2. SYNOPSIS

Title of Study: ESPrES 500 - Evaluation of the safety profile of the new 500 mg film-coated tablet (FCT) formulation of boosted saquinavir (Invirase® 500 mg) in HIV-1 infected patients	
Investigator(s): This multi-center study included 18 principal investigator(s).	
Study Center(s): This study was conducted at 18 study center(s) in 1 country	
Length of Study: 18 months Date of first patient visit: 29 December 2005 Date of last patient visit: 26 June 2007	**Phase of Development:** IIIb
Objectives: The aim of this trial was to gather additional information about the safety on the use of the new 500 mg film-coated tablet (FCT) formulation of boosted saquinavir (Invirase® 500 mg) in HIV infected patients. Efficacy ▪ To evaluate treatment response by CD4 cell count and HIV-RNA viral load. Safety ▪ To assess safety and tolerability ▪ To evaluate the safety and tolerability in different patient types and settings (PI naïve, toxicity switch from other PI).	
Study Design: National, multicenter, open-label, single arm safety study, to evaluate the safety and tolerability of saquinavir/ritonavir (SQV/r) 1000/100 mg bid when using Invirase® 500 mg film-coated tablet (FTC). Each subject was required to be followed for 24 exposure weeks.	
Number of Patients: 111 Planned: 300 Entered: 111 Treated: 87 Completed: 78	
Diagnosis and Main Criteria for Inclusion: ▪ Male and female HIV-1 infected adults (≥ 18 years of age), with detectable HIV-1 RNA viral load. Patients PI naïve or PI experienced still responders to saquinavir on the basis of resistance test or switching another ARV (included PI) for tolerability reasons. ▪ Patients receiving Invirase hard gel capsules (HGC) or soft gel capsules (SGC) 200 mg with or without ritonavir, at any dose prior to study entry were excluded as well as patients receiving double boosted PI regimen including saquinavir. Patients were also excluded in the presence of the following conditions: ▪ if female, pregnant, breast-feeding, or planned to become pregnant or breast-feed during the study; ▪ significant renal dysfunction (creatinine clearance [CrCl] <60 mL/min) and/or hepatic impairment (aspartate aminotransferase/alanine aminotransferase [AST/ALT] >3 X ULN and/or documented liver cirrhosis); ▪ current clinical or laboratory parameter of ACTG Grade 4; asymptomatic grade 4 abnormalities were permitted at the discretion of the investigator, if the potential benefit of treatment outweighed the potential risk; ▪ evidence of active, untreated opportunistic infection, intercurrent illness, drug toxicity or any other condition such that in the judgment of the investigator the patient would not be able to take or continue a prescribed antiretroviral regimen; ▪ malignancy requiring chemotherapy or radiotherapy; ▪ known hypersensitivity to any of the prescribed antiretroviral drugs or formulation components; ▪ evidence of alcohol and/or drug or substance abuse that in the judgment of the investigator would likely result in the patient being unreliable in fulfilling the conditions of the protocol; ▪ history of psychological illness or conditions that in the judgment of the investigator might interfere with the patient's ability to understand the requirements of the study; ▪ history of drug non-adherence that in the judgment of the investigator would result in the patient being unreliable in fulfilling the conditions of this protocol;	

- patients receiving an investigational new drug within the last 4 weeks;
- taking, or anticipate taking during the course of the study, any drug contraindicated with the antiretroviral drugs.

Study Drug, Dose, and Mode of Administration:
Saquinavir mesylate supplied as a salmon-coloured opaque 500-mg hard tablet. Two tablets of saquinavir mesylate administered by mouth twice daily, taken within 2 hours after a meal.
Ritonavir provided as Norvir, a 100-mg white soft gelatine capsule. One capsule of ritonavir administered by mouth twice daily with saquinavir.

Duration of Treatment:
24 weeks

Variables:
Efficacy:
- Changes in HIV-RNA and CD4
  - Number and percentage of patients with an HIV-RNA <50 cp/ml at Week 24
  - Change from baseline in plasma HIV-1 RNA viral load (copies/mL) at Week 24
  - Change from baseline in CD4 at Week 24

Safety:
- Number and percentage of patients with a grade 3 or 4 adverse event (primary endpoint)
- Comparison of AE's by patient type
  - PI naïve but treatment experienced
  - PI experienced still responder to saquinavir
  - Toxicity switch from other regimen
    - Prior PI use (LPV/r; ATV/r; fAPV/r; other)
    - Prior non-PI regimen
- Number and percentage of patients discontinuing study medication due to clinical adverse events
- Adherence assessment
- Incidence of GI AEs of any grade
- Incidence of treatment-emergent clinical (ACTG Grade $\leq$ 2) adverse events and any Grade of laboratory abnormalities.
- Incidence of deaths
- Incidence of AIDS Defining Events (ADEs)
- Changes from baseline in physical examination findings, vital signs, and clinical laboratory tests (hematology, chemistry and lipids)

