

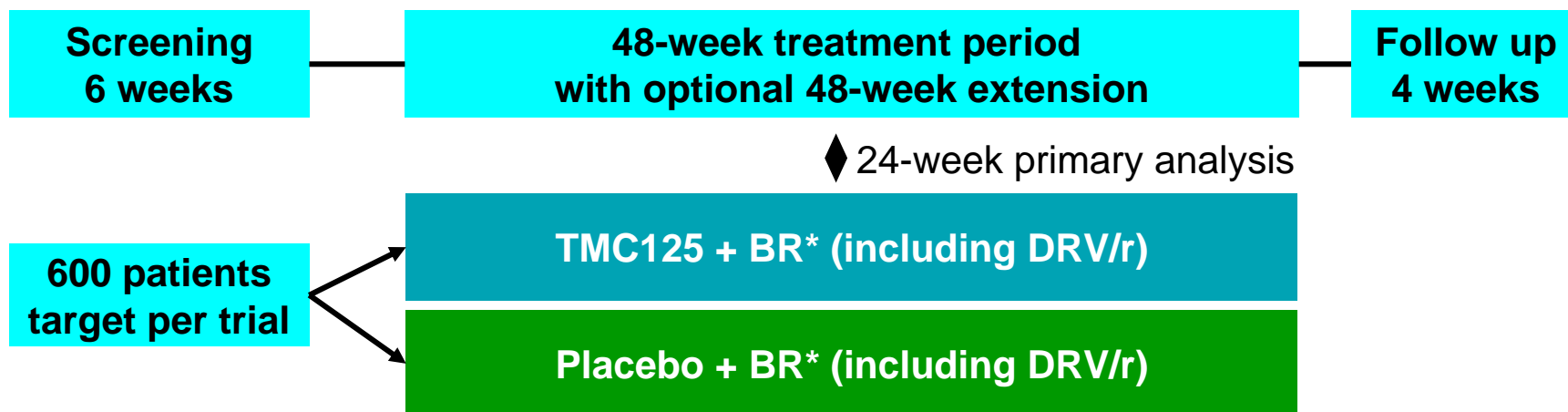
DUET-1 and DUET-2: TMC125 versus placebo in treatment-experienced HIV-1-infected patients

DUET-1: Anthony Mills, Pedro Cahn, Beatriz Grinsztejn, Richard Haubrich, Jacob Lalezari, José Valdez Madruga, Gilles Pialoux, Timothy Wilkin, Monika Peeters, Johan Vingerhoets, Goedele De Smedt, Lorant Leopold, Roberta Trefiglio and Brian Woodfall

DUET-2: Christine Katlama, Thomas Campbell, Bonaventura Clotet, Margaret Johnson, Adriano Lazzarin, Keikawus Arastéh, William Towner, Benoit Trottier, Monika Peeters, Johan Vingerhoets, Goedele De Smedt, Benny Baeten, Greet Beets, Rekha Sinha and Brian Woodfall

DUET-1: Thailand, France, North and South America. Madruga JV, et al. Lancet 2007;370;29–38
DUET-2: Australia, Europe, North America. Lazzarin A, et al. Lancet 2007;370;39–48

DUET-1¹ and DUET-2² trials: design and inclusion criteria



*BR = DRV/r with optimised NRTIs and optional enfuvirtide

- Viral load >5,000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
- ≥1 NNRTI RAM, at screening or in documented historical genotype
- ≥3 primary PI mutations at screening
- Primary endpoint was the proportion of patients achieving viral load <50 HIV-1 RNA copies/mL when all patients had reached Week 24 or discontinued

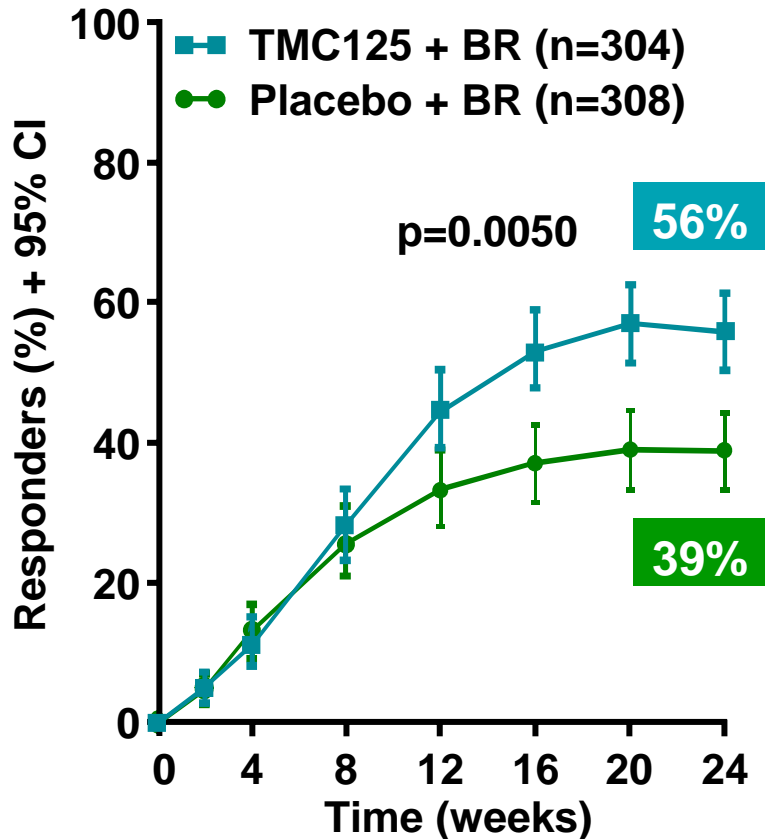
DUET-1 and DUET 2: baseline characteristics and background ARVs

