WP6 (Lead Partner RUG)

Clinical Trial Program

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Double-Blind Randomized Controlled Phase IIb Vaccine Trials

- Aim:

  To evaluate the safety and immunogenicity of two universal influenza vaccines targeting different conserved immunogenic regions of influenza A and B viruses.

- *FLU-v (SEEK, UK) and M-001 (BiondVax, Israel) are both peptide based vaccines containing epitopes identified from the viral internal (structural) proteins.*
- *M-001 contains also epitopes from the viral surface glycoproteins.*
- *While FLU-v is composed of synthetic polypeptides, M-001 is composed of a single recombinant protein.*

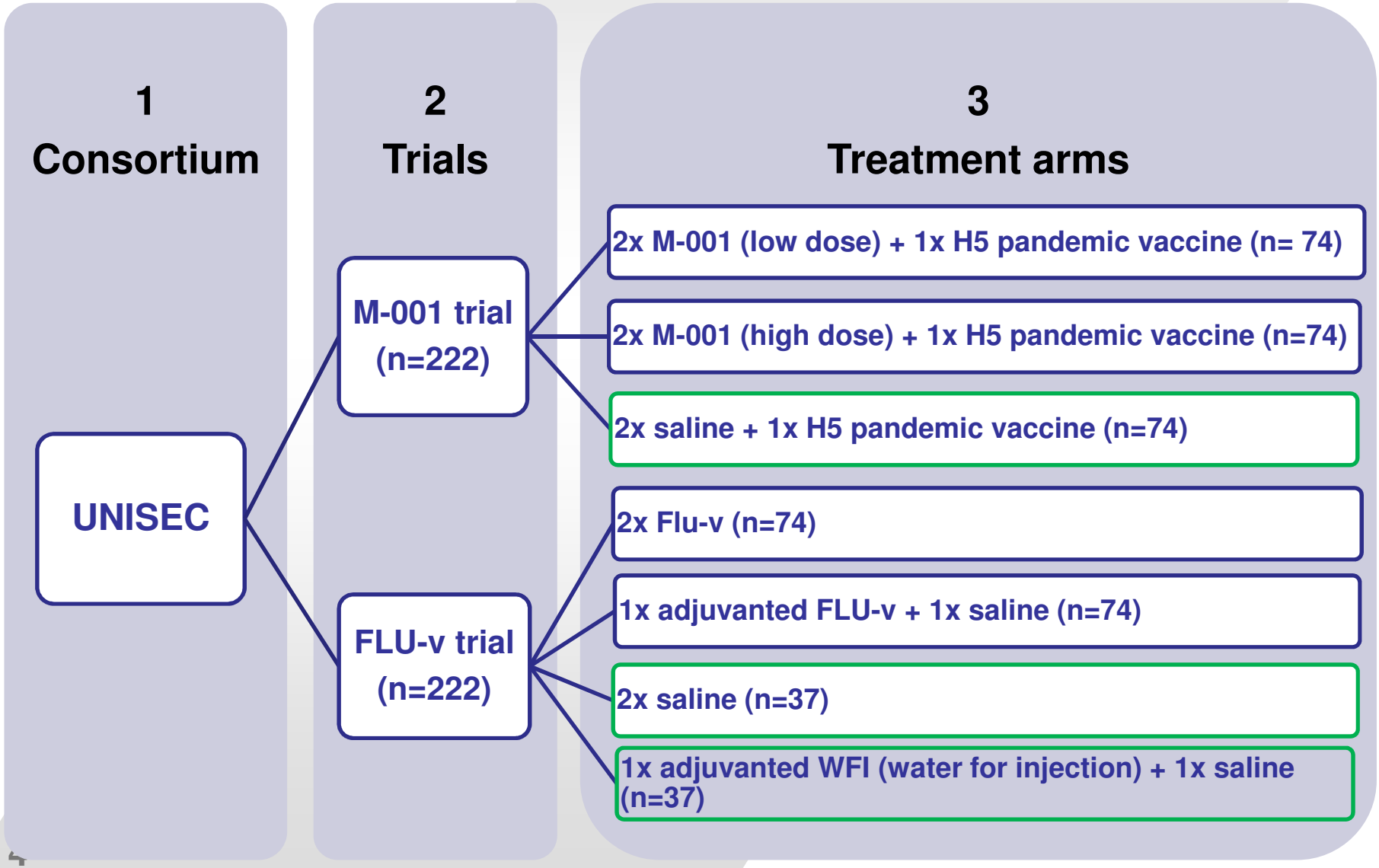
Double-Blind Randomized Controlled Phase IIb Vaccine Trials (cont.)

