

The role of NNRTIs in treatment experienced patients – an update on TMC125

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Introduction

- **Treatment guidelines reflect the well established data for the use of current NNRTIs in treatment naïve patients¹**
- **Limited or negative data exists for the efficacy of current NNRTIs in treatment experienced patients**
 - **Data on the use of current NNRTIs in patients with primary NNRTI resistance is also limited**
- **Unmet medical need to expand the class for the treatment experienced population, including those with NNRTI resistance**
- **Positive Phase II data has been generated with TMC125 as a potential option in these patients²**

1. DHHS, Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents; October, 2006.

2. Cohen C, et al. XVth IAC 2006 (TUPE0061)

NNRTI treatment experienced patients

- **In vitro virology does not support treatment of NNRTI-resistant virus with the current NNRTIs**
 - In vitro, EFV is active (low EC₅₀) against Y181C mutation but this is not substantiated in clinical data¹
- **No randomized clinical trials have been done with current NNRTIs in this setting**
 - Data from EFV expanded access program demonstrated low rates of virologic suppression
 - 18% in the ITT population achieved pVL <400 copies/mL after 6 months of treatment²

1. Antinori A, et al. AIDS Res Hum Retrovir 2002; 18: 835-838.

2. Bachelier L, et al. 39th ICAAC 1999 (Abstract #2201)

Primary NNRTI resistance

- **EFV in primary NNRTI resistance – Gilead 934 trial: treatment outcomes and development of mutations in patients with baseline NNRTI resistance**

Treatment Outcomes and Genotypes	FTC + TDF n (%)	Combivir n (%)
Patients with Baseline NNRTI-R	11	11
On study medication at Week 48 (< 400 copies/mL) ^a	1 (9%)	1 (9%)
Discontinued by Week 48 (< 400 copies/mL) ^b	6 (55%)	5 (45%)
Discontinued by Week 48 (> 400 copies/mL) ^c	4 (36%)	5 (45%)
M184V developed ^d	3	4
Additional EFV-R developed ^e	3	1
Remained as baseline genotype	1	1

NNRTIs with clinical data in NNRTI-resistant patients

- **TMC120 (Tibotec)**
- **Capravirine (Pfizer)**
- **TMC125 (Tibotec)**
- **DPC083 (Dupont – BMS)**
- **GW695634 (pro-drug of GW8248, GSK)**

CPV study 1002: 24 and 48 Week Safety, Tolerability and Efficacy data

- Phase II randomized, double-blind, placebo control
- Failed prior NNRTI-containing regimen, PI naive

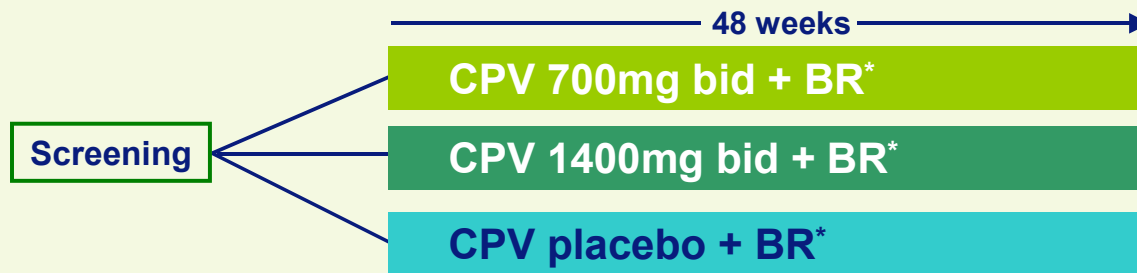
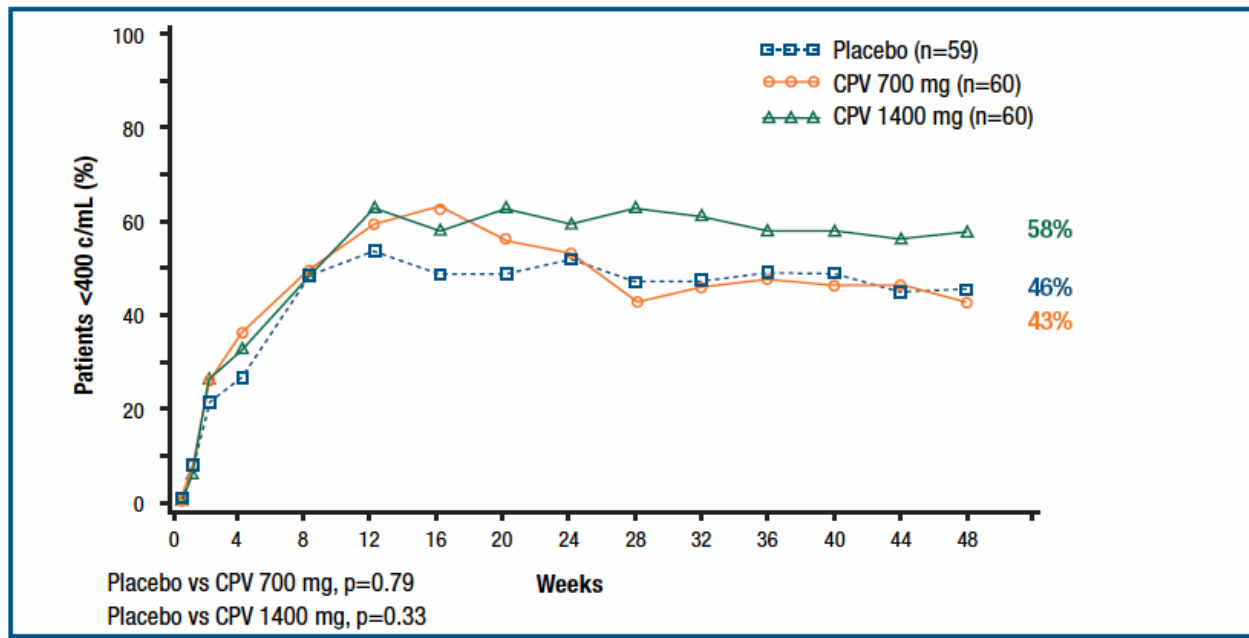


