Statistical Analysis Plan

BiondVax BVX-010

Date 8 July 2020

Version 2.0

Study:

TRIAL FULL TITLE	**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).**
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Abbreviation or special term	Explanation
AE	Adverse Event/Adverse Experience
AESIs	Adverse Events of Special Interest
CDC	Center for Disease Control
CMI	Cell-mediated immunity
CRO	Contract Research Organization
Ct	Cycle threshold
DSMB	Data and Safety Monitoring Board
ICF	Informed Consent Form
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
PP	Per-Protocol
PT	Preferred Term
qRT-PCR	Quantitative Reverse Transcriptase Real Time PCR
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SOC	System Organ Class
TBD	To be determined later
US	United States
VE	Vaccine Efficacy
WHO	World Health Organization

OVERVIEW AND SUMMARY OF CHANGES FROM STATISTICAL ANALYSIS PLAN FINAL 1.0 DATED 17 DECEMBER 2018

The SAP version 1.0 approved on December 17, 2018 is updated to version 2.0

- to incorporate changes made to the protocol through the current version 5.0 - Amendment 1.0.of the protocol,
- to add analyses missing in SAP version 1.0 to be in line with the protocol,
- to describe some conventions following a blinded data review meeting that took place after the end of flu season 2018-2019,
- to clarify one exploratory endpoint, add 2 exploratory endpoints and 2 sensitivity analyses, and
- to incorporate some editorial changes.

Updates to the SAP version 1.0 related to protocol amendment concern:

- the change to the study design with the addition of a second cohort to reach a total of ~12,000 subjects in the study. The second cohort is evaluated during the flu season 2019-2020 while cohort 1 was evaluated during the flu season 2018-2019 (section 3.4). In addition, no subject was participating in two consecutive flu seasons.
- the removal of the long-term efficacy assessment over a second influenza season from the list of secondary objectives. All efficacy and safety analyses related to second flu season were removed from SAP version 1.0 (section 2.2).
- the addition of an immunogenicity objective (section 2.2) and immunogenicity endpoints in section 6.
- the removal of the exploratory objective 2. in SAP version 1.0 concerning the assessment of incidence of clinic visits associated with the ILI episode
- the presentation of safety and efficacy results by cohort (cohort 1 and 2, corresponding to flu season 2018-2019 and 2019-2020, respectively)
- the removal of fever from the list of solicited symptoms. Presence/absence of fever will be evaluated using the reported temperature by the subject (Section 4.1)

The following updates were made to the first version of SAP to be in line with the protocol version 5.0 (these analyses were missing from SAP version 1.0 but are described in the protocol):

- the addition of statistical comparisons between the 2 groups in terms of percentage of subjects with any local or systemic reactogenicity solicited events overall and by vaccination (as specified in the protocol). Within-group comparisons between the percentage of subjects with any local or systemic reactogenicity solicited events after first and second vaccination are specified. The 95% exact CI for the proportion of subjects with unsolicited AEs by SOC and PT will be presented. Within group 95% CI for the proportion

of subjects with serious SAEs will be derived using the exact method by SOC, PT (section 4.4).

- the addition of the analysis comparing the proportion of subjects with ILI symptoms, in addition to the analysis comparing the rate of ILI symptoms over one year (section 5.4.2 – secondary efficacy endpoints)

The following updates were made to the first version of SAP following blinded review of data from season 1:

- the ILI episode for which a nasal or throat swab was collected outside of the allowed window of 3 days post onset date will be considered as a qRT-PCR or culture confirmed ILI if the results of the qRT-PCR or culture are positive. Review of each case will be performed prior to unblinding and documentation provided in the blinded data review meeting memo (see section 5.3).

- the analysis of the secondary efficacy assessment consisting in the between-group comparison of the number of days with respiratory or systemic symptoms among subjects with qRT-PCR- or culture-confirmed influenza illness will be performed on the percentage of subjects with number of days with respiratory or systemic symptoms in the following categories:
  - < 7days
  - At least 7 and < 14 days
  - At least 14 and < 21 days
  - ≥ 21 days

  Cochran-Mantel-Haenszel test with 4 strata corresponding to the combination of age category and cohort will be used.

Clarification of the exploratory analysis :

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

To read:

- Percentage of either qRT-PCR or culture-confirmed influenza cases in the M-001 experimental group *vs.* placebo by virus type (influenza A and B) and Influenza A subtypes (H1N1 and H3N2) as well as Influenza B lineage (B/Yamagata and B/Victoria).

Additional exploratory analyses:

- Reduction, due to vaccination with M-001, in the proportion of subjects with serious ILI with or without confirmation by viral culture or qRT-PCR analysis
- Reduction, due to vaccination with M-001, in the proportion of subjects taking medications due to qRT-PCR- or culture-confirmed ILI

An additional sensitivity analysis for the primary efficacy assessment is added in section 5.4.2. where the following definition is used: influenza is confirmed by a qRT-PCR or culture if the qRT-PCR Ct count corresponding to the detection of any flu type is < 40 or culture is positive for influenza.

An additional sensitivity analysis to the secondary efficacy assessment of proportion of subjects with ILI is added in section 5.4.2.where selection of ILI which occurred prior to March 15th, 2020 will be done.

The following updates made to the first version of SAP are provided for clarity or are editorial:

- section 3 of SAP version 1.0 has been extended to present the study outcome measures as defined in the protocol
- section 4.4 : To match the primary safety objective related to occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each M-001 vaccination (day of the vaccination inclusive), selection of unsolicited AEs will be performed using the cut-off of 22 days after each M-001 vaccination (instead of the 30 days cut-off in SAP version 1). Safety tables reporting all AEs irrespective of the time will be provided also
- the criteria for exclusion from the PP set reported in section 5.3 were clarified.
- section 7 of SAP version 1.0 on handling of missing data is now section 9
- section 8 of SAP version 1.0 on subgroup analysis is now section 7, more details on subgroup analyses are provided in version 2.0.
- section 9 of SAP version 1.0 on assessment of study population has been extended to include section 10 of SAP version 1.0 and is section 8 in version 2.0
- new section section 8.2.1 has been added in SAP 2.0 to define Medical History reporting.
- new section section 8.2.2 has been added in SAP 2.0 to define prior medication and concomitant medication selection and reporting.
- section 11 of SAP version 1.0 is section 10 in version 2.0
- section 12 of SAP version 1.0 on interim analyses and data monitoring committee was removed. Section 12 in the SAP version 2.0 presents the tables, figures, and listings to be provided
- section 13 of SAP version 1.0 on changes of analysis from protocol is section 11 in version 2.0

1. INTRODUCTION

This study compares the safety and clinical efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (≥50 years of age) versus placebo.

