STUDY PROTOCOL

A pivotal, multicentre, randomized, modified double-blind, placebo-controlled phase 3 trial to assess the safety and clinical efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (≥50 years of age).

Sponsor: BiondVax Pharmaceuticals Ltd.
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EudraCT number: 2018-000468-27

ClinicalTrials.gov identifier: NCT03450915

Version and date of the Protocol: Version 5.0 final dated 08th May2019

STATEMENT OF COMPLIANCE

This study will be performed in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and local legal and regulatory requirements

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to Good Clinical Practice (GCP), the Declaration of Helsinki (with amendments) and the laws and regulations of the countries in which the study takes place

Sponsor	Tamar Ben-Yedidia, PhD
Representative	Chief Scientific officer
	BiondVax Pharmaceuticals ltd
	Jerusalem Biopark, Hadassah Ein Kerem, Jerusalem, Israel.

Date May 9th, 2019 Signature 

INVESTIGATOR'S COMPLIANCE DECLARATION

I have read this protocol and agree to conduct the study as outlined herein, and as implemented by any future protocol amendment/update, according to the terms of the clinical trial contract, and in accordance with supplementary study: conduct procedures and/or guidance or documents provided by the study sponsor, complying with the obligations and requirements of clinical investigators and all other requirements listed in relevant national and international regulations including 21 CFR part 312 and ICH GCP guidelines.
I assume responsibility for the compliance of the site personnel reporting to me or assisting me with the study.
I confirm that I am aware of my obligations towards relevant regulatory authorities as it concerns my participation in this trial as investigator.
I agree to disclose and provide information to the Sponsor on any potential conflict of interest I may have participating in this study as investigator.
I declare that I will co-operate with the Sponsor personnel and/or representatives, and vendors managing or supporting the study, including CRO, timely and adequately to ensure timely study conduct and compliance with study documents and relevant regulations.

Protocol: BVX-010, version 5.0 dated May 08th 2019 EudraCT number: 2018-000468-27

_____
Investigator's signature

_____
Date

_____
Investigator's Name (Please print)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
AESIs	Adverse Events of Special Interest
CFR	Code of Federal Regulations
CMI	Cell-mediated immunity
CRF	Case Report Form
CRO	Contract Research Organization
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EMA	European Medicinal Authority
EU	European Union
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAI/HI	Hemagglutinin Inhibition
ICS	Intra Cellular Staining
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFN-g	Interferon gamma
IIV	Inactivated influenza vaccine
IIV3	Trivalent inactivated influenza vaccine
ILI	Influenza-like illness
ITT	Intent-to-treat
M-001	Multimeric-001
MedDRA ®	Medical Dictionary for Regulatory Activities
N	Number (typically refers to subjects)
NOCI	New Onset of Chronic Illness
NP	Nasopharyngeal
PBMC	Peripheral Blood Mononuclear Cell(s)
PBS	Phosphate Buffered Saline
PCR	Polymerase Chain Reaction
Ph.Eur.	European Pharmacopoeia (Pharmacopoeia Europaea)
PHI	Personal Health Information
PI	Principal Investigator
PK	Pharmacokinetics
p.r.n.	*Pro re nata* (dosing as needed)
QA	Quality Assurance
QC	Quality Control
qRT-PCR	Quantitative Reverse Transcriptase Real Time PCR
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SI	Sub-Investigator
TBD	To be determined later
US	United States
WHO	World Health Organization

PROTOCOL SYNOPSIS

<table>
<tr><td colspan="2">Title of the study: A pivotal, multicentre, randomized, modified double-blind, placebo-controlled phase 3 trial to assess the safety and clinical efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (≥50 years of age).</td></tr>
<tr><td>EudraCT number: 2018-000468-27
ClinicalTrial.gov identifier: NCT03450915</td><td>Protocol code: BVX-010</td></tr>
<tr><td colspan="2">Sponsor:
BiondVax Pharmaceuticals LTD, Jerusalem Biopark, Hadassah Ein Kerem, Jerusalem, ISRAEL.</td></tr>
<tr><td colspan="2">Central Study Site:
The trial will be conducted at approximately 85 institutions in Europe (including, but not limited to Bulgaria, Hungary, Poland, Ukraine, Latvia, Georgia and Croatia)</td></tr>
<tr><td>Planned study duration: up to 2 years (2 consecutive flu seasons). It is designed to be completed after 2 influenza seasons unless stopped earlier or extended following recommendation of the DSMB.
Subject participation duration: planned - up to 2 years.</td><td>Phase of Development: Phase III</td></tr>
<tr><td colspan="2">Study population: Older adults and elderly (≥50 years of age). Randomization will be stratified by cohort and age of <65>. For season 2, randomization will also be stratified by participation (or not) to the sub-study. At least half of the participants will be ≥65 years old.</td></tr>
<tr><td colspan="2">Study design: A pivotal multicentre, randomized, modified double-blind, placebo-controlled study.</td></tr>
</table>

Planned number of subjects:
Adaptive design (flexible enrolment); initially assumed to be 9,630 with an increase to 12,000 if the influenza attack rate in Season 1 is lower than expected. At least half of the participants will be ≥65 years of age at the time of the randomization.

Year 1 - cohort 1 (flu season 2018-2019): 4,055 subjects enrolled, as follows:
M-001: n = 2,027 (Lot #1, vials); Placebo: n = 2,028
Year 2 - cohort 2 (flu season 2019-2020): Approximately 8,000 subjects will be enrolled, as follows:
M-001: n = 4,000 (Lot#2, pre-filled syringes); Placebo: n = 4,000

PBMC (CMI) sub-study:
To assess the immune response to the vaccine, blood samples will be collected pre- and post-vaccination from a subset of 350 participants selected at random in pre-specified sites participating in Season 2. Approximately two hundred sixty three (263) will be selected from the M-001 group and 87 from the placebo group.
The endpoint for assessing the immune response will be the change from baseline in the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001 measured at 14 ± 2 days after the day of the second vaccination (Visit 3) (Day 36).

Rationale for sample size:
The initial study sample size of 9,630 subjects is based on the lower bound of the two-sided 95% confidence interval for Vaccine Efficacy (VE) being above 40% with 80% probability when true VE is 62%. It assumes 1:1 randomization, a 3% attack rate in the study population, and no more than 10% of subjects lost to follow-up or excluded from the per protocol population. Under these assumptions, 182 first episodes of either qRT-PCR or culture-confirmed influenza of any strain occurring at least 15 days after the second dose of study vaccine or control will be needed to demonstrate efficacy is at least 40%.
In Year 1, about 4,000 subjects will be enrolled. If during the first flu season a substantially reduced attack rate is anticipated, the Sponsor may elect to increase the total sample size to 12,000. If the average attack rate across Year 1 and Year 2 is at least 2.4%, the study should maintain power at 80%. If during the second flu season another mild season is expected, the Sponsor may consider extending the trial to Year 3 with a third cohort based on an amendment to the protocol which will be submitted for ethics/regulatory approval.
In Year 2, an immunogenicity sub-study will be conducted at select sites. Assuming the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001 measured at Day 36 (14 ± 2 days after the day of the second vaccination) has a mean (standard deviation) of 25% (12%), the sub-study should have reasonable power with 210 evaluable vaccinees to demonstrate the non-inferiority of the immune response in other populations with a non-inferiority margin of 5%. Power calculations are based on an equally sized trial in the population to which vaccine efficacy is being bridged.

Medical condition or disease under investigation: Influenza disease

Inclusion criteria

1. Male and female subjects 50 years of age (inclusive) or older, willing and able to give the written informed consent prior to study entry.
2. Able to comply with the trial procedures and be available for all study visits including answering phone calls and coming to the site as defined by the Protocol.
3. Medically stable (subjects may have underlying systemic chronic conditions such as hypertension, diabetes, ischemic heart disease, or hypothyroidism, as long as their symptoms/signs are controlled; if they are on systemic pharmacological treatment for such condition, the treatment must have been stable for at least 3 months preceding first vaccination).
4. Women of childbearing potential (not surgically sterile or postmenopausal for greater than or equal to one year) and men must agree to practice adequate effective contraception - barrier or hormone-based methods or intra uterine device (IUD) for women and a condom for males -whose female partner has childbearing potential - throughout the study treatment and for at least up to day 81 (for females) and day 111 (for males) of the trial (i.e. 60 (for females) and 90 (for males) days after the last dose of the IMP). In addition, women of childbearing potential must have practiced the contraception for a minimum of 30 days prior to study product exposure.
5. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 24 hours prior to both study vaccinations.

Exclusion criteria

1. History of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine.
2. Known or suspected (or have a high risk of developing) significant impairment/alteration of immune function (excluding that normally associated with advanced age) as judged by PI/SI.
3. Receipt of: a) Current (including within 60 days before Visit 1 or planned during the study) daily use of immunosuppressive drugs: i) systemic glucocorticoids ≥ 10 mg prednisone per day ii) cytotoxic drugs b) Investigational drugs within 30 days before, or planned during, the study c) Blood products within 3 months before, or planned during, the study d) Influenza vaccine within 6 months before the study or planned during the study e) Other vaccines within 30 days before, or planned during, the study.
4. Any serious disease such as: cancer, autoimmune disease, advanced arteriosclerotic disease or complicated diabetes mellitus, chronic obstructive pulmonary disease (COPD) that requires oxygen therapy, acute or progressive hepatic disease, acute or progressive renal disease, or congestive heart failure, as judged by the PI/SI.
5. An acute illness, which occurred within 1 week before first vaccination, as judged by the PI/SI, or body temperature greater than: for participants age 50-59 37.9ºC (axillary or forehead) or 38.4 ºC (oral), or 38.9ºC (ear/tympanic or rectal); for participants of age 60 or more, greater than 37.2ºC (axillary or forehead) or 37.7 ºC (oral), or 38.2ºC (ear/tympanic or rectal), which occurred within 1 week before first vaccination.
6. Anatomical deficiencies which exclude possibility of taking NP swab or throat and nasal swab.
7. Women who are breastfeeding or planning pregnancy during the period of the study.
8. Institutionalized subjects or subjects unable to come to the study site as expected by the Protocol.

Test product, dose and mode of administration: M-001 vaccine, 1.0 mg. Administered twice intramuscularly at 21 days interval (recommended range: 21-30 days)
Reference product, dose and mode of administration: Normal Saline, Placebo. Administered twice intramuscularly at 21 days interval (recommended range: 21-30 days)
Duration of treatment: Approximately 22 (+9) days for 2 vaccination visits.Cohort 2 participants will attend 3 site visits. Subset of Cohort 2 participants will attend , including additional Visit 3 for immunogenicity testing, and remaining Cohort 2 participants will have the third visit as safety assessment focused site visit. The Visit 3 is planned 14±2 days after Visit 2 day. The total duration of this trial for each subject will be up to 1 year. Shall the optional study extension have occurred for the purpose of follow up on efficacy (subject to future protocol amendment), the participants will have no obligation to continue their follow up thru Year 3.
Criteria for evaluation: ***Primary endpoint:*** <u>Safety</u> To assess M-001 Safety by solicited local and systemic reactogenicity events occurring within 8 days (day of the vaccination inclusive) following receipt of each of the two doses of M-001 or placebo and to assess SAEs, and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group. To assess M-001 Safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each study vaccination (day of the vaccination inclusive). <u>Clinical Efficacy</u> Compare the occurrence of either qRT-PCR or culture confirmed influenza in the M-001 experimental group *vs.* placebo (≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness (ILI is defined as symptoms that include one of the following respiratory symptoms (sore throat, cough, sputum production, nasal discharge or congestion, wheezing or difficult breathing) **<u>and</u>** at least one additional systemic symptom [fever (oral temperature >37.2°C for age 50-59, or >36.7°C for age 60 or more, or increased ≥ 1.3°C from baseline), headache, myalgia and/or arthralgia, chills, and fatigue (tiredness for at least 12 hours)]. NP (Nasopharyngeal) or combined nasal and throat swab will be collected from participants who meet the ILI definition for qRT-PCR analysis of influenza A and/or B virus. Influenza positive samples by PCR will be further analysed for culture confirmation

Secondary endpoints:

1. Compare the occurrence of culture confirmed influenza in the M-001 experimental group *vs.* placebo (≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined ILI. Nasopharyngeal swab will be collected from participants who meet the ILI definition within 24 hours from ILI being reported to or identified by study personnel for qRT-PCR confirmation of influenza A and/or B virus (a nasal and throat sample can be collected as alternative method), and the samples identified with qRT-PCR as positive for influenza A or B virus will be verified with virus culture.

2. Reduced Severity of influenza illness
   Reduction of either qRT-PCR or Culture-confirmed influenza illness severity: The reduction due to M-001 in the average number of days with respiratory or systemic symptoms during the first laboratory-confirmed influenza illness episode.
3. The percentage of subjects having ILI symptoms in the experimental and control group
4. The change from baseline in the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001. This endpoint will be assessed within a randomly selected subset of participants from pre-selected sites participating to the substudy in Year 2.

Exploratory endpoints:

- Incidence of antibiotics use due to post-influenza secondary infections of respiratory tract
- Incidence of hospitalization associated with the ILI (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director)
- Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation of presence of influenza virus by viral culture and qRT-PCR analysis
- To determine the specific influenza strains in flu cases in experimental and control group

Statistical methods:

For the primary analysis of vaccine efficacy (VE), the efficacy of M-001 after a first influenza season in each cohort will be estimated by

$$VE = 1 - [(C_V / N_V) / (C_P / N_P)]$$

where C_V and C_P are the number of per protocol cases of influenza meeting the primary case definition in the vaccine and placebo group, respectively, and N_V and N_P are the number of per protocol subjects in the vaccine and placebo group, respectively. The confidence interval for VE will be calculated by the Clopper-Pearson exact method conditional on the total number of cases in the vaccine and placebo groups combined. Similarly, vaccine efficacy and its 95% confidence interval will be calculated for the ITT population.

Determination of sample size for the CMI substudy: The endpoint for assessing immune response to the vaccine will be the change from baseline in the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001. Based on preliminary immunogenicity data, the percentage of CD4+ lymphocytes is approximately normally distributed with a mean of 25% and standard deviation 12%. A sample size of 210 M-001 subjects will provide an estimate of the change from baseline in percentage of CD4+ lymphocytes producing e.g. INF-γ with a precision (1/2 width of the 95% CI) at most 2% .

Table 1: Trial Design(Cohort 1flu season 2018/2019)

	Year 1 **Interim data analysis after Year 1**		
	Visit 1 Day 0	Visit 2 Day 22	Visit 4 Day 202
Experimental	1mg M-001	1mg M-001	Safety, qRT-PCR /Culture confirmation in ILI cases (through passive surveillance period)
Control	Placebo	Placebo	

Table 2: Trial Design (Cohort 2, flu season 2019/2020)

	Year 2 (flu season 2019/2020)			
	Visit 1 (Day 0)*	Visit 2 (Day 22) (site)	Visit 3 (Day 36)* (site)	Visit 4 (Day 202) (phone)

	(site)			
Experimental	1mg M-001	1mg M-001	Safety, phone call no treatment; procedures depend on study group	Safety (phone call), qRT-PCR in ILI cases (through passive surveillance period
Control	Placebo	Placebo		

Flu season 2	**Interim Data Review 2**	**Flu season 3**
≥ Cutoff[1]	YES	No season 3. Study completed.
	NO	Cohort 3 initiation will be considered

Flexible enrollment scheme according to interim data review that will be available after Year 1 and 2. Flu season 3 (Year 3) is not planned. If decided that it is needed after Year 2, protocol amendment will be issued and submitted for relevant approvals.

the cutoff will be at most 182 and will be defined precisely in the DSMB charter

* In subset of subjects – visits at selected sites with collection of blood for CMI assessment at Visit 1 and 3. Visit 3 should take place in 14 days +/-2 since date of Visit 2

Table 3: Schedule of Events (Season 1, 2018/2019) for Cohort 1

Study Visit (V)	01	02	04
Study Day	**0**	**22**	**202 (180 days after last vaccination day) (Phone call or email)**
Visit Windows		(+9)	(±14)
Consent process and Signed Consent Form[1]	X		
Assess eligibility	X	X	
Demographic data and Review Medical & flu vaccination History[2]	X	X	
Concomitant meds	X	X	
Vital signs	X		
Oral temperature	X	X	
Physical examination	X		
Randomization	X		
Review contraception/ Counseling[3]	X	X	
Pregnancy Test[4]	X	X	
Solicited/reactogenicity events assessment	X*	X*	

Unsolicited AEs/ Assessment	X#	X#	
NOCIs, AESIs, SAE	X	X	X
Vaccination[5]	X	X	
Evaluate vaccination site	X	X	
Postvaccination procedures[6]	X	X	
Provision of Memory Aid	X	X	
Review of Memory Aid Data		X	
Interim report	End of Season 2018/19, June 2019		
Collection of ILI symptoms through passive and active surveillance	Passive Surveillance: Subjects will be instructed to contact the study site if they experience symptoms of a respiratory illness from Day 14 post-second vaccination day until 15 May the following year. Active Surveillance: Between November 15, 2018 and March 31, 2019, the dedicated study staff will contact subjects twice a week (see 7.3).		
Collection of nasopharyngeal (or nasal and throat) swabs for laboratory confirmation of influenza	From Day 14 post second vaccination day until 30 April of the following year. Every effort must be made to obtain the NP or nasal and throat swab specimen on the same or following day after reporting of qualifying ILI symptoms and no later than 4 days (sample to be collected within 24 hours from ILI being reported to or identified by study personnel through Day 3 of the illness, considering that Day 0 is the day of illness onset) after onset of qualifying ILI symptoms (start date). NP or nasal and throat swab collection according to: https://www.cdc.gov/flu/pdf/freeresources/healthcare/flu-specimen-collection-guide.pdf. A combination of deep nasal and throat swab will be sampled from participant that will not allow for or cannot have NP swab collection, however NP swab is preferred. Swabs collection period starting on September 15, 2018).		
Collection of disease burden data and concomitant medications	At any time during the study a disease burden and concomitant medications in association with respiratory disease, ILI or AE, and for up to 30 days following the start of a qualifying ILI symptoms. All other concomitant medications from 3 months before V1.		
Collection of information on AESIs, NOCIs, and SAEs	At any time during the study period.		

Table 4: Schedule of Events (Season 2, 2019/2020) for Cohort 2

Study Visit (V)	1	2	3 **(site visit[9])**	4 **(Phone call or email)**
Study Day	**0**	**22**	**36 (14 days post date of Visit 2))**	**202 (180 days after last vaccination day)**
Visit Windows		(+9)	(±2)	(±14)
Consent process and Signed Consent Form[1]	X			
Assess eligibility	X	X		
Demographic data, Review Medical & flu vaccination History[2]	X	X		
Concomitant meds	X	X		
Vital signs	X			

Oral temperature	X	X		
Physical examination	X			
Randomization	X			
Review contraception/ Counseling[3]	X	X	X	
Pregnancy Test[4]	X	X		
Blood sample for CMI (40 mL, Subset)	X		X	
Solicited/Reactogenicity Events Assessment	X*	X*		
Unsolicited AEs	X#	X#		
NOCIs, AESIs, SAE	X	X	X	X
Vaccination[5]	X	X		
Evaluate vaccination site	X	X		
Postvaccination procedures[6]	X	X		
Provision of Memory Aid[7]	X	X		
Review of Memory Aid Data		X	X	
Interim Report/Final Report[8]	End of Season 2019/20, June 2020			
Collection of ILI symptoms through passive and active surveillance for participants from season 2.	**Passive Surveillance**: Subjects will be instructed to contact the study site if they experience symptoms of influenza-like illness from Day 14 post-second vaccination day until 15 May the following year **Active Surveillance**: Between December 1st , 2019 and March 31st, 2020, the dedicated study staff will contact subjects up to twice a week (see 7.3)			
Collection of nasopharyngeal (or nasal and throat) swabs for laboratory confirmation of influenza for participants from season 2	From Day 14 post second vaccination day, until 30 April of the following year. Every effort must be made to obtain the NP or nasal and throat swab specimen on the same or following day after qualifying ILI symptoms being reported to or identified by study personnel and no later than 4 days (sample to be collected through Day 3 of the illness, considering that Day 0 is the day of illness onset) after onset of qualifying ILI symptoms (start date). NP or nasal and throat swab collection according to: https://www.cdc.gov/flu/pdf/freeresources/healthcare/flu-specimen-collection-guide.pdf.. A nasal and throat swab will be sampled from participant that will not allow NP swab collection.			
Collection of disease burden data and concomitant medications for participants from season 2	At any time during the study year disease burden data and concomitant medications in association with respiratory disease, ILI or AE, and for up to 30 days following the start of a qualifying ILI symptoms. All other concomitant medications from 3 months before V1			
Collection of information on AESIs, NOCIs, and SAEs for participants from season 2.	At any time during the study period			

[1] Consent process completed and form signed before any study-related procedures are conducted.

[2] Information on past influenza vaccinations for at least 3 years prior to study entry.

[3] Counseling on avoidance of pregnancy for women of childbearing potential.

[4] Urine pregnancy test must be completed within 24 hours prior to vaccination for women of childbearing potential. If urine pregnancy test is positive, subject is not eligible unless local laboratory performed serum pregnancy test is negative.

[5] All subjects will be observed for a minimum of 20 minutes following vaccination.

[6] Post-vaccination procedures will include documentation of any reactogenicity during the observation period and any AEs/SAEs post-vaccination (i.e. with onset before the participant leaves the site after receipt of the study drug injection), as well as provision of memory aid and instructions on completion.

[7] Paper diaries will be used as memory aid

[8] If study is not extended for season 3 final report will be produced after season 2

[9] In subset of subjects – visit at site with collection of blood for CMI assessment at Visit 1 and 3. For remaining subjects only– site visit or - if site visit not feasible - phone call. Blood sampling applicable only for on site visits in a subset of subjects participating in the CMI assessment.

[10] If indicated by medical interview on period between Visit 1 and 2

[*] **Occurence and severity of reactogenicity events will be collected through seven days after each study vaccination day (8 days in total)**

 # Occurrence of unsolicited AEs will be analyzed from the time of first study vaccination through 22 days after each study vaccination (day of the vaccination inclusive).

Note: within exploratory outcome measures, endpoints and objectives: “dosing” to be understood as second vaccination received (unless second dose will not be administered to given subject); “≥15 days after” is to be understood as ≥15 days after the vaccination, including the day of the vaccination.

1. KEY ROLES

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2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

2.1.1. Influenza

Influenza is a common acute viral respiratory illness. Influenza is the eights leading cause of deaths in the western world[1] resulting in worldwide death toll of 250,000-500,000 annually[2]. The continued emergence of novel influenza A viruses in humans including pandemic subtypes underscores the need for focused efforts to prepare for the next influenza pandemic[3] since each emergence of a new subtype of influenza virus in the human population has the potential to result in a global public health emergency.

Increased morbidity and mortality of elderly individuals from influenza infections poses a major medical and public health concern. US CDC estimated the seasonal influenza vaccine effectiveness during the 2004–17 season to be only 40% among the general population[4] and much lower among the elderly[5]. Even when most circulating flu viruses are well matched to the flu vaccine the vaccine can reduce the risk of flu illness by between 40-60% among the overall population during seasons[6].

Use of influenza vaccines is the primary means for preventing influenza. Current licensed inactivated vaccines are good for preventing influenza but are less effective than desirable. In general, the older age group is more vulnerable to the disease and its complications due to concomitant medical conditions and a senescent immune system. People's immune system becomes weaker with age, placing people 65 years and older are at high risk of serious flu-related complications. Accordingly, elderly individuals are also less responsive to the seasonal vaccine and particularly susceptible to other strains that are not incorporated in the seasonal vaccine [7] [8]. It is estimated that 70-85% of flu-related deaths in the US have occurred among this age group posing a more effective influenza vaccine as a very large unmet medical need. Similar findings were observed in Europe, where the European monitoring of excess mortality for public health action (EuroMOMO) network (www.euromomo.eu) monitors weekly 'real-time' all-cause age-specific excess mortality in countries in Europe through a standardized approach, allowing pooling of results. It is expected that a winter season with predominance of influenza A(H3N2) has higher mortality impact on the elderly than a season with predominant influenza A(H1N1) or a season with low influenza A transmission[9]. The reasons for that are that (1) influenza A(H1N1)pdm09 has less impact on the elderly and (2) since 2009 this strain is contained in the seasonal vaccine. Whereas current vaccines focus on enhancement of humoral immunity against the virus, it is known that cellular immunity also can have a role in preventing influenza-associated illness[10].

An approach to improve vaccine efficacy especially in the old adults and elderly is the use of a broadening vaccine that enhances cellular immunity against multiple influenza viruses (a universal vaccine) and that might also prime serological responses to influenza antigens.

2.1.2. Multimeric-001 (M-001)

The use of epitope-based vaccines is an approach that may be used to improve protection of elderly by activating cell mediated immunity and prime for immune responses to influenza antigens[11]. The M-001 vaccine from BiondVax consists of 3 repetitions of 9 conserved linear epitopes from the hemagglutinin, nucleoprotein and matrix 1 (M1) protein that are prepared as a single recombinant

protein. The epitopes in the vaccine are common to a large majority of influenza virus strains, and the epitopes are recognized by both the *humoral* and *cellular* arms of the immune system[12]. Based upon these characteristics, the M-001 vaccine is hypothesized to provide immunity against both existing as well as future emergent virus strains[13].

The M-001 vaccine is produced as a recombinant protein in *E. coli*. In the current study, the vaccine is intended to be administered in a non-adjuvanted formulation at a 1 mg/dose level that has been found to be safe and immunogenic in previous clinical trials performed by BiondVax.

Preclinical studies using adjuvanted M-001 demonstrated both vaccine immunogenicity and protection from lethal challenge in a mouse model using highly pathogenic influenza A/H5N1[14]. The safety and efficacy results of M-001 in the preclinical studies led to its evaluation in people as detailed in the Investigator Brochure [15]. Additional information on the clinical trials conducted with M-001 is listed below and in the Investigator Brochure.

The initial study of M-001 in humans (BVX-002) was conducted in 63 healthy adults as a Phase 1 trial that evaluated the safety and immunogenicity of two doses of M-001 administered by the intramuscular (IM) route at 3 different dosage levels (125, 250 and 500 mcg) with or without Montanide ISA 51 VG adjuvant[16]. No safety concerns were identified. Recipients of the adjuvanted 500 mcg dose of M-001 had 22-28% more frequent antibody-dependent, complement-mediated lysis of cells infected with influenza virus strains contained in seasonal vaccines compared to placebo recipients. This group also had significantly higher cellular (PBMC proliferation) responses after exposure to vaccine compared to unprimed groups.

The next study (BVX-003) was performed in 60 older adults (55-75 years of age) and evaluated the safety and ability of M-001 to improve humoral and cellular responses when used for priming prior to administration of a trivalent seasonal inactivated influenza vaccine [IIV3]. Participants (n=10 per group) either received Montanide ISA 51 VG-adjuvanted or non-adjuvanted M-001 or placebo 3 weeks prior to IIV3. A greater proportion of recipients of an adjuvanted 250 mcg M-001 dose (50-80%) had HAI seroresponses to the seasonal vaccine strains than did participants who only received IIV3 (20-30%). Following this study and based upon the lack of safety concerns, the 500 mcg dosage of M-001 was selected for further study.

BVX-004 evaluated the safety and immunogenicity of Montanide ISA 51 VG-adjuvanted M-001 when it was co-administered with IIV3 or used in a priming strategy in 200 healthy adults 18-49 years of age. Adjuvanted M-001, when administered twice before delivery of IIV3 and when administered in combination with partial IIV3 (either co-administered or in a prime-boost approach) was found to be safe and induced immune responses that exceeded those exhibited by subjects immunized with placebo or IIV3 alone.

The fourth study of M-001 (BVX-005) compared two priming doses of M-001 with one priming dose of alum-adjuvanted or non-adjuvanted M-001 administered 3 weeks prior to seasonal IIV3 in 120 elderly individuals (see Atsmon et al ref. #11). Seroconversion rates were significantly higher in the two-dose M-001 regimen for the seasonal A (H1N1) and B strains compared to placebo (IIV3 alone), and cellular immune responses (IFN-g expressing CD4 and CD8 lymphocytes) were also significantly increased from pre-immunization levels after exposure to influenza antigens. No safety concerns were identified.

A fifth placebo-controlled study (BVX-006) examining two different dosage levels (0.5 mg and 1 mg) of M-001 as a three-dose prime for seasonal IIV3 has been conducted in 36 adults. No SAEs were observed and no safety concerns were identified. Elevated HAI responses were demonstrated in the experimental group receiving 1 mg M-001 before the IIV3 and hence, this dosage was selected for future trials.

The recent Phase 2b clinical trial was conducted (BVX-007) was conducted by UNISEC consortium in which BiondVax participated. 219 adults (18-65 years old) were divided into 3 groups and vaccinated with either low (0.5mg) or high (1 mg) M-001 or saline twice, next, all the participants were immunized with a sub-optimal dose of H5N1 vaccine[17]. No SAEs were observed and no safety concerns were identified, a significant Th1 cell mediated immunity was induced in the group that was immunized with the M-001 at the high dose[18].

2.2. Rationale

Seasonal influenza poses continuous threats to human populations and especially to elderly and toddlers. The rapid and constant evolution of influenza viruses likewise poses challenges to the development of vaccines for the prevention and control of influenza. Recent vaccine development efforts have focused on the development of "universal" influenza vaccines; that is, vaccines which could offer protection against multiple influenza subtypes. BiondVax has developed a novel vaccine, M-001, that has been shown in preclinical and clinical trials to stimulate directly the cellular arms of the immune system and indirectly, when used as a primer ahead of a strain-specific boost, M-001 enhances immunity to strains contained within the boost and to drifted strains. In view of these immunological outcomes and the good safety profile of the M-001 vaccine candidate, the purposes of the study are to determine the safety and clinical efficacy of M-001 in a large population of older adults and elderly. Cell-mediated immunity expected to be induced by the M-001 will also be evaluated based on samples from subset of participants from Cohort 2. Blood samples will be collected from approximately 263 participants receiving M-001 and 87 participants receiving the placebo (to maintain the blinding). The blood samples from all 350 participants will be collected at baseline (visit 1) and on Visit 3 -14 ± 2 days after the day of the Visit 2 (second vaccination).

2.3. Potential Risks and Benefits

2.3.1. Potential Risks

The potential risks of this study are mostly those associated with having blood drawn and receiving an IM injection that may result in injection site or other adverse reactions, and risk associated with swab collection.

Drawing blood may cause transient discomfort and fainting. Fainting is usually transient and managed by having the subject lie down. Bruising at the blood draw site may occur, but can be prevented or lessened by applying pressure to the draw site for several minutes. IM injection also may cause transient discomfort and fainting. Drawing blood and IM injection may also cause infection. The use of sterile technique will make infection at the site where blood will be drawn or where the study vaccination is given extremely unlikely.

Six previous trials in which approximately 460 participants received M-001 intramuscularly have been completed to date in addition to 2027 who participated in season 1 of the current trial (see Investigator Brochure). AEs described following receipt of M-001 have been similar to those seen in placebo recipients. These included rhinitis/nasal congestion, malaise, myalgia, sore throat, injection site pain and erythema, cough, headache, diarrhea, neck pain, fever, back pain, arthralgia, nausea, vomiting, rash, flushing, dizziness and decreased blood pressure. Analgesics (e.g., acetaminophen, or ibuprofen or similar non-steroidal anti-inflammatory drugs (NSAIDs)) and rest may generally relieve or lessen these reactions. Bruising can sometimes occur due to the vaccination procedure. There were no treatment related SAEs.

The procedure for collection of an NP, deep nasal or throat swab is associated with a slight discomfort, and may, in some instances, cause watering of the eyes or gag reflex. Other than that, there is little to no risk involved.

It is unknown if the M-001 vaccine poses any risks to an unborn child. Female subjects of childbearing potential who are not surgically sterile via tubal sterilization, bilateral oophorectomy, hysterectomy, or successful Essure® placement, or who are not postmenopausal for ≥ 1 year must agree to practice highly effective contraception that may include, but is not limited to, abstinence from intercourse with a male partner, monogamous relationship with a vasectomized partner, male condoms with the use of applied spermicide, intrauterine devices, and licensed hormonal methods, with use of a highly effective method of contraception for a minimum of 30 days prior to study product exposure and agree to practice highly effective contraception for the duration of study product exposure, including 2 months (defined as 60 days) after the last study vaccination. A highly effective method of contraception is defined as one which results in a low failure rate when used consistently and correctly. In addition to contraceptive use, all female subjects of childbearing potential will be required to have a negative serum or urine pregnancy test within 24 hours prior to receiving each dose of study vaccine. Urine pregnancy test must be completed within 24 hours prior to vaccination for women of childbearing potential. If urine pregnancy test is positive, subject is not eligible unless serum pregnancy test is negative. If a female subject becomes pregnant while participating in this study, she will be asked for permission to follow-up with her about her health and the health of her baby through pregnancy outcome.

Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of applicable laws including European Union General Data Protection Regulation 2016/679 (GDPR) where applicable. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects by name. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as EMA and local regulatory authorities.

There may be other unknown risks, discomforts, or side effects.

2.3.2. Known Potential Benefits

There are no known benefits attributable to the receipt of the M-001 vaccine, but there is a prospect of benefit. It is possible that vaccination with M-001 will prime the participant for improved responses to future seasonal or pandemic influenza vaccines.

There may be influenza preparedness benefits to society in the future if the M-001 is shown to have a long-lasting efficacy based on the improved cellular immune responses to influenza.

3. OBJECTIVES

3.1. Study Objectives

3.1.1. Primary Objectives

Safety

To assess M-001 Safety by solicited local and systemic reactogenicity events occurring within 8 days (day of the vaccination inclusive) following receipt of each of the two doses of M-001 or placebo and to assess SAEs and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group. To assess M-001 safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each study vaccination (day of the vaccination inclusive).

Clinical Efficacy

To assess efficacy of M-001 in the prevention of influenza disease by comparing the occurrence of either qRT-PCR or culture confirmed influenza in the M-001 experimental group *vs.* placebo caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness (ILI)

3.1.2. Secondary Objectives

Clinical efficacy

- Compare the occurrence of culture confirmed influenza in the M-001 experimental group *vs.* placebo caused by any influenza A or B virus in association with a protocol defined ILI.
- Assess reduction of severity of either qRT-PCR or culture -confirmed influenza illness by the reduction due to M-001 in the average number of days with respiratory or systemic symptoms during the first laboratory-confirmed influenza illness episode.
- To assess proportion of subjects having ILI symptoms in the experimental or control group.

Immunogenicity

- To assess in at least a subset of samples in season 2 the change from baseline in the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001. This endpoint will be assessed within a randomly selected subset of participants from pre-selected sites participating to the substudy in Year 2.

3.1.3. Exploratory Objectives

- Incidence of antibiotics use due to post-influenza secondary infections of respiratory tract as evidenced with medical records or declared by the participant

- Incidence of hospitalization associated with the ILI (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director).
- Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture or qRT-PCR analysis.
- To determine the specific influenza strains in confirmed flu cases in experimental and control group

3.2. Study Outcome Measures

3.2.1. Primary Outcome Measures

Safety

- Occurrence of vaccine-related SAEs from the time of the first study vaccination (M-001 or placebo) until end of first passive surveillance period
- Occurrence of NOCIs from the time of the first study vaccination (M-001 or placebo) until end of first passive surveillance period
- Occurrence of solicited injection site and systemic reactogenicity events on the day of each study vaccination through 8 days after each study vaccination (day of the vaccination inclusive)
- Occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each study vaccination (day of the vaccination inclusive)
- Occurrence of all SAEs, regardless of the assessment of relatedness, from the time of receiving the first M-001 study vaccination until end of first passive surveillance period

Clinical Efficacy

- Percentage of either qRT-PCR or culture-confirmed influenza cases in the M-001 experimental group *vs.* placebo (during period of ≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness (ILI is defined as symptoms that include one of the respiratory symptoms (sore throat, cough, sputum production, nasal discharge or congestion, wheezing or difficult breathing) and at least one additional systemic symptom [fever (oral temperature >37.2°C for age 50-59, or >36.7°C for age 60 or more, or increased ≥ 1.3°C from baseline), headache, myalgia and/or arthralgia, chills, and fatigue (tiredness for at least 12 hours)]. NP or combined nasal and throat swab will be collected from participants who meet the ILI definition within 24 hours from ILI being reported to or identified by study personnel for qRT-PCR analysis of influenza A and/or B virus. PCR confirmed samples will be further analyzed for culture confirmation.

3.2.2. Secondary Outcome Measures

1. Clinical efficacy

- Percentage of culture confirmed influenza cases in the M-001 experimental group *vs.* placebo (during period of ≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness. NP or nasal and throat swab will be collected from participants who meet the ILI definitions within 24 hours from ILI being reported to or identified by study personnel for Culture confirmation of influenza A and/or B virus (a nasal and throat sample will be collected if the participant object the NP swab collection), and the samples identified with qRT-PCR as positive for influenza A or B virus will be verified with virus culture

- Average time to all symptoms alleviation/fever resolution in the experimental vs control group expressed as reduction (in group with M-001 vs. control group) of number of days with respiratory or systemic symptoms during the first laboratory-confirmed influenza illness episode. "Alleviation/resolution" time is defined as the first time point at which all of the following influenza symptoms (body aches (myalgia and/or arthralgia), cough, fatigue/tiredness, headache, nasal congestion/ runny nose/ sputum production, wheezing or difficult breathing, chills and sore throat) were absent and fever had resolved, with both (resolution of all symptoms and fever) maintained for at least 1 day.

- Percentage of subjects having ILI symptoms in the experimental or control group

2. Immunogenicity In Sub-Study

- Change from baseline in the percentage of T cell expressing e.g. interferon gamma (IFN-g) in CD4+ PBMCs after stimulation with M-001 16 days after the second dose of M-001 (day of the vaccination inclusive) . This endpoint will be evaluated in a subset of participants in the experimental group and will further be compared to the percentage of T cell expressing e.g. interferon gamma (IFN-g) in CD4+ PBMCs after stimulation in another study.