Parameter		DUET-1		DUET-2	
		TMC125 + BR (n=304)	Placebo + BR (n=308)	TMC125 + BR (n=295)	Placebo + BR (n=296)
Patient demographics	Male	87	86	94	92
	Caucasian	65	65	77	76
Disease characteristics	Viral load (log ₁₀ c/mL)*	4.8 (2.7–6.2)	4.9 (2.4–6.5)	4.8 (3.0–6.8)	4.8 (2.2–6.3)
	CD4 cells (cells/μL)*	99 (1–789)	109 (1–694)	100 (1–708)	108 (0–912)
	CDC category C	61	63	55	55
Prior ARV use	10–15 ARVs (%)	67	65	62	67
	Darunavir/r (%)	5	5	3	5
Detectable mutations	≥2 NNRTI RAMs (%)	66	67	65	65
	≥4 primary PI RAMs (%)	60	59	65	66
Background regimen	Used ENF (total) (%)	40	41	52	53
	Used ENF <i>de novo</i> (%)	24	26	27	27
	PSS = 0 (%)	15	15	16	16
	PSS = 1 (%)	35	31	35	42

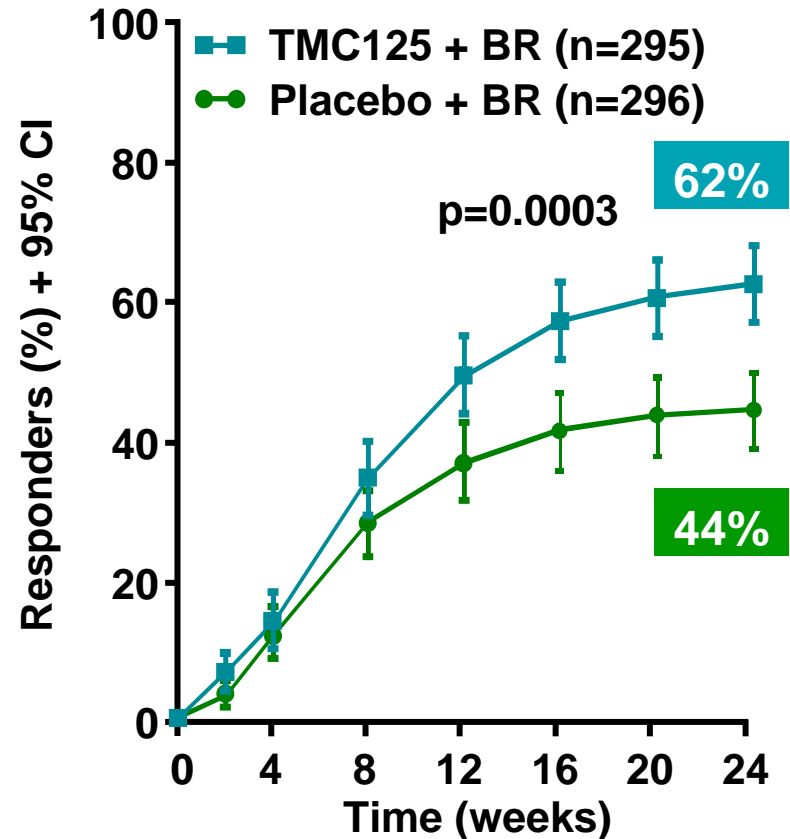
c/mL = HIV-1 RNA copies/mL; PSS = phenotypic sensitivity score

DUET-1 and DUET-2 primary endpoint: patients with viral load <50 copies/mL at Week 24 TLOVR

