P068

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A Phase IIIb Pilot Study Substituting Darunavir/ritonavir (DRV/r) and Etravirine (ETR) for Enfuvirtide (ENF) and Current PI in a Suppressive Regimen

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Abstract

Early clinical experience with DRV/r plus ETR in several small pharmacokinetic and efficacy studies as well as the ongoing DUET trials demonstrated antiretroviral (ARV) activity and tolerability in treatment-experienced patients (pts). ENF has shown activity in treatment-experienced pts but requires twice daily subcutaneous injections, commonly leading to dosing fatigue and injection site reactions. This ongoing 48 week (wk) pilot study evaluates the efficacy and tolerability of the combination of DRV/r and ETR when substituted for ENF and current PI (and NNRTI, if applicable) in a virologically suppressive regimen. We report efficacy, safety and tolerability of the DRV/r and ETR-containing regimen at Wk 24.

Eligible HIV-infected adults were on a PI-based regimen including ENF, had viral load (VL) ≤ 400 copies/mL for at least 6 months, and had a history of 3-class drug resistance or ARV failure. Pts declined to continue ENF or had physicians recommendation to discontinue. At study entry, all pts discontinued ENF, PI(s) and NNRTI(s), if applicable (NRTIs were continued), and substituted DRV/r 600/100mg bid plus ETR 200mg bid. Primary endpoint: proportion of pts maintaining VL ≤ 400 copies/mL at 24 and 48 weeks. Virologic response, CD4 count, and lab values are reported as missing equals failure, last observation carried forward, and observed, respectively.

Target enrollment (40 pts) was not reached due to shortage of eligible pts. Ten male pts enrolled: median age 48y; 6 Caucasian and 4 Hispanic; all baseline (BL) VL < 50 copies/mL; median BL CD4 301 cells/mm^3. One pt discontinued due to dizziness (doubtfully-related) at Wk 8. All 9 pts completing Wk 24 maintained VL < 50 copies/mL. Median increase in CD4 count was 17 cells/mm^3. Most common treatment-related AEs were fatigue (n = 4), rash (n = 3), headache (n = 3) and diarrhea (n=3). One serious AE (cholecystitis; doubtfully-related) and 2 grade 3/4 AEs (nausea and weight loss; not related) were reported. Median changes (min;max) in mg/dL from baseline to Wk 24 for triglycerides, total cholesterol (TC), HDL, LDL and TC/HDL ratio were -13 (-228;118), -15 (-31;60), -2 (-15;17), -7 (-27;6) and 0 (-1.16;1.20), respectively.

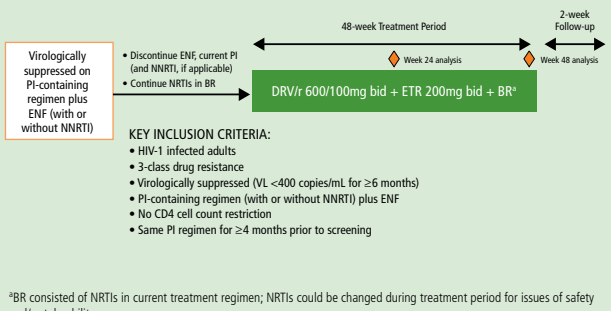
In this study, following substitution of DRV/r and ETR for ENF, PI(s) and NNRTI(s), 9 of 9 previously suppressed pts who completed Wk 24 maintained VL < 50 copies/mL. DRV/r and ETR were generally safe and well tolerated.

Introduction

- Etravirine (ETR; INTELENCE™) and darunavir (DRV; PREZISTA™) are FDA-approved antiretrovirals with proven activity against drug-resistant HIV-1 virus[1,2]
  - Early clinical experience in several small pharmacokinetic and efficacy studies suggested that the combination of ETR and DRV with low-dose ritonavir (DRV/r) was well tolerated and effective in treatment-experienced patients
  - Subsequently, in the phase III DUET-1 and DUET-2 trials, the safety and tolerability of ETR was found to be comparable to placebo at Week 48, with the exception of rash which occurred early in treatment. In the pooled analysis, a significantly higher proportion of patients in the ETR group achieved viral suppression (HIV-1 RNA < 50 copies/mL) compared to the placebo group (61% vs 40% respectively; $P < .0001$) at Week 48[3]
  - At Week 96 in the phase III TITAN trial in treatment-experienced patients, 67% of DRV/r-treated patients achieved HIV-1 RNA <400 copies/mL compared with 59% of LPV/r-treated patients (ITT-TLOVR); 60% and 55% of DRV/r- and LPV/r-treated patients, respectively, achieved HIV-1 RNA <50 copies/mL[4]
- Enfuvirtide (ENF) has shown activity in treatment-experienced patients but requires twice daily subcutaneous injections, commonly leading to injection site reactions and dosing fatigue which can contribute to non-adherence[5]
- This open-label, phase IIIb, 48-week pilot study (TMC114-HIV3009) evaluates the efficacy and tolerability of the combination of DRV/r and ETR when substituted for ENF and current protease inhibitor (PI) – and NNRTI, if applicable – in patients with viral suppression but who are intolerant to ENF
- We report efficacy, safety and tolerability of the DRV/r and ETR-containing regimen at Week 24

