Impact of the hepatitis B virus (HBV) capsid inhibitor, AB-506, on the single dose pharmacokinetics (PK) of a combined oral contraceptive (COC)

Poster #32

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BACKGROUND

- HBV capsid inhibitors are being developed as potential components of new combination regimens for the treatment of chronic hepatitis B (CHB) infection.
- AB-506 is an oral, class II, selective HBV capsid inhibitor for the treatment of CHB infection.
  - AB-506 development was discontinued due to transaminase elevations following treatment ≥14 days that were initially observed in Asian subjects with CHB that were subsequently replicated in healthy subjects.
- An important component of care for HBV-infected women includes the use of effective contraceptive methods to reduce the risk of unintended pregnancy and mother-to-child transmission of HBV, which accounts for the majority of new HBV infections in areas of high prevalence.[1]
- Prior to program discontinuation, study AB-506-002 assessed the effect of AB-506 on the single dose PK of a COC containing drospirenone (DRSP) 3 mg and ethinyl estradiol (EE) 0.02 mg.

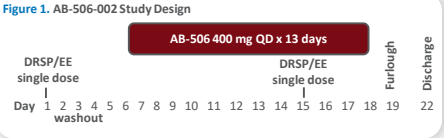
OBJECTIVES

- To assess the effect of AB-506 400 mg once daily (QD) dosing on the single dose PK of DRSP and EE.
- To assess the safety and tolerability of AB-506 in combination with a combined oral contraceptive in healthy female subjects.

MATERIALS AND METHODS

- Study AB-506-002 was a Phase 1, open-label, 2-period, fixed-sequence study in 16 healthy female subjects (see Figure 1).

Figure 1. AB-506-002 Study Design

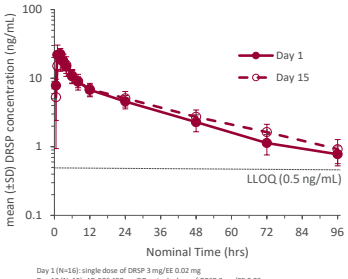


- Subjects were confined to the clinical unit from Day -1 through Day 19, after which they were furloughed until Day 22. Subjects were discharged from the study on Day 22 following completion of all study procedures.
- DRSP/EE tablet administered under fasted conditions on Day 1 and Day 15; AB-506 was administered without regard to food with the exception of coadministration under fasted conditions with DRSP/EE on Day 15.
- Serial blood samples for quantification of DRSP and EE were collected up to 96 hours post-dose on Day 1 and Day 15.
- Concentrations of DRSP and EE were determined via a validated LC/MS/MS assay [QPS LLC, Newark, DE, USA] and single dose PK parameters on Day 1 and Day 15 were derived by noncompartmental methods [Phoenix 8.2, Certara, Princeton, NJ, USA].
- Cmax and Tmax were determined by direct inspection of concentration-time data. AUC parameters were estimated via the linear up log down method. $AUC_{0-\infty}$ was excluded from analysis for an individual subject if %AUC extrapolated > 20%. PK parameters were summarized.
- To assess the impact of AB-506 on exposures, the Bioequivalence Module in Phoenix WinNonlin was used to estimate Day 15/Day 1 ratios and 90% confidence intervals (CIs) for DRSP and EE Cmax, AUC_{0-t}, and $AUC_{0-\infty}$.
- Safety and tolerability were monitored throughout the study via collection of adverse events (AEs), physical examinations, vital signs, ECGs and clinical laboratory testing.
- Study Population
  - Healthy female subjects aged 18 to 50 years, inclusive.
  - BMI ≥18 to ≤30 kg/m^2.

RESULTS

Drospirenone Pharmacokinetics

Figure 2. Mean (± SD) DRSP Plasma Concentration vs Time



Day 1 (N=16): single dose of DRSP 3 mg/EE 0.02 mg
Day 15 (N=15): AB-506 400 mg QD + single dose of DRSP 3 mg/EE 0.02 mg
LLOQ: lower limit of quantitation

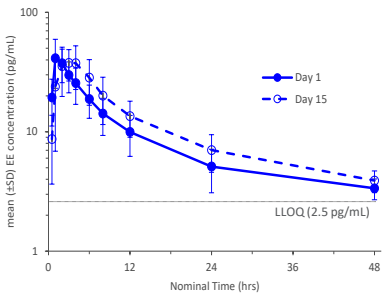
Table 2. DRSP PK Parameter Summary Statistics

DRSP PK parameter	Day 1 [N=16]	Day 15 [N=15]
Cmax (ng/mL) Geometric mean (%CV)	25.2 (20)	21.9 (20)
Tmax (hr) Median (min – max)	2 (1 – 3)	2 (1 – 6)
AUC_{0-t} (ng*hr/mL) Geometric mean (%CV)	337 (20)	372 (18)
$AUC_{0-\infty}$ (ng*hr/mL) Geometric mean (%CV)	366 (20)	403 (18) [N=14]*
$t_{1/2}$ (hr) Mean (SD)	24.7 (4.3)	30.5 (6.7)