DUET-1



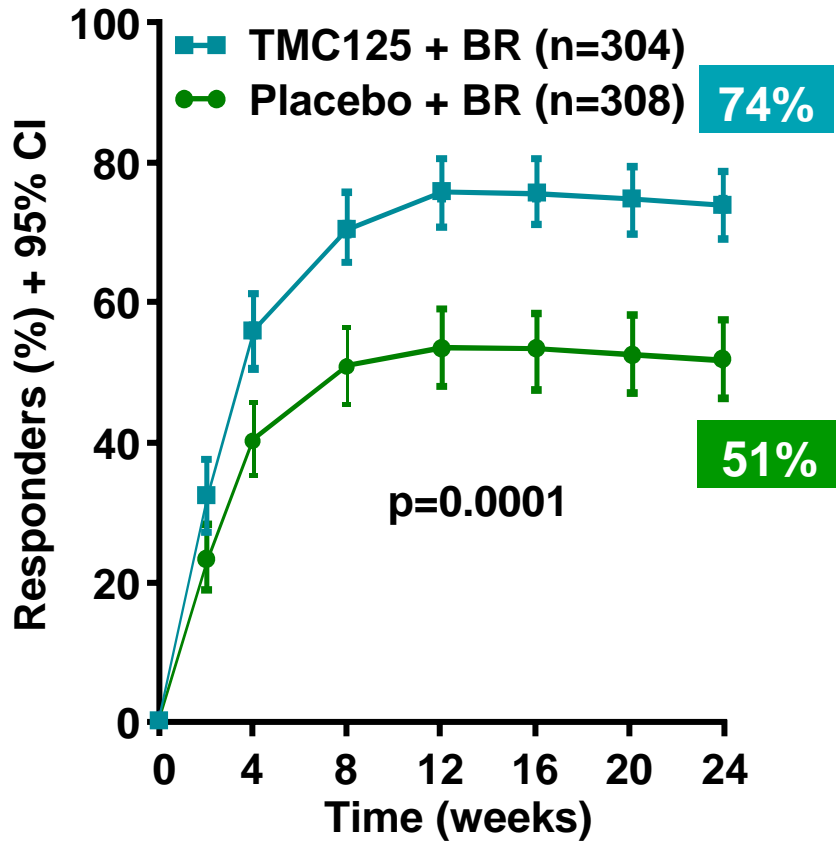
DUET-2



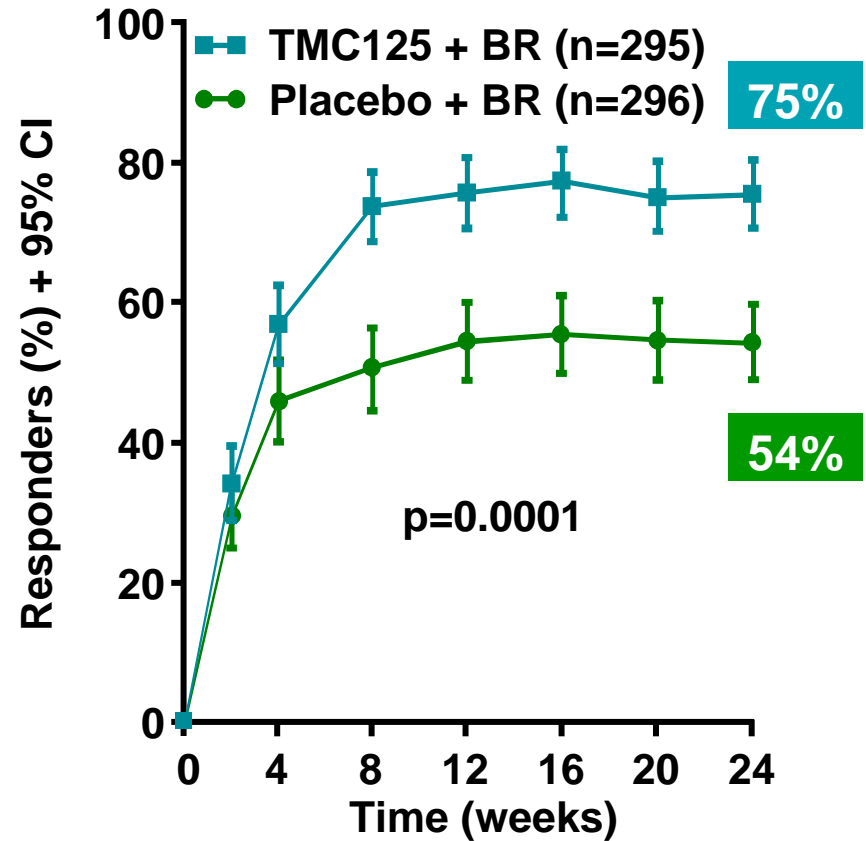
CI = confidence interval; intent-to-treat (ITT) population;
TLOVR = time to loss of virological response imputation algorithm

DUET-1 and -2: patients with HIV-RNA <400 copies/mL to week 24

DUET-1



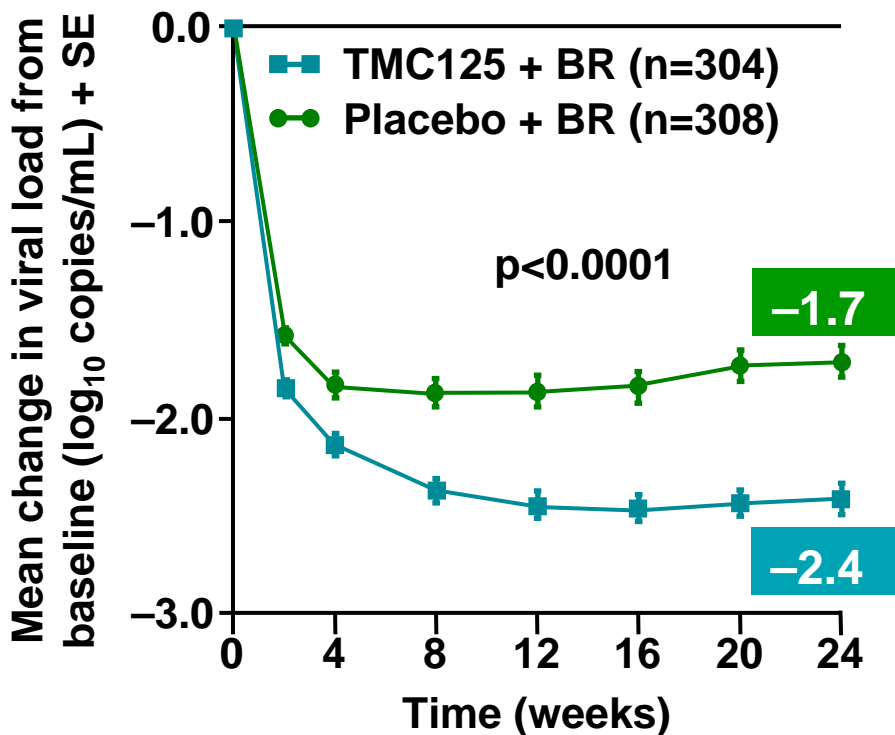
DUET-2



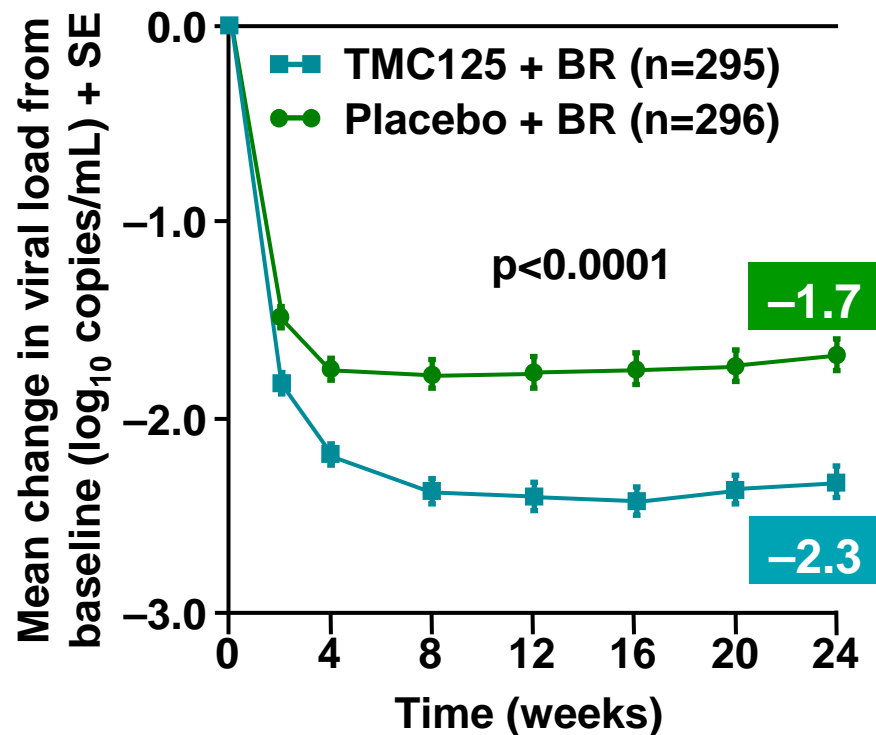
CI = confidence interval; intent-to-treat (ITT) population; time to loss of virological response (TLOVR) imputation algorithm