Figure 2. Patients (%) achieving HIV RNA <400 c/mL over time (ITT, NC=F)



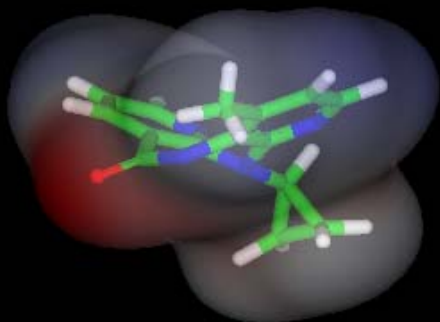
TMC125

- **C207**
 - **Short term proof of principle trial in patients with NNRTI resistant virus**
- **C203**
 - **Phase II dose escalation safety study in 3-class experienced patients**
- **C227**
 - **Phase II exploratory trial in first-line NNRTI failures**
- **C223**
 - **Phase II dose finding efficacy trial in heavily pre-treated patients with extensive multi-drug resistance**

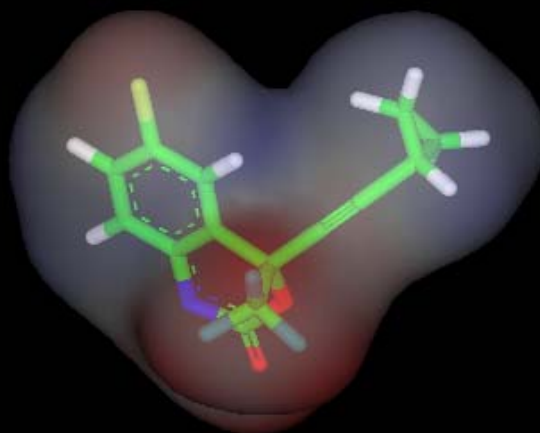
TMC125: In vitro virology data

- High potency and selectivity against wild type HIV
 - $EC_{50} = 1.4 \text{ nM}$ (0.61 ng/ml)
 - $CC_{50} > 100 \text{ }\mu\text{M}$
- Active against HIV-1 with single and double NNRTI-resistant mutations
 - **K103N, Y181C, K103N+Y181C**
- High potency against NNRTI-resistant clinical isolates
 - **EC_{50} below 10 nM for > 80% of ~2,000 NNRTI resistant clinical isolates**
- Increased genetic barrier to development of HIV drug resistance
 - **In vitro selection experiments show virus breakthrough delayed or prevented by TMC125**

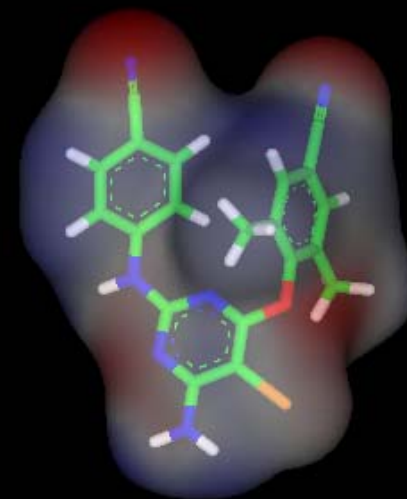
Structures of old and new NNRTI's



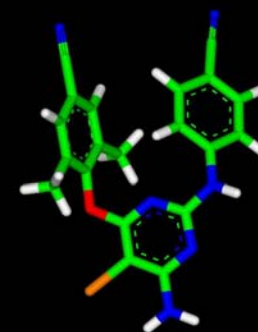
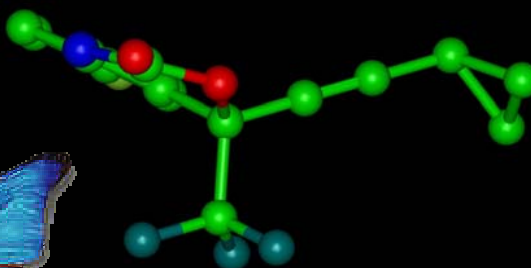
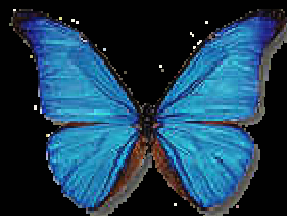
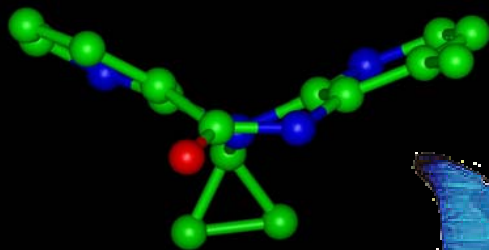
nevirapine



