INTELENCE® (etravirine)
INTELENCE - Once-Daily Dosing

SUMMARY

- In the INROADS study, treatment-experienced patients and treatment-naïve patients were administered INTELENCE 400 mg once daily (QD) and darunavir/ritonavir (DRV/r) 800/100 mg QD. The confirmed virologic response (CVR) rate at week 48 was 89% (95% CI, 79.7-98.1).[1]
- In an observational study[2], the Kaplan-Meyer estimate of efficacy at week 52 was 88.0% in patients with adverse events (AEs) to previous regimens that switched to INTELENCE (mostly QD) in combination with 2 nucleoside/tide reverse transcriptase inhibitors (NRTIs). The estimated response rate was 77.4% in patients treated with INTELENCE that had virologic failure (VF) with a previous NNRTI-based regimen.[2]
- In a prospective study, the virological and immunological efficacy of switching HIV-1-infected patients that received protease inhibitor (PI)-containing triple therapy for ≥12 months and had a viral load (VL)<50 copies/mL for ≥6 months to INTELENCE 400 mg QD was assessed at week 48.[3]
    - In an intention-to-treat (ITT) analysis (missing=failure), 90.9% of patients in the INTELENCE group and 95.2% of patients in the control group achieved a VL<50 copies/mL at week 48 (*P*=0.96).
    - Treatment was discontinued by 2 patients in the INTELENCE group (grade 1 diarrhea and voluntary discontinuation) and 1 patient in the control group (change of regimen to simplify).
- A phase 2 placebo-controlled study (SENSE Study) evaluated neuropsychiatric (NPS) AEs at 12 weeks in treatment-naïve patients randomized to QD INTELENCE or efavirenz (EFV) plus 2 NRTIs.[4] Analysis of NPS AEs and VL suppression continued through week 48.[5]
    - The prevalence of treatment-emergent grade 1-4 drug-related NPS AEs was significantly lower in the INTELENCE arm versus the EFV arm (16.5% versus 46.2%, respectively; *P*<0.0001) at 12 weeks.[4]
    - In the ITT time to loss of virological response (TLOVR) analysis, 60/79 (76%) of patients in the INTELENCE arm and 58/78 (74%) of patients in the EFV arm achieved a VL<50 copies/mL at week 48.[5]
- A single-arm study evaluated the antiretroviral activity, safety and tolerability of INTELENCE 400mg QD with tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) 300mg/200mg QD in treatment-naïve HIV-infected adults.[6]
    - In an ITT analysis, INTELENCE achieved a VL<50 copies/ml at week 48 for 61/79 (77%) of eligible subjects.
    - The prevalence of any Grade 2 or higher AE was 18/79 (23%), with 3 subjects (3.8%) discontinuing INTELENCE because of toxicity.
- In a prospective cohort study, once-daily INTELENCE/raltegravir (RAL) achieved a VL ≤50 copies/mL in 99/111 HIV-1 infected adults who switched from twice-daily INTELENCE/RAL therapy.[7]

CLINICAL STUDIES

INROADS Study

The INROADS (**I**ntelence a**N**d p**R**ezista **O**nce **A** **D**ay) **S**tudy evaluated the efficacy and safety of INTELENCE 400 mg QD with DRV/r 800/100 mg QD as a nucleoside-sparing regimen in treatment-experienced HIV-1-infected patients or treatment-naïve patients with transmitted resistance to at least 1 antiretroviral agent (ARV).[1]

Study Design/Methods

- Single-arm, open-label, multicentered, 48-week, phase 2b study (N=54).[1]

