H-4056

Pharmacokinetics and pharmacodynamics of etravirine in treatment-experienced HIV-1-infected patients: pooled 48-week results of DUET-1 and DUET-2

Thomas N Kakuda,¹ Monika Peeters,² Chris Corbett,² Goedele De Smedt,² Rekha Sinha,² Lorant Leopold,¹ Johan Vingerhoets,² Brian J Woodfall,² Richard MW Hoetelmans² ¹Tibotec Inc., Yardley, PA, USA; ²Tibotec BVBA, Mechelen, Belgium

DUET study design

Abstract

Background

Etravirine (ETR; TMC125) is a next-generation activity against both wild-type and NNRTI-resis and DUET-2 are identically designed, ongoing, blind, randomized trials of ETR versus placebo, investigator-selected background regimen (BR) ritonavir-boosted darunavir (DRV/r). The relation ETR pharmacokinetics and pharmacodynamics from these trials was investigated.

Methods

Population pharmacokinetics for area under th concentration-time curve (AUC) and predose pl concentration (C_{0h}) were estimated using Bayes Analysis of covariance (ANCOVA) and logistic i generalized additive modeling (GAM) were use pharmacokinetic/pharmacodynamic (PK/PD) rel efficacy endpoints and safety.

Results

Of the 1203 patients enrolled, 599 were rando PK data from 575 were available. Mean (standa ETR AUC and Coh were 5506 (4710) ng•h/mL and 393 (391) ng/mL, respectively. In the GAM ana C_{0h} was not significantly associated with reachi <50 copies/mL at Week 48. Other factors, inclu load and CD4 cell count, phenotypic sensitivity adherence, baseline fold-change in EC₅₀ (FC) to age and use of enfuvirtide (ENF) or tenofovir (1 important determinants than pharmacokinetics of ETR was observed in patients with PSS=0 irre pharmacokinetics. No apparent relationships w ETR pharmacokinetics and laboratory changes including rash.

Conclusions

ETR demonstrated superior activity compared DUET trials at Week 48. Achieving viral load < Week 48 in these trials was not influenced by pharmacokinetics, but rather by other drug-, dis patient-related factors. Furthermore, no relation ETR pharmacokinetics and safety was observed

