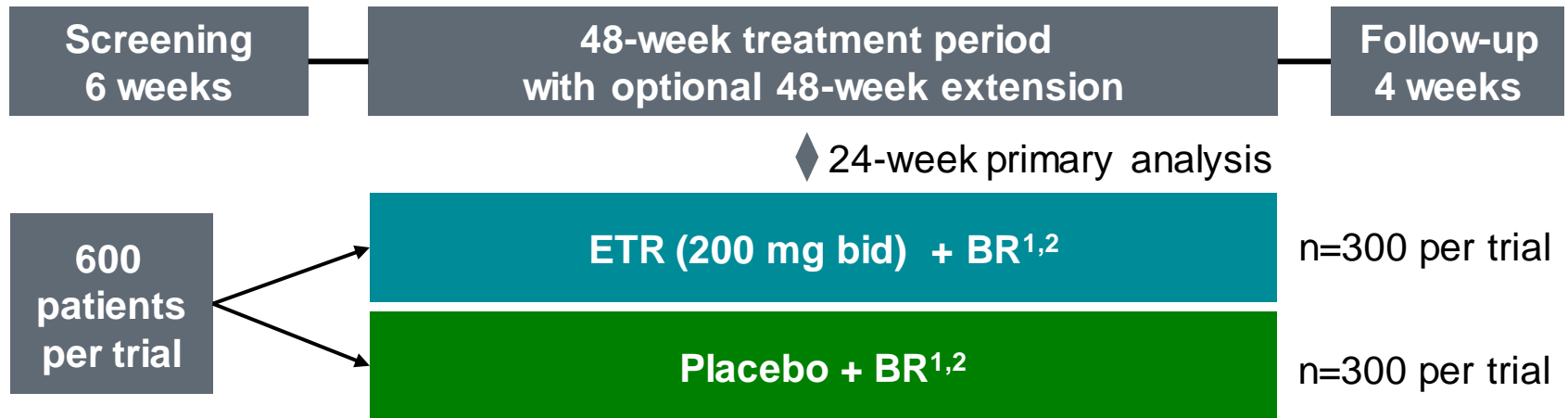


Determination of phenotypic clinical cut-offs for etravirine (ETR): pooled Week 24 results of the DUET-1 and DUET-2 trials

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DUET-1 and DUET-2: trial design and inclusion criteria

