1 SYNOPSIS

Sponsor: BiondVax Pharmaceuticals LTD	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: M-001	**Volume:**	**Not Applicable/Not for Submission**
Name of Active Ingredient: Multimeric peptide-based vaccine	**Page:**	

Study 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)

EudraCT Number:	**Protocol Number:**
2018-000468-27	BVX-010

Study Centre(s):

Total of 110 sites in 7 countries:

Bulgaria: 23 sites	Latvia: 4 sites
Croatia: 7 sites	Poland: 33 sites
Georgia: 7 sites	Ukraine: 24 sites
Hungary: 12 sites	

Publications:
None

Study Design:

This was 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 were assigned randomly to 1 of 2 treatment arms (6231 per study arm during the study) to receive two doses of the M-001 vaccine or placebo (saline) on Day 0 and 22.

Reactogenicity was 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 Adverse Events (SAE) collected from the time of each study vaccination through approximately 22 days after each study vaccination (day of the vaccination inclusive) were analysed separately. SAEs (including Adverse Events of Special Interest (AESI)) and New Onset of Chronic Illnesses (NOCIs) were collected from the time of the first study vaccination through the entire trial period.

The duration of the study was two years covering two flu seasons from August 8th, 2018 to July 2nd, 2020.

The duration of the study for each subject was up to one year (reflecting time between vaccination and end of the flu season as stated in the protocol).

Cell-mediated immunity Sub-study was not assessed as primary endpoint of the study was not achieved.

Subject Number:

Planned: 12000	Randomized: 12462
Screened: 12569	Completed: 11769

Primary Study 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 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: 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).

Criteria for Eligibility:

To be eligible for this study subjects met 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 treatment for 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 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 vaccine. 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 for this study were:

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.

Statistical Methods:

For the primary analysis of vaccine efficacy (VE), the efficacy of M-001 after a first influenza season in each cohort was 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 was calculated by the Clopper- Pearson exact method conditional on the total number of cases in the vaccine and placebo groups combined. Similarly, vaccine efficacy (VE) and its 95% confidence interval were calculated for the ITT Population.

Determination of Sample Size for the CMI Sub-study:

The endpoint for assessing immune response to the vaccine was not assessed due to failure in achieving the primary endpoint. Initially it was supposed to be calculated by 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 were 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%.

Summary of Results

There were no differences in the confirmed influenza cases between the experimental and control groups: ILI Incidence and qRT-PCR or Culture Confirmed Influenza-Like Illness in the per protocol Population were comparable between the groups in both seasons by both methods (qRT-PCR and culture), this was also the conclusion in both age groups (older adults and elderly) and across the different influenza viruses (H1, H3 and B).

Accordingly, M-001 vaccine efficacy could not be demonstrated in both per protocol and ITT Populations. The secondary endpoint, duration of ILI Symptoms were comparable overall, by season, by age group and by confirmation method (qRT-PCR or Culture Confirmed ILI) in both, PP and ITT Population.

There were no safety concerns related to the vaccine. The number of subjects with serious vaccine related AEs were comparable in the experimental and control groups. None of NOCIs was considered as treatment related in the experimental group.

All death cases in the trial (26 in the experimental group and 29 in the control group) were not related to the treatment.

Conclusions

Results did not demonstrate a statistically significant difference between the vaccinated and placebo groups in reduction of flu illness and severity, and therefore failed to meet both the primary and secondary efficacy endpoints. The study's primary safety endpoint was met.

The development programme of M-001 is currently not further followed up.

Final Report Date:

14 June 2021