• ETR is a next-generation NNRTI with potent in-vitro

AUC_{12b} = AUC from time of administration to 12 hours after dosing

both wild-type and NNRTI-resistant HIV-11

PK characteristics²

stract	DUET study design and major inclusion criteria ³	PK/efficacy analysis: GAM (cont'd)	Viral load <50 copies/mL at
round e (ETR; TMC125) is a next-generation NNRTI with potent gainst both wild-type and NNRTI-resistant HIV. DUET-1 T-2 are identically designed, ongoing, Phase III, double- ndomized trials of ETR versus placebo, both with an tor-selected background regimen (BR) including boosted darunavir (DRV/r). The relationship between macokinetics and pharmacodynamics over 48 weeks se trials was investigated.	Screening 8 weeks 48 week treatment period with optional 48 week extension Follow-up 6 weeks 600 patients 100 patients ETR 200mg lid + 8R* Patient Patient 101 Patients Patients Patient Patient 102 Patients Patient Patient Patient Patient 103 Patients Patient Patient Patient Patient 104 Patient Patient Patient Patient Patient 105 Patients Patient Patient Patient Patient 105 Patients Patient Patient Patient Patient 105 Patients Patients Patients Patients 105 Patients <td> Dataset bootstrapped 1000 times Probability of response (viral load <50 copies/mL) was predicted 1000 times for each subject in the original database using the bootstrapped dataset response rate was predicted for each study arm with and without the addition of residual error to each of the individual predictions residual error was added by sampling a random value between zero and one for each subject, assuming a uniform distribution, and comparing this sampled value with the predicted probability of response in that subject if the sampled value was below the predicted probability, the response was considered to have occurred; otherwise the response was considered not to have occurred </td> <td>Week 48 by prognostic factors in final model</td>	 Dataset bootstrapped 1000 times Probability of response (viral load <50 copies/mL) was predicted 1000 times for each subject in the original database using the bootstrapped dataset response rate was predicted for each study arm with and without the addition of residual error to each of the individual predictions residual error was added by sampling a random value between zero and one for each subject, assuming a uniform distribution, and comparing this sampled value with the predicted probability of response in that subject if the sampled value was below the predicted probability, the response was considered to have occurred; otherwise the response was considered not to have occurred 	Week 48 by prognostic factors in final model
on pharmacokinetics for area under the plasma ation-time curve (AUC) and predose plasma ation (C_{0h}) were estimated using Bayesian feedback. of covariance (ANCOVA) and logistic regression with red additive modeling (GAM) were used to analyze okinetic/pharmacodynamic (PK/PD) relationships with endpoints and safety.	Response (viral load <50 copies/mL) at Week 48 (ITT-TLOVR)	 PK/safety analysis Presence or absence of adverse event by DRV or ETR AUC_{12h} rash, skin events of interest, nervous system, psychiatric or gastrointestinal disorders, or the individual events of headeaba disorders, or the 	PC for DRV Afternoo
S 203 patients enrolled, 599 were randomized to ETR, and from 575 were available. Mean (standard deviation [SD]) and C _{0h} were 5506 (4710) ng•h/mL and 1) ng/mL, respectively. In the GAM analysis, ETR AUC or not significantly associated with reaching viral load ies/mL at Week 48. Other factors, including baseline viral CD4 cell count, phenotypic sensitivity score (PSS), te, baseline fold-change in EC _{s0} (FC) to DRV and ETR,	 92% of subjects randomized to ETR who were undetectable (viral load <50 copies/mL) at Week 24 remained undetectable at Week 48 March 24 remained undetectable at Week 48 March 24 remained undetectable at Week 48 	 individual events of headache, dizziness, tachycardia, palpitations or blurred vision Maximum change from baseline in laboratory parameter by DRV or ETR AUC_{12h} pancreatic amylase, lipase, ALT, AST, AP, direct, indirect, total bilirubin, cholesterol, LDL-C, HDL-C, triglycerides and PT or PTT ALT = ataine aminotransferase, AST = asprtate aminotransferase; AP = ataline phosphatase HDL-C = high-density lipopoten cholesterol	A strain of the
use of enfuvirtide (ENF) or tenofovir (TDF), were more it determinants than pharmacokinetics. Antiviral activity as observed in patients with PSS=0 irrespective of okinetics. No apparent relationships were seen between macokinetics and laboratory changes or adverse events, grash. Isions onstrated superior activity compared with placebo in the als at Week 48. Achieving viral load <50 copies/mL at in these trials was not influenced by ETR okinetics, but rather by other drug-, disease- and elated factors. Furthermore, no relationship between macokinetics and safety was observed.	<section-header><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item><list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></list-item></section-header>	ETR population PK and (ovariate analysis) 9. Parameter estimates of the PK model 9. aparent oral clearance (CLF): 43.7L/hou: 9. olume of the central compartment: 422L 9. intersubject variability on CLF: 60% 10. intersubject variability on CLF: 60% 10. intersubject variability on CLF: 60% 10. intersubject variability on fraction absorbed: 40% 10. intersubject variability on fraction absorbed: 40% 10. opulation PK estimates at Week 48 (n=57) 11. <u>Normeter Mean (SD) Median (range</u> <u>AUC₁₂₀, ng·H/mL 5506 (4710) 4380 (458–59,084)</u> <u>Con, ng/mL 393 (391) 298 (2-4852)</u> 10. use of TDF was associated with a ~26% decrease in AUC ₁₂₀ . 11. see of TDF was associated with a ~26% decrease in AUC ₁₂₀ . 12. est of TDF was associated AUC ₁₂₀ , ~1.35-fold 13. or relevant effect of sex, age, race, use of ENF or treatment duration on AUC ₁₂₀ .	$\label{eq:production} \begin{split} & {\rm Viral \ load} < 50 \ {\rm copies/mL \ at}_{\rm Copies/mL} \\ & {\rm upper \$
Introduction R is a next-generation NNRTI with potent in-vitro activity against th wild-type and NNRTI-resistant HIV-11 Characteristics ² ETR must be administered following a meal • AUC _{12n} decreased ~50% under fasting conditions highly protein bound (99.9%) to both albumin and α_1 -acid glycoprotein (orosomucoid) substrate and inducer of CYP3A substrate and inhibitor of CYP2C9 and 2C19 inhibitor of P-glycoprotein, but not a substrate minimal (<1.2%) renal excretion mean terminal elimination half-life of 41 hours	PCGrossic factors	Scheduction of final GAM ••••••••••••••••••••••••••••••••••	Pharmacokinetics and safety • Safety and tolerability of ETR was similar to placebo except for rash over 48 weeks • rash (any type) was more commonly reported with ETR (19%) than with placel • no apparent association between rash and baseline CD4 cell count, previous to NNRTI-related rash or ETR AUC _{12h} • $\frac{43026.7 (n=144)}{9026.7 - 4380 (n=144)}$

 $\label{eq:FCETR} FCETR = FC \text{ in ETR; } BVL = baseline viral load; FCDRV = FC \text{ in DRV} \\ BCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; VL = viral load \\ FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; FCD4 = baseline CD4; s = spline fit with X degrees of freedom; lo = loess fit; loess fit$

