Lessons From The Vicriviroc Clinical Development Program

Wayne L. Greaves, MD

MERCK

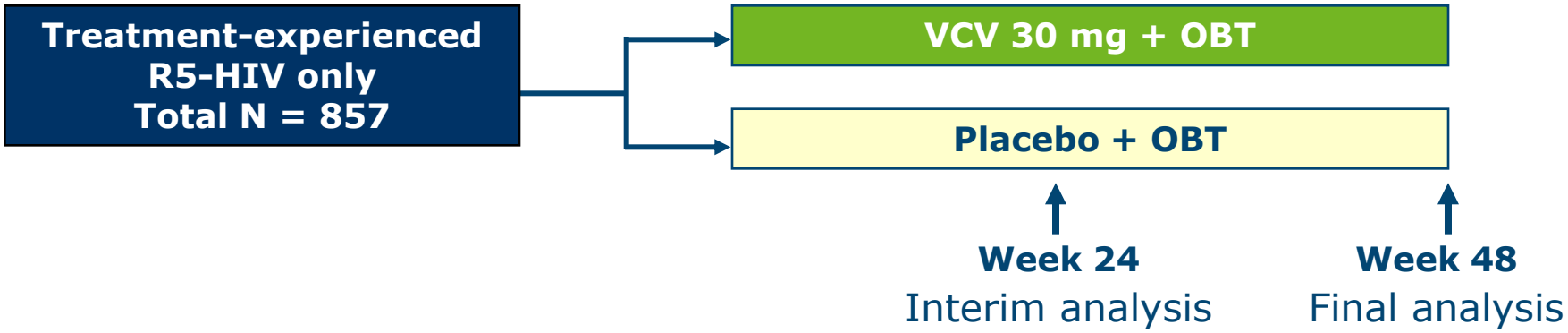
VICTOR-E3 and E4 Phase 3 Trial Design

VICTOR-E3 and 4 were identically designed, randomized, double-blind, placebo-controlled, 48-week multicenter Phase 3 studies

Subjects were ART-experienced with:

- Documented resistance to ≥2 then available drug classes
- OBT that had to include 2 fully active drugs including PI/r
- R5-only virus based on Trofile assay

Primary endpoint: %<50 copies/mL at 48 weeks



Pooled Safety (VICTOR-E3 & E4) FAS, As Treated Topline Summary of AEs Normalized by Total Exposure

Population	VCV n=568 Total Yrs. of Exposure = 454.85 Number (%)	Rate $	Control n=285 Total Yrs. of Exposure = 226.66 Number (%)	Rate $
Subjects reporting any Treatment Emergent Adverse Event	477 (84)	104.87	247 (87)	108.98
Subjects reporting any Treatment related, Treatment Emergent Adverse Event	171 (30)	37.59	83 (29)	36.62
Subjects reporting any Serious Adverse Event #	55 (10)	12.09	26 (9)	11.47
Subjects reporting any Grade 3 / 4 Treatment Emergent Adverse Event	67 (12)	14.73	38 (13)	16.77
Subjects reporting any Adverse Event resulting in Study Discontinuation #	19 (3)	4.18	6 (2)	2.65
Subjects reporting any Adverse Event resulting in Death #	7 (1)	1.54	0 (0)	0.00

$ Rate = incidence per 100 patient years **# All AEs reported regardless of treatment emergence**