- All patients received INTELENCE 400 mg (2 x 200 mg tablets) and DRV/r 800/100 mg QD.
- Treatment-experienced patients (n=42) currently on highly active antiretroviral therapy (HAART) were required to have a baseline VL>500 copies/mL, a CD4+ cell count ≥50 cells/μL, and had ≤2 previous VFs on a PI-containing regimen.
- Treatment-naïve patients (n=12) had documented primary drug resistance that conferred genotypic or phenotypic resistance to either efavirenz or nevirapine.
- Primary endpoint: The proportion of patients with VL<50 copies/mL at week 48 (CVR, non-VF censored).
    - CVR non-VF censored is an adaptation of the TLOVR algorithm that allows subjects who are resuppressed after VF to be counted as virologic successes (CVR) and censors subjects who discontinue for reasons other than VF, except in cases where VF precedes discontinuation for other reasons (non-VF censored).
- 41 patients (76%) completed the study, with AEs and VF being the most common reasons for discontinuation (7% each).

Results

Efficacy

- The CVR rate at week 48 (ITT non-VF censored population; N=45) was 89% (95% CI 79.7-98.1).
    - CVR was achieved early and was sustained in both the treatment-experienced and treatment-naïve patients (ITT non-VF population):
        - Week 12: 69% (27/39) and 78% (7/9), respectively.
        - Week 48: 87% (32/37) and 100% (8/8), respectively
- The median increase in CD4+ cell count from baseline to week 48 was +185 cells/μL.
- Of the 7 patients who experienced VF, 3 were nonresponders and 4 experienced viral rebound.
    - Baseline and withdrawal resistance data was available for 2 of the 7 VFs; both had confirmed treatment-emergent NNRTI/INTELENCE resistance-associated mutations (RAMs). No treatment-emergent PI RAMs were identified.
        - 1 patient had L100I, E138G, and Y181C RAMs.
        - 1 patient had E138K and M230L RAMs.

Safety

- 78% of patients experienced an AE, regardless of severity or causality.
- The most common treatment-emergent AEs (any grade reported in ≥5% of patients, regardless of causality) reported were diarrhea (n=8, 15%), rash (n=8, 15%), and upper respiratory tract infection (n=6, 11%).
- Discontinuation due to AEs occurred in 4 patients (7%):
    - Nausea and vomiting (grade 1), rash (grade 3), fatal pneumonia (grade 4), fatal Hodgkin's disease and dyspnea (grade 4)

Observational Study

López-Cortés et al (2014)[2] conducted an observational study to evaluate the efficacy and safety of INTELENCE plus 2 NRTIs in HIV patients that were seen in HIV clinics in Spain (N=287).

Study Design/Methods

- The study population was divided into 2 groups and received INTELENCE in combination with 2 NRTIs:

- Group A: Patients without VF or no experience with NNRTIs, but switched due to AEs with their prior regimen (n=242). INTELENCE was administered as 400 mg QD in 89% of patients.
- Group B: Patients with virologic failure on a nevirapine or efavirenz-based regimen (n=45). INTELENCE was administered as 400 mg QD in 64% of patients.

- The primary endpoint was efficacy (HIV-RNA levels <50 copies/mL) at 52 weeks using an ITT analysis.
- Treatment failure was defined as treatment interruption for any reason or VF.

Results

Efficacy

- In group A, the Kaplan-Meyer estimate of efficacy at week 52 was 88% (95% CI, 83.9%-92.1%) in the ITT analysis.
  - The 30 treatment failures were due to AEs (n=11; 4.5%), VF (n=8; 3.3%), treatment dropout (n=4; 1.7%), other reasons (n=4; 1.6%), and loss to follow-up (n=3; 1.2%).
  - The VF rate in patients that received INTELENCE QD and twice daily (BID) was 2.8% and 6.9%, respectively (*P*=0.243).
- In group A, the median increase in CD4+ cell count was 58 cells/μL from baseline to week 52.
- In group B, the Kaplan-Meyer estimate of efficacy at week 52 was 77.4% (95% CI, 65%-89.7%) in the ITT analysis.
  - The efficacy in group B was lower compared to group A in the ITT analysis (*P*=0.006).
  - The 10 treatment failures were due to VF (n=4; 8.9%), loss to follow-up (n=3; 6.7%), AEs, treatment dropout, and other reasons (n=1 each; 2.2%).
  - The VF rate in patients that received INTELENCE QD and BID was 3.4% and 21.4%, respectively (*P*=0.094).
  - In group B, the median increase in CD4+ cell count was 61 cells/μL from baseline to week 52.