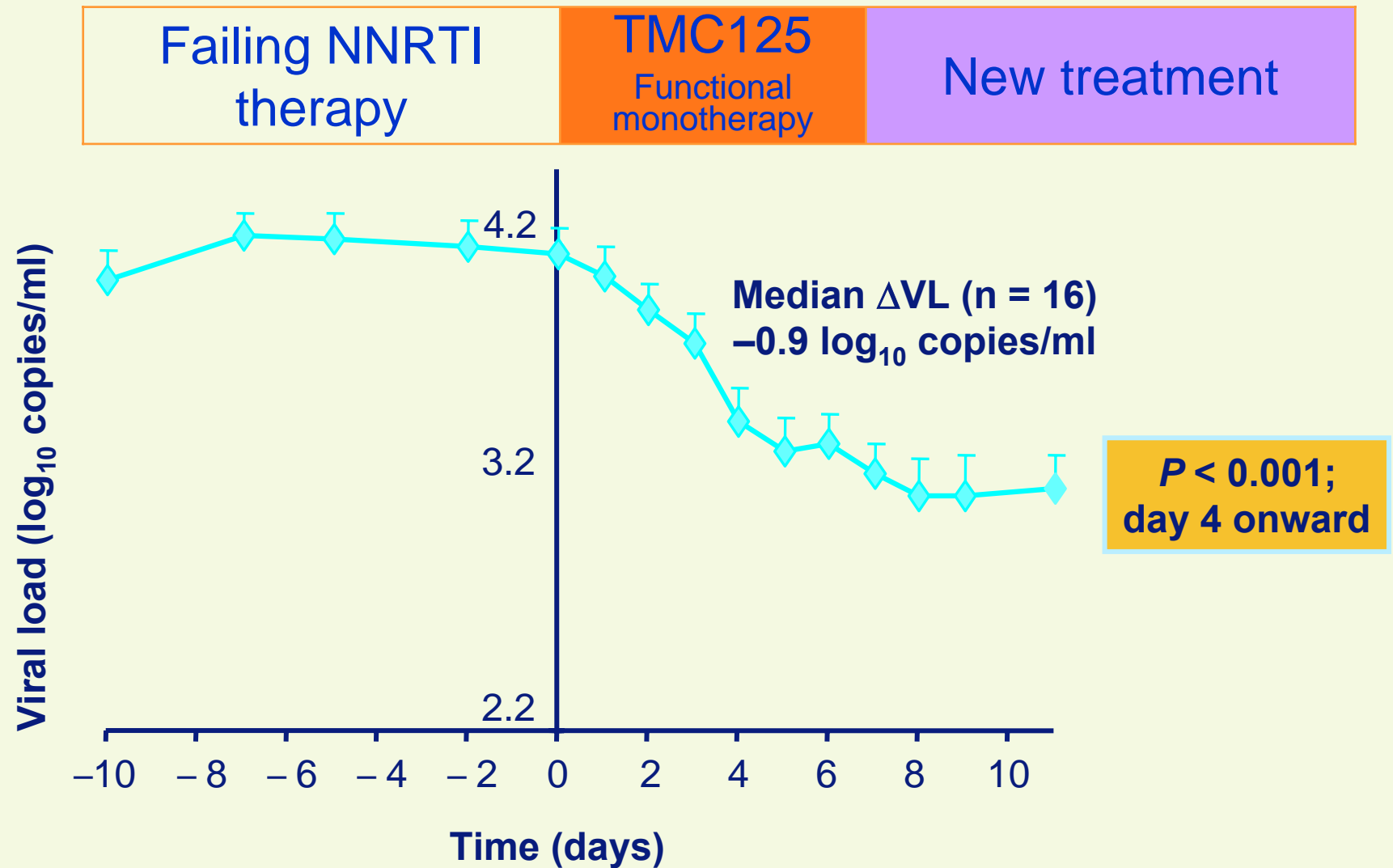
efavirenz



TMC125

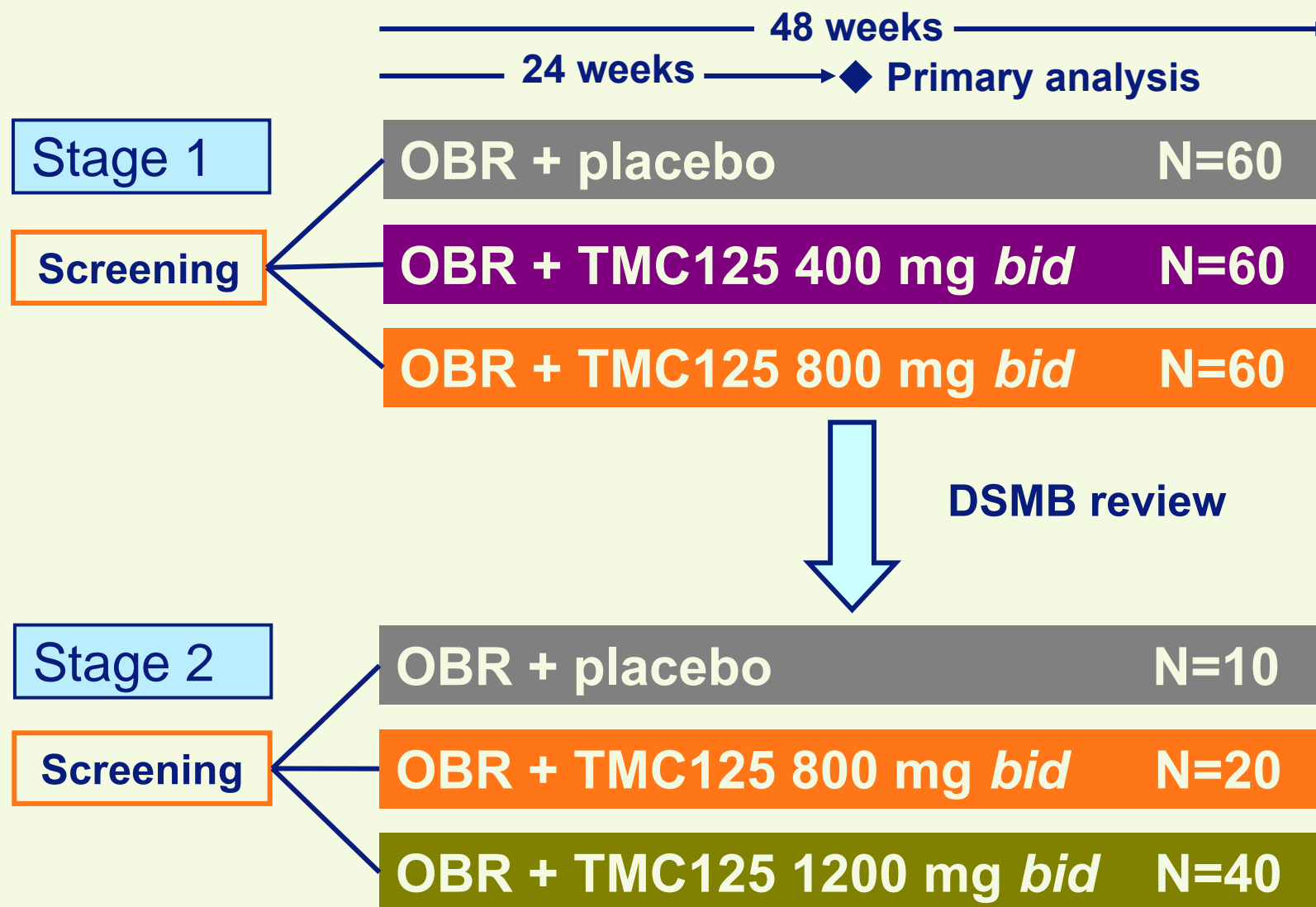


TMC125-C207: PoP trial in patients with NNRTI resistant virus



TMC125-C203

TMC125-C203: Safety trial in 3-class experienced patients



OBR = optimized background regimen; N = enrollment target

TMC125-C203: Conclusions

- **TMC125 was generally safe and well tolerated in this study**
 - **Grade 3/4 AEs – not substantially different from placebo**
 - **Most common AEs were diarrhoea, headache, rash and nausea**
 - **Rashes were generally mild to moderate**
 - **No consistent or frequent neuropsychiatric syndrome associated with TMC125**
- **The TMC125-C223 dose-finding study was designed and conducted based on these data**

TMC125-C203: Safety – most common AEs

Adverse event, %	TMC125				Placebo + OBR (N = 66)	95% CI All TMC125 vs. placebo
	400 mg <i>bid</i> (N = 57)	800 mg <i>bid</i> (N = 74)	1200 mg <i>bid</i> (N = 43)	All TMC125 (N = 174)		
Median treatment duration (weeks)	47	32	24	29	40	–
Any adverse event	88	95	93	92	91	–7.0 to 9.1
Diarrhoea	30	24	26	26	38	– 24.9 to 2.0
Headache	28	18	9	19	17	– 8.4 to 13.0
Rash (grouped term)	16	18	19	17	11	– 2.7 to 15.9
Nausea	18	18	14	17	23	– 17.6 to 5.5
URTI	9	15	12	12	14	– 11.2 to 8.0
Abdominal pain	11	12	12	12	8	– 4.0 to 11.9
Fatigue	12	5	19	11	9	– 6.6 to 10.0

Injection site reactions related to enfuvirtide use were reported in 9% patients

- Incidence of most common AEs not substantially different between TMC125 and placebo
- No clear dose relationship with safety assessments