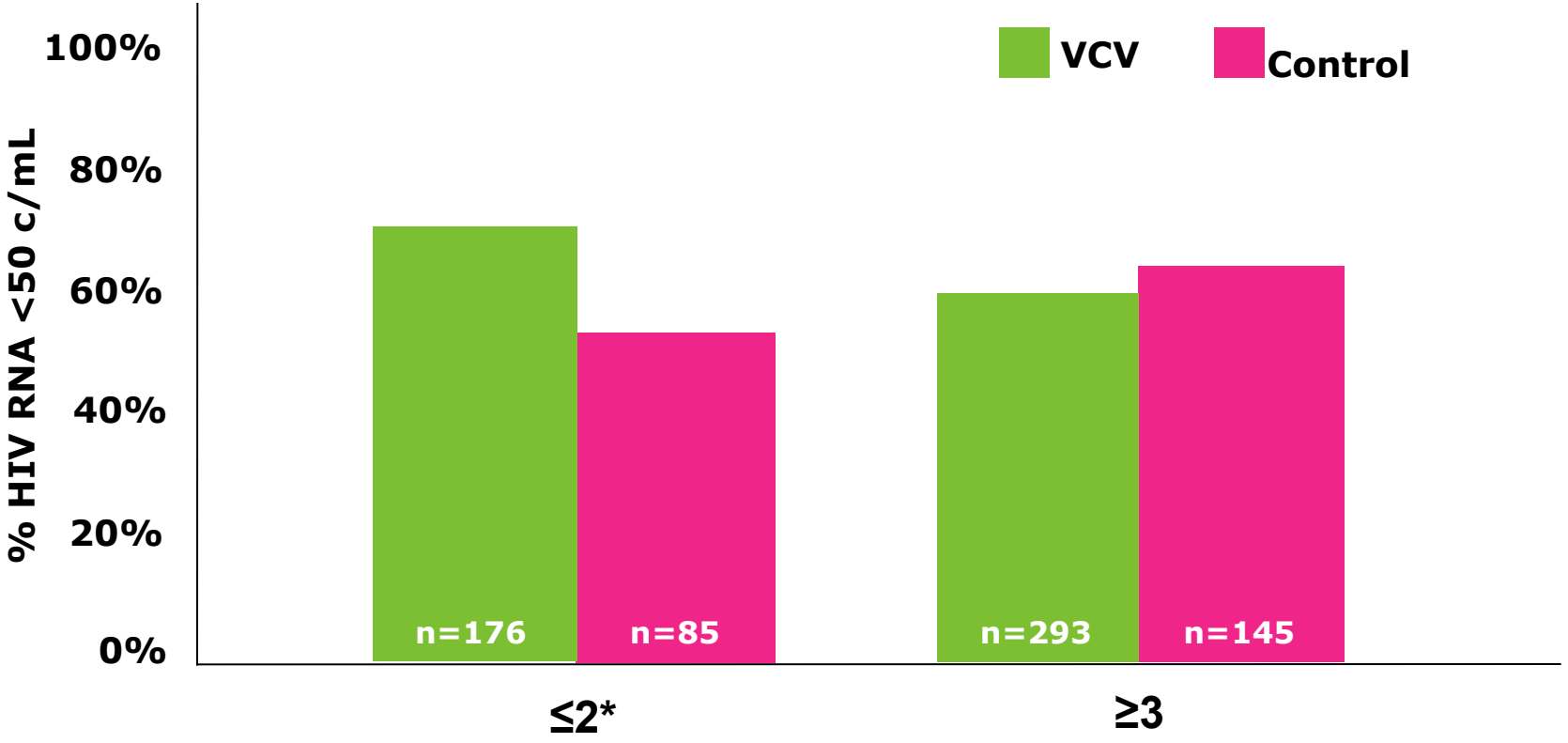
MERCK

Restricted Confidential limited access

Pooled Efficacy (VICTOR-E3 & 4)
MITT Population

	VCV	Control
Overall N = 721	486	235
HIV RNA <50 at week 48, n (%)	313 (64%)	145 (62%)
HIV RNA <400 at week 48, n (%)	352 (72%)	166 (71%)
Mean change in CD4, cells/mm^3 (SE)	+138 (7.3)	+129 (9.4)

Virologic Response by OSS



*Pre-specified subset; not adjusted for multiple analyses; Odds Ratio 1.9, *P* = 0.02.