Safety

- 41 patients (14.3%) reported AEs including dizziness (n=9), nausea or vomiting (n=9), rash (n=6), nightmares or insomnia (n=5), diarrhea (n=4), constipation (n=2), depression (n=2), abdominal discomfort (n=1), lipoatrophy (n=1), lipohypertrophy (n=1), peripheral neuropathy (n=1).
  - All these AEs were grade 1-2 severity.
  - These AEs led to the change of treatment in 12 patients.

ETRASWITCH Study

Echeverria et al (2014)[3] assessed the virological and immunological efficacy at week 48 of switching HIV-1-infected patients, who were receiving PI-containing triple therapy for ≥12 months with VL<50 copies/mL for ≥6 months, to INTELENCE 400 mg QD therapy (N=43).

Study Design/Methods

- Prospective, randomized, pilot study.
- Participants were randomly assigned in a ratio of 1:1 to switch from the PI to INTELENCE 400 mg/day (n=22) or to continue with the same PI-based regimen (control group, n=21).
- The primary efficacy analysis was the proportion of patients achieving a VL ≤50 copies/mL at week 48.

- Patients were required to have no documented NNRTI or NRTI resistance or VF with previous regimens at baseline.
- Patients were eligible to be switched from their PI-containing regimen to INTELENCE 400 mg QD if they had dyslipidemia, were currently using lipid-lowering agents, had ARV-induced gastrointestinal disturbances, or repeatedly expressed dissatisfaction with their current ARV regimen.

Results

Efficacy

- In an ITT analysis (missing=failure), 90.9% of patients in the INTELENCE group and 95.2% of patients in the control group achieved a VL<50 copies/mL at week 48 (*P*=0.96).
- In an on-treatment analysis of patients who completed the study, no significant difference in the rate of patients achieving a VL<50 copies/mL were noted at week 48 (100% in both groups, *P*=0.84).
- The mean CD4+ cell counts at baseline and at week 48 were 702 and 749 cells/L in the INTELENCE group and 717 and 713 in the control group. No significant differences were noted between the treatment groups at any time point.

Safety

- Treatment was discontinued by 2 patients in the INTELENCE group (grade 1 diarrhea and voluntary discontinuation) and 1 patient in the control group (change of regimen to simplify).
- No grade 3 or 4 AEs were reported.
- Patients in the INTELENCE group showed significant reductions in cholesterol (207 to 191 mg/dL, *P*<0.001), triglycerides (186 to 132 mg/dL, *P*<0.001), and blood glucose (97 to 93 mg/dL, *P*=0.03) from baseline to week 48. No significant changes were noted for high-density lipoprotein (HDL), low-density lipoprotein (LDL), or total cholesterol/HDL ratio.
- No significant changes in lipids or blood glucose from baseline to week 48 were noted in the control group.
- No significant changes or grade 3 or 4 elevations in liver enzymes were observed.

SENSE Study

Nelson et al (2011)[4] evaluated NPS AEs at 12 weeks in treatment-naïve patients randomized to QD INTELENCE or EFV, plus 2 NRTIs (N=157). **Gazzard et al (2011)**[5] analyzed NPS AEs and HIV-RNA suppression at week 48.

Study Design/Methods

- Double-blind, placebo-controlled study in treatment-naïve patients randomized to receive INTELENCE 400 mg QD (n=79) or EFV 600 mg QD (n=78) plus 2 NRTIs.[5]
    - NRTIs in the INTELENCE treatment arm: TDF/FTC, 60%; ABC/3TC, 26%; ZDV/3TC, 14%.

