



**Discordance between
virological/immunological and clinical
outcomes at 48 weeks,
in a randomised comparison of
ZDV/3TC/NVP and ZDV/3TC/ABC
in patients with low CD4 counts in Africa**

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on behalf of the **DART** Trial Team



Background - NORA



- A randomised, double-blind, 24 week, phase II trial
- 600 ARV-naïve adults , symptomatic HIV infection, CD4<200 cells/mm³ and no contraindications to ART randomised in a 1:1 ratio to receive:
 - zidovudine/lamivudine (Combivir) twice daily, plus
 - 300 mg ABC and nevirapine placebo twice daily, or
 - 200 mg NVP and abacavir placebo twice daily
- switch to open-label active drug at 24 weeks, then follow-up
- 1° endpoint: Safety



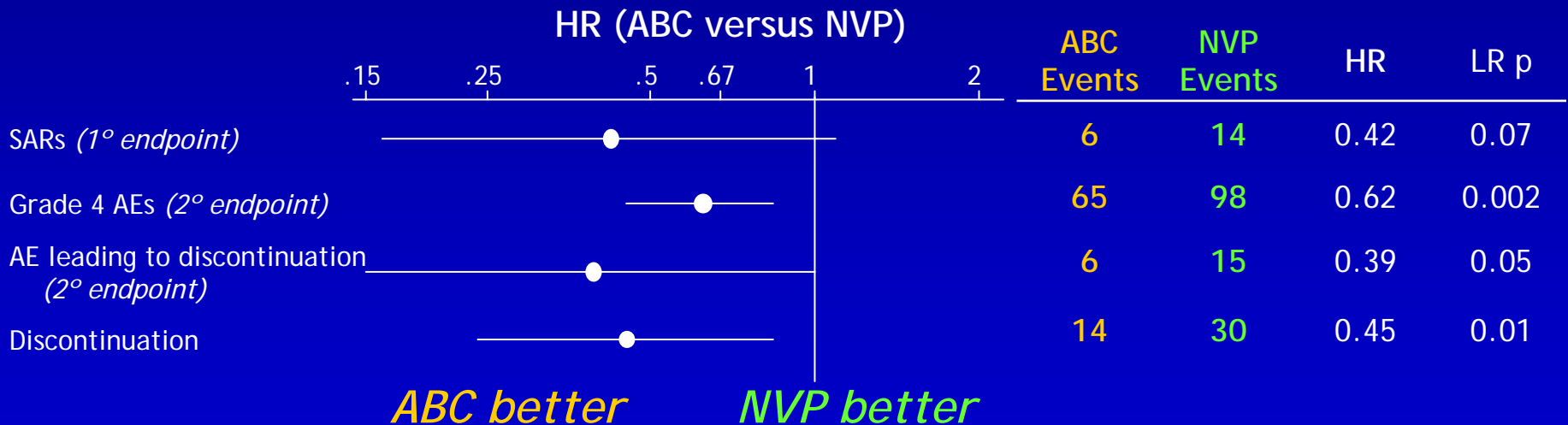
Baseline Characteristics

		ABC	NVP
Total patients		300	300
Women		72%	71%
Prior ART to prevent MTCT (% of women)		2%	5%
Age	median	37	36
CD4 at randomisation (cells/mm ³)	0-99	50%	50%
	100-199	50%	50%
	median	99	100
HIV-1 RNA at randomisation (copies/ml)	median	292,300	283,100
WHO stage at randomisation	2	28%	25%
	3	58%	52%
	4	15%	22%



Safety Outcomes - 24 weeks

- 289 ABC 280 NVP completed 24 weeks
 - a trend towards a lower rate of SARs with ABC
 - a lower discontinuation rate with ABC
 - a lower rate of any grade 4 AE with ABC