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.

1.1 Background

Influenza is a common acute viral respiratory illness. Influenza is the eighth leading cause of death in the western world[i] resulting in worldwide death toll of 250,000-500,000 annually[ii]. 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[iii] 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[iv] and much lower among the elderly[v]. 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[vi].

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 desired. 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 [vii viii]. 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[ix]. 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[x].

An approach to improve vaccine efficacy especially in the older 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.

1.2 Background of the Investigational Product

The use of epitope-based vaccines is an approach that may be used to improve protection of the elderly by activating cell mediated immunity and prime for immune responses to influenza antigens[xi]. 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[xii]. Based upon these characteristics, the M-001 vaccine is hypothesized to provide immunity against both existing as well as future emergent virus strains[xiii].

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[xiv]. The safety and efficacy results of M-001 in the preclinical studies led to its evaluation in people as detailed in the Investigator Brochure [xv]. 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[xvi]. 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-γ 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) 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[xvii]. 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[xviii].

Another Phase 2b trial was recently concluded by NIAID in the US. In this trial, 120 young adults were administered with either M-001 or placebo (1:1) ahead of immunization with QIV. The primary objectives of the trial, to assess safety and T-cell responses to M-001 were achieved.

1.3 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.

2. STUDY OBJECTIVES

2.1 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 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).

2.2 Secondary Objectives

Clinical efficacy

1. To 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. To assess the 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 qRT-PCR- or culture-confirmed influenza illness episode.
3. To assess the proportion of subjects having ILI symptoms in the experimental or control group.

Immunogenicity

1. To assess in at least a subset of samples in season 2019-2020 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 in the substudy in season 2019-2020.

2.3 Exploratory Objectives

Clinical efficacy

1. To assess the incidence of antibiotics use due to post-influenza secondary infections of respiratory tract as evidenced with medical records or declared by the participant
2. To assess the incidence of hospitalization associated with the ILI (≥15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director)
3. To assess the incidence of death due to ILI (≥15 days after the second vaccination until epidemiological levels of influenza are low as defined by the medical director) with or without confirmation by viral culture or qRT-PCR analysis
4. To determine the specific influenza strains in confirmed flu cases in experimental and control groups

3. STUDY OUTCOME MEASURES

3.1 Primary Outcome Measures

Safety

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

3.2 Secondary Outcome Measures

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.
- 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 qRT-PCR or culture-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 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 vs control group

Immunogenicity Sub-Study

- Change from baseline in the percentage of T cell expressing e.g., interferon gamma (IFN-γ) 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-γ) in CD4+ PBMCs after stimulation in another future study.

3.3 Exploratory Outcome Measures

- Reduction in the proportion of subjects taking antibiotics 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 enough.
- Reduction in the percentage of subjects with hospitalization associated with ILI episodes, due to vaccination with M-001 compared to placebo. Hospitalization associated with ILI (≥15 days after the second vaccination 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 qRT-PCR analysis.

- Incidence of death due to influenza-like illness (≥15 days after the second vaccination 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 qRT-PCR analysis.

- Percentage of either qRT-PCR or culture-confirmed influenza cases in the M-001 experimental group *vs.* placebo by virus type (influenza A and B) and subtype (H1N1 and H3N2)

In addition to the above, the following outcome measures will be analysed:

- Reduction, due to vaccination with M-001, in the proportion of subjects with serious ILI with or without confirmation by viral culture or qRT-PCR analysis

- Reduction, due to vaccination with M-001, in the proportion of subjects taking medications due to qRT-PCR- or culture-confirmed ILI

3.4 Study Design

This is a pivotal, multicenter, 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 (2 doses 21 to 30 days apart) in older adults and the elderly (≥50 years of age) who meet all eligibility criteria.

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 are selected to participate to the Cell Mediated Immunity (CMI) substudy. A total of 350 subjects are 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).

The trial spans 2 influenza seasons. In each of the 2 cohorts corresponding to season 2018-2019 and 2019-2020, subjects are randomized in a 1:1 ratio to receive two doses (on Day 0 and 22) of either M-001 or saline placebo prior to start of the influenza season.

In cohort 2, immunogenicity testing is performed and includes 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 are 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, are 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).

At least half of the participants will be ≥ 65 years of age.

Table 1: Schedule of Events (Season 1, 2018) (Cohort 1)

Study Visit (V)	01	02	04
Study Day	**0**	**22**	**202** **(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
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
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 2: Schedule of Events (Season 2, 2019) (Cohort 2)

Study Visit (V)	1	2	3 (site visit[9])	4
Study Day	**0**	**22**	**36 (14 days post date of Visit 2))**	**202**
Visit Windows		(+9)	(±2)	(±14)
Consent process and Signed Consent Form[1]	X			
Assess eligibility	X	X		
Demographic data, Review Medical & flu	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			
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 but not earlier than from September 15th until 15 May the following year Active Surveillance: Between December 1st , 2019 and April 30th, 2020,			

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 , but not earlier than from September 15th 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 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

4. SAFETY ENDPOINTS

4.1 Safety Definitions

The following definitions are taken from the International Conference on Harmonisation (ICH) E6 Guideline.

Adverse Event (AE): An AE as any untoward medical occurrence in a patient or clinical investigation subject administered with a pharmaceutical product regardless of its causal relationship to the study vaccine. An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product.

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.

The severity or intensity of AE was noted as mild, moderate, or severe.

Serious Adverse Event (SAE): 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[1],
- inpatient hospitalization or prolongation of existing hospitalization (excluding pre-planned elective surgeries or other pre-planned hospitalizations),
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- a congenital anomaly/birth defect,
- an important medical event 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

[1] 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.

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.

The definitions below are used by BiondVax:

Local and Systemic Reactogenicity events: these are events which are common and considered as possible to occur following administration of this type of vaccine. These events comprise solicited events which are injection site reactions including Blue spot/ bruising; Induration / Swelling; Redness / Warmth; Itching, Pain/ tenderness , and systemic reactions including Fever (only for the first season (2018-2019); 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).

The intensity of reactogenicity events was mentioned as mild, moderate, or severe, as for AEs.

Local and systemic reactogenicity events could also be non-solicited and would be recorded as AEs.