DUET-1 and DUET-2: viral load reduction from baseline to week 24

DUET-1



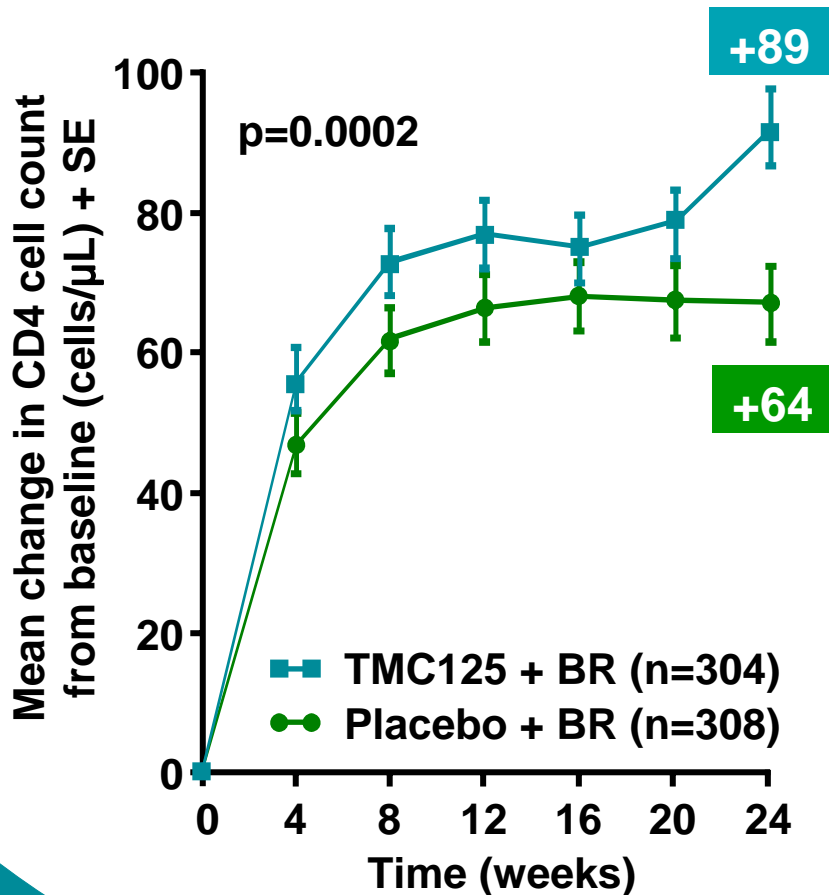
DUET-2



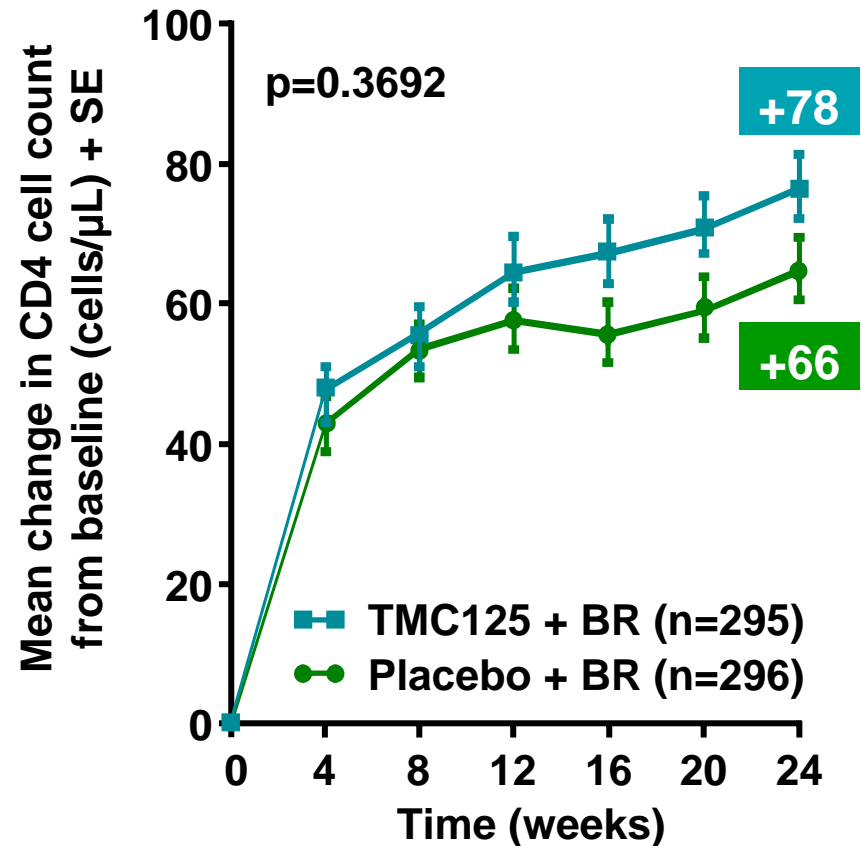
CI = confidence interval; intent-to-treat (ITT) population;
time to loss of virological response (TLOVR) imputation algorithm