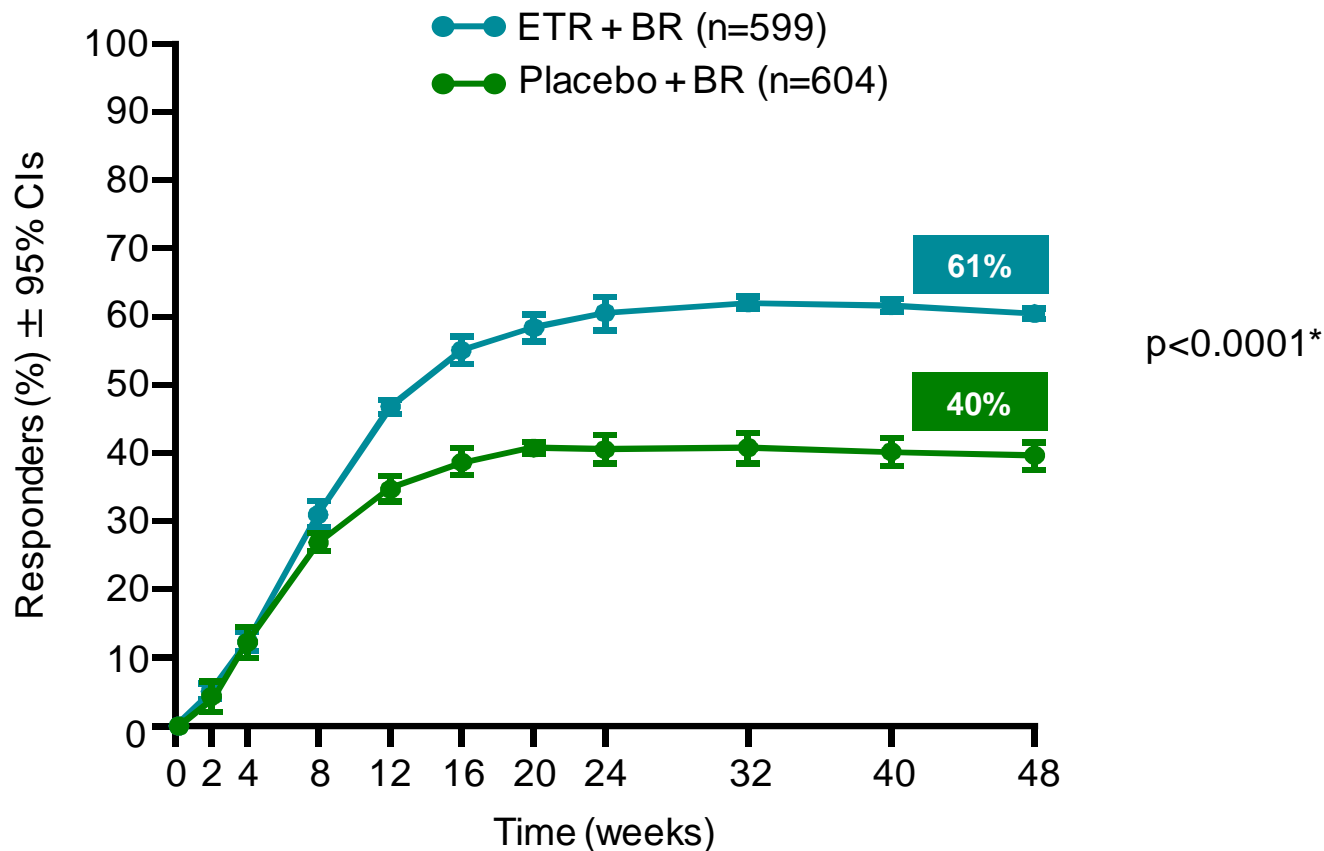


^{1,2}BR = DRV/r with optimised NRTIs and optional ENF

- Plasma VL at screening: >5,000 HIV-1 RNA copies/mL
- Stable antiretroviral therapy for at least 8 weeks prior to screening and until baseline
- At least three primary protease inhibitor mutations at screening
- At least one NNRTI RAM (either at screening or in documented historical genotype)

BR = background regimen; DRV/r = darunavir with low-dose ritonavir;
ENF = enfuvirtide; VL = viral load; RAM = resistance-associated mutation
¹Madruga JV, et al. Lancet 2007;370:29–38; ²Lazarin A, et al. Lancet 2007;370:39–48

Patients with VL <50 copies/mL over Week 48 (ITT-TLOVR)

