

Results obtained by the statistical reviewer using the snapshot approach and the applicant using the TLOVR algorithm appeared to be similar. The statistical reviewer counted all deaths during the observation period (except for patient 193 in study 206), resulting in more deaths in the reviewer's tables than the number of deaths in the applicant's tables. The remaining patients who discontinued up to and including study day 154 were counted as discontinuations, depending on the applicant's reason. Patients who remained in the study up to the beginning of the Week 24 window (after study day 154) were counted as virologic responders if their Week 24 HIV RNA was <50 copies/mL; otherwise they were counted as virologic failures at Week 24.

**Snapshot Classification at Week 24
Pooled Duet Trials**

All patients who discontinued before Week 24 except deaths were counted as discontinuations

Virologic Response Data Specification, n (%)	Placebo N = 604	TMC125 N = 599
<i>Viral Load < 50 copies/mL at Week 24</i>	243 (40.2)	358 (59.8)
Non-Response Reason:		
Virologic failures at Week 24	318 (52.6)	190 (31.7)
Death¹	15 (2.5)	9 (1.5)
Discontinued due to VF before Week 24	4 (0.7)	2 (0.3)
Discontinuation due to AE	11 (1.8)	28 (4.7)
Discontinuation due to other reasons	13 (2.2)	12 (2.0)

N = number of subjects, n = number of observations, VF = virologic failure

¹All deaths except placebo subject 206-0193

Note: The categories are mutually exclusive; no subject can be counted more than once.

Source: Statistical Reviewer's Analysis

Pooled results from the two DUET trials (C206 and C216) using this approach are shown in the table above. Sixty percent (60%) of the TMC125 subjects compared to only 40% of the placebo subjects had viral loads <50 copies/mL. Approximately 53% of the placebo subjects were virologic failures at Week 24 compared to only 32% of the TMC125 subjects. There were 15 placebo deaths and 9 TMC125 deaths. Less than 1% of the subjects in each treatment group were discontinued due to virologic failure prior to Week 24. Approximately 5% of the TMC125 subjects discontinued due to AEs prior to Week 24 compared to approximately 2% of the placebo subjects. Approximately 2% of the patients in each treatment arm discontinued prior to Week 24 due to other reasons.

Snapshot Classification at Week 24

Pooled Duet Trials

Not Counting Patients who were Never Suppressed below 50 copies/mL by Week 12 as Discontinuations or Deaths

Virologic Response Data Specification, n (%)	Placebo N = 604	TMC125 N = 599
<i>Viral Load < 50 copies/mL at Week 24</i>	243 (40.2)	358 (59.8)
<i>Non-Response Reason:</i>		
Virologic failures	346 (57.3)	201 (33.6)
Never Suppressed below 50 copies/mL by Week 12	285 (47.2)	141 (23.5)
Death¹	4 (0.7)	7 (1.2)
Discontinued due to VF before Week 24	0	0
Discontinuation due to AE	7 (1.2)	26 (4.3)
Discontinuation due to other reasons	4 (0.7)	7 (1.2)

N = number of subjects, n = number of observations, VF = virologic failure

¹All remaining deaths except placebo subject 206-0193

Note: The categories are mutually exclusive; no subject can be counted more than once.

Patients who were never suppressed below 50 copies/mL up to the beginning of the Week 12 window (day 71) were not counted as discontinuations or deaths

Source: Statistical Reviewer's Analysis

The statistical reviewer performed a sensitivity analysis that looked at all patients who were not virologic responders at Week 24 and counted the remaining patients who were never suppressed below 50 copies/mL by Week 12 as virologic failures instead of discontinuations or deaths. This group comprised almost half of the placebo subjects and almost one quarter of the TMC125 subjects. The percentage of subjects who were virologic failures increased from 53% to 57% in the placebo treatment arm and from 32% to 34% in the TMC125 treatment arm. There were only 4 remaining deaths in the placebo arm and 7 remaining deaths in the TMC125 treatment arm and there were no remaining discontinuations who were counted as virologic failures prior to Week 24.

**APPEARS THIS WAY
ON ORIGINAL**

Snapshot Classification at Week 24

Pooled Duet Trials

Not Counting Patients who were Never Suppressed below 50
copies/mL as Discontinuations or Deaths

Virologic Response Data Specification, n (%)	Placebo N = 604	TMC125 N = 599
<i>Viral Load < 50 copies/mL at Week 24</i>	243 (40.2)	358 (59.8)
<i>Non-Response Reason:</i>		
Virologic failures	354 (58.6)	223 (37.2)
Never Suppressed below 50 copies/mL	293 (48.5)	163 (27.2)
Death¹	3 (0.5)	6 (1.0)
Discontinued due to VF before Week 24	0	0
Discontinuation due to AE	2 (0.3)	7 (1.2)
Discontinuation due to other reasons	2 (0.3)	5 (0.8)

N = number of subjects, n = number of observations, VF = virologic failure

¹ All deaths except placebo subject 206-0193

Note: The categories are mutually exclusive; no subject can be counted more than once.

Source: Statistical Reviewer's Analysis

The statistical reviewer performed a sensitivity analysis that looked at all patients who were not virologic responders at Week 24 and counted the remaining patients who were never suppressed below 50 copies/mL as virologic failures instead of discontinuations or deaths. This group comprised almost half of the placebo subjects and a little more than one quarter of the TMC125 subjects. Almost 60% of the placebo subjects and 37% of the TMC125 subjects arm were virologic failures. There were only 3 remaining deaths in the placebo arm and 6 remaining deaths in the TMC125 treatment arm and there were no remaining patients who virologic failures and discontinued prior to Week 24.

**APPEARS THIS WAY
ON ORIGINAL**

Snapshot Classification at Week 24

Pooled Duet Trials

Not Counting Patients who Never had at least a 1 log₁₀ reduction
since baseline as Discontinuations or Deaths

Virologic Response Data Specification, n (%)	Placebo N = 604	TMC125 N = 599
<i>Viral Load < 50 copies/mL at Week 24</i>	243 (40.2)	358 (59.8)
<i>Non-Response Reason:</i>		
Virologic failures	330 (54.6)	212 (35.4)
Never Suppressed below 1 log ₁₀ since baseline	104 (17.2)	38 (6.3)
Death¹	12 (2.0)	8 (1.3)
Discontinued due to VF before Week 24	2 (0.3)	0
Discontinuation due to AE	9 (1.5)	13 (2.2)
Discontinuation due to other reasons	8 (1.3)	8 (1.3)

N = number of subjects, n = number of observations, VF = virologic failure

¹ All deaths except placebo subject 206-0193

Note: The categories are mutually exclusive; no subject can be counted more than once.

Source: Statistical Reviewer's Analysis

The statistical reviewer performed a sensitivity analysis that looked at all patients who were not virologic responders at Week 24 and counted the remaining patients who were never suppressed below 1 log₁₀ since baseline as virologic failures instead of discontinuations or deaths. This group comprised 17% of the placebo subjects and 6% of the TMC125 subjects, while 55% of the placebo subjects and 35% of the TMC125 subjects were counted as virologic failures. There were 12 remaining deaths in the placebo arm and 8 remaining deaths in the TMC125 treatment arm, 2 remaining placebo subjects in the placebo arm and no remaining subjects in the TMC125 treatment arm who virologic failures and discontinued prior to Week 24.

**APPEARS THIS WAY
ON ORIGINAL**

**Ordinal Categorical Responses using
Snapshot Classification at Week 24
Trial TMC125-C206**

Virologic Response Data, n (%)	Placebo N = 308	TMC125 N = 304
<i>Viral Load < 50 copies/mL</i>	121 (39)	176 (58)
<i>50 ≤ Viral Load <400 copies/mL</i>	34 (11)	48 (16)
<i>>400 copies/mL and 1 log₁₀ drop</i>	20 (6)	16 (5)
<i>0.5 to <1 log₁₀ drop</i>	21 (7)	17 (6)
<i><0.5 log₁₀ drop</i>	91 (30)	22 (7)
Discontinued prior to Week 24	21 (7)	25 (8)

N = number of subjects, n = number of observations

Note: The categories are mutually exclusive; no subject can be counted more than once.

Source: Statistical Reviewer's Analysis

**Ordinal Categorical Responses using
Snapshot Classification at Week 24
Trial TMC125-C216**

Virologic Response Data, n (%)	Placebo N = 296	TMC125 N = 295
<i>Viral Load < 50 copies/mL</i>	122 (41)	182 (62)
<i>50 ≤ Viral Load <400 copies/mL</i>	34 (11)	37 (13)
<i>>400 copies/mL and 1 log₁₀ drop</i>	24 (8)	12 (4)
<i>0.5 to <1 log₁₀ drop</i>	19 (6)	8 (3)
<i><0.5 log₁₀ drop</i>	81 (27)	31 (11)
Discontinued prior to Week 24	16 (5)	25 (8)

N = number of subjects, n = number of observations

Note: The categories are mutually exclusive; no subject can be counted more than once.

Source: Statistical Reviewer's Analysis

Approximately 60% of TMC125 subjects had HIV RNA viral loads < 50 copies/mL in both DEUT trials compared to 40% of the placebo subjects, while 11% of the TMC125 subjects had viral loads greater than or equal to 50 but <400 copies/mL compared to 16% of the placebo subjects in study C206 and 13% of the placebo subjects in study C216. The percentage of placebo patients with viral loads exceeding 400 copies/mL was greater than the corresponding percentage of TMC125 subjects, particularly for subjects with less than a 0.5 log₁₀ drop from baseline; approximately 30% of the placebo subjects in study C206 had less than a 0.5 log₁₀ drop from baseline in viral load compared to <10% of TMC125 subjects. Seven percent (7%) of the placebo subjects in study C206, 5% of the placebo subjects in study C216 and 8% of the TMC125 subjects in studies C206 and C216 discontinued from the study prior to Week 24.

