



# EuroVacc 02 : A Phase I Trial to Assess the Safety of 4 mg DNA-C (IM), and the Safety and Immunogenicity of DNA-C (IM) Followed by NYVAC-C (IM) in an Open, Randomised Comparison to NYVAC-C Alone in Healthy HIV Negative Volunteers at Low Risk of Infection

Pierre-Alexandre BART, MD  
Division of Immunology  
and Allergy  
BT 06 / CHUV  
1011 Lausanne  
Switzerland  
pierre-alexandre.bart@chuv.ch  
Tel +41 21 314 11 60  
Fax +41 21 314 11 61

476

Pierre-Alexandre Bart<sup>1</sup>, Tristan Barber<sup>2</sup>, Mona Khonkarly<sup>1</sup>, Donatella Ciuffreda<sup>1</sup>, Séverine Burnet<sup>1</sup>, Wolfgang Stöhr<sup>3</sup>, Miranda Cowen<sup>2</sup>, Sheena McCormack<sup>3</sup>, Giuseppe Pantaleo<sup>1</sup>, Jonathan Weber<sup>2</sup> and EUROVACC Program

<sup>1</sup>Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; <sup>2</sup>Imperial College, London, UK; <sup>3</sup>Medical Research Council Clinical Trials Unit, London, UK.

## ABSTRACT

**Background:** EuroVacc 02 is a phase I trial to evaluate the safety of a DNA-C vaccine and the safety and immunogenicity of its combination with a poxvirus-based (NYVAC-C) vaccine, compared to administration of NYVAC-C alone. The same recombinant HIV DNA, consisting of a gag-pol-nef polyprotein and env derived from the genes of the Chinese R5 CRF-07 strain (97CN54), is inserted in the NYVAC-C and DNA-C vaccines.

**Methods:** 40 volunteers were enrolled either to DNA-C IM (weeks 0 and 4) + NYVAC-C IM (weeks 20 and 24) or to NYVAC-C alone (weeks 20 and 24).

The treatment groups were not perfectly balanced due to the differential enrolment across the sites (25 volunteers in Switzerland and 15 in UK), randomization being stratified by site. Immunisations consisted of 4mg of DNA-C (2 mg into each vastus lateralis muscle), and 1ml of NYVAC-C into the deltoid muscle. The primary safety endpoints were grade 3/4 (severe/extreme) local and systemic events, assessed clinically 10 min, 1 h and 1-7 days after each immunisation.

**Results:** 23 volunteers have been allocated to DNA-C + NYVAC-C, of whom 21 received both DNA-C immunisations. All participants completed at least 1 week of follow-up after second DNA-C. Two volunteers discontinued immunisations after the first DNA-C injection, one for a vasovagal (grade 2) reaction and one for a rise in ALT (grade 4 down to grade 1 within a week). Pain and erythema were the most frequent local reactions observed after both DNA-C immunisations, reported in 22 and 17 participants, respectively, and these were mild with only two exceptions (moderate pain). Fifty-seven grade 1 or 2 systemic reactions were reported by 18 volunteers, including malaise (2 of 10 moderate), headache (1 of 9 moderate), myalgia (1 of 5 moderate), nausea and chills. The pattern was broadly similar at weeks 0 and 4 with a median duration of 1 day (range 1-9).

Twenty-eight of 35 volunteers have received the first NYVAC-C immunisation, and 24 have received both, and completed at least 1 week of follow-up. Pain, erythema and itching were the most frequent of the 93 local events (86 mild, 6 moderate) observed after both NYVAC-C immunisations. One participant had erythema and swelling with grade 3 induration following the first NYVAC-C injection, but did not present identical local reaction nor systemic reaction at the second NYVAC-C immunisation. Of 52 solicited systemic reactions, 44 were mild and 8 moderate. The median duration of the solicited events was 2 days (range 1-36).

**Conclusion:** To date 4mg DNA-C and 1ml NYVAC-C appears to be safe and sufficiently well tolerated.

## INTRODUCTION

EuroVacc is a scientific programme to design, manufacture and assess pre-clinically candidate HIV vaccines, and to conduct human clinical trials. The first to emerge from this pipeline into a randomised, blinded clinical trial was a pox-derived viral vector vaccine, NYVAC-C: a recombinant NYVAC (vP866) strain with an insert containing gag-pol-nef polyprotein and env both derived from the Chinese R5 CRF-07 strain (97CN54) [1]. This vaccine has been evaluated in the EuroVacc 01 clinical study, on 20 HIV-negative volunteers, and has shown to be safe and well tolerated. Vaccine-induced immune responses were observed in 50% of the vaccinees [2]. EuroVacc 02 trial proposed to explore the safety and immunogenicity of the prime-boost regimen DNA-C + NYVAC-C compared to the single agent NYVAC-C. DNA-C vaccine containing the same recombinant HIV DNA as the one inserted in the NYVAC-C.

## PRIMARY OBJECTIVES AND ENDPOINTS

Since DNA-C was injected in humans for the first time, one of the objectives of the trial was to explore the safety of 4 mg DNA-C injections (2 mg in each vastus lateralis) on two occasions.

**EuroVacc 02 addressed the following questions:**

- Is 4 mg of DNA-C per immunisation timepoint safe (systemic and local events)
- Is the prime-boost regimen safe compared to NYVAC-C alone
- Does the DNA-C prime improve the immune response to NYVAC-C ?

**Primary endpoints:**

- **Safety:** grade 3 or above local (pain, cutaneous reactions), general (fever, chills, headache, nausea, vomiting, malaise, myalgia) and other unsolicited adverse events.
- **Immunogenicity:** CD4/CD8<sup>+</sup> T cell responses at weeks 26, 28 and 48.