Solicited events (reactogenicity events) which match at least one of the below criteria were to be recorded as AEs:

- symptom/event continued or occurred beyond 7 days post vaccination day,

- reactogenicity symptom/event(s) required medical (i.e. physician's) assistance,

- reactogenicity symptom/event has been graded by subject or by investigator as severe,

- oral body temperature of severe grade, i.e., >38.9°C for subjects aged <60 years and >38.2°C for subjects ≥60 years.

Adverse Event of Special Interest (AESIs): These comprise new onset of Guillain-Barré Syndrome (GBS), Bell's Palsy, encephalitis / myelitis, optic neuritis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis. These AEs will be reported as serious adverse events.

New-onset of Chronic Medical Illnesses (N**OCIs):** 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 SAEs.

4.2 Safety Endpoints Calculation Methods

4.2.1 Causality and Severity of AEs

An intensity, missing for an AE, will be imputed as severe. The summary of AEs by severity will use these imputed values, while the actual ones will be presented in the data listings.

An AE, whose relationship to treatment is missing, will be considered as related. These imputed values for causality will be used for the summary of AEs by relationship to treatment; the actual values will be presented in the data listings.

If the degree of missingness for the severity or relationship to study drug is >5%, then an additional table with non-imputed severity or causality will be provided.

Seriousness, outcome, and action taken, if missing for an AE, will not be imputed.

4.2.2 Start and Stop dates, Time to Onset and Duration of AEs

See section 9. for a complete description of handling of missing dates for AEs.

The analysis of the AEs will be based on the Safety Population (Section 4.3), i.e., will include all subjects who received the study treatment.

Time to onset of an AE will be computed in days using the formula: Time to onset = start date of AE – date of first vaccination. In case the time to onset of the AE is 0, i.e., the AE occurred the day of the first vaccination, the time to onset will be expressed in minutes. Time to onset relative to the second vaccination will also be reported in minutes, if an AE occurred the same day as the second vaccination.

Events that occur before vaccination will not be included in summaries but will be listed separately.

The duration of the AE will be reported in days and be computed as stop date of event – start date of event + 1.

4.2.3 Causality and Severity of Local and Systemic Reactogenicity Events

Local and systemic reactogenicity events are considered to be related to the treatment. Severity, when missing in a reported Local and Systemic Reactogenicity event, will not be imputed.

4.2.4 Start and Stop dates, Time to Onset and Duration of Local and Systemic Reactogenicity Events

For the analysis of solicited systemic and injection site reactions, missing dates will not be replaced. The analysis of the solicited symptoms based on the Safety Population (Section 4.3) will include only subjects with solicited systemic and injection site reactions, retrieved from the diary data.

The time to onset and duration of a specific local and systemic reactogenicity event will be calculated as defined above for an AE.

4.3 Safety Endpoints Population Analysis

All safety analyses will be based on the Safety Population, which will comprise all subjects having received at least one vaccine dose. The safety analyses will be performed by vaccine actually received at visit 1.

For the analyses of local and systemic reactogenicity events, the percentage in each table will be computed using the number of subjects having received the specified vaccination and who returned a diary card for the period of interest.

The safety analyses performed during the season 2018-2019 and 2019-2020 will be based on the subgroup of subjects from the safety set who were enrolled in the specific season.

4.4 Safety Endpoints Analysis

Local and Systemic Reactogenicity Events – Overall Summaries

Each set of tables described below will summarize the occurrence of events over the 3 following periods:

P1. any day over 8-day period following first or second vaccination (Period = Day of the first/second vaccination to 7 days post first/second vaccination)
P2. any day over 8-day period following first vaccination (Period = Day of the first vaccination to 7 days post first vaccination)
P3. any day over 8-day period following second vaccination (Period = Day of the second vaccination to 7 days post second vaccination)

Summary of all the local and systemic reactogenicity **solicited** events provided for

- any local or systemic reactogenicity solicited events,
- any local events and by local event separately (5 events: blue spot/bruising, induration/swelling, redness/warmth, itching, pain/tenderness),
- any systemic reactogenicity events and by systemic reactogenicity event separately (14 events: decreased blood pressure/dizziness, chills/sweating, joint/muscle pain, headache, nasal congestion/runny nose/phlegm production/rhinitis, difficulty breathing/wheezing, general malaise/fatigue/loss of appetite, swelling/tender lymph nodes, irritability, rash, cough, sore throat, abdominal pain/diarrhea/nausea/vomiting, pruritus or itching on the body).

During the first season, fever was one of the solicited symptom and was graded subjectively as mild, moderate, or severe by the subject in addition to the oral body temperature daily record. This symptom was not recorded as such during the season 2019-2020. For homogeneity of reporting, oral body temperature daily records only will be presented for the 2 seasons and a separate table summarizing fever as a solicited symptom will be presented for season 2018-2019.

The tables will present the number and percentage of subjects with any events, the percentage in each table being computed using the number of subjects having received the specified vaccination and with diary data reported for local and systemic reactogenicity in the period of interest as defined in P1, P2, and P3.

For each of the above tables, the number and percentage of subjects will be tabulated by treatment.

The percentage of subjects with any local or systemic reactogenicity solicited events overall and by vaccination will be compared between the groups using the chi-square test. Within-group comparison between the percentage of subjects with any local or systemic reactogenicity solicited events after first and second vaccination will be performed using Mc Nemar test.

Descriptive tables for duration of event will also be provided by solicited event.

Recorded Temperature – Overall Summary

A table summarizing the percentage of subjects experiencing fever will be provided using the temperatures recorded by the subject during the 8-day period post first, second and first or second vaccination. A subject aged <60 years will be said to have fever at a given day if his/her recorded temperature for that day is ≥38.0°C.

A subject aged ≥60 years will be said to have fever at a given day if his/her recorded temperature for that day ≥37.3°C.

Local and Systemic Reactogenicity Events –Summaries by Severity (Grade)

The following grading scale was used by the subject to rate how intense or annoying each symptom was: 1-mild, 2-moderate, 3-severe.
All the above summaries will be provided by severity (or grade) also.

The severity of an event reported within a period (8-day period post first vaccination, 8-day period post second vaccination) will be the maximum severity recorded for the event during the period.

In the case that a subject has more than one event with different levels of severity over the 2 periods considered (first and second vaccination), then the maximum severity level will be used in the analysis over the 2 periods.

The severity, which is missing for an event, will remain missing in the analysis.