Efficacy Outcomes



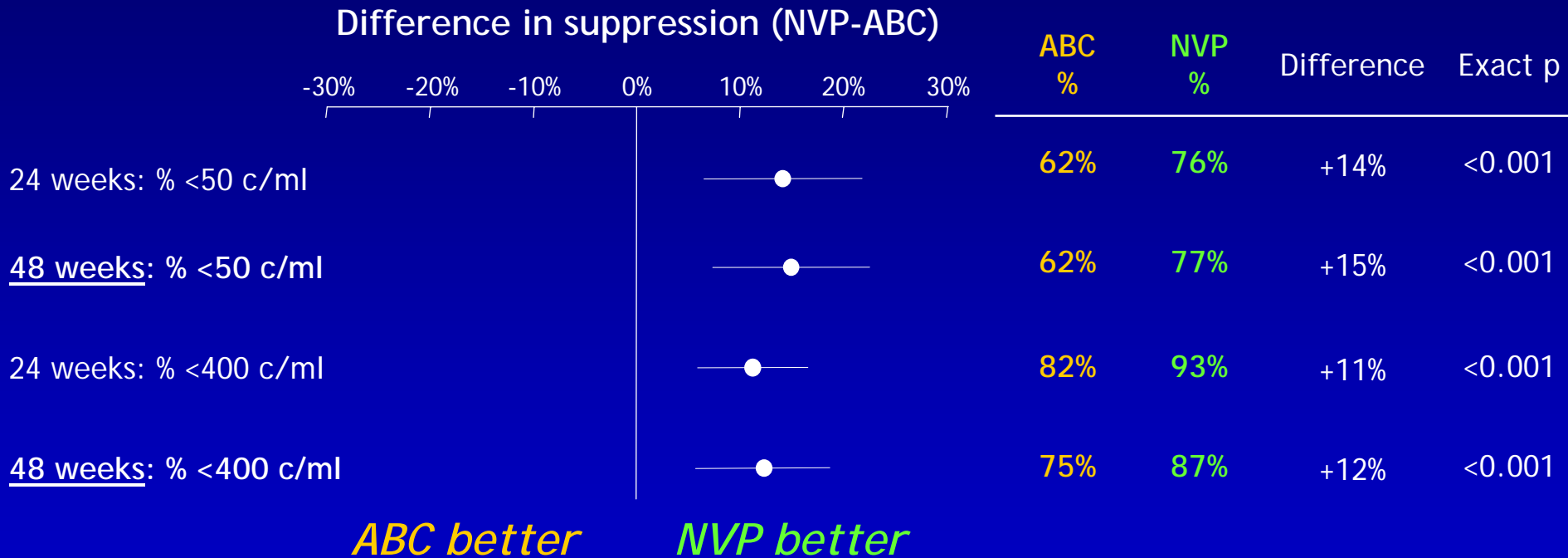
- **Efficacy analysis was not planned as part of NORA protocol**
- Patients continued to be seen in DART study clinic every 4 weeks
- Exploratory ITT analysis of efficacy outcomes to 48 weeks
 - clinical events (WHO 3 and 4 events) and death documented and independently reviewed
 - CD4 cell count (measured in real-time at 0, 12, 24, 36, 48 weeks)
 - plasma HIV-1 RNA (assayed retrospectively at 0, 4, 12, 24, 48 weeks)
- 12 patients (2%) lost to follow-up before 48 weeks



Virological Efficacy to 48 Weeks

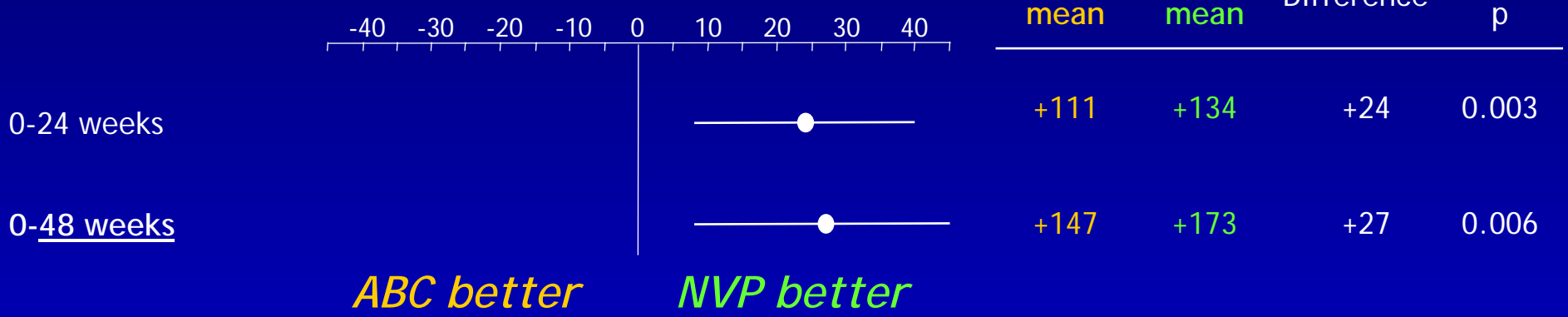


(a) virological efficacy: NVP is superior



(b) immunological efficacy: NVP is superior

Difference in mean cells/mm³ increase (NVP-ABC)