- **Trial participants:**

  Healthy adults aged 18-60 years, not among the target groups for influenza vaccination.

- **Sample size estimation**:
  - Determined on the basis of influenza-specific interferon-γ responses observed from their earlier trials.
    - FLU-v study: fold increase of influenza-specific interferon-γ responses measured by ELISA.
    - M-001 study: fold increase of influenza-specific interferon-γ secreting CD8+ T cells measured by FACS analysis.
  - Two-sided alfa of 5%, power of 80% with continuity correction.
  - Taking a loss to follow up into account, we will include 222 subjects in total (74 subjects per experimental arm).

Study Layout



Study endpoints

Safety

- AE diary cards and questionnaires will be collected until 180 days after the first dosing.

Immune Correlates of Protection

- Cellular immunity will be assessed on day 42 (21 days after the second administration).
- For FLU-v study, cellular immunity on day 180 (159 days after the second administration) will also be assessed. Antibody responses on day 42 and 180 will be evaluated.
- For M-001 study, cellular and humoral immunity (HI) will be assessed 21 days after the H5 pandemic vaccination.

➢ A maximum of 187 days (from screening to study conclusion) study participation, covering one influenza season.

Exploratory endpoints

- **M-001 trial**
  - Additional CMI measures (qRT-PCR assay).
  - Humoral immunity (HI) against drifted H5N1 strains.
  - Association between CMI markers and antibody responses measured in the study.

- **FLU-v trial**
  - Clinical efficacy
    - Clinical symptom score (to be collected during the influenza epidemic season (December-March)).
    - RT-PCR –confirmed influenza infections
  - Additional CMI measures.
  - Antibody responses.
    - Isotyping of antibody responses to FLUv
    - ADCC/ADC assays

Trial Logistics

- Clinical trial sites:
  - St Istvan St Laszlo Hospital (Hungary) will perform the M-001 study.
  - Isala (Zwolle, NL) is the potential site for the FLU-v study.

- PBMC processing sites:
  - National Center of Epidemiology (Hungary) will process clinical samples for the M-001 study.
  - Isala is able to process clinical samples for the FLU-v study.

- Laboratories for clinical sample analysis:
  - Robert Koch Institute is the central analytic center for clinical studies run under the UNISEC consortium (WP5 leader). Perform multi-parametric intracellular cytokine FACS analysis and IFN-γ ELISA (primary CMI endpoint).
  - National Center of Epidemiology will analyze HAI assay and additional (exploratory) CMI endpoints for the M-001 study.
  - National Institute Public Health (Norway) is able to measure additional (exploratory) CMI endpoints for the FLU-v study.

Data Management

- Will be performed by UMCG Trial Coordination Center (Iso-certified);
- Project manager Denise Mailly, part of WP6-team;
- In close collaboration with sponsors and WP partners;
- Case report forms on secured website;
- Check of data consistency and reliability;
- Pseudo-anonymization;
- Data Safety and Monitoring Board not required.

Action points BVX

- Submission BVX dossier to Hungarian authorities.
- Development of recruitment strategies in Hungary.
- GMP vaccine manufacturing.
- Development and testing IT tool data management.
- Statistical Analysis Plan.

Action points SEEK

- Further tendering GMP manufacturers.
- Tendering CRO.
- Meeting with Zwolle Isala Clinics.
- Meeting with National Institute Public Health.
- Submission SEEK dossier to NL authorities.
- Development of recruitment strategies in Zwolle.
- GMP vaccine manufacturing.
- Development and testing IT tool datamanagement.
- Statistical Analysis Plan.

Timelines

Protocols/ Audits
Oct 2013- Mar 2015

ERB/ Trial no.
Mar 2015-Jun 2015

BVX Trial
Aug 2015- May 2016

Comparative (meta-analytic) study
July-Sept 2017

Report
2016- Oct 2017

Batch information needed from GMP producer

SEEK trial possibly delayed with 6-12 months