Recorded Temperature by Severity – Overall Summary

A table summarizing the grading of the temperatures will also be provided using the temperatures recorded by the subject during the 8-day post first, second and first or second vaccination. Temperature will be graded as in Table 3.

The severity, which is missing for an event, will remain missing in the analysis.

The percentage of subjects with temperature overall and by vaccination will be compared between the groups using the chi-square test. Within-group comparison between the percentage of subjects with temperature after first and second vaccination will be performed using Mc Nemar test.

Table 3: Quantitative Systemic Reactogenicity Grading

Systemic (Quantitative)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
(Age <60 years) Fever - oral	38.0°C – 38.4°C	38.5°C – 38.9°C	>38.9°C
(Age ≥60 years) Fever - oral	37.3.0°C – 37.7°C	37.8°C – 38.2°C	>38.2°C

Unsolicited Adverse Events

All unsolicited AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.

Unsolicited AEs – which do not meet SAE criteria, nor ILI, AESI or NOCI definition – were to be reported until ~22 days post each study vaccination. The cut-off of 22 days post each study vaccination will be used; however, tables including all unsolicited AEs started up to 30 days after Visit 4 or after discontinuation will be provided. SAEs and NOCIs reported from the time of the first study vaccination and up to 30 days after Visit 4 or after discontinuation will be included in all SAEs and NOCIs tables.

The following ordering will be used to define the maximum level for intensity, action taken, outcome, causality, or seriousness, when needed :

- Intensity: Mild < Moderate < Severe
- Causality: No (None or Unlikely) < Yes (Possible, Probable, Certain)
- Seriousness: No < Yes
- Action taken: None – Not Applicable < Drug withdrawn
- Outcome: Unknown < Recovered/resolved < Recovered/resolved with sequelae < Recovering/resolving < Not recovered/not resolved < Fatal.

The intensity, missing for an AE, will be imputed as severe. These imputed values will be used for the summary of AEs by severity, while the actual values will be presented in the data listings.

An AE, whose relationship to vaccine is missing, will be considered as related. These imputed values will be used for the summary of AEs by relationship to vaccine; the actual values will be presented in data listings.

Local and systemic reactogenicity **solicited** events will be included in the table for unsolicited adverse events with the severity provided by the investigator, which may differ from that given by the subject's diary. Also, the relationship to vaccine for solicited events will be that recorded by the investigator.

A second set of tables for unsolicited adverse events will be generated in which the local and systemic reactogenicity events are excluded unless the event is considered serious or it is ongoing at the end of the observation period for solicited events. The first set of tables follows the guidelines of the EMA while the second set follows those of the US Food and Drug Administration.

A general summary of all AEs occurring after the first vaccination will show the number and percentage of subjects with

- Any AE,
- Any AE with death as outcome,
- Any severe AE,
- Any AE causally related to vaccine (Relationship to Study vaccine Possible, Probable, or Certain),
- Any serious AE,
- AE leading to vaccine withdrawal,
- Not recovered or not resolved AE,
- AE of special interest,
- New onset of chronic illness,
- New onset of serious chronic illness.

The number and percentage of subjects who experienced one or more AEs will be tabulated by group and by:

- SOC, and PT
- SOC, and PT (Severe AEs)
- SOC, and PT (AEs causally related with the vaccine)

All the above tables will be presented for the entire safety population (2 seasons) and by season as well. All the above tables will report the number of AE by group in addition of the number and percentage of subjects who experience the AE. Tables by age category will be provided also.

Tables by SOC and PT will be sorted by descending percentage of events (by SOC, and By PT within SOC) for the vaccine group. In case of same percentages, sorting will be done descending number of events. In case of same percentages and number of events, sorting will be done by alphabetical order.

Serious Adverse Events and NOCIs

SAEs and NOCIs from the time of the first study vaccination (Day 0 (Visit 1)) and up to 30 days after Visit 4 or after discontinuation (Visit 4) will be described. Any SAE or NOCI occurring more than 30 days after Visit 4 or after discontinuation will <u>not</u> be reported in the below analyses, but will be listed.

Three set of tables will be provided reporting:

- All SAEs,
- Adverse events of special interest (AESIs) captured as SAEs will be reported separately. These include a new onset of Guillain-Barré Syndrome (GBS), Bell's Palsy, encephalitis / myelitis, optic neuritis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis,
- NOCIs events (serious or not).

For all tables, rules about multiple occurrences of an AE in the same subject and about missing intensity, action taken, outcome, causality, or seriousness level are identical to those described above.

A general summary of all SAEs will show by group the number and percentage of subjects with

- Any SAE,
- Any SAE with death as outcome,
- Any SAE causally related to vaccine.

The number and percentage of subjects who experienced one or more SAEs will be tabulated by group :

- SOC, and PT
- SOC, and PT (AEs causally related with the vaccine (Possible, Probable, or Certain))

Within group 95% CI for the proportion of subjects with serious SAEs will be derived using the exact method by SOC, PT.

The number and percentage of subjects who experienced one or more AESIs will be tabulated by group and:

- PT

Specific tables will be provided for NOCIs.

A general summary of all NOCIs will show the number and percentage of subjects with

- Any NOCI,
- Any NOCI with death as outcome
- Any NOCI causally related to vaccine,

The number and percentage of subjects who experience one or more NOCIs will be tabulated by group:

- SOC, and PT
- SOC, and PT (NOCIs causally related with the vaccine (Possible, Probable, or Certain))

All the above tables will be presented for the entire safety population (2 seasons) and by season as well. All the above tables will report the number of AE by group in addition of the number and percentage of subjects who experience the AE. Tables by age category will be provided also.

Tables by SOC and PT will be sorted by descending percentage of events (by SOC, and By PT within SOC) for the vaccine group. In case of same percentages, sorting will be done descending number of events. In case of same percentages and number of events, sorting will be done by alphabetical order.

Any SAE or NOCI occurring more than 30 days after Visit 4 or after discontinuation will be listed separately.

Key subject information (age/sex/race/medical history) for subjects experiencing SAEs or NOCIs will be presented in a listing together with all recorded information about the SAE or NOCI.

5. EFFICACY ENDPOINTS

5.1 Efficacy Endpoints – Definition

Surveillance for respiratory illness – Flu season 2018-2019

- *Active Surveillance:* All subjects were contacted twice a week by a call center starting on November 15th of the vaccination year until the week of March 31th the following year.
- *Passive Surveillance:* All subjects were instructed to contact their study site if they experienced symptoms of a respiratory illness from Day 14 post-second vaccination day until May 15th the following year.