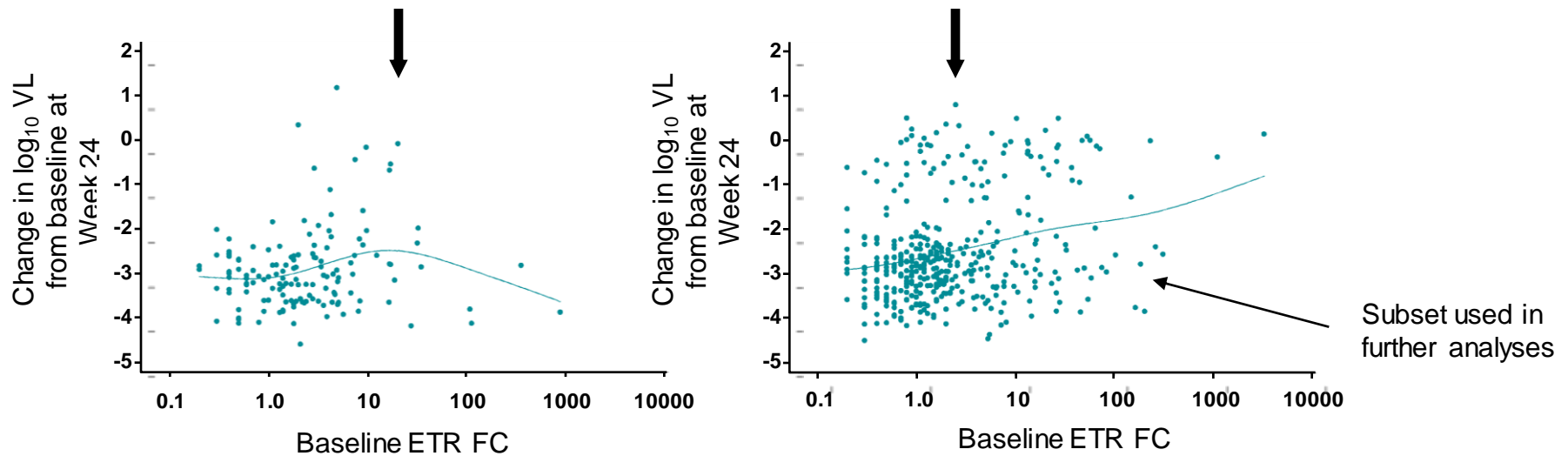


- 61% of patients in the ETR group achieved confirmed undetectable VL (<50 copies/mL) compared with 40% in the placebo group at Week 48

ITT = intent-to-treat; TLOVR = time to loss of virologic response; CI = confidence interval; *Logistic regression model

Determination of ETR FC CCO: data used in the analysis

- Pooled DUET-1 and DUET-2 studies – Week 24 response data
- Patients who discontinued for reasons other than virologic failure (non-virologic failure excluded population) were excluded
- Subgroups of patients
 - DRV FC >40 (n=51): ideal but small sample size
 - *de-novo* ENF (n=143) / *not de-novo* ENF (n=403)