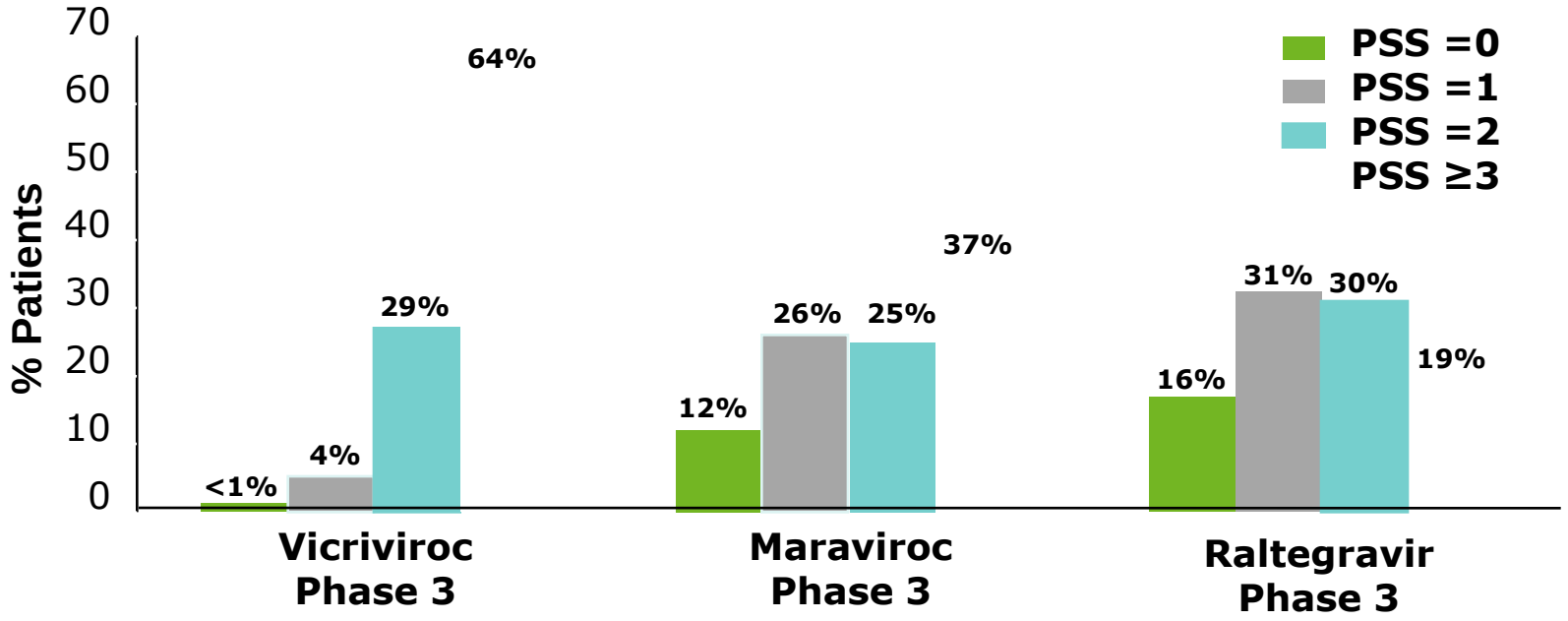
MERCK

Phenotypic Sensitivity Scores in Recent HIV Trials

PSS = total number of phenotypically active drugs in background regimen

Most vicriviroc trial participants had fully active background regimens

- 461 (64%) of patients had ≥3 active drugs in OBT

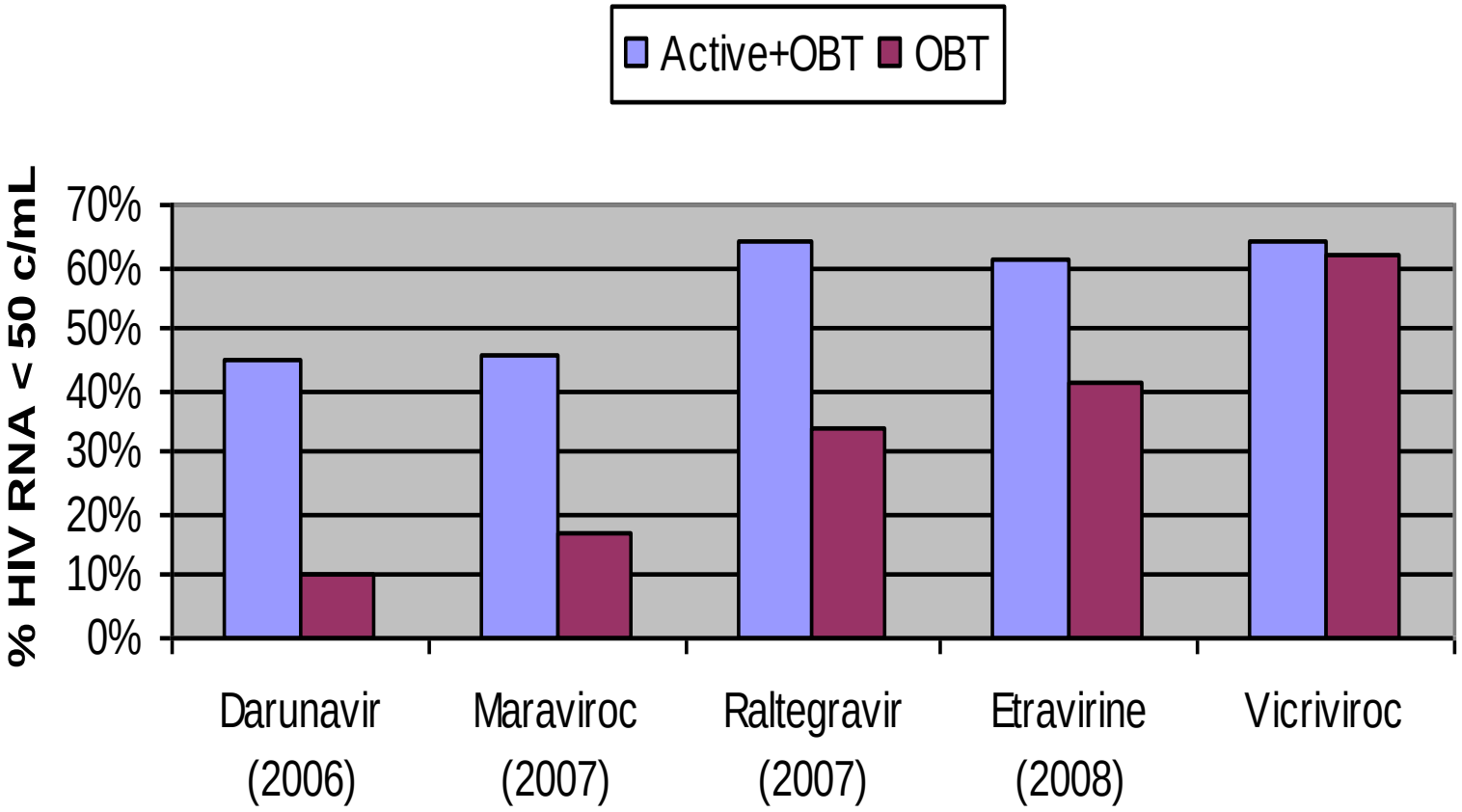


NEJM 2008;359:1429-1441, *NEJM* 2008;359:339-354, *AIDS* 2009;23(17):2289-2300, CROI 2010, abstract # 54LB

MERCK

Restricted Confidential limited access

Efficacy of Recent HIV Trials in Treatment Experienced Subjects



***Lancet* 2007;369(9581):39-48, *NEJM* 2008;359:1429-1441, *NEJM* 2008;359:339-354, *AIDS* 2009;23(17):2289-2300, CROI 2010, abstract # 54LB**

MERCK

Summary and Conclusions

VCV did not meet the primary efficacy endpoint

- OBT in the phase 3 trials included more potent antiretroviral drugs than in the VCV Phase 2 trial or Phase 3 trials of recently approved HIV drugs
- 64% of subjects had ≥3 fully active drugs in OBT

For subjects with 2 or fewer available active drugs, VCV provided additional benefit for viral suppression (<50 copies/mL)

Implications for Drug Development

- With the success of recently available therapies, studies of newer agents will require non-inferiority studies or novel designs to demonstrate efficacy and meet criteria for Regulatory approval
- Placebo control trials may no longer be an ethically acceptable option
- In placebo add-on trials, an increasingly potent background regimen diminishes the likelihood of showing incremental benefit of a new drug.
- Evolving standards of care and corresponding changes in study design and entry criteria can have a major impact on study outcome and drug development.
- Recruitment of TE patients is likely to become more difficult with over-representation of individuals with adherence problems.