3.2.3. Exploratory Outcome Measures

- Reduction in the proportion of subjects taking antibiotics use due to a post-influenza secondary infections of respiratory tract, due to vaccination with M-001 as compared to the control group. In case of lack of documented medical record subject's provided information will be sufficient.

- Reduction in the number of hospitalizations associated with ILI episodes, due to vaccination with M-001 compared to Placebo. Hospitalization associated with ILI (≥15 days after dosing* until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group.

- Incidence of death due to influenza-like illness (≥15 days after dosing* until epidemiological levels of influenza are low as defined by the medical director) in the

experimental group as compared to the control group, with or without confirmation by viral culture and qRT-PCR analysis.

- Define influenza virus subtype in the swab samples to compare the viruses causing disease in the experimental vs control group

* - within exploratory outcome measures, endpoints and objectives: “dosing” to be understood as second vaccination received.; ≥15 days after” is to be understood as ≥15 days after the second vaccination, including the day of the vaccination.

4. STUDY DESIGN

This is a pivotal, multicentre, randomized, modified double-blind, placebo-controlled phase 3 trial to assess the safety and clinical efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (≥50 years of age) who meet all eligibility criteria.

Subjects will be assigned randomly to 1 of 2 treatment arms (6000 per study arm during the study) to receive two doses of the M-001 vaccine or placebo (saline). Group A will receive two doses of M-001, each containing 1 mg of M-001, on Day 0 and 22. Group B will receive saline placebo on the same days.

Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination with M-001 (or placebo) through 8 days after the study vaccination (inclusive of vaccination day). Unsolicited non-serious AEs collected from the time of each study vaccination through approximately 22 days after each study vaccination (day of the vaccination inclusive) will be analyzed separately. SAEs (including AESIs)and NOCIs will be collected from the time of the first study vaccination through the entire trial period.

In cohort 2, immunogenicity testing will be performed and will include performing CMI assays on blood samples obtained immediately at baseline (Day 0) and on samples collected on Visit 3 (referred to as Day 36, taking place 14±2 days since day of the administration of second dose of the vaccine/placebo). At sites participating in the CMI sub-study, data will be obtained from a subset of approximately 263 participants randomly selected from the experimental group and from a subset of 87 participants randomly selected from the placebo group. Cell mediated immune responses to influenza antigens, including epitopes represented in the M-001 vaccine, will be assessed at baseline (Day 0, before vaccination), and at 14±2 days since day of the administration of second dose of the vaccine/placebo (Day 36).

The duration of this trial for each subject will be up to 1 year (reflecting time between vaccination and end of the flu season as stated in the protocol).

For additional details on study procedures and evaluations and study schedule by study visits/days, see Sections 7 and 8 as well as Table 3 and Table 4 – Schedule of events.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Subject Inclusion Criteria

Subjects eligible to participate in this study must meet all of the following inclusion criteria:

1. Male and female subjects 50 years of age (inclusive) or older, willing and able to give and sign the written Informed consent form (ICF) prior to study entry.
2. Able to comply with the trial procedures and be available for all study visits including answering phone calls and coming to the site as defined by the Protocol.
3. Medically stable (subjects may have underlying systemic chronic conditions such as hypertension, diabetes, ischemic heart disease, or hypothyroidism, as long as their symptoms/signs are controlled;. if they are on systemic pharmacological treatmentfor such condition, the treatment must have been stable for at least 3 months preceding vaccination).
4. Women of childbearing potential (not surgically sterile or postmenopausal for greater than or equal to one year) and men must agree to practice adequate effective contraception – barrier or hormone-based methods or intra uterine device (IUD) for women and a condom for males -whose female partner has childbearing potential - throughout the study treatment and for at least up to day 81 (for female) and day 111 (for male) of the trial (i.e. 60 (for females) and 90 (for males) days after the last dose of the IMP). In addition, women of childbearing potential must have practiced the contraception for a minimum of 30 days prior to study product exposure.
5. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 24 hours prior to both study vaccinations.

5.2. Subject Exclusion Criteria

Subjects eligible to participate in this study must not meet any of the following exclusion criteria:

1. History of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine.
2. Known or suspected (or have a high risk of developing) significant impairment/alteration of immune function (excluding that normally associated with advanced age) as judged by PI/SI.
3. Receipt of: a) Current (including within 60 days before Visit 1 or planned during the study) daily use of immunosuppressive drugs: i) systemic glucocorticoids ≥ 10 mg prednisone per day ii) cytotoxic drugs b) Investigational drugs within 30 days before, or planned during, the study c) Blood products within 3 months before, or planned during, the study d) Influenza vaccine within 6 months before the study or planned during the study e) Other vaccines within 30 days before, or planned during, the study.
4. Any serious disease such as: cancer, autoimmune disease, advanced arteriosclerotic disease or complicated diabetes mellitus, chronic obstructive pulmonary disease (COPD) that requires oxygen therapy, acute or progressive hepatic disease, acute or progressive renal disease, or congestive heart failure, as judged by the PI.
5. An acute illness, which occurred within 1 week before first vaccination, as judged by the PI/SI, or body temperature greater than: for participants age 50-59 37.9ºC (axillary or

forehead) or 38.4 ºC (oral), or 38.9ºC (ear/tympanic or rectal); for participants of age 60 or more greater than 37.2ºC (axillary or forehead) or 37.7 ºC (oral), or 38.2ºC (ear/tympanic or rectal); which occurred within 1 week before first vaccination.

6. Anatomical deficiencies which exclude possibility of taking NP swab or throat and nasal swab.
7. Women who are breastfeeding or planning pregnancy during the period of the study.
8. Institutionalized* subjects unable to come to the study site as expected by the Protocol.

*except for institutionalization without subsequent overnight stays

5.3. Treatment Assignment Procedures

5.3.1. Randomization Procedures

Central randomization will be implemented in this study. Subjects will be randomized to 1 of 2 treatment arms, based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be stratified by cohort and age group (i.e., 50- 65, ≥ 65) and balanced by using permuted blocks. At least 50% of study participants will be 65 or older in each randomization cohort. The Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit(s) for the subject.

For season 2, the randomization will be further stratified by sub-study participation (i.e. Yes or No).

For the CMI substudy, 350 subjects from sites participating to the sub-study (sub-study sites) are randomly chosen among 700 sub-study sites subjects with appoximately 263 subjects selected at random from 350 M-001 sub-study sites subjects and approximately 87 from 350 placebo sub-study sites subjects.

Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subject will be enrolled. A total of 12,000 subjects will be randomly assigned to one of 2 arms: experimental and control. A total of 700 subjects will be randomly chosen to participate to the sub-study, with approximately 263 subjects selected at random from 350 M-001 sub-study sites subjects and approximately 87 from 350 placebo sub-study sites subjects.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject, if necessary.

Per International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP), screening records will be kept at each participating site to document the reason why an individual was screened, but failed trial entry criteria.

5.3.2. Masking Procedures

This is a modified double-blind study. Blinding will prevent conscious or unconscious misclassification of study endpoints based on subjective perceptions; blinding will be accomplished by using a randomization scheme for the participants.

Subjects, investigators, and study personnel performing any study-related assessments following study injection, as well as collecting swab specimends or blood samples, will be blinded to study group and treatment assignment to both: M-001 or placebo. Laboratory personnel will be blinded to treatment assignment. Separate unblinded laboratory personnel will be assigned if needed.

As the M-001 and placebo solutions differ in appearance (see section 6.1), at each study site, an appropriately qualified person, who will otherwise not be involved in the treatment or follow-up of trial patients, will not be blinded to study treatment. The person will be responsible for the preparation of the study treatment syringe. This will in most cases be the site nurse.

The site unblinded staff member will be responsible for preparing the syringe and covering it or making it (the content) in other way not visible for the subject before its administration to keep the subject blinded. This un-blinded staff member will not participate in the assessment of respiratory illnesses or ILI, or in the collection of safety information.

The Data and Safety Monitoring Board (DSMB) may receive data in aggregate and by treatment arm, or may be unblinded to individual subject treatment assignments, as needed, to adequately assess safety issues.

Refer to the relevant Unblinding Plan for unblinding procedures.

5.3.3. Reasons for Withdrawal

Subjects may voluntarily withdraw their consent for study participation at any time and for any reason, without penalty.

A subject may withdraw or be withdrawn from the study for any of the following reasons:

- Medical disease or condition, or any new clinical findings for which continued participation, in the opinion of the site PI or appropriate SI, would compromise the safety of the subject, or would interfere with the subject's successful completion of the study, or would interfere with the evaluation of responses.
- Subject no longer meets eligibility criteria.
- As deemed necessary by the site PI or appropriate SI for noncompliance or other reasons.
- Subject withdrawal of consent.
- Subject lost to follow-up.
- Termination of the study or the study cohort.
- New information becomes available that makes further participation unsafe.

Subsequent study vaccinations will not be administered to a subject if any of the following criteria are met:

- Medical condition for which continued participation, in the opinion of the site PI or appropriate SI, would pose a risk to the subject or would be likely to confound interpretation of the results.

- Presence of signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity. For subjects with injection site or systemic signs or symptoms, or with an acute illness, the subsequent study vaccinations should be postponed/deferred until signs, symptoms, or acute illness have sufficiently resolved as per PI/SI judgment, and if within the expected protocol-specified window for that visit. If outside this window, the PI must first obtain approval for the second study vaccination from the study sponsor and the documentation of the approval should be filed in the subject's file.

- Any unresolved by or continuing at Visit 2 Grade 3 AE. An unresolved or continuing Grade 1 or 2 AE (grade 2 except for temperature which at grade 2 is not acceptable for vaccination) is permissible unless, in the opinion of the PI or SI, it would render study vaccination unsafe or interfere with the evaluation of responses.

- Solicited reactogenicity event grade 3 or AE grade 3 AE, within the 8 days following study vaccination (day of the vaccination inclusive), that has no alternative (to the vaccination) etiology.

- Subject no longer meets eligibility criteria.

- As deemed necessary by the site PI or appropriate SI for noncompliance or other reasons.

- Subject refusal of further study vaccination.

- Subject withdrawal of consent.

- Subject lost to follow-up.

- Termination of the study.

- New information becomes available that makes further participation unsafe.

5.3.4. Handling of Withdrawals

The primary reason for withdrawal from the study will be recorded on the Study Status data collection form. Subjects will be encouraged to complete the Early Termination Visit. The Early Termination Visit procedures are listed in Section 7.7. Although subjects are free to withdraw at any time or may be withdrawn by the site PI or appropriate SI at any time, subjects who receive at least one dose of study vaccine will be encouraged to remain in the study for follow-up safety assessments and – in cohort 2 - collection of venous blood samples for immunogenicity testing. Every attempt will be made to follow all AEs, including solicited injection site and systemic reactions, SAEs, ongoing at the time of early withdrawal to resolution.

In the case of subjects who fail to appear for a follow-up safety assessment, extensive effort (i.e., three documented contact attempts via e.g. phone calls, e-mails, etc., made on separate occasions and followed by a certified letter, as applicable per local law) will be made to locate or recall them, or at least to determine their health status. These efforts will be documented in the subjects' records. See the protocol-specific manual for alternate follow-up requirements.

Subjects who withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the ICF, randomization, and receipt of study vaccine will not be replaced. Subjects who withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the ICF and randomization but before receipt of study vaccine may be replaced.

Subjects who do not receive second vaccination dose but have not withdrawn the consent for paritіcpation in the study are allowed to remain in the study upon PI's decision.

5.3.5. Termination of Study

Although the study Sponsor has every intention of completing the study, it reserves the right to terminate the study or the study cohort at any time for clinical or administrative reasons. Reasons for termination include, but are not limited to, study closure due to DSMB review and recommendation.

6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

6.1. Study Product Description

M-001

Multimeric-001 (M-001) vaccine developed by BiondVax is a multimeric peptide-based vaccine, a single chain recombinant protein containing 9 B and T cell epitopes derived from HA, Nucleoprotein and M1 sequences that are conservatively expressed among influenza A and B viruses.
It has been produced under aseptic conditions and according to the rules of current Good Manufacturing Practice and guidelines applicable to investigational medicinal products (IMPs). The vaccine lots used in this trial have been tested and released by the quality control department of BiondVax.

Placebo

Sterile normal saline will be used as the placebo.

6.1.1. Acquisition

M-001 will be provided by BiondVax. Packaging, labeling and distribution will be performed by Klifo A/S.

Placebo (normal saline) will be provided by BiondVax. Packaging, labeling and distribution will be performed by Klifo A/S.

M-001

In Season 1, M-001 is supplied as a sterile, cloudy-white suspension in single-dose vials of volume sufficient to dose 1 mg of M-001 (1mg is a single dose).
Each vial contains a fill volume (less than 1 mL) of concentration provided in the study manual for respective product batch that should be transferred to a 1mL syringe for injection according to the study manual. It contains no preservative (i.e. non-thimerosal).
Volume of the product containing 1mg of M-001 (1 mg of M-001 is the dose to be administered per each vaccination) will be provided in the study manual for respective product batch.

In Season 2, M-001 is supplied in single-dose pre-filled syringes containing 1mg of M-001. Each syringe contains a fill volume (0.6 mL) of concentration provided in the study manual for respective product batch that should injected according to the study manual. It contains no preservative (i.e. non-thimerosal).

Study product must be stored at 2°C to 8°C. Do not freeze.

Placebo (Normal Saline)

0.9% Sodium Chloride, USP, Ph.Eur. or "normal" saline is a sterile, nonpyrogenic, isotonic solution; each mL contains sodium chloride 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied in single-dose ready to use syringes, containing

0.6 mL. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5-7.0). The normal saline will be stored according to storage conditions defined in product-specific Summary of Product Characteristics.

The packaging and labelling of study treatment will be performed according to GMP (Good Manufacturing Practice) and GCP (Good Clinical Practice). In addition, the content of the labels to be affixed on the study treatment packs will be in accordance with local regulations for clinical trials. A sticker on the outer study treatment pack will indicate that the study treatment pack must only be opened by unblinded study personnel.

Each treatment pack will be identified by a treatment number. Once allocated to a patient, the study treatment packs should not be used for any other patient. The patient's identification number (i.e. PatID number) must be written on the label by hand by the person who prepares the study treatment.

6.1.2. Product Storage and Stability Procedures

The temperature of the storage unit must be recorded daily (excluding non-business days and holidays as applicable), monitored during the duration of this trial per the participating sites' standard operating procedures, and documentation will be maintained. If the temperature fluctuates outside of the required range, the affected study product(s) must be quarantined at the correct storage temperature and labeled as 'Do Not Use' (until further notice). If any study product appears to have been damaged, contaminated or discolored, contains visible particulate matter (for normal saline), or if there are any concerns regarding its integrity, do NOT use the affected study product(s). The pharmacist or dedicated nurse must alert the site PI and study coordinator, if the temperature fluctuates outside of the required range. The site PI or responsible person should immediately contact the Sponsor for further instructions before any additional study vaccinations are administered. Based on the information collected, the Sponsor will determine whether the affected study product(s) can be used. If it cannot be used, the site will receive specific instructions on how to return the affected study product(s) to the Sponsor or destroy it on site. Dosage, Preparation and Administration of Study Intervention/ Investigational Product

See the protocol-specific manuals for detailed information on the preparation, labeling, storage, and administration of study vaccine. Study vaccine preparation will be performed by the participating site's research pharmacist or nurse on the same day of study vaccine administration. Each dose of study vaccine must be administered within 120 minutes from removing the IMP from the refrigerator, the prepared syringe must be stored at room temperature until administered

M-001 investigational influenza vaccine product:

The 1 mg of M-001 dose will be administered as a single intramuscular injection according to the study manual. The M-001 will be provided in vials (Season 1) or syringes (in Season 2) as described in paragraph 6.1.1 of the protocol.

Visually inspect M-001 vaccine vial (Season 1)/ ready to use syringe (Season 2) upon receipt and prior to use. After shaking, the suspension will be cloudy white in appearance. For season 2, if the M-001 vaccine precipitated, it should be re-suspended by tapping on the pre-filled syringe

strongly with the finger or by intensive shaking until the suspension looks homogeneous.
If the M-001 vaccine appears to have been damaged, contaminated or discolored, or if there are any concerns regarding its integrity, do NOT use the affected study product(s).

Normal Saline (Placebo):

The saline placebo dose will be administered as a single intramuscular injection. Exact volume to be injected will be defined in the study manual and will be equal to the volume of the M-001 defined for the active treatment (M-001) study arm.

The saline will be provided in ready to use syringes as described in paragraph 6.1.1 of the protocol.
Visually inspect the placebo (normal saline) upon receipt and prior to use. The solution will be clear to colorless in appearance. If the placebo appears to have been damaged, contaminated or discolored, contain visible particulate matter, or if there are any concerns regarding its integrity, do NOT use the affected study product(s).

Study vaccine preparation will be performed by an unblinded study personnel member. Details on administration of the IMP will be described in relevant study manual. Briefly, vaccination will be performed by a person credentialed to administer medications/vaccines. The syringe containing the dose of study vaccine (or placebo) will be inverted a few times, and the air bubble removed before administered via a single IM injection given in the deltoid muscle of the subjects' non dominant arm. Subject will be maintained blinded to the contents of the syringe. The site of injection (right or left arm) will be recorded on the appropriate data collection form. Aseptic technique will be used for the preparation and administration of each dose of study vaccine/placebo using a disposable sterile needle appropriate in length and size for each subject.
Each dose of study vaccine must be administered within 120 minutes from removing the IMP from the refrigerator, the prepared syringe must be stored at room temperature until administered.

6.2. Modification of Study Intervention/Investigational Product for a Participant

Individuals must meet the appropriate inclusion and exclusion criteria prior to receiving the subsequently scheduled study injections. There will be no replacement of individuals who do not qualify to receive study dose 2. There will be no dose modifications. If a subject's second study vaccination (study dose 2) cannot occur on Day 22, vaccination should be rescheduled to occur within the expected protocol-specified window for that visit (Day 22 + 9 days), if possible.

6.3. Accountability Procedures for the Study Intervention/ Investigational Product

After receipt of the M-001 and placebo vials or syringes, the site PI is responsible for study product distribution and disposition, and has ultimate responsibility for study product accountability. The Site PI may delegate to another study site team member(s) the responsibility for study product accountability. Such person(s) will be responsible for maintaining complete records and documentation of product receipt, accountability, dispensation, temperature and storage conditions, and final disposition of study product. All study product, whether administered or not, must be documented on the appropriate study product accountability record or dispensing log.

Accountability and study product handling must follow blinded/unblinded personnel assignment at the site level.

Used and unused vials or syringes of M-001 will be retained until monitored and released for disposition as applicable. Upon completion or termination of the study and after the final monitoring visit, final disposition of unused study products and empty vials or syringes will be determined by the Sponsor. For details regarding final disposition of study products see the relevant manual.

6.4. Assessment of Subject Compliance with Study Intervention/ Investigational Product

Study product will be administered to subjects by an unblinded vaccine administrator via IM injection at all dosing times according to subject treatment assignment and as described in sections 5.3 and 6 of the protocol. Thus, subject compliance with appropriate administration is not anticipated to be an issue. Deviations from the dose schedule may only occur as described in Section 6.2.

6.5. Concomitant Medications/Treatments

Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Records of concomitant medications will include at least all current medications and medications taken within 3 months prior to Day 0 through 21 days after last vaccination day. After this period, only concomitant medications relevant for background chronic respiratory illness as per PI judgment, or related to AE or ILI, will be recorded. Subjects who do not receive both M-001/placebo study vaccinations will have all concomitant medications collected through approximately 22 days after the first study vaccination, day of the vaccination inclusive, or early termination, whichever occurs first. Prescription and over-the-counter drugs will be included as well as herbals, vitamins and supplements. In addition, information on receipt of other influenza or non-influenza study vaccines will be solicited at each subject's visit at the site or phone call by PI/SI or delegated study site personnel, and, if confirmed, such vaccination will be reported in the eCRF. Past use of influenza vaccinations should be recorded for at least 3 years prior to study entry.

Identified use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.

Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. However, as the study concerns elderly population use of such medications cannot be excluded. Medications in this category include the prohibited medications per the Subject Exclusion Criteria (see Section 5.2). In addition, the site PI or appropriate SI may identify other mediations that should not be used due to a risk to subject safety or assessment of reactogenicity and immunogenicity.

Subjects may be on chronic or as needed (p.r.n.) medications if, in the opinion of the site principal investigator or appropriate SI, they pose no additional risk to subject safety or assessment of reactogenicity and immunogenicity. Note: Topical, nasal, and inhaled medications, vitamins, and contraceptives are permitted.

Medications which require relatively frequent dose adjustments, like insulin, hormones, anti-inflammatory or pain relieve medications, are considered as stable treatment for a chronic condition for the purpose of Inclusion Criterion number 3 compliance assessment as long as the treatment (regular or p.r.n.) has been continued for at least 3 months prior to first vaccination. Switch within the same therapeutic class or type of treatment is not automatically considered as an unstable treatment but is subject to PI's assessment and decision.

7. STUDY SCHEDULE

7.1. Enrollment/Baseline (Visit 1, Day 0, Dose 1, Site Visit)

- Subjects will be provided with a description of the study (purpose and study procedures) and asked to read and sign the ICF. The ICF will be signed prior to performing any study procedures, including administration of the first study vaccination.
- Eligibility criteria will be reviewed with subjects prior to the first study vaccination.
- History of receipt of licensed seasonal influenza vaccine(s) from at least last 3 years, and approximate date of vaccination will be recorded on the appropriate data collection form, if known.
- Complete medical history will be obtained by interview of subjects prior to the first study vaccination to assure eligibility.
- All concomitant medications taken before signing the ICF (at minimum those taken within 3 months prior to it, if applicable) will be recorded on the appropriate data collection form prior to the first study vaccination.
- Vital signs, including oral temperature and pulse, will be obtained prior to the first study vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- Height and weight will be collected on Day 0 prior to the first study vaccination for the calculation of Body Mass Index (BMI).
- Standard physical examination (PE) will be performed on day 0 prior to the first study vaccination. If subject's medical history is known based on medical records (but not if there are no medical records available at all), a limited, targeted physical examination may be performed instead of standard scope PE prior to the first study vaccination by a study clinician, however in any case neurologic component of PE and physical examination of head/upper respiratory tract must be performed. Except for neurologic, head and upper respiratory tract physical examination, for other body systems only findings relevant from the study perspective and not obvious from medical history need to recorded in the eCRF
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- A urine pregnancy test will be performed within 24 hours prior to the first study vaccination on all female subjects of childbearing potential. Results must be negative and known prior to randomization and first study vaccination.
- Approximately 40 mL of venous blood will be collected prior to the first study vaccination for isolation of PBMCs from a subset from Cohort 2 intended for CMI testing (applicable only for selected study sites).
- Subjects entered into EDC system will be randomly assigned to a treatment arm prior to the first study vaccination.
- In study sites participating in CMI assessment, additional, nested randomization is planned to assign certain number of subjects to one of the subset substudy groups.

- Pre-administration reactogenicity assessments will be performed prior to the first study vaccination to establish baseline. Subjects will then receive a single dose of study vaccine via IM injection in the deltoid muscle of the non-dominant arm. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 20 minutes after the first study vaccination. The study vaccination site will be examined, and observed reactions, AEs, SAEs (as applicable) will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic.
- Subjects will be provided with a memory aid (paper diaries) and other study-related materials to record daily oral temperature (e.g. thermometers), solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their temperature on the vaccination day in the evening and then at selected approximately the same time each day for next 7 days after the vaccination day. Subjects will be instructed on how to use the provided materials, prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any reactions after the first study vaccination. PI or appropriate SI will assess the reaction and will give the subject further instructions on the proper course of action, including request for return to the clinic for immediate evaluation. The participants will be instructed to return the completed diary, covering period between Visit 1 and Visit 2 to the site for Visit 2, and to bring their study thermometer with them to the Visit 2.

7.2. Second Vaccination

7.2.1. Visit 2, Day 22, Site Visit (22 days [+9 days] post first study vaccination day)

- Study personnel will review the memory aid information with subjects and assess and record all solicited, reported reactions, AEs, SAEs (as applicable) and concomitant medications on the appropriate data collection form.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- If indicated by review of memory aid or recent medical history, obtain vital signs
- A targeted physical examination should be performed by a study physician if assessed as needed based on medical interview concerning period between Visit 1 and Visit 2 .
- Examine the vaccination site for Dose 1.
- Eligibility criteria will be reviewed with subjects prior to the second study vaccination to assure continued eligibility.
- Obtain interim medical history by interview of subjects prior to the second study vaccination and note any changes since the previous visit.
- All concomitant medications will be recorded on the appropriate data collection form prior to the second study vaccination.
- Oral temperature will be obtained prior to the second study vaccination. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

- All unsolicited AEs/ SAEs will be assessed and recorded on the appropriate data collection form prior to the second study vaccination.
- A urine pregnancy test will be performed within 24 hours prior to the second study vaccination on all female subjects of childbearing potential. Results must be negative and known prior to the second study vaccination.
- Pre-administration reactogenicity assessments will be performed prior to the second study vaccination to establish baseline. Subjects will then receive a single dose of study vaccine via IM injection into the deltoid muscle of the same arm that received Dose 1 as long as there is no interference with the reactogenicity assessment. The site of injection (right or left arm) and time of administration will be recorded on the appropriate data collection form. Subjects will be observed in the clinic for at least 20 minutes after the second study vaccination. The study vaccination site for Dose 2 will be examined, and any reactions, AEs or SAEs (as applicable) will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic.
- Subjects will be provided with a memory aid (paper diaries) in a stamped envelope to record daily oral temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their temperature on the vaccination day in the evening and then at selected approximately the same time each day for next 7 days after the vaccination day. Subjects will be instructed on how to use the memory aid and how to measure and record solicited events and / or unsolicited AEs prior to discharge from the clinic. Subjects will be instructed to notify the study center if they develop any significant reactions after the second study vaccination. If the site PI or appropriate SI deems the reaction severe enough, s/he will give further instructions on the proper course of action, including a return to the clinic for immediate evaluation if appropriate. The participants will be instructed to return the diary to the site after completion of the diary. The participants that are coming for visit 3 to the site will be requested to bring the diary to that visit.

7.2.2. Visit 3, Day 36, Site Visit (14 days [±2 days] post second study vaccination day(visit 3 - in season 2019/20 only)

- This is a visit in study site for the subset of subjects selected for immunogenicity evaluation and site visit or a phone call (if site visit is not feasible) for the rest of the participants. The following #4 and #6 points refer to those actually visiting the clinic:
- Study personnel will review the memory aid information with subjects and assess and record all solicited events / unsolicited reactions, AEs, SAEs and concomitant medications on the appropriate data collection form.
- Counsel women of childbearing potential on contraception and avoidance of pregnancy.
- [site visits only] A targeted physical examination and/or vital signs collection may be performed by a study clinician if assessed as needed based on review of recent medical history.

- Study personnel will review interim medical history (other than reactogenicity events) with subjects and assess and record all unsolicited AE/SAEs and concomitant medications on the appropriate data collection form.
- [site visits only] Approximately 40 mL of venous blood will be collected for isolation of PBMCs from a subset of subjects from Cohort 2.

7.3. Follow up period for safety and efficacy:

Safety surveillance:

All serious adverse events (SAEs) and new onset of chronic medical illness (NOCIs) will be collected from Day 0 until the end of the participation in the trial by the subject.
Adverse events of special interest (AESIs) will be captured as SAEs. These include new onset of Guillain-Barré Syndrome (GBS), Bell's Palsy, encephalitis / myelitis, optic neuritis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

Passive efficacy surveillance: Following randomization and vaccinations, subjects will be instructed to contact the site if they experience symptoms of a respiratory illness or influenza-like illness during the annual surveillance periods defined as from Day 14 after second vaccination day until 15 May of the following year.

Active efficacy surveillance will be performed from November 15th (in Season 1) or from December 1st (in Season 2) until the week of 30 March the following year, the most likely period of influenza virus circulation in the Northern Hemisphere.
The participants will be contacted by a dedicated study staff up to twice a week between approximately November 15th through March 31st .
Participants will be contacted as described above by non-site study staff to monitor for influenza-like illness (ILI).; participants identified this way as potentially having ILI will be followed up by relevant study site personnel to confirm if the participant's symptoms and signs meet study ILI definition.
ILI is NOT to be understood as condition caused specifically by influenza virus. The etiology of ILI may be very different, and only after analysis of swabs taken from subjects , the presence or absence of influenza virus in swab sample can be determined. Hence, even if it is suspected that ILI is caused by e.g. a bacteria, or by some other virus than influenza virus, such ILI remains valid reason for swab collection, also because in some cases there may be a superinfection or parallel infection with influenza virus.
However, if an Investigator is sure that an ILI-qualifying symptom/sign comes purely from underlying chronic condition (e.g. arthritis, COPD, asthma), including also the severity of the symptoms/signs, or belongs to clinical presentation of another, known, completely non-infectious condition (e.g. toxicity, injury, cancer), then it is understood that the investigator may decide to NOT recognize the case as meeting ILI criteria, and to NOT qualify the subject for swab collection. The rationale behind disqualifying such cases from ILI is preference for avoidance of exposing subjects to swab collection procedure in case when it is absolutely sure *a priori* that infectious etiology of the symptoms/signs is highly unlikely.
During the period from Day 14 after second vaccination day until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), the site will arrange for an NP/nasal and throat swab to be collected if the subject

experiences a new onset of the above mentioned symptoms of ILI (that persist for or reoccur after a period of at least 12 hours).
During the passive and active efficacy surveillance period participants suffering from ILI will be asked to provide information on the symptoms that they developed using also standardized sets of questions.

NP/nasal and throat swab collection:

NP swab (or nasal and throat swab) specimens will be collected during the period from Day 14 after second vaccination day until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), within 24 hours from ILI being reported to or identified by study personnel and up to 4 days of the onset of ILI qualifying symptom(s) for confirmation of influenza virus A or B via qRT-PCR followed by culture (Rhesus Monkey Kidney or Madin–Darby Canine Kidney tissue cultures) confirmation for qRT-PCR positive samples as described in Vesikari et al [19]. Every effort must be made to obtain the NP(or nasal and throat) swab specimen within 24 hours from ILI being reported to or identified by study personnel according to the qualifying ILI symptoms, and no later than 4 days (sample to be collected through Day 3 of the illness, considering that Day 0 is the day of the illness onset) following the onset of the ILI.

The end of influenza season will be defined for each participating country by the Medical director based on national surveillance and study data.

The Sponsor's Responsible Medical Director will base the decision on the following criteria:

1) The influenza activity level for the region/zone where the research site is located has to be evident by increased ILI and laboratory confirmed influenza detection together with e.g. outbreaks in schools, hospitals, residential institutions and/or other types of facilities occurring in less than 50% of the influenza surveillance region), based on the most updated report.
2) The percentage of specimens tested that are positive for influenza has to be at least 10% for the country where the site is located, based on data present in the most updated report.

If the 2 criteria are met for the region/zone where the research site is located, the site will be instructed to continue obtaining NP/nasal and throat swabs if a subject has a new influenza-like illness.

On 15 May (unless other instructions are given by the medical director), all surveillance and the swab collection procedures will end.

Any influenza A or B strain will be included in the vaccine efficacy analysis. Culture confirmation of influenza will be performed only for qRT-PCR highly positive samples.

After 30th of April, passive surveillance will continue, with subjects expected to call the research site to report the occurrence of any new respiratory illness or influenza-like illness symptoms. However, the research site will schedule the collection of the NP/ nasal and throat swab only if the Sponsor has categorized the site as requiring continued testing based

on DSMB recommendation which will be based on influenza epidemiologic data. The Sponsor's Responsible Medical Director will perform weekly assessments of the applicable influenza surveillance system to determine whether a particular research site needs to continue collecting the swabs.

ILI follow-up calls:

Any ILI must be followed up for up to 30 days following the start date or until resolved. Site personnel will follow up the participant with ILI at 10±3 days after ILI start date. Follow up information on symptoms associated with the ILI will be collected by study staff through a telephone call performed at 10±3 days (and up to 30 days) (unless collected at unscheduled site visit at relevant time point) following the illness start date.
Protocol defined ILI end date is the date when for at least 24 hours ILI symptoms are no longer present. Of note, some symptoms may persist after ILI for a long time, but the duration of ILI is to be determined by presence of symptoms of ILI understood as active disease, or "influenza symptom", contrary to symptoms being part of an underlying chronic condition (e.g. COPD, arthritis), and contrary to chronic complications and/or sequelae of the ILI. When no clear end of ILI can be observed, the PI is requested to make rational judgment and determine the ILI end date based on available data and his/her experience. It is expected, that normally, ILI should not last longer than 2-3 weeks, and in case of suspected overlapping new infection, the two infection episodes should be recognized by PI as separate ILI cases.

Laboratory testing for the confirmation of influenza:

All NP/nasal and throat swab specimens will be submitted for analysis by polymerase chain reaction (qRT-PCR), and when the result is found positive, and if there is a sufficient content of viruses (as determined by Ct value ≤35)" [Ct= cycle threshold] another aliquot from such specimen will be also examined by culture confirmation test. Typing and subtyping of the influenza virus will be performed with PCR based method.
Optional test: Positive cultures samples will be stored and may undergo additional testing in the future (subtyping or strain identification, utilizing genetic sequencing and antigenic analysis using hemagglutination inhibition [HAI] against a panel of known standard ferret reference antisera to different viral strains) to further determine the breadth of protection provided by M-001.
Out of study influenza infection confirmation: in cases when no swab collection was performed within study framework, but valid, relevant external medical documentation exists confirming recent or ongoing influenza infection (laboratory confirmation – PCR, culture or serology - IgM antibodies), such medical documentation will be subject to sponsor's approval as surrogate proofs of influenza infection, and if approved as valid, may be taken into account for exploratory analyzes. Details of exploratory analyzes will be defined in statistical analysis plan.

7.4. Safety Follow Up Visit, Visit 4, Day 202: Phone Call/ Electronic Communication (180 days [+/-14 days] post last study vaccination day)

Subjects will be contacted by phone or electronic communication (e.g., email, text message) to query for safety events. In case follow-up contact is needed based on the responses, subjects will be asked to provide further details to the follow-up by phone. AEs limited to NOCIs and SAEs that have occurred since the previous visit will be solicited. Based on the information, subjects may be asked to return to the clinic for evaluation.

7.5. Follow Up Period for Efficacy Season 2

Passive surveillance will take place starting 14 days after the second injection and until May 15, 2020.

Active surveillance for cohort 2 will take place between December 1st , 2019 and March 31, 2020. During this period, the dedicated study staff will contact the participants up to twice a week to monitor for ILI symptoms as detailed above in 7.3. (Follow up calls in season 2019/20 will be for participants in cohort 2 only).

As of the end of the season 1, the follow up for Cohort 1 subjects in season 2019/2020 is not planned and participation of all Cohort 1 subjects will be assumed as completed with the end of Season 1, i.e. the latest on May 15th except for cases defined elsewhere (e.g. ongoing ILI, SAE follow-up).

7.6. Follow Up Period for Efficacy Season 3

Season 3 is not planned and is not encompassed by this study protocol.

7.7. Early Termination Visit

The following activities will be performed at the early termination visit for subjects who withdraw, or are withdrawn or terminated from the study:

- Obtain interim medical history by interview of subjects and note any changes since the previous visit.
- Memory aid information will be reviewed with subjects (if within 22 days after the last study vaccination, day of the vaccination inclusive).
- If indicated by medical history, perform physical examination and/or obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- Review and record all concomitant medications (if within 22 days after the last study vaccination, day of the vaccination inclusive).
- Information regarding reactions recorded in diary/-ies, AEs and SAEs will be recorded on the appropriate data collection form. Recording of AEs in the EDC will be limited to SAEs if after 21 days following the last study vaccination day.

- Examine study vaccination site, and perform post- administration reactogenicity assessment (if within 8 days after the last study vaccination, day of the vaccination inclusive).

7.8. Unscheduled Visit

Unscheduled visits may occur at any time during the study. Any of the following activities may be performed:

- Review memory aid (if within 22 days after the last study vaccination day, inclusive of the vaccination day).
- Review and record all concomitant medications (if within 22 days after the last study vaccination day, inclusive of the vaccination day).
- All reactions recorded in diary/-ies, AEs, SAEs will be recorded on the appropriate data collection form. Recording of AEs in the EDC will be limited to SAEs if after 21 days after the last study vaccination day.
- Obtain interim medical history by interview of subjects and note any changes since the previous visit (if indicated).
- If deemed as relevant and/or needed, perform physical examination and/or obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
- Examine study vaccination site and perform post- administration reactogenicity assessment (if within 8 days after the last study vaccination, inclusive of vaccination day).

8. STUDY PROCEDURES/EVALUATIONS

8.1. Clinical Evaluations

Medical History: Will be obtained by interview of the subjects. Subjects will be queried regarding a history of significant – clinically or from the study protocol perspective - medical disorders of the head, eyes, ears, nose, throat, mouth, cardiovascular system, lungs, gastrointestinal tract, liver, pancreas, kidney, nervous system, blood, lymph glands, endocrine system, musculoskeletal system, skin, and genital/reproductive tract. A history of any allergies, cancer, immunodeficiency, psychiatric illness, and substance abuse will be solicited. The collection of medical history information will include a review of vaccine history and plans for vaccinations. All Past influenza vaccinations should be recorded (up to 3 years). Other vaccines history should include at least 30 days before the study and any other study-relevant vaccination received in the past.

Concomitant Medications: All current medications and medications taken within 3 months before Study Day 0 (prescription and over-the-counter drugs) will be included, as well as vitamins and supplements, through 21 days after the last study injection day, unless relevant for chronic background respiratory illness, as per PI judgment, or related to AE or ILI.

Vital signs: blood pressure, oral temperature and pulse will be collected at study visit 1, and as needed at any other study visits Only oral temperature is required to be measured on visit 2. Measurement of oral temperature should be performed with thermometers provided by the study Sponsor. Oral temperature should be measured by keeping the tip of the thermometer under the tongue for sufficient amount of time until the temperature reading stabilizes. In cases when level of oral temperature seems too low the measurement should be repeated and care should be taken to correctly place the tip of the thermometer and to keep it under the tongue for sufficient amount of time (until the temperature stops growing).