Results

Efficacy

- In the ITT-TLOVR analysis, 60/79 (76%) of patients in the INTELENCE arm and 58/78 (74%) of patients in the EFV arm had a VL<50 copies/mL at week 48.[5]
    - Baseline VL≤100,000 copies/mL: 77% (n=52) in the INTELENCE arm and 78% (n=51) in the EFV arm.

    - Baseline VL>100,000 copies/mL: 74% (n=27) in the INTELENCE arm and 67% (n=27) in the EFV arm.
- The mean CD4+ count change from baseline to week 48 was +232 cells/μL and +236 cells/μL in the INTELENCE and EFV arms, respectively.[5]
- At 48 weeks there were fewer VFs (TLOVR) in the INTELENCE arm (n=4) than the EFV arm (n=7).[5]
    - None of the INTELENCE VFs had treatment-emergent NRTI or NNRTI mutations. In the EFV arm, 3 of the VFs had treatment-emergent NRTI or NNRTI mutations.
- In the on-treatment analyses, which excluded discontinuations due to non-VF reasons, 92% and 89% of patients achieved a VL<50 copies/mL in the INTELENCE and EFV arms, respectively.[5]

NPS Events - Week 12

- At week 12, The prevalence of treatment-emergent grade 1-4 drug-related NPS AEs was significantly lower for the INTELENCE arm than the EFV arm (16.5% and 46.2%, respectively; $P<0.001$).[4]
- At least 1 grade 1-4 nervous system disorder (all-cause) was reported in 20.2% of INTELENCE patients and 33.4% of EFV patients.
    - Dizziness, the most common nervous system AE, was reported in 3 (4%) INTELENCE patients and 15 (19%) EFV patients.
- At least 1 grade 1-4 psychiatric disorder (all-cause) was reported in 11% of INTELENCE patients and 39% of EFV patients.
    - Sleep disorder was the most common psychiatric AE reported: INTELENCE (9%) and EFV (32%).
- 18 patients discontinued the study by week 12 (10 in the INTELENCE arm and 8 in the EFV arm).
    - All patients in the EFV arm discontinued due to AEs.
    - Patients in the INTELENCE arm withdrew due to: withdrawal of consent (n=3), AEs (n=4), loss to follow-up (n=1), and other non-virological reasons (n=2).
    - 1 patient in the INTELENCE arm and 5 in the EFV arm discontinued due to NPS AEs.

NPS Events - Week 48

- 4/79 patients (5%) in the INTELENCE arm and 12/78 patients (15%) in the EFV arm reported ≥1 grade 2-4 drug-related psychiatric AE up to week 48 ($P<0.05$).
- The percentage of patients with ≥1 grade 2-4 drug-related nervous system AE was 1/79 (1%) of patients in the INTELENCE arm and 13/78 (17%) in the EFV arm ($P<0.01$).[5]
- At the week 48 visit, the percentage with an ongoing grade 1-4 drug-related NPS AEs was 6.3% with INTELENCE and 21.5% with EFV; $P=0.011$.

Pharmacokinetics

- 71 of the 79 patients who received INTELENCE had evaluable pharmacokinetic (PK) data.[8]
- The area under the plasma-concentration time curve (AUC_{24h}) of etravirine from the SENSE study was similar to other INTELENCE studies in which INTELENCE 400 mg QD and INTELENCE 200 mg BID were assessed.[8]
- No correlation between etravirine exposure and viral suppression or the incidence of AEs at week 48 was observed.[8]

48-Week Results for Once-Daily INTELENCE

Floris-Moore et al (2016)[6] evaluated the antiretroviral activity, safety and tolerability of INTELENCE 400mg QD with TDF/FTC 300mg/200mg QD in treatment-naïve HIV-infected adults at 48 weeks.

