SYNOPSIS

Trial Identification and Protocol Summary

Company: Tibotec Pharmaceuticals **Trade Name**: INTELENCE® **Indication**: HIV-1 infection	**Drug Substance**: etravirine **Trial no**.: CR017038 **Clinical Phase**: I
Title: A study to survey the swallowability of non-coated 200-mg tablets of etravirine in HIV-1 infected subjects	
Investigator: B. Rashbaum, Capital Medical Associates, 1640 Rhode Island Avenue, NW800, Washington DC 20036	**Country**: USA
Trial Period: Start: 29-MAR-2010 End: 06-MAY-2010	**No. of Investigators**: 3 **No. of Subjects**: 49

Objectives:

The primary objective of this study was to assess the swallowability of non-coated 200-mg ETR tablets (F068), expressed as an acceptability rate and its 95% confidence interval (CI).

The secondary objectives of this study were:

- To assess the swallowability of film-coated 200-mg ETR tablets (F074);
- To compare the swallowability between the non-coated (F068) and film-coated (F074) 200-mg ETR tablets;
- To elicit patient preferences between the non-coated (F068) and film-coated (F074) 200-mg ETR tablets;
- To compare the swallowability between dosing with the 200-mg ETR tablets and the commercially available 100-mg tablets (F060);
- To evaluate safety and tolerability of the non-coated and film-coated 200-mg ETR tablets, as assessed by limited safety evaluations.

Design: This was a study to assess the swallowability of uncoated (F068, described as non-coated hereafter) and film-coated (F074) 200-mg etravirine (ETR) tablets in HIV-1 infected subjects who are currently virologically suppressed on an ETR-containing regimen.

The study consisted of a screening visit and an assessment visit, followed by a 1-week post-treatment follow up period. The screening visit took place maximally 2 weeks before the assessment visit. The total study duration was a maximum of 3 weeks. Preferably, screening visit and assessment visit were combined into one visit, unless results needed to complete screening were not available prior to dosing.

The study population consisted of 49 HIV-1 infected subjects who were, at the time, taking ETR at a total daily dose of 400 mg (F060, commercial, as whole tablets orally) as part of a virologically suppressive antiretroviral regimen (HIV-1 RNA < 50 copies/mL for at least 3 months).

Subjects were instructed not to take their usual ETR dosing on the assessment day. The assessment visit included dosing with two 200-mg ETR tablets: a non-coated tablet (F068) followed by a film-coated tablet (F074). The second tablet was to be taken within approximately 30 minutes after intake of the first tablet. Tablets were administered in a single-blinded fashion to the subjects such that on the assessment day, ETR dosing was 400 mg q.d. A swallowability questionnaire was given immediately following each intake to assess the swallowability of each tablet. The questionnaire also contained a question to assess the swallowability of the commercially available 100-mg ETR tablet (F060) and on patient preferences. It was estimated that the survey would take no longer than approximately 30 minutes to complete.

Subjects continued their other antiretrovirals without interruption or change in administration schedules. Subjects resumed their normal ETR regimen the day after the assessment day..

Subject Selection

Inclusion Criteria

1. Male or female, aged 18 years or above.
2. All women had to have a negative serum or urine pregnancy test at screening. Women of childbearing potential had to have a negative urine pregnancy test at the assessment visit.
3. Subjects had to sign an informed consent document indicating that they understood the purpose of and procedures required for the study and were willing to participate in the study.
4. Subject had to be able to comply with the protocol requirements.
5. Subject with documented HIV-1 infection.
6. Subject was receiving an ETR-containing regimen which was taken by swallowing the ETR tablets (4 x 100-mg) whole.
7. Subject had HIV-1 RNA < 50 copies/mL at their last two assessments, with the last HIV-1 RNA < 50 copies/mL within the last 3 months prior to study start.
8. General medical condition, in the investigator's opinion, did not interfere with the assessments and completion of the trial.

Exclusion Criteria

1. Any condition that, in the opinion of the investigator, would compromise the study or the well-being of the subject or prevent the subject from meeting or performing study requirements
2. Any active clinically significant disease (e.g., pancreatitis, cardiac dysfunction) or findings during screening that, in the investigator's opinion, would compromise the subject's safety, ability to swallow (e.g., candidiasis), or outcome of the study
3. Pregnant or breastfeeding female subject.

Treatment	**Etravirine**	**Etravirine**
Concentration	200 mg	200 mg
Dosage Form (F No.)	Non-coated tablet F068	Film-coated tablet F074
Usage	Oral	Oral
Batch Number	9EL22	9EL4L
Dose Regimen	On the morning of the assessment day, within approximately 10 minutes of finishing breakfast, all subjects were given a single dose of the ETR non-coated 200-mg tablet (F068) in a single-blinded fashion (blindfolded, using a cup to hold the tablet). The subjects were given a (200 mL) glass of water to assist in swallowing the tablet. After intake of the tablet they were given a questionnaire to assess the swallowability of the tablet. Within approximately 30 minutes after the first tablet intake, a single dose of the ETR film-coated 200-mg tablet (F074) was administered in a single-blinded fashion (blindfolded, using a cup to hold the tablet). The subjects were given a (200 mL) glass of water to assist in swallowing the tablet. After intake of the tablet the questionnaire was again to be completed. Subjects were to continue their other antiretrovirals without interruption or change in administration schedules. On the day of the assessments, subjects were instructed not to take their usual ETR dosing. Subjects were to resume their normal ETR regimen the day after the assessment day.	

