interferes with eating and/or drinking
	3	Severe - Significant discomfort/prevents eating and/or drinking or seeks medical encounter
Headache	0	No symptoms
	1	Mild - No interference with daily activity
	2	Moderate - Some interference with daily activity
	3	Severe - Significant interference, prevents daily activity and/or seeks medical encounter
Cough	0	No symptoms
	1	Mild - Noticeable but does not interfere with daily activity or sleeping
	2	Moderate - Moderate discomfort/interferes with daily activity or sleeping
	3	Severe - Significant discomfort/prevents daily activity or seeks medical encounter
Nausea	0	No symptoms
	1	Mild - Transient (<24 hours) or intermittent AND No or minimal interference with oral intake
	2	Moderate - Persistent nausea resulting in decreased oral intake for 24 to 48 hours
	3	Severe - Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)
Vomiting	0	No symptoms
	1	Mild - Transient or intermittent AND no interference with daily activity; minimal interference with oral intake
	2	Moderate - Frequent episodes with no dehydration and interferes with some daily activity

	3	**Severe - Persistent vomiting, resulting in orthostatic hypotension (low blood pressure that happens when you stand up from sitting or lying down) or requiring rapid rehydration (e.g., IV fluids) or prevents normal daily activity**

Symptom Memory Aid **Protocol: FluGen-H3N2-V003** **Subject #: __ __ __ - __ __ __**

Date (dd/mmm/2019)	Training Entry (Pre-Dose) ___/_____/2019	Day 1 (Dosing Day) ___/_____/2019	Day 2 ___/_____/2019	Day 3 ___/_____/2019	Day 4 ___/_____/2019	Day 5 ___/_____/2019	Day 6 ___/_____/2019	Day 7 ___/_____/2019
Record Oral Temperature (°C)	___ ___.___°C	___ ___.___°C	___ ___.___°C	___ ___.___°C	___ ___.___°C	___ ___.___°C	___ ___.___°C	___ ___.___°C
Feverish	☐	☐	☐	☐	☐	☐	☐	☐
Tiredness	☐	☐	☐	☐	☐	☐	☐	☐
Body/Muscle Aches	☐	☐	☐	☐	☐	☐	☐	☐
Joint Pain	☐	☐	☐	☐	☐	☐	☐	☐
Body Rash	☐	☐	☐	☐	☐	☐	☐	☐
Stuffy Nose/Nasal Congestion	☐	☐	☐	☐	☐	☐	☐	☐
Runny Nose	☐	☐	☐	☐	☐	☐	☐	☐
Nasal Irritation (Pain or Dryness)	☐	☐	☐	☐	☐	☐	☐	☐
Nasal Bleeding	☐	☐	☐	☐	☐	☐	☐	☐
Sore/Scratchy/Itchy Painful Throat	☐	☐	☐	☐	☐	☐	☐	☐
Headache	☐	☐	☐	☐	☐	☐	☐	☐
Cough	☐	☐	☐	☐	☐	☐	☐	☐

Nausea	☐	☐	☐	☐	☐	☐	☐	☐
Vomiting	☐	☐	☐	☐	☐	☐	☐	☐

Important: If you experience **any events of concern**, contact the study staff immediately.

Other Symptoms

Other symptoms to report following vaccination: ☐ No ☐ Yes (Complete chart below)

INTENSITY LEVEL	DESCRIPTION
0	No symptoms
1	Mild - events require minimal or no treatment and do not interfere with daily activities
2	Moderate - events may cause some interference with daily activities
3	Severe - events may require medication or other treatment. Severe events usually prevent daily activities.

	Study Day Date (dd/mmm/2019)	Day 1 (Dosing Day) ___/_____/2019	Day 2 ___/_____/2019	Day 3 ___/_____/2019	Day 4 ___/_____/2019	Day 5 ___/_____/2019	Day 6 ___/_____/2019	Day 7 ___/_____/2019
Other Symptoms (Describe)								
Include Intensity Level (0-3)	☐	☐	☐	☐	☐	☐	☐	☐