Study Design/Methods

- Single arm, open-label study, enrolling 79 treatment-naïve HIV-infected adults.
  - All subjects received INTELENCE 400mg and TDF/FTC 300mg/200mg once daily.
  - Subjects were assessed at screening, baseline, and at weeks 2, 4, 8, 12, 24 and 48 and a planned follow-up for a total of 96 weeks.
  - The primary outcome measure was the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 (intention-to-treat [ITT] analysis, with missing counted as failure)
  - Secondary outcome measures included proportion of subjects with HIV RNA <50 copies/mL at Week 48 and Week 96, proportion with HIV RNA <200 copies/mL at all three time points, and change in CD4+ cell count from baseline to Weeks 24, 48 and 96.

Results

Efficacy

- In an ITT analysis, INTELENCE achieved a VL<50 copies/ml at week 48 for 61/79 (77%, 95% CI: 66 - 86%) of eligible subjects with 11 subjects (14%) experiencing virologic failure.
  - A VL result was unavailable for 10 of the 79 subjects at the week 48 visit, because of either premature study discontinuation (n=7) or missed evaluation (n=3). A missing result was treated as a failure.
  - 3 of the 5 subjects with VL ≥ 500 copies/ml at week 48 had genotype testing showing RAMs (2 with E138K (1 alone and 1 with additional mutations)), which were not present at baseline. The other 2 subjects did not have samples available for testing.
  - The median increase in CD4+ cell count from baseline was 163 (136, 203) cells/mm^3 at week 48 (n= 69).

Safety

- The prevalence of any Grade 2 or higher AE was 18/79 (23%), with 3 subjects (3.8%) discontinuing INTELENCE because of toxicity.
  - Rash and transaminase elevation were the most commonly reported Grade 2 or higher AE's. Both events were reported by 5 subjects (6.3%).
  - A new sign/symptom or lab abnormality (≥ Grade 3) was reported by 15 subjects (18.9%).
  - Three participants permanently discontinued INTELENCE due to toxicity: one had Grade 2 rash alone; one had Grade 2 rash and concomitant Grade 1 aspartate aminotransferase elevation; and the third had elevated aspartate aminotransferase and alanine aminotransferase (Grade 2) as well as total bilirubin (Grade 1) levels.
  - No deaths were reported during this study.
- A substudy was conducted evaluating lipid profiles, insulin resistance and body fat distribution.
  - At week 48, there was a 5 (2 to 8) mg/dL median increase in HDL-C (n=58).
  - There was a 4.3 (0.3 to 8.4) µU/mL median increase in insulin levels at week 48 (n=24).
  - No significant changes in body fat distribution were observed at week 24, using a Whole-Body Dual X-ray Absorptiometry Scan (n=37).

Palich et al (2021)[7] evaluated the virological efficacy of switching HIV-1 infected patients that received twice-daily INTELENCE 200 mg/RAL 400 mg for at least 96 weeks to once-daily INTELENCE 400 mg/RAL 800 mg at week 48.

Study Design/Methods

- A total of 111 participants, including those previously enrolled in the ANRS-163 ETRAL study (n=51), with a HIV-RNA VL <50 copies/mL were included in the prospective cohort study.
- The primary endpoint (ITT population) was the proportion of participants with virological failure (VF), defined as a VL >50 copies/mL, at week 48.

Results

- Ninety-nine participants reported a VL ≤50 copies/mL at week 48.
- Protocol-defined VF occurred in 2 participants, resulting in a VF rate of 2.0% (95% CI, 0.5-7.8) at week 48.
    - Resistance mutations associated with integrase strand transfer inhibitor (INSTI) were found in one of the participants with VF.
- Ten participants discontinued treatment due to the following reasons: adverse events (n=2), investigator or patient decisions (n=3), death due to myocardial infarction (n=1), lost to follow-up (n=3) or pregnancy (n=1).
- Overall, at week 48, the strategy success rate of viral suppression was 89% (95% CI, 81.5-93.6).
- In a subgroup of 64 participants with plasma concentration data, median (interquartile range [IQR]) plasma C_{24h} concentrations for INTELENCE and RAL were 401 ng/mL (280-603) and 62 ng/mL (31-140), respectively.
- In a subgroup of 74 participants with weight data, there was no significant change in median body weight or body mass index (BMI) reported at week 48.
- There was no significant change observed in the CD4+ cell count or CD4/CD8+ ratio.