Height, weight: These parameters will be measured at Day 0 (Visit 1).

Physical Examination: On Visit 1 standard physical examination should be performed prior to the first study vaccination, but if subject's medical history is known based on medical records, a limited, targeted physical examination may be performed instead of standard scope PE prior to the first study vaccination by a study clinician, however in any case neurologic component of PE and physical examination of head/upper respiratory tract must be performed. On visits other than 1 limited, targeted physical examination may be performed if assessed by investigator as needed.

Reactogenicity Assessments: This will include an assessment of solicited events occurring from the time of each M-001 study vaccination [Day 0 (Visit 1), Day 22 (Visit 2] through 8 days after the study vaccination (inclusive of vaccination day), which includes an assessment of systemic reactions (Fever; Decreased blood pressure and/or dizziness; Chills and/or sweating; Joint and/or muscle pain; Headache; Nasal congestion, runny nose, phlegm production, rhinitis; Problems with breathing (difficulty breathing, wheezing); General malaise, fatigue, loss of appetite; Itching on body/ pruritus; Swelling/tender lymph nodes; Irritability; Rash; Cough; Sore throat; Stomach problems (abdominal pain, diarrhea, nausea, vomiting)) and local – injection site reactions (Blue spot/ bruising; Induration / Swelling; Redness / Warmth; Itching),Pain/ tenderness

Memory Aids: All subjects will complete a subject memory aid (paper diary) from the time of each study vaccination [Day 0 (Visit 1), Day 22 (Visit 2)] through 8 days after the study vaccination (study vaccination day inclusive). Subject memory aids will be reviewed with the subject for AEs at the site visit following the first study injection, and over the phone after the second study

injection (unless the subject comes to the site for Visit 3). If a subject noted ongoing injection site or systemic reactogenicity on the 7th day following the study injection day, the memory aid will continue to be completed and reviewed until resolved. Subjects will be requested to deliver memory aids filled in after the second vaccination when completed – to the site.

Questionnaires: information on ILI clinical presentation, duration etc. will be collected in the study by study personnel.

8.2. Laboratory Evaluations

Schedules and volumes of clinical laboratory tests and immunogenicity assays are specified in Schedule of events (Table in the Synopsis).

8.2.1. Clinical Laboratory Evaluations

Urine pregnancy tests will be performed by the local or site laboratory within 24 hours prior to each study vaccination (Day 0 (Visit 1) and approximately Day 22 (Visit 2) on all female subjects of childbearing potential. Result must be negative and known prior to randomization on Day 0 (Visit 1) and administration of each study vaccination to be eligible for participation in the study and receipt of each dose of study vaccine.

8.2.2. Nasopharyngeal Samples

For assessment of influenza virus through culture and qRT-PCR, an NP/nasal and throat swab sample will be collected from both nasal passages using two different swab applicators; both swabs are then placed in the same tube of universal transport medium (UTM). Optionally, if NP swab cannot be collected, combined swabs collection from deep nasal (both nostrils) and throat - can be collected instead of NP with three separate applicators, and all three swabs are then placed into the same tube of UTM. Immediately prior to taking the sample, the person performing the procedure will verify the subject's identity and will confirm that the subject number and any other required information on the laboratory request form are those of the subject. Each tube of UTM will be clearly labeled with the self-adhesive bar-coded label provided on the Swab Requisition form that will be applied to the tube immediately before collection of the NP/nasal and throat swab. The subject's identification number and any other required information, the date of sampling, and the date and time of preparation will be clearly documented.

Detailed instructions for the preparation of NP (or combination of nasal and throat swabs) samples are contained in the relevant study manual provided to the sites and relevant study personnel.

8.2.3. Special Assays or Procedures

<u>Cellular (CMI) Studies</u>

Assays to measure T cell responses will be performed by a qualified laboratory. Venous blood samples for isolation of PBMCs will be collected from a subset of cohort 2, immediately prior to the first study vaccination (Day 0, visit 1 in season 2), and approximately 15 days (day of the vaccination inclusive) after the second study vaccination (Day 36, visit 3, season 2).

8.2.4. Specimen Preparation, Handling, and Shipping

8.2.4.1. Instructions for Specimen Preparation, Handling, and Storage

Instructions for specimen preparation, handling, and storage are included in the relevant study manual, as appropriate.

8.2.4.2. Specimen Shipment

Swab samples will be shipped and stored according to applicable regulations and according to the technical requirements aiming at preserving good quality of the material before it is processed for qRT-PCR and (where applicable) for culture confirmation. Swab samples will be analyzed in a qualified laboratory. Details will be contained in the relevant laboratory and study manuals.

Swab samples will be shipped in batches regularly during the course of this study.

Samples for PBMC will be shipped from the sites to the qualified laboratory in a blinded fashion for PBMC isolation and storage before the planned cellular assays take place. Details on shipment and PBMC isolation will be contained in the relevant laboratory and study manuals.

Samples for PBMC will be shipped from sites on ongoing basis aiming at same day or next day delivery, as possible.

9. ASSESSMENT OF SAFETY

9.1. Specification of Safety Parameters

Safety will be assessed by the frequency and severity of:

1. SAEs and NOCIs occurring from the time of the first study vaccination through subjects' participation in the trial.

2. Solicited events – reactogenicity events occurring on the day of each study vaccination through 8 days* after each study vaccination:
   **Vaccination day is considered Day 0, with 7 days following (8 days in total)*

   a) Injection site reactions including pruritus, ecchymosis, erythema,warmth, induration, swelling, pain and tenderness.

   b) Systemic reactions including fever, feverishness, general malaise, fatigue, loss of appetite, myalgia or arthralgia, decreased blood pressure or dizziness, chills and/or sweating, nasal congestion, runny nose, phlegm production, rhinitis, problems with breathing (difficulty breathing, wheezing), itching on body/ pruritus, swelling/tender lymph nodes, irritability, rash, cough, sore throat, headache and stomach problems (abdominal pain, diarrhea, nausea, vomiting).

3. Unsolicited AEs/SAEs – unsolicited AEs/SAEs occurring from the time of the study vaccination through approximately 22 days after each study vaccination (day of the vaccination inclusive) .

9.2. Safety Assessment

9.2.1. Adverse Events

Adverse Event (AE): International Conference on Harmonisation (ICH) E6 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product. The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

AEs, will be captured on the appropriate data collection form and electronic case report form (eCRF) as described below in terms of reporting periods. Information to be collected for AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product and considered etiology (if case not related or unlikely related to study product) date of resolution of the event, seriousness and outcome. AEs while on study will be documented appropriately regardless of relationship. AEs will be followed to resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it may be recorded as an AE or SAE.

AEs must be graded for severity and assessed for relationship to study product (see definitions below). AEs characterized as intermittent require documentation in the subject's file of onset and duration of each episode. It is up to PI's decision whether the episodes are recorded in the eCRF as separate events or under one event with comment added on the intermittent (or similar) nature of the event. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF within study periods as described below.

•Unsolicited AEs – which do not meet SAE criteria, nor ILI, AESI or NOCI definition should be reported only until ~22 days post each study vaccination, thus - per protocol – such AEs, if they occurred later then 22 days post study vaccination day, should not be recorded in the AE section of the eCRF. They still need to be documented in the subject's study file at the site.

Adverse events of special interest (AESIs) will be captured as SAEs and within the same timelines throughout the subject's participation in the trial. These include new onset of Guillain-Barré Syndrome (GBS), Bell's Palsy, encephalitis / myelitis, optic neuritis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis.

NOCIs should be collected from the time of the first study vaccination throughout the subject's participation in the trial. NOCI is defined as diagnosis of a chronic medical condition where the symptoms commenced or worsened following exposure to the study vaccine. NOCIs meeting criteria of SAE will be recorded as SAE.

Events classified as ILI will not be recorded as AEs/SAEs unless they occur during period from first or second vaccination within 8 days (the vaccination day inclusive) post the respective vaccination or if they meet seriousness criteria - then they are also (in addition to being reported as ILI) reported as SAEs, because ILI cases are to be recorded separately and analyzed for efficacy assessment.

Severity of Event: AEs will be assessed by a licensed study physician using a protocol-defined grading system (see section 9.2.2). For events not included in the protocol-defined grading system, the following guidelines will be used by PI/SI to quantify severity, taking into account subject's medical history, concomitant medications, and baseline values:

- Mild (Grade 1): Events require minimal or no treatment and do not interfere with the subject's daily activities.
- Moderate (Grade 2): Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning and daily activities.
- Severe (Grade 3): Events interrupt the subject's usual daily activities and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Relationship to Study Product: The study physician's assessment of an AE's relationship to study product 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. The relationship to study product must be assessed for AEs using the terms: none, unlikely, possible, probable, certain. In a clinical trial, the study product should be considered as potential suspect. To help assess, the following guidelines are used:

- NONE no evidence of any causal relationship is present
- UNLIKELY There is only little evidence to suggest there may be a causal relationship. Another reasonable explanation for the event exists (medical history, treatment)
- POSSIBLE There is some evidence to suggest a causal relationship but the influence of other factors has been reasonably possible
- PROBABLE There is a reasonable evidence to suspect a causal relationship, and the relevant influence of other factors is less likely.
- CERTAIN - There is clear evidence for the causal relationship, and other reason is very unlikely

9.2.2. Reactogenicity

Reactogenicity events are solicited events which are common and considered as possible to occur following administration of this type of vaccine. Reactogenicity (solicited) events are recorded only for 8 days post vaccination (day of the vaccination inclusive). Solicited events (reactogenicity events) which match at least one of the below criteria must be also recorded as AE/SAE or unsolicited AE/SAE:

- symptom/event continues/occurs beyond 7 days post vaccination day (unsolicited AE/SAE)
- reactogenicity symptom/event(s) required medical (i.e. physician's) assistance (AE/SAE)
- reactogenicity symptom/event has been graded by subject or by investigator as severe (AE/SAE)
- oral body temperature of severe grade as per section 9.2.2 Table 8 (AE/SAE)

Per PI/SI's judgment, also cases of symptoms/events occurring within 8 days post vaccination (day of the vaccination inclusive) not meeting the above criteria can be recorded as SAE.

The following Toxicity Grading Scales will be used by PI/SI to grade solicited injection site and systemic (subjective and quantitative) reactions in order to assess whether they qualify as AE/SAE, and if they are severe enough to delay administration of second dose:

Table 5: Injection Site Reactogenicity Grading

Injection Site Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain – experienced without touching the injection site (spontaneous discomfort)	Subject is aware of pain, but it does not interfere with daily activity, **and** no pain medication is taken	Subject is aware of pain; there is interference with daily activity **or** it requires repeated use of a non-	Subject is aware of pain, **and** it prevents daily activity or requires any use of a narcotic pain reliever

Injection Site Reaction	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
		narcotic pain reliever for >24 hours	
Tenderness – hurts only when injection site is touched or the arm is moved	The area immediately surrounding the injection site hurts only when touched or with arm motion, **and** it does **not** interfere with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it interferes with daily activity	The area immediately surrounding the injection site hurts when touched or with arm motion, **and** it prevents daily activity
Pruritus (Itching)	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Ecchymosis (Bruising)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Erythema (Redness)*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity
Induration (Hardness)/Swelling*	Does not interfere with daily activity	Interferes with daily activity	Prevents daily activity

* Will be also measured in mm but size will not be used as criterion for stopping the trial

Ecchymosis, erythema, and induration /swelling as analyzed by measurement will be graded as follows:

Table 6: Injection Site Reactogenicity Measurements

Injection Site Reaction	Small	Medium	Large
Ecchymosis *	<20 mm	20 mm – 50 mm	>50 mm
Erythema*	<20 mm	20 mm – 50 mm	>50 mm
Induration /Swelling*	<20 mm	20 mm – 50 mm	>50 mm

* Will not be used as criterion for stopping the trial.

Table 7: Subjective Systemic Reactogenicity Grading

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Feverishness (Chills/Shivering/Sweating)	No interference with daily activity	Nonsignificant interference with daily activity	Significant interference, prevents daily activity
Fatigue (Tiredness)	No interference with daily activity	Nonsignificant interference with daily activity	Significant interference, prevents daily activity
Malaise (General Unwell Feeling)	No interference with daily activity	Nonsignificant interference with daily activity	Significant interference, prevents daily activity

Systemic (Subjective)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Myalgia (Body Aches/Muscular Pain)*	No interference with daily activity	Nonsignificant interference with daily activity	Significant interference, prevents daily activity
Arthralgia (Joint Pain)*	No interference with daily activity	Nonsignificant interference with daily activity	Significant interference, prevents daily activity
Headache	No interference with daily activity	Nonsignificant interference with daily activity	Significant interference, prevents daily activity
Nausea	No interference with daily activity	Nonsignificant interference with daily activity	Significant interference, prevents daily activity

* Not at injection site.

Oral temperature# will be graded as follows:

Table 8: Quantitative Systemic Reactogenicity Grading [20,21]

Systemic (Quantitative)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
(Age <60) Fever* - oral†	38.0°C – 38.4°C	38.5°C – 38.9°C	>38.9°C
(Age 60+) Fever* - oral†	37.3°C – 37.7°C	37.8°C – 38.2°C	>38.2°C

Oral temperature assessed on Day 0 prior to the first primary series study vaccination will be considered as baseline.
* A fever can be considered not related to the study product if an alternative etiology can be documented.
† Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.

9.2.3. Additional Adverse Event Severity Grading

Pulse and Blood pressure changes will be graded according to the PI/SI judgment taking into consideration subject's medical history, concomitant medications, and baseline values.

9.2.4. Serious Adverse Events

An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes/meets any of the following:

- death,
- a life-threatening AE*,
- inpatient hospitalization or prolongation of existing hospitalization (excluding pre-planned elective surgeries or other pre-planned hospitalizations; for this option it is not required that they were pre-planned solely before Visit 1, they might be pre-planned also after Visit 1),
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect

- an important medical events that may not result in death, be life-threatening, or require hospitalizations may be considered serious when, based upon appropriate medical judgment they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- Note: all AESIs will also be considered SAEs as within the confines of this protocol are deemed as important medical events

- Note: cases of NOCIs which meet criteria of SAE will be recorded as SAE with annotation that they are also considered NOCIs.

- Note: ILI cases meeting seriousness criterion/criteria should be recorded as SAE in parallel with recording them as ILI cases, except for periods of 8 days post vaccination day (day of the vaccination inclusive) for both vaccine doses when such cases will only be recorded as SAE.

* Life-threatening AE. An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

All SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician.

- Recorded on the appropriate paper SAE form and in eCRF.

- Followed through resolution by a licensed study physician.

- Reviewed and evaluated by the DSMB (periodic review unless related)

9.3. Reporting Procedures

Solicited injection site and systemic reactogenicity events will be documented from the time of each study vaccination (Day 0 (Visit 1) and approximately Day 22 (Visit 2) through 8 days after each study vaccination (day of the vaccination inclusive).

Unsolicited non-serious AEs (excluding NOCIs) will be documented from the time of the study vaccination until 22 days after the study vaccination (day of the vaccination inclusive).

ILI will be documented as AE if occurs within 8 days post vaccination (day of the vaccination inclusive).

SAEs and NOCIs will be documented from the time of the first study vaccination (Day 0 (Visit 1)) through subject's participation in the trial.

SAEs occurring after the participant completes the study or after early termination need not be reported unless the Investigator believes that the event may have been caused by the study product or a protocol procedure.

9.3.1. Serious Adverse Events

Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the CRO representative at the following:

KCR S.A.
Email: SAE@kcrcro.com

FAX: +48 22 203 56 58

In addition to the SAE form, selected SAE data fields must also be entered into EDC,

Other supporting documentation of the event may be requested by the DSMB and should be provided as soon as possible.

All SAE report(s) will be reviewed and assessed for regulatory reporting purposes and potential impact on study subject safety and protocol whithin 1 business day from receipt. SAE reports will beshared with DSMB.

At any time after completion of the study, if the site PI or appropriate SI becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate SI will report the event to the study Sponsor directly.

9.3.2. Reporting of Pregnancy

Pregnancies occurring in study subjects will be reported via Pregnancy Report Form (paper) and recorded in the EDC under SAE category. No further study vaccinations will be administered to pregnant subjects, but, with the subject's permission, all study mandated blood samples will be obtained and the subject will continue in follow-up for safety events. Efforts will be made to follow all pregnancies reported during the course of the study to pregnancy outcome pending the subject's permission.

9.4. Type and Duration of Follow-up of Subjects after Adverse Events

AE will be followed until it reaches a satisfactory resolution, or becomes stable, or clinical judgment indicates that further evaluation is not warranted. Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.

Follow-up procedures, evaluations, and outcomes will be recorded on the appropriate data collection form.

9.5. Safety Oversight (DSMB)

Safety oversight will be conducted by a DSMB that is an independent group of experts that monitors subject safety and advises the sponsor. The DSMB members will be separate and independent of study personnel participating in this trial and should not have scientific, financial or other conflict of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of the data from this trial.

The DSMB will review study progress and participant, clinical, safety, and reactogenicity data at the following time points.

- Data review for safety at study specific time frames; at least annually (shortly after each influenza season).
- After all 8-day post second study vaccination safety data are available for all study participants.
- Interim review meeting: Review the blinded safety data for the interim report for this trial. The data will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to questions posed by the sponsor.
- Final review meeting: After clinical database lock to review the cumulative unblinded safety and efficacy data for this trial. The data will be provided in a standard summary format. The DSMB may be asked to provide recommendations in response to questions posed by the sponsor.
- Ad hoc, for evaluation of immediate concerns regarding observations during this trial, or as needed.

The DSMB will operate under the Medical director that will forward information and organize meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. Procedures for DSMB reviews/meetings will be defined in a charter prepared by the Medical director. The DSMB will review applicable data to include, but not limited to, study progress and participant, clinical (total number of influenza confirmed cases), safety, and reactogenicity data. Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited/reactogenicity events and AE/SAEs. Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by the sponsor. The DSMB may receive data in aggregate and presented by treatment arm. The DSMB may also be provided with expected and observed rates of the expected AEs in an unblinded fashion, and may request the treatment arm be unblinded for an individual subject if required for safety assessment. The DSMB will review grouped and unblinded data in the closed session only. The DSMB will meet and review this data at scheduled time points or ad hoc as needed during this trial as defined in the DSMB charter. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study vaccinations (as applicable), and to continue, modify, or terminate this trial.

Upon completion of this review and receipt of the advice of the DSMB, the sponsor will determine if study entry or study dosing should be interrupted or if study entry and study dosing may continue according to the protocol.

9.6. Efficacy Assessment

9.6.1. Molecular Detection and Sequencing Methodology (qRT-PCR):

Clinical samples collected during the study period will undergo an extraction procedure to isolate the viral RNA from the NP/nasal and throat swab prior to testing.
The initial test will be a qRT-PCR-based assay to determine if Influenza strains are present in the clinical sample. A multiplex qRT-PCR will be performed to define Influenza A/H1 or A/H3 or B in a single test, Influenza B samples will be re-tested by qRT-PCR to define the Victoria/Yamagate lineage specification.
For samples that are found positive for influenza in the qRT-PCR assay, further testing by culture confirmation will be performed if there is a sufficient content of viruses (as determined by Ct value <35)" [Ct= cycle threshold].

If swab specimen was not collected but infection with influenza virus has been confirmed outside of the study framework and valid medical documentation exists confirming such virus identification (e.g. hospital discharge), such cases may be recognized by study sponsor as valid confirmed influenza cases. Extent to which such results will be included in the statistical analyses will be defined in statistical analysis plan.

9.6.2. Influenza Virus Culture:

Swab samples from subjects with ILI that were found positive in qRT-PCR, will be used to inoculate and infect influenza virus susceptible tissue culture cell lines (e.g. MDCK). Optionally, Influenza positive cultures will be confirmed by using direct immunofluoresence techniques with influenza type–specific (i.e., for influenza A and influenza B) antibodies.

10. CLINICAL MONITORING

10.1. Site Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study center visit log that will be kept at the site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the eCRF are consistent with the original source data. Findings from this review of eCRF and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

Please refer to Monitoring Plan for further details.

11. STATISTICAL CONSIDERATIONS

This section provides an overview of the statistical considerations for the design, conduct, and analysis of the phase 3 trial of Multimeric-001 influenza vaccine. A formal statistical analysis plan will be developed and finalized prior to first DSMB meeting for Year 1 cohort and will be amended to reflect changes made to previous version of the protocol.

11.1. Study Hypotheses

The null hypothesis of vaccine efficacy (VE) equals 40% against the alternative hypothesis VE > 40% will be tested using the two-sided, 95% Clopper-Pearson confidence interval for VE. If the lower bound of the 95% confidence interval is above 40%, adequate efficacy will have been established.

11.2. Study Outcome Measures

Please refer to Section 3.2.

11.3. Sample Size Considerations

11.3.1. Study Design

This is a pivotal, multicentre, randomized, modified double-blind, placebo-controlled phase 3 trial to assess the safety and clinical efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (≥50 years of age). Subjects will be randomized 1:1 to vaccine or placebo with randomization stratified by cohort and age group. For season 2, stratification will also be performed for participation to the sub-study. All doses will be administered IM approximately 21 days apart (recommended window is 21-30 days). All subjects from cohort 1 will be followed for up to two consecutive influenza seasons with no obligation to continue in season 3 if the study is extended to third season with protocol amendment. It is not planned to extend the participation of the cohort 1 subjects beyond season 1. Subjects from cohort 2 will be followed up for one season. If the study is extended to third season with protocol amendment, it will be determined by the amendment if they are offered possibility to continue their participation in the next season and new, relevant consent will be then collected.

A total of up to 10 sites will be selected to participate to the CMI substudy. Blood samples will be collected prior to the first study vaccination (Day 0) and approximately 15 days (day of the vaccination inclusive) after the second vaccination (Day 36, 14±2 days since day of the second vaccination) in 350 randomly chosen subset of subjects from these sites. M-001 subjects will be 3 times more likely to be selected in the subset than placebo subjects and T cell responses will be measured only in subjects who receive M-001.

11.3.2. Study Population and Sample Size

The study population for this clinical trial includes 12,000 males and non-pregnant females, ≥50 years old, inclusive, who meet all eligibility criteria. The participants will be recruited from the general population. At least half of the participants will be ≥65 years old.

The study sample size of 12,000 subjects is based on the lower bound of the two-sided 95% confidence interval for vaccine efficacy (VE) being above 40% with 80% probability when true VE is 62%. It assumes 1:1 randomization, a 2.41% attack rate in the study population, and no more than 10% of subjects lost to follow-up or excluded from the per protocol population. Under these assumptions, 182 first episodes of qRT-PCR -confirmed influenza of any strain occurring at least 15 days after the second dose of study vaccine or control and prior to the end of the first influenza season will be needed to demonstrate efficacy is at least 40%.

A total of up to 10 sites will be selected to participate to the CMI substudy. A total of 350 subjects will be randomly chosen among 700 subjects from the selected sites: approximately 263 subjects selected at random from 350 M-001 subjects and approximately 87 from 350 placebo subjects; placebo subjects being selected to maintain the study blind. Assuming that among the 263 M-001 selected subjects, 210 will have valid measurement for the change from baseline in percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001, then this endpoint can be estimated with a precision of at most 2% (1/2 width of the 95% CI).

11.3.3. Subject Enrollment and Follow-up

Based on the accrual rate for similar studies, it seems reasonable to expect that the participating sites will be able to enroll this trial in a timely fashion. Prior experience suggests up to 10% of subjects may be excluded from the per protocol analysis for the primary outcome either because they were lost-to-follow-up or otherwise do not have data available following the study vaccination or because they had a protocol deviation requiring their exclusion from the per protocol analysis.

11.4. Planned Interim Analyses

Interim unblinded analyses would be used to terminate this trial in the event that unanticipated safety events deemed to be of sufficient concern require such action by the sponsor. Sample size re-estimation at the end of Year 1 and possibly at the end of Year 2 will be based on the pooled number of influenza cases in the PP population and not on any interim estimate of efficacy or the observed attack rate in the control group. Details of the sample size re-estimation will be provided in the DSMB charter.

11.4.1. Interim Safety Review

A DSMB will be convened by the sponsor to review study progress and participant, clinical, safety, reactogenicity, and efficacy data as described in section 9.5. Once the last subject in Year 1 completes the visit that occurs approximately at Day 202, the clinical database will be cleaned, monitored and analyzed in blinded manner. The first partly unblinded report will be issued to the DSMB at the end of the first influenza season of the trial approximately in June 2019, though some

data may be requested by DSMB to be provided to them earlier. Based on the interim review of safety data, the DSMB may recommend continuing the study as planned, stopping the study for safety concerns, or modifying the study to ensure study objectives are followed.

11.4.2. Interim Efficacy Review

There are no plans to stop the trial for futility or for efficacy at the end of Year 1. However if after the first flu season the total number of per protocol cases of confirmed influenza infection is substantially fewer than there may be a decision made by the Sponsor about increasing the sample size for Year 2.

11.5. Final Analysis Plan

At the end of Year 2 a clinical study report (CSR) will be prepared (unless the study is decided to be continued for Year 3) summarizing the efficacy, safety, reactogenicity, and immunogenicity data. The clinical database will be cleaned, monitored, and locked prior to analysis.

A formal statistical analysis plan for the efficacy and immunogenicity data will be developed and finalized prior to start of the study. Any changes to the plan including post hoc analyses will be documented and clearly indicated in the CSR.

11.5.1. Analysis Populations

The Safety Analysis population includes all subjects who received at least one dose of study vaccine. Subjects in the safety population will be analyzed according to the treatment actually received.

The intent-to-treat (ITT) population includes all subjects who received at least one dose of study vaccine. Subjects in the ITT population will be analyzed according to their randomization.

The per protocol (PP) population includes all subjects in the ITT subset satisfying the following criteria:

- Subject met all protocol-specified inclusion criteria and met no exclusion criterion,
- Subject received both doses of M-001/placebo as randomized, in the protocol-specified time frame, and at the intended dose level,
- Subject did not receive M-001/placebo that was not properly handled or was otherwise not acceptable for administration,
- Subject had at least one successful surveillance contact 15 days or more after the second dose of M-001/placebo, or attended at least one ILI visit due to ILI symptoms
- Subject did not receive a seasonal influenza vaccine between randomization and end of the surveillance period for Season 1,
- Subject did not receive a licensed live vaccine within 30 days of any dose of M-001/placebo, and
- Subject did not receive a licensed non-live vaccine within 21 days of any dose of M-001/placebo.

11.5.2. Analysis of Safety Data

Summaries and analysis of safety data will be presented for the Safety Analysis Population.

Solicited events will be summarized by severity for each day after each study vaccination (Days 0-7 post each study vaccination, 8 days in total) and as the maximum severity over all 8 days (day of the vaccination inclusive). Additionally, solicited events will be analyzed by taking the most severe response over the follow-up period and using standard techniques, such as exact confidence intervals, to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom. Summaries of solicited events will be presented separately for each study vaccination as well as overall study vaccinations by treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact test, as appropriate. The proportion of subjects reporting solicited symptoms between the different study vaccinations (e.g., dose 1 vs. dose 2) will be compared using McNemar's test.

Unsolicited AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA®) for preferred term and system organ class (SOC). The number of SAEs is expected to be small in this trial and SAEs will be reported by detailed listings showing the event description, MedDRA® preferred term and SOC, relevant dates (study vaccinations and AEs), severity, relatedness, and outcome for each event. Non-serious unsolicited AEs will be summarized as number and percentage of subjects reporting at least one event in each MedDRA® preferred term and SOC, cross tabulated by severity and relationship to study product. Additionally, the proportion of subjects and exact 95% confidence intervals of AEs in aggregate and by MedDRA® categories will be computed.

Graphical presentations may include box plots and shift plots.

11.5.3. Analysis of Efficacy Data

Primary Efficacy Assessment

For the primary analysis of vaccine efficacy (VE), the efficacy of M-001 after a first influenza season in each cohort will be estimated by

$$VE = 1 - [(C_V / N_V) / (C_P / N_P)]$$

where C_V and C_P are the number of per protocol cases of influenza meeting the primary case definition in the vaccine and placebo group, respectively, and N_V and N_P are the number of per protocol subjects in the vaccine and placebo group, respectively. The confidence interval for VE will be calculated by the Clopper-Pearson exact method conditional on the total number of cases in the vaccine and placebo groups combined. Similarly, vaccine efficacy and its 95% confidence interval will be calculated for the ITT population.

VE and its 95% confidence interval will be estimated by age group (i.e., < 65 years, ≥ 65 years) for both the PP and ITT analysis populations. Given VE for a specific age group can be approximated

by 1 minus the age group specific odds ratio, the Breslow-Day test for the homogeneity of the odds ratios will be used to test for a common VE across age groups. In addition, given that circulating strains of flu may vary over the course of the trial, VE and its 95% confidence interval will be estimated by flu season as well for both the PP and ITT analysis populations; Breslow-Day test for the homogeneity of the odds ratios will be used to test for a common VE across cohort (flu season).

If the study discontinuation or loss to follow-up rate varies by vaccine group, a Cox proportional hazards model will be used to estimate vaccine efficacy. For this analysis, time from 15 days after the second dose of study vaccine or placebo to the first episode of culture or PCR confirmed influenza caused by any influenza A or B virus in association with a protocol-defined influenza like illness (ILI) will be the endpoint. All subjects will be censored at the earliest of their date of study withdrawal, date of lost to follow-up, or end of their first influenza season defined as April 30th for countries in the northern hemisphere. The model will have a single covariate for vaccine group and will be stratified by age group. Vaccine efficacy will be estimated by 1 minus the estimated hazard ratio from this model. If the lower limit of the 95% confidence interval for vaccine efficacy based on the PP population is above 40%, the vaccine will have demonstrated sufficient efficacy.

Kaplan-Meier plots of time to first episode by vaccine group will be generated.

Secondary Efficacy Assessments

The first secondary efficacy assessment will be analyzed using the same methodology than the one used for the primary endpoint (including the supportive and sensitivity analyses). Notice that samples with Ct ≤35 only will be grown for culture.

The second secondary efficacy assessment consisting in the between-group difference in average number of days with respiratory or systemic symptoms among subjects with laboratory-confirmed influenza illness will be tested in an ANOVA model with vaccine group, age category, and season/cohort as main factors.

The risk ratio for the total number of ILI events during the flu season will be compared between the vaccine groups using an overdispersed Poisson model with offset being the duration of follow-up in days and factors for vaccine group, age category and season/cohort.

All secondary efficacy assessments will be performed on the ITT and PP sets.

Exploratory efficacy assessments:

For both vaccine groups, the following proportions will be estimated with an exact 95% CI within the PP set

- Proportions of subjects taking antibiotics due to a post-influenza (laboratory confirmed) respiratory tract infection
- Proportions of subjects who died due to influenza-like illness with or without confirmation by viral culture and qRT-PCR analysis due to vaccination with M-001

Between-groups comparisons will be performed using Fisher's exact test.

For both vaccine groups, the following rates will be estimated on the PP set using a 95% CI based on

a Poisson model on the number of events with duration of follow-up (in days) as offset

- Rate of hospitalizations associated with ILI episodes over the flu season

Comparisons between the 2 groups will be performed on the basis of an overdispersed Poisson model with group as factor and duration of follow-up (in days) as offset. Incidence rate ratios between the 2 groups will be estimated and their 95% CI provided. Because it is expected that very few hospitalizations cases will occur, no additional factor will be included in the Poisson model.

Descriptive statistics for the specific influenza strains in confirmed flu cases in experimental and control groups will also be provided.

In addition, the following descriptive statistics will be provided to describe the ILI episodes:

- For the PP set, the distribution of influenza confirmed episodes
- For the PP set, the distribution of influenza confirmed episodes by severity.

Exploratory CMI assessment in substudy:

A subset of patients will be be enrolled in Season 2 to assess immunogenicity: the average percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001 measured at Day 36 (14±2 days since day of the second vaccination) and its two-sided 95% confidence interval will be calculated. Additional exploratory analyses to be performed on the immunogenicity data from these subjects will be detailed in a separate SAP for immunogenicity.

11.5.4. Missing Values and Outliers

All attempts will be made to collect all data per protocol. As missing data are expected to be minimal, no imputation will be performed for missing values. Any data point that appears to be erroneous or inexplicable based on clinical judgment will be investigated as a possible outlier. If data points are identified as outliers, sensitivity analyses will be performed to examine the impact of including or excluding the outliers. Any substantive differences in these analyses will be reported.

11.5.5. Statistical Software

Statistical analyses will be performed using SAS® version 9.4 or later under a Windows operating system.

12. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6, Section 4.9, and regulatory and institutional requirements for the protection of confidentiality of subjects. Each participating site will permit authorized representatives of the sponsor, its designees, and appropriate regulatory agencies to examine (and when required by applicable law, to copy) clinical study records for the purposes of quality assurance reviews, audits, monitoring and evaluation of the study safety and progress. These representatives will be permitted access to all source data, which include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the sponsor. Written instructions will be provided for collection, preparation, and shipment of blood samples and NP/nasal and throat swabs.

Guidelines for eCRF completion will be provided and reviewed with study personnel before the start of the study.

The sponsor will review eCRFs 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 entry of the data into the clinical study database they will be verified for accuracy.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

The investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

14.2. Ethics Committees and Competent Authorities

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities and ethics committees in each respective country, as applicable. The study may not be initiated until all local regulatory requirements are met.

At the end of the study, the investigator (or sponsor where required) will notify the relevant ethics committee about the study completion.

14.3. Informed Consent Process

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 by the reviewing ethics committee. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor's policy.

Before enrollment in the study, the investigator or an authorized member of the investigational staff must explain to potential subjects (or their legal representatives) 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 withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject can expect. Subjects will be told that alternative vaccines are available if they refuse to take part and that such refusal will not prejudice future access to an influenza vaccination as normally available country-specific. 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 and authorized sponsor staff without violating their confidentiality, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject (or legal representative) is authorizing such access, and agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent for additional safety evaluations, if needed, or to obtain information about his or her survival status.

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 the consent, a copy of the ICF must be given to the subject.

Depending on local regulations, if the subject is unable to read or write, an impartial witness should be present for the entire informed consent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent of the subject is obtained.

14.4. Exclusion of Women, Minorities, and Children (Special Populations)

This trial will be inclusive of all adults who meet the Subject Inclusion/Exclusion Criteria, regardless of religion, sex, or ethnic background. Should the outcome of this trial be deemed acceptable, additional trials may be initiated in other populations.

It is unknown if the M-001 vaccine poses any risks to an unborn child. Female subjects of childbearing potential who are not surgically sterile via tubal sterilization, bilateral oophorectomy, hysterectomy, or successful Essure® placement, or who are not postmenopausal for ≥ 1 year must agree to practice highly effective contraception that may include, but is not limited to, abstinence from intercourse with a male partner, monogamous relationship with a vasectomized partner, male condoms with the use of applied spermicide, intrauterine devices, and licensed hormonal methods, with use of a highly effective method of contraception for a minimum of 30 days prior to study product exposure and agree to practice highly effective contraception for the duration of study product exposure, including 2 months (defined as 60 days) after the last study vaccination (at least up to day 81 of the trial). A highly effective method of contraception is defined as one which results in a low failure rate when used consistently and correctly. In addition to contraceptive use, all female subjects of childbearing potential will be required to have a negative serum or urine pregnancy test within 24 hours prior to receiving each dose of study vaccine. If a female subject becomes pregnant while participating in this study, we will ask her permission to follow-up with her about her health and the health of her baby through pregnancy outcome.

In selected, individual cases, PI, where justified, may accept complete abstinence from sexual activity in women not having male partner as basis for considering such female subject as of no childbearing potential. Rationale for such decision must be available and documented.

Males whose female partner has childbearing potential, if not after vasectomy, must use condoms throughout the study treatment and for at least up to day 111 of the trial 90 days after the last dose of the IMP.

Children will not be included in this trial as presently there are no safety or efficacy data on this regimen in adults. Should the outcome of this trial be deemed acceptable, additional trials may be initiated in other populations.

14.5. Subject Confidentiality

Subjects will have code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the participating site PIs, their study personnel, the sponsor(s), and their agents according to the applicable laws including European Union General Data Protection Regulation 2016/679 (GDPR) where applicable. This confidentiality is extended to cover testing of biological samples, 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 trial or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All information provided by the Sponsor and all data and information generated by the participating sites as part of the trial (other than a subject's medical records) will be kept confidential by the site PI and other study personnel to the extent permitted by law. This information and data will not be used by the site PI or other study personnel for any purpose other than conducting the trial. These restrictions do not apply to: (1) information which becomes publicly available through no fault of the site PI or other study personnel; (2) information which is necessary to disclose in confidence to an ethics and/regulatory bodies solely for the evaluation of the trial (3) information which is necessary to disclose in order to provide appropriate medical care to a study subject; or (4) study results which may be published as described in Section 16. If a written contract for the conduct of the trial which includes confidentiality provisions inconsistent with this statement is executed, that contract's confidentiality provisions shall apply rather than this statement.

The study monitor, applicable regulatory authorities, such as the EMA, the FDA, or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the site PI. This includes, but is not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this trial. The participating sites will permit access to such records.

14.6. Study Discontinuation

If the trial is discontinued, subjects who have signed the ICF, and are randomized and vaccinated will continue to be followed for safety assessments. No further study vaccinations will be administered.

14.7. Costs, Subject Compensation, and Research Related Injuries

There is no cost to subjects for taking part in this trial.

Subjects may be compensated for their participation in this trial. Compensation will be in accordance with the local requirements and procedures, and subject to Ethics Committee approval.

If it is determined by the participating site and the site PI that an injury occurred to a subject as a direct result of the tests or treatments that are done for this trial, then referrals to appropriate health care facilities will be provided to the subject. Study personnel will try to reduce, control, and treat any complications from this trial. Immediate medical treatment may be provided by the participating site, such as giving emergency medications to stop immediate allergic reactions to the study vaccine. No financial compensation will be provided to the subject by the participating site for any injury suffered due to participation in this trial beyond that provided by clinical trial insurance.

