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<b>Study No.:</b> AZLF 3003	
<b>Title:</b> A Pilot, Multicentre Study to Evaluate the Efficacy and Safety of an Antiretroviral Therapy with <i>Trizivir</i> [abacavir, lamivudine, zidovudine] and Efavirenz after a 14-week Structured Antiretroviral Treatment Interruption, in HIV-1 Infected Subjects with a Viral Load > 5000 copies/mL and a Total CD4 Count > 300/mm <sup>3</sup>	
<b>Rationale:</b> Suboptimal antiretroviral regimens lead to the selection of resistant mutants, which could be a limiting factor in obtaining long-term benefit. Data have shown that wild-type virus can predominate after 3 months of treatment interruption in subjects with virological failure. The Renaissance study was designed to assess the effect of a 14-week treatment interruption before antiretroviral therapy resumption as a new strategy for subjects with virological failure.	
<b>Phase:</b> III	
<b>Study Period:</b> 12 October 2000 – 15 November 2002	
<b>Study Design:</b> Multicentre, open-label, pilot study.	
<b>Centres:</b> 13 French centres	
<b>Indication:</b> HIV-1 infection	
<b>Treatment:</b> Fixed combination of abacavir 300mg, lamivudine 150mg, and zidovudine 300mg (TZV) bid in combination with efavirenz (EFZ) 600mg once daily for 24 weeks treatment.	
<b>Objectives:</b> The primary objective was to evaluate the efficacy of a combination of TZV and EFZ for 24-weeks in HIV-infected adults after a treatment interruption of 14 weeks.	
<b>Primary Outcome/Efficacy Variable:</b> Proportion of subjects with plasma viral load (pVI) < 400 copies/mL after 12 weeks of treatment following shift of virus to wild type.	
<b>Secondary Outcome/Efficacy Variables:</b> Proportions of subjects with pVI < 400 copies/mL and < 50 copies/mL after 12 and 24 weeks of treatment resumption, increase in CD4 cell count after 12 and 24 weeks of treatment, safety and tolerability of the TZV-EFZ combination regimen.	
<b>Statistical Methods:</b> Baseline pVI and CD4 count were calculated using the mean between values at Week –16 (screening) and Week –14. During the treatment interruption period, median change for pVI and CD4 count was calculated from the baseline value as defined above. After treatment resumption, median change was calculated from the day the treatment was restarted (Day 1). Quantitative variables are summarized in tables displaying sample sizes, means, medians, standard deviations, minimum and maximum values. Qualitative variables are described in terms of frequencies of each response category and frequencies converted into percentages. The percentages of subjects with undetectable viral load are presented with the associated exact 95% CI. All subjects followed from Week –16 to Week –2 during the treatment interruption period were included in the ITP (Interrupted Treatment Population) and were the primary population for the analysis of structured treatment interruption period data. All subjects who started the study drug regimen from Day 1 were included in the Intent-to-Treat population (ITT). The ITT Population was the primary population for efficacy analysis of the study drug period. The Safety Population consisted of all subjects who received at least one dose of the study medication. It was assumed that a subject was in the Safety Population, unless evidence existed that the subjects did not take any study medication.	
<b>Study Population:</b> To be enrolled, subjects must have previously received antiretroviral treatment and must have presented virological failure defined as a pVI > 5000 copies/mL at screening visit (Week -16), CD4 count had to be >300 cells/mm <sup>3</sup> , and have interrupted their current treatment for 14 weeks (Week -14). Subjects for whom a shift was not observed were not enrolled (genotyping of virus was performed at Week – 2 to evaluate the shift in virus population from drug resistant to wild-type virus).	
	<b>TZV/EFZ</b>
<b>Number of Subjects:</b>	
Planned, N	60
Screened, n	51
Structured treatment interruption	30
Entered, N	20
Completed, n (%)	14 (70)
Total Number Subjects Withdrawn, N (%)	6 (30)
Withdrawn due to Adverse Events n (%)	5 (25)
Withdrawn due to Lack of Efficacy n (%)	1 (5)
Withdrawn for other reasons n (%)	0

