NOVEL MULTIVALENT MVA-BN-RSV VACCINE INDUCES BROAD HUMORAL AND CELLULAR IMMUNE RESPONSES

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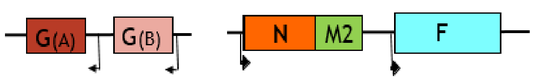
BACKGROUND

MVA-BN-RSV Vaccine Design



MVA-BN-RSV was designed to induce RSV-specific immune responses against 5 RSV proteins (F, G [A and B subtype], M2 and N), based on an established, safe viral vector. We present clinical phase 1, phase 2 and annual boosting results.

RESULTS

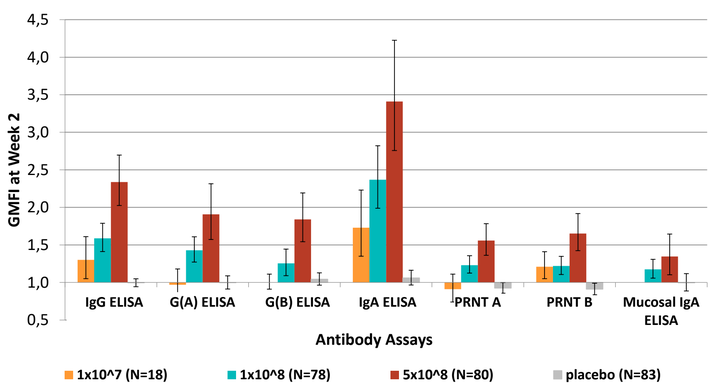
MVA-BN-RSV elicited broad, dose-dependent, RSV-specific cellular and antibody immune responses, which could be boosted after 1 year. Serum antibody assays showed highest fold-increases after administration of $5x10^8$ Inf.U, with GMFI ranging from 1.6 (RSV[A] PRNT) to 3.4 (IgA ELISA). GMFI of 1.4 was detected for mucosal IgA responses ($5x10^8$ Inf.U). Cellular immune responses were achieved against all encoded RSV proteins, with 65% of subjects responding to all 5 proteins ($5x10^8$ Inf.U). No relevant differences were observed between age groups.

CONCLUSIONS

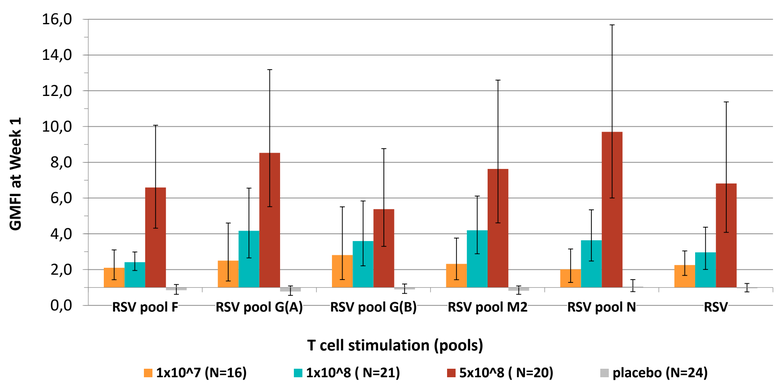
MVA-BN-RSV induced broad and robust humoral and cellular immune responses, thus appears to be mimicking a natural response to RSV infection. Data from the 1-year extension study support a durable response lasting ≥6 months and suggest a seasonal vaccination approach.

MVA-BN-RSV - antibody responses fold increases at week 2

- Trend towards higher antibody and T cell immune responses with higher doses of MVA-BN-RSV
- Data shown are fold increases from baseline at the peak post vaccination visits observed, namely week 2 (2 weeks after first vaccination) for antibody based responses and week 1 for T cell responses
- GMFI (geometric mean fold increases) are displayed to address the observation of baseline variability between the groups (different GMTs at week 0)
- MVA-BN-RSV induced antibody based (ELISA, PRNT) and T cell (IFN-γ ELISPOT) immune responses against RSV subtypes A and B
- MVA-BN-RSV induced T cell responses against all RSV inserts in the vaccine