3.2 Evaluation of Safety

Adverse Events Summary (Pooled DUET Analysis)

AE Summary, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
<i>Subject years of exposure</i>	171.5	173.1	187.7	184.4	359.5	357.7
Any AE	287 (93.2)	282 (92.8)	272 (91.9)	272 (92.2)	559 (92.5)	554 (92.5)
Any grade 1 or 2 AE	282 (91.6)	277 (91.1)	268 (90.5)	264 (89.5)	550 (91.1)	541 (90.3)
Grade 1 AE	243 (78.9)	251 (82.6)	240 (81.1)	238 (80.7)	483 (80.0)	489 (81.6)
Grade 2 AE	210 (68.2)	189 (62.2)	174 (58.8)	197 (66.8)	384 (63.6)	386 (64.4)
Any grade 3 or 4 AE	85 (27.6)	64 (21.1)	79 (26.7)	84 (28.5)	164 (27.2)	148 (24.7)
Grade 3 AE	78 (25.3)	56 (18.4)	71 (24.0)	73 (24.7)	149 (24.7)	129 (21.5)
Grade 4 AE	29 (9.4)	19 (6.3)	25 (8.4)	24 (8.1)	54 (8.9)	43 (7.2)
Treatment-related AE^a	139 (45.1)	144 (47.4)	119 (40.2)	152 (51.5)	258 (42.7)	296 (49.4)
Death	8 (2.6)	4 (1.3)	7 (2.4)	4 (1.4)	15 (2.5)	8 (1.3)
Death in posttreatment phase	1 (0.3)	1 (0.3)	0	0	1 (0.2)	1 (0.2)
Any SAE	62 (20.1)	35 (11.5)	51 (17.2)	44 (14.9)	113 (18.7)	79 (13.2)
AE leading to permanent stop	16 (5.2)	16 (5.3)	11 (3.7)	19 (6.4)	27 (4.5)	35 (5.8)
AE leading to temporary stop	26 (8.4)	23 (7.6)	19 (6.4)	25 (8.5)	45 (7.5)	48 (8.0)
AEs of interest						
Any skin event of interest	51 (16.6)	78 (25.7)	46 (15.5)	56 (19.0)	97 (16.1)	134 (22.4)
Rash (any type) ^b	30 (9.7)	61 (20.1) ^c	27 (9.1)	41 (13.9)	57 (9.4)	102 (17.0) ^c
Any neuropsychiatric event of interest	94 (30.5)	69 (22.7)	88 (29.7)	83 (28.1)	182 (30.1)	152 (25.4)
Nervous system event of interest	61 (19.8)	46 (15.1)	51 (17.2)	43 (14.6)	112 (18.5)	89 (14.9)
Psychiatric event	42 (13.6)	31 (10.2)	49 (16.6)	46 (15.6)	91 (15.1)	77 (12.9)
Any hepatic event	20 (6.5)	16 (5.3)	11 (3.7)	16 (5.4)	31 (5.1)	32 (5.3)
Any cardiac event	14 (4.5)	15 (4.9)	18 (6.1)	20 (6.8)	32 (5.3)	35 (5.8)
Coronary artery disorder	1 (0.3)	3 (1.0)	5 (1.7)	5 (1.7)	6 (1.0)	8 (1.3)
Any pancreatic event	12 (3.9)	11 (3.6)	9 (3.0)	9 (3.1)	21 (3.5)	20 (3.3)
Any bleeding event	12 (3.9)	11 (3.6)	16 (5.4)	12 (4.1)	28 (4.6)	23 (3.8)

N = number of subjects, n = number of subjects with observations

^a AEs assessed by the investigator as possible, probable or very likely related to the investigational medication.

^b Grouped term: combining all rash-related events, refer to Section 3.1.1.6.1 for details on grouped term.

^c Incidence includes rash AEs emerging or deteriorating in the follow-up phase of the trial, see Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Add-Anal2/Display SAF.18.

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.1, Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE /Display SAF.12 (only lists AEs during the treatment period), Module 5.3.5.1/TMC125-C206 and Module 5.3.5.1/TMC125-C216.

Source: Table 19, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

At the time of the cut-off of the analyses (12 January 2007), the same percentage of patients had at least one AE (92.5%) in placebo and TMC125 treatment groups. Compared to placebo patients, there were a somewhat larger percentage of TMC125 patients with treatment-related AEs and a lower percentage of TMC125 patients who died in the post-treatment phase and with any SAE. Compared to placebo, there were more TMC125 patients with rashes.

**Adverse Events in at Least 5% of Subjects in the TMC125 Group
(Pooled DUET Analysis)**

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
Any AE	287 (93.2)	282 (92.8)	272 (91.9)	272 (92.2)	559 (92.5)	554 (92.5)
Infections and infestations	185 (60.1)	167 (54.9)	151 (51.0)	161 (54.6)	336 (55.6)	328 (54.8)
Nasopharyngitis	21 (6.8)	22 (7.2)	24 (8.1)	26 (8.8)	45 (7.5)	48 (8.0)
Herpes simplex	22 (7.1)	30 (9.9)	18 (6.1)	17 (5.8)	40 (6.6)	47 (7.8)
Oral candidiasis	15 (4.9)	16 (5.3)	15 (5.1)	20 (6.8)	30 (5.0)	36 (6.0)
Bronchitis	14 (4.5)	10 (3.3)	13 (4.4)	25 (8.5)	27 (4.5)	35 (5.8)
Gastrointestinal disorders	142 (46.1)	125 (41.1)	126 (42.6)	139 (47.1)	268 (44.4)	264 (44.1)
Diarrhea	63 (20.5)	36 (11.8)	60 (20.3)	54 (18.3)	123 (20.4)	90 (15.0)
Nausea	38 (12.3)	42 (13.8)	29 (9.8)	41 (13.9)	67 (11.1)	83 (13.9)
Vomiting	17 (5.5)	15 (4.9)	16 (5.4)	26 (8.8)	33 (5.5)	41 (6.8)
General disorders and administration site conditions	111 (36.0)	94 (30.9)	136 (45.9)	122 (41.4)	247 (40.9)	216 (36.1)
Injection site reaction	22 (7.1)	20 (6.6)	44 (14.9)	38 (12.9)	66 (10.9)	58 (9.7)
Fatigue	20 (6.5)	16 (5.3)	31 (10.5)	26 (8.8)	51 (8.4)	42 (7.0)
Injection site nodule	23 (7.5)	26 (8.6)	17 (5.7)	15 (5.1)	40 (6.6)	41 (6.8)
Pyrexia	26 (8.4)	14 (4.6)	28 (9.5)	21 (7.1)	54 (8.9)	35 (5.8)
Skin and subcutaneous tissue disorders	82 (26.6)	106 (34.9)	86 (29.1)	85 (28.8)	168 (27.8)	191 (31.9)
Rash ^a	18 (5.8)	35 (11.5)	15 (5.1)	25 (8.5)	33 (5.5)	60 (10.0)
Nervous system disorders	82 (26.6)	77 (25.3)	82 (27.7)	75 (25.4)	164 (27.2)	152 (25.4)
Headache	40 (13.0)	29 (9.5)	34 (11.5)	27 (9.2)	74 (12.3)	56 (9.3)
Musculoskeletal and connective tissue disorders	70 (22.7)	57 (18.8)	65 (22.0)	67 (22.7)	135 (22.4)	124 (20.7)
Investigations	62 (20.1)	50 (16.4)	71 (24.0)	58 (19.7)	133 (22.0)	108 (18.0)
Respiratory, thoracic and mediastinal disorders	36 (11.7)	47 (15.5)	56 (18.9)	56 (19.0)	92 (15.2)	103 (17.2)
Cough	11 (3.6)	17 (5.6)	24 (8.1)	22 (7.5)	35 (5.8)	39 (6.5)
Metabolism and nutrition disorders	39 (12.7)	46 (15.1)	42 (14.2)	48 (16.3)	81 (13.4)	94 (15.7)
Psychiatric disorders	42 (13.6)	31 (10.2)	50 (16.9)	47 (15.9)	92 (15.2)	78 (13.0)
Insomnia	17 (5.5)	13 (4.3)	23 (7.8)	20 (6.8)	40 (6.6)	33 (5.5)
Blood and lymphatic system disorders	46 (14.9)	34 (11.2)	37 (12.5)	35 (11.9)	83 (13.7)	69 (11.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (4.2)	15 (4.9)	22 (7.4)	30 (10.2)	35 (5.8)	45 (7.5)
Renal and urinary disorders	30 (9.7)	22 (7.2)	24 (8.1)	23 (7.8)	54 (8.9)	45 (7.5)
Eye disorders	18 (5.8)	12 (3.9)	17 (5.7)	26 (8.8)	35 (5.8)	38 (6.3)
Injury, poisoning and procedural complications	22 (7.1)	11 (3.6)	23 (7.8)	25 (8.5)	45 (7.5)	36 (6.0)
Vascular disorders	21 (6.8)	18 (5.9)	16 (5.4)	14 (4.7)	37 (6.1)	32 (5.3)

N = number of subjects. n = number of subjects with observations

^a Individual preferred term: refer to Section 3.1.1.6.1 for details on grouped term.

Source: Module 5.3.5.3 TMC125-C909-SCS-PhIb-III-Main-Anal-AE/Display SAF.1, Module 5.3.5.3 TMC125-C909-SCS-PhIb-III-Main-Anal-AE/Display SAF.2, Module 5.3.5.1 TMC125-C206 and Module 5.3.5.1 TMC125-C216

Source: Table 20, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

Compared to placebo, there were nearly twice as many TMC125 subjects with rash (10% of TMC125 subjects vs. only 5.5% of placebo subjects) and fewer TMC125 subjects with

pyrexia (6% of the TMC125 subjects compared to 9% of placebo subjects) and headaches (9% of TMC125 subjects compared to 12% of placebo subjects).

Adverse Events at Least Possibly Related to TMC125/Placebo in at Least 2% of Subjects in the TMC125 Group (Pooled DUET Analysis)

System Organ Class Preferred Term, n (%)	DUET 1		DUET 2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
Any AE at least possibly related^a	139 (45.1)	144 (47.4)	119 (40.2)	152 (51.5)	258 (42.7)	296 (49.4)
Gastrointestinal disorders	59 (19.2)	57 (18.8)	47 (15.9)	67 (22.7)	106 (17.5)	124 (20.7)
Nausea	14 (4.5)	31 (10.2)	16 (5.4)	28 (9.5)	30 (5.0)	59 (9.8)
Diarrhea	26 (8.4)	13 (4.3)	21 (7.1)	29 (9.8)	47 (7.8)	42 (7.0)
Vomiting	2 (0.6)	7 (2.3)	6 (2.0)	11 (3.7)	8 (1.3)	18 (3.0)
Flatulence	10 (3.2)	5 (1.6)	5 (1.7)	9 (3.1)	15 (2.5)	14 (2.3)
Skin and subcutaneous tissue disorders	31 (10.1)	60 (19.7)	30 (10.1)	43 (14.6)	61 (10.1)	103 (17.2)
Rash ^b	9 (2.9)	28 (9.2)	5 (1.7)	17 (5.8)	14 (2.3)	45 (7.5)
Nervous system disorders	43 (14.0)	36 (11.8)	30 (10.1)	27 (9.2)	73 (12.1)	63 (10.5)
Headache	21 (6.8)	15 (4.9)	18 (6.1)	15 (5.1)	39 (6.5)	30 (5.0)
Investigations	21 (6.8)	22 (7.2)	22 (7.4)	27 (9.2)	43 (7.1)	49 (8.2)
General disorders and administration site conditions	18 (5.8)	13 (4.3)	25 (8.4)	26 (8.8)	43 (7.1)	39 (6.5)
Fatigue	9 (2.9)	8 (2.6)	16 (5.4)	13 (4.4)	25 (4.1)	21 (3.5)
Metabolism and nutrition disorders	15 (4.9)	20 (6.6)	12 (4.1)	18 (6.1)	27 (4.5)	38 (6.3)
Psychiatric disorders	11 (3.6)	6 (2.0)	16 (5.4)	14 (4.7)	27 (4.5)	20 (3.3)
Musculoskeletal and connective tissue disorders	10 (3.2)	2 (0.7)	8 (2.7)	10 (3.4)	18 (3.0)	12 (2.0)

N = number of subjects, n = number of subjects with observations

^a AEs assessed by the investigator as possible, probable or very likely related to the investigational medication.