14.8. Future Use of Stored Specimens

Subjects will be asked for permission to keep any remaining samples for possible use in future research studies, such as examining additional immunological assessments or testing for antibodies against other viruses or bacteria. Samples will be stored at a central clinical storage facility for future use and may be shared with investigators at the participating sites and with other investigators at other institutions. The samples will not be sold or used directly for production of any commercial product. No human genetic tests will be performed on samples. Each sample will be encoded (labeled) only with a barcode and a unique tracking number to protect subject's confidentiality.

There are no benefits to subjects in the collection, storage and subsequent research use of specimens. Reports about future research done with subject's samples will NOT be kept in their health records.

Any unused part of the NP/nasal and throat swab samples (including retention vials of universal transport media, tissue culture amplified isolates, and any repeat amplification harvests) will be securely stored at the CRO's site (including initial sample receiving laboratories and different testing laboratories) at least until publication of the final clinical study report (CSR). At any time during the 3 to 6 months before expiration of the CRO contract, the Sponsor may request that the CRO store these samples for a longer period, based on needs or requests. At any time during storage, the samples may be transferred to another Sponsor-approved laboratory.

14.9. Disclosure of Individual Research Information

In this protocol, it is not planned to provide each participant with a summary of overall study results as these will be generally published by the sponsor. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by international and local regulations. Disclosure of assignment to study arms for individual subjects can be provided during the study only based on justified urgent medical need as assessed by the sponsor, and after the study has been completed, as per local regulations and based on sponsor's decision.

15. DATA HANDLING AND RECORD KEEPING

The site PI is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported.

Data collection forms will be derived from the eCRF to record and maintain data for each subject enrolled in the study. All data collection forms should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making a change or correction, cross out the original entry with a single line and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the eCRF derived from the data collection forms should be consistent with the data collection forms or the discrepancies should be explained.

The sponsor and/or its designee will provide guidance to site PIs and other study personnel on making corrections to the data collection forms and eCRF.

15.1. Data Management Responsibilities

All data collection forms and laboratory reports must be reviewed by the site clinical team, who will ensure that they are accurate and complete. AEs must be recorded and assessed for severity and relationship, and reviewed by the site PI or appropriate SI.

Data collection is the responsibility of the study personnel at the participating sites under the supervision of the respective site PI. During the study, the site PI must maintain complete and accurate documentation for the study.

15.2. Data Capture Methods

All clinical trial information collected by the study personnel will be recorded electronically by the authorized persons using a web-based CRF (i.e., using an eCRF within the EDC system). The eCRF has been designed specifically for this trial under the responsibility of the Sponsor, using a validated Electronic Records/Electronic Signature-compliant platform (21 CFR Part 11). To ensure the correct and consistent completion of the eCRFs, the Sponsor will provide all necessary instructions, and training to all staff involved in data entry prior to granting them access to the EDC. Additional instructional documents such as training manuals and completion guidelines will be provided to assist with data entry during the course of the trial. Upon completion of training, each user requiring access to the EDC system will be issued individual username and password. In the event of a change in trial personnel, each newly assigned individual will receive individual, dedicated username and password. In case a user is no longer authorized to access the EDC, e.g. in case of departure from the study team, the Investigator or appropriate manager is responsible for informing the Sponsor immediately so that their access is deactivated. An audit trail will be available in the EDC system at the time of the first data entry in order to track all modifications and to ensure database integrity.

The study personnel performing data entry are responsible for the timeliness, completeness, and accuracy of the information in the eCRFs and must provide explanations for all missing information as requested by Sponsor or its designees.

15.3. Types of Data

Data for this study will include clinical, safety, and outcome measures (e.g., reactogenicity, efficacy (influenza confirmation) and possibly, immunogenicity data).

15.4. Timing/Reports

The primary clinical study report (CSR) will include clinical, safety, reactogenicity, efficacy and possibly, cellular immunogenicity data through the end of the last follow up period. At this time, the clinical database will be cleaned, monitored and locked. Unblinded analyses of safety, reactogenicity, and available PBMCs, including all primary and secondary endpoint data will be performed after the clinical database is locked. The CSR will be completed when all efficacy data are available.

Given the higher complexity of the data generation and analysis and increased time frame for completion of the exploratory studies, compared to the primary and secondary safety and efficacy assessments and analyses, the exploratory endpoint analysis will be optionally summarized in one or more addenda to the primary CSR. Of note, several of the exploratory studies are contingent upon the study team's approval for moving forward based on the results from the interim immunogenicity report.

After full analysis and final reporting is complete, and upon request and upon sponsor approval, the PIs from participating sites may be provided with a summary of results by treatment arm and/or subject treatment assignments. In this regard, the participating sites requesting such information to share with study subjects must do so in compliance with their respective legal regulations.

15.5. Study Records Retention

Study records and reports, including, but not limited to, eCRFs, source documents, ICFs, and study drug disposition records, shall be maintained for 2 years (or as required per applicable local regulations) after a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for the drug, until 2 years (or as required per applicable local regulations) after the investigation is discontinued and EMA has been so notified. The participating site must contact the sponsor for authorization prior to the destruction of any study records. Informed consent forms for future use will be maintained as long as the sample exists.

15.6. Protocol Deviations

As protocol deviation will be considered any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), or study manuals requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Sites are expected to maintain vigilance to identify deviations from the Protocol and address them as soon as possible including reporting of suspected major protocol deviations within 5 working days of its identification, or for deviations related to study schedule - within 5 working days of the scheduled protocol-required activity. Suspected major protocol deviations must be reported to the sponsor directly or to the sponsor's contracted representative (e.g. clinical research monitor or medical monitor). All deviations from the protocol must be addressed in study subject source documents. Protocol deviations must be sent to the local ethics committees per their requirements. The site PI/study staff is responsible for knowing and adhering to their ethics committees' requirements.

16. PUBLICATION POLICY.

Following completion or during the trial, the sponsor will be responsible for any publication. This clinical trial will be registered in a public trials registry.

17. SUPPLEMENTS/APPENDICES

None

18. SUMMARY OF CHANGES

List of changes vs. study protocol version 1.0 dated 21st February 2018

Description	Wording
Title page	
ClinicalTrials.gov identifier	
Original wording	TBD
New wording	NCT03450915
Version and date of the Protocol	
Original wording	Version 1.0 dated 21st February 2018
New wording	Version 2.0 dated 28th March 2018
INVESTIGATOR'S COMPLIANCE DECLARATION	
Change description	Whole paragraph and page removed from the protocol
New wording	
Protocol Synopsis	
ClinicalTrials.gov identifier	
Original wording	TBD
New wording	NCT03450915
Planned study duration	
Original wording	up to 3 years (3 consecutive flu seasons
New wording	up to 2 years (2 consecutive flu seasons)
Rationale for sample size	
Original wording	If after the first flu season the relative number of cases is **not met** (i.e., less than 82 cases), the DSMB may, following issuance of interim report #1, recommend increasing the sample size for Year 2. Otherwise, the sample size for Year 2 will remain at 5,296 subjects. The same methodology will be used after the second flu season by issuing interim report #2 and optionally extending the trial to year 3 with a third cohort.
New wording	If after the first flu season the total number of per protocol cases of confirmed influenza infection is substantially fewer than 82 cases, the DSMB may, following issuance of interim report #1, recommend increasing the sample size for Year 2. Otherwise, the sample size for Year 2 will remain at 5,296 subjects. Details for sample size re-estimation will be defined in the DSMB charter. The same methodology will be used after the second flu season by issuing interim report #2 and optionally extending the trial to year 3 with a third cohort based on amendment to the protocol which will be

	submitted in such case for ethics/regulatory approval.
Inclusion criteria	
#4	
Original wording	Women of childbearing potential (not surgically sterile or postmenopausal for greater than or equal to one year) and men must agree to practice adequate contraception
New wording	Women of childbearing potential (not surgically sterile or postmenopausal for greater than or equal to one year) and men must agree to practice adequate effective contraception
Exclusion criteria	
#5	
Original wording	An acute illness, including an axillary temperature greater than 38ºC, occurred within 1 week before first vaccination
New wording	An acute illness, including body temperature greater than 37.5ºC (axillary or forehead) or greater than 38.0 ºC (oral), or greater than 38.5ºC (ear/tympanic or rectal), occurred within 1 week before first vaccination
Criteria for evaluation	
Primary endpoint	
Original wording	To assess M-001 Safety by solicited local and systemic reactogenicity events occurring between 0 and 7 days following receipt of each of the two doses of M-001 or placebo and to assess SAEs, Medically Attended AEs (MAAEs) and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group.
New wording	To assess M-001 Safety by solicited local and systemic reactogenicity events occurring between 0 and 7 days following receipt of each of the two doses of M-001 or placebo and to assess SAEs, and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group. To assess M-001 Safety by occurrence of unsolicited AEs from the time of first study vaccination through 21 days after each M-001 vaccination
Original wording	protocol defined Influenza Like Illness (ILI is defined as symptoms that interfere with normal daily activities and that include one of the following respiratory symptoms (sore throat, cough, sputum production, nasal discharge, wheezing or difficult breathing) **and** at least one additional systemic symptom [fever (oral temperature >37.2°C), headache, myalgia and/or arthralgia, chills, and fatigue (tiredness for at least 12 hours)
New wording	protocol defined Influenza Like Illness (ILI is defined as symptoms that include one of the following respiratory symptoms (sore throat, cough, sputum production, nasal discharge or congestion, wheezing or difficult breathing) **and** at least one additional systemic symptom [fever (oral temperature >37.2°C for age 50-59, or >36.7°C for age

	60 or more, or increased ≥ 1.3°C from baseline), headache, myalgia and/or arthralgia, chills, and fatigue (tiredness for at least 12 hours)
Secondary endpoints	
Original wording	4. Compare the occurrence of qualitative PCR confirmed influenza in the M-001 experimental group *vs.* placebo (≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined ILI (ILI is defined as symptoms that interfere with normal daily activities and that include one of the following respiratory symptoms (sore throat, cough, sputum production, wheezing or difficult breathing) **and** at least one additional systemic symptom [fever (oral temperature >37.2°C), headache, myalgia and/or arthralgia, chills, and fatigue (tiredness)]. Nasopharyngeal swab will be collected from participants who meet the ILI definitions for PCR analysis of influenza A and/or B virus. 5. Reduced Severity of influenza illness ("breakthrough illness") Reduction of illness severity: The time to symptom alleviation/fever resolution ("alleviation/resolution"), which can be defined as the first time point at which all of the six influenza symptoms (body aches and pains, cough, fatigue, headache, nasal congestion, and sore throat) were either absent or mild and fever had resolved, with both (resolution of all 6 symptoms and fever) maintained for at least 21.5 hours (i.e., 24 hours minus 10%, i.e., lower limit of detection of an [approximately] 1 day improvement in resolution of illness). 6. To assess in at least a subset of samples the consistency of manufacturing between 3 batches of M-001 according to their T cell responses by ICS and FACS analysis for IFN-g production in PBMCs.
New wording	1. Compare the occurrence of qualitative PCR confirmed influenza in the M-001 experimental group *vs.* placebo (≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined ILI. Nasopharyngeal swab will be collected from participants who meet the ILI definition within 24 hours from ILI being reported to or identified by study personnel for PCR analysis of influenza A and/or B virus. (a nasal and throat sample will be collected if the participant object NP

	swab collection). 2. Percentage of subjects having ILI symptoms in the experimental and control group. 3. <u>Reduced Severity of influenza illness</u> Reduction of PCR confirmed influenza illness severity: The time to symptoms alleviation/fever resolution ("alleviation/resolution"), which can be defined as the first time point at which all of the following influenza symptoms (body aches (myalgia and/or arthralgia), cough, fatigue/tiredness, headache, nasal congestion/ runny nose/ sputum production, wheezing or difficult breathing, chills and sore throat) were absent and fever had resolved, with both (resolution of the symptoms and fever) maintained for at least one day. 4. To assess in at least a subset of samples the consistency of manufacturing between 3 batches of M-001 according to their T cell responses by ICS and FACS analysis for IFN-g production in PBMCs. 5. To assess the durability of vaccine efficacy over a second influenza season.
Exploratory endpoints	
Original wording	• Time to alleviation of <u>each</u> influenza symptom and time to resolution of fever • Incidence of physician-diagnosed secondary respiratory tract infections leading to a prescription for antibiotic therapy • Time to return to normal activity, as assessed on an 11-point visual analogue scale (VAS) • Incidence of clinic visits associated with the ILI episode (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director); A possibility of multiple visits per subject; each visit will be counted once in the analysis. • Incidence of hospitalization (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) • Incidence of confirmed pneumonia (by clinical diagnosis ≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) • Validated tool-based evaluation of change in severity of influenza-like illness • Incidence of death due to influenza-like illness (≥15 days after

	dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture or PCR analysis • Define influenza virus subtype in the swab samples
New wording	• Incidence of secondary respiratory tractinfectionsleading to a prescription for antibiotic therapy • Incidence of clinic visits associated with the ILI episode (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director); A possibility of multiple visits per subject; each visit will be counted once in the analysis. • Incidence of hospitalization associated with the ILI (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) • Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation of presence of influenza virus by viral culture or PCR analysis • To determine the specific influenza strains in flu cases in experimental and control group
Table 1	
Change description	Removed last column (titled "Season 3 (optional)")
Graph embedded within Table 1	
Original wording	≥82 cases observed
New wording	≥Cutoff[1]
Graph embedded within Table 1	
Change description	Removed last column from the graph (titled "Flu season 3?")
Table 1 *(text)*	
Original wording	Flexible enrollment scheme according to interim reports that will be issued after seasons 1 and 2.
New wording	Flexible enrollment scheme according to interim reports that will be issued after seasons 1 and 2. Flu season 3 is not planned. If decided that it is needed, protocol amendment will be issued and submitted for relevant approvals.
Table 2 *(list of procedures in column 1)*	
Original wording	Sign Consent Form1 Assess eligibility Review Medical & flu vaccination History2 Concomitant meds Vital signs, oral temp and pulse Physical examination Randomization Review contraception/ Counseling3 Pregnancy Test4

	AE/SAE Assessment Vaccination5 Evaluate vaccination site Postvaccination procedures6 Provision of Memory Aid Review of Memory Aid Data Collection of reportable medications Interim report Collection of ILI symptoms through passive and active surveillance Collection of nasopharyngeal swabs for laboratory confirmation of influenza Collection of disease burden and health care information Collection of information on SAEs
New wording	Consent process and Signed Consent Form1 Assess eligibility Demographic data and Review Medical & flu vaccination History2 Concomitant meds Vital signs Oral temperature Physical examination Randomization Review contraception/ Counseling3 Pregnancy Test4 AE/SAE Assessment Vaccination5 Evaluate vaccination site Postvaccination procedures6 Provision of Memory Aid Review of Memory Aid Data Interim report Collection of ILI symptoms through passive and active surveillance Collection of nasopharyngeal swabs for laboratory confirmation of influenza Collection of disease burden data and concomitant medications Collection of information on AEs, NOCIs, and SAEs
Table 2 *(plan of procedures)*	
Description of change	Procedure **Vital signs, oral temp and pulse** split to two procedures **Vital signs** and **Oral temperature. Vital signs** marked as to be done at **Visit 1, Oral temperature** marked as to be done at **Visit 1 and 2**
Table 2	
Collection of ILI symptoms through passive and active surveillance	

Original wording	**Active Surveillance:** Between November 15, 2018 and April 30, 2019, the dedicated study staff will contact subjects twice a week (see 7.3). Both passive and active surveillance will be replicated during second season (passive one starting on September 15, 2019).
New wording	**Active Surveillance:** Between November 15, 2018 and March 31, 2019, the dedicated study staff will contact subjects twice a week (see 7.3). Both passive and active surveillance for cohort 1 subjects will be replicated during second season (passive one starting on September 15, 2019).
Table 2	
Collection of nasopharyngeal swabs for laboratory confirmation of influenza	
Original wording	From Day 14 post vaccination until 30 April of the following year. Every effort must be made to obtain the NP specimen on the same or following day after reporting of qualifying symptoms and no later than 4 days (sample to be collected through Day 3 of the illness, considering that Day 0 is the day of illness onset) after onset of qualifying respiratory illness symptoms (start date).
New wording	From Day 14 post vaccination until 30 April of the following year. Every effort must be made to obtain the NP specimen on the same or following day after reporting of qualifying ILI symptoms and no later than 4 days (sample to be collected within 24 hours from ILI being reported to or identified by study personnel through Day 3 of the illness, considering that Day 0 is the day of illness onset) after onset of qualifying ILI symptoms (start date).
Table 2	
Collection of disease burden and health care information	
Original wording	At any time during the study year in association with a respiratory illness, and for up to 30 days following the start of a qualifying symptom.
New wording	At any time during the study a disease burdenand concomitant medications in association with ILI, and for up to 30 days following the start of a qualifying ILI symptoms. All other concomitant medications from 3 months before V1.
Table 3 *(list of procedures in column 1)*	
Original wording	Sign Consent Form1

	Assess eligibility Review Medical & flu vaccination History2 Concomitant meds Vital signs, oral temp and pulse Physical examination Randomization Review contraception/ Counseling3 Pregnancy Test4 Blood sample for CMI (40 mL, Subset) AE/SAE Assessment Vaccination5 Evaluate vaccination site Postvaccination procedures6 Provision of Memory Aid7 Review of Memory Aid Data Collection of reportable medications Interim Report8 Collection of ILI symptoms through passive and active surveillance for a total of 9,630 participants from seasons 1 and 2. Collection of nasopharyngeal swabs for laboratory confirmation of influenza for a total of 9,630 participants from seasons 1 and 2. Collection of disease burden and health care information for a total of 9,630 participants from seasons 1 and 2. Collection of information on SAEs for a total of 9,630 participants from seasons 1 and 2.
New wording	Consent process and Signed Consent Form1 Assess eligibility Demographic data, Review Medical & flu vaccination History2 Concomitant meds Vital signs Oral temperature Physical examination Randomization Review contraception/ Counseling3 Pregnancy Test4 Blood sample for CMI (40 mL, Subset) AE/SAE Assessment Vaccination5 Evaluate vaccination site Postvaccination procedures6 Provision of Memory Aid7 Review of Memory Aid Data Interim Report/Final Report8

	Collection of ILI symptoms through passive and active surveillance for all participants from seasons 1 and 2. Collection of nasopharyngeal swabs for laboratory confirmation of influenza for all participants from seasons 1 and 2. Collection of disease burden data and concomitant medications for all participants from seasons 1 and 2. Collection of information on AEs, NOCIs, and SAEs for all participants from seasons 1 and 2.
Table 3 *(plan of procedures)*	
Description of change	Procedure **Vital signs, oral temp and pulse** split to two procedures **Vital signs** and **Oral temperature. Vital signs** marked as to be done at **Visit 1, Oral temperature** marked as to be done at **Visit 1 and 2**
Table 3	
Collection of ILI symptoms through passive and active surveillance	
Original wording	**Active Surveillance:** Between November 15, 2019 and April 30, 2020, the dedicated study staff will contact subjects twice a week (see 7.3).
New wording	**Active Surveillance:** Between November 15, 2018 and March 31, 2019, the dedicated study staff will contact subjects twice a week (see 7.3).
Table 3	
Collection of nasopharyngeal swabs for laboratory confirmation of influenza	
Original wording	From Day 14 post vaccination until 30 April of the following year. Every effort must be made to obtain the NP specimen on the same or following day after reporting of qualifying symptoms and no later than 4 days (sample to be collected through Day 3 of the illness, considering that Day 0 is the day of illness onset) after onset of qualifying respiratory illness symptoms (start date).
New wording	From Day 14 post vaccination until 30 April of the following year. Every effort must be made to obtain the NP specimen on the same or following day after qualifying ILI symptoms being reported to or identified by study personnel and no later than 4 days (sample to be collected through Day 3 of the illness, considering that Day 0 is the day of illness onset) after onset of qualifying ILI symptoms (start date).

Table 3	
Collection of disease burden and health care information	
Original wording	At any time during the study year in association with a respiratory illness, and for up to 30 days following the start of a qualifying symptom.
New wording	At any time during the study a disease burdenand concomitant medications in association with ILI, and for up to 30 days following the start of a qualifying ILI symptoms. All other concomitant medications from 3 months before V1.
Denotes for Table 2 and 3	
Original wording	[6] Post-vaccination procedures will include documentation of any reactogenicity during the observation period and any AEs/SAEs post-vaccination, as well as provision of memory aid and instructions on completion. (…) **#AEs will be limited to SAEs if after 21 days after the last study vaccination.**
New wording	[6] Post-vaccination procedures will include documentation of any reactogenicity during the observation period and any AEs/SAEs post-vaccination (i.e. with onset before the participant leaves the site after receipt of the study drug injection), as well as provision of memory aid and instructions on completion. (…) **#From seven days after the study vaccination AEs related to vaccination will no longer be collected as solicited AEs Occurrence of unsolicited AEs will be analyzed from the time of first study vaccination through 21 days after each M-001 vaccination.**
BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE	
Potential Risks	
Original wording	The procedure for collection of an NP, nasal or throat swab is associated with a slight discomfort, and may, in some instances, cause watering of the eyes or gag reflex. Other than that, there is little to no risk involved. (…)

	A highly effective method of contraception is defined as one which results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly.
New wording	The procedure for collection of an NP, deep nasal or throat swab is associated with a slight discomfort, and may, in some instances, cause watering of the eyes or gag reflex. Other than that, there is little to no risk involved. (…) A highly effective method of contraception is defined as one which results in a low failure rate when used consistently and correctly.
OBJECTIVES	
Primary Objectives	
Original wording	To assess M-001 Safety by solicited local and systemic reactogenicity events occurring between 0 and 7 days following receipt of each of the two doses of M-001 or placebo and to assess SAEs, Medically Attended AEs (MAAEs) and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group.
New wording	To assess M-001 Safety by solicited local and systemic reactogenicity events occurring between 0 and 7 days following receipt of each of the two doses of M-001 or placebo and to assess SAEs and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group.
Secondary Objectives	
Original wording	2. Reduced Severity of influenza illness (“breakthrough illness”) by the time to symptom alleviation/fever resolution (“alleviation/resolution”). (…) 5. To assess influenza strain specific vaccine efficacy.
New wording	2. Reduced Severity of PCR-confirmed influenza illness by the time to symptom alleviation/fever resolution (“alleviation/resolution”). (…) 5. To assess proportion of subjects having ILI symptoms in the experimental or control group.
Exploratory Objectives	
Original wording	• Time to alleviation of <u>each</u> influenza symptom and time to resolution of fever • Incidence of physician-diagnosed secondary respiratory tract infections leading to a prescription for antibiotic therapy • Time to return to normal activity, as assessed on an 11-point visual analogue scale (VAS) • Incidence of clinic visits associated with the ILI episode (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director); A possibility of

	multiple visits per subject; each visit will be counted once in the analysis. • Incidence of hospitalization (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) • Incidence of confirmed pneumonia (by clinical diagnosis ≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) • Change in severity of influenza-like illness (using validated tool) • Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture or PCR analysis • Define influenza virus subtype in the swab samples
New wording	• Incidence of secondary respiratory tract infections leading to a prescription for antibiotic therapy • declared by the participant • Incidence of clinic visits associated with the ILI episode (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director); A possibility of multiple visits per subject; each visit will be counted once in the analysis. • Incidence of hospitalization associated with the ILI (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) • Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture or PCR analysis • To determine the specific influenza strains in flu cases in experimental and control group
Study Outcome Measures	
Primary Outcome Measures	
Clinical efficacy	
Original wording	protocol defined Influenza Like Illness (ILI is defined as symptoms that interfere with normal daily activities and that include one of the respiratory symptoms (sore throat, cough, sputum production, nasal discharge, wheezing or difficult breathing) and at least one additional systemic symptom [fever (oral temperature >37.2°C), headache, myalgia and/or arthralgia, chills, and fatigue (tiredness for at least 12 hours)]. NP swab will be collected from participants who meet the ILI definitions for qualitative PCR analysis of influenza A and/or B virus. PCR confirmed samples will be further analyzed by culture confirmed influenza testing.

New wording	protocol defined Influenza Like Illness (ILI is defined as symptoms that include one of the respiratory symptoms (sore throat, cough, sputum production, nasal discharge or congestion, wheezing or difficult breathing) and at least one additional systemic symptom [fever (oral temperature >37.2°C for age 50-59, or >36.7°C for age 60 or more, or increased ≥ 1.3°C from baseline), headache, myalgia and/or arthralgia, chills, and fatigue (tiredness for at least 12 hours)]. NP swab will be collected from participants who meet the ILI definitions within 24 hours from ILI being reported to or identified by study personnel for qualitative PCR analysis of influenza A and/or B virus. PCR confirmed samples will be further analyzed by culture confirmed influenza testing.
Secondary Outcome Measures	
Clinical efficacy	
Original wording	protocol defined Influenza Like Illness (ILI is defined as symptoms that interfere with normal daily activities and that include one of the respiratory symptoms (sore throat, cough, sputum production, nasal discharge, wheezing or difficult breathing) and at least one additional systemic symptom [fever (oral temperature >37.2°C), headache, myalgia and/or arthralgia, chills, and fatigue (tiredness for at least 12 hours)]. NP swab will be collected from participants who meet the ILI definitions for qualitative PCR analysis of influenza A and/or B virus. (…) • Average time to symptom alleviation/fever resolution in the experimental vs control group. “alleviation/resolution” time is defined as the first time point at which all of the six influenza symptoms (body aches and pains, cough, fatigue, headache, nasal congestion, and sore throat) were either absent or mild and fever had resolved, with both (resolution of all 6 symptoms and fever) maintained for at least 21.5 hours (i.e., 24 hours minus 10%, i.e., lower limit of detection of an [approximately] 1 day improvement in resolution of illness).
New wording	protocol defined Influenza Like Illness. NP swab will be collected from participants who meet the ILI definitions within 24 hours from ILI being reported to or identified by study personnel for qualitative PCR analysis of influenza A and/or B virus. (…) • Average time to symptom alleviation/fever resolution in the experimental vs control group. “alleviation/resolution” time is defined as the first time point at which all of the following influenza symptoms (body aches (myalgia and/or arthralgia), cough, fatigue/tiredness, headache, nasal congestion/ runny nose/ sputum production, wheezing or difficult breathing, chills and sore throat)

	were absent and fever had resolved, with both (resolution of all symptoms and fever) maintained for at least 1 day. • To assess the durability of vaccine efficacy over a second influenza season
Exploratory Outcome Measures	
Original wording	• Average time to alleviation of each influenza symptom and time to resolution of fever • Reduced incidence of physician-diagnosed secondary respiratory tract infections leading to a prescription for antibiotic therapy in the experimental group as compared to the control group. • Shorter time to return to normal activity, as assessed on an 11-point visual analog scale (VAS) in the experimental group as compared to the control group. • Lower incidence of clinic visits (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director) in the experimental group as compared to the control group; A possibility of multiple visits per subject; each visit will be counted once in the analysis. • Lower incidence of hospitalization (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group. • Lower incidence of confirmed pneumonia as defined by a physician (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group. • Lower severity of influenza-like illness according to a validated tool-based evaluation of change in severity in the experimental group as compared to the control group, with or without confirmation by viral culture or PCR analysis. • Lower incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group, with or without confirmation by viral culture or PCR analysis. • Define influenza virus subtype in the swab samples to compare the viruses causing disease in the experimental vs control group
New wording	• Incidence of secondary respiratory tract infections leading to a prescription for antibiotic therapy in the experimental group as compared to the control group. In case of lack of documented medical record subject's provided information will be sufficient. • Incidence of clinic visits (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director) in the experimental group as compared to the control group;

	A possibility of multiple visits per subject; each visit will be counted once in the analysis. • Incidence of hospitalization associated with ILI (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group. • Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group, with or without confirmation by viral culture or PCR analysis. • Define influenza virus subtype in the swab samples to compare the viruses causing disease in the experimental vs control group
STUDY DESIGN	
Original wording	Unsolicited non-serious AEs will be collected from the time of each M-001 vaccination through approximately 21 days after each study vaccination. SAEs will be collected from the time of the first study vaccination through approximately 6 months after the last study vaccination. Immunogenicity testing will include performing CMI assays on blood samples obtained immediately at baseline (Day 1) and on samples collected on Days 37 from a subset of 275 participants randomly selected from experimental group receiving each of the 3 batches used in the trial (total of 825). Cell mediated immune responses to influenza antigens, including epitopes represented in the M-001 vaccine, will be assessed at baseline (Day 1), at 16 days after the second M-001 vaccination (Days 37).
New wording	Unsolicited non-serious AEs collected from the time of each M-001 vaccination through approximately 21 days after each study vaccination will be analyzed separately. SAEs will be collected from the time of the first study vaccination through the entire trial period. In cohort 2, immunogenicity testing will be performed and will include performing CMI assays on blood samples obtained immediately at baseline (Day 1) and on samples collected on Days 37 from a subset of 275 participants randomly selected from experimental group receiving each of the 3 batches used in the trial (total of 825). Cell mediated immune responses to influenza antigens, including epitopes represented in the M-001 vaccine, will be assessed at baseline (Day 1), at 16 days after the second M-001 vaccination (Days 37).
STUDY ENROLLMENT AND WITHDRAWAL	

Subject Inclusion Criteria	
#4	
Original wording	Women of childbearing potential (not surgically sterile or postmenopausal for greater than or equal to one year) and men must agree to practice adequate contraception
New wording	Women of childbearing potential (not surgically sterile or postmenopausal for greater than or equal to one year) and men must agree to practice adequate effective contraception
Subject Exclusion Criteria	
#5	
Original wording	5. An acute illness, including an axillary temperature greater than 38ºC, occurred within 1 week before first vaccination
New wording	5. An acute illness, including body temperature greater than 37.5ºC (axillary or forehead) or greater than 38.0 ºC (oral), or greater than 38.5ºC (ear/tympanic or rectal), occurred within 1 week before first vaccination.
STUDY INTERVENTION/INVESTIGATIONAL PRODUCT	
Concomitant Medications/Treatments	
Original wording	Used and unused vials of M-001 will be retained until monitored and released for disposition as applicable. Upon completion or termination of the study and after the final monitoring visit, final disposition of unused study products and sterile empty vials will be determined by the CRO. (…) Subjects who do not receive both M-001 study vaccinations will have concomitant medications collected through approximately 21 days after the first study vaccination, or early termination, whichever occurs first. Medications reported in the electronic case report form (eCRF) are limited to those taken within 30 days prior to the first study vaccination through approximately 21 days after the last M-001 study vaccination. (…) Use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.
New wording	Used and unused vials of M-001 will be retained until monitored and released for disposition as applicable. Upon completion or termination of the study and after the final monitoring visit, final disposition of unused study products and sterile empty vials will be determined by the Sponsor.

	(…) After Day 43 only concomitant medications relevant for respiratory illness as per PI judgment, or related to AE or ILI will be recorded. Subjects who do not receive both M-001 study vaccinations will have all concomitant medications collected through approximately 21 days after the first study vaccination, or early termination, whichever occurs first. (…) Identified use of new medication should prompt evaluation for the presence of a new diagnosis of chronic medical disease or condition.
STUDY SCHEDULE	
Enrollment/Baseline	
Original wording	All concomitant medications taken within 30 days prior to signing the ICF will be recorded on the appropriate data collection form prior to the first study vaccination
New wording	All concomitant medications taken within 3 months prior to signing the ICF will be recorded on the appropriate data collection form prior to the first study vaccination
Second Vaccination	
Original wording	• If indicated by review of memory aid, obtain vital signs and temperature.
New wording	• If indicated by review of memory aid, obtain vital signs • Measure oral temperature.
Follow up period for safety and efficacy	
Original wording	*Active efficacy surveillance* will be performed from November 15th until the week of 30 April the following year (…) During the passive and active efficacy surveillance period participants suffering from ILI will be asked to provide information on the symptoms as they develop using standardized sets of questions (…) NP swab specimens will be collected within 4 days of the onset of ILI symptoms (…) following the onset of the respiratory illness. (…) **The influenza peak season will be defined for each participating country by the Medical director based on national surveillance and study data** (…) Respiratory Illness follow-up calls: Any ILI must be followed up for 30 days following the start date or until resolved. Information on symptom type and duration, occurrence of pneumonia and new onset or exacerbations of cardio-respiratory conditions, healthcare utilization, and medication use

	temporally associated with the respiratory illness will be collected by study staff through a telephone call performed up to 30 days following the illness start date. (…) All NP specimens will be submitted for analysis by polymerase chain reaction (RT-PCR), and when the result is found positive, the second aliquot from such specimen will be also examined by culture confirmation test
New wording	Active efficacy surveillance will be performed from November 15th until the week of 30 March the following year (…) During the passive and active efficacy surveillance period participants suffering from ILI will be asked to provide information on the symptoms as they develop using also standardized sets of questions (…) NP swab specimens will be collected within 24 hours from ILI being reported to or identified by study personnel and up to 4 days of the onset of ILI symptoms (…) following the onset of the ILI (…) **The end of influenza season will be defined for each participating country by the Medical director based on national surveillance and study data** (…) ILI follow-up calls: Any ILI must be followed up for up to 30 days following the start date or until resolved. Sites will follow up the participant with ILI at 10±3 days after ILI start date. Follow up information on symptoms associated with the ILI will be collected by study staff through a telephone call performed at 10±3 days (and up to 30 days) (unless collected at unscheduled clinic visit at relevant time point) following the illness start date. (…) All NP specimens will be submitted for analysis by polymerase chain reaction (RT-PCR), and when the result is found positive, another aliquot from such specimen will be also examined by culture confirmation test.
Follow Up Period for Efficacy Season 2	
Original wording	Active surveillance will take place between November 15, 2019 and April 30, 2020.
New wording	Active surveillance will take place between November 15, 2019 and March 30, 2020.

Follow Up Period for Efficacy Season 3	
Original wording	This 3rd season follow up period will take place according to the sponsor decision based on the outcomes of interim report #2. If the ILI attack rate in the study population is too low in season 1 and season 2, the sponsor will advise if and how to proceed. If the primary endpoints are achieved, this follow-up period will take place to complete the 2nd year follow up for cohort 2 to define the 2 years duration of the protection. Passive and active surveillance will take place as detailed for season 1 (see 7.3). Passive surveillance will take place between September 15, 2020 till May 15, 2021. Active surveillance will take place between November 15 2020 until the week of 30 April 2021. During this period, the dedicated study staff will contact the participants twice a week to remind and record ILI and respiratory symptoms as detailed above.
New wording	Season 3 is not planned and is not encompassed by this study protocol.
Unscheduled Visit	
Original wording	Review memory aid (if within 8 days after the previous study vaccination, inclusive of vaccination day). (…) • If indicated by medical history, obtain vital signs and oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. • A targeted physical examination may be performed by a study clinician, if indicated based on review of interim medical history.
New wording	Review memory aid (if within 21 days after the previous study vaccination, inclusive of vaccination day). (…) • If deemed as relevant and/or needed, perform physical examination and obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature.
STUDY PROCEDURES/EVALUATIONS	
Original wording	*Concomitant Medications*: All current medications and medications taken in the 30 days before Study Day 1 (prescription and over-the-counter drugs) will be included, as well as vitamins and supplements, through 21 days after the last study injection. Assessment of eligibility also will include a review of prohibited medications (per the exclusion criteria).

	Vital signs: oral temperature and pulse will be collected at each of the study visits when a study vaccination is scheduled [Day 1 (Visit 1)] and as needed at the other study visits. (…) *Reactogenicity Assessments*: This will include an assessment of solicited AEs occurring from the time of each M-001 study vaccination [Day 1 (Visit 1), Day 22 (Visit 2] through 8 days after the study vaccination (inclusive of vaccination day), which includes an assessment of erythema/redness, induration/swelling, pain, tenderness, ecchymosis and pruritus at the injection site; fever, chills, fatigue, malaise, body aches (exclusive of injection site), arthralgia (exclusive of injection site), headache, and nausea. (…) *Questionnaires*: questionnaire(s) for collection of information on ILI clinical presentation, impact on subject, duration etc. will be used in the study.
New wording	*Concomitant Medications*: All current medications and medications taken within 3 months before Study Day 1 (prescription and over-the-counter drugs) will be included, as well as vitamins and supplements, through 21 days after the last study injection *Vital signs*: blood pressure, oral temperature and pulse will be collected at study visit 1,on early termination visit and as needed at the other study visits. Only oral temperature will be measured on visit 2. (…) *Reactogenicity Assessments*: This will include an assessment of solicited AEs occurring from the time of each M-001 study vaccination [Day 1 (Visit 1), Day 22 (Visit 2] through 8 days after the study vaccination (inclusive of vaccination day), which includes an assessment of systemic reactions (Fever; Decreased blood pressure and/or dizziness; Chills and/or sweating; Joint and/or muscle pain; Headache; Nasal congestion, runny nose, phlegm production, rhinitis; Problems with breathing (difficulty breathing, wheezing); General malaise, fatigue, loss of appetite; Itching on body/ pruritus; Swelling/tender lymph nodes; Irritability; Rash; Cough; Sore throat; Stomach problems (abdominal pain, diarrhea, nausea, vomiting)) and local – injection site reactions (Blue spot/ bruising; Induration / Swelling; Redness / Warmth; Itching),Pain/ tenderness (…) *Questionnaires*: information on ILI clinical presentation, duration etc. will be collected in the study by study personnel.