Note: Active surveillance might be extended by the medical monitor for those countries in which influenza does not reach low levels by March 30.

Surveillance for respiratory illness – Flu season 2019-2020

- *Active Surveillance:* All subjects will be contacted twice a week by a call center starting on December 1st, 2019 until the week of April 30th.

- *Passive Surveillance:* All subjects will be instructed to contact their study site if they experience symptoms of a respiratory illness from September 15, 2019 to May 15, 2020.

Protocol-defined Influenza-Like Illness (ILI)

An ILI episode was identified if at least one respiratory symptom and at least one systemic symptom occurred concurrently; the respiratory symptoms being either

- sore throat,
- cough,

- sputum production,
- nasal discharge or congestion,
- wheezing or difficult breathing

and the systemic symptoms being either

- fever (oral temperature >37.2°C for age 50-59 years, or >36.7°C for age 60 years or more, or increased ≥ 1.3°C from baseline),
- headache,
- myalgia and/or arthralgia,
- chills,
- fatigue (tiredness for at least 12 hours).

The time of onset for an ILI episode is defined as the time from 14 days after the second vaccination to the date when at least one respiratory symptom and at least one systemic symptom occurred concurrently. For subjects who received only one vaccination, the time of onset for the ILI episode will be defined from 35 days after first vaccination. New episodes of ILI are defined as occurring at least 14 days after the end of a previous episode.

The duration of the ILI episode (days) is defined as follows: last stop date of ILI symptoms for the episode - onset date of the ILI episode + 1.

Confirmed influenza in association with protocol-defined ILI

A subject is said to have a laboratory-confirmed influenza in association with protocol-defined ILI, if

- the subject had a protocol-defined ILI;
- the subject had a nasopharyngeal (NP) or nasal and throat swab; and
- the NP or nasal and throat swab was qRT-PCR- or culture-positive for influenza of any type.

A subject is said to have a culture-confirmed influenza in association with protocol-defined ILI if

- the subject had a protocol-defined ILI;
- the subject had a NP or nasal and throat swab; and
- the NP or nasal and throat swab was culture positive for influenza of any type.

Although the protocol required the nasal or throat swab to be performed during a window of 3 days post onset date, positive results from nasal or throat swabs obtained out of the widow of 3 days will be used in the analysis and the subject will be considered as having laboratory confirmed influenza.
Number of subjects with missing swab results will be reported. The number of swabs performed out of the window of 3 days post onset date will be reported.

The time to onset and duration of the confirmed case of influenza with protocol-defined ILI will be identical to the time to onset and duration of the associated ILI episode.

5.2 Efficacy Assessment

The assessment of vaccine efficacy will be performed over one flu season and will focus on events which occurred during the flu season in cohorts 1 and 2. Given the surveillance plan, only events which occurred at least 14 days after the second vaccination will be captured.

Primary efficacy assessment:

Vaccine efficacy (VE) against qRT-PCR- or culture-confirmed influenza illness is defined as $VE = 1 - [p_V/p_P]$, where p_V and p_P are the proportions of subjects with qRT-PCR- or culture-confirmed influenza caused by any influenza A or B virus in association with a protocol-defined Influenza-Like Illness (ILI) in the M-001 experimental and placebo groups, respectively.

Secondary efficacy assessment:

1. Vaccine efficacy against culture-confirmed influenza illness, defined as $VE^c = 1 - [p_V^c/p_P^c]$, where p_V^c and p_P^c are the proportions of subjects with culture-confirmed influenza in association with a protocol-defined Influenza-Like Illness (ILI) in the M-001 experimental and placebo groups, respectively.

2. Average duration of the ILI episode or average number of days with respiratory or systemic symptoms during the first qRT-PCR- or culture-confirmed influenza illness episode in the M-001 experimental group and placebo group.

3. Proportion of subjects with ILI episodes in the M-001 experimental group and placebo group.

For the primary efficacy and secondary assessments 1 and 2 in case of multiple qRT-PCR- or culture-confirmed ILI events observed for the same subject, only the first qRT-PCR- or culture-confirmed ILI event will be considered. For the secondary assessment 3, the number of ILI episodes in the M-001 experimental group and placebo group will also be assessed.

Exploratory efficacy assessments:

- Reduction, due to vaccination with M-001, in the proportion of subjects taking antibiotics due to a post-influenza respiratory tract infection (ILI with confirmation by viral culture or qRT-PCR analysis)
- Reduction, due to vaccination with M-001, in the proportion of subjects taking medications due to qRT-PCR- or culture-confirmed ILI

- Reduction, due to vaccination with M-001, in the number of hospitalizations associated with ILI with or without confirmation by viral culture or qRT-PCR analysis
- Reduction, due to vaccination with M-001, in the incidence of death due to ILI with or without confirmation by viral culture or qRT-PCR analysis
- Reduction in the proportion of subjects with serious ILI with or without confirmation by viral culture or qRT-PCR analysis

In addition to the above exploratory endpoints, the following exploratory subgroup analyses will be performed based on the first qRT-PCR- or culture-confirmed ILI event.

- VE against qRT-PCR-confirmed Type A influenza illness, VE against qRT-PCR-confirmed Type B influenza illness
- VE against qRT-PCR-confirmed Type A/H1N1 influenza illness
- VE against qRT-PCR-confirmed Type A/H3N2 influenza illness

Sensitivity analyses of primary efficacy assessment:

As a sensitivity analysis to the primary efficacy assessment, the time to first qRT-PCR- or culture-confirmed influenza in association with a protocol-defined ILI will be analyzed.

An additional sensitivity analysis to the primary efficacy assessment will be performed where qRT-PCR- or culture-confirmed influenza is defined if the qRT-PCR Ct count corresponding to the detection of any flu type is < 40.

5.3 Efficacy Analysis Populations

The subjects with major and minor protocol deviations will be reported in the CSR.

Below is the list of major protocol deviations that lead to exclusion from the from PP set.