^b Individual preferred term; refer to Section 3.1.1.6.1 for details on grouped term.

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.1, Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.5, Module 5.3.5.1/TMC125-C206 and Module 5.3.5.1/TMC125-C216

Source: Table 21, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

Compared to the placebo treatment group, there were more than 3 times as many TMC125 subjects with rashes that were thought to be possibly related to TMC125. Compared to placebo patients, there were also more TMC125 patients with treatment-related nausea and vomiting.

Adverse Events of Severity Grade 2 or More at Least Possibly Related to TMC125/Placebo in at Least 2% of Subjects in the TMC125 Group (Pooled DUET Analysis)

System Organ Class Preferred Term, n (%)	DUET 1		DUET 2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
Any AE with grade 2 or more and at least possibly related^a	86 (27.9)	86 (28.3)	62 (20.9)	94 (31.9)	148 (24.5)	180 (30.1)
Skin and subcutaneous tissue disorders	13 (4.2)	32 (10.5)	13 (4.4)	21 (7.1)	26 (4.3)	53 (8.8)
Rash ^b	3 (1.0)	17 (5.6)	3 (1.0)	12 (4.1)	6 (1.0)	29 (4.8)
Gastrointestinal disorders	28 (9.1)	19 (6.3)	15 (5.1)	26 (8.8)	43 (7.1)	45 (7.5)
Nausea	5 (1.6)	7 (2.3)	3 (1.0)	12 (4.1)	8 (1.3)	19 (3.2)
Diarrhea	12 (3.9)	4 (1.3)	7 (2.4)	12 (4.1)	19 (3.1)	16 (2.7)
Investigations	17 (5.5)	16 (5.3)	19 (6.4)	19 (6.4)	36 (6.0)	35 (5.8)
Metabolism and nutrition disorders	6 (1.9)	15 (4.9)	5 (1.7)	13 (4.4)	11 (1.8)	28 (4.7)
Nervous system disorders	20 (6.5)	15 (4.9)	6 (2.0)	12 (4.1)	26 (4.3)	27 (4.5)
General disorders and administration site conditions	9 (2.9)	5 (1.6)	10 (3.4)	13 (4.4)	19 (3.1)	18 (3.0)

N = number of subjects, n = number of subjects with observations

^a AEs with grade 2, 3 or 4, assessed by the investigator as possible, probable or very likely related to the investigational medication.

^b Individual preferred term; refer to Section 3.1.1.6.1 for details on grouped term.

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.1, Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.6, Module 5.3.5.1/TMC125-C206 and Module 5.3.5.1/TMC125-C216

Source: Table 22, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

Compared to placebo patients, there were a somewhat larger percentage of TMC125 patients with treatment-related AEs of at least grade 2 or more, including skin and subcutaneous tissue disorders (rash) and metabolism and nutrition disorders. Compared to the placebo treatment group, there were more than almost 5 times as many TMC125 subjects with rashes of grade 2 or more that were thought to be possibly related to TMC125.

Grade 3 or 4 Adverse Events in at Least 0.5% of Subjects in the TMC125 Group (Pooled DUET Analysis)

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
Any grade 3 or 4 AE	85 (27.6)	64 (21.1)	79 (26.7)	84 (28.5)	164 (27.2)	148 (24.7)
Investigations*	31 (10.1)	19 (6.3)	27 (9.1)	21 (7.1)	58 (9.6)	40 (6.7)
Infections and infestations	26 (8.4)	18 (5.9)	24 (8.1)	17 (5.8)	50 (8.3)	35 (5.8)
<i>Pneumocystis jiroveci pneumonia</i>	1 (0.3)	2 (0.7)	3 (1.0)	2 (0.7)	4 (0.7)	4 (0.7)
<i>Pneumonia</i>	1 (0.3)	3 (1.0)	3 (1.0)	0	4 (0.7)	3 (0.5)
Metabolism and nutrition disorders	9 (2.9)	13 (4.3)	9 (3.0)	15 (5.1)	18 (3.0)	28 (4.7)
<i>Hypertriglyceridemia</i>	2 (0.6)	4 (1.3)	2 (0.7)	7 (2.4)	4 (0.7)	11 (1.8)
<i>Hypercholesterolemia</i>	2 (0.6)	2 (0.7)	2 (0.7)	2 (0.7)	4 (0.7)	4 (0.7)
<i>Diabetes mellitus</i>	0	3 (1.0)	0	0	0	3 (0.5)
Blood and lymphatic system disorders	18 (5.8)	8 (2.6)	12 (4.1)	12 (4.1)	30 (5.0)	20 (3.3)
<i>Neutropenia</i>	11 (3.6)	5 (1.6)	7 (2.4)	4 (1.4)	18 (3.0)	9 (1.5)
<i>Anemia</i>	4 (1.3)	3 (1.0)	2 (0.7)	4 (1.4)	6 (1.0)	7 (1.2)
<i>Thrombocytopenia</i>	2 (0.6)	1 (0.3)	1 (0.3)	4 (1.4)	3 (0.5)	5 (0.8)
General disorders & administration site conditions	10 (3.2)	2 (0.7)	11 (3.7)	13 (4.4)	21 (3.5)	15 (2.5)
<i>Injection site reaction</i>	1 (0.3)	0	3 (1.0)	4 (1.4)	4 (0.7)	4 (0.7)
<i>Pyrexia</i>	4 (1.3)	0	4 (1.4)	3 (1.0)	8 (1.3)	3 (0.5)

Continued

Source: Table 23, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

Compared to placebo, there were a somewhat lower percentage of TMC125 subjects with any grade 3 or 4 AE, including investigations, blood and lymphatic system disorders, general disorders & administrations site conditions, and gastrointestinal disorders.

The percentage of TMC125 subjects with grade 3 or 4 metabolism and nutrition disorders (including hypertriglyceridemia and diabetes mellitus) and nervous system disorders was only somewhat higher than placebo; 4.7% of TNC125 subjects reported grade 3 or 4 metabolism and nutrition disorders compared to 3.0% of placebo subjects.

Grade 3 or 4 Adverse Events in at Least 0.5% of Subjects in the TMC125 Group (Pooled DUET Analysis), Cont'd

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
Gastrointestinal disorders	9 (2.9)	7 (2.3)	10 (3.4)	7 (2.4)	19 (3.1)	14 (2.3)
Pancreatitis	0	2 (0.7)	0	2 (0.7)	0	4 (0.7)
Nausea	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.3)	3 (0.5)
Nervous system disorders	10 (3.2)	8 (2.6)	1 (0.3)	5 (1.7)	11 (1.8)	13 (2.2)
Neuropathy peripheral	0	4 (1.3)	0	2 (0.7)	0	6 (1.0)
Cardiac disorders	2 (0.6)	4 (1.3)	6 (2.0)	6 (2.0)	8 (1.3)	10 (1.7)
Acute myocardial infarction	0	2 (0.7)	0	1 (0.3)	0	3 (0.5)
Myocardial infarction	0	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.2)	3 (0.5)
Renal and urinary disorders	5 (1.6)	7 (2.3)	3 (1.0)	2 (0.7)	8 (1.3)	9 (1.5)
Renal failure	0	3 (1.0)	2 (0.7)	1 (0.3)	2 (0.3)	4 (0.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	4 (1.3)	5 (1.7)	4 (1.4)	8 (1.3)	8 (1.3)
Skin and subcutaneous tissue disorders	1 (0.3)	3 (1.0)	2 (0.7)	5 (1.7)	3 (0.5)	8 (1.3)
Rash ^b	0	2 (0.7)	0	4 (1.4)	0	6 (1.0)
Respiratory, thoracic and mediastinal disorders	2 (0.6)	3 (1.0)	5 (1.7)	4 (1.4)	7 (1.2)	7 (1.2)
Musculoskeletal and connective tissue disorders	4 (1.3)	2 (0.7)	4 (1.4)	3 (1.0)	8 (1.3)	5 (0.8)
Vascular disorders	4 (1.3)	2 (0.7)	1 (0.3)	2 (0.7)	5 (0.8)	4 (0.7)
Hepatobiliary disorders	3 (1.0)	0	2 (0.7)	3 (1.0)	5 (0.8)	3 (0.5)
Surgical and medical procedures	0	0	1 (0.3)	3 (1.0)	1 (0.2)	3 (0.5)

N = number of subjects, n = number of subjects with observations.

^a This table does not contain AEs from the SOC of investigations; however, AEs in other SOCs with a laboratory component are included (e.g. anemia). Refer to Section 3.1.2.3 for laboratory-related AEs.

^b Individual preferred term; refer to Section 3.1.1.6.1 for details on grouped term.

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.4, Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.1, Module 5.3.5.1/TMC125-C206 and Module 5.3.5.1/TMC125-C216

Source: Table 23, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

One percent (1%, n=6) of TMC125 subjects reported grade 3 rashes. None of the placebo patients reported such rashes.

Triglyceride Values (mmol/L) for Pooled Data from TMC125 Duet Trials

Week	Treatment Group	N	Mean	Mean Change from Baseline	Standard Error of Change from Baseline
0	Placebo	604	3.3	0	0
	TMC125	599	3.5	0	0
2	Placebo	599	2.5	-0.83	0.09
	TMC125	591	2.8	-0.80	0.12
4	Placebo	609	2.5	-0.79	0.09
	TMC125	591	2.7	-0.82	0.12
8	Placebo	597	2.5	-0.78	0.10
	TMC125	583	2.9	-0.67	0.13
12	Placebo	583	2.5	-0.75	0.11
	TMC125	565	3.0	-0.59	0.15
16	Placebo	580	2.6	-0.75	0.10
	TMC125	565	3.1	-0.51	0.16
20	Placebo	577	2.7	-0.69	0.11
	TMC125	549	3.1	-0.51	0.14
24	Placebo	583	2.6	-0.74	0.10
	TMC125	571	3.1	-0.51	0.15
32	Placebo	246	2.7	-0.30	0.17
	TMC125	255	3.3	-0.03	0.25

Source: Statistical Reviewer's Analysis

Since Grade 3 hypertriglyceridemia appeared to be more prevalent among TMC125 subjects, laboratory datasets were used to compare change from baseline for all available triglyceride values.

After 24 weeks, mean triglyceride levels declined by 0.7 mmol/L from baseline to 2.6 mmol/L in the placebo treatment group and by 0.5 mmol/L from baseline to 3.1 mmol/L in the TMC125 treatment group. At week 32, when less than half the randomized subjects remained, mean triglycerides declined by 0.3 mmol/L from baseline in the placebo treatment group to 2.7 mmol/L and remained almost the same as baseline levels in the TMC125 treatment group.