Phase 2a Study

DeJesus et al (2010)[9] evaluated the PK, short-term safety, and efficacy of INTELENCE 400 mg QD in treatment-naïve, HIV-1-infected patients (N=23).

Study Design/Methods

- Phase 2a, multicenter, open-label, single-arm study through day 42.
- All patients received 3 treatments sequentially, each regimen consisting of a combination of ≥2 of the following ARVs: INTELENCE 400 mg QD, DRV/r 800/100 mg QD and/or TDF/FTC 300/200 mg QD.

Results

Pharmacokinetic Analysis

- Mean plasma concentrations for etravirine following coadministration of INTELENCE + DRV/r and TDF/FTC were comparable to INTELENCE + TDF/FTC without DRV/r (Table: PK Parameters for Etravirine 400 mg QD).

PK Parameters for Etravirine 400 mg QD[9]

Parameter, mean (SD)	INTELENCE + TDF/FTC (n=21)	INTELENCE + TDF/FTC + DRV/r (n=20)
C_{min}, ng/mL	233 (130)	236 (168)
C_{max}, ng/mL	790 (287)	801 (327)
t_{max}, h [median (range)]	4 (2–6)	4 (3–9)

AUC_{24h}, ng•h/mL	10,410 (4186)	10,720 (5459)

Abbreviation: AUC_{24h}, area under the plasma concentration-time curve at 24 hours; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; PK, pharmacokinetic; QD, once daily; SD, standard deviation; t_{max}, time to maximum plasma concentration.

- Overall, the etravirine C_{max} was higher, the C_{min} was lower, and the AUC was similar when comparing INTELENCE QD dosing in the current study to INTELENCE BID dosing in treatment-experienced patients in the historical control.
    - DUET-1 and DUET-2 were two randomized, double-blind, placebo-controlled, multinational, phase 3 studies (N=1,203). Treatment-experienced, HIV-1-infected patients were randomized (1:1) to receive INTELENCE 200 mg BID (n=599) or placebo (n=604), each in combination with a background regimen (BR) of DRV/r 600/100 mg BID and ≥ 2 investigator-selected ARVs: N[t]RTIs or enfuvirtide (ENF) based on screening genotypic resistance assay and treatment history.

Efficacy

- The mean VL decline for all patients on INTELENCE QD was 1.7 log_{10} copies/mL at day 14, 1.8 log_{10} copies/mL at day 28 and 2.0 log_{10} copies/mL at day 42.[9]
- The median increase in CD4+ cell count from baseline was 56 cells/mm^3 at day 42 (n=19).[9]

Safety

- At least 1 AE was reported in 60.9% (14/23) of patients in the INTELENCE + TDF/FTC group and in 47.6% (10/21) of the INTELENCE + TDF/FTC + DRV/r group.
- There were no reports of serious AEs, grade 3 or 4 AEs, or AEs leading to discontinuation.
- The impact on metabolic parameters is presented in Table: Median Change in Metabolic Parameters and Laboratory Abnormalities.

Median Change in Metabolic Parameters and Laboratory Abnormalities[9]

Parameter, median (range)	Baseline (n=23)	INTELENCE + TDF/FTC (n=21)	INTELENCE + TDF/FTC + DRV/r (n=21)	TDF/FTC + DRV/r (n=20)
Triglycerides, mg/dL	70 (35, 249)	1 (-124, 103)	24 (-80, 104)	33 (-88, 166)
Total cholesterol, mg/dL	145 (110, 222)	-3 (-45, 44)	1 (-51, 47)	11 (-64, 58)
Direct LDL cholesterol, mg/dL	92 (59, 139)	-8 (-43, 29)	-6 (-36, 32)	2 (-39, 49)
HDL cholesterol, mg/dL	41 (30, 60)	0 (-12, 17)	-2 (-26, 14)	-1 (-30, 8)
TC/HDL ratio	3.67 (2.20, 4.95)	-0.05 (-1, 0.72)	0.10 (-0.58, 4.82)	0.36 (-0.38, 7.65)
Glucose, mg/dL	91 (75, 107)	-2 (-36, 42)	-2 (-31, 12)	-2 (-22, 43)
Insulin, µU/mL	5 (1.9, 23)	-1 (-13.3, 11.3)	0 (-16, 20)	0 (-10, 32.2)

Abbreviation: LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol.