DUET-1 and DUET-2: change in CD4 cell count from baseline

DUET-1



DUET-2

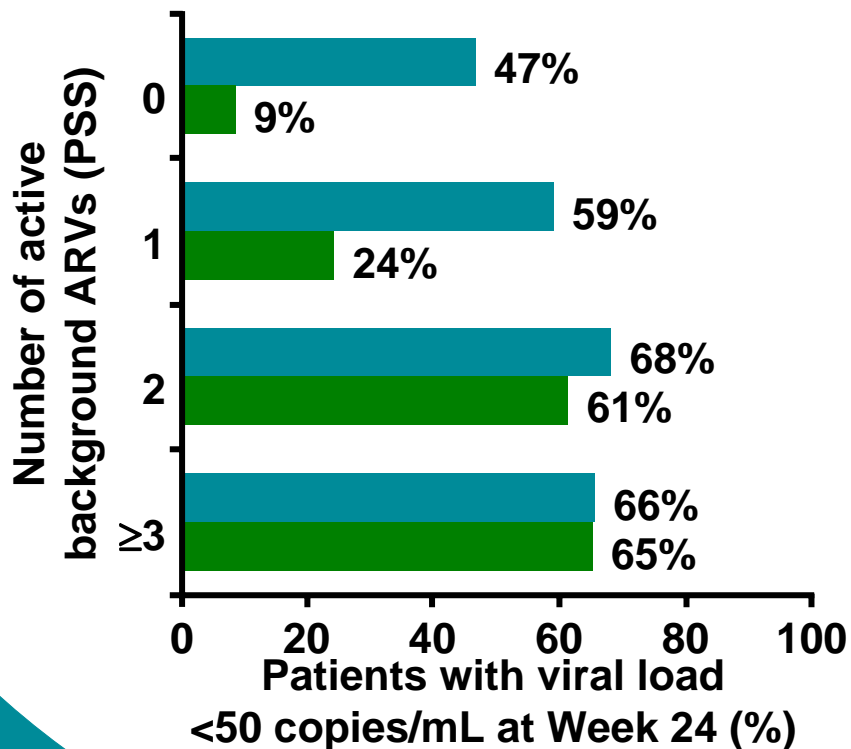


SE = standard error; intent-to-treat (ITT) population; non-completer = failure (NC=F) imputation

DUET-1 and DUET-2: response (VL <50 copies/mL) according to number of active background ARVs

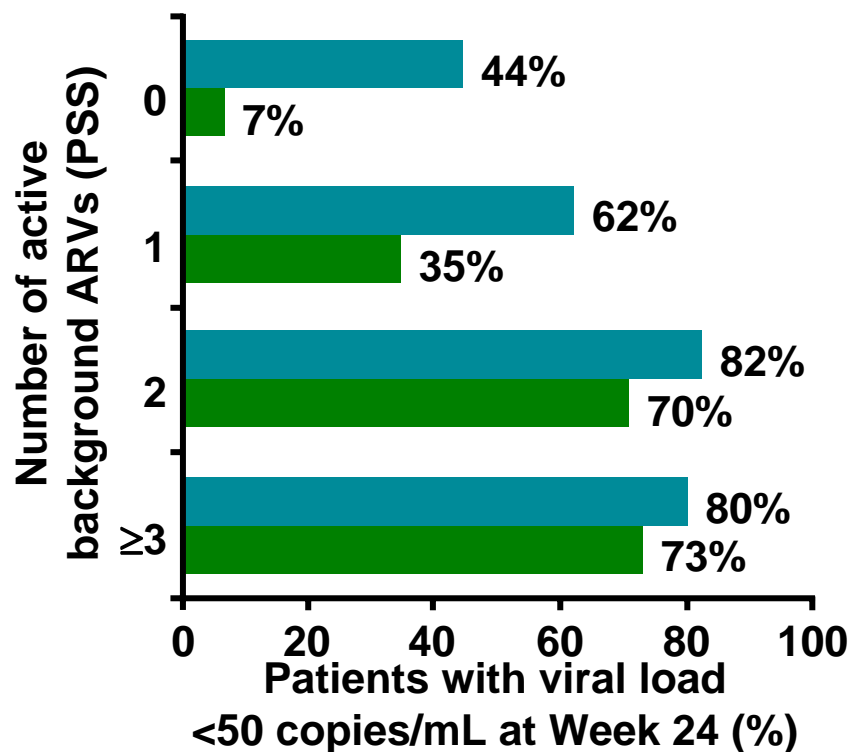
DUET-1

- TMC125 + BR (n=304)
- Placebo + BR (n=308)



DUET-2

- TMC125 + BR (n=295)
- Placebo + BR (n=296)