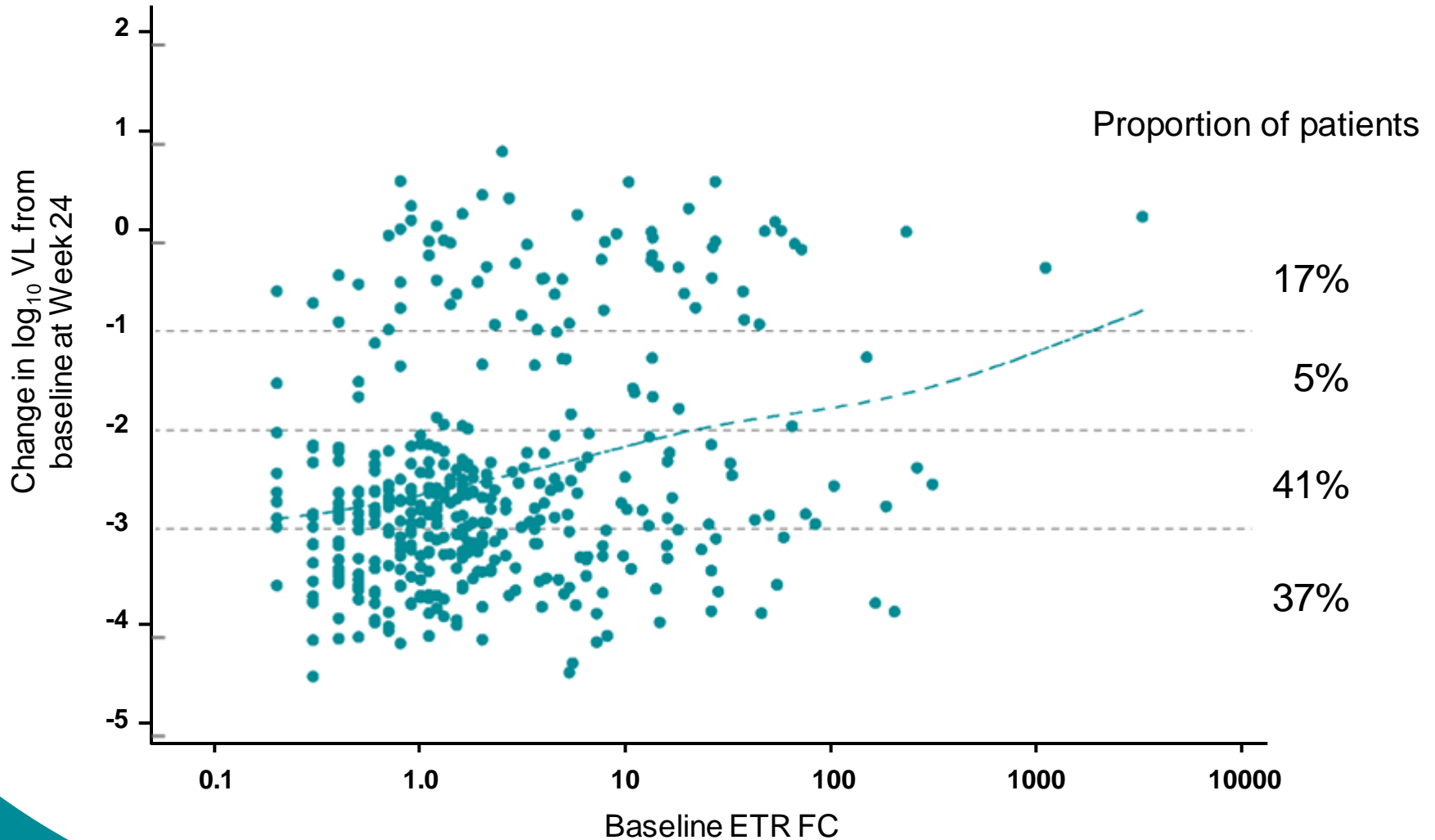


LOESS smoothed spline fitted to the raw data

Analysis outline: methods

- Phenotypic susceptibility determined by antivirogram
- Efficacy parameters at Week 24
 - VL <50 copies/mL (TLOVR)
 - change in \log_{10} VL (NC=F)
- ANCOVA model for change in \log_{10} VL with covariate \log_{10} FC ETR
 - accounting for factors