<b>Demographics</b>	
N (ITT)	17
Females: Males	5: 12
Mean Age, years (SD)	41.4 (8.4)
Race, n (%)	n/a
Other relevant demographic criteria	n/a
<b>Primary Efficacy Results:</b>	
	<b>TZV/EFZ</b>
Proportion of subjects with pVI < 400 copies/mL after 12 weeks of treatment following shift of virus to wild type	
ITT Switch included, n (%) [95%CI]	12 (71%) {44%; 90%}
ITT Switch/missing=failure, n (%) [95%CI]	11 (65%) [38%; 86%]
<b>Secondary Outcome Variables:</b>	
	<b>TZV/EFZ</b>
Proportion of subjects with a pVI < 400 copies/mL after 12 weeks of treatment resumption	
ITT Switch included, n (%) [95%CI]	12 (71%) [44%; 90%]
ITT Switch/missing=failure, n (%) [95%CI]	11 (65%) [38%; 86%]
Proportion of subjects with a pVI < 400 copies/mL after 24 weeks of treatment resumption	
ITT Switch included, n (%) [95%CI]	10 (59%) [33%; 82%]
ITT Switch/missing=failure, n (%) [95%CI]	9 (53%) [28%; 77%]
Proportion of subjects with a pVI < 50 copies/mL after 12 weeks of treatment resumption	
ITT Switch included, n (%) [95%CI]	9 (53%) [28%; 77%]
ITT Switch/missing=failure, n (%) [95%CI]	8 (47%) [23%; 72%]
Proportion of subjects with a pVI < 50 copies/mL after 24 weeks of treatment resumption	
ITT Switch included, n (%) [95%CI]	10 (59%) [33%; 82%]
ITT Switch/missing=failure, n (%) [95%CI]	9 (53%) [28%; 77%]
Median increase in CD4 cell count after 12 weeks of treatment (min; max) –: cells/mm <sup>3</sup>	+105.5 (-135; 305)
Median increase in CD4 cell count after 24 weeks of treatment (min; max) –: cells/mm <sup>3</sup>	+171.5 (-40; 382)
<b>Safety Results:</b> An on-therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on-therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to the last dose of medication.	
	<b>TZV/EFZ N=20</b>
<b>Most Frequent Adverse Events – On-Therapy</b>	
Subjects with any AE(s), n (%)	18 (90)
Sleep disorders	3 (15)
Vertigo	3 (15)
Dreams	2 (10)
Malaise & Fatigue	6 (30)
Allergies & Allergic reactions	2 (10)
Temperature regulation disturbances	2 (10)
Skin rashes	3 (15)
Throat & Tonsil discomfort & Pain	2 (10)
Disorders of lipid metabolism	2 (10)
Hypertension	2 (10)
<b>Serious Adverse Events - On-Therapy</b>	
n (%) [n considered by the investigator to be related to study medication]	
	<b>TZV/EFZ N=20</b>

	n (%) [related]
Subjects with non-fatal SAEs	3 (15) [2]
Allergies & Allergic Reactions	2 (10) [1]
Hypertension	1 (5) [1]
Subjects with fatal SAEs	0

**Conclusion:**

These data show that a large proportion of subjects experienced substantial plasma viral load suppression after resumption of a combination of TZV+EFZ following a shift in HIV genotypic resistance profile. Adverse events were reported in 18 (90%) subjects, with the most frequently reported being sleep disorders, and vertigo. Three (15%) subjects reported serious adverse events. No fatal serious adverse events were reported.

**Publications:**

Genotypic mutations in HIV-1 adult patients with treatment failure before and after antiviral therapy interruption. P. Massip, J. Izopet, G. Force, B. Delmas, H. Gallais, C. H. Aquilina, E. David, J. P. Mamet on behalf of AZLF3003 Study group. 14th International AIDS Conference: Knowledge and Commitment for Action; Barcelona; Spain. 2002 Jul 7

Shift in HIV-1 resistance after treatment interruption in patients with virological failure and antiviral effect following trizivir plus efavirenz. Izopet, Jacques; Massip, Patrice; Force, Gilles; Delmas, Benedicte; Gallais, Herve; Aquilina, Christian, and David, Frederique, 3/21/2005. 6th International Congress on Drug Therapy in HIV Infection; Glasgow; Scotland. 2002 Nov 17

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