Per-Protocol (PP) Set

The primary efficacy analysis set (PP Set) will exclude

- Subjects who did not satisfy all protocol-specified inclusion criteria or met at least one exclusion criterion,
- Subjects who did not receive both doses of M-001/placebo as randomized,
- Subjects who did not receive M-001/placebo that was properly handled or was otherwise not acceptable for administration (unblinded subjects will be excluded),
- Subjects or their representative who were not contacted by the surveillance center, did not have any phone call, or any visit 15 days or more after second injection,

- Subjects who received a seasonal influenza vaccine between randomization and end of the surveillance period,
- Subjects who received a licensed live vaccine within 30 days of any dose of M-001/placebo that interfered with the evaluation of the investigational product, and
- Subjects who received a licensed non-live vaccine within 21 days of any dose of M-001/placebo that interfered with the evaluation of the investigational product.

Data from the database will be used to flag the protocol violations.

The results of the NP or nasal and throat swab collected outside of the allowed window following the ILI will be considered valid.

List of subjects excluded from the per-protocol analysis will be finalyzed prior to unblinding the database and described in the blinded data analysis memo.

Intention-to-Treat (ITT) Set

The intention-to-treat set comprises all subjects who received at least one dose of the vaccine or placebo. Subjects in the ITT population will be analysed according to their randomization.

5.4 Efficacy Endpoints Analysis Methods

5.4.1 Hypothesis

The hypothesis to be tested is: $H_0 : VE \leq 40\%$

where VE denotes the vaccine efficacy of M-001 against qRT-PCR- or culture-confirmed influenza in association with protocol-defined ILI over a first season of influenza.

The hypothesis will be rejected and the superiority of M-001 demonstrated if the lower bound of the two-sided 95% CI for VE is >40% for the primary per-protocol analysis.

5.4.2 Statistical Methods

Primary efficacy endpoint:

The main analysis will be performed using data from cohort 1 (Season 2018-2019) and cohort 2 (Season 2019-2020) combined.

Efficacy will be assessed for the qRT-PCR- or culture-confirmed influenza caused by any influenza A or B virus in association with a protocol-defined ILI. The vaccine efficacy (VE) is defined as

$VE = 1 - [p_V / p_P]$, where p_V and p_P are the proportions of subjects with qRT-PCR or culture-confirmed influenza caused by any influenza A or B virus in association with a protocol-defined ILI in the M-001 experimental group and placebo group, respectively.

For the main analysis performed on the PP set, $p_V = C_V / N_V$ with N_V = number of subjects in the PP set in vaccine M-001 group and C_V = number of cases of qRT-PCR- or culture-confirmed

influenza in association with a protocol-defined ILI in the set of N_V subjects, and similarly for the placebo group with $p_P = C_P / N_P$.

The two-sided confidence interval for VE will be calculated by an exact method conditional on the total number of cases in both groups. VE can also be written as

$VE = 1 - \left[\frac{N_P}{N_V} x \frac{q}{1-q}\right]$, where $q = \frac{C_V}{C_V + C_P}$.

Given the total number of cases, an exact confidence interval for q can be derived by the exact Clopper-Pearson method for the binomial proportion from which an exact 95% CI for VE can be derived.

The exact 95% CI for p_V and p_P within each group will be derived using the Clopper-Pearson exact method.

The conditional binomial test is testing about the probability an event falls in the vaccine rather than placebo group ($q = \frac{C_V}{C_V + C_P}$).

The p-value resulting from the test of H_0: $q <= 0.6*N_v/(0.6*N_v + N_P)$ versus H_a : $q > 0.6*N_v/(0.6*N_v + N_P)$ will be reported (test will be performed at the one-sided level 0.025).

The p-value of the exact test will be reported together with the exact 95% CI for the VE.

The main analysis performed on the PP set will be supported by an analysis on the ITT set. For the ITT set, N_V and N_P correspond to the number of subjects in the ITT set in the M-001 and placebo groups, respectively.

VE and 95% CI will be provided by cohort, age group, and combination of cohort and age group as well for the PP and ITT population.

Descriptive statistics of $p_V = C_V / N_V$ and $p_P = C_P / N_P$ by country and site within country will be provided, N_V et N_P being the number of subjects and C_v and C_P being the number of cases, within each country, and site within country.

Sensitivity analyses for the primary efficacy endpoint:

Time to first qRT-PCR- or culture-confirmed influenza in association with a protocol-defined ILI will be considered.

For this analysis, performed on the PP set, the following proportional hazard model will be fitted:

$$h(t) = h_0(t)\exp\left[\beta_1 \, Group\right]$$

where $h_0(t)$ is the baseline hazard function, Group is the treatment variable, (0 for placebo and 1 for M-001), and β_1 is the group effect.

The proportional hazard model assumes that the ratio of the hazard functions associated with M-001 and placebo is constant over time.
Under this model, the VE between M-001 and placebo is estimated by $100(1 - e^{\beta_1})$ and its associated 95% CI will be derived as $100\left(1 - e^{\beta_1 \pm z_{0.975}\, sterr(\beta_1)}\right)$,
where *sterr* and $z_{0.975}$ represents the standard error and 97.5% quantile for the normal distribution, respectively.

The p-value resulting from the test of H_0: $\beta >= \ln(0.6)$ versus H_a : $\beta < \ln(0.6)$ will be reported (test will be performed at the one-sided level 0.025).

In addition, the time to first qRT-PCR- or culture-confirmed influenza in association with a protocol-defined ILI will be presented using a Kaplan-Meier plot, with x-axis values at 30, 60, 90, 120, 150, 180, 210 and 240 days.

For the time-to-event analysis, the time of the first qRT-PCR or culture confirmed influenza in association with a protocol-defined ILI is the time of the first symptom associated with the ILI episode. This time will be calculated in days from the start of the surveillance period (14 days post second vaccination). Subjects without qRT-PCR- or culture-confirmed influenza will be censored at the last successfull contact and the associated time in the analysis will be the number of days from the start of the surveillance period (14 days post second vaccination) until censoring time. For the ITT analysis, subjects with no surveillance contact will be censored at day 1.

Additional analyses will be performed to assess the effect of the 2 cohorts (season 2018-2019 and season 2019-2020) and the age stratification factor (<65 years and ≥65 years) in the model applied to time to first qRT-PCR- or culture-confirmed influenza in association with a protocol-defined ILI. The methodology will be based on the paper by Mehrotra, Lu, and Li[xix]. The hazard ratio will first be estimated separately for each of the 4 strata (combinations of cohort and age group) using an unstratified Cox model and the stratum-specific estimates will be combined using the minimum risk weights.

qRT-PCR Cut-off for confirmation of influenza in association with a protocol-defined ILI

An additional sensitivity analysis to the primary efficacy assessment will be performed where qRT-PCR- confirmed influenza is defined if the qRT-PCR Ct count corresponding to the detection of any flu type is < 40.