 - baseline disease characteristics (baseline VL, CD4)
 - baseline resistance (\log_{10} FC DRV, ENF use, number of sensitive NRTIs)
- Data mining using graphical presentations

Increasing baseline ETR FC was associated with a gradual loss in virologic response at Week 24



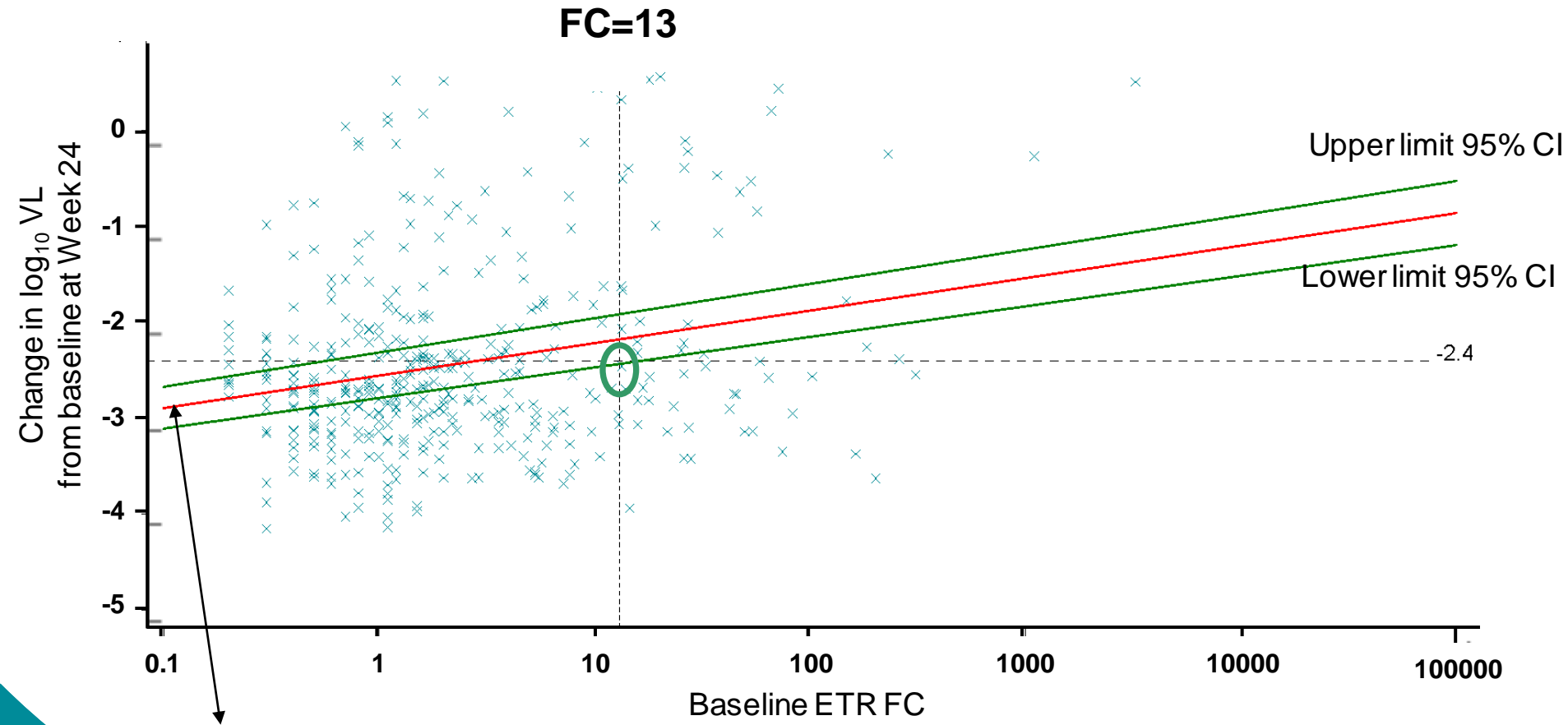
LOESS smoothed spline fitted to the raw data