Calculated LDL Values (mg/dL) for Pooled Data from TMC125 Duet Trials					
Week	Treatment Group	N	Mean	Mean Change from Baseline	Standard Error of Change from Baseline
0	Placebo	531	92.3	0	0
	TMC125	520	92.5	0	0
2	Placebo	494	98.3	+6.3	0.026
	TMC125	473	99.2	+6.5	0.027
4	Placebo	509	100.1	+7.2	0.029
	TMC125	470	102.8	+8.9	0.033
8	Placebo	489	101.3	+8.5	0.032
	TMC125	460	105.6	+11.3	0.035
12	Placebo	472	102.4	+9.3	0.033
	TMC125	441	106.6	+13.4	0.038
16	Placebo	469	104.9	+11.0	0.037
	TMC125	446	107.0	+13.7	0.037
20	Placebo	462	103.8	+9.8	0.036
	TMC125	423	108.3	+14.3	0.040
24	Placebo	474	103.8	+10.6	0.036
	TMC125	441	108.3	+13.9	0.037
32	Placebo	203	110.7	+9.2	0.056
	TMC125	202	116.7	+17.9	0.061

Source: Statistical Reviewer's Analysis

Laboratory datasets were used to compare change from baseline for all available calculated low density lipoprotein (LDL) values.

After 24 weeks, mean calculated LDL levels increased from baseline by 11 mg/dL to 104 mg/dL in the placebo treatment group and by 14 mg/dL to 108 mg/dL in the TMC125 treatment group. At week 32, when less than half the randomized subjects remained, mean calculated LDL levels increased by 9 mg/dL in the placebo treatment group to 111 mg/dL and increased by 18 mg/dL in the TMC125 treatment group to 117 mg/dL.

Number of patients using new Lipid Lowering Agents in the Treatment and Follow-up Phases of the TMC125 Duet Trials

Treatment Group	Number	%	p-value¹
Placebo	78/604	12.9	
TMC125	99 / 599	16.5	0.09

¹ Fisher's Exact Test comparing placebo and TMC125 treatment groups
Source: Statistical Reviewer's Analysis

Thirteen percent (13%) of the 604 placebo subjects and 16.5% of the 599 TMC125 subjects used new lipid lowering agents after randomization during the treatment and follow-up phases of the two TMC125 Duet Trials. The difference was not statistically significant but the p-value was small enough to be indicative of a possible trend.

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Number of patients with increases from baseline in calculated LDL exceeding 10 mg/dL in the TMC125 Duet Trials

Week	Treatment Group	Number	%	p-value ¹
2	Placebo	202 / 494	40.9	0.36
	TMC125	208 / 473	44.0	
4	Placebo	223 / 509	43.8	0.34
	TMC125	221 / 470	47.0	
8	Placebo	222 / 489	45.4	0.60
	TMC125	217 / 460	47.2	
12	Placebo	210 / 472	44.5	0.06
	TMC125	224 / 441	50.8	
16	Placebo	230 / 469	49.0	0.11
	TMC125	243 / 446	54.5	
20	Placebo	214 / 462	46.3	0.002
	TMC125	241 / 423	57.0	
24	Placebo	228 / 474	48.1	0.02
	TMC125	246 / 441	55.8	
32	Placebo	96 / 203	47.3	0.01
	TMC125	122 / 202	60.4	

¹ Fisher's Exact Test comparing placebo and TMC125 treatment groups
Source: Statistical Reviewer's Analysis

After 24 weeks, the proportion of patients with increases in calculated LDL levels from baseline exceeding 10 mg/dL was 48% in the placebo treatment group and 56% in the TMC125 treatment group. This difference was statistically significant (p=0.02).

Statistically significant differences between TMC125 and placebo were also observed at Week 20 and 32 with non-significant statistical trends favoring placebo at Weeks 12 and 16.

Number of patients with increases from baseline in calculated LDL exceeding 10 mg/dL at last visit up to and including Week 24 prior to first new lipid lowering agent in the TMC125 Duet Trials

Treatment Group	Number	%	p-value ¹
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Placebo	248 / 502	49.4	
TMC125	266 / 479	55.5	0.06

¹ Fisher's Exact Test comparing placebo and TMC125 treatment groups
Source: Statistical Reviewer's Analysis

An additional analysis used the last calculated LDL value up to and including Week 24 but prior to use of any new lipid lowering agents. In this analysis, the proportion of patients with increases in calculated LDL levels from baseline exceeding 10 mg/dL was 49% in the placebo treatment group and 56% in the TMC125 treatment group. These results were quite similar to the Week 24 results in the previous table except they were not quite statistically significant (p=0.06).

Number and % of patients using new Lipid Lowering Agents in the Treatment or Follow-up Phases of the TMC125 Duet Trials by treatment group and increase in LDL

Treatment Group	Δ LDL ¹ >10 mg/dL	N	%
Placebo	No	12 / 254	4.7
	Yes	18 / 248	7.3
TMC125	No	14 / 213	6.6
	Yes	26 / 266	9.8

¹ Changes in LDL from Baseline exceeded 10 mg/dL at last visit up to and including Week 24 prior to first new Lipid Lowering Agent
Source: Statistical Reviewer's Analysis

The percentage of patients using new Lipid Lowering Agents in post-randomization phases of the two Duet Trials was higher for patients with more than a 10 mg/dL increase in calculated LDL (from baseline up to the last visit through Week 24) than for patients with a 10 mg/dL or lower increase and greater for TMC125 patients than for placebo patients.

**Adverse Events Reported in the Treatment Phase and Leading to Death
(Pooled DUET Analysis)**

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
Any AE leading to death	8 (2.6)	4 (1.3)	7 (2.4)	4 (1.4)	15 (2.5)	8 (1.3)
Infections and infestations	5 (1.6)	2 (0.7)	3 (1.0)	3 (1.0)	8 (1.3)	5 (0.8)
Central line infection ^g	0	1 (0.3)	0	0	0	1 (0.2)
HIV wasting syndrome	0	0	0	1 (0.3)	0	1 (0.2)
Acquired immunodeficiency syndrome	1 (0.3)	0	0	0	1 (0.2)	0
<i>Mycobacterium avium</i> complex infection ^g	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Progressive multifocal leukoencephalopathy	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Respiratory tract infection ^h	0	1 (0.3)	0	0	0	1 (0.2)
Septic shock ^g	0	1 (0.3)	0	0	0	1 (0.2)
Bacterial sepsis	0	0	1 (0.3)	0	1 (0.2)	0
Esophageal candidiasis ^a	1 (0.3)	0	0	0	1 (0.2)	0
<i>Pneumocystis jirovecii</i> pneumonia	1 (0.3)	0	0	0	1 (0.2)	0
Pneumonia ^{a, f}	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0
Sepsis ^{d, f}	0	0	2 (0.7)	0	2 (0.3)	0
Cardiac disorders	1 (0.3)	2 (0.7)	0	1 (0.3)	1 (0.2)	3 (0.5)
Cardiac failure congestive ^e	0	1 (0.3)	0	0	0	1 (0.2)
Cardiogenic shock	0	1 (0.3)	0	0	0	1 (0.2)
Myocardial infarction	0	0	0	1 (0.3)	0	1 (0.2)
Cardiac arrest ^e	1 (0.3)	0	0	0	1 (0.2)	0
General disorders and administration site conditions	1 (0.3)	1 (0.3)	0	0	1 (0.2)	1 (0.2)
Sudden death	0	1 (0.3)	0	0	0	1 (0.2)
Multi-organ failure ^b	1 (0.3)	0	0	0	1 (0.2)	0
Pyrexia ^b	1 (0.3)	0	0	0	1 (0.2)	0

Continued

Source: Table 24, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

At the time of the cut-off of the analyses (12 January 2007), there were 15 patients in the placebo group and 8 patients in the TMC125 treatment group who had AEs reported in the treatment phase and leading to death. More than half of these deaths were infections and infestations.

**Adverse Events Reported in the Treatment Phase and Leading to Death
(Pooled DUET Analysis), Cont'd**

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
Renal and urinary disorders	1 (0.3)	1 (0.3)	0	0	1 (0.2)	1 (0.2)
Renal impairment ^d	0	1 (0.3)	0	0	0	1 (0.2)
Renal failure acute	1 (0.3)	0	0	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)	2 (0.7)	0	2 (0.3)	1 (0.2)
Respiratory failure ^b	0	1 (0.3)	0	0	0	1 (0.2)
Dyspnea ^c	0	0	1 (0.3)	0	1 (0.2)	0
Hemoptysis ^c	0	0	1 (0.3)	0	1 (0.2)	0
Lung infiltration ^c	0	0	1 (0.3)	0	1 (0.2)	0
Pulmonary hemorrhage	0	0	1 (0.3)	0	1 (0.2)	0
Blood and lymphatic system disorders	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0
Anemia ^c	0	0	1 (0.3)	0	1 (0.2)	0
Lymphadenopathy ^b	1 (0.3)	0	0	0	1 (0.2)	0
Neutropenia ^b	1 (0.3)	0	0	0	1 (0.2)	0
Gastrointestinal disorders	0	0	1 (0.3)	0	1 (0.2)	0
Intestinal perforation ^d	0	0	1 (0.3)	0	1 (0.2)	0
Musculoskeletal and connective tissue disorders	1 (0.3)	0	0	0	1 (0.2)	0
Back pain ^b	1 (0.3)	0	0	0	1 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0	2 (0.7)	0	3 (0.5)	0
Central nervous system lymphoma	0	0	1 (0.3)	0	1 (0.2)	0
Malignant neoplasm progression	0	0	1 (0.3)	0	1 (0.2)	0
Non-hodgkin's lymphoma ^b	1 (0.3)	0	0	0	1 (0.2)	0
Vascular disorders	1 (0.3)	0	0	0	1 (0.2)	0
Shock ^c	1 (0.3)	0	0	0	1 (0.2)	0

N = number of subjects, n = number of subjects with observations

a, b, c, d, e, f, g, h subject having 2 or more events with fatal outcome. These subjects are, for placebo: ^aTMC125-C206-0103, ^bTMC125-C206-0156, ^cTMC125-C206-0646, ^dTMC125-C216-0490, ^eTMC125-C216-0584, ^fTMC125-C216-0730; and for TMC125: ^gTMC125-C206-0424, ^hTMC125-C206-0569.