ASSESSMENT OF SAFETY	
Specification of Safety Parameters	
Original wording	1. SAEs, MAAEs, and NOCIs occurring from the time of the first study vaccination through subjects' participation in the trial. 2. Solicited AEs – reactogenicity events occurring on the day of each study vaccination through 7 days* after each study vaccination: *Vaccination day is considered Day 1, with 7 days following (8 total days) a) Injection site reactions including pruritus, ecchymosis, erythema, induration, swelling, pain and tenderness. b) Systemic reactions including fever, feverishness, fatigue, malaise, myalgia, arthralgia, headache and nausea.
New wording	1. SAEs and NOCIs occurring from the time of the first study vaccination through subjects' participation in the trial. 2. Solicited AEs – reactogenicity events occurring on the day of each study vaccination through 7 days* after each study vaccination: *Vaccination day is considered Day 1, with 7 days following (8 total days) a) Injection site reactions including pruritus, ecchymosis, erythema,warmth, induration, swelling, pain and tenderness. b) Systemic reactions including fever, feverishness, general malaise, fatigue, loss of appetite, myalgia or arthralgia, decreased blood pressure or dizziness, chills and/or sweating, nasal congestion, runny nose, phlegm production, rhinitis, problems with breathing (difficulty breathing, wheezing), itching on body/ pruritus, swelling/tender lymph nodes, irritability, rash, cough, sore throat, headache and stomach problems (abdominal pain, diarrhea, nausea, vomiting).
Safety Assessment	
Original wording	Information to be collected for unsolicited AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product and alternate etiology (…) The relationship to study product must be assessed for AEs using the terms: related or not related. In a clinical trial, the study product should be considered as potential 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 – There is not a reasonable possibility that the administration of the study product caused the event. (…)

	9.2.3. Additional Adverse Event Severity Grading Pulse will be graded according to the PI/SI judgment taking into consideration subject's medical history, concomitant medications, and baseline values
New wording	Information to be collected for AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product and alternate etiology (…) . The relationship to study product must be assessed for AEs using the terms: none, unlikely, possible, probable, certain. In a clinical trial, the study product should be considered as potential suspect. To help assess, the following guidelines are used: • NONE no evidence of any causal relationship is present. • UNLIKELY There is only little evidence to suggest there may be a causal relationship. Another reasonable explanation for the event exists (medical history, treatment) • POSSIBLE There is some evidence to suggest a causal relationship but the influence of other factors has been reasonably possible • PROBABLE There is a reasonable evidence to suspect a causal relationship, and the relevant influence of other factors is less likely. • CERTAIN - There is clear evidence for the causal relationship, and other reason is very unlikely (…) 9.2.3. Additional Adverse Event Severity Grading Pulse and Blood pressure changes will be graded according to the PI/SI judgment taking into consideration subject's medical history, concomitant medications, and baseline values.
Table 7	
Description of change	One row added to the table. Two references added to the title of the table (20 and 21)
Table 7	
Original wording	Fever* - oral† 38.0°C – 38.4°C 38.5°C – 38.9°C >38.9°C
New wording	(Age <60) Fever* - oral† 38.0°C – 38.4°C 38.5°C – 38.9°C >38.9°C (Age 60+) Fever* - oral† 37.3.0°C – 37.7°C 37.8°C – 38.2°C >38.2°C
Reporting Procedures	

Original wording	Unsolicited non-serious AEs will be documented from the time of the first study vaccination (Day 0 (Visit 1)) through approximately 8 days after the last study vaccination (approximately Day 30.
New wording	Unsolicited non-serious AEs will be documented from the time of the first study vaccination until study completion by the subject.
Serious Adverse Events	
Original wording	Medical Monitor will review SAE report(s) within 24 hours from receipt and assess the SAE for regulatory reporting and potential impact on study subject safety and protocol conduct together with Sponsor. SAE reports are shared with DSMB.
New wording	SAE report(s) within 24 hours from receipt will be reviewed and assessed for regulatory reporting and potential impact on study subject safety and protocol. SAE reports are shared with DSMB.
Reporting of Pregnancy	
Original wording	Pregnancies occurring in study subjects will be reported via Pregnancy Report Form (paper) and thru EDC
New wording	Pregnancies occurring in study subjects will be reported via Pregnancy Report Form (paper) and recorded in the EDC under SAE category
Type and Duration of Follow-up of Subjects after Adverse Events	
Original wording	AEs will be followed from the time of the first study vaccination (Day 1 (Visit 1)) through approximately 8 days after the last study vaccination (approximately Day 30). SAEs will be followed from the time of the first study vaccination (Day 1 (Visit 1)) through resolution even if this extends beyond the study-reporting period. Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.
New wording	AE will be followed until it reaches a satisfactory resolution, or becomes stable, or clinical judgment indicates that further evaluation is not warranted. Resolution of an AE/SAE is defined as the return to pretreatment status or stabilization of the condition with the expectation that it will remain chronic.
STATISTICAL CONSIDERATIONS	
Sample Size Considerations	
Study design	
Original wording	All subjects from cohort 1 will be followed for up to two consecutive influenza seasons with no obligation to continue in season 3 if the study is extended to third season. Subjects from cohort 2 will be followed up for two consecutive influenza seasons if such decision

	(of study extension to season 3) is made based on review of study data available after season 2.
New wording	All subjects from cohort 1 will be followed for up to two consecutive influenza seasons with no obligation to continue in season 3 if the study is extended to third season with protocol amendment. Subjects from cohort 2 will be followed up for one season. If the study is extended to third season with protocol amendment, it will be determined by the amendment if they are offered possibility to continue their participation in the next season and new, relevant consent will be then collected.
Interim Efficacy Review	
Original wording	There are no plans to stop the trial for futility or for efficacy at the end of Year 1. However, if fewer than 80 per protocol cases of influenza are observed at the end of Year 1, the DSMB may recommend increasing the sample size for Year 2. The sample size re-estimation plan will be detailed in the DSMB charter. The final analysis of vaccine efficacy will be carried out at the end of Year 2 unless the number of per protocol cases by the end of Year 2 is remarkably less than the planned 182 events. If too few influenza cases are observed, the DSMB may recommend extending enrollment and stud conduct for a third year (season). The exact increase in sample size will be detailed in the charter. Subjects enrolled in Year 3 would be vaccinated using Lot 2 (produced in Israel).
New wording	There are no plans to stop the trial for futility or for efficacy at the end of Year 1. However if after the first flu season the total number of per protocol cases of confirmed influenza infection is substantially fewer than 82 cases, the DSMB may recommend increasing the sample size for Year 2. The sample size re-estimation plan will be detailed in the DSMB charter. The final analysis of vaccine efficacy will be carried out at the end of Year 2 unless the number of per protocol cases by the end of Year 2 is remarkably less than the planned 182 events. If too few influenza cases are observed, the DSMB may recommend extending enrollment and stud conduct for a third year (season). The exact increase in sample size will be detailed in the charter.
Final Analysis Plan	
Original wording	At the end of Year 2 (or Year 3 if a third cohort is enrolled), a clinical study report (CSR) will be prepared summarizing the efficacy, safety, reactogenicity, and immunogenicity data. The clinical database will be cleaned, monitored, and locked prior to analysis.
New wording	At the end of Year 2 a clinical study report (CSR) will be prepared summarizing the efficacy, safety, reactogenicity, and immunogenicity data. The clinical database will be cleaned, monitored, and locked prior to analysis.
Analysis of Safety Data	

Original wording	The numbers of SAEs and MAAEs are expected to be small in this trial and will be reported by detailed listings showing the event description, MedDRA® preferred term and SOC, relevant dates (study vaccinations and AEs), severity, relatedness, and outcome for each event.
New wording	The numbers of SAEs is expected to be small in this trial and will be reported by detailed listings showing the event description, MedDRA® preferred term and SOC, relevant dates (study vaccinations and AEs), severity, relatedness, and outcome for each event.
ETHICS/PROTECTION OF HUMAN SUBJECTS	
Exclusion of Women, Minorities, and Children (Special Populations)	
Original wording	Female subjects of childbearing potential who are not surgically sterile via tubal sterilization, bilateral oophorectomy, or hysterectomy or who are not postmenopausal for ≥ 1 year must agree to practice highly effective contraception that may include, but is not limited to, abstinence from intercourse with a male partner, monogamous relationship with a vasectomized partner, male condoms with the use of applied spermicide, intrauterine devices, and licensed hormonal methods, with use of a highly effective method of contraception for a minimum of 30 days prior to study product exposure and agree to practice highly effective contraception for the duration of study product exposure, including 2 months (defined as 60 days) after the last study vaccination.
New wording	Female subjects of childbearing potential who are not surgically sterile via tubal sterilization, bilateral oophorectomy, hysterectomy, or successful Essure® placement, or who are not postmenopausal for ≥ 1 year must agree to practice highly effective contraception that may include, but is not limited to, abstinence from intercourse with a male partner, monogamous relationship with a vasectomized partner, male condoms with the use of applied spermicide, intrauterine devices, and licensed hormonal methods, with use of a highly effective method of contraception for a minimum of 30 days prior to study product exposure and agree to practice highly effective contraception for the duration of study product exposure, including 2 months (defined as 60 days) after the last study vaccination (at least up to day 81 of the trial).
Study Discontinuation	
Original wording	If the trial is discontinued, subjects who sign the ICF, and are randomized and vaccinated will continue to be followed for safety assessments.

New wording	If the trial is discontinued, subjects who have signed the ICF, and are randomized and vaccinated will continue to be followed for safety assessments.
DATA HANDLING AND RECORD KEEPING	
Timing/Reports	
Original wording	The CSR will be completed when all efficacy data for day 202 and for the follow up period of season 2 or season 3 are available.
New wording	The CSR will be completed when all efficacy data for day 202 and for the follow up period of season 2 are available.
LITERATURE REFERENCES	
Description of change	Two literature positions added: [20] https://www.ncbi.nlm.nih.gov/pubmed/19886869 [21] http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0110927#pone.0110927-Katz1
SUMMARY OF CHANGES	
Description of change	Summary of changes vs previous version of the protocol added.

List of changes of study protocol version 3.0 vs. study protocol version 2.0 dated 28th March 2018

Description	Wording
Title page	
Version and date of the Protocol	
Original wording	Version 2.0 dated 28th March 2018
New wording	Version 3.0 dated 02nd June 2018
Investigator's compliance declaration	
Original wording	Protocol: BVX-010,
New wording	Protocol: BVX-010, version 3.0 dated June 02nd 2018
TABLE OF CONTENTS	
Description of change	Updated
LIST OF ABBREVIATIONS	
Description of change	Added abbreviations: CMI- Cell-mediated immunity, ICS - Intra Cellular Staining, IFN-g - Interferon gamma, NOCI - New Onset of Chronic Illness, p.r.n. - Pro re nata (dosing as needed), qRT-PCR -

	Quantitative Reverse Transcriptase Real Time PCR, SI - Sub-Investigator
PROTOCOL SYNOPSIS	
Study population:	
Original wording	Older adults and elderly (≥50 years of age). A stratification for age of <65> will be performed for each endpoint.
New wording	Older adults and elderly (≥50 years of age). Randomization will be stratified by cohort and age of <65>.
Planned number of subjects	
Original wording	At least half of the participants will be ≥65 years of age
New wording	At least half of the participants will be ≥65 years of age at the time of the randomization.
Rationale for sample size	
Original wording	Under these assumptions, 182 first episodes of PCR and/or culture-confirmed influenza of any strain occurring at least 15 days after the second dose of study vaccine or control will be needed to demonstrate efficacy is at least 40%.
New wording	Under these assumptions, 182 first episodes of either qRT-PCR or culture-confirmed influenza of any strain occurring at least 15 days after the second dose of study vaccine or control will be needed to demonstrate efficacy is at least 40%.
Inclusion criteria	
Original wording	1. Male and female subjects 50 years of age (inclusive) or older, mentally competent, willing and able to give the written informed consent prior to study entry
New wording	1. Male and female subjects 50 years of age (inclusive) or older, willing and able to give the written informed consent prior to study entry
Exclusion criteria	
Original wording	3. Receipt of: a) Current (including within 60 days or planned during the study) daily use of immunosuppressive drugs: i) systemic glucocorticoids ≥ 10 mg prednisone per day ii) cytotoxic drugs b) Investigational drugs within 30 days before, or planned during, the study c) Blood products within 3 months before, or planned during, the study d) Influenza vaccine within 6 months before the study) Other vaccines within 30 days before, or planned during, the study. (…) 5. An acute illness, including body temperature greater than 37.5ºC (axillary or forehead) or greater than 38.0 ºC (oral), or greater than 38.5ºC (ear/tympanic or rectal) , occurred within 1 week before first vaccination. 6. Anatomical deficiencies which exclude possibility of taking NP swab.

New wording	3. Receipt of: a) Current (including within 60 days or planned during the study) daily use of immunosuppressive drugs: i) systemic glucocorticoids ≥ 10 mg prednisone per day ii) cytotoxic drugs b) Investigational drugs within 30 days before, or planned during, the study c) Blood products within 3 months before, or planned during, the study d) Influenza vaccine within 6 months before the study e) Other vaccines within 30 days before, or planned during, the study. (…) 5. An acute illness, which occurred within 1 week before first vaccination, as judged by the PI/SI, or including body temperature greater than: for participants age 50-59 37.95ºC (axillary or forehead) or greater than 38.04 ºC (oral), or greater than 38.59ºC (ear/tympanic or rectal); for participants of age 60 or more, greater than 37.2ºC (axillary or forehead) or 37.7 ºC (oral), or 38.2ºC (ear/tympanic or rectal), which occurred within 1 week before first vaccination. 6. Anatomical deficiencies which exclude possibility of taking NP swab or throat and nasal swab.
Duration of treatment	
Original wording	Approximately 21 (+9) days for 2 vaccination visits
New wording	Approximately 22 (+9) days for 2 vaccination visits
Criteria for evaluation	
Original wording	Primary endpoint: Safety To assess M-001 Safety by solicited local and systemic reactogenicity events occurring between 0 and 7 days following receipt of each of the two doses of M-001 or placebo (…) To assess M-001 Safety by occurrence of unsolicited AEs from the time of first study vaccination through 21 days after each M-001 vaccination. Clinical Efficacy Compare the occurrence of culture confirmed influenza (…) Secondary endpoints: 1. Compare the occurrence of qualitative PCR confirmed influenza in the M-001 experimental group vs. placebo (≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined ILI. Nasopharyngeal swab will be collected from participants who meet the ILI definition within 24 hours from ILI being reported to or identified by study personnel for PCR analysis of influenza A and/or B virus. (a nasal and throat sample will be collected if the participant object NP swab collection)

	(…) Reduced Severity of influenza illness Reduction of PCR confirmed influenza illness severity: The time to symptoms alleviation/fever resolution ("alleviation/resolution"), (…) To assess in at least a subset of samples the consistency of manufacturing between 3 batches of M-001 according to their T cell responses by ICS and FACS analysis for IFN-g production in PBMCs. (…) Exploratory endpoints: (…) Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation of presence of influenza virus by viral culture or PCR analysis
New wording	Safety To assess M-001 Safety by solicited local and systemic reactogenicity events occurring within 8 days (day of the vaccination inclusive) following receipt of each of the two doses of M-001 or placebo (…) To assess M-001 Safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each M-001 vaccination (day of the vaccination inclusive). Clinical Efficacy Compare the occurrence of either qRT-PCR or culture confirmed influenza (…) Secondary endpoints: 1. Compare the occurrence of culture confirmed influenza in the M-001 experimental group vs. placebo (≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined ILI. Nasopharyngeal swab will be collected from participants who meet the ILI definition within 24 hours from ILI being reported to or identified by study personnel for qRT-PCR confirmation of influenza A and/or B virus. (a nasal and throat sample will be collected if the participant object NP swab collection), and the samples identified with qRT-PCR as positive for influenza A or B virus will be verified with virus culture. (…) 2. Reduced Severity of influenza illness Reduction of either qRT-PCR or Culture-confirmed influenza illness severity: The time to all symptoms alleviation/fever resolution ("alleviation/resolution")

	(…) To assess in at least a subset of samples in season 2 the consistency of manufacturing between 3 batches of M-001 according to their T cell responses by ICS and FACS analysis for IFN-g production in PBMCs *Exploratory endpoints:* (…) • Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation of presence of influenza virus by viral culture and qRT-PCR analysis
Criteria for evaluation	
Description of change	In *Secondary endpoints* section rearranged order of the endpoints.
Table 1	
Original wording	Day 180 Safety, Culture and PCR on any ILI (flu season) (…) Follow up Culture and PCR on any ILI (flu season)
New wording	Day 180 Safety, qRT-PCR on any ILI (flu season) (…) Follow up qRT- PCR on any ILI (flu season)
Table 2	
Description of change	Added tick "X" for Demographic data and Review Medical & flu vaccination History and Concomitant meds at Visit 2 Replaced/split AE/SAE Assessment line into Solicited/reactogenicity events assessment Unsolicited AEs Assessment NOCIs, AESIs, SAE [Note: for Solicited/reactogenicity events assessment AND Unsolicited AEs/ Assessment – tick "X" at Visit 1 and 2, for NOCIs, AESIs, SAE – tick "X" at Visits 1, 2 and 4] [Note: for Solicited/reactogenicity events assessment denote added for visits 1 and 2: * Occurence and severity of reactogenicity events will be collected through seven days after each study vaccination day (8 days in total)] [Note: for Unsolicited AEs Assessment denote added for visits 1 and 2: # Occurrence of unsolicited AEs will be analyzed from the time of first study vaccination through 22 days after each M-001 vaccination (day of the vaccination inclusive).]
Table 2	
Original wording	Passive Surveillance:

	Subjects will be instructed to contact the study site if they experience symptoms of respiratory illness from Day 14 post-vaccination (…) From Day 14 post vaccination until 30 April of the following year. (…) Collection of information on AEs, NOCIs, and SAEs
New wording	Passive Surveillance: Subjects will be instructed to contact the study site if they experience symptoms of a respiratory illness from Day 14 post-second vaccination day (…) From Day 14 post second vaccination day until 30 April of the following year (…) Collection of information on AESIs, NOCIs, and SAEs
Table 3	
Description of change	Added tick "X" for Demographic data and Review Medical & flu vaccination History and Concomitant meds at Visit 2 Replaced/split AE/SAE Assessment line into Solicited/reactogenicity events assessment Unsolicited AEs Assessment NOCIs, AESIs, SAE [Note: for Solicited/reactogenicity events assessment AND Unsolicited AEs/ Assessment – tick "X" at Visit 1 and 2, for NOCIs, AESIs, SAE – tick "X" at Visits 1, 2, 3 and 4] [Note: for Solicited/reactogenicity events assessment denote added for visits 1 and 2: * Occurence and severity of reactogenicity events will be collected through seven days after each study vaccination day (8 days in total)] [Note: for Unsolicited AEs Assessment denote added for visits 1 and 2: # Occurrence of unsolicited AEs will be analyzed from the time of first study vaccination through 22 days after each M-001 vaccination (day of the vaccination inclusive).]
Table 3	
Original wording	Sub-set of 925
New wording	(Sub-set of participants, only)
Table 3	
Original wording	Passive Surveillance: Subjects will be instructed to contact the study site if they experience symptoms of respiratory illness from Day 14 post-vaccination (…) From Day 14 post vaccination until 30 April of the following year. (…) Collection of information on AEs, NOCIs, and SAEs
New wording	Passive Surveillance:

	Subjects will be instructed to contact the study site if they experience symptoms of a respiratory illness from Day 14 post-second vaccination day (…) From Day 14 post second vaccination day until 30 April of the following year (…) Collection of information on AESIs, NOCIs, and SAEs
Table 3 [denotes under table]	
Original wording	#From seven days after the study vaccination AEs related to vaccination will no longer be collected as solicited AEs Occurrence of unsolicited AEs will be analyzed from the time of first study vaccination through 21 days after each M-001 vaccination.
New wording	* Occurence and severity of reactogenicity events will be collected through seven days after each study vaccination day (8 days in total) # Occurrence of unsolicited AEs will be analyzed from the time of first study vaccination through 22 days after each M-001 vaccination (day of the vaccination inclusive). Note: within exploratory outcome measures, endpoints and objectives: "dosing" to be understood as second vaccination received.; "≥15 days after" is to be understood as ≥15 days after the vaccination, including the day of the vaccination.
2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE	
2.3.1. Potential Risks	
Original wording	All attempts will be made to keep this PHI confidential within the limits of applicable laws.
New wording	All attempts will be made to keep this PHI confidential within the limits of applicable laws including European Union General Data Protection Regulation 2016/679 (GDPR) where applicable.
3. OBJECTIVES	
3.1.1. Primary Objectives	
Original wording	Safety To assess M-001 Safety by solicited local and systemic reactogenicity events occurring between 0 and 7 days following receipt of each of the two doses of M-001 or placebo and to assess SAEs and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group. Clinical Efficacy To assess efficacy of M-001 in the prevention of influenza disease by comparing the occurrence of culture confirmed influenza in the M-

	001 experimental group vs. placebo caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness (ILI)
New wording	Safety To assess M-001 Safety by solicited local and systemic reactogenicity events occurring within 8 days (day of the vaccination inclusive) following receipt of each of the two doses of M-001 or placebo and to assess SAEs and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group. To assess M-001 safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each M-001 vaccination (day of the vaccination inclusive). Clinical Efficacy To assess efficacy of M-001 in the prevention of influenza disease by comparing the occurrence of either qRT-PCR or culture confirmed influenza in the M-001 experimental group vs. placebo caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness (ILI)
3.1.2. Secondary Objectives	
Original wording	Clinical efficacy 1. Compare the occurrence of qualitative PCR confirmed influenza in the M-001 experimental group vs. placebo caused by any influenza A or B virus in association with a protocol defined ILI. 2. Reduced Severity of PCR-confirmed influenza illness by the time to symptom alleviation/fever resolution (“alleviation/resolution”). 3. To assess in at least a subset of samples the consistency of manufacturing between 3 batches of M-001 according to their T cell responses by IFN-g production in PBMCs. 4. To assess the durability of vaccine efficacy over a second influenza season. 5. To assess proportion of subjects having ILI symptoms in the experimental or control group.
New wording	Clinical efficacy 1. Compare the occurrence of culture confirmed influenza in the M-001 experimental group vs. placebo caused by any influenza A or B virus in association with a protocol defined ILI. 2. Reduced Severity of either qRT-PCR or culture -confirmed influenza illness by the time to all symptoms alleviation/fever resolution (“alleviation/resolution”). 3. To assess the durability of vaccine efficacy over a second influenza season.

	4. To assess proportion of subjects having ILI symptoms in the experimental or control group. Immunogenicity and lots consistency To assess in at least a subset of samples in season 2 the consistency of manufacturing between 3 batches of M-001 according to their T cell responses by IFN-g production in PBMCs
3.1.3. Exploratory Objectives	
Original wording	- Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture or PCR analysis - To determine the specific influenza strains in flu cases in experimental and control group
New wording	• Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture and qRT-PCR analysis • To determine the specific influenza strains in confirmed flu cases in experimental and control group
3.2.1. Primary Outcome Measures	
Original wording	Safety - Occurrence of vaccine-related SAEs from the time of the first study vaccination (M-001 or placebo) until end of first passive surveillance period - Occurrence of solicited injection site and systemic reactogenicity events on the day of each study vaccination through approximately 7 days after each M-001 vaccination - Occurrence of unsolicited AEs from the time of first study vaccination through 21 days after each M-001 vaccination (…) Clinical Efficacy - Percentage of culture confirmed influenza cases in the M-001 experimental group vs. placebo (…) NP swab will be collected from participants who meet the ILI definitions within 24 hours from ILI being reported to or identified by study personnel for qualitative PCR analysis of influenza A and/or B virus. PCR confirmed samples will be further analyzed by culture confirmed influenza testing.
New wording	Safety

	• Occurrence of vaccine-related SAEs from the time of the first study vaccination (M-001 or placebo) until end of first passive surveillance period • Occurrence of NOCIs from the time of the first study vaccination (M-001 or placebo) until end of first passive surveillance period • Occurrence of solicited injection site and systemic reactogenicity events on the day of each study vaccination through approximately 8 days after each M-001 vaccination (day of the vaccination inclusive) • Occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each M-001 vaccination (day of the vaccination inclusive) (…) Clinical Efficacy • Percentage of either qRT-PCR or culture-confirmed influenza cases in the M-001 experimental group vs. placebo (during (…) NP or combined nasal and throat swab will be collected from participants who meet the ILI definition within 24 hours from ILI being reported to or identified by study personnel for qRT-PCR analysis of influenza A and/or B virus. PCR confirmed samples will be further analyzed for culture confirmation.
3.2.2. Secondary Outcome Measures	
Original wording	1. Clinical efficacy - Percentage of PCR confirmed influenza cases in the M-001 experimental group vs. placebo (during ≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness. NP swab will be collected from participants who meet the ILI definitions within 24 hours from ILI being reported to or identified by study personnel for qualitative PCR analysis of influenza A and/or B virus. - Percentage of subjects having ILI symptoms in the experimental or control group - Average time to symptom alleviation/fever resolution in the experimental vs control group. “alleviation/resolution” time is defined as the first time point at which all of the following influenza symptoms (body aches (myalgia and/or arthralgia), cough, fatigue/tiredness, headache, nasal congestion/ runny nose/ sputum production, wheezing or difficult breathing, chills and sore throat) were absent and fever had resolved, with both (resolution of all symptoms and fever) maintained for at least 1 day. - To assess the durability of vaccine efficacy over a second influenza season 2. Immunogenicity and lots consistency

	Frequency of T cell subsets from participants in the experimental group, expressing interferon gamma (IFN-g) in CD4+ PBMCs after stimulation with M-001 16 days after the second dose of M-001 as compared to baseline.
New wording	1. Clinical efficacy • Percentage of culture confirmed influenza cases in the M-001 experimental group vs. placebo (during ≥ 15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness. NP or nasal and throat swab will be collected from participants who meet the ILI definitions within 24 hours from ILI being reported to or identified by study personnel for culture confirmation of influenza A and/or B virus (a nasal and throat sample will be collected if the participant object the NP swab collection), and the samples identified with qRT-PCR as positive for influenza A or B virus will be verified with virus culture. • Average time to all symptoms alleviation/fever resolution in the experimental vs control group. "Alleviation/resolution" time is defined as the first time point at which all of the following influenza symptoms (body aches (myalgia and/or arthralgia), cough, fatigue/tiredness, headache, nasal congestion/ runny nose/ sputum production, wheezing or difficult breathing, chills and sore throat) were absent and fever had resolved, with both (resolution of all symptoms and fever) maintained for at least 1 day. • To assess the durability of vaccine efficacy over a second influenza season • Percentage of subjects having ILI symptoms in the experimental or control group 2. Immunogenicity and lots consistency Frequency of T cell subsets from participants in the experimental group, expressing interferon gamma (IFN-g) in CD4+ PBMCs after stimulation with M-001 16 days after the second dose of M-001 (day of the vaccination inclusive) as compared to baseline.
3.2.3. Exploratory Outcome Measures	
Original wording	3.2.3. Exploratory Outcome Measures - Incidence of secondary respiratory tract infections leading to a prescription for antibiotic therapy in the experimental group as compared to the control group. In case of lack of documented medical record subject's provided information will be sufficient. - Incidence of clinic visits (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director) in the experimental group as compared to the control group;

	A possibility of multiple visits per subject; each visit will be counted once in the analysis. - Incidence of hospitalization associated with ILI (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group. - Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group, with or without confirmation by viral culture or PCR analysis. - Define influenza virus subtype in the swab samples to compare the viruses causing disease in the experimental vs control group
New wording	3.2.3. Exploratory Outcome Measures • Incidence of secondary respiratory tract infections leading to a prescription for antibiotic therapy in the experimental group as compared to the control group. In case of lack of documented medical record subject's provided information will be sufficient. • Incidence of clinic visits (≥15 days after dosing* until epidemiological influenza levels are low as defined by the medical director) in the experimental group as compared to the control group; A possibility of multiple visits per subject; each visit will be counted once in the analysis. • Incidence of hospitalization associated with ILI (≥15 days after dosing* until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group. • Incidence of death due to influenza-like illness (≥15 days after dosing* until epidemiological levels of influenza are low as defined by the medical director) in the experimental group as compared to the control group, with or without confirmation by viral culture or and qRT-PCR analysis. • Define influenza virus subtype in the swab samples to compare the viruses causing disease in the experimental vs control group * - within exploratory outcome measures, endpoints and objectives: "dosing" to be understood as second vaccination received.; ≥15 days after" is to be understood as ≥15 days after the second vaccination, including the day of the vaccination.
4. STUDY DESIGN	
Original wording	Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination with M-001 (or placebo) through 7 days after the study vaccination (inclusive of vaccination day). Unsolicited non-serious AEs collected from the time of each M-001 vaccination through approximately 21 days after each study vaccination will be analyzed

	separately. SAEs will be collected from the time of the first study vaccination through the entire trial period
New wording	Reactogenicity will be measured by the occurrence of solicited injection site and systemic reactions from the time of each study vaccination with M-001 (or placebo) through 8 days after the study vaccination (inclusive of vaccination day). Unsolicited non-serious AEs collected from the time of each M-001 vaccination through approximately 22 days after each study vaccination (day of the vaccination inclusive) will be analyzed separately. SAEs (including AESIs) and NOCIs will be collected from the time of the first study vaccination through the entire trial period.
5. STUDY ENROLLMENT AND WITHDRAWAL	
5.1 Subject Inclusion Criteria	
Original wording	1. Male and female subjects 50 years of age (inclusive) or older, mentally competent, willing and able to give the written informed consent form (ICF) prior to study entry
New wording	1. Male and female subjects 50 years of age (inclusive) or older, willing and able to give the written informed consent prior to study entry
5.2 Subject Exclusion criteria	
Original wording	3. Receipt of: a) Current (including within 60 days or planned during the study) daily use of immunosuppressive drugs: i) systemic glucocorticoids ≥ 10 mg prednisone per day ii) cytotoxic drugs b) Investigational drugs within 30 days before, or planned during, the study c) Blood products within 3 months before, or planned during, the study d) Influenza vaccine within 6 months before the study) Other vaccines within 30 days before, or planned during, the study. (…) 5. An acute illness, including body temperature greater than 37.5ºC (axillary or forehead) or greater than 38.0 ºC (oral), or greater than 38.5ºC (ear/tympanic or rectal) , occurred within 1 week before first vaccination. 6. Anatomical deficiencies which exclude possibility of taking NP swab.
New wording	3. Receipt of: a) Current (including within 60 days or planned during the study) daily use of immunosuppressive drugs: i) systemic glucocorticoids ≥ 10 mg prednisone per day ii) cytotoxic drugs b) Investigational drugs within 30 days before, or planned during, the study c) Blood products within 3 months before, or planned during, the study d) Influenza vaccine within 6 months before the study e) Other vaccines within 30 days before, or planned during, the study. (…)

	5. An acute illness, which occurred within 1 week before first vaccination, as judged by the PI/SI, or including body temperature greater than: for participants age 50-59 37.95ºC (axillary or forehead) or greater than 38.04 ºC (oral), or greater than 38.59ºC (ear/tympanic or rectal); for participants of age 60 or more, greater than 37.2ºC (axillary or forehead) or 37.7 ºC (oral), or 38.2ºC (ear/tympanic or rectal), which occurred within 1 week before first vaccination. 6. Anatomical deficiencies which exclude possibility of taking NP swab or throat and nasal swab.
5.3 Treatment Assignment Procedures	
Original wording	5.3.1. Randomization Procedures Central randomization will be implemented in this study. Subjects will be randomized to 1 of 2 treatment arms, based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be stratified by age group (i.e., 50- 65, ≥ 65) and balanced by using permuted blocks
New wording	5.3.1. Randomization Procedures Central randomization will be implemented in this study. Subjects will be randomized to 1 of 2 treatment arms, based on a computer-generated randomization schedule prepared by or under the supervision of the sponsor before the study. The randomization will be stratified by cohort and age group (i.e., 50- 65, ≥ 65) and balanced by using permuted blocks
5.3.3. Reasons for Withdrawal	
Original wording	• Presence of signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity. For subjects with injection site or systemic signs or symptoms, or with an acute illness, including an oral temperature greater than or equal to 37.5°C, the subsequent study vaccinations should be postponed/deferred until signs, symptoms, or acute illness have resolved and if within the acceptable protocol-specified window for that visit. If outside this window, the PI must first approve the subsequent study vaccination and the documentation of approval should be filed in the subject's chart. •Any unresolved by or continuing solicited or unsolicited Grade 2 or 3 AE. An unresolved or continuing Grade 1 AE is permissible unless, in the opinion of the site PI or sub-I, it would render study vaccination unsafe or interfere with the evaluation of responses. • Grade 3 within the 8 days following a study vaccination, that has no alternative (to the vaccination) etiology.
New wording	•Presence of signs or symptoms that could confound or confuse assessment of study vaccine reactogenicity. For subjects with

	injection site or systemic signs or symptoms, or with an acute illness, the subsequent study vaccinations should be postponed/deferred until signs, symptoms, or acute illness have sufficiently resolved as per PI/SI judgment, and if within the acceptable protocol-specified window for that visit. If outside this window, the PI must first obtain approval for the second study vaccination from the study sponsor and the documentation of the approval should be filed in the subject's file. • Any unresolved or continuing at Visit 2 Grade 3 AE. An unresolved or continuing Grade 1 or 2 AE (grade 2 except for temperature which at grade 2 is not acceptable for vaccination) is permissible unless, in the opinion of the PI or SI, it would render study vaccination unsafe or interfere with the evaluation of responses. • Solicited reactogenicity event grade 3 or AE grade 3 AE, within the 8 days following study vaccination (day of the vaccination inclusive), that has no alternative (to the vaccination) etiology.
5.3.4. Handling of Withdrawals	
Original wording	Subjects who withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the ICF and randomization but before receipt of study vaccine may be replaced. Subjects who withdraw after randomization will not be replaced.
New wording	Subjects who withdraw, or are withdrawn or terminated from the study, or are lost to follow-up after signing the ICF and randomization but before receipt of study vaccine may be replaced.
6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT	
Original wording	M-001 M-001 is supplied as a sterile, cloudy-white suspension in single-dose vials containing:1 mg M-001 per 0.4 mL (dose for injection). Each vial contains a fill volume of 0.7 mL at a concentration of 2.5mg/mL that should be transferred to a 1mL syringe for injection. It contains no preservative (i.e., non-thimerosal). Study product must be stored at 2°C to 8°C. Do not freeze. (…) M-001 investigational influenza vaccine product: The 1 mg of M-001 dose will be administered as a single 0.4 mL intramuscular injection. The M-001 will be provided in a vial containing 0.7 mL of solution containing the exact dose for immunization. Visually inspect M-001 vaccine vial upon receipt and prior to use. After gentle shaking, the suspension will be cloudy white in appearance. If the M-001 vaccine precipitated, it should be resuspended by tapping on the vial with the finger or mixing by vortex until the suspension looks homogeneous, then it should be

	transferred to a syringe. If the M-001 vaccine appears to have been damaged, contaminated or discolored, or if there are any concerns regarding its integrity, do NOT use the affected study product(s). Normal Saline (Placebo): The saline placebo dose will be administered as a single 0.4 mL intramuscular injection. Visually inspect the placebo (normal saline) upon receipt and prior to use. The solution will be clear to colorless in appearance. If the placebo appears to have been damaged, contaminated or discolored, contain visible particulate matter, or if there are any concerns regarding its integrity, do NOT use the affected study product(s). (…) 6.4. Assessment of Subject Compliance with Study Intervention/ Investigational Product Study product will be administered to subjects by a blinded vaccine administrator via IM injection at all dosing times according to subject treatment assignment and as described in section 0. Thus, subject compliance with appropriate administration is not anticipated to be an issue. Deviations from the dose schedule may only occur as described in Section 6.2. 6.5. Concomitant Medications/Treatments Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include all current medications and medications taken within 30 days prior to Day 1 through approximately Day 43. After Day 43 only concomitant medications relevant for respiratory illness as per PI judgment, or related to AE or ILI will be recorded. Subjects who do not receive both M-001 study vaccinations will have all concomitant medications collected through approximately 21 days after the first study vaccination, or early termination, whichever occurs first. Prescription and over-the-counter drugs will be included as well as herbals, vitamins and supplements. In addition, information on receipt of non-study influenza vaccines will be solicited at each clinic visit or phone call, and reported in the eCRF.
New wording	M-001 M-001 is supplied as a sterile, cloudy-white suspension in single-dose vials of volume sufficient to dose: 1 mg of M-001 (1mg is a single dose). Each vial contains a fill volume (less than 1 mL) of concentration provided in the study manual for respective product batch that should be transferred to a 1mL syringe for injection according to the study manual. It contains no preservative (i.e., non-thimerosal).