Methods

- Study design and inclusion criteria are shown in **Figure 1**
- Major exclusion criteria:
  - Prior experience with DRV/r or ETR
  - Pregnancy or breast feeding
  - AST or ALT >5 times upper limit of normal
  - Prior documentation of ≥3 DRV resistance-associated mutations (RAMs) from the following list: V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V, and L89V
- Patients were considered intolerant to ENF if they declined to continue therapy with ENF or if their physician recommended discontinuation due to persistent injection site reactions



[a]BR consisted of NRTIs in current treatment regimen; NRTIs could be changed during treatment period for issues of safety and/or tolerability

Figure 1. Study design

- Following a screening period of 7 to 42 days, all eligible patients at study entry discontinued ENF, PI(s) and NNRTI(s), if applicable, and initiated treatment with DRV/r 600/100mg bid plus ETR 200mg bid for 48 weeks
  - NRTIs were continued as part of the background regimen (BR) but could be changed during the treatment period for safety and/or tolerability issues
- In the event of virologic rebound, antiretroviral resistance was assessed to determine alternative therapeutic options, including the possible resumption of ENF use
- The primary endpoint is the proportion of patients maintaining virologic suppression ≤400 copies/mL at 24 and 48 weeks
- Secondary endpoints include:
  - Virologic suppression <50 copies/mL
  - Time to virologic failure
  - Immunologic response
  - Changes in lipid and glucose levels from baseline
  - Resistance at failure
- Virologic response and CD4 count are reported as missing equals failure, last observation carried forward (LOCF), respectively. Lab abnormalities are reported as LOCF, the same as CD4 cell count

Results

- Ten men were enrolled in the study (**Table 1**)
  - Enrollment goal of 40 patients was not reached due to a shortage of eligible patients
  - All patients had VL <50 copies/mL at baseline

Table 1. Baseline demographics and disease characteristics

Parameter	All patients N = 10
Age, median (range), years	48 (35–61)
Males, n (%)	10 (100)
Race/ethnicity, n (%)	
Caucasian	6 (60)
Hispanic	4 (40)
VL <50 copies/mL, n (%)	10 (100)
CD4 count, median (range), cells/mm^3	301 (187–663)
VL, viral load	

- Prior to study entry, 8 patients had 1 PI, 2 patients had 2 PIs and 5 patients had an NNRTI included in their treatment regimens (**Table 2**)

Table 2. Historical resistance data, ARV regimen at screening, and background ARVs

	Historical genotype				
Patient	DRV RAMs	IAS-USA primary PI mutations	ETR RAMs	PI +/-NNRTI at screening (all receiving ENF)	NRTIs in BR
1	—	V82A, L90M	G190A, A98G	LPV, SQV	ABC, 3TC[a]
2	I84V	M46I, I84V, L90M	—	TPV	TDF, FTC
3	I84V	I84V, L90M	Y181C, G190A	TPV	d4T, TDF, FTC
4	V32I, I47V, I54M, I84V	V32I, M46I, I47V, I54M, I84V, L90M	K101H, G190A	LPV, DLV	ddC, ABC, 3TC
5	—	M46L, V82A, V82T	—	LPV, SQV, NVP	TDF, 3TC
6	L33F, I84V	L33F, M46I, V82A, V82T, I84V	K101H, Y181C, G190A	LPV	ZDV, ABC, 3TC, TDF
7	I84V	I84V, L90M	—	LPV, EFV	d4T, ddI, ABC
8	—	M46I, L90M	Y181C, G190A, A98G	LPV, EFV	TDF, FTC
9	I84V	M46I, I84V, L90M	K101P	TPV, NVP	TDF, ABC
10	I84V	M46I, V82A, I84V	Y181C, G190A	TPV	TDF

[a]NRTIs were started at Week 7 and patient discontinued at Week 8

RAMs, resistance-associated mutations

- One patient discontinued the study at Week 8 due to dizziness (doubtfully related to study drug)
- At Week 24, all 9 patients remaining on study maintained VL <50 copies/mL (**Table 3**)

Table 3. Proportion of patients maintaining virologic response (VL <50 copies/mL) from baseline through Week 24 (ITT, missing = failure)