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.1, Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.3, Module 5.3.5.1/TMC125-C206 and Module 5.3.5.1/TMC125-C216

Source: Table 24, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

**Serious Adverse Events in at Least 0.5% of the Subjects in the TMC125 Group
(Pooled DUET Analysis)**

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 = (3-55)	30.0 (1-60)
Any SAE	62 (20.1)	35 (11.5)	51 (17.2)	44 (14.9)	113 (18.7)	79 (13.2)
Infections and infestations	27 (8.8)	13 (4.3)	26 (8.8)	18 (6.1)	53 (8.8)	31 (5.2)
Pneumonia	3 (1.0)	3 (1.0)	6 (2.0)	2 (0.7)	9 (1.5)	5 (0.8)
<i>Pneumocystis jirovecii</i> pneumonia	1 (0.3)	2 (0.7)	4 (1.4)	2 (0.7)	5 (0.8)	4 (0.7)
Cellulitis	3 (1.0)	2 (0.7)	1 (0.3)	1 (0.3)	4 (0.7)	3 (0.5)
Cardiac disorders	3 (1.0)	5 (1.6)	5 (1.7)	6 (2.0)	8 (1.3)	11 (1.8)
Acute myocardial infarction	0	2 (0.7)	0	1 (0.3)	0	3 (0.5)
Myocardial infarction	0	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.2)	3 (0.5)
Blood and lymphatic system disorders	7 (2.3)	5 (1.6)	6 (2.0)	5 (1.7)	13 (2.2)	10 (1.7)
Anemia	2 (0.6)	3 (1.0)	4 (1.4)	2 (0.7)	6 (1.0)	5 (0.8)
General disorders and administration site conditions	7 (2.3)	4 (1.3)	5 (1.7)	5 (1.7)	12 (2.0)	9 (1.5)
Pyrexia	6 (1.9)	3 (1.0)	4 (1.4)	4 (1.4)	10 (1.7)	7 (1.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.0)	5 (1.6)	4 (1.4)	4 (1.4)	7 (1.2)	9 (1.5)
Nervous system disorders	8 (2.6)	7 (2.3)	1 (0.3)	1 (0.3)	9 (1.5)	8 (1.3)
Investigations	5 (1.6)	5 (1.6)	3 (1.0)	2 (0.7)	8 (1.3)	7 (1.2)
Gastrointestinal disorders	9 (2.9)	0	11 (3.7)	6 (2.0)	20 (3.3)	6 (1.0)
Respiratory, thoracic and mediastinal disorders	4 (1.3)	2 (0.7)	5 (1.7)	4 (1.4)	9 (1.5)	6 (1.0)
Metabolism and nutrition disorders	7 (2.3)	3 (1.0)	4 (1.4)	2 (0.7)	11 (1.8)	5 (0.8)
Renal and urinary disorders	5 (1.6)	3 (1.0)	3 (1.0)	2 (0.7)	8 (1.3)	5 (0.8)
Surgical and medical procedures	2 (0.6)	0	1 (0.3)	5 (1.7)	3 (0.5)	5 (0.8)
Injury, poisoning and procedural complications	3 (1.0)	0	1 (0.3)	3 (1.0)	4 (0.7)	3 (0.5)

N = number of subjects, n = number of subjects with observations

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.1, Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.3, Module 5.3.5.1/TMC125-C206 and Module 5.3.5.1/TMC125-C216

Source: Table 25, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

Nineteen percent (19%) of the placebo subjects and 13% of TMC125 subjects had at least one serious AE (SAE), where the majority of these SAEs were infections and infestations like pneumonia.

Serious Adverse Events at Least Possibly Related to Investigational Medication (TMC125/Placebo) (Pooled DUET Analysis)

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
Treatment-related SAE^a	8 (2.6%)	9 (3.0%)	7 (2.4%)	5 (1.7%)	15 (2.5%)	14 (2.3%)
Cardiac disorders	0	2 (0.7)	0	2 (0.7)	0	4 (0.7)
Acute myocardial infarction	0	2 (0.7)	0	1 (0.3)	0	3 (0.5)
Atrial fibrillation	0	0	0	1 (0.3)	0	1 (0.2)
Nervous system disorders	1 (0.3)	3 (1.0)	0	0	1 (0.2)	3 (0.5)
Convulsion	0	1 (0.3)	0	0	0	1 (0.2)
Dizziness	0	1 (0.3)	0	0	0	1 (0.2)
Partial seizures	0	1 (0.3)	0	0	0	1 (0.2)
Headache	1 (0.3)	0	0	0	1 (0.2)	0
Hepatobiliary disorders	1 (0.3)	0	2 (0.7)	2 (0.7)	3 (0.5)	2 (0.3)
Cytolytic hepatitis	0	0	0	1 (0.3)	0	1 (0.2)
Hepatitis	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.2)
Hepatic cirrhosis	0	0	1 (0.3)	0	1 (0.2)	0
Immune system disorders	1 (0.3)	2 (0.7)	0	0	1 (0.2)	2 (0.3)
Drug hypersensitivity	0	1 (0.3)	0	0	0	1 (0.2)
Immune reconstitution syndrome	1 (0.3)	1 (0.3)	0	0	1 (0.2)	1 (0.2)
Investigations^b	2 (0.6)	2 (0.7)	0	0	2 (0.3)	2 (0.3)
Gastrointestinal disorders	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Pancreatitis	0	0	0	1 (0.3)	0	1 (0.2)
Diarrhea	1 (0.3)	0	0	0	1 (0.2)	0
General disorders and administration site conditions	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Pyrexia	1 (0.3)	0	0	1 (0.3)	1 (0.2)	1 (0.2)
Fatigue	1 (0.3)	0	0	0	1 (0.2)	0
Metabolism and nutrition disorders	0	1 (0.3)	0	0	0	1 (0.2)
Diabetes mellitus	0	1 (0.3)	0	0	0	1 (0.2)
Skin and subcutaneous tissue disorders	0	1 (0.3)	0	0	0	1 (0.2)
Rash ^c	0	1 (0.3)	0	0	0	1 (0.2)
Surgical and medical procedures	0	0	0	1 (0.3)	0	1 (0.2)
Coronary angioplasty	0	0	0	1 (0.3)	0	1 (0.2)
Vascular disorders	0	1 (0.3)	1 (0.3)	0	1 (0.2)	1 (0.2)
Hypotension	0	1 (0.3)	0	0	0	1 (0.2)
Vaculitis	0	0	1 (0.3)	0	1 (0.2)	0
Blood and lymphatic system disorders	2 (0.6)	0	1 (0.3)	0	3 (0.5)	0
Pancytopenia	0	0	1 (0.3)	0	1 (0.2)	0
Thrombocytopenia	2 (0.6)	0	0	0	2 (0.3)	0
Infections and infestations	0	0	1 (0.3)	0	1 (0.2)	0
Cytomegalovirus chorioretinitis	0	0	1 (0.3)	0	1 (0.2)	0
Psychiatric disorders	0	0	1 (0.3)	0	1 (0.2)	0
Disorientation	0	0	1 (0.3)	0	1 (0.2)	0

Continued

Source: Table 26, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

Approximately 2.5% of the subjects in each treatment group had SAEs that were at least possibly related to investigational medication. Less than 1% (n=4) of the TMC125

subjects and no placebo subjects had cardiac disorders while 0.5% (n=3) of the placebo subjects and no TMC125 subjects had blood and lymphatic system disorders.

Serious Adverse Events at Least Possibly Related to Investigational Medication (TMC125/Placebo) (Pooled DUET Analysis), Cont'd

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
Renal and urinary disorders	1 (0.3)	0	0	0	1 (0.2)	0
Renal failure acute	1 (0.3)	0	0	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.3)	0	1 (0.2)	0
Pulmonary embolism	0	0	1 (0.3)	0	1 (0.2)	0

N = number of subjects, n = number of subjects with observations

* AEs assessed by the investigator as possible, probable or very likely related to the investigational medication.

^b This table does not contain AEs from the SOC of investigations; however, AEs in other SOCs with a laboratory component (e.g. thrombocytopenia) are included. Refer to Section 3.1.2.3 for laboratory-related AEs.

^c Individual preferred term; refer to Section 3.1.1.6.1 for details on grouped term.

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.5, , Module 5.3.5.1/TMC125-C206 and Module5.3.5.1/TMC125-C216

Source: Table 26, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

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ON ORIGINAL**

Adverse Events Leading to Permanent Discontinuation in at Least 0.3% of Subjects in the TMC125/Placebo Group (Pooled DUET Analysis)

System Organ Class Preferred Term, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks); Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
Any AE leading to permanent stop	16 (5.2)	16 (5.3)	11 (3.7)	19 (6.4)	27 (4.5)	35 (5.8)
Skin and subcutaneous tissue disorders	1 (0.3)	6 (2.0)	0	7 (2.4)	1 (0.2)	13 (2.2)
Rash ^a	0	2 (0.7)	0	5 (1.7)	0	7 (1.2)
Rash maculo-papular	0	2 (0.7)	0	0	0	2 (0.3)
Infections and infestations	4 (1.3)	4 (1.3)	3 (1.0)	3 (1.0)	7 (1.2)	7 (1.2)
Pneumonia	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.3)
Sepsis	0	0	2 (0.7)	0	2 (0.3)	0
Gastrointestinal disorders	0	1 (0.3)	1 (0.3)	4 (1.4)	1 (0.2)	5 (0.8)
Nausea	0	1 (0.3)	0	3 (1.0)	0	4 (0.7)
Diarrhea	0	0	0	2 (0.7)	0	2 (0.3)
Blood and lymphatic system disorders	3 (1.0)	1 (0.3)	1 (0.3)	2 (0.7)	4 (0.7)	3 (0.5)
Anemia	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.2)	2 (0.3)
Thrombocytopenia	2 (0.6)	0	0	0	2 (0.3)	0
Cardiac disorders	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.3)	3 (0.5)
Cardiac failure congestive	0	2 (0.7)	0	0	0	2 (0.3)
Cardiac arrest	0	2 (0.7)	0	0	0	2 (0.3)
General disorders and administration site conditions	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)	2 (0.3)	3 (0.5)
Renal and urinary disorders	1 (0.3)	2 (0.7)	0	1 (0.3)	1 (0.2)	3 (0.5)
Renal failure	0	1 (0.3)	0	1 (0.3)	0	2 (0.3)
Respiratory, thoracic and mediastinal disorders	2 (0.6)	2 (0.7)	1 (0.3)	1 (0.3)	3 (0.5)	3 (0.5)
Hepatobiliary disorders	1 (0.3)	0	2 (0.7)	2 (0.7)	3 (0.5)	2 (0.3)
Hepatitis	1 (0.3)	1 (0.3)	1 (0.3)	0	2 (0.3)	1 (0.2)
Investigations^b	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.3)	3 (0.5)	2 (0.3)
Nervous system disorders	5 (0.8)	0	1 (0.3)	1 (0.3)	6 (1.0)	1 (0.2)
Metabolism and nutrition disorders	1 (0.3)	0	1 (0.3)	0	2 (0.3)	0
Musculoskeletal and connective tissue disorders	2 (0.6)	0	0	1 (0.3)	2 (0.3)	1 (0.2)

N = number of subjects, n = number of subjects with observations

^a Individual preferred term; refer to Section 3.1.1.6.1 for details on grouped term

^b This table does not contain AEs from the SOC of investigations; however, AEs in other SOCs with a laboratory component (e.g. anemia) are included. Refer to Section 3.1.2.3 for laboratory-related AEs.