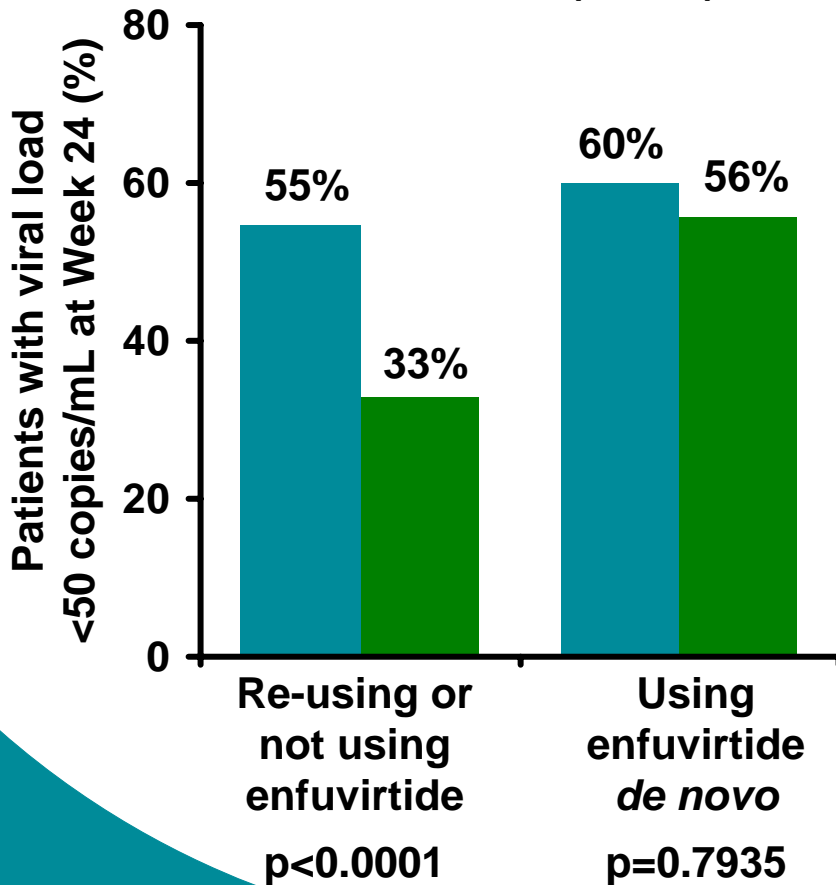


Darunavir and enfuvirtide are counted as active if FC<10 or used *de novo*, respectively;
PSS = phenotypic sensitivity score

DUET-1 and DUET-2: response according to enfuvirtide use (primary analysis)

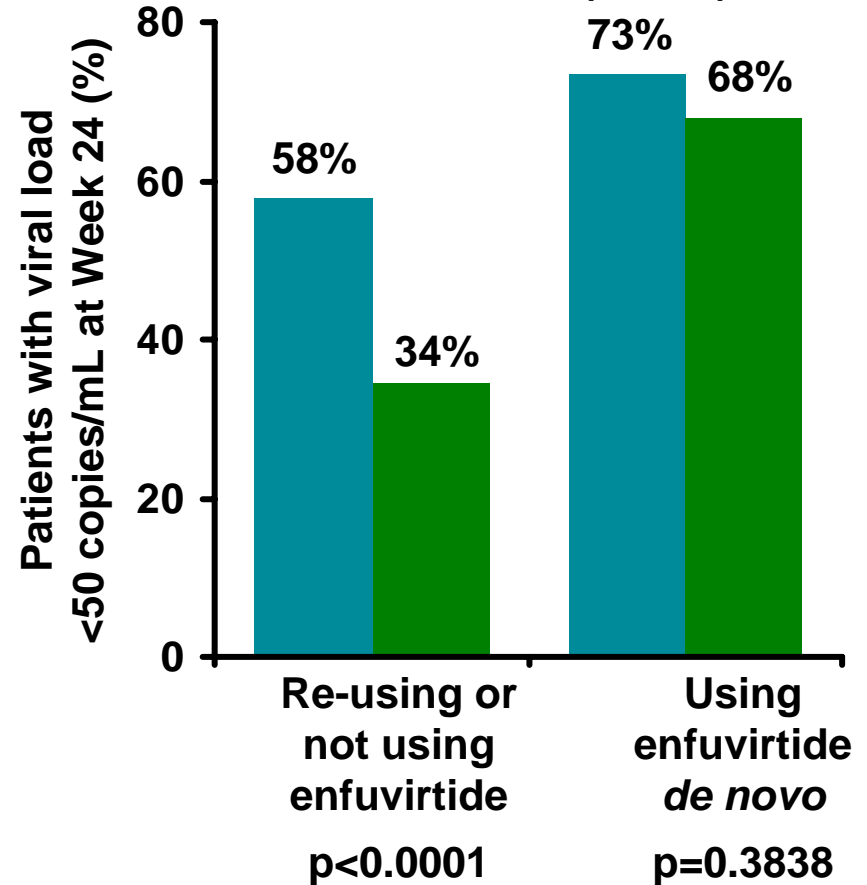
DUET-1

- TMC125 + BR (n=304)
- Placebo + BR (n=308)