TMC125-C203: Rash

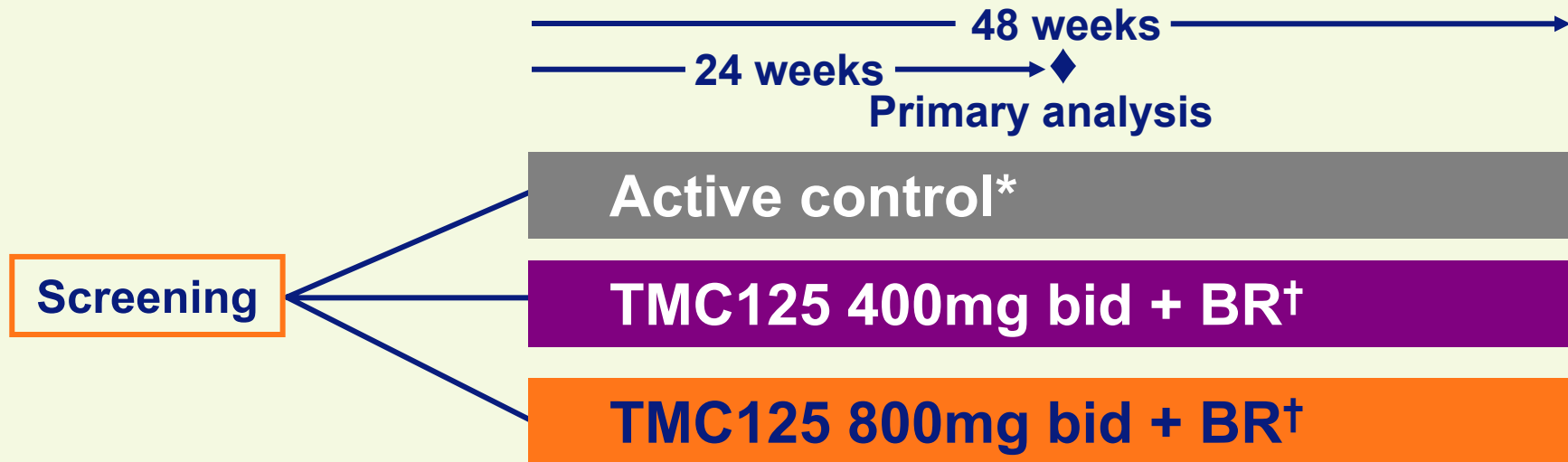
- **Overall incidence:**
 - 17% TMC125 vs. 11% placebo (95% CI: -2.7 to 15.9)
 - No dose differentiation
- **Relatedness and severity:**
 - At least possibly related to TMC125: 8%
 - Grade 3 rash plus fever: 1 in 400 mg group; no SAEs
 - No Stevens-Johnson syndrome, toxic epidermal necrolysis or erythema multiforme
- **Permanent discontinuation:**
 - 3 (2%) TMC125 vs. 1 (2%) placebo
- **Time to onset / duration (at least possibly related rash):**
 - Median time to onset 13 days and median duration 4 days
- **No association between rash and higher baseline CD4 cell count**
- **No difference in the incidence of rash between male and female patients receiving TMC125**

TMC125-C203: neuropsychiatric summary

- **Nervous system disorders occurred in 40% of TMC125-treated patients and 35% of placebo-treated patients**
 - the most common nervous system AEs were headache, dizziness and insomnia. Only dizziness was more common compared with placebo
 - headache, dizziness and insomnia generally occurred within the first month of TMC125 administration
 - there was no association between TMC125 dose and incidence or severity of nervous system events
- **Psychiatric AEs occurred in 13% of TMC125-treated patients and 11% of placebo-treated patients**
 - the most common psychiatric AEs were depression, anxiety and sleep disorder; the incidence was low and not different from placebo
 - there was no pattern in the time of onset for the most common psychiatric events
 - for TMC125-treated patients, there was an overall trend for increased incidence with the highest dose (1,200mg bid). A pre-trial history of psychiatric disorder(s) was also most frequent in the TMC125 1,200mg bid group

TMC125-C223

TMC125-C223: study design



*Active control: best available regimen from licensed agents

†BR: investigator selected NRTIs ± LPV/r ± ENF

- Documented NNRTI resistance and ≥ 3 primary PI mutations
- Partially blinded, US, randomization 1:2:2 (active control versus 400mg bid versus 800mg bid)
- VL >1,000 copies/mL