Evaluation Methods:
Statistical: All the analyses were performed on treated patients.
Baseline characteristics were analyzed by means of count and percentage for categorical variables and means, standard deviation, median and range for continuous variables.
Efficacy analysis and treatment compliance were performed on patients evaluable for efficacy, defined as those completing a minimum of 10 exposure days.
Safety analyses were performed analyzing adverse events rate and the rate of abnormal laboratory values.
Adverse Events were coded using MedDRA Version 10.
No formal tests of statistical inference were performed.
The analysis was performed using SAS System 9.1.

Sample size determination Not Planned / Not Applicable

Results

Analyses of secondary efficacy variables
The primary objective of this non controlled study was related to safety, and efficacy was investigated as a secondary objective.
The treatment resulted effective in decreasing the HIV-RNA, significantly versus baseline values, at all time points (4, 12 and 24 weeks) in both groups: Treatment Experienced and Naïve. As a consequence, the number of patients with an HIV-RNA < 50 cp/ml continuously increased by reaching the proportion of about 70% in both groups at the end of treatment.
In addition, CD4 count significantly increased at all time points compared to baseline, in both groups: Treatment Experienced and Naïve patients.
Therefore, the study achieved its efficacy objective.

Safety:
The treatment was well tolerated: grade 3-4 AEs occurred in 5.7% of patients, with similar distribution between Treatment Experienced (5.7%) and Naïve (5.9%) patients. Treatment related AEs occurred in 16.1% of patients, again with similar distribution between the two groups (Treatment Experienced: 15.1%, Naïve 17.6%).
Three patients experienced a Serious Adverse Event (SAE); among these one was considered having a 'remote' drug-relationship (depression, patient nr. [redacted] in the Treatment Experienced group, Grade 3).
Treatment related SAEs occurred only in two patients of Treatment Experienced group (3.8%).
Four more patients in the Treatment Experienced group, in addition to patient [redacted] experienced an AE of grade 3-4:

- [redacted] Hypercolesterolemia, possibly drug-related (227 mg/dl at study entry);
- [redacted] Hypercolesterolemia, possibly drug-related (152 mg/dl at study entry);
- [redacted] High level of Transaminases, defined as drug-relationship 'remote' (28 U/L at study entry);
- [redacted] Hypertrigliceridemia, probably drug-related (694 mg/dl at study entry).

Overall, diarrhoea and nausea were complained of by 4.6% and 3.4% patients, respectively. Those AEs were never severe (grade 1-2).

Conclusions:
This was a national, multicenter, open-label, single arm safety study on 87 HIV Treatment- Experienced or Naïve patients, to assess the safety and the efficacy of a total daily dose of 2000 mg of saquinavir, using Invirase FCT 500 mg, boosted with 200 mg of ritonavir (divided into two daily doses), chosen as appropriate treatment in combination with other ARV.
Eligibility was determined at a screening visit within 28 days before the baseline visit. Protocol-defined study assessments took place at clinic visits at the end of weeks 4, 12 and 24. Patients returned for a follow-up visit 4 weeks after the end of treatment.
The primary objective of the study was to assess safety and tolerability of saquinavir/ritonavir 1000/100 mg bid when using Invirase film-coated tablet 500 mg (Invirase® 500 mg). Secondary objectives were the evaluation of treatment response by CD4 cell count and HIV-RNA viral load, and to evaluate the safety and tolerability in different patient types and settings (PI naïve, toxicity switch from other PI).
The treatment was well tolerated: grade 3-4 AEs occurred in a minority of patients, with similar distribution between Treatment Experienced and Naïve patients. Treatment-related AEs occurred in about 16.% of patients of both groups. Treatment related SAEs occurred only in two patients of Treatment Experienced group (3.8%). Overall, diarrhoea and nausea were complained of by 4.6% and 3.4% patients and were never severe (grade 1-2). Hypertriglyceridemia was graded as severe in 1.9% and hypercholesterolemia in 3.8% of Treatment Experienced patients.
The study met its efficacy objective, in fact the treatment resulted effective in decreasing the HIV-RNA, significantly versus baseline values, at all time points in both groups: Treatment Experienced and Naïve. As a consequence, number of patients with an HIV-RNA < 50 cp/ml continuously increased by reaching the proportion of about 70% in both groups at the end of treatment.
In addition, CD4 count significantly increased at all time points compared to baseline, in both groups: Treatment Experienced and Naïve patients.

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