FLU-v: Universal Influenza Vaccine Clinical Development

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FLU-v composition

An equimolar admixture of four individual synthetic polypeptides (20 to 32 aa long) covering conserved immunogenic regions in M1, M2 and NP.

Criteria for selection of immunogenic sequences:

- LENGTH: Short Regions (<40 aa)
- CONSERVATION: Present in >70% of all animal and human influenza strains.
- IMMUNOREACTIVITY: Each region contains >5 potential T cell epitopes.
- UNIVERSALITY: Absence of all epitopes in any Flu strain: $p<10^{-10}$

Previous clinical data

- **Phase I**
  - **FLU-v was safe and well tolerated with no vaccine associated severe adverse events.**
  - **Dose-dependent IFN-gamma responses >2-fold the pre-vaccination level were detected in 80% and 100% of volunteers receiving, respectively, the low (250ug) and high dose (500ug) adjuvanted FLU-v formulations.**

- **Challenge study**
  - **FLU-v was safe and well tolerated.**
  - **Day-19 post-vaccination, the FLU-v group, but not the Placebo, developed FLU-v specific IFN-g responses (8.2±3.9 vs 1.3±0.1 fold increase, respectively).**
  - **FLU-v specific cellular responses correlated with reductions in both viral titre (p=0.01) and symptom score (p=0.02) post-challenge.**

UNISEC Clinical trial protocol

- Single centre double-blind randomised trial
- 4 arms:
  - Single dose adjuvanted FLUv (500ug) n=74
  - Two doses non-adjuvanted FLUv (500ug) n=74
  - Placebo: single dose adjuvanted water for injection n=37
  - Placebo: two doses saline n=37

- Visits:
  - Screening /Inclusion/ Exclusion criteria / Blood chemistry (approx day -7)
  - Randomisation/ Blood sample/ first dose (day 0)
  - Second dose (day 21)
  - Blood sample (day 42)
  - Blood sample (day 180)

Study end points

- **Immunogenicity:** Measured at prevaccination, post vaccination (day 42) and long term (day 180)

  - <u>Cellular</u>
    - **CMI studies: multiparametric FACS analyisis CD4+/CD8+ cells and cytokines (IFNg, TNF) (Primary Endpoint)**
    - **Additional assays (Granzyme B secretion)(Exploratory)**

  - <u>Humoral</u>
    - **Isotyping of antibody responses to FLUv**
    - **ADCC/ADC assays**

Study end points

- **Efficacy:**
  - Reduction in influenza symptom scores (daily diary score during influenza season)
  - Reduction in the number of RT-PCR –confirmed influenza infections (nasal and throat swab when predefined symptom scores persist for 24h)

- **Safety:**
  - Solicited Adverse effects until 21 days post -vaccination
  - Unsolicited Adverse Effects and Severe Adverse effects during the entire duration of the study.

Trial progress

- Study Protocol in the final stages.
- Peptide GMP Manufacturing: American Peptide, San Diego, US. Ready to sign contract.
- Sterile vialling company and Analytical & Stability studies: Symbiosis, Scotland. Ready to sign contract.
- Trial centre: Isala Clinics, Zwolle, The Netherlands. Negotiations to start immediately.
- Ethics & Regulatory: Information on manufacturing (CMC) required in order to update IMP Dossier to add to Clinical Trial Application and submit to Ethics and Regulatory boards.
- Support to WP5 in protocol development (PBMC isolation and flow cytometry assays)