SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
SYMTUZA - Drug Interaction with Ethinyl Estradiol

SUMMARY

- No studies have evaluated a drug-drug interaction between ethinyl estradiol and SYMTUZA administered as either the fixed-dose combination product or the individual drug components administered simultaneously.
- A phase 1 pharmacokinetic (PK) study in 18 healthy women evaluated a potential drug interaction between darunavir (DRV) + cobicistat (COBI) and a hormonal contraceptive containing drospirenone/ethinyl estradiol.[1]
    - When the hormonal contraceptive was administered with DRV + COBI, the systemic exposure of drospirenone increased by 58% which was attributed to inhibition of the cytochrome P450 enzyme 3A by COBI.
    - The systemic exposure of ethinyl estradiol decreased by 30% when the hormonal contraceptive was administered with DRV + COBI.

CLINICAL STUDIES

DRV + COBI and Drospirenone/Ethinyl Estradiol

Majeed et al (2020)[1] evaluated the potential drug interaction between DRV + COBI and a hormonal contraceptive that contained drospirenone/ethinyl estradiol.

Study Design/Methods

- Phase 1, open-label, fixed-sequence, single-center study (N=18)
- Participants in the study were healthy, non-pregnant, nonlactating, premenopausal females aged 18-45 years of age with a body mass index 19-30 kg/m^2.
- Participants received a single dose of drospirenone 3 mg/ethinyl estradiol 0.02 mg on day 1, DRV 800 mg + COBI 150 mg on days 5-17, and a single dose of drospirenone 3 mg/ethinyl estradiol 0.02 mg on day 17.
- Study treatments were administered in the morning with approximately 240 mL of water following an overnight fast, within 5 minutes of completion of a standardized moderate fat breakfast (~600 kcal and 27% fat).
- On PK assessment days, food intake was restricted until after the 4-hour blood sample was collected, and water intake was restricted 1 hour before and 2 hours after dosing of study drug.
- Blood samples for PK analysis were collected over 96 hours after study drug administration on day 1 and day 17.

Results

Efficacy

- Drospirenone and ethinyl estradiol PK are noted in Table: Drospirenone and Ethinyl Estradiol PK Parameters.
- The steady state PK parameters of DRV and COBI are noted in Table: DRV and COBI PK Parameters.

Drospirenone and Ethinyl Estradiol PK Parameters[1]

PK Parameter Mean (% CV)	DRV + COBI + Drospirenone/Ethinyl Estradiol (Test) n=15	Drospirenone/Ethinyl Estradiol (Reference) n=18	GLSM Ratio % (90% CI) (Test/Reference)
Drospirenone			
AUC_{∞} (h·ng/mL)	895 (24)	567 (24)	158 (147-171)
C_{max} (ng/mL)	36 (21)	31 (20)	115 (105-126)
$T_{1/2}$ (h)[a]	43 (30-56)	39 (29-43)	-
CL/F (L/h)	4 (26)	6 (19)	-
Ethinyl Estradiol			
AUC_{∞} (h·ng/mL)	308 (28)	439 (32)	70 (63-77)
C_{max} (pg/mL)	29 (35)	33 (36)	86 (77-95)
$T_{1/2}$ (h)[a]	10 (9-18)	17 (14-20)	-
CL/F (L/h)	70 (30)	49 (27)	-

Abbreviations: AUC_{∞}, area under the concentration versus time curve extrapolated to infinity; CI, confidence interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; COBI, cobicistat; CV, coefficient of variation; DRV, darunavir; GLSM, geometric least squares mean; PK, pharmacokinetic; $T_{1/2}$, terminal elimination half-life.
[a]$T_{1/2}$ presented as median (quartile 1, quartile 3).

DRV and COBI PK Parameters[1]

PK Parameter Mean (% CV)	DRV + COBI + Drospirenone/Ethinyl Estradiol n=15
DRV	
AUC_{tau} (h·ng/mL)	100568 (28)
C_{max} (ng/mL)	8850 (17)
C_{tau} (ng/mL)	2759 (46)
COBI	
AUC_{tau} (h·ng/mL)	11065 (32)
C_{max} (ng/mL)	1378 (18)
C_{tau} (ng/mL)	54 (72)

Abbreviations: AUC_{tau}, area under the concentration versus time curve over the dosing interval; C_{max}, maximum plasma concentration; COBI, cobicistat; C_{tau}, observed plasma concentration at the end of the dosing interval; CV, coefficient of variation; DRV, darunavir; PK, pharmacokinetic.

Safety

- A total of 13 participants had an adverse event.
- Four participants experienced adverse events that were considered by the investigator to be drug related.
- Three participants (16.7%) discontinued the study due to grade 1 maculopapular rash.
    - All rash events were assessed by the investigator as related to study treatment and resolved following treatment with topical and/or oral antihistamines or

corticosteroids (ie, hydrocortisone 1% cream, oral diphenhydramine, or oral methylprednisolone).

- There were no clinically relevant changes in median laboratory values throughout the study; all laboratory abnormalities were grade 1 or 2 in severity.
- There were increases in serum creatinine and corresponding decreases in estimated glomerular filtration rate calculated using the Cockroft-Gault equation while participants were receiving DRV + COBI (median creatinine increase from baseline of 0.15 mg/dL) that recovered to near baseline at day 21.

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal/external databases) was conducted on 07 October 2023.

REFERENCES

1. Majeed SR, West S, Ling KH, et al. Confirmation of the drug-drug interaction potential between cobicistat-boosted antiretroviral regimens and hormonal contraceptives. *Antivir Ther*. 2019;24(8):557-566.