

# Boosting Adenovirus Serotype 5 (Ad5) HIV-gag Primed Subjects with ALVAC HIV (vCP205)

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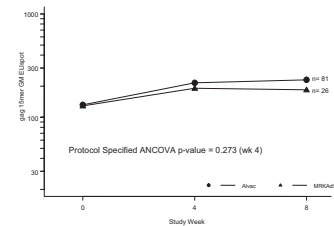
## Abstract

**Background:** Recombinant viral vectors can elicit CMI responses, but immunity to the vector limits their immunogenicity. The use of a heterologous prime-boosting regimen is one potential strategy to circumvent this problem. CMI response in animals primed with an adenovirus vector can be efficiently boosted with a poxvirus vector. To test this strategy in humans, subjects previously primed with an adenovirus vector were boosted with a poxvirus vector.

**Methods:** A randomized, double-blind, comparative multicenter study involving 135 subjects who had previously participated in Merck Protocol 007 (Ad5 HIV-1 gag) or Protocol 012 (MRKAd5 HIV-1 gag). Subjects who received placebo in the parent study received ALVAC-HIV (vCP205). Subjects who received the adenovirus vector in the parent study were randomized at a 3:1 ratio to receive ALVAC-HIV (vCP205) or MRKAd5 HIV-1 gag vaccine. Subjects were pre-stratified at entry based on their ELISPOT responses in the parent study. The primary immunogenicity assessment was the difference in the geometric mean ELISPOTs between treatment groups 4 weeks after the study vaccination.

**Results:** Both vaccines were generally safe and well tolerated. Recall responses were elicited by both vaccines. There was no significant difference in the proportion of responders or the magnitude of the ELISPOT responses between the treatment groups. Responses in individual subjects were consistent with the overall response in the treatment groups.

### ALVAC-HIV vCP205 vs. MRKAd5 gag 15mer ELISPOT Summaries

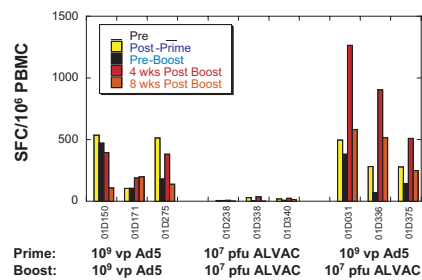


**Conclusions:** The heterologous adenovirus prime/poxvirus boost regimen was generally safe and well tolerated. Boosting adenovirus vector-primed subjects with a poxvirus vector elicited recall CMI responses, but this was not more effective than boosting with a homologous vector.

### Rationale for the study

- Cell mediated immune (CMI) responses may be key to control of HIV
- Adenovirus vectors elicit potent CMI responses, but:
  - Pre-existing immunity may blunt response rate
  - Induced immunity may impair subsequent boost
- Heterologous prime/boost regimen may overcome immunity to vector
  - Supported by preliminary data in macaques

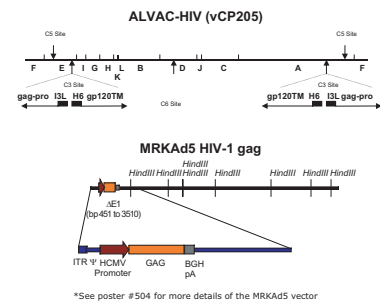
### ELISPOT Responses in Rhesus Monkeys Poxvirus boost following low dose Ad5-gag prime



## Study Design

- Study population: eligible subjects who had participated in 2 previous studies (the "Parent Studies") of Merck's adenovirus type 5 HIV-1 gag vaccines (see poster #504)
  - Protocol 007: Ad5 HIV-1 gag vaccine
  - Protocol 012: MRKAd5 HIV-1 gag vaccine
- Study regimen: a single booster dose of either
  - ALVAC vCP205 vaccine at 1x10<sup>8</sup> TCID<sub>50</sub> QR
  - MRKAd5 HIV-1 gag at 1 x 10<sup>10</sup> vp
- Randomization
  - Stratification based on status in Parent Study

### Study Vaccines



### Randomization

Treatment	Status in Parent Study	Responder?	Week 30 ELISPOT	Randomization Ratio ALVAC/MRKAd5	Stratum
Placebo	N/A <sup>1</sup>	N/A <sup>1</sup>	N/A <sup>1</sup>	4/0	Stratum 1
Adenovirus	No	N/A <sup>1</sup>	N/A <sup>1</sup>	3/1	Stratum 2
Adenovirus	Low	Week 30 ≤250 SFC <sup>2</sup>	Week 30 ≤250 SFC <sup>2</sup>	3/1	Stratum 3
Adenovirus	High	Week 30 >250 SFC <sup>2</sup>	Week 30 >250 SFC <sup>2</sup>	3/1	Stratum 4

<sup>1</sup> N/A = Not Applicable  
<sup>2</sup> SFC = Spot Forming Cells

### Demographics

	ALVAC (N=109) n (%)	MRKAd5 (N=26) n (%)
<b>Gender</b>		
Male	59 (54%)	13 (50%)
Female	50 (46%)	13 (50%)
<b>Age</b>		
Mean	36.2	35.8
SD	9.4	9.0
Median	37.0	35.5
Range	19 TO 51	23 TO 50
Male	19 TO 51	23 TO 50
Female	21 TO 52	23 TO 50
<b>Race/Ethnicity</b>		
Asian/Pacific	1 (1%)	1 (4%)
Black	10 (9%)	1 (4%)
Caucasian	94 (86%)	24 (92%)
Hispanic	2 (2%)	0 (0%)
Indian	0 (0%)	0 (0%)
Native American	1 (1%)	0 (0%)
Other	1 (1%)	0 (0%)