PHARMACOKINETIC STUDIES (HIV-1-NEGATIVE SUBJECTS)

INTELENCE QD vs BID PK Data

Schöller-Gyüre et al (2007)[10] evaluated the PK of dosing INTELENCE (phase 3 formulation) QD and BID in 2 separate phase 1 studies (C168 and C178).

Study Design/Methods

- 2 randomized, crossover, multiple dose PK studies in HIV-negative subjects.
  - Study C168 was an open-label study (N=24).
  - Study C178 was a double-blind study (N=41).
- In both studies, all subjects were randomized to receive INTELENCE following a meal for 7 days with a morning dose on day 8 in 2 separate treatment regimens (C168 [INTELENCE 100 mg BID and INTELENCE 200 mg QD); C178 [INTELENCE 200 mg BID and INTELENCE 400 mg QD]). The regimens were separated by a washout period of 14 days.

Results

- On day 8 of C168, the etravirine C_{min} for the INTELENCE 200 mg QD dose was 26% lower and the C_{max} was 42% higher compared with INTELENCE 100 mg BID.
- On day 8 of C178, the etravirine C_{min} for the INTELENCE 400 mg QD dose was 25% lower and the C_{max} was 44% higher compared with INTELENCE 200 mg BID.

PK of INTELENCE QD Switch from Efavirenz

Boffito et al (2009)[11] evaluated the PK of INTELENCE QD and BID following the use of EFV in HIV-negative subjects.

Study Design/Methods

- Phase 1, randomized, open-label, parallel assignment study (N=25).
- All subjects were randomized to 1 of 2 treatment arms containing INTELENCE 400 mg QD (n=12) or 200 mg BID (n=13).
- Subjects received their randomized INTELENCE treatment for 14 days, followed by a 14-day washout period, then EFV 600 mg QD for 14 days.
- EFV was discontinued on day 42 and EFV concentrations were determined daily from days 42 through 56.
- INTELENCE was restarted on day 42 and continued for the final 14 days of the study.
- 12-hour INTELENCE PK assessments were determined on days 1, 14, 43, and 56; C_{trough} concentrations were assessed up to 12 hours post-dose in the INTELENCE 200 mg BID group and 24 hours post-dose in the INTELENCE 400 mg QD group.

Results

- Comparable reductions from baseline (day 14) in steady-state etravirine PK parameters (C_{max}, C_{trough}, AUC_{0-24h}) were observed in both the INTELENCE QD (C_{max} ↓ 22%, C_{trough} ↓ 33% and AUC_{0-24h} ↓ 29%) and BID arms (C_{max} ↓ 21%, C_{trough} ↓ 37% and AUC_{0-24h} ↓ 28%) following 2 weeks of EFV 600 mg QD (day 56).
- Significant differences from baseline (day 14) were observed between male and female subjects for reductions in etravirine AUC (26.5% and 7.5%, respectively; *P*=0.05) and C_{trough} (35% and 2.4%, respectively; *P*=0.017).
- All subjects had detectable EFV plasma concentrations 7 days (day 50) after the last administered dose of EFV (day 43).
- EFV induction effects on INTELENCE were still observed after discontinuation of EFV.
  - EFV plasma concentrations were negatively correlated with etravirine AUC and C_{trough} plasma concentrations.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 13 September 2023. Patient-reported outcomes studies, studies of male patients with

continuing central nervous system AEs, intracellular studies, and laboratory analyses are not summarized.

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