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIb-III-Main-Anal-AE/Display SAF.8, Module 5.3.5.1/TMC125-C206 and Module 5.3.5.1/TMC125-C216

Source: Table 27, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

Four and a half percent (4.5%) of the placebo subjects and 5.8% of the TMC125 subjects had AEs that led to permanent discontinuation of investigational medication. The most common AEs that led to permanent discontinuation of investigational medication in the TMC125 treatment group were skin and subcutaneous tissue disorders (rash and maculo-papular rash). Infections and infestations were the most common reason for permanent discontinuation of investigational medication in the placebo treatment group and the second most common reason for permanent discontinuation of investigational medication in the TMC125 treatment group.

Skin Events of Interest Reported in at Least 0.3% of Subjects in the TMC125 Group (Pooled DUET Analysis)

Rash (Any Type) (Pooled DUET Analysis)

AE Summary, n (%)	DUET-1		DUET-2		Pooled DUET	
	Placebo N = 308	TMC125 N = 304	Placebo N = 296	TMC125 N = 295	Placebo N = 604	TMC125 N = 599
<i>Treatment duration (weeks), Median (range)</i>	26.6 (3-55)	26.6 (1-60)	32.2 (3-55)	33.1 (2-56)	29.1 (3-55)	30.0 (1-60)
Rash (any type)	30 (9.7)	61 (20.1)^a	27 (9.1)	41 (13.9)	57 (9.4)	102 (17.0)^a
Grade 1	21 (6.8)	34 (11.2)	19 (6.4)	22 (7.5)	40 (6.6)	56 (9.3)
Grade 2	11 (3.6)	29 (9.5)	8 (2.7)	18 (6.1)	19 (3.1)	47 (7.8)
Grade 3	0	4 (1.3) ^a	0	4 (1.4)	0	8 (1.3) ^a
Onset in days, median	67.0	11.0	17.0	15.0	45.0	12.0
Duration in days, median	22.5	10.0	15.5	13.0	17.0	11.0
Any SAE	0	1 (0.3)	0	0	0	1 (0.2)
Leading to permanent stop	0	6 (2.0) ^a	0	7 (2.4)	0	13 (2.2) ^a
Leading to temporary stop	0	6 (2.0)	0	5 (1.7)	0	11 (1.8)
Vesicular rash (SJS)	0	0	1 (0.3)	0	1 (0.3)	0

N = number of subjects, n = number of subjects with observations

^a Incidence includes one rash AE which emerged and one which deteriorated in the follow-up phase of the trial, see Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Add-Anal2/Display SAF.18 and Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Add-Anal2/Display SAF.19

Source: Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.12 (only lists AEs during the treatment period) and Module 5.3.5.3/TMC125-C909-SCS-PhIIb-III-Main-Anal-AE/Display SAF.11, Module 5.3.5.1/TMC125-C206 and Module 5.3.5.1/TMC125-C216

Source: Table 29, Module 2.7 Clinical Summary, 2.7.4 Summary of Clinical Safety

Seventeen percent (17%) of the TMC125 subjects (n=102) and 9% of the placebo subjects (n=57) developed a rash; 8% (n=47) of the TMC125 subjects and 3% (n=19) of the placebo subjects developed a Grade 2 rash; 1% (n=8) of the TMC125 subjects and none of the placebo subjects developed a Grade 3 rash.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analyses by Gender, Race, and Region

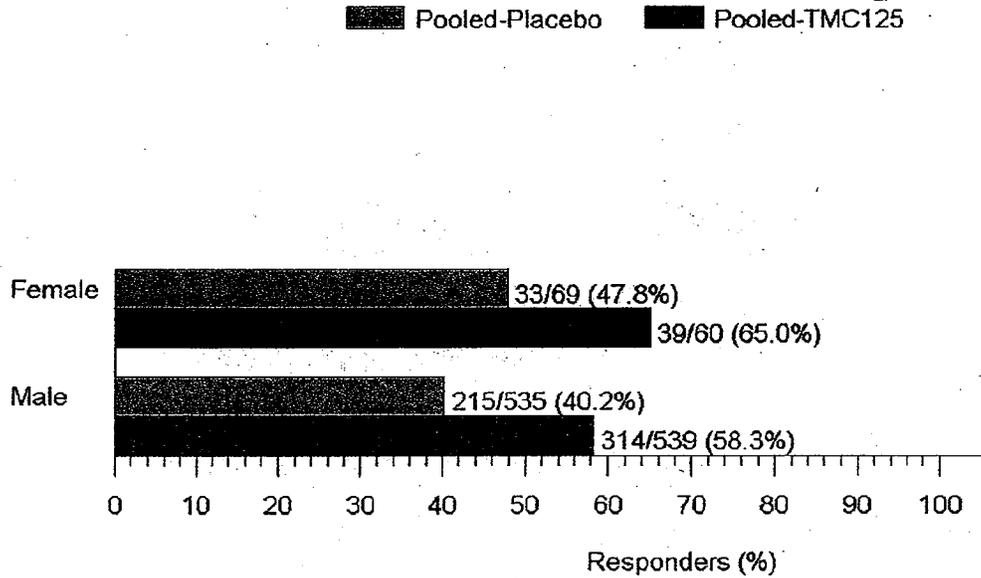


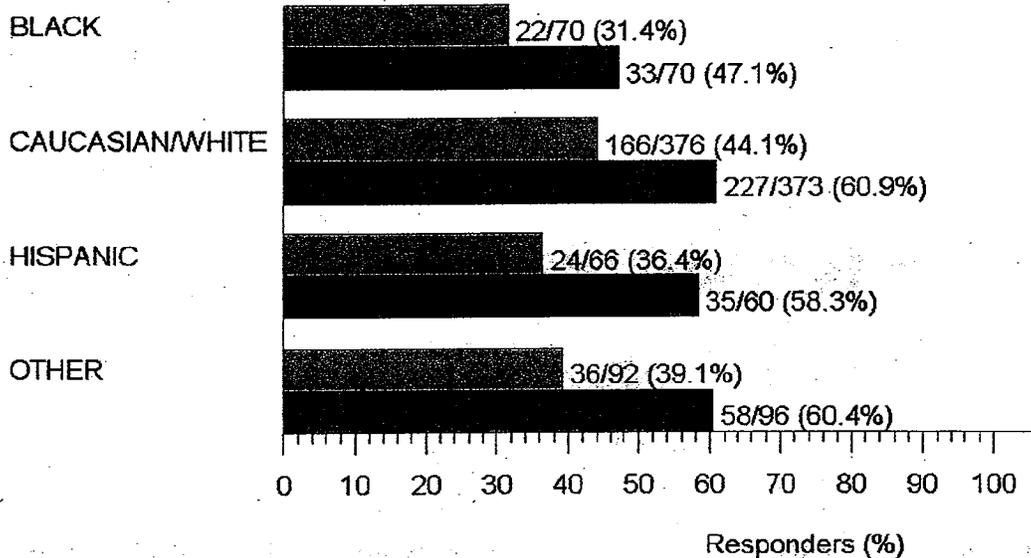
Figure 52: Virologic Response (viral load < 50 copies /mL [TLOVR]) at Week 24 by Gender in the DUET-1 and DUET-2 Trials – Pooled DUET Data

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 52

Compared to placebo, TMC125 appeared to be more effective than placebo in Males and Females, and in Blacks, Whites, Hispanics and other race groups.

APPEARS THIS WAY
ON ORIGINAL

Pooled-Placebo
 Pooled-TMC125



Virologic Response (viral load < 50 copies /mL [TLOVR]) at Week 24 by Race in the DUET-1 and DUET-2 Trials – Pooled DUET Data
 Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 53

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 ON ORIGINAL

**TLOVR Classification of Viral Load < 50 copies/mL
at Week 24 by Country
Trial TMC125-C206**

Country, n/N (%)	Placebo N = 308	TMC125 N = 304
Argentina	15/37 (41%)	20/29 (69%)
Brazil	51/118 (43%)	67/119 (57%)
Chile	0/1	1/3 (33%)
France	11/21 (52%)	12/21 (57%)
Mexico	5/7 (71%)	4/7 (57%)
Panama	0/2	2/4 (50%)
Puerto Rico	1/2 (50%)	0/1
Thailand	2/2	0/2
United States	34/118 (29%)	64/119 (54%)

N = number of subjects, n = number of observations, VF = virologic failure
Source: Statistical Reviewer's Analysis

The percentage of patients with viral loads < 50 copies/mL was higher for TMC125 than placebo in all of the largest countries and most of the smaller countries.

**APPEARS THIS WAY
ON ORIGINAL**

**TLOVR Classification of Viral Load < 50 copies/mL
at Week 24 by Country
Trial TMC125-C216**

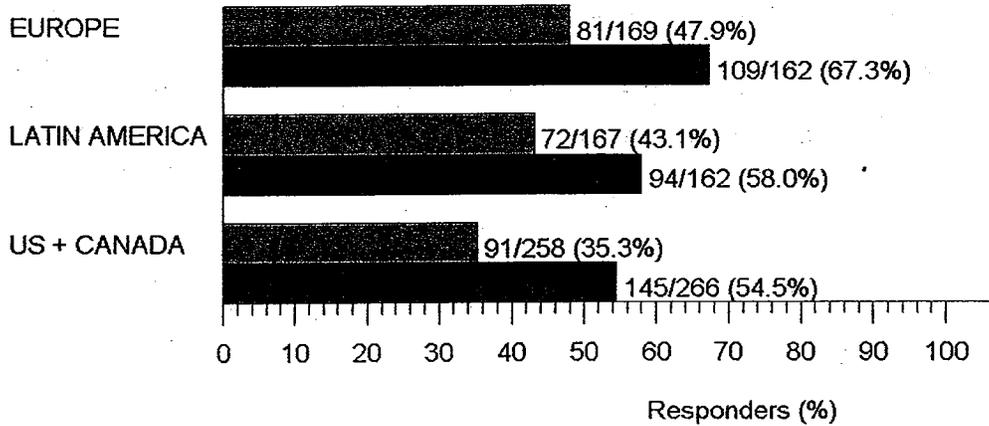
Country, n/N (%)	Placebo N = 308	TMC125 = N = 304
Australia	2/8 (25%)	5/7 (71%)
Belgium	4/8 (50%)	6/6 (100%)
Canada	12/22 (55%)	10/20 (50%)
France	19/49 (39%)	34/53 (64%)
Germany	15/26 (58%)	21/35 (60%)
Italy	19/39 (49%)	22/31 (71%)
Netherlands	2/4 (50%)	2/2 (100%)
Poland	0/1	1/1
Portugal	0/1	0/0
Spain	7/14 (50%)	8/9 (89%)
United Kingdom	4/6 (67%)	3/4 (75%)
United States	45/118 (38%)	71/127 (56%)

N = number of subjects, n = number of observations, VF = virologic failure

Source: Statistical Reviewer's Analysis

**APPEARS THIS WAY
ON ORIGINAL**

■ Pooled-Placebo ■ Pooled-TMC125



Note: Thailand and Australia are excluded from this sub-grouping due to low subject numbers and not fitting into the major regional groupings
Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 54

Virologic Response (viral load < 50 copies /mL [TLOVR]) at Week 24 by Region in the DUET-1 and DUET-2 Trials

The percentage of patients with viral loads < 50 copies/mL was higher for TMC125 than placebo in each geographic region.