Definition of ETR CCO

- **Reference:** At Week 24, patients in the **placebo arm** who were not using ENF *de novo*, had a mean change in \log_{10} VL of **$-1.4 \log$**
- The ETR CCO was determined as a **1 log better** response than placebo = **$-2.4 \log$**
 - using the ANCOVA model, backward prediction was used to define a cut-off that was associated with at least -2.4 reduction in \log_{10} VL

Change in \log_{10} VL at Week 24 vs ETR FC

FC: identification of CCO at FC=13

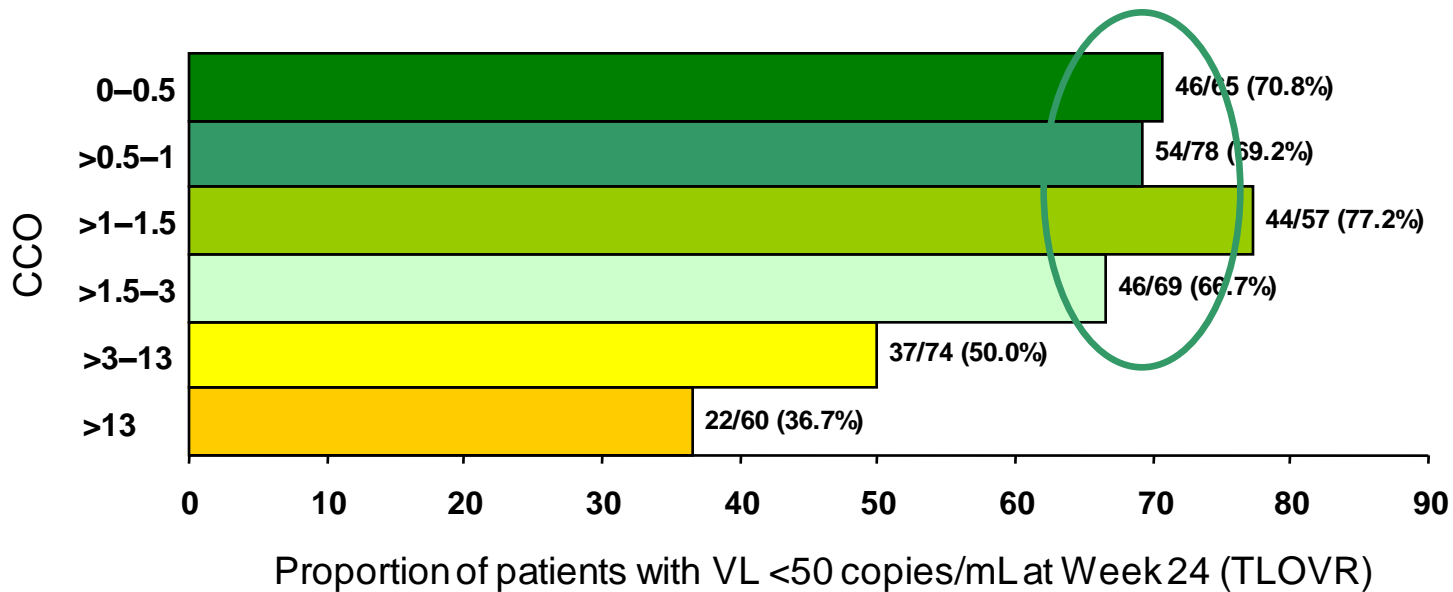


Regression line from ANCOVA model with factors baseline VL, CD4, \log_{10} FC ETR, \log_{10} FC DRV, ENF use, # sensitive NRTIs in ART

ART = antiretroviral therapy

Identification of CCOs lower than 13

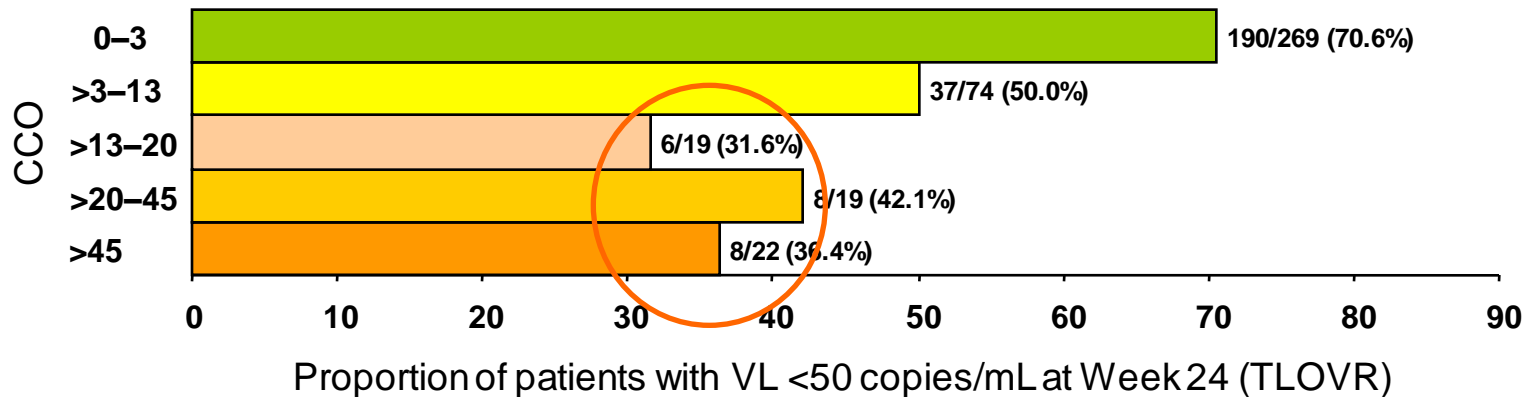
- Look for baseline ETR FC **below** which virologic response (<50 copies/mL) is maximal