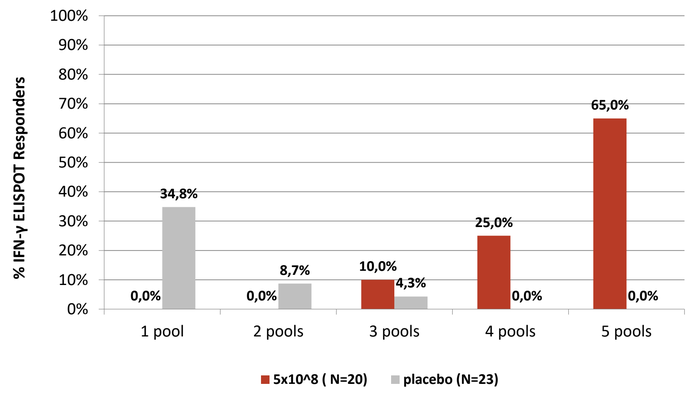


MVA-BN-RSV - T cell responses fold increases at week 1



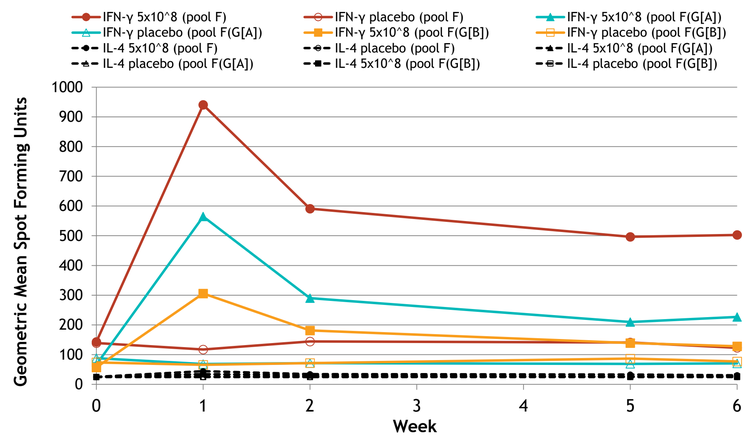
IFN-γ ELISPOT responders to RSV peptide pools

- Majority of subjects responded to multiple RSV proteins at the same time, demonstrating a broad MVA-BN-RSV induced T cell response on a subject level
- In the $5x10^8$ dose group 100% of the subjects responded to at least 3 RSV proteins, and 65% to all 5 RSV proteins

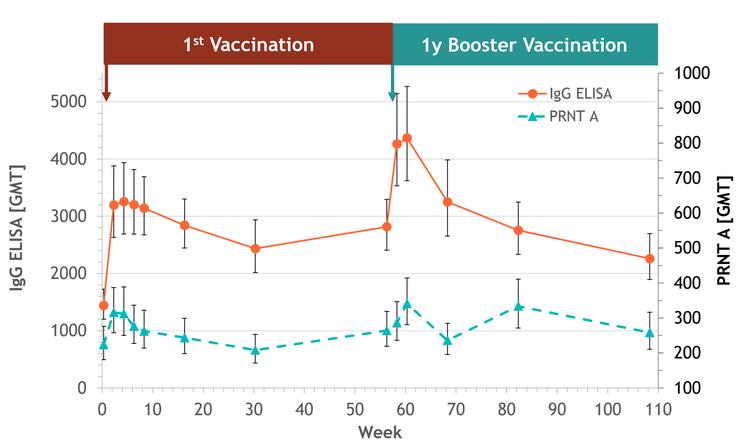


T cells - kinetic of IFN-γ and IL-4 responses

- Kinetics of T cell responses and (selected) antibody responses reflect (recall) immune response in RSV experienced subjects
- Quick increase after first vaccination; peak of T cell response at week 1 and of humoral response at week 2
- Booster vaccination given at week 56 induces further immune response booster to levels similar or higher as after initial vaccination
- T cell responses: IL-4 signals were low or below the detection limit, indicating a Th1 biased T cell response. Placebo group showed no changes in GMSFU over time for either IFN-γ or IL-4