APPEARS THIS WAY
ON ORIGINAL

4.2 Distribution of HIV RNA Data by Inspected Sites

**TLOVR Classification of Viral Load < 50 copies/mL
at Week 24 by Inspected Sites**

Center	Location	Placebo n/N (%)	TMC125 n/N (%)
Study 206			
BR00006	Curitiba PR	4/8 (50%)	7/9 (78%)
BR00027	Rio de Janiero RJ	11/19 (58%)	10/17 (59%)
US00092	San Diego, CA	2/7 (29%)	5/6 (83%)
Study 216			
US00176	Los Angeles, CA	2/13 (15%)	6/10 (60%)

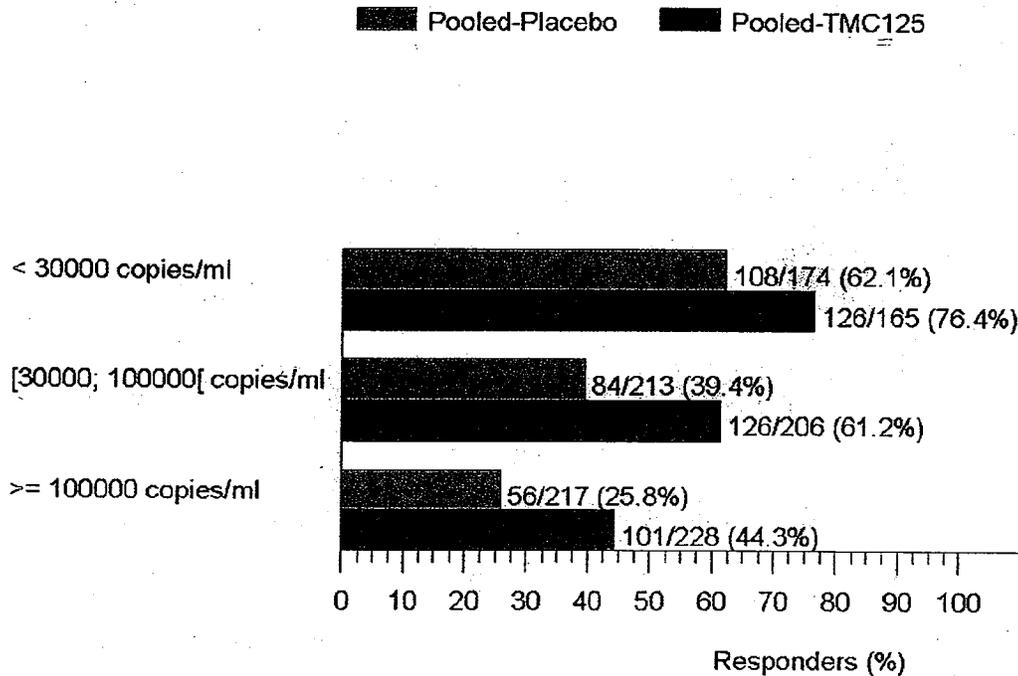
N = number of subjects, n = number of observations, VF = virologic failure

Source: Statistical Reviewer's Analysis

There were four sites that were inspected by DSI. TMC125 had a larger percentage of subjects with viral loads <50 copies/mL than placebo in all but one site.

**APPEARS THIS WAY
ON ORIGINAL**

4.3 Subgroup Analyses by Selected Baseline Characteristics



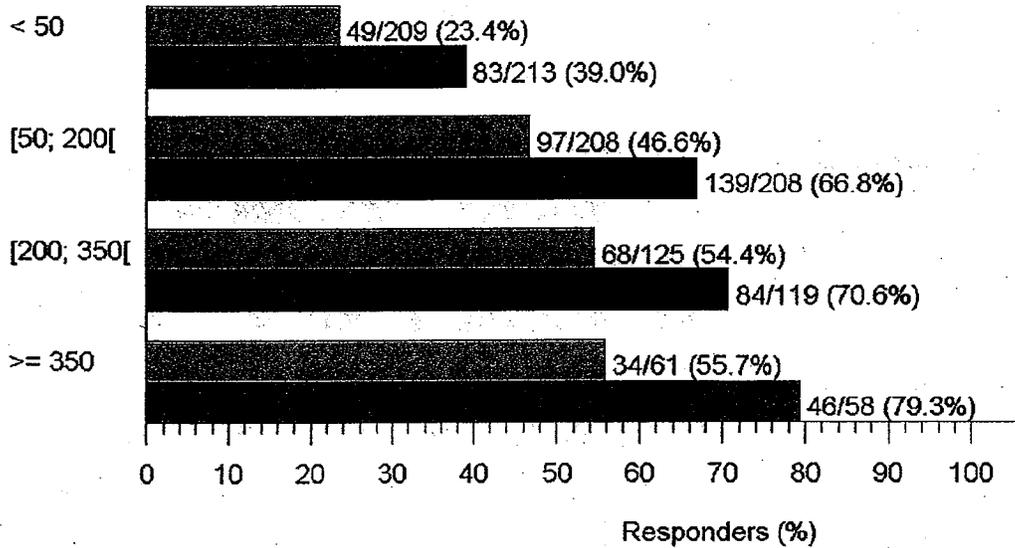
Virologic Response (< 50 copies/mL, TLOVR) at Week 24 by Baseline Viral Load in the DUET-1 and DUET-2 Trials – Pooled DUET Data

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 55

In studies C206 and C216, the percentage of TMC125 responders was higher than placebo in each baseline plasma viral load subgroup.

APPEARS THIS WAY
ON ORIGINAL

Pooled-Placebo
 Pooled-TMC125



Virologic Response (< 50 copies/mL, TLOVR) at Week 24 by Baseline CD4 Count in the DUET-1 and DUET-2 Trials – Pooled DUET Data

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 57

TMC125 appeared to be more efficacious than placebo regardless of baseline CD4 count.

**APPEARS THIS WAY
ON ORIGINAL**

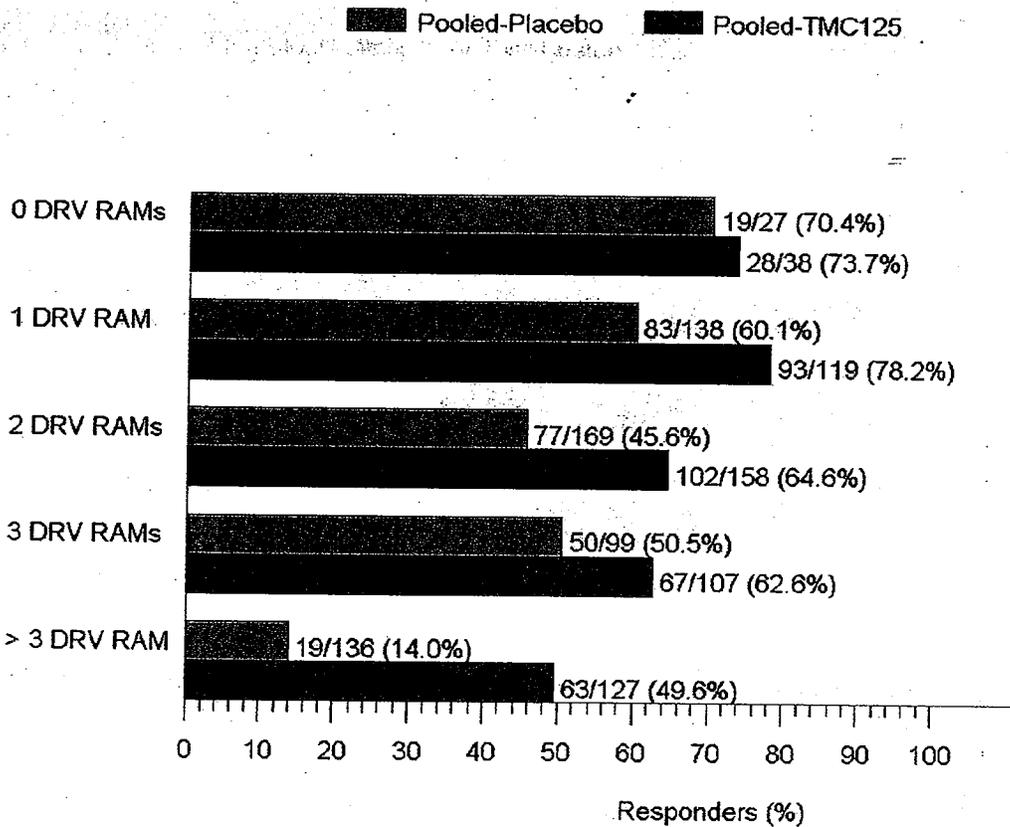
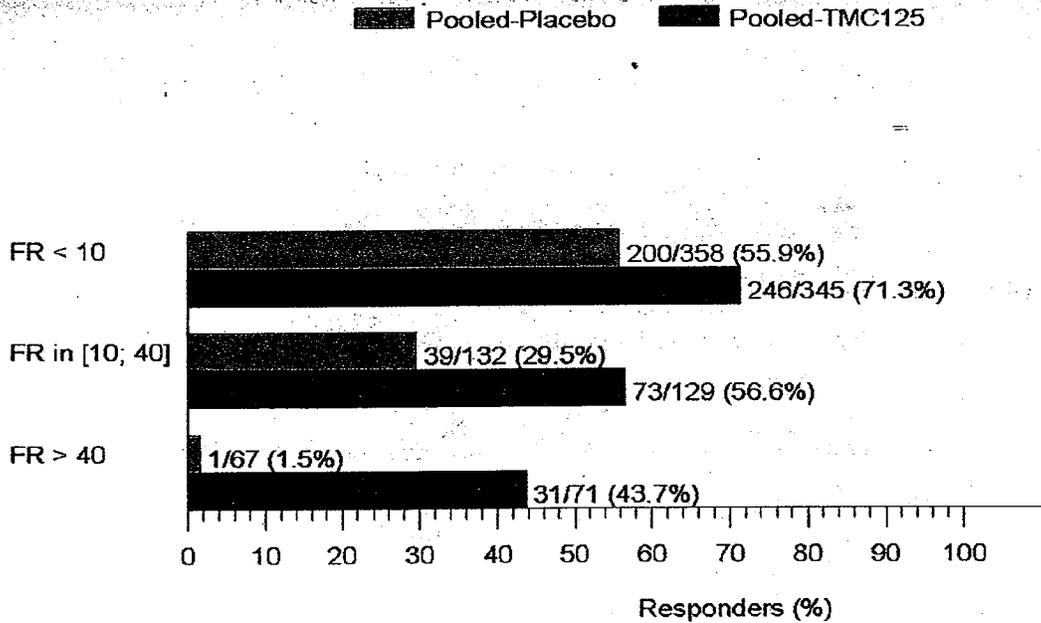


Figure 63: Virologic Response (Viral load < 50 copies/mL TLOVR) at Week 24 by Baseline DRV RAMs – Pooled DUET Trials

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 63

Compared to placebo, the treatment effect of TMC125 appeared to be largest in patients with >3 DRV RAMs and smallest in the small number of patients with 0 DRV RAMs.