*$AUCD_{\infty}$ for one subject excluded due to % AUC extrapolated > 20%

Ethinyl Estradiol Pharmacokinetics

Figure 3. Mean (± SD) EE Plasma Concentration vs Time



Day 1 (N=16): single dose of DRSP 3 mg/EE 0.02 mg
Day 15 (N=15): AB-506 400 mg QD + single dose of DRSP 3 mg/EE 0.02 mg
Samples collected post-48 hours were <LLOQ

Table 3. EE PK Parameter Summary Statistics

EE PK parameter	Day 1 [N=16]	Day 15 [N=15]
Cmax (pg/mL) Geometric mean (%CV)	40.2 (39)	45.8 (28)
Tmax (hr) Median (min – max)	1 (1 – 2)	3 (1 – 6)
AUC_{0-t} (pg*hr/mL) Geometric mean (%CV)	313 (43)	448 (36)
$AUC_{0-\infty}$ (pg*hr/mL) Geometric mean (%CV)	381 (40) [N=15]*	549 (33) [N=14]*
$t_{1/2}$ (hr) Mean (SD)	10.2 (3.3)	14.3 (5.4)

*$AUC_{0-\infty}$ for one subject excluded from Day 1 and one subject excluded from Day 15 due to % AUC extrapolated > 20%

Table 4. PK Parameter Day 15/Day 1 Ratios and 90% CIs

COC Component	Cmax	AUC_{0-t}	$AUC_{0-\infty}$
DRSP	0.87 (0.78 – 0.97)	1.14 (1.11 – 1.18)	1.12 (1.08 – 1.15)
EE	1.15 (1.03 – 1.29)	1.41 (1.29 – 1.54)	1.45 (1.32 – 1.60)

- In the presence of AB-506, DRSP Cmax was reduced 13%. The 90% confidence intervals for the AUC ratios were within 0.8 – 1.25 suggesting no statistically significant impact on DRSP AUC (Table 4).
- In the presence of AB-506, EE Cmax increased 15%, while AUC_{0-t} and $AUC_{0-\infty}$ increased 41% and 45%, respectively (Table 4).

RESULTS

- 16 subjects received study drugs and 15 (93.8%) subjects completed the study.
  - 2 (12.5%), 12 (75.0%) and 2 (12.5%) were Asian, White, or Other, respectively. Mean (SD) age and body weight were 28.5 (5.56 years) and 64.4 (7.59) kg, respectively.

Table 1. Most commonly reported AEs (N, %) in Study AB-506-002

AE	DRSP/EE (N=16)	AB-506 (N=16)	DRSP/EE + AB-506 (N=15)	Total (N=16)
Headache	1 (6.3)	4 (25.0)	3 (20.0)	6 (37.5)
Abdominal pain	0	3 (17.7)	2 (13.3)	5 (31.3)
Acne	3 (18.8)	1 (6.3)	0	4 (25.0)
Nausea	0	1 (6.3)	2 (13.3)	3 (18.8)
Diarrhea	0	0	3 (20.0)	3 (18.8)

- There were no deaths or serious AEs.
- There were no ≥Grade 3 AEs or laboratory abnormalities.
- One subject was withdrawn from the study due to Grade 1 influenza, not related to treatment.
- 14 subjects (87.5%) reported at least 1 AE (see Table 1 for most commonly reported). 5 subjects (31.3%) had AEs considered related to study drug administration (AB-506 and/or DRSP/EE):
  - Grade 2 abdominal pain (AB-506), Grade 1 constipation (DRSP/EE), Grade 1 myalgia (AB-506 + DRSP/EE), Grade 1 headache (AB-506 + DRSP/EE), Grade 1 oligomenorrhea (AB-506), and Grade 2 ALT increase (AB-506 + DRSP/EE).
  - The Grade 2 ALT increase occurred on Day 22 and resolved on Day 57.
- There were no clinically significant changes from baseline in hematology, serum chemistry, coagulation, or urinalysis laboratory parameters.

CONCLUSIONS

- AB-506 400 mg orally administered once daily had no clinically meaningful impact on single dose exposures to DRSP when coadministered with a COC containing DRSP and EE.
- AB-506 400 mg orally administered once daily increased single dose EE exposures approximately 40%.
  - EE is subject to presystemic conjugation with metabolism primarily occurring through aromatic hydroxylation mediated by CYP3A4; however numerous hydroxylated and methylated metabolites are formed as free metabolites and conjugates of sulfate and glucuronide.[2,3]
  - Based on in vitro data, AB-506 has a low potential to impact CYP3A4; however impact on sulfation or glucuronidation has not been assessed.
- AB-506 given once daily for 13 days and single doses of DRSP/EE both with and without AB-506 were well tolerated in this study.
- Due to the increase in EE exposures in the presence of AB-506, combination oral contraceptives containing EE doses no higher than 0.02 mg would have been recommended had development of AB-506 been continued.

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