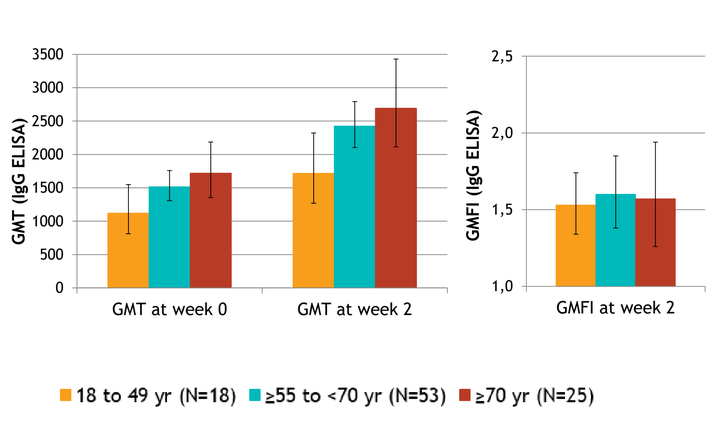
Antibody responses – GMT kinetic



Age groups – IgG ELISA antibody responses

GMTs (week 0 & 2; left) GMFI (week 2; right)

- No significant / meaningful difference found in both, Ab responses and T cell responses in different age groups
- MVA-BN-RSV vaccine is immunogenic (with favourable safety profile), even for elderly ≥70 years



METHODS

Healthy subjects of different age groups were enrolled in Phase 1 (N=63) (18-49, 50-65 years) and Phase 2 (N=420) (55-69, ≥70 years) clinical trials. They received either 1 or 2 doses of MVA-BN-RSV vaccine ($1x10^7$; $1x10^8$; $5x10^8$ Inf.U/0.5mL per dose, IM) or placebo.

- Phase 1 trial was a safety study with 63 subjects in three groups receiving 1 dose of vaccine or placebo at Day 0 and Day 28. Each group included 18 subjects receiving verum and 3 subjects receiving placebo (TBS): (1) 18-45 years receiving a dose of $1x10^7$ Inf.U; (2) 18-45 years receiving $1x10^8$ Inf.U and (3) 55-65 years receiving $1x10^8$ Inf.U
- Phase 2 was a dose finding study in a total of 420 subjects ≥55 years with 5 treatment groups receiving 2 doses (0.5mL, IM) at Day 0 and Day 28 as follows: (Group 1): $1x10^8$ Inf.U /placebo; (Group 2): $1x10^8$ Inf.U / $1x10^8$ Inf.U; (Group 3): $5x10^8$ Inf.U /placebo; (Group 4): $5x10^8$ Inf.U / $5x10^8$ Inf.U; (Group 5): placebo / placebo.
- 88 subjects vaccinated in the Phase 2 trial who had previously received a single dose of $1x10^8$ Inf.U or $5x10^8$ Inf.U of MVA-BN-RSV received an equivalent booster dose at month 12. A subgroup of 20 subjects per group had additional blood draws to determine T cell responses (PBMC subset).

Safety and RSV-specific humoral, mucosal and cellular immune responses were assessed before and after the booster vaccination using:

- Serum PRNT (for subtype A and B),
- Serum ELISA: total IgG and IgA, IgG against G protein (subtype A and B)
- Mucosal ELISA: IgA
- IFN-y/IL-4 ELISPOT assays (PBMC subset)

Serum samples and nasal swab samples (for mucosal antibody response) were collected at each visit whereas whole blood for PBMC preparation was drawn until 4 weeks after vaccination. For PRNT and ELISA, geometric mean titers (GMT) and geometric mean fold increases (GMFI) over baseline with 95% confidence intervals (CI) were calculated. For the ELISPOT assay, response was defined as ≥2-fold increase in number of spot forming units (SFU) over baseline (baseline positive) or the appearance of a positive signal (baseline negative).

ACKNOWLEDGEMENT:
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