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ON ORIGINAL



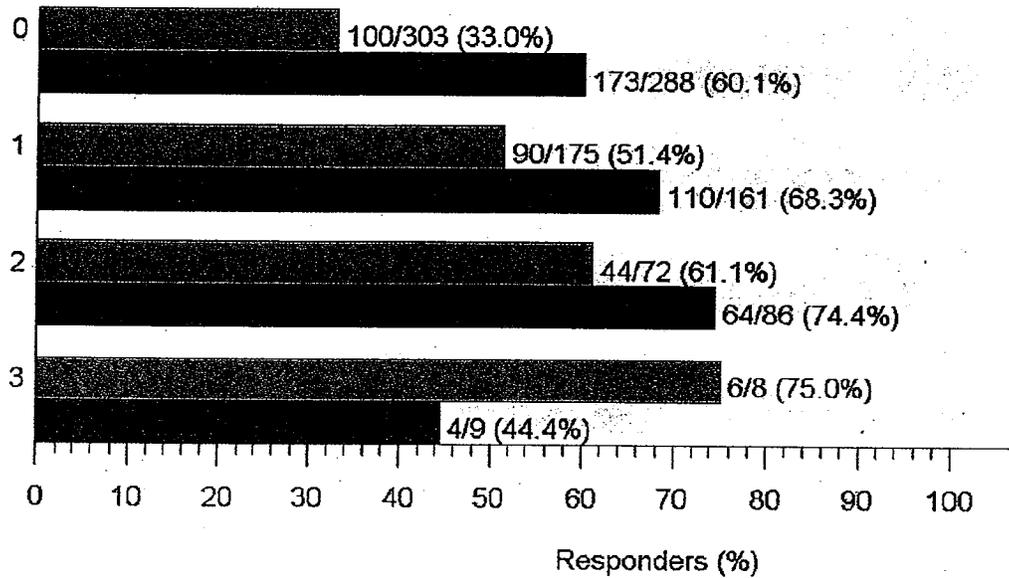
Virologic Response (Viral Load < 50 copies/mL, TLOVR) at Week 24 by DRV FC – Pooled DUET Trials

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 64

The treatment effect of TMC125 appeared to be larger than placebo in all baseline strata by FC for DRV in studies C206 and C216. Compared to placebo, the largest treatment effect in favor of TMC125 was observed in patients with baseline FR>40.

APPEARS THIS WAY
ON ORIGINAL

Pooled-Placebo
 Pooled-TMC125



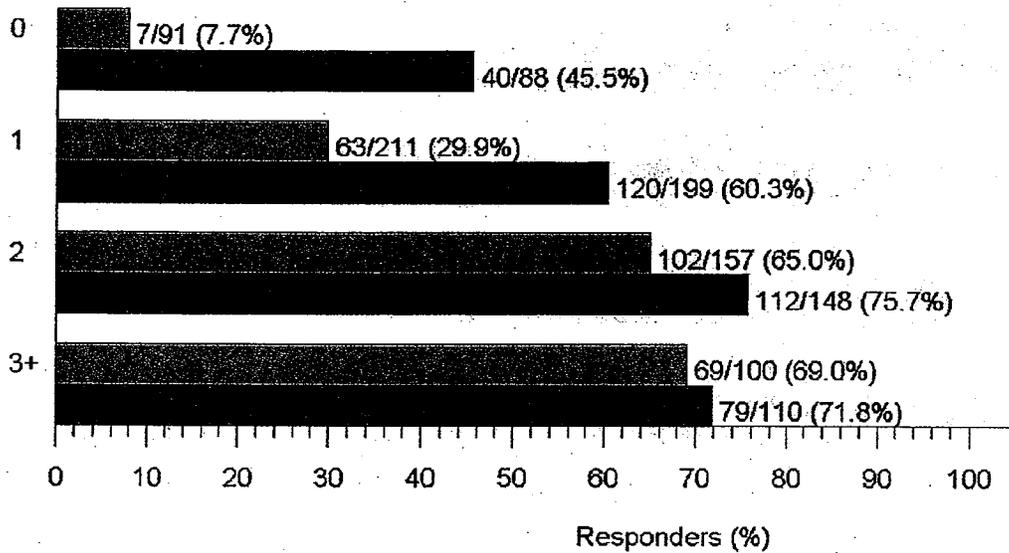
Virologic Response (Viral Load < 50 copies/mL, TLOVR) at Week 24 by Sensitive NRTIs – Pooled DUET Data

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 65

Compared to placebo, the treatment effect of TMC125 appeared to be largest in patients with 0 sensitive NRTIs.

APPEARS THIS WAY
ON ORIGINAL

Pooled-Placebo
 Pooled-TMC125



Virologic Response (Viral Load < 50 copies/mL, TLOVR) at Week 24 by Total Number of Sensitive ARVs – Pooled DUET Trials

Source: Module 2.7.3 Summary of Clinical Efficacy, Figure 66

Compared to placebo, the treatment effect of TMC125 appeared to be largest in patients with 0 sensitive ARTs and smallest in the small number of patients with 3 or more sensitive ARTs.

**APPEARS THIS WAY
ON ORIGINAL**

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Overall, based on the data submitted, the following results were observed:

- In the two pivotal Phase III studies (TMC125-C206 and TMC125-C216), approximately 60% of the patients in the TMC125 treatment group had HIV RNA viral load <50 copies/mL at Week 24 compared to 40% of the placebo patients.
- TMC125 efficacy compared to placebo was more impressive for patients who never used or were re-using enfuvirtide than for de-novo enfuvirtide patients. Among the de-novo ENF subgroup, 67% of the TMC125 subjects had HIV RNA viral loads <50 copies/mL at Week 24 compared to 62% of the placebo subjects ($p=0.427$) while among the non de-novo ENF subjects, 56% of the TMC125 subjects had HIV viral loads <50 copies/mL at Week 24 compared to only 34% of the placebo subjects ($p<0.0001$).

To evaluate the robustness of the efficacy results of the two Phase III trials in the treatment-experienced patients, the applicant used different approaches to impute missing data and the statistical reviewer used a snapshot approach instead of the TLOVR algorithm and different rules of counting non-responders who discontinued early as virologic failures. The statistical reviewer's results were quite similar to the applicant's.

With regards to the mortality, there were 15 placebo deaths and 9 TMC125 deaths based on the database lock for the NDA submission.

Rash (any type) combining all rash-related terms reported during treatment and/or follow-up was reported in 17% of the subjects in the TMC125 treatment group compared to only 9% of the placebo group. AEs with at least grade 2 severity, determined by the investigator to be at least possibly related to the investigational medication occurring in at least 2.0% of subjects in the TMC125 group that appeared to be higher in TMC125 patients included rash (individual preferred term, 4.8% vs. 1.0% in the placebo group), nausea (3.2% vs. 1.3%) and metabolism and nutrition disorders (4.7% vs. 1.8%). None of the placebo subjects and 6 (1%) of the TMC125 subjects had grade 3 or 4 rashes.

After 24 weeks, mean calculated LDL levels increased from baseline by 11 mg/dL to 104 mg/dL in the placebo treatment group and by 14 mg/dL to 108 mg/dL in the TMC125 treatment group. At week 32, when less than half the randomized subjects remained, mean calculated LDL levels increased by 9 mg/dL in the placebo treatment group to 111 mg/dL and increased by 18 mg/dL in the TMC125 treatment group to 117 mg/dL.

After 24 weeks, the proportion of patients with increases in calculated LDL levels from baseline exceeding 10 mg/dL was 48% in the placebo treatment group and 56% in the TMC125 treatment group. This difference was statistically significant ($p=0.02$).

Statistically significant differences between TMC125 and placebo were also observed at Week 20 and 32 with non-significant statistical trends favoring placebo at Weeks 12 and 16.

An additional analysis used the last calculated LDL value up to and including Week 24 but prior to use of any new lipid lowering agents. In this analysis, the proportion of patients with increases in calculated LDL levels from baseline exceeding 10 mg/dL was 49% in the placebo treatment group and 56% in the TMC125 treatment group. These results were quite similar to the Week 24 results except they were not quite statistically significant ($p=0.06$).

As part of the review process, the FDA requested the copies of original source documents for treatment randomization schedules generated for each patient in the two DUET trials. In addition, the review team requested Tibotec's standard operating procedures for randomization schedule generation, unblinding and release of randomization codes along with corresponding flow charts.

The FDA asked the applicant to provide the address and phone number of the central laboratory used for the two DUET trials. The FDA asked the applicant if external vendors were used to generate randomization codes for the two studies, and if so, to provide their addresses and telephone numbers and to disclose to the FDA any financial or partnering agreements between Tibotec and the external vendors. If external vendors were used to generate the treatment allocation codes for the two DUET trials, the FDA asked to have the external vendors send the treatment allocation codes directly to the FDA along with information on when the vendors received/generated the original codes. The FDA also requested certification (from the external vendors, if they were used to generate treatment allocation codes for studies TMC125-C206 and TMC125-C216) that the documents of the treatment allocation codes were the original source documents and that the treatment allocation codes were generated prior to study initiations.

In addition, the FDA requested all other source documents of treatment allocation codes. (e.g., from the applicant's Clinical Pharmaceutical Operations or drug packaging group).

5.2 Conclusions and Recommendations

On July 17, 2007, Tibotec submitted the NDA to seek the Agency's accelerated approval of TMC125 (Intelence[®]; etravirine); a non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 infection in treatment-experienced adults. The dosage was TMC125 200 mg administered orally, twice daily (bid) following a meal.

The statistical reviewer evaluated efficacy results based on all 24-week data from two pivotal Phase III trials in treatment-experienced [i.e., Studies TMC125-C206 (DUET-1) and TMC125-C216 (DUET-2)] in the original submission which included the data up to database cutoff dates of February 9, 2007 for DUET-1 and January 18, 2007 for DUET-2.

The statistical reviewer concluded that TMC125 200 mg bid in combination of the

background regimen (BR) had superior efficacy over the placebo in combination of BR for the treatment of HIV treatment-experienced adults who had previously taken or were retaking enfuvirtide. Among the non de-novo ENF subjects, 56% of the TMC125 subjects had HIV viral loads <50 copies/mL at Week 24 compared to only 34% of the placebo subjects.

In contrast, TMC125 200 mg bid appeared to offer less benefit compared to placebo in de novo enfuvirtide subjects. Among the de-novo ENF subgroup, 67% of the TMC125 subjects had HIV RNA viral loads <50 copies/mL at Week 24 compared to 62% of the placebo subjects.

The overall percentage of subjects with any adverse events was comparable in TMC125 and placebo treatment groups. However, rashes were more prevalent in TMC125 subjects than placebo subjects. Compared to placebo, the statistical reviewer also found somewhat higher increases in LDL cholesterol from baseline in TMC125 subjects.

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