The analysis will be the same than the one described for the primary efficacy endpoint.

Secondary efficacy endpoints:

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

The second secondary efficacy assessment consisting in the between-group difference in number of days with respiratory or systemic symptoms will be assessed within the subjects with qRT-PCR- or culture-confirmed influenza illness from the per-protocol population. The number of days with respiratory or systemic symptoms during the first qRT-PCR- or culture-confirmed ILI event will be used in the analysis.

The between-group comparison will be done on the percentage of subjects with number of days with respiratory or systemic symptoms in the following categories:

- < 7days
- ≥ 7 and < 14 days
- ≥ 14 and < 21 days
- > 21 days

using Cochran-Mantel-Haenszel test (general association statistic) with 4 strata corresponding to the combination of age category and cohort.

The percentage of subjects with ILI symptoms in each vaccine group and its 95% CI will be derived using the stratified Wilson's method with 4 strata (4 combinations of age category and cohort); the difference in percentages between the 2 groups (with 95% CI) will be estimated using the stratified Newcombe confidence limits, the strata being weighted by Mantel-Haentzel weights[xx]. The percentage of subjects with ILI symptoms in each vaccine group, the between-group group differences with their 95% CI within each combination of cohort and age stratum will be provided also using the same approach as above. The 95% CI for each combination of age category and cohort will be derived using Wilson's method.

An additional analysis comparing the rates (/year) of ILI events during the flu season will be performed between the vaccine groups using an overdispersed Poisson model: the offset will be the duration of follow-up in the flu season for a given subject and the scale parameter will be estimated by the Pearson method. The model will include the vaccine group, cohort, and age group as factors, as well as the interactions between cohort and vaccine group and between age group and vaccine. The event rate (/year) will be estimated in each group (a month being defined as 365 days) as well as the rate ratio for the M-001 group compared with the placebo group; 95% CI will be provided. Event rates (/year) and rate ratios will be derived within each cohort, age group and combination of cohort and age group.

A sensitivity analysis of the percentage of subjects with ILI symptoms selecting ILI with a start date prior to March 15th, 2020 will be performed.

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

Exploratory efficacy endpoints:

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

- Proportion of subjects taking antibiotics due to a post-influenza (qRT-PCR- or culture-confirmed) respiratory tract infection,
- Proportion of subjects hospitalized due to an ILI, with or without confirmation by viral culture or qRT-PCR analysis.
- Proportion of subjects who died due to an ILI, with or without confirmation by viral culture or qRT-PCR analysis.
- Proportion of subjects with serious ILI with or without confirmation by viral culture or qRT-PCR analysis
- Proportion of subjects taking medications due to qRT-PCR- or culture-confirmed ILI

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

For both vaccine groups, if the number of subjects having more than 1 hospitalization is at least 10, in addition to the analysis defined above, the rate of hospitalizations associated with ILI episodes over the flu season and its 95% CI will be estimated for the PP set by means of a Poisson model, applied on the number of events with duration of follow-up as offset. The event rate (/year) will be estimated in each group (a year being defined as 365 days).

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

- For the PP set, the distribution of influenza confirmed episodes

6. IMMUNOGENICITY ENDPOINTS

A subset of subjects was enrolled in Season 2 to assess immunogenicity.

The endpoint for assessing the immune response is 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.

Immunogenicity analyses will be detailed in a separate SAP.

7. SUBGROUP ANALYSES

7.1 Vaccine-by-Subgroup Interaction

To assess the consistency of the vaccine efficacy across different subgroups, Breslow-Day test for the homogeneity of the odds ratios will be used; this analysis will be performed on the PP population.

The following subgroups will be tested:

- Cohort : 1 and 2, corresponding to season 2018-2019 and 2019-2020
- Age: <65 years and ≥65 years overall and by age within each cohort
- Gender: M and F : overall and by sex within each cohort
- Flu Type (A, B)

7.2 VE Subgroup Estimates

In addition to testing the consistency of vaccine efficacy across the subgroups, estimates of VE within the subgroups will be obtained using the Clopper-Pearson method for the binomial proportion from which an exact 95% CI for VE will be derived. These estimates will be obtained on the PP population.
Estimates of VE within the subgroup of Cohort will also be provided for the ITT population.
Also, estimates of VE and exact 95% CI by subtype (Type A/H1N1 and Type A/H3N2) or by lineage (Type B/Yamagata) and Type B/Victoria) will be provided if sufficient data is available.
Descriptive statistics will be provided for all subgroups including influenza sub-type or lineage.

8. ASSESSMENT OF STUDY POPULATION

8.1 Disposition of Subjects

The number and percent of subjects will be summarized for the following categories: subjects screened, screening failed, enrolled subjects, enrolled and not randomized, randomized subjects, completed, and discontinued.

Reasons for screen failure will be summarized in the screened population.

All subjects who fail to complete the study will be categorized by their primary reason for discontinuation and summarized by group. Disposition of subjects and reasons for withdrawal will also be summarized separately. Supportive listings will be provided.

The number and percent of randomized subjects with protocol deviations and the number of protocol deviations will be summarized by group, broken down by main deviation category (major/minor) and sub-categories in the randomized population. Subjects will be counted once per deviation category, and can be counted for more than one deviation category.

In addition to the number of subjects included in each analysis set (Safety, ITT, PP), will be summarised overall and by group.

8.2 Demographic and Baseline Characteristics

Analyses of demographic and baseline characteristics will be performed on the ITT, PP and safety populations.

Standard descriptive statistics will be presented at least for the continuous variables of:

- Age (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

The total counts and percentages of subjects will be presented at least for the categorical variables of:

- Cohort
- Age (<65 years, ≥ 65 years)
- Sex
- Race
- Ethnicity

8.2.1 Medical History

Medical history is defined as any condition that started prior to the ICF signature at V1. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 and listed separately by group, System Organ Class (SOC) and Preferred Term (PT) within SOC.

Percentage of subjects with any medical history will be summarised for the ITT analysis set overall, by SOC and PT.

8.2.2 Prior and Concomitant Medications

Prior and concomitant medications are collected in the CRF at each study visit. A prior medication has started and ended prior to the first vaccine dose. A concomitant medication has started on or after the first study vaccine dose or is continuing after the first vaccine dose.

Any medications with an unknown start or stop date will be assumed to be concomitant medications, unless a partial start date or stop date indicates otherwise.