## METHODS

We enrolled 40 healthy low risk HIV-negative volunteers, recruited from two clinical sites: 25 in Switzerland (CHUV, Lausanne) and 15 in the United Kingdom (Imperial College, London). Immunisations began in both sites in February 2005.

➢ **Safety:** Local and systemic adverse events are assessed at 10 minutes, 1 hour, and 1 to 7 days after each vaccination (grading defined according to internationally agreed criteria for HIV trials).

➢ **Immunogenicity** is evaluated by IFN-γ ELISpot assays on cryo-preserved blood mononuclear cells at weeks 0, 4, 5, 20, 24, 26, 28 and 48. Response is defined as positive according to internationally agreed criteria.

The analysis plan is to compare the safety and immunogenicity of the prime-boost regimen to the NYVAC-C alone, in terms of proportion of participants with grade 3 or above adverse event and the proportion with positive ELISpot responses after completing the immunisation schedule.

## STUDY DESIGN AND REGIMEN

40 volunteers were allocated either to DNA-C (weeks 0 and 4) + NYVAC-C (weeks 20 and 24) or to NYVAC-C alone (weeks 20 and 24). The trial was randomised, stratified by clinical site.

REGIMEN	Allocated	Week 0	Week 4	Week 20	Week 24
DNA-C 4 mg IM + NYVAC-C 1 ml IM	n = 23	DNA C	DNA C	NYVAC C	NYVAC C
NYVAC-C 1 ml IM alone	n = 17			NYVAC C	NYVAC C

Table 1 : EV02 immunisations regimen and allocation to these regimens

The clinical staff and the participants are aware of allocation to one or the other regimen but laboratory staff is blind to the regimen throughout the study, although do know the week of the study.

WEEKS	-6	0	1	4	5	8	18	20	21	24	25	26	28	48
Immunisation		X		X				X	X					
ELISpot		X		X	X			X	X		X	X	X	X
Antibodies		X		X				X	X		X	X	X	X

Table 2 : Schedule of immunisations, timepoints for ELISpot and antibodies assays

## STUDY POPULATION

40 (20 Female) of 59 volunteers screened have been enrolled.

Characteristic	Centre		Total
	CHUV	St Mary's	
Total eligible	25	15	40
Sex			
Male	10 (40%)	10 (67%)	20 (50%)
Female	15 (60%)	5 (33%)	20 (50%)
Median age (range) in years	23 (21-49)	42 (21-56)	32 (21-56)

Table 3 : EV02 Trial Population

No of participants who have received:	Centre		Total
	CHUV	St Mary's	
1st DNA or nothing	25 (100%)	15 (100%)	40 (100%)
2nd DNA or nothing	25 (100%)	15 (100%)	40 (100%)
1st NYVAC	18 (72%)	10 (67%)	28 (70%)
2nd NYVAC	18 (72%)	6 (40%)	24 (60%)

Table 4 : Vaccinations Received (Ongoing Study)

## SAFETY RESULTS : DNA-C Immunisations

Safety results for DNA-C include those of 17 participants who received nothing at weeks 0 and 4. Separation by randomisation arm will be done at the end of the trial.

**Results:** Pain and erythema were the most frequent local reactions reported in 55% and 43% of the participants respectively. 45% of participants reported systemic reactions including malaise, headache, myalgia, nausea and chills. Two volunteers discontinued immunisations after the 1<sup>st</sup> DNA-C injection, one for a vasovagal (grade 2) reaction and one for a rise in ALT, but remained in the study for follow-up.

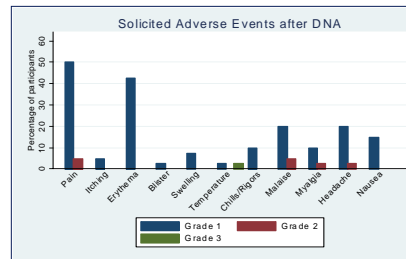


Figure 1 : Solicited Adverse Events after DNA-C vaccinations

## SAFETY RESULTS : NYVAC-C Immunisations

At the time of NYVAC-C immunisations, 38 of 40 volunteers were scheduled to receive injections at weeks 20 and 24 (2 were discontinued for safety reasons, as described above). Additionally, 2 volunteers were lost to follow-up, and 1 volunteer did not show at NYVAC-C immunisation timepoints but remained in the study for follow-up visits.

So far, 28 of 35 volunteers have received the first NYVAC-C immunisation and 24 have received the second one. One participant had erythema and swelling with grade 3 induration following the first NYVAC-C. This volunteer received second NYVAC-C injection and presented no identical local reaction nor systemic reaction at the second NYVAC-C immunisation.

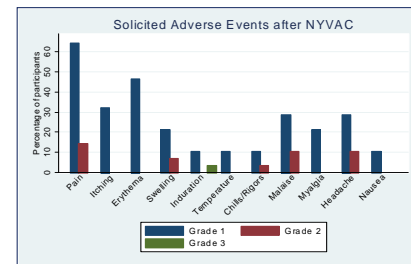


Figure 2 : Solicited Adverse Events after NYVAC-C vaccinations

## CONCLUSIONS

- Injection of 4 mg of DNA-C (2 mg into each vastus lateralis muscle) on two occasions appears to be safe and well tolerated in terms of systemic and local events.
- So far, the injection of NYVAC-C following DNA-C priming is safe.
- Immunogenicity results are currently under evaluation and will be available soon.

## REFERENCES

1. Su L. et al. J Virol 2000;74:11367-76
2. P.-A. Bart et al. Poster #507, CROI 2005, Boston

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