→ Lower CCO = 3

Identification of CCOs higher than 13

- Look for ETR FC above which response (<50 copies/mL) is minimal

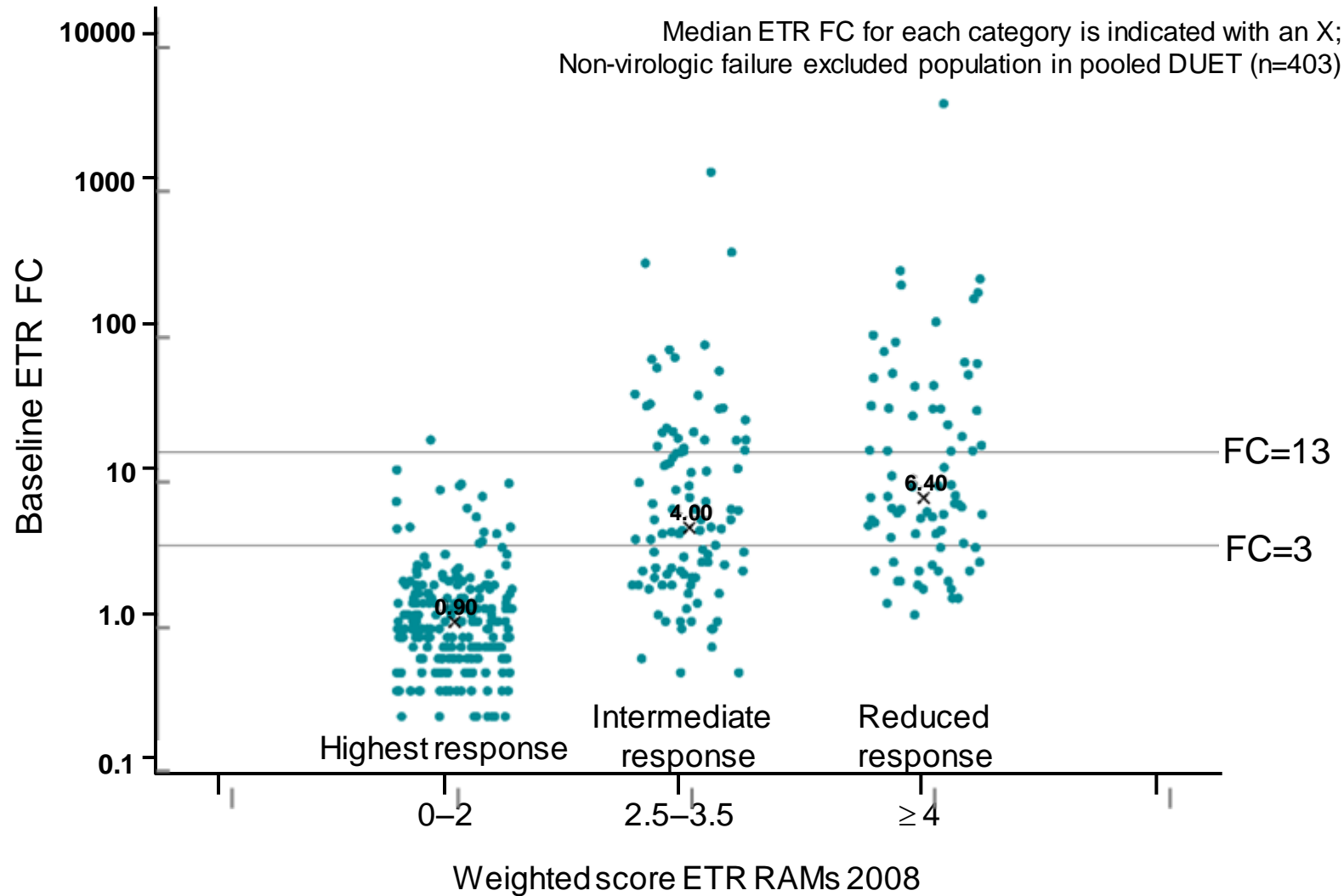


- Substantial response was observed above baseline FC=13, thus this represents an intermediate CCO
- Limited data above baseline FC=13, thus a higher CCO could not be established

Response according to phenotypic ETR CCOs: pooled Week 24 DUET – patients not using ENF *de novo**

ETR CCO	Proportion of patients with VL <50 copies/mL (TLOVR), % (n)	Mean (SE) decrease in log ₁₀ VL from baseline (NC=F)
≤3	71 (190/269)	-2.67 (1.03)
3–13	50 (37/74)	-2.39 (1.21)
>13	37 (22/60)	-1.79 (1.42)

ETR FC vs ETR weighted mutation score – pooled DUET



Conclusions

- ETR is the first NNRTI for which phenotypic CCOs could be determined
- Based on the analysis of the Week 24 DUET virologic response data, two CCOs were determined for ETR
- A lower CCO of 3 and an intermediate CCO of 13 were identified for ETR
 - the ‘highest’ response rate (71% VL <50 copies/mL) was observed in patients with baseline ETR FC ≤ 3
 - an ‘intermediate’ response rate (50% VL <50 copies/mL) was observed in patients with baseline ETR FC between 3 and 13
 - an upper CCO above which patients would no longer benefit from ETR could not yet be determined in this dataset, due to the small number of patients with FC >13 and the substantial virologic response rate in this subset of patients (37% VL <50 copies/mL)
- The majority of patients in DUET had an ETR baseline FC ≤ 3 : 66% (779/1190)

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