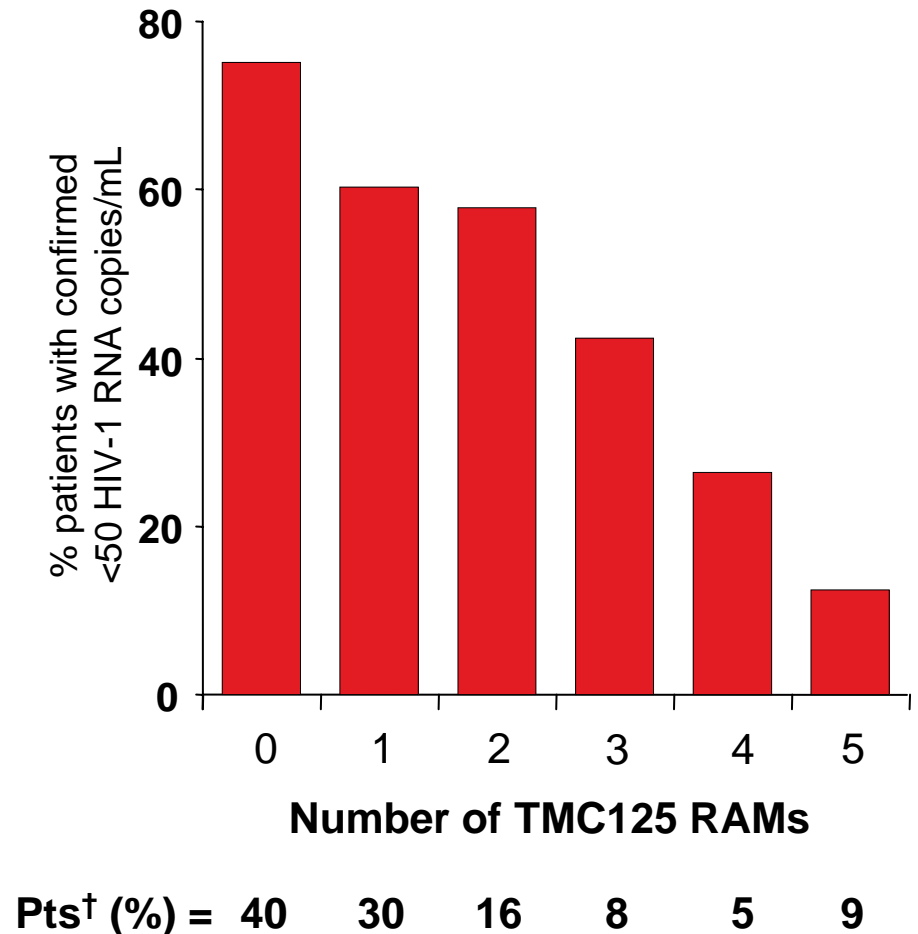
DUET-2

- TMC125 + BR (n=295)
- Placebo + BR (n=296)



DUET-1 and DUET-2: virological response (<50 copies/mL) according to baseline mutations

- 13 baseline **Resistance-Associated Mutations** were associated with a decreased response to TMC125 (TMC125 RAMs):
V90I **A98G**
L100I **K101E/P**
V106I **V179D/F**
Y181C/I/V **G190A/S**
- When 3 of these TMC125 RAMs were present the response rate was comparable to the overall placebo response*
- Only 14% of patients had 3 or more TMC125 RAMs

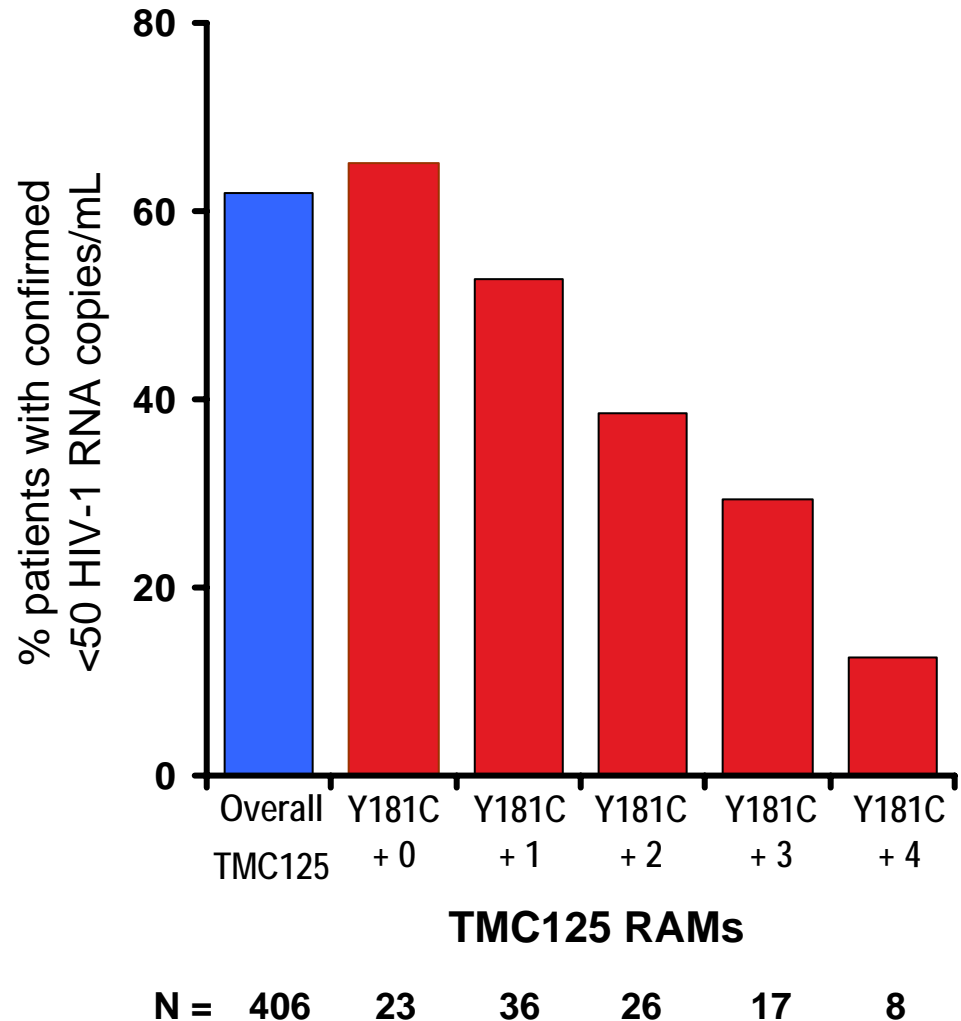


†analysis performed in n=406 (100%); *overall placebo response = 36%

What is the effect of Y181C on TMC125 response rates?

What is the effect of Y181C on TMC125 response rates?

- Y181C is a common mutation conferring resistance to currently available NNRTIs
- The TMC125 response rate is not compromised when Y181C is present, with either 0 or 1 other TMC125 RAM
- When Y181C is present with two or more TMC125 RAMs (13% of all patients), response rates were substantially reduced



DUET-1 and DUET-2: overview of adverse events (AEs)

Parameter	DUET-1		DUET-2		
	TMC125 + BR (n=304)	Placebo + BR (n=308)	TMC125 + BR (n=295)	Placebo + BR (n=296)	
Any AE (any cause)	93	93	92	92	
Grade 3/4 AE	21	28	28	27	
Discontinuation due to AE, %	5	5	6	4	
Serious AE, %	12	20	15	17	
Death (any cause), n (%)	4 (1.3%)	8 (2.6%)	4 (1.4%)	7 (2.4%)	
Most common AEs*	Rash (any type), %	20	10	14	9
	Nausea, %	14	12	14	10
	Diarrhoea, %	12	20	18	20
	Headache	10	13	9	11
	Injection site reaction	7	7	13	15
AEs of interest	Nervous system disorders	15	20	15	17
	Psychiatric disorders	10	14	16	17
	Hepatic AEs	5	7	5	4