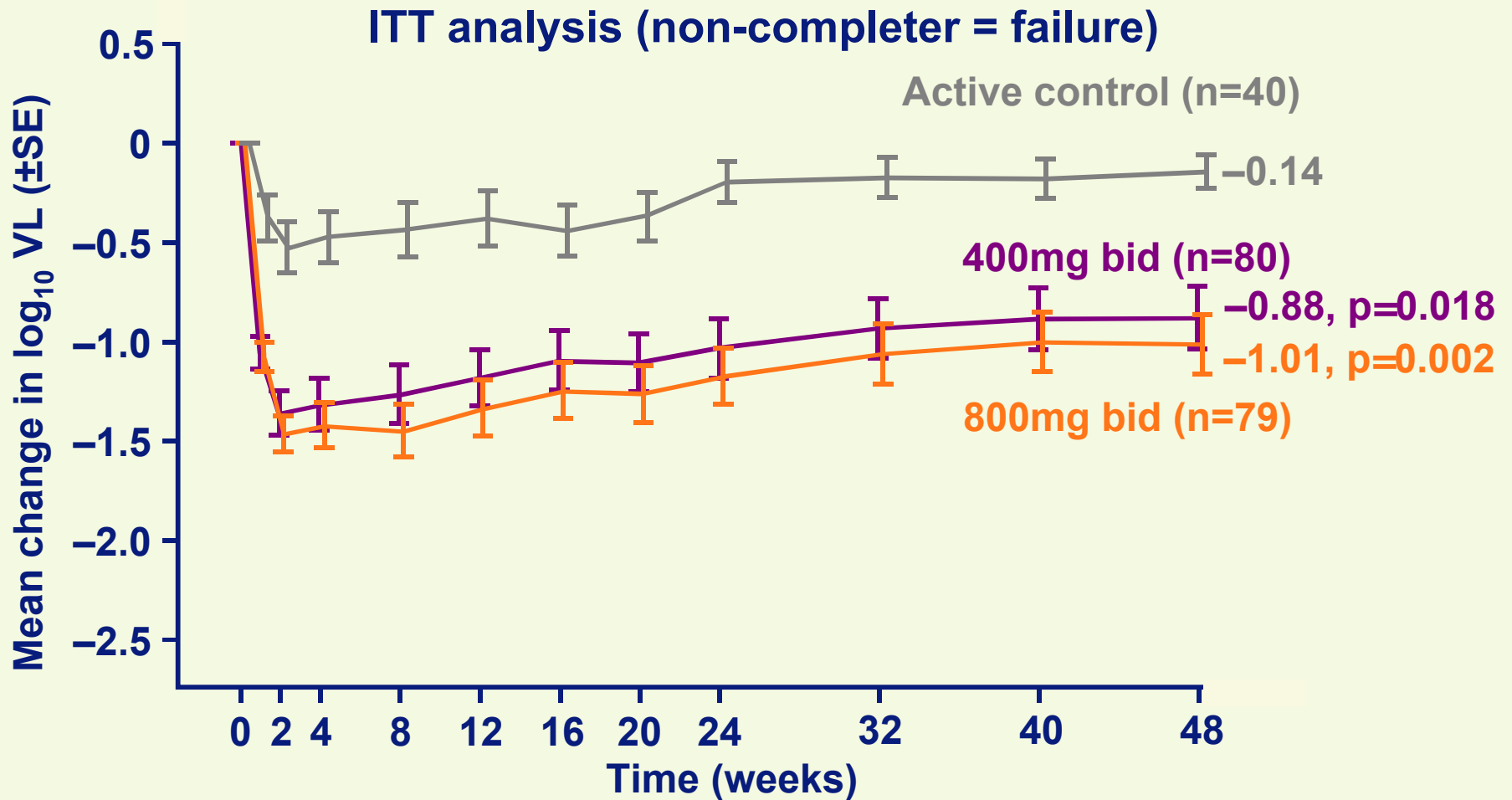
BR = background regimen; LPV = lopinavir; ENF = enfuvirtide

TMC125-C223: treatment-experienced population

	Median (range)
VL (log ₁₀ copies/mL)	4.7 (2.6–7.1)
CD4 count (cells/mm ³)	99 (1–660)
Duration of HIV infection (years)	14.6 (2.2–22.7)
Number of mutations	
NNRTI resistance-associated mutations	2 (0–5)
NRTI resistance-associated mutations	6 (0–12)
Primary PI mutations	4 (0–6)
PI resistance-associated mutations	9 (0–13)
Resistant to all currently approved PIs (excluding tipranavir)*	83% [†]
Phenotypic susceptibility score (PSS)	1 (0–4) [‡]
FC to TMC125	1.7 (0.1–399)
FC to lopinavir	83.6 (not different between groups)

*Tipranavir was not approved when study TMC125-C223 was started; [†]FC to LPV was 83.6 (82.7–84.3 across study arms); [‡]ENF is included in this PSS and scored as sensitive if not previously used; TMC125 is excluded from the PSS; PSS was 1 for all study arms