<sup>1</sup> No statistical differences between groups

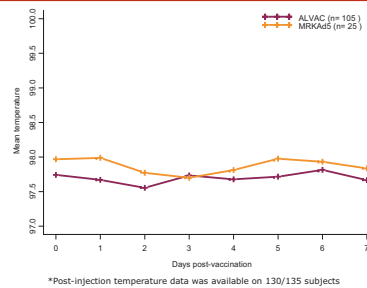
### Disposition of Enrolled Subjects

- 135 Subjects Enrolled in Study
- 135 Subjects Continuing at Week 4
- 133 Subjects Currently Continuing in the Study

### Most Common (>2.5%) Adverse Events

AE	ALVAC (%) (N=109)	MRKAd5 (%) (N=26)
Injection site	86.2	84.6
Fatigue	9.2	23.1
Headache	18.3	23.1
Diarrhoea	6.4	15.4
Arthralgia	7.3	11.5
Back pain	3.7	11.5
Pain	3.7	11.5
Chills	1.8	7.7
Myalgia	4.6	7.7
Nausea	7.3	7.7
Pharyngolaryngeal pain	9.2	7.7
Cough	5.5	3.8
Pyrexia	5.5	3.8
Insomnia	3.7	0.0
Nasal congestion	6.4	0.0
Pain in extremity	5.5	0.0
Rhinorrhoea	5.5	0.0
Sinus congestion	3.7	0.0
Upper resp. tract infection	5.5	0.0

### Observed mean temperature\* after vaccination by regimen



### ALVAC vs. MRKAd5 gag 15mer ELISPOT Summaries

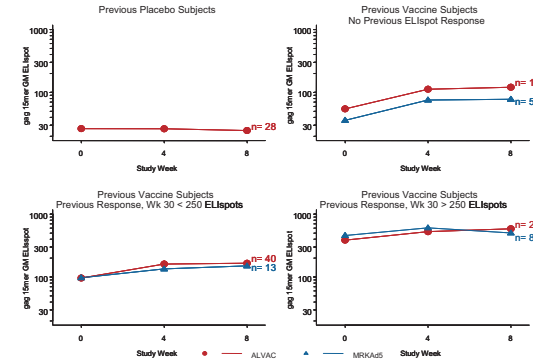
Response Freqs. (%) and Geom. Mean of Responders

Strata	Parent Study Trt*	Prev. Resp.†	Wk 30 Resp.†	Regimen	wk			% Responders			Geometric Mean (Responders)		
					0	4	8	wk 0	wk 4	wk 8	wk 0	wk 4	wk 8
1	P	N/A	N/A	ALVAC	28	28	27	4%	4%	4%	180	256	186
				MRKAd5	16	16	16	25%	44%	44%	174	207	173
3	V	Yes	Low	ALVAC	40	40	39	45%	75%	77%	144	206	221
				MRKAd5	13	13	13	54%	69%	85%	155	180	155
4	V	Yes	High	ALVAC	25	25	25	96%	92%	92%	387	620	623
				MRKAd5	8	8	7	88%	100%	100%	493	604	500
<b>Pooled</b>				<b>ALVAC</b>	<b>81</b>	<b>81</b>	<b>80</b>	<b>57%</b>	<b>74%</b>	<b>75%</b>	<b>245</b>	<b>314</b>	<b>319</b>
<b>2,3,4</b>				<b>MRKAd5</b>	<b>26</b>	<b>26</b>	<b>25</b>	<b>54%</b>	<b>65%</b>	<b>72%</b>	<b>276</b>	<b>318</b>	<b>244</b>

\* P = Placebo; V = Vaccine (Ad5 or MRKAd5)  
† At least one positive IFN-γ ELISPOT response between weeks 4 and 30 of parent study.  
‡ Week 30 ELISPOT response of parent study.  
§ Dosing regimen: wks 0, 4, 26 (parent protocol) + wk 0 (Protocol 019 booster)  
|| ELISPOT Responder: ≥55 SFC/10<sup>6</sup> PBMCs and ≥4-fold over media control for 15mer peptide pool; summaries are based on 15mer ELISPOTs.

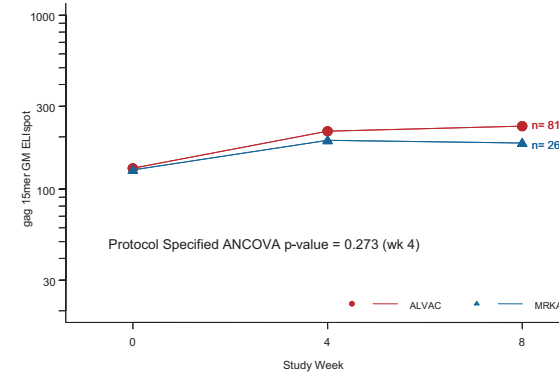
### ALVAC vs. MRKAd5 gag 15mer ELISPOT Summaries

Geom. Mean of all subjects by Strata



### ALVAC vs. MRKAd5 gag 15mer ELISPOT Summaries

Geom. Mean of all previously vaccinated subjects (strata 2, 3, and 4)



## Summary/Conclusions

- Both vaccines were generally safe and well tolerated
- Each vaccine elicited recall responses in subjects previously primed with an adenovirus type 5 HIV-1 gag vaccine
- An Ad5 gag/ALVAC-HIV heterologous prime/boost vaccination regimen does not produce a synergistic immune response in man

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