No deaths in the TMC125 group were considered at least possibly related to trial medication;

*In >10% patients in TMC125 group in either trial

DUET-1 and DUET-2: summary of rash

- **Overall incidence**
 - 17% in TMC125 group vs 9% in placebo group
- **Onset:** most frequent in 2nd week of therapy
- **Severity**
 - usually mild to moderate; 1% grade 3 and 0% grade 4
 - no rashes with mucosal involvement
- **Infrequently lead to discontinuation (2%)**
 - most self-limiting with continued treatment
- Higher incidence in women, **but no gender difference in severity or treatment discontinuations**
- **No association** between rash and **baseline CD4 cell count**
- In patients with a **history of NNRTI-related rash**, there was **no apparent increased risk**

DUET-1 and DUET-2: incidence of treatment-emergent lipid and liver abnormalities

Grade 3/4 abnormalities	DUET-1		DUET-2	
	TMC125 + BR (n=304)	Placebo + BR (n=308)	TMC125 + BR (n=295)	Placebo + BR (n=296)
Triglycerides increased, %	7	5	7	4
Total cholesterol increased, %	6	5	5	4
LDL increased, %	3	4	7	7
ALT, %	3	2	2	1
AST, %	2	2	3	1

- The profile of abnormalities was generally **similar between the TMC125 and placebo groups** with **no consistent or clinically-relevant trends** in laboratory, vital signs or ECG data

Conclusions

- In **treatment-experienced** patients, including those with NNRTI resistant virus, TMC125 consistently demonstrated **superiority over placebo**
 - **56%** (DUET-1) and **62%** (DUET-2) of patients achieved confirmed undetectable VL (<50 copies/mL) with TMC125 plus BR at Week 24
- Even in the absence of any **other fully active background agents**, with TMC125, **over 40% of patients** achieved **undetectable** (<50 copies/mL) viral load
 - response rates increased as more active agents were used in the background regimen
- Thirteen TMC125 resistance-associated mutations (TMC125 RAMs) were identified
 - in the **presence of 0, 1 and 2 TMC125 RAMs**, virological responses were **greater than** the overall **placebo** response
 - **only 14%** of **all** patients had **≥3 TMC125 RAMs**
- Except for rash, incidence and severity of AEs with TMC125 were similar to placebo
- TMC125 has the ability to extend and enhance the NNRTI class and provide a new treatment option for patients with resistance to and/or unable to tolerate other NNRTI's

DUET-1 and DUET-2: acknowledgements

- We express our gratitude to the patients that participated in the study, as well as the study centre staff, DSMB, Tibotec personnel and following principal investigators:

DUET-1

Argentina: H Ariza, J Benetucci, L Calanni, L Cassetti, J Corral, D David, A Krolewiecki, M Losso, P Patterson, R Teijeiro; **Brazil:** C A da Cunha, E Kallas, E Netto, J H Pilotto, M Schechter, J Suleiman, A Timerman; **Chile:** J Ballesteros, R Northland; **Costa Rica:** A Alvilés Montoya, G Herrera Martinez, A Solano Chinchilla; **France:** M Dupon, C Katlama, J M Livrozet, P Morlat, C Piketty, I Poizot-Martin; **Mexico:** J Andrade-Villanueva, G Reyes-Terán, J Sierra-Madero; **Panama:** A Canton, A Rodriguez, N Sosa; **Puerto Rico:** J O Morales Ramirez, J L Santana Bagur, R Soto-Malave; **Thailand:** T Anekthananon, P Mootsikapun, K Ruxrungtham; **USA:** M Albrecht, N Bellos, R Bolan, P Brachman, C Brinson, F Cruickshank, R Elion, W J Fessel, T Hawkins, S Hodder, T Jefferson, H Katner, C Kinder, M Kozal, J Leider, D McDonough, K Mounzer, D Norris, W O'Brien, G Pierone, K Raben, B Rashbaum, M Rawlings, B Rodwick, P Ruane, J Sampson, S Schrader, A Scribner, M Sension, D Sweet, B Wade, D Wheeler, A Wilkin, T Wills, M Wohlfeiler, K Workowski.

DUET-2

Australia: J Chuah, D Cooper, B Eu, J Hoy, C Workman; **Belgium:** N Clumeck, R Colebunders, M Moutschen; **Canada:** J Gill, K Gough, P Junod, D Kilby, J Montaner, A Rachlis, C M Tsoukas, S L Walmsley; **France:** C Arvieux, L Cotte, J F Delfraissy, P M Girard, B Marchou, J M Molina, D Vittecoq, Y Yazdanpanah, P Yeni; **Germany:** S Esser, G Fätkenheuer, H Gellermann, K Göbels, F D Goebel, H Jäger, A Moll, J K Rockstroh, D Schuster, S Staszewski, A Stoehr; **Italy:** A Antinori, G Carosi, G Di Perri, R Esposito, F Mazzotta, G Pagano, E Raise, S Rusconi, L Sighinolfi, F Suter; **Netherlands:** P H J Frissen, J M Prins, B J A Rijnders; **Poland:** A Horban; **Portugal:** F Antunes, M Miranda, J Vera; **Spain:** P Domingo, G Garcia, J M Gatell, J González-Lahoz, J López-Aldeguer, D Podzamczar; **UK:** P Easterbrook, M Fisher, C Orkin, E Wilkins; **USA:** B Barnett, J Baxter, G Beatty, D Berger, C Borkert, C Cohen, M Conant, J Ernst, C Farthing, T File, M Frank, J E Gallant, A E Greenberg, C Hicks, D T Jayaweera, S Kerkar, N Markowitz, C Martorell, C McDonald, D McMahan, M Mogyoros, R A Myers Jr, G Richmond, K Sathasivam, S Schneider, H Schragar, P Shalit, F P Siegal, L Sloan, K Smith, S Smith, P Tebas, L S Tkatch.