TMC125-C223 primary endpoint: change in VL at 48 weeks

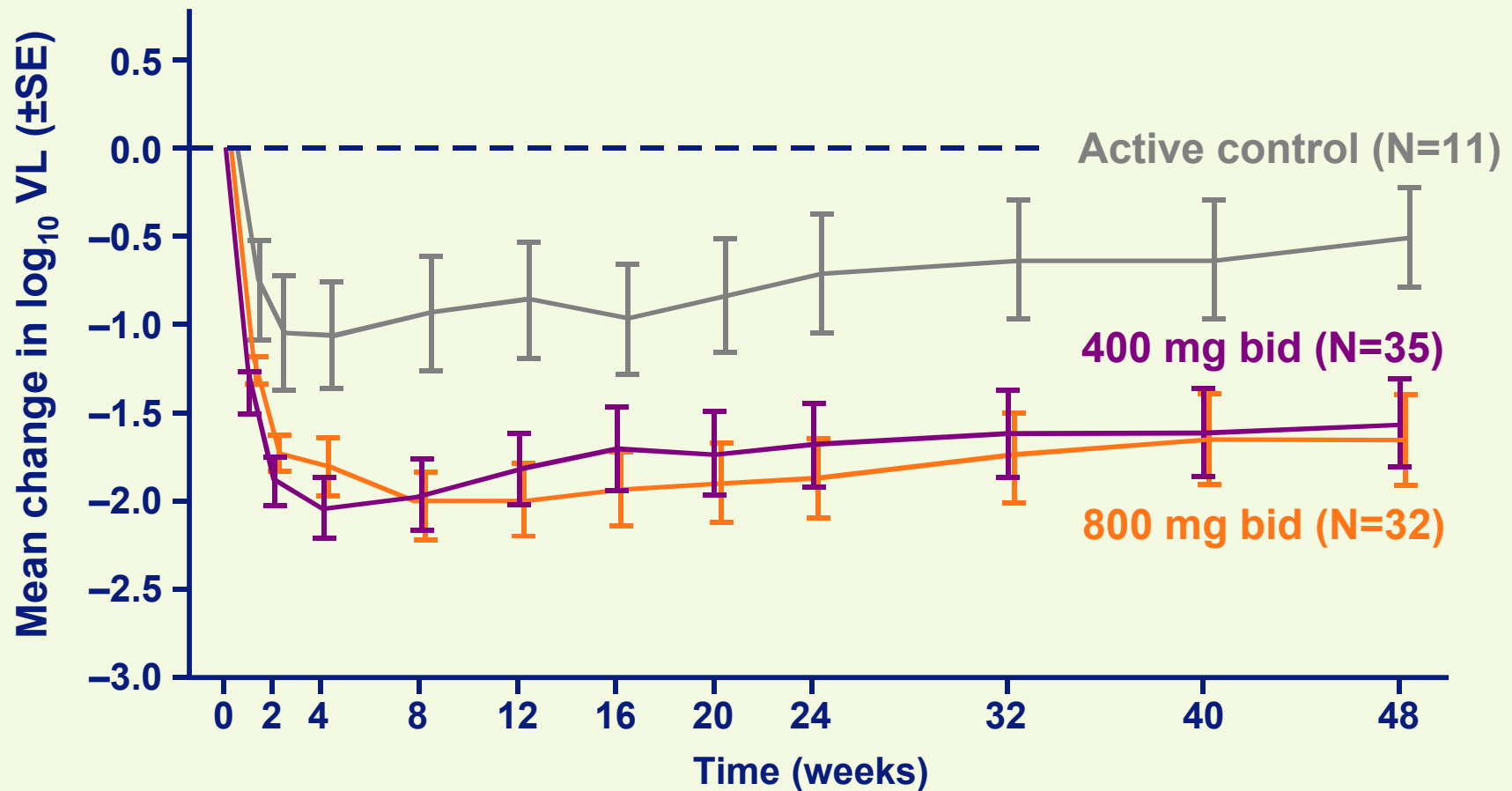


No statistical difference between the TMC125 groups was observed
EDTA samples and Roche Amplicor® version 1.5 used for HIV RNA analyses

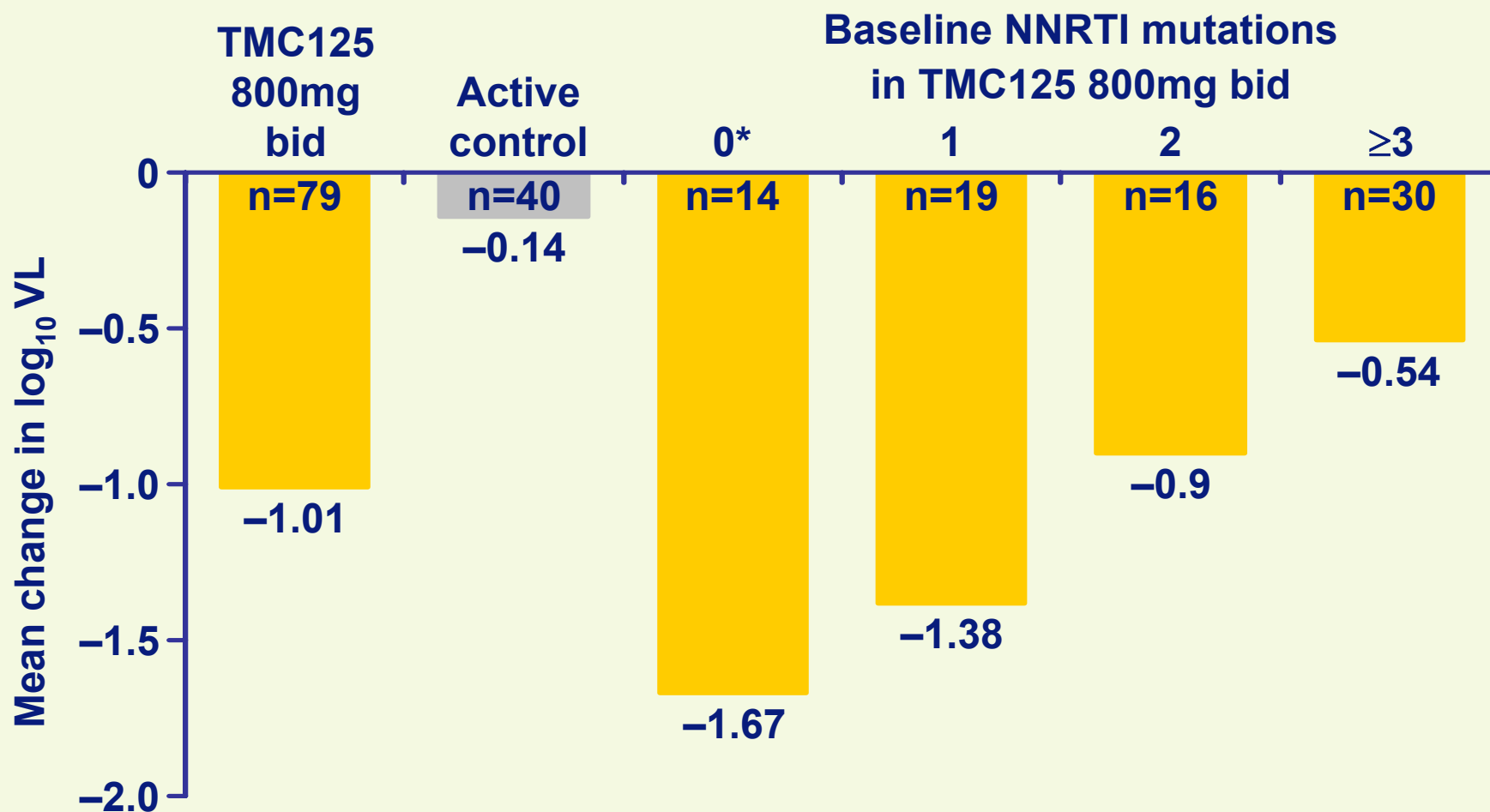
p values versus active control; SE = standard error