	Volume of the product containing 1mg of M-001 (1 mg of M-001 is the dose to be administered per each vaccination) will be provided in the study manual for respective product batch. Study product must be stored at 2°C to 8°C. Do not freeze. (…) M-001 investigational influenza vaccine product: The 1 mg of M-001 dose will be administered as a single intramuscular injection according to the study manual. The M 001 will be provided in vials as described in paragraph 6.1.1 of the protocol. Visually inspect M-001 vaccine vial upon receipt and prior to use. After shaking, the suspension will be cloudy white in appearance. If the M-001 vaccine precipitated, it should be re-suspended by tapping on the vial with the finger or mixing until the suspension looks homogeneous, then it should be transferred to a syringe. If the M-001 vaccine appears to have been damaged, contaminated or discolored, or if there are any concerns regarding its integrity, do NOT use the affected study product(s). Normal Saline (Placebo): The saline placebo dose will be administered as a single intramuscular injection. Exact volume to be injected will be defined in the study manual and will be equal to the volume of the M-001 defined for the active treatment (M-001) study arm. The saline will be provided in vials as described in paragraph 6.1.1 of the protocol. Visually inspect the placebo (normal saline) upon receipt and prior to use. The solution will be clear to colorless in appearance. If the placebo appears to have been damaged, contaminated or discolored, contain visible particulate matter, or if there are any concerns regarding its integrity, do NOT use the affected study product(s). (…) 6.4. Assessment of Subject Compliance with Study Intervention/ Investigational Product Study product will be administered to subjects by a blinded vaccine administrator via IM injection at all dosing times according to subject treatment assignment and as described in sections 5.3 and 6 of the protocol. Thus, subject compliance with appropriate administration is not anticipated to be an issue. Deviations from the dose schedule may only occur as described in Section 6.2. 6.5. Concomitant Medications/Treatments Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include all current medications and medications

	taken within 3 months days prior to Day 0 through approximately Day 43. After Day 43 only concomitant medications relevant for respiratory illness as per PI judgment, or related to AE or ILI will be recorded. Subjects who do not receive both M-001 study vaccinations will have all concomitant medications collected through approximately 22 days after the first study vaccination, day of the vaccination inclusive, or early termination, whichever occurs first. Prescription and over-the-counter drugs will be included as well as herbals, vitamins and supplements. In addition, information on receipt of other influenza or non-influenza study vaccines will be solicited at each clinic visit or phone call by PI/SI or delegated study site personnel, and, if confirmed, such vaccination will be reported in the eCRF.
7. STUDY SCHEDULE	
Original wording	• Subjects will be entered into EDC system randomly assigned to a treatment arm prior to the first study vaccination (…) Subjects will be encouraged to take their temperature around the same time each day for 8 days post vaccination. (…) 7.2.1. Visit 2, Day 22, Clinic Visit (21 days [+9 days] post first study vaccination) (…) Subjects will be instructed on how to use the memory aid and how to measure and record AEs prior to discharge from the clinic. (…) 7.2.2. Visit 3, Day 37, Clinic Visit (16 days [±3 days] post second study vaccination for a subset, in season 2019/20) (…) Study personnel will review the memory aid information with subjects and assess and record all AEs/SAEs and concomitant medications on the appropriate data collection form (…) Study personnel will review interim medical history with subjects and assess and record all AE/SAEs and concomitant medications on the appropriate data collection form (…) Safety surveillance: All serious adverse events (SAEs) will be collected from Day 0 until the last telephone call of the study year. Adverse events of special interest (AESIs) will be captured as SAEs. These include new onset of Guillain-Barré Syndrome (GBS), Bell's Palsy, encephalitis / myelitis, optic neuritis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis. Passive efficacy surveillance: Following randomization and vaccinations, subjects will be instructed to contact the site if they

	experience symptoms of a respiratory illness during the annual surveillance periods, from Day 14 after vaccination until 15 May of the following year. Another period of follow up will take place in the influenza season that follows (total of 2 years follow up). Active efficacy surveillance will be performed from November 15th until the week of 30 March the following year, the most likely period of influenza virus circulation in the Northern Hemisphere. Another period of follow up will take place in the influenza season that follows (total of 2 years follow up). The participants will be contacted by a dedicated study staff twice a week between approximately November 15th through March 30th; Another period of follow up may take place in the influenza season that follows (up to 2 years follow up). Participants will be contacted as described above to monitor for influenza-like illness (ILI)), and any related symptom causing hospitalization or urgent care visit, and serious or specified adverse events. ILI was defined as listed above. During the period from Day 14 after vaccination until 30 April of the following year, the site will arrange for an NP swab to be collected if the subject experiences a new onset of the above mentioned symptoms of ILI (that persist for or reoccur after a period of at least 12 hours). During the passive and active efficacy surveillance period participants suffering from ILI will be asked to provide information on the symptoms as they develop using also standardized sets of questions. NP swab collection: NP swab specimens will be collected within 24 hours from ILI being reported to or identified by study personnel and up to 4 days of the onset of ILI symptoms for confirmation of influenza virus A or B via reverse transcriptase polymerase chain reaction RT-PCR followed by culture (Rhesus Monkey Kidney or Madin–Darby Canine Kidney tissue cultures) confirmation for PCR positive samples as described in Vesikari et al . Every effort must be made to obtain the NP swab specimen within 24 hours from ILI being reported to or identified by study personnel according to the qualifying ILI symptoms, and no later than 4 days (sample to be collected through Day 3 of the illness, considering that Day 0 is the day of the illness onset) following the onset of the ILI. (…) Laboratory testing for the confirmation of influenza: All NP specimens will be submitted for analysis by polymerase chain reaction (RT-PCR), and when the result is found positive, another aliquot from such specimen will be also examined by culture confirmation test.

	Optional test: Positive cultures samples will be stored and may undergo additional testing in the future (typing, subtyping or strain identification, utilizing genetic sequencing and antigenic analysis using hemagglutination inhibition [HAI] against a panel of known standard ferret reference antisera to different viral strains) to determine the breadth of protection provided by M-001 (…) 7.4. Safety Follow Up Visit, Visit 4, Day 202: Phone Call/ Electronic Communication (180 days +/-14 post last study vaccination) Subjects will be contacted by phone or electronic communication (e.g., email, text message) to query for safety events. Subjects will be asked to provide positive responses to the follow-up by phone. AEs limited to SAEs that have occurred since the previous visit will be solicited. Based on the information, subjects may be asked to return to the clinic for evaluation. 7.5. Follow Up Period for Efficacy Season 2 (…) Active surveillance will take place between November 15, 2019 and March 30, 2020. During this period, the dedicated study staff will contact the participants twice a week to remind and record ILI and respiratory symptoms as detailed above (Follow up calls in season 2019/20 will be for all 9,630 participants). (…) • Memory aid information will be reviewed with subjects (if within 21 days after the last study vaccination). • If indicated by interim medical history, perform physical examination and obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. • Review and record all concomitant medications (if prior to 21 days after the last study vaccination). (…) • Examine study vaccination site, and perform post- administration reactogenicity assessment (if within 7 days after the last study vaccination). 7.8. Unscheduled Visit Unscheduled visits may occur at any time during the study. Any of the following activities may be performed: • Review memory aid (if within 21 days after the previous study vaccination). • Review and record all concomitant medications (if prior to 21 days after the last study vaccination).

	• All AEs/SAEs will be recorded on the appropriate data collection form. AEs will be limited to SAEs if after 21 days after the last study vaccination.
New wording	Subjects entered into EDC system will be randomly assigned to a treatment arm prior to the first study vaccination (…) Subjects will be encouraged to take their temperature around the same time each day for 8 days post vaccination (day of the vaccination inclusive). (…) 7.2.1. Visit 2, Day 22, Clinic Visit (22 days [+9 days] post first study vaccination day) (…) Subjects will be instructed on how to use the memory aid and how to measure and record solicited events and / or unsolicited AEs prior to discharge from the clinic. (…) Visit 3, Day 37, Clinic Visit (16 days [±3 days] post second study vaccination for subset of subjects from Cohort 2, in season 2019/20) (…) Study personnel will review the memory aid information with subjects and assess and record all solicited events / unsolicited AEs/SAEs and concomitant medications on the appropriate data collection form (…) Study personnel will review interim medical history (other than reactogenicity events) with subjects and assess and record all unsolicited AE/SAEs and concomitant medications on the appropriate data collection form/ (…) Safety surveillance: All serious adverse events (SAEs) and new onset of chronic medical illness (NOCIs) will be collected from Day 0 until the end of the participation in the trial by the subject. Adverse events of special interest (AESIs) will be captured as SAEs. These include new onset of Guillain-Barré Syndrome (GBS), Bell's Palsy, encephalitis / myelitis, optic neuritis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis. Passive efficacy surveillance: Following randomization and vaccinations, subjects will be instructed to contact the site if they experience symptoms of a respiratory illness during the annual surveillance periods, from Day 14 after second vaccination day until 15 May of the following year. Another period of follow up will take place in the influenza season that follows (total of 2 years follow up). Active efficacy surveillance will be performed from November 15th until the week of 30 March the following year, the most likely period

	of influenza virus circulation in the Northern Hemisphere. Another period of follow up will take place in the influenza season that follows (total of 2 years follow up). The participants will be contacted by a dedicated study staff twice a week between approximately November 15th through March 30th; Another period of follow up may take place in the influenza season that follows (up to 2 years follow up). Participants will be contacted as described above by non-site study staff to monitor for influenza-like illness (ILI)); participants identified this way as potentially having ILI will be followed up by relevant study site personnel to confirm if the participant's symptoms and signs meet study ILI definition. During the period from Day 14 after second vaccination day until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), the site will arrange for an NP/nasal and throat swab to be collected if the subject experiences a new onset of the above mentioned symptoms of ILI (that persist for or reoccur after a period of at least 12 hours). During the passive and active efficacy surveillance period participants suffering from ILI will be asked to provide information on the symptoms as that they developed using also standardized sets of questions. NP swab collection: NP swab (or nasal and throat swab) specimens will be collected during the period from Day 14 after second vaccination until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), within 24 hours from ILI being reported to or identified by study personnel and up to 4 days of the onset of ILI symptoms for confirmation of influenza virus A or B via qRT-PCR followed by culture (Rhesus Monkey Kidney or Madin–Darby Canine Kidney tissue cultures) confirmation for qRT-PCR positive samples as described in Vesikari et al . Every effort must be made to obtain the NP(or nasal and throat) swab specimen within 24 hours from ILI being reported to or identified by study personnel according to the qualifying ILI symptoms, and no later than 4 days (sample to be collected through Day 3 of the illness, considering that Day 0 is the day of the illness onset) following the onset of the ILI. (…) Laboratory testing for the confirmation of influenza: All NP/nasal and throat swab specimens will be submitted for analysis by polymerase chain reaction (qRT-PCR), and when the result is found positive, another aliquot from such specimen will be also examined by culture confirmation test. Typing and subtyping of the influenza virus will be performed with PCR based method.

	Optional test: Positive cultures samples will be stored and may undergo additional testing in the future (subtyping or strain identification, utilizing genetic sequencing and antigenic analysis using hemagglutination inhibition [HAI] against a panel of known standard ferret reference antisera to different viral strains) to further determine the breadth of protection provided by M-001 (…) 7.4. Safety Follow Up Visit, Visit 4, Day 202: Phone Call/ Electronic Communication (180 days +/-14 post last study vaccination) Subjects will be contacted by phone or electronic communication (e.g., email, text message) to query for safety events. Subjects will be asked to provide positive responses to the follow-up by phone. AEs limited to NOCIs and SAEs that have occurred since the previous visit will be solicited. Based on the information, subjects may be asked to return to the clinic for evaluation. 7.5. Follow Up Period for Efficacy Season 2 (…) Active surveillance will take place between November 15, 2019 and March 30, 2020. During this period, the dedicated study staff will contact the participants twice a week to monitor for ILI symptoms as detailed above in 7.3. (Follow up calls in season 2019/20 will be for all 9,630 participants). (…) • Memory aid information will be reviewed with subjects (if within 22 days after the last study vaccination, day of the vaccination inclusive). • If indicated by interim medical history, perform physical examination and obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. • Review and record all concomitant medications (if within 22 days after the last study vaccination, day of the vaccination inclusive). (…) • Examine study vaccination site, and perform post- administration reactogenicity assessment (if within 8 days after the last study vaccination, day of the vaccination inclusive). 7.8. Unscheduled Visit Unscheduled visits may occur at any time during the study. Any of the following activities may be performed: • Review memory aid (if within 22 days after the last study vaccination day, inclusive of the vaccination day). • Review and record all concomitant medications (if within 22 days after the last study vaccination day, inclusive of the vaccination day).

	• All AEs/SAEs will be recorded on the appropriate data collection form. AEs will be limited to SAEs if after 21 days after the last study vaccination day.
8. STUDY PROCEDURES/EVALUATIONS	
Original wording	8.1. Clinical Evaluations (…) The collection of medical history information will include a review of vaccine history and plans for vaccinations. Concomitant Medications: All current medications and medications taken within 3 months before Study Day 1 (prescription and over-the-counter drugs) will be included, as well as vitamins and supplements, through 21 days after the last study injection (…) Reactogenicity Assessments: This will include an assessment of solicited AEs occurring from the time of each M-001 study vaccination [Day 1 (Visit 1), Day 22 (Visit 2] through 7 days after the study vaccination (inclusive of vaccination day), (…) Memory Aids: All subjects will complete a subject memory aid (paper diary) from the time of each study vaccination [Day 1 (Visit 1), Day 22 (Visit 2)] through 7 days after the study vaccination. Subject memory aids will be reviewed with the subject for AEs at the clinic visit following the first study injection. If a subject noted ongoing injection site or systemic reactogenicity on the 7th day following the study injection, the memory aid will continue to be completed and reviewed until resolved. (…) 8.2.1. Clinical Laboratory Evaluations Urine or serum pregnancy tests will be performed by the local or site laboratory within 24 hours prior to each study vaccination (Day 1 (Visit 1) and approximately Day 22 (Visit 2) on all female subjects of childbearing potential. Result must be negative and known prior to randomization on Day 1 (Visit 1) and administration of each study vaccination to be eligible for participation in the study and receipt of each dose of study vaccine. 8.2.2. Nasopharyngeal Samples For assessment of influenza virus through culture and PCR, an NP swab sample will be collected from both nasal passages using two different swab applicators; that are then placed in the same tube of universal transport medium (UTM). Optionally, if NP swab cannot be collected, combined swabs collection from deep nasal and throat - can be collected instead of NP, however NP swab is preferred method of collection of material for assessment of influenza virus infection. Immediately prior to taking the sample, the person

	performing the procedure will verify the subject's identity and will confirm that the subject number and any other required information on the laboratory request form are those of the subject. Each tube of UTM will be clearly labeled with the self-adhesive bar-coded label provided on the NP Requisition form that will be applied to the tube immediately before collection of the NP swab. (…) 8.2.3. Special Assays or Procedures Cellular (CMI) Studies Assays to measure T cell responses will be performed by a qualified laboratory. Venous blood samples for isolation of PBMCs will be collected from a subset, immediately prior to the first study vaccination (Day 1, visit 1 in season 2), and 16 days after the second M-001 vaccination (Day 37, visit 3, season 2). 8.2.4. Specimen Preparation, Handling, and Shipping (…) 8.2.4.2. Specimen Shipment Swab samples will be shipped and stored according to applicable regulations and according to the technical requirements aiming at preserving good quality of the material before it is processed for RT-PCR and/or culture confirmation
New wording	8.1. Clinical Evaluations (…) The collection of medical history information will include a review of vaccine history and plans for vaccinations. All past influenza vaccinations should be recorded (up to 3 years). Other vaccines history should include at least 30 days before the study and any other study-relevant vaccination received in the past. Concomitant Medications: All current medications and medications taken within 3 months before Study Day 0 (prescription and over-the-counter drugs) will be included, as well as vitamins and supplements, through 21 days after the last study injection day (…) Reactogenicity Assessments: This will include an assessment of solicited events occurring from the time of each M-001 study vaccination [Day 0 (Visit 1), Day 22 (Visit 2] through 8 days after the study vaccination (inclusive of vaccination day), (…) Memory Aids: All subjects will complete a subject memory aid (paper diary) from the time of each study vaccination [Day 0 (Visit 1), Day 22 (Visit 2)] through 8 days after the study vaccination (study vaccination day inclusive). Subject memory aids will be reviewed with the subject for AEs at the clinic visit following the first study injection. If a subject noted ongoing injection site or systemic reactogenicity on the 7th day following the study injection day, the

	memory aid will continue to be completed and reviewed until resolved. (…) 8.2.1. Clinical Laboratory Evaluations Urine pregnancy tests will be performed by the local or site laboratory within 24 hours prior to each study vaccination (Day 0 (Visit 1) and approximately Day 22 (Visit 2) on all female subjects of childbearing potential. Result must be negative and known prior to randomization on Day 0 (Visit 1) and administration of each study vaccination to be eligible for participation in the study and receipt of each dose of study vaccine. 8.2.2. Nasopharyngeal Samples For assessment of influenza virus through culture and qRT-PCR, an NP/nasal and throat swab sample will be collected from both nasal passages using two different swab applicators; both swabs are then placed in the same tubes of universal transport medium (UTM). Optionally, if NP swab cannot be collected, combined swabs collection from deep nasal (both nostrils) and throat - can be collected instead of NP with three separate applicators, and all three swabs are then placed into the same tube of UTM. Immediately prior to taking the sample, the person performing the procedure will verify the subject's identity and will confirm that the subject number and any other required information on the laboratory request form are those of the subject. Each tube of UTM will be clearly labeled with the self-adhesive bar-coded label provided on the Swab Requisition form that will be applied to the tube immediately before collection of the NP/nasal and throat swab. (…) 8.2.3. Special Assays or Procedures Cellular (CMI) Studies Assays to measure T cell responses will be performed by a qualified laboratory. Venous blood samples for isolation of PBMCs will be collected from a subset of cohort 2, immediately prior to the first study vaccination (Day 0, visit 1 in season 2), and 16 days (day of the vaccination inclusive) after the second M-001 vaccination (Day 37, visit 3, season 2). 8.2.4. Specimen Preparation, Handling, and Shipping (…) 8.2.4.2. Specimen Shipment Swab samples will be shipped and stored according to applicable regulations and according to the technical requirements aiming at preserving good quality of the material before it is processed for qRT-PCR and (where applicable) for culture confirmation
9. ASSESSMENT OF SAFETY	

9.1. Specification of Safety Parameters	
Original wording	2. Solicited AEs – reactogenicity events occurring on the day of each study vaccination through 7 days* after each study vaccination: *Vaccination day is considered Day 1, with 7 days following (8 total days) (…) Unsolicited AEs – non-serious AEs occurring from the time of the first study vaccination through approximately 21 days after the last study vaccination
New wording	2. Solicited events – reactogenicity events occurring on the day of each study vaccination through 8 days* after each study vaccination: *Vaccination day is considered Day 0, with 7 days following (8 days in total) (…) Unsolicited AEs/SAEs – non-serious AEs/SAEs occurring from the time of the study vaccination through approximately 22 days after the study vaccination (day of the vaccination inclusive)
9.2. Safety Assessment	
Original wording	All unsolicited AEs, including solicited injection site and systemic (subjective and quantitative) reactions, not meeting the protocol-defined criteria for SAEs , will be captured on the appropriate data collection form and electronic case report form (eCRF). Information to be collected for AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product and alternate etiology (if not related to study product) date of resolution of the event, seriousness and outcome. AEs while on study will be documented appropriately regardless of relationship. AEs will be followed to resolution. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it will be recorded as an AE. AEs must be graded for severity and assessed for relationship to study product (see definitions below). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF. Events classified as ILI will not be recorded as AEs unless they occur within 8 days post vaccination or if they meet seriousness criteria - then they are reported as AEs/SAEs, because ILI cases are to be recorded separately and analyzed for efficacy endpoints. Severity of Event: AEs will be assessed by a licensed study physician using a protocol-defined grading system (see section 9.2.2). For

	events not included in the protocol-defined grading system, the following guidelines will be used to quantify severity: (…) 9.2.2. Reactogenicity Reactogenicity events are AEs that are common and known to occur following administration of this type of study vaccine. The following Toxicity Grading Scales will be used to grade solicited injection site and systemic (subjective and quantitative) reactions (…) 9.2.4. Serious Adverse Events An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: (…) • all events described as Guillain-Barré syndrome will also be considered SAEs as within the confines of this protocol are deemed as important medical events (…) 9.3. Reporting Procedures Solicited injection site and systemic reactogenicity events will be documented from the time of each study vaccination (Day 1 (Visit 1) and approximately Day 22 (Visit 2) through 7 days after each study vaccination. Unsolicited non-serious AEs will be documented from the time of the study vaccination until study completion by the subject. SAEs will be documented from the time of the first study vaccination (Day 1 (Visit 1)) through subject's participation in the trial. SAEs occurring after the participant completes the study or after early termination need not be reported unless the Investigator believes that the event may have been caused by the study product or a protocol procedure. 9.3.1. Serious Adverse Events Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the CRO representative at the following address: KCR S.A. 6 Postepu Str. 02-676 Warsaw, Poland Email: SAE@kcrcro.com FAX: +48 22 203 56 58 Email: SAE@kcrcro.com In addition to the SAE form, selected SAE data fields must also be entered into EDC,

	Other supporting documentation of the event may be requested by the DSMB and should be provided as soon as possible. SAE report(s) within 24 hours from receipt will be reviewed and assessed for regulatory reporting and potential impact on study subject safety and protocol. SAE reports are shared with DSMB. At any time after completion of the study, if the site PI or appropriate sub-I becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate sub-I will report the event to the study Sponsor. (…) 9.5. Safety Oversight (DSMB) (…) Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited and unsolicited AE/SAEs.
New wording	AEs will be captured on the appropriate data collection form and electronic case report form (eCRF) as described below in terms of reporting periods. Information to be collected for AEs includes event description, date of onset, licensed study physician's assessment of severity and relationship to study product and considered etiology (if case not related or unlikely related to study product) date of resolution of the event, seriousness and outcome. AEs while on study will be documented appropriately regardless of relationship. AEs will be followed to resolution. Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the severity of any pre-existing medical condition increases, it may be recorded as an AE or SAE. AEs must be graded for severity and assessed for relationship to study product (see definitions below). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF within study periods as described below. Unsolicited AEs will be collected occurring from the time of the study vaccination through approximately 22 days after the study vaccination (day of the study vaccination inclusive). Adverse events of special interest (AESIs) will be captured as SAEs and within the same timelines throughout the subject's participation in the trial. These include new onset of Guillain-Barré Syndrome (GBS), Bell's Palsy, encephalitis / myelitis, optic neuritis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis. NOCIs should be collected from the time of the first study vaccination throughout the subject's' participation in the trial. NOCI is defined as diagnosis of a chronic medical condition where the

	symptoms commenced or worsened following exposure to the study vaccine. NOCIs meeting criteria of SAE will be recorded as SAE. Events classified as ILI will not be recorded as AEs/SAEs unless they occur during period from first or second vaccination within 8 days (the vaccination day inclusive) post the respective vaccination or if they meet seriousness criteria - then they are also (in addition to being reported as ILI) reported as SAEs, because ILI cases are to be recorded separately and analyzed for efficacy assessment. Severity of Event: AEs will be assessed by a licensed study physician using a protocol-defined grading system (see section 9.2.2). For events not included in the protocol-defined grading system, the following guidelines will be used by PI/SI to quantify severity, taking into account subject's medical history, concomitant medications, and baseline values: (…) 9.2.2. Reactogenicity Reactogenicity events are solicited events which are common and considered as possible to occur following administration of this type of vaccine. Reactogenicity (solicited) events are recorded only for 8 days post vaccination (day of the vaccination inclusive). Solicited events (reactogenicity events) which match at least one of the below criteria must be also recorded as AE/SAE or unsolicited AE/SAE: - symptom/event continues/occurs beyond 7 days post vaccination day (unsolicited AE/SAE) - reactogenicity symptom/event(s) required medical (i.e. physician's) assistance (AE/SAE) - reactogenicity symptom/event has been graded by subject or by investigator as severe (AE/SAE) - oral body temperature of severe grade as per section 9.2.2 Table 7 (AE/SAE) Per PI/SI's judgment, also cases of symptoms/events occurring within 8 days post vaccination (day of the vaccination inclusive) not meeting the above criteria can be recorded as SAE. The following Toxicity Grading Scales will be used by PI/SI to grade solicited injection site and systemic (subjective and quantitative) reactions in order to assess whether they qualify as AE/SAE, and if they are severe enough to delay administration of second dose (…) 9.2.4. Serious Adverse Events An AE or suspected AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes/meets any of the following:

	(…) • Note: all AESIs will also be considered SAEs as within the confines of this protocol are deemed as important medical events • Note: cases of NOCIs which meet criteria of SAE will be recorded as SAE with annotation that they are also considered NOCIs. • Note: ILI cases meeting seriousness criterion/criteria should be recorded as SAE in parallel with recording them as ILI cases, except for periods of 8 days post vaccination day (day of the vaccination inclusive) for both vaccine doses when such cases will only be recorded as SAE. (…) 9.3. Reporting Procedures Solicited injection site and systemic reactogenicity events will be documented from the time of each study vaccination (Day 0 (Visit 1) and approximately Day 22 (Visit 2) through 8 days after each study vaccination (day of the vaccination inclusive). Unsolicited non-serious AEs (excluding NOCIs) will be documented from the time of the study vaccination until 22 days after the study vaccination (day of the vaccination inclusive). ILI as AE will be documented if occur within 8 days post vaccination (day of the vaccination inclusive). SAEs and NOCIs will be documented from the time of the first study vaccination (Day 0 (Visit 1)) through subject's participation in the trial. SAEs occurring after the participant completes the study or after early termination need not be reported unless the Investigator believes that the event may have been caused by the study product or a protocol procedure. 9.3.1. Serious Adverse Events Any AE that meets a protocol-defined serious criterion must be submitted immediately (within 24 hours of site awareness) on an SAE form to the CRO representative at the following: KCR S.A. Email: SAE@kcrcro.com FAX: +48 22 203 56 58 In addition to the SAE form, selected SAE data fields must also be entered into EDC, Other supporting documentation of the event may be requested by the DSMB and should be provided as soon as possible. All SAE report(s) will be reviewed and assessed for regulatory reporting purposes and potential impact on study subject safety and protocol whithin 1 business day from receipt. SAE reports will be shared with DSMB.

	At any time after completion of the study, if the site PI or appropriate SI becomes aware of an SAE that is suspected to be related to study product, the site PI or appropriate SI will report the event to the study Sponsor directly. (…) 9.5. Safety Oversight (DSMB) (…) Reports may include enrollment and demographic information, medical history, concomitant medications, physical assessments, clinical laboratory values, dosing compliance, and solicited/reactogenicity events and AE/SAEs.
9.6. Efficacy Assessment	
Original wording	9.6.1. Molecular Detection and Sequencing Methodology (PCR): Clinical samples collected during the study period will undergo an extraction procedure to isolate the viral RNA from the NP swab prior to testing. The initial test will be a qualitative reverse transcriptase polymerase chain reaction (RT-PCR-) based assay to determine if Influenza strains are present in the clinical sample. For samples that are found positive for influenza in the RT-PCR assay, further testing by culture confirmation will be performed, to avoid false positive results. 9.6.2. Influenza Culture and Virus Isolation: Nasopharyngeal (NP) swab samples from subjects with ILI that were found positive in RT-PCR
New wording	9.6.1. Molecular Detection and Sequencing Methodology (qRT-PCR): Clinical samples collected during the study period will undergo an extraction procedure to isolate the viral RNA from the NP/nasal and throat swab prior to testing. The initial test will be a qRT-PCR- based assay to determine if Influenza strains are present in the clinical sample. A multiplex qRT-PCR will be performed to define Influenza A/H1 or A/H3 or B in a single test, Influenza B samples will be re-tested by qRT-PCR to define the Victoria/Yamagate lineage specification. For samples that are found positive for influenza in the qRT-PCR assay, further testing by culture confirmation will be performed. 9.6.2. Influenza Culture and Virus Isolation: Swab samples from subjects with ILI that were found positive in qRT-PCR
11. STATISTICAL CONSIDERATIONS	
Original wording	11.3.1. Study Design This is a pivotal, multicentre, randomized, modified double-blind, placebo-controlled phase 3 trial to assess the safety and clinical

	efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (≥50 years of age). Subjects will be randomized 1:1 to vaccine or placebo with randomization stratified by age group. (…) For these 925 subjects, blood samples will be collected prior to the first study vaccination (Day 1) and approximately 16 days after the second vaccination (Day 37). (…) Under these assumptions, 182 first episodes of PCR and/or culture-confirmed influenza of any strain occurring at least 15 days after the second dose of study vaccine or control and prior to the end of the first influenza season will be needed to demonstrate efficacy is at least 40%. (…) • Receipt of non-study licensed inactivated vaccine within 21 days before or anytime after each study vaccination (…) 11.5.2. Analysis of Safety Data Summaries and analysis of safety data will be presented for the Safety Analysis Population. Solicited AEs will be summarized by severity for each day after each study vaccination (Days 1-8 post each study vaccination) and as the maximum severity over all 8 days . Additionally, solicited AEs will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence intervals, to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom. Summaries of solicited AEs will be presented separately for each study vaccination as well as overall study vaccinations by treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact test, as appropriate. The proportion of subjects reporting solicited symptoms between the different study vaccinations (e.g., dose 1 vs. dose 2) will be compared using McNemar's test. Unsolicited AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA®) for preferred term and system organ class (SOC). The numbers of SAEs is expected to be small in this trial and will be reported (…) VE and its 95% confidence interval will be estimated by age group (i.e., < 65 years, ≥ 65 years) for both the PP and ITT analysis populations. Given VE for a specific age group can be approximated by 1 minus the age group specific odds ratio, the Breslow-Day test

	for the homogeneity of the odds ratios will be used to test for a common VE across age groups.
New wording	11.3.1. Study Design This is a pivotal, multicentre, randomized, modified double-blind, placebo-controlled phase 3 trial to assess the safety and clinical efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (≥50 years of age). Subjects will be randomized 1:1 to vaccine or placebo with randomization stratified by cohort and age group. (…) For these 925 subjects, blood samples will be collected prior to the first study vaccination (Day 0) and approximately 16 days (day of the vaccination inclusive) after the second vaccination (Day 37). (…) Under these assumptions, 182 first episodes of qRT-PCR -confirmed influenza of any strain occurring at least 15 days after the second dose of study vaccine or control and prior to the end of the first influenza season will be needed to demonstrate efficacy is at least 40%. (…) • Receipt of non-study licensed inactivated vaccine within 21 days before or anytime after each study vaccination day (…) 11.5.2. Analysis of Safety Data Summaries and analysis of safety data will be presented for the Safety Analysis Population. Solicited events will be summarized by severity for each day after each study vaccination (Days 0-7 post each study vaccination, 8 days in total) and as the maximum severity over all 8 days (day of the vaccination inclusive). Additionally, solicited events will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence intervals, to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom. Summaries of solicited events will be presented separately for each study vaccination as well as overall study vaccinations by treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact test, as appropriate. The proportion of subjects reporting solicited symptoms between the different study vaccinations (e.g., dose 1 vs. dose 2) will be compared using McNemar's test. Unsolicited AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA®) for preferred term and system organ class

	(SOC). The numbers of SAEs is expected to be small in this trial and SAEs will be reported (…) VE and its 95% confidence interval will be estimated by age group (i.e., < 65 years, ≥ 65 years) for both the PP and ITT analysis populations. Given VE for a specific age group can be approximated by 1 minus the age group specific odds ratio, the Breslow-Day test for the homogeneity of the odds ratios will be used to test for a common VE across age groups. In addition, given that circulating strains of flu may vary over the course of the trial, VE and its 95% confidence interval will be estimated by flu season as well for both the PP and ITT analysis populations; Breslow-Day test for the homogeneity of the odds ratios will be used to test for a common VE across cohort (flu season).
14.5. Subject Confidentiality	
Original wording	Subjects will have code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the participating site PIs, their study personnel, the sponsor(s), and their agents.
New wording	Subjects will have code numbers and will not be identified by name. Subject confidentiality is strictly held in trust by the participating site PIs, their study personnel, the sponsor(s), and their agents according to the applicable laws including European Union General Data Protection Regulation 2016/679 (GDPR) where applicable.
Across the protocol	
Original wording	Sub-I
New wording	SI
Across the protocol	
Original wording	Day 21
New wording	Day 22 [note: change applied to increase consistency regarding duration of relevant period from the time/day of the first vaccination]
Across the protocol	
Original wording	Day 7
New wording	Day 8 [note: change applied to increase consistency regarding duration of relevant period from the time/day of the vaccination]
Across the protocol	
Original wording	Day 1
New wording	Day 0 [note: change applied to increase consistency regarding numbering of the day of first vaccination]
Across the protocol	
Original wording	NP swab, NP (Nasopharyngeal)
New wording	NP (Nasopharyngeal) or combined nasal and throat swab; NP/nasal and throat swab
Across the protocol	
Original wording	PCR, qualitative PCR
New wording	qRT-PCR

List of changes of study protocol version 4.0 vs. study protocol version 3.0 dated 02nd June 2018

Description	Wording
Title page	
Version and date of the Protocol	
Original wording	Version 3.0 dated 02nd June 2018
New wording	Version 4.0 dated 27th March 2019
Sponsor	
Original wording	BiondVax Pharmaceuticals Ltd. Kiryat Weizmann, 14 Einstein Street Ness Ziona, POB 4143, 7414002, Israel
New wording	BiondVax Pharmaceuticals Ltd. Jerusalem Biopark, Hadassah Ein Kerem, Jerusalem, Israel
Investigator's compliance declaration	
Original wording	Protocol: BVX-010, version 3.0 dated June 02nd 2018
New wording	Protocol: BVX-010, version 4.0 dated March 27th 2019
TABLE OF CONTENTS and LIST OF TABLES	
Description of change	Updated
PROTOCOL SYNOPSIS	
Description of changes	Updated Sponsor's address. Updated information on planned study allocation – change from 66 to 85 institutions, added one new country – Georgia. Deleted information on planned subject participation duration "(including 2 consecutive flu seasons for cohort 1 participants)." Added information in study population section: "For season 2, randomization will also be stratified by participation (or not) to the sub-study"
PROTOCOL SYNOPSIS	
Original wording	Adaptive design (flexible enrolment); initially assumed to be 9,630 (including 10% dropouts). At least half of the participants will be ≥65 years of age at the time of the randomization. <u>Year 1 - cohort 1</u> (flu season 2018-2019): Approximately 4,334 subjects will be enrolled, as follows: M-001: n = 2,167 (Lot #1); Placebo: n = 2,167 <u>Year 2 - cohort 2</u> (flu season 2019-2020): Approximately 5,296 subjects will be enrolled, as follows:

	M-001: n = 2,648 ((Lot #1, #2 & #3); Placebo: n = 2,648
New wording	Year 1 - cohort 1 (flu season 2018-2019): 4,055 subjects enrolled, as follows: M-001: n = 2,027 (Lot #1, vials); Placebo: n = 2,028 Year 2 - cohort 2 (flu season 2019-2020): Approximately 8,000 subjects will be enrolled, as follows: M-001: n = 4,000 (Lot#2, pre-filled syringes); Placebo: n = 4,000
Original wording	**PBMC sub-study**: In addition to the main trial, blood samples will be collected pre- and post-vaccination from a subset of 925 participants to confirm lots consistency: 275 participants receiving each lot (Lot #1 produced by Cytovance; Lots #2 & #3 produced by BiondVax, IL facility) and additional 100 participants from control group (to maintain the blinding). Lot-to-lot consistency testing will occur during Year 2 (in Cohort 2).
New wording	**PBMC (CMI) sub-study**: To assess the immune response to the vaccine, blood samples will be collected pre- and post-vaccination from a subset of 350 participants selected at random in pre-specified sites participating in Season 2. Approximately two hundred sixty two (263) will be selected from the M-001 group and 87 from the placebo group. The endpoint for assessing the immune response will be the change from baseline in the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001 measured at 14 ± 2 days after the day of the second vaccination (Visit 3) (Day 36).
Original wording	**Rationale for sample size:** The study sample size of 9,630 subjects is based on the lower bound of the two-sided 95% confidence interval for Vaccine Efficacy (VE) being above 40% with 80% probability when true VE is 62%. (…). If after the first flu season the total number of per protocol cases of confirmed influenza infection is substantially fewer than 82 cases, the DSMB may, following issuance of interim report #1, recommend increasing the sample size for Year 2. Otherwise, the sample size for Year 2 will remain at 5,296 subjects. Details for sample size re-estimation will be defined in the DSMB charter. The same methodology will be used after the second flu season by issuing interim report #2 and optionally extending the trial to year 3 with a third cohort based on amendment to the protocol which will be submitted in such case for ethics/regulatory approval. In the event vaccine efficacy for a single influenza season is demonstrated, a lot consistency analysis will be performed on Year 2. The endpoint for assessing lot consistency will be the percentage of

	CD4+ lymphocytes producing INF-γ in response to any of the 9 peptides in M-001 measured at Day 37.
New wording	**Rationale for sample size:** The initial study sample size of 9,630 subjects is based on the lower bound of the two-sided 95% confidence interval for Vaccine Efficacy (VE) being above 40% with 80% probability when true VE is 62% (…). In Year 1, about 4,000 subjects will be enrolled. If during the first flu season a substantially reduced attack rate is anticipated, the Sponsor may elect to increase the total sample size to 12,000. If the average attack rate across Year 1 and Year 2 is at least 2.4%, the study should maintain power at 80%. If during the second flu season another mild season is expected, the Sponsor may consider extending the trial to Year 3 with a third cohort based on an amendment to the protocol which will be submitted for ethics/regulatory approval. In Year 2, an immunogenicity sub-study will be conducted at select sites. Assuming the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001 measured at Day 36 (14 ± 2 days after the day of the second vaccination) has a mean (standard deviation) of 25% (12%), the sub-study should have reasonable power with 210 evaluable vaccinees to demonstrate the non-inferiority of the immune response in other populations with a non-inferiority margin of 5%. Power calculations are based on an equally sized trial in the population to which vaccine efficacy is being bridged.
PROTOCOL SYNOPSIS	
Inclusion criteria	
Original wording	1. Male and female subjects 50 years of age (inclusive) or older, willing and able to give the written informed consent prior to study entry. 2. Able to comply with the trial procedures and be available for all study visits. 3. Medically stable (subjects may have underlying chronic conditions such as hypertension, diabetes, ischemic heart disease, or hypothyroidism, as long as their symptoms/signs are controlled; if they are on medication for a condition, the medication dose must have been stable for at least 3 months preceding vaccination). 4. Women of childbearing potential (not surgically sterile or postmenopausal for greater than or equal to one year) and men must agree to practice adequate effective contraception - barrier or hormone-based methods or intra uterine device (IUD) for women and a condom for males -whose female partner has childbearing potential - throughout the study treatment and for at least up to day 81 (for females) and day 111 (for males) of the trial (i.e. 60

	(for females) and 90 (for males) days after the last dose of the IMP). In addition, women of childbearing potential must have practiced the contraception for a minimum of 30 days prior to study product exposure. 5. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 24 hours prior to study vaccination.
New wording	1. Male and female subjects 50 years of age (inclusive) or older, willing and able to give the written informed consent prior to study entry. 2. Able to comply with the trial procedures and be available for all study visits including answering phone calls and coming to the site as defined by the Protocol. 3. Medically stable (subjects may have underlying systemic chronic conditions such as hypertension, diabetes, ischemic heart disease, or hypothyroidism, as long as their symptoms/signs are controlled; if they are on systemic pharmacological treatment for such condition, the treatment must have been stable for at least 3 months preceding first vaccination). 4. Women of childbearing potential (not surgically sterile or postmenopausal for greater than or equal to one year) and men must agree to practice adequate effective contraception - barrier or hormone-based methods or intra uterine device (IUD) for women and a condom for males -whose female partner has childbearing potential - throughout the study treatment and for at least up to day 81 (for females) and day 111 (for males) of the trial (i.e. 60 (for females) and 90 (for males) days after the last dose of the IMP). In addition, women of childbearing potential must have practiced the contraception for a minimum of 30 days prior to study product exposure. 5. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 24 hours prior to both study vaccinations.
Exclusion criteria	
Original wording	1. History of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine. 2. Known or suspected (or have a high risk of developing) impairment/alteration of immune function (excluding that normally associated with advanced age). 3. Receipt of: a) Current (including within 60 days or planned during the study) daily use of immunosuppressive drugs: i) systemic glucocorticoids ≥ 10 mg prednisone per day ii) cytotoxic drugs b) Investigational drugs within 30 days before, or planned during, the study c) Blood products within 3 months before, or planned during, the study d) Influenza vaccine within 6 months before the study e) Other vaccines within 30 days before, or planned during,

	the study. 4. Any serious disease such as: cancer, autoimmune disease, advanced arteriosclerotic disease or complicated diabetes mellitus, chronic obstructive pulmonary disease (COPD) that requires oxygen therapy, acute or progressive hepatic disease, acute or progressive renal disease, or congestive heart failure, as judged by the PI/SI. 5. An acute illness, which occurred within 1 week before first vaccination, as judged by the PI/SI, or body temperature greater than: for participants age 50-59 37.9ºC (axillary or forehead) or 38.4 ºC (oral), or 38.9ºC (ear/tympanic or rectal); for participants of age 60 or more, greater than 37.2ºC (axillary or forehead) or 37.7 ºC (oral), or 38.2ºC (ear/tympanic or rectal), which occurred within 1 week before first vaccination. 6. Anatomical deficiencies which exclude possibility of taking NP swab or throat and nasal swab. 7. Women who are breastfeeding or planning pregnancy during the period of the study
New wording	1. History of neurological symptoms or signs, or anaphylactic shock following administration of any vaccine. 2. Known or suspected (or have a high risk of developing) significant impairment/alteration of immune function (excluding that normally associated with advanced age) as judged by PI/SI. 3. Receipt of: a) Current (including within 60 days before Visit 1 or planned during the study) daily use of immunosuppressive drugs: i) systemic glucocorticoids ≥ 10 mg prednisone per day ii) cytotoxic drugs b) Investigational drugs within 30 days before, or planned during, the study c) Blood products within 3 months before, or planned during, the study d) Influenza vaccine within 6 months before the study or planned during the study e) Other vaccines within 30 days before, or planned during, the study. 4. Any serious disease such as: cancer, autoimmune disease, advanced arteriosclerotic disease or complicated diabetes mellitus, chronic obstructive pulmonary disease (COPD) that requires oxygen therapy, acute or progressive hepatic disease, acute or progressive renal disease, or congestive heart failure, as judged by the PI/SI. 5. An acute illness, which occurred within 1 week before first vaccination, as judged by the PI/SI, or body temperature greater than: for participants age 50-59 37.9ºC (axillary or forehead) or 38.4 ºC (oral), or 38.9ºC (ear/tympanic or rectal); for participants of age 60 or more, greater than 37.2ºC (axillary or forehead) or 37.7 ºC (oral), or 38.2ºC (ear/tympanic or rectal), which occurred within 1 week before first vaccination. 6. Anatomical deficiencies which exclude possibility of taking NP swab or throat and nasal swab.