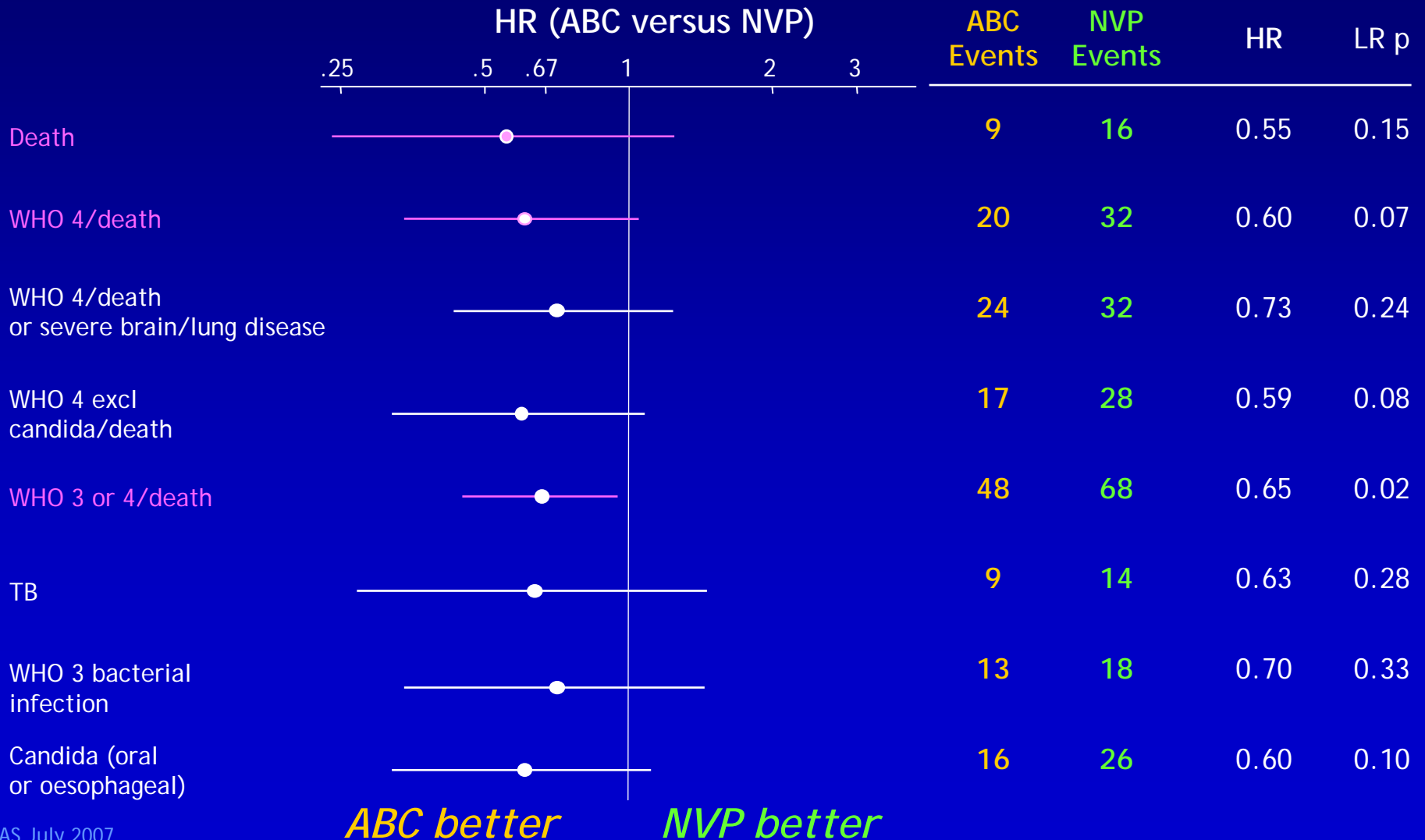




Clinical Efficacy to 48 Weeks



(c) clinical efficacy: trend towards superiority of ABC





Discussion



Possible explanations for these results

- increased toxicity of NVP led to more clinical events on NVP - **unlikely**
 - most clinical events not related to ARV toxicity (HIV related)
- Was there a difference in rate of 'switching' to alternative regimens (with altered potency) ? - **No**
 - more ART substitutions in NVP arm (34 vs 21)
- These differences between outcomes are a chance finding (Type I error)
 - cannot be ruled out



Discussion cont ..



No evidence that excess events in NVP arm were due to IRIS

- Events were not classified as IRIS or not IRIS
- Surrogate markers for IRIS e.g early vs late events

Number of new or recurrent WHO 4 events or death	ABC	NVP	HR
Before 12 weeks	15	25	0.58
After 12 weeks	5	7	0.67
<i>test for heterogeneity p=0.84</i>			

- Similar results for CD4 or WHO stage at ART initiation
- Similar changes in HIV-1 RNA at week 4 in both groups



Conclusion



- **NVP** has superior virological/immunological efficacy compared to **ABC** over 48 weeks
- Trend towards clinical superiority of the **ABC** arm to 48 weeks
- No clear explanation so far for this apparent discordance
 - it may be a chance finding
 - if real, it suggests a disconnect between early clinical and virological/immunological outcomes which may influence the way surrogate markers are interpreted