TMC125-C223: Change in viral load with *de novo* enfuvirtide, without a (sensitive) PI

ITT analysis (non-completer = failure)



TMC125-C223: number of NNRTI mutations and virologic response at Week 48



- Patients discontinuing the trial for any reason had their VL response imputed as no change from baseline (NC=F)

*All patients had NNRTI mutations from prior genotyping

Drug-drug interactions

Interaction data - TMC125 and other ARVs

ALLOWED

No dose adjustment

- NRTIs
 - TDF
 - ddl
- RTV boosted PIs
 - ATV
 - DRV
 - LPV
 - SQV
 - LPV/SQV

Dose adjustment may be required

- fosAPV/r

NOT RECOMMENDED

- NNRTIs
 - EFV
 - NVP
- TPV/r
- RTV (full dose)
- Unboosted PIs
 - ATV
 - IDV

Interaction data - TMC125 and other drugs

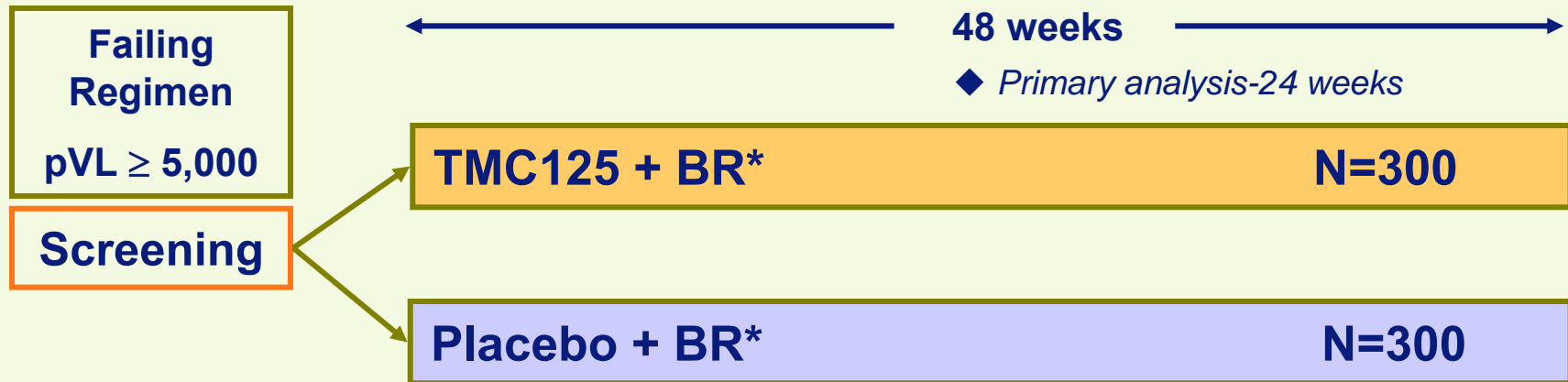
ALLOWED

- pH modifiers
 - omeprazole
 - ranitidine
- Methadone
- Oral contraceptives
- Rifabutin
- Clarithromycin
 - Alternative should be considered for treatment of *MAC*

Dose adjustment may be required

- Sildenafil

DUET trials: TMC125-C206 and -C216



- Two identical Phase III trials in heavily treatment experienced patients
- Randomized, double blind, placebo controlled
- *Background regimen: DRV/r + Investigator selected NRTIs +/- ENF
- Primary objective: TMC125 superior over placebo for proportion of subjects with undetectable viral load (<50 copies/ml)
- TMC125 dosed at 200 mg bid (new formulation) which provides comparable exposure to 800 mg bid (Phase II formulation) selected from the Phase II program

TMC125: Other ongoing activities

- **Phase I interaction trial with investigational agents ongoing or planned**
 - **MK0518, maraviroc, GS-9137**
- **Early Access Program (EAP) open and enrolling in 11 countries**
 - **Additional countries and sites added on ongoing basis**
- **Pediatric dose finding**
 - **HIV-1 infected children/adolescents age 6-18 inclusive**

Acknowledgements

- **Patients (and their families) who have participated in TMC125 trials**
- **Investigators and study site staff**
- **TMC125 clinical team colleagues at Tibotec**