Medication terms will be coded according to WHO Drug Dictionary 01Mar2018.

Table summaries will be provided for prior and concomitant medications; a further distinction between concomitant medications starting after first vaccination and continuing medications will be done.

Previous vaccination history will be summarised similarly. The presence of severe vaccination reactions that occurred during previous vaccination will be summarized by SOC, PT for the subjects having received previous vaccinations.

8.3 Duration of Follow-Up

Duration of follow-up defined for the flu season (cohorts 1 and 2) as the time (in days) between the first dose of vaccination and last date at which the subject answered to the center call, last date of site visit, last date of phone contact, date of early discontinuation visit, or date of death for subjects known to have died (whichever comes last).

The distribution of days under active surveillance, i.e., the number of days between the date of last vaccination day + 14 and the date where the last call was answered within the active surveillance period will be summarised overall and by group.

The distribution of days until last contact, i.e., the number of days between the date of last vaccination day + 14 and the date where the last call was answered within the active surveillance period or last phone contact (received by subject or representative) or last visit will be summarised overall and by group.

8.4 Vital Signs

Systolic and diastolic blood pressure (BP), Pulse, Respiratory Rate, and Body Temperature recorded at Visit 1 will be summarized overall and by group for the safety population.

8.5 Vaccine Received By Subject

The number and percentage of subjects who received one or 2 doses of vaccine will be presented. The distribution of time between the 2 vaccinations will be described.

9. DETAILS ON MISSING DATA

9.1 Handling of Missing Dates for Adverse Events

The following imputation rules apply to cases in which the start date is incomplete (i.e., partial or completely missing) for adverse events. In addition to the following rules, if the stop date is complete and the imputed start date is after the stop date, then the start date will be imputed using the stop date. If the stop date is on or after the date of first dose of vaccine in the study, but the start date is completely missing, then the start date will be imputed with the date of first dose of vaccine. If the stop date is prior to the date of first dose of vaccine in the study, but the start date is completely missing, then the start date will be imputed with the stop date.

For start dates with missing day and month (year is present):

- If the year of the incomplete start date is the same as the year of the date of the first dose of IP, then the day and month of the date of the first dose of vaccine will be assigned to the missing fields.
- If the year of the incomplete start date is prior to the year of the date of the first dose of vaccine, then December 31 will be assigned to the missing fields.
- If the year of the incomplete start date is after the year of the date of the first dose of vaccine, then January 1 will be assigned to the missing fields.

For start dates with missing month only (day and year are present):

- The day will be treated as missing and both month and day will be replaced according to the above procedure.

For start dates with missing day only (month and year are present):

- If the month and year of the incomplete start date are the same as the year and month of the date of the first dose of vaccine, then the date of the first dose of vaccine will be assigned to the missing day.
- If either the year of the incomplete start date is before the year of the date of the first dose of vaccine or if both years are the same but the month is before the month of the date of the first dose of vaccine, then the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of vaccine or if both years are the same but the month is after the month of the date of the first dose of vaccine, then the first day of the month will be assigned to the missing day.

9.2 Handling of Missing Dates for Solicited Systemic and Injection Site Reactions

For the analysis of solicited systemic and injection site reactions, missing dates will not be replaced. The denominator will be the number of subjects who returned their diary card for the period of assessment. Missing responses on the card will be treated as if no event occurred.

10. GENERAL PRINCIPLES FOR REPORTING RESULTS

10.1 Statistical Testing

No adjustment of the Type I error for multiple comparisons will be made in the study; indeed, all analyses, estimations are supportive to the results of the primary endpoint.

10.1.1 Presentation of Results

All analyses will use SAS® version 9.3 or higher. Unless otherwise specified, summary tables will be presented by vaccine group, labelled as follows: M-001 and Placebo.

All data will be presented in listings, sorted by country, site number and subject number, and group. Continuous variables will be summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding group.

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, and standard deviation will be reported to one more decimal place than the raw data recorded in the database. The maximum number of decimal places presented for any statistic shall be four.

Percentages will be presented to one decimal place except if percentage are smaller than 0.1%.

All confidence intervals (CIs) will be two-sided 95% CIs, unless stated otherwise, and presented to one more decimal place than the raw data recorded in the database. If a model is used to estimate the treatment difference, the corresponding CI according to the model will be presented. Otherwise, the unadjusted CI will be used. Nominal p-value will be presented for the main efficacy variable, but these cannot be interpreted in terms of statistical significance.

The presentation of p-values will be to three decimal places unless a p-value is less than 0.001, in which case "<0.001" will be displayed.

A month is operationally defined to be 30.4 days. A year defined to be 365 days.

11. CHANGES OF ANALYSIS FROM PROTOCOL

Protocol version 1.0

No lot consistency analysis will be performed in a subset of subjects from Cohort 2, since all lots needed for the entire study will be produced by Cytovance. Immunogenicity analyses to be performed in a subset of subjects from Cohort 2 will be defined in a separate document (SAP for immunogenicity analyses).

Protocol version 5.0 – Amendment 1

The following changes were made compared to the analyses described in the protocol.

- the ILI episode for which a nasal or throat swab was collected outside of the allowed window of 3 days post onset date will be considered as a qRT-PCR or culture confirmed ILI if the results of the qRT-PCR or culture were positive. Review of each case will be performed prior to unblinding and documentation provided in the blinded data review meeting memo (see section 5.3).
- the analysis of the secondary efficacy assessment consisting in the between-group comparison of the number of days with respiratory or systemic symptoms among subjects with qRT-PCR- or culture-confirmed influenza illness will be performed on the percentage of subjects with number of days with respiratory or systemic symptoms in the following categories:
  - < 7days
  - At least 7 and < 14 days
  - At least 14 and < 21 days
  - > 21 days

  Cochran-Mantel-Haenszel test with 4 strata corresponding to the combination of age category and cohort will be used.

- these exploratory endpoints have been added :
  - Reduction, due to vaccination with M-001, in the proportion of subjects with serious ILI with or without confirmation by viral culture or qRT-PCR analysis
  - Reduction, due to vaccination with M-001, in the proportion of subjects taking medications due to qRT-PCR- or culture-confirmed ILI

In addition, more details are provided in the SAP compared to the protocol.

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[i] http://www.cdc.gov/nchs/fastats/deaths.htm;

[ii] http://www.who.int/mediacentre/factsheets/fs211/en/

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