Patient	BL	Wk 1	Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 24
1	<50	<50	<50	<50	—	—	—	—
2	<50	<50	<50	<50	<50	<50	<50	<50
3	<50	<50	<50	<50	<50	735	<50	<50
4	<50	<50	<50	<50	<50	<50	<50	<50
5	<50	<50	<50	<50	<50	<50	<50	<50
6	<50	<50	<50	<50	<50	<50	<50	<50
7	<50	<50	<50	<50	<50	<50	<50	<50
8	<50	<50	<50	<50	<50	<50	<50	<50
9	<50	<50	50	65	<50	<50	<50	<50
10	<50	<50	<50	<50	<50	<50	<50	<50
Patients with VL <50 copies/mL, n/N (%)		10/10 (100%)	9/10 (90%)	9/10 (90%)	9/10 (90%)	8/10 (80%)	9/10 (90%)	9/10 (90%)

- The median (range) increase in CD4 count from baseline to Week 24 was 19 (-36, 71) cells/mm^3 (**Figure 2**)

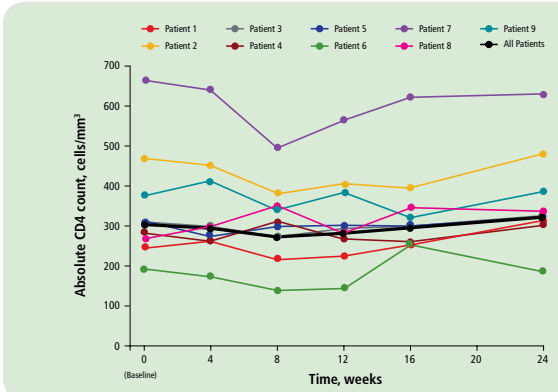


Figure 2. Immunologic response: absolute CD4 cell count from baseline through Week 24

- Adverse events (AEs) were generally mild to moderate in severity and are summarized in **Table 4**
- Two AEs graded as severe (nausea and weight loss; not related to study drug) and one serious AE also graded as severe (acute cholecystitis; doubtfully related) were reported in the same patient
  - All 3 events resolved

Table 4. Adverse events

Parameter, n (%)	All patients N = 10
Median duration of exposure, weeks	*48.1*
Serious AEs, regardless of causality	
Acute cholecystitis	1 (10)
Clinical AEs graded as severe	2 (20)
Nausea[a]	1 (10)
Decreased weight[a]	1 (10)
Acute cholecystitis[b]	1 (10)
AEs leading to discontinuation, regardless of causality	1 (10)
AEs (>1 patient) at least possibly related to study drug, any grade	
Fatigue	4 (40)
Rash	3 (30)
Headache	3 (30)
Diarrhea	3 (30)
Depression	2 (20)
Insomnia	2 (20)

One patient discontinued due to dizziness (doubtfully related to study drug); [a]not related to study drug; [b]doubtfully related to study drug

- Changes in lipid parameters and glucose levels from baseline to Week 24 are shown in **Table 5**

Table 5. Metabolic parameters and laboratory abnormalities

Parameter	Baseline, median (range) N = 10	Week 24 Median change from baseline, (range) N = 10
Triglycerides		
mg/dL	229 (121, 402)	–10 (–228, 118)
mmol/L	2.59 (1.37, 4.54)	–0.11 (–2.57, 1.33)
Total cholesterol		
mg/dL	189 (159, 244)	–13 (–31, 60)
mmol/L	4.89 (4.11, 6.31)	–0.32 (–0.80, 1.55)
LDL cholesterol		
mg/dL	100 (63, 149)	–5 (–27, 6)
mmol/L	2.59 (1.63, 3.85)	–0.13 (–0.70, 0.16)
HDL cholesterol		
mg/dL	48 (25, 54)	–2 (–15, 17)
mmol/L	1.23 (0.65, 1.40)	–0.05 (–0.39, 0.44)
TC/HDL ratio	4.7 (2.9, 6.4)	0 (–1.16, 1.20)
Glucose		
mg/dL	93 (74, 105)	–2 (–13, 31)
mmol/L	5.14 (4.11, 5.83)	–0.08 (–0.72, 1.72)

Conclusions

- In this study, following substitution of DRV/r and ETR for ENF and other PIs and NNRTIs in virologically suppressed treatment-experienced patients with documented PI and NNRTI resistance:
  - 9 of 9 patients who completed Week 24 maintained virologic suppression (<50 copies/mL)
  - DRV/r and ETR were generally safe and well tolerated
  - The most common treatment related AEs (fatigue, rash, headache and diarrhea) were generally mild to moderate
  - Changes in metabolic parameters from baseline were generally favorable, similar to what has been observed in larger trials of DRV/r and ETR in treatment-experienced patients
- This regimen containing DRV/r and ETR:
  - Obviated the need for ENF and simplified the ARV regimen, potentially leading to reduced ARV-associated costs
  - Maintained virologic suppression in patients with a history of both PI and NNRTI resistance without the need for new classes

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