Duration of Treatment	1 day.
Duration of Trial	Maximum 3 weeks (maximum 2 week screening period, 1 day of treatment and 1 week follow-up period).
Disallowed Medication	The investigator provided subjects with information concerning prohibited medications during studies with ETR, using reference to the Investigator's Brochure (IB). In addition, all disallowed medication as mentioned in the package insert of drugs included in the antiretroviral therapy (ART) was prohibited medication in this study.

Assessments

Type of Visit	Screening Visit* (≤ 2 weeks before Assessment Visit)	Assessment Visit*	Posttreatment Follow-Up Visit** (1 week after Assessment Visit)
Time of Visit	**Week -2**	**Day 1**	**Week 1**
Visit	1	2	3
Informed consent	X		
Demographic data, height	X		
Weight	X		
Pregnancy test, if applicable[a]	X	X	
Inclusion/exclusion criteria	X		
Dosing of investigational medication on site		X[b]	
Swallowability Questionnaire		X[c]	
Collection of AEs	X	X	X

* Preferably, screening visit and assessment visit were combined into one visit, unless results needed to complete screening were not available prior to dosing. Duplicate assessments were not repeated if screening and assessment visit were on the same day.

** In case no AEs were observed, this follow-up visit could be done by phone.

[a] Serum test or urine dipstick at screening for all female subjects. Urine test at the assessment visit for female subjects of childbearing potential (only if screening visit and assessment visit were not on the same day).

[b] Subjects received a non-coated 200-mg ETR tablet (F068), followed by a film-coated 200-mg ETR tablet (F074). The second tablet was to be administered within approximately 30 minutes after intake of the first tablet. The first tablet intake was to take place within approximately 10 minutes after finishing breakfast.

[c] A swallowability questionnaire was to be completed immediately after each tablet intake. Subjects unable to read and/or write were to be provided assistance with completing the questionnaire.

Statistical Methods	The Intent-to-treat analysis was mainly descriptive; descriptive statistics, frequency tabulations, Cohen's kappa statistic.

Main Features of the Subject Sample and Summary of the Results

Baseline demographics	All subjects (N = 49)
Age, years	
Median (range)	49.0 (32-72)
Sex, n (%)	
Male	45 (91.8)
Female	4 (8.2)
Height, cm	
Median (range)	173.0 (155-188)
Weight, kg	
Median (range)	81.0 (61-117)
BMI, kg/m²	
Median (range)	27.3 (20-45)
Ethnic origin, n (%)	
Black	10 (20.4)
Caucasian/White	30 (61.2)
Hispanic	9 (18.4)
Education level, n (%)	
Some high school	3 (6.1)
High school or equivalent degree (includes GED)	7 (14.3)
Some college	12 (24.5)
College degree	17 (34.7)
Postgraduate degree	10 (20.4)
Discontinuations	0

GED = General Educational Development

Parameter	200mg F068 (Non-coated)	200mg F074 (Film Coated)	100mg F060 (Commercial)
How difficult/easy to swallow tablet, n (%)			
1: very difficult	1 (2.0)	1 (2.0)	8 (16.3)
2: moderately difficult	5 (10.2)	4 (8.2)	10 (20.4)
3: slightly difficult	9 (18.4)	5 (10.2)	10 (20.4)
4: neither difficult nor easy	6 (12.2)	3 (6.1)	7 (14.3)
5: slightly easy	1 (2.0)	2 (4.1)	0
6: moderately easy	4 (8.2)	6 (12.2)	7 (14.3)
7: very easy	23 (46.9)	28 (57.1)	7 (14.3)
How difficult/easy to swallow tablet			
Mean (SE)	5.1 (0.29)	5.7 (0.27)	3.6 (0.30)
95% Confidence Interval	4.56, 5.73	5.13, 6.22	3.02, 4.21
Median (Range)	6.0 (1-7)	7.0 (1-7)	3.0 (1-7)
Swallowing acceptability: dichotomization 1[a], n (%)			
Acceptable	34 (69.4)	39 (79.6)	21 (42.9)
Not acceptable	15 (30.6)	10 (20.4)	28 (57.1)

[a] Dichotomization 1: All scores 4 or higher were considered “acceptable” and all answers below 4 as “not acceptable”. Note: a higher score indicates greater swallowing acceptability.

Safety (n = number of subjects with data)	
Adverse Events (AEs)	
n (%) with 1 or more AEs (sinusitis)	1 (2.0%)
n (%) of deaths	0
n (%) with 1 or more other serious AEs	0
n (%) of treatment stopped due to AEs	0
n (%) with 1 or more grade 3 or 4 AEs	0

Conclusions

The results of the present trial demonstrate that in this etravirine-experienced population, 69.4% (95% CI: 54.6%-81.7%) of subjects assessed the non-coated 200-mg tablet (F068) as 'acceptable to swallow', compared with 79.6% (65.7%, 89.8%) and 42.9% (28.8%, 57.8%) for the 200-mg coated (F074) and 100-mg (F060) tablets, respectively. No relevant difference was observed in acceptability between film-coated (F074) and non-coated (F068) 200-mg tablets.

Subjects indicated a preference for the film-coated 200-mg (F074) tablets over their current etravirine 100-mg (F060) tablets and the non-coated 200-mg (F068) tablet. Subjects also indicated a preference for the non-coated 200-mg (F068) tablet over the current 100-mg tablet.

A single intake of 2 consecutive doses of 200-mg of ETR, administered as the non-coated formulation F068 followed by the film-coated formulation F074, was generally safe and well tolerated.

Disclaimer

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