Thomas N Kakuda, PharmD Tibotec Inc 1020 Stony Hill Road Suite 300 Yardley, PA 19067 USA tkakuda@its.jnj.com

















Pharmacokinetics and safety (cont'd)

- no apparent relationship between ETR AUC12h and any of the other adverse events
- no apparent relationship between ETR AUC on and maximum change from baseline in any of the laboratory parameters, including hepatic and lipid parameters

Conclusions

- ETR 200mg bid demonstrated superior activity than placebo in this treatment-experienced patient population
- Moderate-to-high inter and intrapatient variability in ETR pharmacokinetics
- ETR pharmacokinetics do not vary by sex, age or race - changes in ETR pharmacokinetics due to TDF or hepatitis
- co-infection are not clinically relevant • ETR AUC_{12b} or C_{0b} was not associated with viral load
- <50 copies/mL at Week 48
- prognostic factors retained in the final model (baseline CD4 cell count, baseline viral load, use of active agents,6 adherence, age and FC to DRV and ETR) are more important determinants than pharmacokinetics
- No apparent relationships were seen between pharmacokinetics and adverse events or laboratory changes - rash does not appear to be related to ETR AUC_{12h}

References

- 1. Vingerhoets J. et al. J Virol 2005;79:12773-82.
- 2. Schöller-Gyüre M, et al. Clin Pharmacokinet. Manuscript submitted
- 3. Cahn P, et al. XVIIth International AIDS Conference 2008. Abstract TUPE0047.
- 4. Kakuda TN, et al. XVIIth International AIDS Conference 2008. Abstract TUPE0082.
- 5. Mills A, et al. XVIIth International AIDS Conference 2008. Abstract TUPE0059.
- 6. Di Perri G. et al. XVIIth International AIDS Conference 2008. Abstract TUPE0061

Acknowledgments

We express our gratitude to the patients who participated in the study, as well as the study center staff, DSMB, Tibotec personnel and the following principal investinators: DUET-1

DUET-1
Argentina: H Ariza, J Benetucci, L Calami, L Cassetti, J Corral, D David, A Krolewiecki, M Losso, P Patterson, R Teijeiro, Brazil:
CA da Cunha, E Kallas, E Netto, JH Pilotto, M Schechter, J Suleiman, A Timerman, Chile: J Ballesteros, R Northland; Costa Rica:
A Alvilés Montoja, G Artenez Martinez, A Solano Chinchila; Trance: M Dupon, C Katlama, M Livrozet, P Morlat, C Piketty,
I Prolazi-Matrin; Mexico: J Andrade Villaueva, G Reyer Ferari, J Sterr-Madero, Panama: A Canton, A Rodinguez, N Sosa;
Puerto Rico: JO Morales Ramirez, J. Santana Bagur, R Sotor-Malave; Thailand: Tanekthananon, P Mootskapun,
K Ruxungtham; USA: M Albrecht, P Bellos, R Bolan, P Brachman, C Brimon, F CruicScham, R Elion, WJ Feser, I Tawkins,
S Hodder, T Jeffesson, H Katmer, C Kinder, M Kozal, D McDonough, K Mourzet, D Noris, 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 Wilk, M Wohlfeller, K Workowski.

DUET-2 Australia: Chuah, D Caoper, 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, CM Tsoukas, SJ Walmsley, France: C Arvieux, L Cotte, JF Delfraissy, PM Grard, B Marchou, JM Molina, D Vittercon, Y Yazdanpanah, P Veni; Germany: S Esser, G Faitenheuer, H Gellemman, K Göbels, PD Goebe H Jager, A Moli, IR Rockstrol, D Solutuse; S Stazewski, A Steher, Haly: -Antinni, G Carosi, G D Ierni, F Repositi, F Mazzuka, G Pagano, E Raise, S Rusconi, L Sighinofi, F Stuter; The Netherlands: PH IFissen, JM Prins, BJA Rijnders; Poland: A Horban; Portugal: F Antunes; M Miranda, J Vene; Spain: P Doming, G Garcia, M Gatel, J González-Jahoz, I Lápez-Aldegue; D Podzamiczer; UK: P Easterbook, M Fisher, C Otkin, EWilkins; USA: B Barnet, J Barter, G Beatty, D Berger, C Borkert, C Cohen, M Conant, J Ernst, C Farthing, T File, M Frank, JE Gaillant, AE Greenberg, C Hicks, DT Jayaween, S Kerka, N Markowitz, C Martorell, C McDonald, D McMachon, M Mogroors, R Myers Jr, G Richmond, K Sathasivam, S Schneider, H Schrager, P Shailt, FP Siegal, L Sloan, K Smith, S Smith, P Tebas, LS Tkatch.