	7. Women who are breastfeeding or planning pregnancy during the period of the study. 8. Institutionalized subjects or subjects unable to come to the study site as expected by the Protocol.
PROTOCOL SYNOPSIS	
Test and reference product administration	
Original wording	Administered twice intramusculary at 21 days interval (acceptable range: 21-30 days)
New wording	Administered twice intramuscularly at 21 days interval (recommended range: 21-30 days)
Duration of treatment	
Original wording	For the subset of Cohort 2 participants who will attend 3 visits for immunogenicity testing for lot-to-lot consistency, the duration is 37±3 days. The total duration of this trial for each subject will be approximately 8 months and up to 2 years of follow-up (planned are 2 consecutive flu seasons for cohort 1 participants). Shall the optional study extension occurred (subject to future protocol amendment), cohort 1 participants will have no obligation to continue their follow up thru Year 3.
New wording	Cohort 2 participants will attend 3 site visits. Subset of Cohort 2 participants will attend , including additional Visit 3 for immunogenicity testing, and remaining Cohort 2 participants will have the third visit as safety assessment focused site visit. The Visit 3 is planned 14±2 days after Visit 2 day. The total duration of this trial for each subject will be up to 1 year. Shall the optional study extension have occurred for the purpose of follow up on efficacy (subject to future protocol amendment), the participants will have no obligation to continue their follow up thru Year 3
Criteria for evaluation	
Original wording	(a nasal and throat sample will be collected if the participant object NP swab collection),
New wording	(a nasal and throat sample can be collected as alternative method)
Original wording	<u>2. Reduced Severity of influenza illness</u> Reduction of either qRT-PCR or Culture-confirmed influenza illness severity: The time to all symptoms alleviation/fever resolution (“alleviation/resolution”), which can be defined as the first time point at which all of the following influenza symptoms (body aches (myalgia and/or arthralgia), cough, fatigue/tiredness, headache, nasal congestion/ runny nose/ sputum production, wheezing or difficult breathing, chills and sore throat) were absent and fever had resolved, with both (resolution of the symptoms and fever) maintained for at least one day.

	3. To assess the durability of vaccine efficacy over a second influenza season. 4. Percentage of subjects having ILI symptoms in the experimental and control group 5. To assess in at least a subset of samples in season 2 the consistency of manufacturing between 3 batches of M-001 according to their T cell responses by ICS and FACS analysis for IFN-g production in PBMCs.
New wording	2. Reduced Severity of influenza illness Reduction of either qRT-PCR or Culture-confirmed influenza illness severity: The reduction due to M-001 in the average number of days with respiratory or systemic symptoms during the first laboratory-confirmed influenza illness episode. 3. The percentage of subjects having ILI symptoms in the experimental and control group 4. The change from baseline in the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001. This endpoint will be assessed within a randomly selected subset of participants from pre-selected sites participating to the substudy in Year 2.
Original wording	***Exploratory endpoints:*** • Incidence of secondary respiratory tract infections leading to a prescription for antibiotic therapy • Incidence of clinic visits associated with the ILI episode (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director); A possibility of multiple visits per subject; each visit will be counted once in the analysis.
New wording	***Exploratory endpoints:*** • Incidence of antibiotics use due to post-influenza secondary infections of respiratory tract
Statistical methods	
Original wording	For the primary analysis of vaccine efficacy (VE), the efficacy of M-001 after a first influenza season will be estimated (…) **Determination of sample size for lot consistency:** The endpoint for assessing lot consistency will be the percentage of CD4+ lymphocytes producing INF-γ in response to any of the 9 peptides in M-001. Based on preliminary immunogenicity data, the percentage of CD4+ lymphocytes is approximately normally distributed with a mean of 25% and standard deviation 12%.

	Assuming an equivalence margin of 5%, 250 subjects per lot would need to be enrolled to have 90% probability that the 95% confidence interval for the difference in mean percentage for each of 3 pair-wise comparisons falls between -5% and 5% when there is no true difference. Assuming, that no more than 10% of samples are not evaluable, 275 subjects per lot will be targeted.
New wording	For the primary analysis of vaccine efficacy (VE), the efficacy of M-001 after a first influenza season in each cohort will be estimated (…) **Determination of sample size for the CMI substudy:**The endpoint for assessing immune response to the vaccine will be the change from baseline in the percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001. Based on preliminary immunogenicity data, the percentage of CD4+ lymphocytes is approximately normally distributed with a mean of 25% and standard deviation 12%. A sample size of 210 M-001 subjects will provide an estimate of the change from baseline in percentage of CD4+ lymphocytes producing e.g. INF-γ with a precision (1/2 width of the 95% CI) at most 2% .
Table 1	
Description of changes	Trial Design tables for Cohort 1 and 2 split between two separate tables (Table 1 and 2). Headers changed from: Season 1 Interim report issued after season 1 Season 2 Interim or final report issued after season 2 To: Year 1 Interim data analysis after Year 1 And Year 2 (flu season 2019/2020) In addition, updated subheaders and added Visit 3 column. Deleted column reflecting season 2 for cohort 1 subjects. In addition: Graph updated to reflect decision tree for after flu season 2 completion timepoint. Updated text below the graph: Original wording: Flexible enrollment scheme according to interim reports that will be issued after seasons 1 and 2. Flu season 3 is not planned. If decided that it is needed, protocol amendment will be issued and submitted for relevant approvals. [1] the cutoff will be at most 82 and will be defined precisely in the DSMB charter

	New wording: Flexible enrollment scheme according to interim data review that will be available after Year 1 and 2. Flu season 3 (Year 3) is not planned. If decided that it is needed after Year 2, protocol amendment will be issued and submitted for relevant approvals. [1] the cutoff will be at most 182 and will be defined precisely in the DSMB charter * In subset of subjects – visits at selected sites with collection of blood for CMI assessment at Visit 1 and 3. Visit 3 should take place in 14 days +/-2 since date of Visit 2.
Table 2 Schedule of Events for Cohort 1	
Description of changes	Changed to Table 3. Deleted: Both passive and active surveillance for cohort 1 subjects will be replicated during second season (passive one starting on September 15, 2019). Original wording: A combination of deep nasal and throat swab will be sampled from participant that will not allow for or cannot have NP swab collection, however NP swab is preferred. The process will be replicated for cohort 1 during second season (…) At any time during the study a disease burdenand concomitant medications in association withILI, and for up to 30 days following the start of a qualifying ILI symptoms. New wording: At any time during the study a disease burdenand concomitant medications in association withILI, and for up to 30 days following the start of a qualifying ILI symptoms. (…) At any time during the study a disease burden and concomitant medications in association with respiratory disease, ILI or AE, and for up to 30 days following the start of a qualifying ILI symptoms.
Table 3 Schedule of Events for Cohort 2	
Description of changes	Changed to Table 4. Updated headers Added Visit 3 details Minor corrections made to list of procedures on Visit 2 Updated wording of headers narrowing the contents fo season 2 instead of season 1 and 2. Original wording:

	A nasal and throat swab will be sampled from participant that will not allow NP swab collection (…) At any time during the study year disease burden data and concomitant medications in association with ILI, and for up to 30 days following the start of a qualifying ILI symptoms. New wording: A nasal and throat swab will be sampled from participant that will not allow NP swab collection. Swabs collection period starting on September 15, 2019 (…) At any time during the study year disease burden data and concomitant medications in association with respiratory disease, ILI or AE, and for up to 30 days following the start of a qualifying ILI symptoms.
Denotes under the Tables with schedule of events	
Description of changes	Added two positions: [9] In subset of subjects – visit at site with collection of blood for CMI assessment at Visit 1 and 3. For remaining subjects only– site visit or - if site visit not feasible - phone call. Blood sampling applicable only for on site visits in a subset of subjects participating in the CMI assessment. [10] If indicated by medical interview on period between Visit 1 and 2 Original wording: Note: within exploratory outcome measures, endpoints and objectives: "dosing" to be understood as second vaccination received.; "≥15 days after" is to be understood as ≥15 days after the vaccination, including the day of the vaccination. New wording: Note: within exploratory outcome measures, endpoints and objectives: "dosing" to be understood as second vaccination received (unless second dose will not be administered to given subject); "≥15 days after" is to be understood as ≥15 days after the vaccination, including the day of the vaccination.
2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE	
2.2. Rationale	
Original wording:	In addition, long term efficacy (up to 2 seasons) will be assessed. Lot-to-lot consistency between three batches (produced by Cytovance (OK, US) and by BiondVax (IL) will be evaluated. To compare the 3 lots in terms of immunogenicity, participants in season 2019/20 will be vaccinated with the 3 M-001 batches (equally randomized, 1:1:1

	for each batch). Blood samples will be collected from 825 participants receiving M-001 (275 participants for each batch) and from 100 participants receiving the placebo (to maintain the blinding). The blood samples from all 925 participants will be collected at baseline (visit 1) and 16±3 days after the second immunization (visit 3). Lots consistency will be confirmed by comparing cell mediated immune parameters in the samples from the experimental groups only.
New wording:	Cell-mediated immunity expected to be induced by the M-001 will also be evaluated based on samples from subset of participants from Cohort 2. Blood samples will be collected from approximately 263 participants receiving M-001 and 87 participants receiving the placebo (to maintain the blinding). The blood samples from all 350 participants will be collected at baseline (visit 1) and on Visit 3 -14 ± 2 days after the day of the Visit 2 (second vaccination).
Original wording:	Six previous trials in which approximately 460 participants received M-001 intramuscularly have been completed to date (see Investigator Brochure). (…) Bruising can sometimes occur due to the vaccination procedure.
New wording:	Six previous trials in which approximately 460 participants received M-001 intramuscularly have been completed to date in addition to 2027 who participated in season 1 of the current trial (see Investigator Brochure). (…) Bruising can sometimes occur due to the vaccination procedure. There were no treatment related SAEs.
3. OBJECTIVES	
3.1. Study Objectives	
Original wording	<u>Clinical efficacy</u> • Compare the occurrence of culture confirmed influenza in the M-001 experimental group *vs.* placebo caused by any influenza A or B virus in association with a protocol defined ILI. • Reduced Severity of either qRT-PCR or culture -confirmed influenza illness by the time to all symptoms alleviation/fever resolution (“alleviation/resolution”). • To assess the durability of vaccine efficacy over a second influenza season. • To assess proportion of subjects having ILI symptoms in the experimental or control group. <u>Immunogenicity and lots consistency</u>

	To assess in at least a subset of samples in season 2 the consistency of manufacturing between 3 batches of M-001 according to their T cell responses by IFN-g production in PBMCs. (…) 3.1.3 Exploratory Objectives • Incidence of secondary respiratory tract infections leading to a prescription for antibiotic therapy declared by the participant • Incidence of clinic visits associated with the ILI episode (≥15 days after dosing until epidemiological influenza levels are low as defined by the medical director); A possibility of multiple visits per subject; each visit will be counted once in the analysis. • Incidence of hospitalization associated with the ILI (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) • Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture and qRT-PCR analysis • To determine the specific influenza strains in confirmed flu cases in experimental and control group
New wording	Clinical efficacy • Compare the occurrence of culture confirmed influenza in the M-001 experimental group *vs.* placebo caused by any influenza A or B virus in association with a protocol defined ILI. • Assess reduction of severity of either qRT-PCR or culture - confirmed influenza illness by the reduction due to M-001 in the average number of days with respiratory or systemic symptoms during the first laboratory-confirmed influenza illness episode. • To assess proportion of subjects having ILI symptoms in the experimental or control group. Immunogenicity • To assess in at least a subset of samples in season 2 the change from baseline in the percentage of CD4+

	lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001. This endpoint will be assessed within a randomly selected subset of participants from pre-selected sites participating to the substudy in Year 2. (…) 3.1.3. Exploratory Objectives • Incidence of antibiotics use due to post-influenza secondary infections of respiratory tract as evidenced with medical records or declared by the participant • Incidence of hospitalization associated with the ILI (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director). • Incidence of death due to influenza-like illness (≥15 days after dosing until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture or qRT-PCR analysis. • To determine the specific influenza strains in confirmed flu cases in experimental and control group
Decription of changes	Study outcome measures changed accordingly to reflect changes in text defining study endpoints and study objectives as indicated in the Summary of Changes above.
4. STUDY DESIGN	
Original wording:	Subjects will be assigned randomly to 1 of 2 treatment arms (4815 per study arm during the study) to receive two doses of the M-001 vaccine or placebo (saline). Group A will receive two doses of M-001, each containing 1 mg of M-001, on Day 0 and 22. Group B will receive saline placebo on the same days. (…) In cohort 2, immunogenicity testing will be performed and will include performing CMI assays on blood samples obtained immediately at baseline (Day 0) and on samples collected on Days 37 from a subset of 275 participants randomly selected from experimental group receiving each of the 3 batches used in the trial (total of 825). Cell mediated immune responses to influenza antigens, including epitopes represented in the M-001 vaccine, will be assessed at baseline (Day 0), at 16 days after the second M-001 vaccination (Day 37). The duration of this trial for each subject will be approximately 8 months (reflecting time between vaccination and end of the flu

	season as stated in the protocol) and up to additional 2 years of follow up. For additional details on study procedures and evaluations and study schedule by study visits/days, see Sections 7 and 8 as well as Table and Table 3 – Schedule of events.
New wording:	Subjects will be assigned randomly to 1 of 2 treatment arms (6000 per study arm during the study) to receive two doses of the M-001 vaccine or placebo (saline). Group A will receive two doses of M-001, each containing 1 mg of M-001, on Day 0 and 22. Group B will receive saline placebo on the same days. (…) In cohort 2, immunogenicity testing will be performed and will include performing CMI assays on blood samples obtained immediately at baseline (Day 0) and on samples collected on Visit 3 (referred to as Day 36, taking place 14±2 days since day of the administration of second dose of the vaccine/placebo). At sites participating in the CMI sub-study, data will be obtained from a subset of approximately 263 participants randomly selected from the experimental group and from a subset of 87 participants randomly selected from the placebo group. Cell mediated immune responses to influenza antigens, including epitopes represented in the M-001 vaccine, will be assessed at baseline (Day 0, before vaccination), and at 14±2 days since day of the administration of second dose of the vaccine/placebo (Day 36). The duration of this trial for each subject will be up to 1 year (reflecting time between vaccination and end of the flu season as stated in the protocol). For additional details on study procedures and evaluations and study schedule by study visits/days, see Sections 7 and 8 as well as Table 3 and Table 4 – Schedule of events.
5. STUDY ENROLLMENT AND WITHDRAWAL	
Description of changes	Inclusion and exclusion criteria updated as indicated above. Clarification added to the last Exclusion Criterion: (…) Institutionalized* subjects unable to come to the study site as expected by the Protocol. *except for institutionalization without subsequent overnight stays
5.3. Treatment Assignment Procedures	
Original wording	Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subject will be enrolled. A total of 9,630

	subjects will be randomly assigned to one of 2 arms: experimental and control. The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject, if necessary.
New wording	For season 2, the randomization will be further stratified by sub-study participation (i.e. Yes or No). For the CMI substudy, 350 subjects from sites participating to the sub-study (sub-study sites) are randomly chosen among 700 sub-study sites subjects with appoximately 263 subjects selected at random from 350 M-001 sub-study sites subjects and approximately 87 from 350 placebo sub-study sites subjects. Once consented and upon entry of demographic data and confirmation of eligibility for this trial, the subject will be enrolled. A total of 12,000 subjects will be randomly assigned to one of 2 arms: experimental and control. A total of 700 subjects will be randomly chosen to participate to the sub-study, with approximately 263 subjects selected at random from 350 M-001 sub-study sites subjects and approximately 87 from 350 placebo sub-study sites subjects. The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual subject, if necessary.
5.3.2. Masking Procedures	
Original wording	Subjects, investigators, and study personnel performing any study-related assessments following study injection will be blinded to treatment assignment to the two M-001 dosing regimen or placebo. Laboratory personnel will be blinded to treatment assignment. Separate unblinded laboratory personnel will be assigned if needed. (…) The site unblinded staff member will be responsible for preparing the syringe and covering it or making it (the content) in other way not visible for the subject before its administration to keep the subject blinded. This un-blinded staff member will not participate in the assessment of respiratory illnesses or ILI, or in the collection of safety information.
New wording	Subjects, investigators, and study personnel performing any study-related assessments following study injection, as well as collecting

	swab specimends or blood samples, will be blinded to study group and treatment assignment to both: M-001 or placebo. Laboratory personnel will be blinded to treatment assignment. Separate unblinded laboratory personnel will be assigned if needed. (…) The site unblinded staff member will be responsible for preparing the syringe and covering it or making it (the content) in other way not visible for the subject before its administration to keep the subject blinded. This un-blinded staff member will not participate in the assessment of respiratory illnesses or ILI, or in the collection of safety information.
5.3.3. Reasons for Withdrawal and 5.3.5 Termination of Study	
Original wording	Termination of the study (…) Although the study Sponsor has every intention of completing the study, it reserves the right to terminate the study at any time for
New wording	• Termination of the study or the study cohort. (…) Although the study Sponsor has every intention of completing the study, it reserves the right to terminate the study or the study cohort at any time for
6. STUDY INTERVENTION/INVESTIGATIONAL PRODUCT	
6.1. Study Product Description To 6.4. Assessment of Subject Compliance with Study Intervention/ Investigational Product	
Original wording	Placebo (normal saline) will be sourced from the European Union (marketed product). It will be labelled and distributed by Klifo A/S. **M-001** M-001 is supplied as a sterile, cloudy-white suspension in single-dose vials of volume sufficient to dose 1 mg of M-001 (1mg is a single dose). Each vial contains a fill volume (less than 1 mL) of concentration provided in the study manual for respective product batch that should

	be transferred to a 1mL syringe for injection according to the study manual. It contains no preservative (i.e. non-thimerosal). Volume of the product containing 1mg of M-001 (1 mg of M-001 is the dose to be administered per each vaccination) will be provided in the study manual for respective product batch. Study product must be stored at 2°C to 8°C. Do not freeze. **Placebo (Normal Saline)** 0.9% Sodium Chloride, USP, Ph.Eur. or "normal" saline is a sterile, nonpyrogenic, isotonic solution; each mL contains sodium chloride 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied only in single-dose containers. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH 5.3, range 4.5-7.0). The normal saline will be stored according to storage conditions defined in product-specific Summary of Product Characteristics. (…) **M-001 investigational influenza vaccine product:** The 1 mg of M-001 dose will be administered as a single intramuscular injection according to the study manual. The M-001 will be provided in vials as described in paragraph 6.1.1 of the protocol. Visually inspect M-001 vaccine vial upon receipt and prior to use. After shaking, the suspension will be cloudy white in appearance. If the M-001 vaccine precipitated, it should be re-suspended by tapping on the vial with the finger or mixing until the suspension looks homogeneous, then it should be transferred to a syringe. If the M-001 vaccine appears to have been damaged, contaminated or discolored, or if there are any concerns regarding its integrity, do NOT use the affected study product(s). **Normal Saline (Placebo):** The saline placebo dose will be administered as a single intramuscular injection. Exact volume to be injected will be defined in the study manual and will be equal to the volume of the M-001 defined for the active treatment (M-001) study arm. The saline will be provided in vials as described in paragraph 6.1.1 of the protocol. (…) The syringe containing the dose of study vaccine (or placebo) will be inverted a few times before administered (…)

	Aseptic technique will be used for the preparation and administration of each dose of study vaccine using a disposable sterile needle appropriate in length and size for each subject and a disposable sterile 1 mL syringe. (…) If a subject's study vaccination (study dose 2) is deferred, vaccination should be rescheduled to occur within the acceptable protocol-specified window for that visit (22 + 9 days). (…) After receipt of the M-001 and placebo vials, the site (…) Used and unused vials of M-001 (…) Study product will be administered to subjects by a blinded vaccine administrator
New wording	Placebo (normal saline) will be provided by BiondVax. Packaging, labeling and distribution will be performed by Klifo A/S. **M-001** In Season 1, M-001 is supplied as a sterile, cloudy-white suspension in single-dose vials of volume sufficient to dose 1 mg of M-001 (1mg is a single dose). Each vial contains a fill volume (less than 1 mL) of concentration provided in the study manual for respective product batch that should be transferred to a 1mL syringe for injection according to the study manual. It contains no preservative (i.e. non-thimerosal). Volume of the product containing 1mg of M-001 (1 mg of M-001 is the dose to be administered per each vaccination) will be provided in the study manual for respective product batch. In Season 2, M-001 is supplied in single-dose pre-filled syringes containing 1mg of M-001. Each syringe contains a fill volume (0.6 mL) of concentration provided in the study manual for respective product batch that should injected according to the study manual. It contains no preservative (i.e. non-thimerosal). Study product must be stored at 2°C to 8°C. Do not freeze. **Placebo (Normal Saline)** 0.9% Sodium Chloride, USP, Ph.Eur. or "normal" saline is a sterile, nonpyrogenic, isotonic solution; each mL contains sodium chloride 9 mg. It contains no bacteriostatic agent, antimicrobial agent, preservatives, or added buffer and is supplied in single-dose ready to use syringes, containing 0.6 mL. The solution may contain hydrochloric acid and/or sodium hydroxide for pH adjustment (pH

	5.3, range 4.5-7.0). The normal saline will be stored according to storage conditions defined in product-specific Summary of Product Characteristics. (…) **M-001 investigational influenza vaccine product:** The 1 mg of M-001 dose will be administered as a single intramuscular injection according to the study manual. The M-001 will be provided in vials (Season 1) or syringes (in Season 2) as described in paragraph 6.1.1 of the protocol. Visually inspect M-001 vaccine vial (Season 1)/ ready to use syringe (Season 2) upon receipt and prior to use. After shaking, the suspension will be cloudy white in appearance. For season 2, if the M-001 vaccine precipitated, it should be re-suspended by tapping on the pre-filled syringe strongly with the finger or by intensive shaking until the suspension looks homogeneous. If the M-001 vaccine appears to have been damaged, contaminated or discolored, or if there are any concerns regarding its integrity, do NOT use the affected study product(s). **Normal Saline (Placebo):** The saline placebo dose will be administered as a single intramuscular injection. Exact volume to be injected will be defined in the study manual and will be equal to the volume of the M-001 defined for the active treatment (M-001) study arm. The saline will be provided in ready to use syringes as described in paragraph 6.1.1 of the protocol. (…) The syringe containing the dose of study vaccine (or placebo) will be inverted a few times, and the air bubble removed before administered (…) Aseptic technique will be used for the preparation and administration of each dose of study vaccine/placebo using a disposable sterile needle appropriate in length and size for each subject. (…) If a subject's second study vaccination (study dose 2) cannot occur on Day 22, vaccination should be rescheduled to occur within the expected protocol-specified window for that visit (Day 22 + 9 days), if possible. (…) After receipt of the M-001 and placebo vials or syringes, (…) Used and unused vials or syringes of M-001 (…)

	Study product will be administered to subjects by an unblinded vaccine administrator
6.5. Concomitant Medications/Treatments	
Original wording	Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include all current medications and medications taken within 3 months days prior to Day 0 through approximately Day 43. After Day 43 only concomitant medications relevant for respiratory illness as per PI judgment, (…) . Prescription and over-the-counter drugs will be included as well as herbals, vitamins and supplements. In addition, information on receipt of other influenza or non-influenza study vaccines will be solicited at each clinic visit or phone call by PI/SI or delegated study site personnel, and, if confirmed, such vaccination will be reported in the eCRF. (…) Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely necessary. Medications in this category include the prohibited medications per the Subject Exclusion Criteria (see Section 5.2). (…) contraceptives are permitted.
New wording	Administration of any medications, therapies, or vaccines will be recorded on the appropriate data collection form. Concomitant medications will include at least all current medications and medications taken within 3 months prior to Day 0 through approximately Day 43 or 21 days after second vaccination day whichever occurs later. After Day 43 (or 21 days after V2 day) only concomitant medications relevant for background chronic respiratory illness as per PI judgment, (…) Prescription and over-the-counter drugs will be included as well as herbals, vitamins and supplements. In addition, information on receipt of other influenza or non-influenza study vaccines will be solicited at each subject's visit at the site or phone call by PI/SI or delegated study site personnel, and, if confirmed, such vaccination will be reported in the eCRF. Past use of influenza vaccinations should be recorded for at least 3 years prior to study entry. (…) Medications that might interfere with the evaluation of the investigational product should not be used unless absolutely

	necessary. However, as the study concerns elderly population use of such medications cannot be excluded. Medications in this category include the prohibited medications per the Subject Exclusion Criteria (see Section 5.2). (…) contraceptives are permitted. Medications which require relatively frequent dose adjustments, like insulin, hormones, anti-inflammatory or pain relieve medications, are considered as stable treatment for a chronic condition for the purpose of Inclusion Criterion number 3 compliance assessment as long as the treatment (regular or p.r.n.) has been continued for at least 3 months prior to first vaccination. Switch within the same therapeutic class or type of treatment is not automatically considered as an unstable treatment but is subject to PI's assessment and decision.
7. STUDY SCHEDULE	
Original wording	7. STUDY SCHEDULE 7.1. Enrollment/Baseline (Visit 1, Day 0, Dose 1, Clinic Visit) • (…). •. Subject receipt of licensed seasonal influenza vaccine, and approximate date of vaccination will be recorded on the appropriate data collection form, if known. • (…) • All concomitant medications taken within 3 months prior to signing the ICF will be recorded on the appropriate data collection form prior to the first study vaccination. • (…) • A targeted physical examination may be performed prior to the first study vaccination by a study clinician, if indicated based on review of complete medical history. • (…) • Approximately 40 mL of venous blood will be collected prior to the first study vaccination for isolation of PBMCs from a subset from Cohort 2 intended for CMI testing. • (…) • (…). The study vaccination site will be examined, and any AE/SAEs will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic. • (…). Subjects will be encouraged to take their temperature around the same time each day for 8 days post vaccination (day of the vaccination inclusive). (…). The participants will be instructed to return the completed diary, covering period between Visit 1 and Visit 2 to the site for Visit 2. 7.2. Second Vaccination

	7.2.1. Visit 2, Day 22, Clinic Visit (22 days [+9 days] post first study vaccination day) • Study personnel will review the memory aid information with subjects and assess and record all AE/SAEs and concomitant medications on the appropriate data collection form. •(…) • If indicated by review of memory aid, obtain vital signs • Measure oral temperature. • A targeted physical examination may be performed by a study physician, if indicated based on review of interim medical history. • (…). • (…)The study vaccination site for Dose 2 will be examined, and any AE/SAEs will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic. • Subjects will be provided with a memory aid in a stamped envelope to record daily oral temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their temperature around the same time each day. (…) The participants that are required for visit 3 will be notified and will be requested to bring the diary on visit 3. 7.2.2. Visit 3, Day 37, Clinic Visit (16 days [±3 days] post second study vaccination for subset of subjects from Cohort 2, in season 2019/20) • Study personnel will review the memory aid information with subjects and assess and record all solicited events / unsolicited AEs/SAEs and concomitant medications on the appropriate data collection form. • Counsel women of childbearing potential on contraception and avoidance of pregnancy. • A targeted physical examination and vital signs collection may be performed by a study clinician if indicated based on review of interim medical history. • (…) • Approximately 40 mL of venous blood will be collected for isolation of PBMCs from a subset of subjects from Cohort 2. 7.3. Follow up period for safety and efficacy: Safety surveillance: (…) Passive efficacy surveillance: Following randomization and vaccinations, subjects will be instructed to contact the site if they experience symptoms of a respiratory illness during the annual surveillance periods, from Day 14 after second vaccination day until

	15 May of the following year. Another period of follow up will take place in the influenza season that follows (total of 2 years follow up). Active efficacy surveillance will be performed from November 15th until the week of 30 March the following year, the most likely period of influenza virus circulation in the Northern Hemisphere. Another period of follow up will take place in the influenza season that follows (total of 2 years follow up). The participants will be contacted by a dedicated study staff twice a week between approximately November 15th through March 30th; Another period of follow up may take place in the influenza season that follows (up to 2 years follow up). Participants will be contacted as described above by non-site study staff to monitor for influenza-like illness (ILI).; participants identified this way as potentially having ILI will be followed up by relevant study site personnel to confirm if the participant's symptoms and signs meet study ILI definition. During the period from Day 14 after second vaccination day until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), the site will arrange for an NP/nasal and throat swab to be collected if the subject experiences a new onset of the above mentioned symptoms of ILI (that persist for or reoccur after a period of at least 12 hours). (…) NP/nasal and throat swab collection: NP swab (or nasal and throat swab) specimens will be collected during the period from Day 14 after second vaccination until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), within 24 hours from ILI being reported to or identified by study personnel and up to 4 days of the onset of ILI symptoms for confirmation of influenza virus (…) **The end of influenza season will be defined for each participating country by the Medical director based on national surveillance and study data.** The Sponsor's Responsible Medical Director will base the decision on the following criteria: (…) If the 2 criteria are met for the region/zone where the research site is located, the site will be instructed to continue obtaining NP/nasal and throat swabs if subjects report a new respiratory illness. (…)

	After 30th of April, passive surveillance will continue, with subjects expected to call the research site to report the occurrence of any new respiratory illness symptoms. (…) ILI follow-up calls: Any ILI must be followed up for up to 30 days following the start date or until resolved. Site personnel will follow up the participant with ILI at 10±3 days after ILI start date. Follow up information on symptoms associated with the ILI will be collected by study staff through a telephone call performed at 10±3 days (and up to 30 days) (unless collected at unscheduled clinic visit at relevant time point) following the illness start date. Laboratory testing for the confirmation of influenza: All NP/nasal and throat swab specimens will be submitted for analysis by polymerase chain reaction (qRT-PCR), and when the result is found positive, another aliquot from such specimen will be also examined by culture confirmation test. Typing and subtyping of the influenza virus will be performed with PCR based method. (…). 7.4. Safety Follow Up Visit, Visit 4, Day 202: Phone Call/ Electronic Communication (180 days +/-14 post last study vaccination) Subjects will be contacted by phone or electronic communication (e.g., email, text message) to query for safety events. Subjects will be asked to provide positive responses to the follow-up by phone. (…) 7.5. Follow Up Period for Efficacy Season 2 Participants from cohort 1 who did not withdraw during season 1 (2018-2019) will be followed up for ILI during the subsequent season (2019-2020), to define the duration of the protection unless during initial call for the season 2 a participant decides not to continue or is determined as being not able to comply with the study protocol. Passive and active surveillance will take place as detailed for season 1 (see 7.3(. Passive surveillance will take place between September 15, 2019 and May 15, 2020. Active surveillance will take place between November 15, 2019 and March 30, 2020. During this period, the dedicated study staff will contact the participants twice a week to monitor for ILI symptoms as detailed above in 7.3. (Follow up calls in season 2019/20 will be for all 9,630 participants). (…) 7.7. Early Termination Visit

	(…) • If indicated by interim medical history, perform physical examination and obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. • (…). • Information regarding AEs/SAEs will be recorded on the appropriate data collection form. AEs will be limited to SAEs if after 21 days following the last study vaccination day. • A targeted physical examination may be performed by a study clinician licensed to make medical diagnoses, if indicated based on review of interim medical history. • Examine study vaccination site, and perform post-administration reactogenicity assessment (if within 8 days after the last study vaccination, day of the vaccination inclusive). 7.8. Unscheduled Visit (…). • All AEs/SAEs will be recorded on the appropriate data collection form. AEs will be limited to SAEs if after 21 days after the last study vaccination day. • (…). • If deemed as relevant and/or needed, perform physical examination and obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. • (…).
New wording	7.1. Enrollment/Baseline (Visit 1, Day 0, Dose 1, Site Visit) • (…) • History of receipt of licensed seasonal influenza vaccine(s) from at least last 3 years, and approximate date of vaccination will be recorded on the appropriate data collection form, if known. • (…) • All concomitant medications taken before signing the ICF (at minimum those taken within 3 months prior to it, if applicable) will be recorded on the appropriate data collection form prior to the first study vaccination. • (…) • Standard physical examination (PE) will be performed on day 0 prior to the first study vaccination. If subject's medical history is known based on medical records (but not if there are no medical records available at all), a limited, targeted physical examination may be performed instead of standard scope PE prior to the first study vaccination by a study clinician, however in any case neurologic component of PE and physical examination of head/upper respiratory tract must be performed. Except for neurologic, head and upper

	respiratory tract physical examination, for other body systems only findings relevant from the study perspective and not obvious from medical history need to recorded in the eCRF • (…) • Approximately 40 mL of venous blood will be collected prior to the first study vaccination for isolation of PBMCs from a subset from Cohort 2 intended for CMI testing (applicable only for selected study sites). • (…) • In study sites participating in CMI assessment, additional, nested randomization is planned to assign certain number of subjects to one of the subset substudy groups. • (…). The study vaccination site will be examined, and observed reactions, AEs, SAEs (as applicable) will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic. • (…). Subjects will be encouraged to take their temperature on the vaccination day in the evening and then at selected approximately the same time each day for next 7 days after the vaccination day. (…) The participants will be instructed to return the completed diary, covering period between Visit 1 and Visit 2 to the site for Visit 2, and to bring their study thermometer with them to the Visit 2. 7.2. Second Vaccination 7.2.1. Visit 2, Day 22, Site Visit (22 days [+9 days] post first study vaccination day) • Study personnel will review the memory aid information with subjects and assess and record all solicited, reported reactions, AEs, SAEs (as applicable) and concomitant medications on the appropriate data collection form. • (…) • If indicated by review of memory aid or recent medical history, obtain vital signs • A targeted physical examination should be performed by a study physician if assessed as needed based on medical interview concerning period between Visit 1 and Visit 2 . • (…). • (…) The study vaccination site for Dose 2 will be examined, and any reactions, AEs or SAEs (as applicable) will be assessed and recorded on the appropriate data collection form prior to discharge from the clinic. • Subjects will be provided with a memory aid (paper diaries) in a stamped envelope to record daily oral temperature, solicited injection site and systemic reactions, any unsolicited AEs, and concomitant medications. Subjects will be encouraged to take their

	temperature on the vaccination day in the evening and then at selected approximately the same time each day for next 7 days after the vaccination day. (…) The participants that are coming for visit 3 to the site will be requested to bring the diary to that visit. 7.2.2. Visit 3, Day 36, Site Visit (14 days [±2 days] post second study vaccination day(visit 3 - in season 2019/20 only) • This is a visit in study site for the subset of subjects selected for immunogenicity evaluation and site visit or a phone call (if site visit is not feasible) for the rest of the participants. The following #4 and #6 points refer to those actually visiting the clinic: • Study personnel will review the memory aid information with subjects and assess and record all solicited events / unsolicited reactions, AEs, SAEs and concomitant medications on the appropriate data collection form. • Counsel women of childbearing potential on contraception and avoidance of pregnancy. • [site visits only] A targeted physical examination and/or vital signs collection may be performed by a study clinician if assessed as needed based on review of recent medical history. • (…) • [site visits only] Approximately 40 mL of venous blood will be collected for isolation of PBMCs from a subset of subjects from Cohort 2. 7.3. Follow up period for safety and efficacy: Safety surveillance: (…) Passive efficacy surveillance: Following randomization and vaccinations, subjects will be instructed to contact the site if they experience symptoms of a respiratory illness or influenza-like illness during the annual surveillance periods defined as from Day 14 after second vaccination day or from September 15 (the later of them) until 15 May of the following year. Active efficacy surveillance will be performed from November 15th (in Season 1) or from December 1st (in Season 2) until the week of 30 March the following year, the most likely period of influenza virus circulation in the Northern Hemisphere. The participants will be contacted by a dedicated study staff up to twice a week between approximately November 15th through March 31st . Participants will be contacted as described above by non-site study staff to monitor for influenza-like illness (ILI).; participants identified this way as potentially having ILI will be followed up by relevant study site personnel to confirm if the participant's symptoms and signs meet study ILI definition.