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Dame Anne McLaren



Chair of DART DSMC

April 26 1927 - July 7 2007









First new/recurrent WHO 4 event



	ABC	NVP
Oesophageal candida	4	6
Extrapulmonary TB	2	5
Cryptococcus	2	3
PCP	2	1
Herpes Simplex	2	1
Toxoplasmosis	1	1
KS		2
Cryptosporidia		1
Wasting		1
Died without WHO 4 event	7	11
Total	20	32

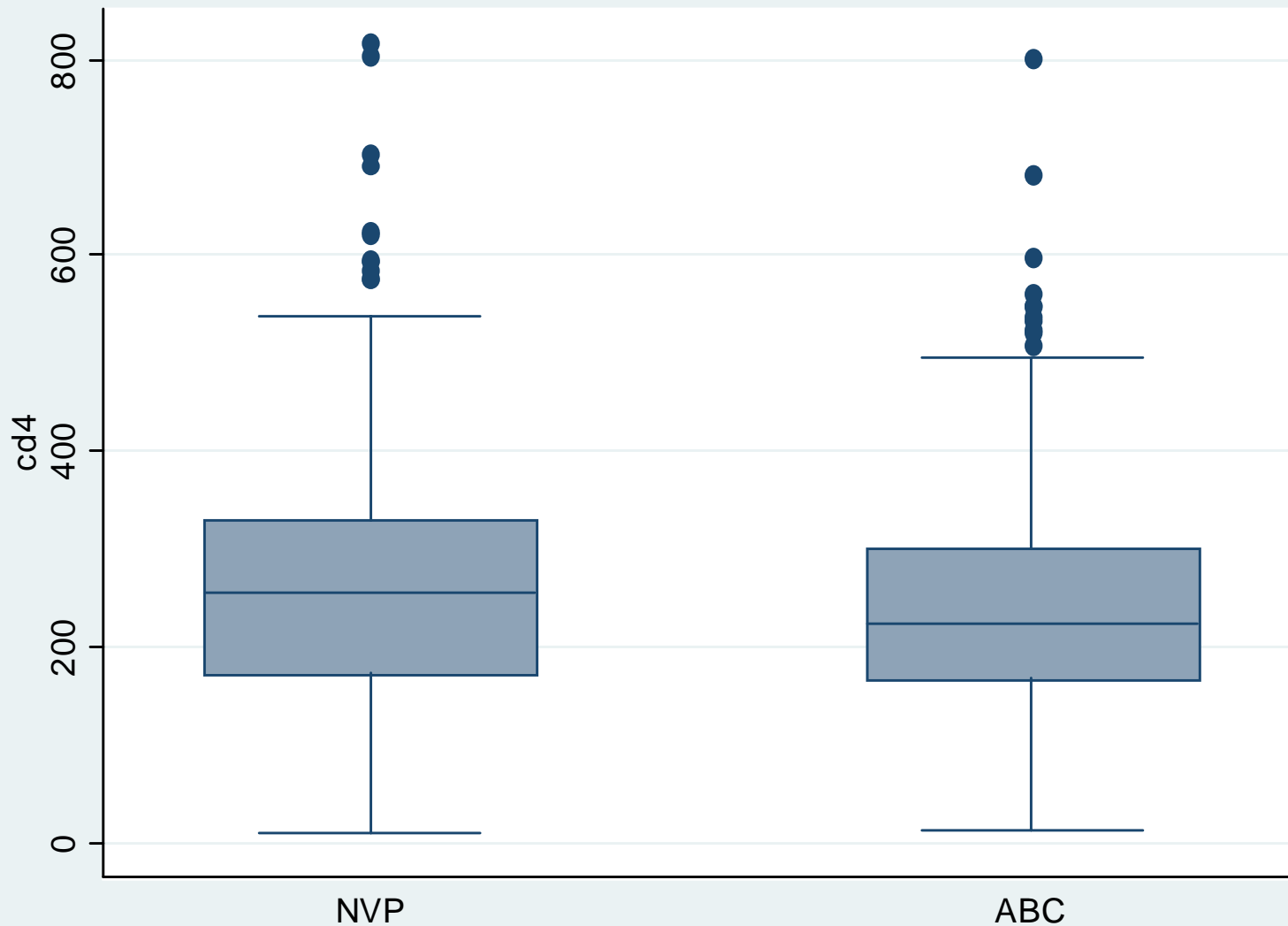


Causes of death

	ABC	NVP
Cryptosporidia		1
Cryptococcal meningitis		1
Other Meningitis	2	
Septicaemia/Bacteraemia ± Neutropenia	3	6
Pneumonia		3
Pulmonary TB	1	1
Haematemesis		1
Fits / Convulsions - judged not HIV related	1	
HIV- related indeterminate cerebral disease	1	1
Uncertain	1	2
Total	9	16



Absolute CD4 at week 48



Change in CD4 from baseline to week 48