	ILI is NOT to be understood as condition caused specifically by influenza virus. The etiology of ILI may be very different, and only after analysis of swabs taken from subjects , the presence or absence of influenza virus in swab sample can be determined. Hence, even if it is suspected that ILI is caused by e.g. a bacteria, or by some other virus than influenza virus, such ILI remains valid reason for swab collection, also because in some cases there may be a superinfection or parallel infection with influenza virus. However, if an Investigator is sure that an ILI-qualifying symptom/sign comes purely from underlying chronic condition (e.g. arthritis, COPD, asthma), including also the severity of the symptoms/signs, or belongs to clinical presentation of another, known, completely non-infectious condition (e.g. toxicity, injury, cancer), then it is understood that the investigator may decide to NOT recognize the case as meeting ILI criteria, and to NOT qualify the subject for swab collection. The rationale behind disqualifying such cases from ILI is preference for avoidance of exposing subjects to swab collection procedure in case when it is absolutely sure a priori that infectious etiology of the symptoms/signs is highly unlikely. During the period from Day 14 after second vaccination day (not earlier than from September 15th) until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), the site will arrange for an NP/nasal and throat swab to be collected if the subject experiences a new onset of the above mentioned symptoms of ILI (that persist for or reoccur after a period of at least 12 hours). (…) NP/nasal and throat swab collection: NP swab (or nasal and throat swab) specimens will be collected during the period from Day 14 after second vaccination day (but not earlier than from September 15th) until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), within 24 hours from ILI being reported to or identified by study personnel and up to 4 days of the onset of ILI qualifying symptom(s) for confirmation of influenza virus (…) **The end of influenza season will be defined for each participating country by the Medical director based on national surveillance and study data.** The Sponsor's Responsible Medical Director will base the decision on the following criteria: (…)

	If the 2 criteria are met for the region/zone where the research site is located, the site will be instructed to continue obtaining NP/nasal and throat swabs if a subject has a new influenza-like illness. (…) After 30th of April, passive surveillance will continue, with subjects expected to call the research site to report the occurrence of any new respiratory illness or influenza-like illness symptoms. (…) ILI follow-up calls: Any ILI must be followed up for up to 30 days following the start date or until resolved. Site personnel will follow up the participant with ILI at 10±3 days after ILI start date. Follow up information on symptoms associated with the ILI will be collected by study staff through a telephone call performed at 10±3 days (and up to 30 days) (unless collected at unscheduled site visit at relevant time point) following the illness start date. Protocol defined ILI end date is the date when for at least 24 hours ILI symptoms are no longer present. Of note, some symptoms may persist after ILI for a long time, but the duration of ILI is to be determined by presence of symptoms of ILI understood as active disease, or "influenza symptom", contrary to symptoms being part of an underlying chronic condition (e.g. COPD, arthritis), and contrary to chronic complications and/or sequelae of the ILI. When no clear end of ILI can be observed, the PI is requested to make rational judgment and determine the ILI end date based on available data and his/her experience. It is expected, that normally, ILI should not last longer than 2-3 weeks, and in case of suspected overlapping new infection, the two infection episodes should be recognized by PI as separate ILI cases. Laboratory testing for the confirmation of influenza: All NP/nasal and throat swab specimens will be submitted for analysis by polymerase chain reaction (qRT-PCR), and when the result is found positive, and if there is a sufficient content of viruses (as determined by Ct value ≤35)" [Ct= cycle threshold] another aliquot from such specimen will be also examined by culture confirmation test. Typing and subtyping of the influenza virus will be performed with PCR based method. (…). Out of study influenza infection confirmation: in cases when no swab collection was performed within study framework, but valid, relevant external medical documentation exists confirming recent or ongoing

	influenza infection (laboratory confirmation – PCR, culture or serology - IgM antibodies), such medical documentation will be subject to sponsor's approval as surrogate proofs of influenza infection, and if approved as valid, may be taken into account for exploratory analyzes. Details of exploratory analyzes will be defined in statistical analysis plan. 7.4. Safety Follow Up Visit, Visit 4, Day 202: Phone Call/ Electronic Communication (180 days +/-14 post last study vaccination) Subjects will be contacted by phone or electronic communication (e.g., email, text message) to query for safety events. In case follow-up contact is needed based on the responses, subjects will be asked to provide further details to the follow-up by phone. (…) 7.5. Follow Up Period for Efficacy Season 2 Passive surveillance will take place between September 15, 2019 and May 15, 2020. Active surveillance for cohort 2 will take place between December 1st , 2019 and March 31, 2020. During this period, the dedicated study staff will contact the participants up to twice a week to monitor for ILI symptoms as detailed above in 7.3. (Follow up calls in season 2019/20 will be for participants in cohort 2 only). As of the end of the season 1, the follow up for Cohort 1 subjects in season 2019/2020 is not planned and participation of all Cohort 1 subjects will be assumed as completed with the end of Season 1, i.e. the latest on May 15th except for cases defined elsewhere (e.g. ongoing ILI, SAE follow-up). (…) 7.7. Early Termination Visit (…) • If indicated by medical history, perform physical examination and/or obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. • (…). • Information regarding reactions recorded in diary/-ies, AEs and SAEs will be recorded on the appropriate data collection form. Recording of AEs in the EDC will be limited to SAEs if after 21 days following the last study vaccination day. • Examine study vaccination site, and perform post-administration reactogenicity assessment (if within 8 days after the last study vaccination, day of the vaccination inclusive). 7.8. Unscheduled Visit

	(…) • All reactions recorded in diary/-ies, AEs, SAEs will be recorded on the appropriate data collection form. Recording of AEs in the EDC will be limited to SAEs if after 21 days after the last study vaccination day. • (…). • If deemed as relevant and/or needed, perform physical examination and/or obtain vital signs including oral temperature. Subjects must not eat or drink anything hot or cold, or smoke within 10 minutes prior to taking oral temperature. • (…).
8. STUDY PROCEDURES/EVALUATIONS	
Original wording	8.1. Clinical Evaluations (…). Concomitant Medications: All current medications and medications taken within 3 months before Study Day 0 (prescription and over-the-counter drugs) will be included, as well as vitamins and supplements, through 21 days after the last study injection day Vital signs: blood pressure, oral temperature and pulse will be collected at study visit 1,on early termination visit and as needed at the other study visits. Only oral temperature will be measured on visit 2. Height, weight: These parameters will be measured at Day 0 (Visit 1). Targeted Physical Examination: This may be conducted at any study visit based on indicated symptoms. (…) Subject memory aids will be reviewed with the subject for AEs at the clinic visit following the first study injection. (…). 8.2. Laboratory Evaluations Schedules and volumes of clinical laboratory tests and immunogenicity assays are specified in Schedule of events (Table 2). (…). Refer to the relevant instruction included in the relevant study manual for further details. Detailed instructions for the preparation of NP (or combination of nasal and throat swabs) samples are contained in the relevant study manual provided to the sites and relevant study personnel. 8.2.3. Special Assays or Procedures Cellular (CMI) Studies

	Assays to measure T cell responses will be performed by a qualified laboratory. Venous blood samples for isolation of PBMCs will be collected from a subset of cohort 2, immediately prior to the first study vaccination (Day 0, visit 1 in season 2), and 16 days (day of the vaccination inclusive) after the second M-001 vaccination (Day 37, visit 3, season 2). 8.2.4. Specimen Preparation, Handling, and Shipping (…). Swab samples will be shipped on ongoing basis or in batches shipped regularly (at least once a month) during the course of this study. (…) Samples for PBMC will be shipped from sites on ongoing basis aiming at same day or next day delivery.
New wording	8.1. Clinical Evaluations (…). Concomitant Medications: All current medications and medications taken within 3 months before Study Day 0 (prescription and over-the-counter drugs) will be included, as well as vitamins and supplements, through 21 days after the last study injection day, unless relevant for chronic background respiratory illness, as per PI judgment, or related to AE or ILI. Vital signs: blood pressure, oral temperature and pulse will be collected at study visit 1, and as needed at any other study visits Only oral temperature is required to be measured on visit 2. Measurement of oral temperature should be performed with thermometers provided by the study Sponsor. Oral temperature should be measured by keeping the tip of the thermometer under the tongue for sufficient amount of time until the temperature reading stabilizes. In cases when level of oral temperature seems too low the measurement should be repeated and care should be taken to correctly place the tip of the thermometer and to keep it under the tongue for sufficient amount of time (until the temperature stops growing). Height, weight: These parameters will be measured at Day 0 (Visit 1). Physical Examination: On Visit 1 standard physical examination should be performed prior to the first study vaccination, but if subject's medical history is known based on medical records, a limited, targeted physical examination may be performed instead of standard scope PE prior to the first study vaccination by a study clinician, however in any case neurologic component of PE and physical examination of head/upper respiratory tract must be performed. On visits other than 1 limited, targeted physical examination may be performed if assessed by investigator as needed. (…)

	Subject memory aids will be reviewed with the subject for AEs at the site visit following the first study injection, and over the phone after the second study injection (unless the subject comes to the site for Visit 3). (…). 8.2. Laboratory Evaluations Schedules and volumes of clinical laboratory tests and immunogenicity assays are specified in Schedule of events (Table 3 and 4 in the Synopsis). (…). Detailed instructions for the preparation of NP (or combination of nasal and throat swabs) samples are contained in the relevant study manual provided to the sites and relevant study personnel. 8.2.3. Special Assays or Procedures Cellular (CMI) Studies Assays to measure T cell responses will be performed by a qualified laboratory. Venous blood samples for isolation of PBMCs will be collected from a subset of cohort 2, immediately prior to the first study vaccination (Day 0, visit 1 in season 2), and approximately 15 days (day of the vaccination inclusive) after the second M-001 vaccination (Day 36, visit 3, season 2). 8.2.4. Specimen Preparation, Handling, and Shipping (…. Swab samples will be shipped in batches regularly during the course of this study. (…). Samples for PBMC will be shipped from sites on ongoing basis aiming at same day or next day delivery, as possible.
9. **ASSESSMENT OF SAFETY**	
Original wording	Unsolicited AEs/SAEs – non-serious AEs/SAEs occurring from the time of the study vaccination through approximately 22 days after the study vaccination (day of the vaccination inclusive) (…) AEs must be graded for severity and assessed for relationship to study product (see definitions below). AEs characterized as intermittent require documentation of onset and duration of each episode. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF within study periods as described below.

	Unsolicited AEs will be collected occurring from the time of the study vaccination through approximately 22 days after the study vaccination (day of the study vaccination inclusive). (…) Tables numbered 4,5,6,7 (…) inpatient hospitalization or prolongation of existing hospitalization (excluding pre-planned elective surgeries or other pre-planned hospitalizations), (…) ILI as AE will be documented if occur within 8 days post vaccination (day of the vaccination inclusive). (…) 9.6. Efficacy Assessment 9.6.1. Molecular Detection and Sequencing Methodology (qRT-PCR): (…). For samples that are found positive for influenza in the qRT-PCR assay, further testing by culture confirmation will be performed. 9.6.2. Influenza Culture and Virus Isolation: .
New wording	Unsolicited AEs/SAEs – unsolicited AEs/SAEs occurring from the time of the study vaccination through approximately 22 days after each study vaccination (day of the vaccination inclusive) (…) AEs must be graded for severity and assessed for relationship to study product (see definitions below). AEs characterized as intermittent require documentation in the subject's file of onset and duration of each episode. It is up to PI's decision whether the episodes are recorded in the eCRF as separate events or under one event with comment added on the intermittent (or similar) nature of the event. The start and stop date of each reported AE will be recorded on the appropriate data collection form and eCRF within study periods as described below. •Unsolicited AEs – which do not meet SAE criteria, nor ILI, AESI or NOCI definition should be reported only until ~22 days post each study vaccination, thus - per protocol – such AEs, if they occurred later then 22 days post study vaccination day, should not be recorded in the AE section of the eCRF. They still need to be documented in the subject's study file at the site. (…)

	Desription of changes: Tables numbered 4,5,6,7 re-numbered as 5,6,7,8 respectively (…) inpatient hospitalization or prolongation of existing hospitalization (excluding pre-planned elective surgeries or other pre-planned hospitalizations; for this option it is not required that they were pre-planned solely before Visit 1, they might be pre-planned also after Visit 1), (…) ILI will be documented as AE if occurs within 8 days post vaccination (day of the vaccination inclusive). (…) 9.6. Efficacy Assessment 9.6.1. Molecular Detection and Sequencing Methodology (qRT-PCR): (…) For samples that are found positive for influenza in the qRT-PCR assay, further testing by culture confirmation will be performed if there is a sufficient content of viruses (as determined by Ct value <35)" [Ct= cycle threshold]. If swab specimen was not collected but infection with influenza virus has been confirmed outside of the study framework and valid medical documentation exists confirming such virus identification (e.g. hospital discharge), such cases may be recognized by study sponsor as valid confirmed influenza cases. Extent to which such results will be included in the statistical analyses will be defined in statistical analysis plan. 9.6.2. Influenza Culture:
11. STATISTICAL CONSIDERATIONS	
Original wording	This section provides an overview of the statistical considerations for the design, conduct, and analysis of the phase 3 trial of Multimeric-001 influenza vaccine. A formal statistical analysis plan will be developed and finalized prior to or shortly after enrollment starts in Year 1. 11.1 Study Hypotheses (…). 11.3 Sample Size Considerations 11.3.1 Study Design (…)

	All doses will be administered IM approximately 21 days apart. All subjects from cohort 1 will be followed for up to two consecutive influenza seasons with no obligation to continue in season 3 if the study is extended to third season with protocol amendment. (…) A lots consistency study is nested within the second year of the trial. In Year 1, a single lot of vaccine produced by Cytovance will be used. In Year 2, the lot produced by Cytovance as well as 2 lots produced by BiondVax in Israel will be employed. Thus, subjects randomized to vaccine in Year 2 will be further randomized 1:1:1 to one of the three lots of vaccines. A random sample of subjects enrolled in Year 2 will be selected to provide blood samples for the lots consistency study. For each vaccine lot, 275 (34.4%) of the roughly 800 subjects randomized to that lot will be selected. In order to maintain the study blind, 100 (4.2%) of the roughly 2,400 subjects randomized to placebo will be selected and bled as well. For these 925 subjects, blood samples will be collected prior to the first study vaccination (Day 0) and approximately 16 days (day of the vaccination inclusive) after the second vaccination (Day 37). However, T cell responses will be measured only in subjects who receive M-001. 11.3.2 Study Population and Sample Size The study population for this clinical trial includes 9,630 males and non-pregnant females, ≥50 years old, inclusive, who meet all eligibility criteria. The participants will be recruited from the general population. At least half of the participants will be ≥65 years old. The study sample size of 9,630 subjects is based on the lower bound of the two-sided 95% confidence interval for vaccine efficacy (VE) being above 40% with 80% probability when true VE is 62%. It assumes 1:1 randomization, a 3% attack rate in the study population, and no more than 10% of subjects lost to follow-up or excluded from the per protocol population. Under these assumptions, 182 first episodes of qRT-PCR -confirmed influenza of any strain occurring at least 15 days after the second dose of study vaccine or control and prior to the end of the first influenza season will be needed to demonstrate efficacy is at least 40%. In the event vaccine efficacy for a single influenza season is demonstrated, a lot consistency analysis will be performed at the end of Year 2. The endpoint for assessing lot consistency will be the percentage of CD4+ lymphocytes producing INF-g in response to any

	of the 9 peptides in M-001 measured at Day 37. Based on preliminary immunogenicity data, the percentage of CD4+ lymphocytes is approximately normally distributed with a mean of 25% and standard deviation of 12%. Assuming an equivalence margin of 5%, 250 subjects per lot would need to be enrolled to have 90% probability that the 95% confidence interval for the difference in mean percentage for each of 3 pair-wise comparisons falls between -5% and 5% when there is no true difference. Assuming no more than 10% of samples is missing or not evaluable, 275 subjects per lot will be targeted. 11.3.3 Subject Enrollment and Follow-up (…). 11.4.1 Interim Safety Review A DSMB will be convened by the sponsor to review study progress and participant, clinical, safety, reactogenicity, and efficacy data as described in section 9.5. Once the last subject in Year 1 completes the visit that occurs approximately at Day 202, the interim clinical database will be cleaned, monitored and locked. The first unblinded interim report will be issued to the DSMB at the end of the first influenza season of the trial approximately in June 2019). Based on the interim safety data, the DSMB may recommend continuing the study as planned, stopping the study for safety concerns, or modifying the study to ensure study objectives are followed. 11.4.2 Interim Efficacy Review There are no plans to stop the trial for futility or for efficacy at the end of Year 1. However if after the first flu season the total number of per protocol cases of confirmed influenza infection is substantially fewer than 82 cases, the DSMB may recommend increasing the sample size for Year 2. The sample size re-estimation plan will be detailed in the DSMB charter. (…). 11.5 Final Analysis Plan At the end of Year 2 a clinical study report (CSR) will be prepared summarizing the efficacy, safety, reactogenicity, and immunogenicity data. The clinical database will be cleaned, monitored, and locked prior to analysis. A formal statistical analysis plan will be developed and finalized prior to start of the study. Any post hoc analyses will be documented and clearly indicated in the CSR.

	11.5.1 Analysis Populations
	
	(…).
	
	The per protocol (PP) population includes all subjects in the ITT subset with the following exclusions:
	
	• Data from all available visits for subjects found to be ineligible at baseline
	• Data from all visits subsequent to major protocol deviations, such as:
	  • Second study vaccination not received
	  • Second study vaccination received out of window
	  • Receipt of non-study licensed live vaccine within 30 days before or anytime after each study vaccination
	  • Receipt of non-study licensed inactivated vaccine within 21 days before or anytime after each study vaccination day
	  • Receipt of non-study influenza vaccine (live or inactivated) within 30 days before or anytime after each study vaccination
	  • Receipt of immunosuppressive therapy (e.g., corticosteroids) within 30 days before or after each study vaccination
	
	Data from any visit that occurs substantially out of window.
	
	11.5.2 Analysis of Safety Data
	
	(…).
	
	Additionally, solicited events will be analyzed by taking the most severe response over the follow-up period, dichotomizing into a binary variable (none versus mild, moderate, or severe) and using standard techniques, such as exact confidence intervals, to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom. Summaries of solicited events will be presented separately for each study vaccination as well as overall study vaccinations by treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact test, as appropriate. The proportion of subjects reporting solicited symptoms between the

different study vaccinations (e.g., dose 1 vs. dose 2) will be compared using McNemar's test.

(…)

11.5.3 Analysis of Efficacy Data

For the primary analysis of vaccine efficacy (VE), the efficacy of M-(…).

To assess the ability of M-001 to prevent culture or PCR confirmed influenza in association with an ILI during a second influenza season without revaccination, we will extend the follow-up time for a first episode to include a second influenza season. Average vaccine efficacy over two seasons will be calculated as

$$VE[(0,2)] = 1 - [(C_V^*/ N_V) /(C_P^*/N_P)]$$

where C^*_V and C^*_P are the number of first episodes of influenza during 2 years of follow-up meeting the primary case definition in the vaccine and placebo group, respectively, and N_V and N_P are the number of per protocol subjects in the vaccine and placebo group, respectively. VE(2) assumes loss to follow-up is similar between the vaccine and placebo groups. It also assumes subjects will not receive a licensed influenza vaccine prior to or during the second season. If either assumption is violated, a Cox regression analysis of time to first episode over 2 years of follow-up will be performed. In addition to an indicator variable for randomization to the vaccine group (Z_1), the model will include a time dependent variable Z_2 that indicates the subject is in the vaccine group and under follow-up for a second season. Subjects who are known to receive a licensed influenza vaccine will be censored at the time of this vaccination. To test whether vaccine efficacy is different in the second season, we test whether the coefficient associated with Z_2 is equal to zero. For the Cox model, vaccine efficacy for a first season is estimated by

$$VE[(0,1)] = 1 - \exp\{-\beta_1\}$$

while vaccine efficacy over the second season is estimated by

$$VE[(1,2)] = 1 - \exp\{-\beta_1 - \beta_2\}.$$

11.5.4 Analysis of Cell Mediated Immunity Data

	For each pair of vaccine lots, the pairwise difference in the average percentage of CD4+ lymphocytes producing INF-γ in response to any of the 9 peptides in M-001 measured at Day 37 and its two-sided 95% confidence interval will be calculated. The un-pooled estimate of the variance of the difference will be used in the construction of the confidence intervals. Subjects with missing Day 37 data will be excluded. If all three confidence intervals fall within -5% and 5%, lot consistency will be demonstrated. In the event more than 10% of samples is missing or not evaluable, a sensitivity analysis will be performed in which multiple imputation is employed to impute missing Day 37 percentage of CD4+ cells. Details of the imputation procedure will be described in the statistical analysis plan. Please see the separate document "Statistical Analysis Plan" for additional information. 11.5.5 Missing Values and Outliers (…) 11.5.6 Statistical Software
New wording	This section provides an overview of the statistical considerations for the design, conduct, and analysis of the phase 3 trial of Multimeric-001 influenza vaccine. A formal statistical analysis plan will be developed and finalized prior to first DSMB meeting for Year 1 cohort and will be amended to reflect changes made to previous version of the protocol. 11.1 Study Hypotheses (…). 11.3 Sample Size Considerations 11.3.1 Study Design (…) For season 2, stratification will also be performed for participation to the sub-study. All doses will be administered IM approximately 21 days apart (recommended window is 21-30 days). All subjects from cohort 1 will be followed for up to two consecutive influenza seasons with no obligation to continue in season 3 if the study is extended to third season with protocol amendment. It is not planned to extend the participation of the cohort 1 subjects beyond season 1.

	(…). A total of up to 10 sites will be selected to participate to the CMI substudy. Blood samples will be collected prior to the first study vaccination (Day 0) and approximately 15 days (day of the vaccination inclusive) after the second vaccination (Day 36, 14±2 days since day of the second vaccination) in 350 randomly chosen subset of subjects from these sites. M-001 subjects will be 3 times more likely to be selected in the subset than placebo subjects and T cell responses will be measured only in subjects who receive M-001. 11.3.2 Study Population and Sample Size The study population for this clinical trial includes 12,000 males and non-pregnant females, ≥50 years old, inclusive, who meet all eligibility criteria. The participants will be recruited from the general population. At least half of the participants will be ≥65 years old. The study sample size of 12,000 subjects is based on the lower bound of the two-sided 95% confidence interval for vaccine efficacy (VE) being above 40% with 80% probability when true VE is 62%. It assumes 1:1 randomization, a 2.41% attack rate in the study population, and no more than 10% of subjects lost to follow-up or excluded from the per protocol population. Under these assumptions, 182 first episodes of qRT-PCR -confirmed influenza of any strain occurring at least 15 days after the second dose of study vaccine or control and prior to the end of the first influenza season will be needed to demonstrate efficacy is at least 40%. A total of up to 10 sites will be selected to participate to the CMI substudy. A total of 350 subjects will be randomly chosen among 700 subjects from the selected sites: approximately 263 subjects selected at random from 350 M-001 subjects and approximately 87 from 350 placebo subjects; placebo subjects being selected to maintain the study blind. Assuming that among the 263 M-001 selected subjects, 210 will have valid measurement for the change from baseline in percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001, then this endpoint can be estimated with a precision of at most 2% (1/2 width of the 95% CI). 11.3.3 Subject Enrollment and Follow-up (…) 11.4.1 Interim Safety Review A DSMB will be convened by the sponsor to review study progress and participant, clinical, safety, reactogenicity, and efficacy data as

	described in section 9.5. Once the last subject in Year 1 completes the visit that occurs approximately at Day 202, the clinical database will be cleaned, monitored and analyzed in blinded manner. The first partly unblinded report will be issued to the DSMB at the end of the first influenza season of the trial approximately in June 2019, though some data may be requested by DSMB to be provided to them earlier. Based on the interim review of safety data, the DSMB may recommend continuing the study as planned, stopping the study for safety concerns, or modifying the study to ensure study objectives are followed. 11.4.2 Interim Efficacy Review There are no plans to stop the trial for futility or for efficacy at the end of Year 1. However if after the first flu season the total number of per protocol cases of confirmed influenza infection is substantially fewer than there may be a decision made by the Sponsor about increasing the sample size for Year 2. 11.5 Final Analysis Plan At the end of Year 2 a clinical study report (CSR) will be prepared (unless the study is decided to be continued for Year 3) summarizing the efficacy, safety, reactogenicity, and immunogenicity data. The clinical database will be cleaned, monitored, and locked prior to analysis. A formal statistical analysis plan for the efficacy and immunogenicity data will be developed and finalized prior to start of the study. Any changes to the plan including post hoc analyses will be documented and clearly indicated in the CSR. 11.5.1 Analysis Populations (…). The per protocol (PP) population includes all subjects in the ITT subset satisfying the following criteria: • Subject met all protocol-specified inclusion criteria and met no exclusion criterion, • Subject received both doses of M-001/placebo as randomized, in the protocol-specified time frame, and at the intended dose level, • Subject did not receive M-001/placebo that was not properly handled or was otherwise not acceptable for administration,

	• Subject had at least one successful surveillance contact 15 days or more after the second dose of M-001/placebo, or attended at least one ILI visit due to ILI symptoms • Subject did not receive a seasonal influenza vaccine between randomization and end of the surveillance period for Season 1, • Subject did not receive a licensed live vaccine within 30 days of any dose of M-001/placebo, and • Subject did not receive a licensed non-live vaccine within 21 days of any dose of M-001/placebo. 11.5.2 Analysis of Safety Data (…) Additionally, solicited events will be analyzed by taking the most severe response over the follow-up period and using standard techniques, such as exact confidence intervals, to summarize the proportion of subjects reporting each symptom, any injection site symptom, and any systemic symptom. Summaries of solicited events will be presented separately for each study vaccination as well as overall study vaccinations by treatment arm. The proportion of subjects reporting symptoms may be compared between treatment arms using Chi-square or Fisher's exact test, as appropriate. The proportion of subjects reporting solicited symptoms between the different study vaccinations (e.g., dose 1 vs. dose 2) will be compared using McNemar's test. (…) 11.5.3 Analysis of Efficacy Data Primary Efficacy Assessment For the primary analysis of vaccine efficacy (VE), the efficacy of M-(…). **Secondary Efficacy Assessments** The first secondary efficacy assessment will be analyzed using the same methodology than the one used for the primary endpoint (including the supportive and sensitivity analyses). Notice that samples with Ct ≤35 only will be grown for culture.

	The second secondary efficacy assessment consisting in the between-group difference in average number of days with respiratory or systemic symptoms among subjects with laboratory-confirmed influenza illness will be tested in an ANOVA model with vaccine group, age category, and season/cohort as main factors. The risk ratio for the total number of ILI events during the flu season will be compared between the vaccine groups using an overdispersed Poisson model with offset being the duration of follow-up in days and factors for vaccine group, age category and season/cohort. All secondary efficacy assessments will be performed on the ITT and PP sets. **Exploratory efficacy assessments:** For both vaccine groups, the following proportions will be estimated with an exact 95% CI within the PP set • Proportions of subjects taking antibiotics due to a post-influenza (laboratory confirmed) respiratory tract infection • Proportions of subjects who died due to influenza-like illness with or without confirmation by viral culture and qRT-PCR analysis due to vaccination with M-001 Between-groups comparisons will be performed using Fisher's exact test. For both vaccine groups, the following rates will be estimated on the PP set using a 95% CI based on a Poisson model on the number of events with duration of follow-up (in days) as offset • Rate of hospitalizations associated with ILI episodes over the flu season Comparisons between the 2 groups will be performed on the basis of an overdispersed Poisson model with group as factor and duration of follow-up (in days) as offset. Incidence rate ratios between the 2 groups will be estimated and their 95% CI provided. Because it is expected that very few hospitalizations cases will occur, no additional factor will be included in the Poisson model. Descriptive statistics for the specific influenza strains in confirmed flu cases in experimental and control groups will also be provided.

	In addition, the following descriptive statistics will be provided to describe the ILI episodes: • For the PP set, the distribution of influenza confirmed episodes • For the PP set, the distribution of influenza confirmed episodes by severity. **Exploratory CMI assessment in substudy:** A subset of patients will be be enrolled in Season 2 to assess immunogenicity: the average percentage of CD4+ lymphocytes producing Th1 cytokine (e.g. INF-γ) in response to any of the 9 peptides in M-001 measured at Day 36 (14±2 days since day of the second vaccination) and its two-sided 95% confidence interval will be calculated. Additional exploratory analyses to be performed on the immunogenicity data from these subjects will be detailed in a separate SAP for immunogenicity. 11.5.4 Missing Values and Outliers (…) 11.5.5 Statistical Software
14.4. Exclusion of Women, Minorities, and Children (Special Populations)	
Original wording	. If a female subject becomes pregnant while participating in this study, we will ask her permission to follow-up with her about her health and the health of her baby through pregnancy outcome. Males whose female partner has childbearing potential, if not after vasectomy, must use condoms throughout the study treatment and for at least up to day 111 of the trial 90 days after the last dose of the IMP.
New wording	. If a female subject becomes pregnant while participating in this study, we will ask her permission to follow-up with her about her health and the health of her baby through pregnancy outcome.

	In selected, individual cases, PI, where justified, may accept complete abstinence from sexual activity in women not having male partner as basis for considering such female subject as of no childbearing potential. Rationale for such decision must be available and documented. Males whose female partner has childbearing potential, if not after vasectomy, must use condoms throughout the study treatment and for at least up to day 111 of the trial 90 days after the last dose of the IMP.
15.4. Timing/Reports	
Original wording	The primary clinical study report (CSR) will include clinical, safety, reactogenicity, efficacy and cellular immunogenicity data through the end of the last follow up period. At this time, the clinical database will be cleaned, monitored and locked. Unblinded analyses of safety, reactogenicity, and available PBMCs, including all primary and secondary endpoint data will be performed after the clinical database is locked. The CSR will be completed when all efficacy data for day 202 and for the follow up period of season 2 are available.
New wording	The primary clinical study report (CSR) will include clinical, safety, reactogenicity, efficacy and possibly, cellular immunogenicity data through the end of the last follow up period. At this time, the clinical database will be cleaned, monitored and locked. Unblinded analyses of safety, reactogenicity, and available PBMCs, including all primary and secondary endpoint data will be performed after the clinical database is locked. The CSR will be completed when all efficacy data are available.
15.6. Protocol Deviations	
Original wording	It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be promptly reported to the sponsor.
New wording	Sites are expected to maintain vigilance to identify deviations from the Protocol and address them as soon as possible including reporting of suspected major protocol deviations within 5 working days of its identification, or for deviations related to study schedule - within 5 working days of the scheduled protocol-required activity. Suspected major protocol deviations must be reported to the sponsor directly or to the sponsor's contracted representative (e.g. clinical research monitor or medical monitor).

List of changes of study protocol version 5.0 vs. study protocol version 4.0 dated 27Mar2019

Description	Wording
Version and Date of the protocol	
Original Wording	Version 4.0 final dated 27th March 2019
New Wording	Version 5.0 final dated 08th May2019
INVESTIGATOR'S COMPLIANCE DECLARATION	
Original Wording	Protocol: BVX-010, version 4.0 dated 27th March 2019…
New Wording	Protocol: BVX-010, version 5.0 dated 08th May 2019…
PROTOCOL SYNOPSIS PBMC (CMI) sub-study	
Original Wording	Approximately two hundred sixty two (263) will be selected….
New Wording	Approximately two hundred sixty three (263) will be selected….
PROTOCOL SYNOPSIS PBMC *Primary endpoint*	
Original Wording	To assess M-001 Safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after M-001 study vaccination (day of the vaccination inclusive).
New Wording	To assess M-001 Safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each study vaccination (day of the vaccination inclusive).
Table 3: Schedule of Events (Season 1, 2018/2019 for Cohort 1)	
Original Wording	Study Day…202
New Wording	Study Day…202 (180 days after last vaccination day)
Table 4: Schedule of Events (Season 2, 2019/2020 for Cohort 2)	
Original Wording	Study Day…202
New Wording	Study Day…202 (180 days after last vaccination day)

Original Wording	**Passive Surveillance:** Subjects will be instructed to contact the study site if they experience symptoms of influenza-like illness from Day 14 post-second vaccination day but not earlier than from September 15th until 15 May the following year **…** From Day 14 post second vaccination day, but not earlier than from September 15th until **30 April** of the following year. … Swabs collection period starting on September 15, 2019.
New Wording	**Passive Surveillance:** Subjects will be instructed to contact the study site if they experience symptoms of influenza-like illness from Day 14 post-second vaccination day until 15 May the following year … From Day 14 post second vaccination day, until **30 April** of the following year. …
Original Wording	# Occurrence of unsolicited AEs will be analyzed from the time of first study vaccination through 22 days after M-001 study vaccination (day of the vaccination inclusive).
New Wording	# Occurrence of unsolicited AEs will be analyzed from the time of first study vaccination through 22 days after each study vaccination (day of the vaccination inclusive).
Section 3.1.1 Primary Objectives	
Original Wording	To assess M-001 safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after M-001 study vaccination (day of the vaccination inclusive).
New Wording	To assess M-001 safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each study vaccination (day of the vaccination inclusive).
Section 3.2.1 Primary Outcome Measures	
Original Wording	• Occurrence of solicited injection site and systemic reactogenicity events on the day of each study vaccination through 8 days after M-001 study vaccination (day of the vaccination inclusive) • Occurrence of unsolicited AEs from the time of first study vaccination through 22 days after M-001 study vaccination (day of the vaccination inclusive)
New Wording	• Occurrence of solicited injection site and systemic reactogenicity events on the day of each study vaccination

	through 8 days after each study vaccination (day of the vaccination inclusive) • Occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each study vaccination (day of the vaccination inclusive)
Section 4. Study Design	
Original Wording	Unsolicited non-serious AEs collected from the time of each study vaccination through approximately 22 days after M-001 study vaccination (day of the vaccination inclusive) will be analyzed separately.
New Wording	Unsolicited non-serious AEs collected from the time of each study vaccination through approximately 22 days after each study vaccination (day of the vaccination inclusive) will be analyzed separately.
Section 6.5 Concomitant Medications/Treatments	
Original Wording	Concomitant medications will include at least all current medications and medications taken within 3 months prior to Day 0 through approximately Day 43 or 21 days after second vaccination day whichever occurs later. After Day 43, only concomitant medications relevant for background chronic respiratory illness as per PI judgment, or related to AE or ILI, will be recorded. Subjects who do not receive both M-001 study vaccinations will have all concomitant medications collected through approximately 22 days after the first study vaccination, day of the vaccination inclusive, or early termination, whichever occurs first.
New Wording	Records of concomitant medications will include at least all current medications and medications taken within 3 months prior to Day 0 through 21 days after last vaccination day. After this period, only concomitant medications relevant for background chronic respiratory illness as per PI judgment, or related to AE or ILI, will be recorded. Subjects who do not receive both M-001/placebo study vaccinations will have all concomitant medications collected through approximately 22 days after the first study vaccination, day of the vaccination inclusive, or early termination, whichever occurs first.
Section 7.3 Follow up period for safety and efficacy	
Original Wording	*Passive efficacy surveillance:* Following randomization and vaccinations, subjects will be instructed to contact the site if they experience symptoms of a respiratory illness or influenza-like illness during the annual surveillance periods defined as from Day 14 after second vaccination day or from September 15 (the later of them) until 15 May of the following year. …

	During the period from Day 14 after second vaccination day (not earlier than from September 15th) until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), the site will … … **NP/nasal and throat swab collection:** NP swab (or nasal and throat swab) specimens will be collected during the period from Day 14 after second vaccination day (but not earlier than from September 15th) until 30 April of the following year…
New Wording	*Passive efficacy surveillance:* Following randomization and vaccinations, subjects will be instructed to contact the site if they experience symptoms of a respiratory illness or influenza-like illness during the annual surveillance periods defined as from Day 14 after second vaccination day until 15 May of the following year. … During the period from Day 14 after second vaccination day until 30 April of the following year (or longer if decided by the medical director based on actual influenza season duration), the site will… … **NP/nasal and throat swab collection:** NP swab (or nasal and throat swab) specimens will be collected during the period from Day 14 after second vaccination day until 30 April of the following year…
Section 7.4. Safety Follow Up Visit, Visit 4, Day 202: Phone Call/ Electronic Communication (180 days +/-14 post last study vaccination)	
Original Wording	7.4. Safety Follow Up Visit, Visit 4, Day 202: Phone Call/ Electronic Communication (180 days +/-14 post last study vaccination)
New Wording	7.4. Safety Follow Up Visit, Visit 4, Day 202: Phone Call/ Electronic Communication (180 days [+/-14 days] post last study vaccination day)
Section 7.5 Follow Up Period for Efficacy Season 2	
Original Wording	Passive surveillance will take place between September 15, 2019 and May 15, 2020.
New Wording	Passive surveillance will take place starting 14 days after the second injection and until May 15, 2020.

Section 8.2.3 Special Assays or Procedures	
Original Wording	Venous blood samples for isolation of PBMCs will be collected from a subset of cohort 2, immediately prior to the first study vaccination (Day 0, visit 1 in season 2), and approximately 15 days (day of the vaccination inclusive) after the second M-001 vaccination (Day 36, visit 3, season 2).
New Wording	Venous blood samples for isolation of PBMCs will be collected from a subset of cohort 2, immediately prior to the first study vaccination (Day 0, visit 1 in season 2), and approximately 15 days (day of the vaccination inclusive) after the second study vaccination (Day 36, visit 3, season 2).
Section 9.6.2 Infuenza Culture	
Original Wording	9.6.2 Influenza Culture
New Wording	9.6.2 Influenza Virus Culture

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