SYMTUZA® (darunavir, cobicistat, emtricitabine, and tenofovir alafenamide)
Use of SYMTUZA for the Treatment of COVID-19

SUMMARY

- Janssen does not believe there is sufficient clinical and pharmacological evidence at this time to support the inclusion of darunavir (DRV), boosted with either ritonavir (r) or cobicistat (COBI), in treatment guidelines for coronavirus disease 2019 (COVID-19), nor is there sufficient data on the safety and efficacy profile of DRV in the treatment of COVID-19.
- The in vitro antiviral activity of DRV against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was assessed. DRV showed no activity against SARS-CoV-2 at clinically relevant concentrations. These data do not support the use of DRV for treatment of COVID-19.[1, 2]
- Results from a single-center, open-label, randomized, controlled trial conducted at Shanghai Public Health Clinical Center in patients with laboratory-confirmed COVID-19 showed that DRV/COBI was not effective.[3]
- For additional information regarding the lack of evidence to support use of DRV-based treatments for SARS-CoV-2, please visit https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus.

PRE-CLINICAL DATA

In a previously reported experiment, preliminary in vitro data show that DRV inhibited viral replication of SARS-CoV-2 at a concentration of 300 µM, a concentration that is much higher than what is usually achieved with oral administration of boosted DRV[4] As explained by the investigator of this in vitro experiment, this does not imply efficacy *in-vivo*.[5] In fact, when DRV/COBI is administered at the indicated dose (800/150 mg once daily) to treat HIV infection, the mean trough concentration of DRV in plasma is 3.4 µM, 88-fold lower than the 300 µM concentration at which antiviral activity against SARS-CoV-2 has been reported. Based on these data, it is unlikely that DRV will have significant activity against SARS-CoV-2.

Furthermore, based on structural analyses it is unlikely that DRV will have significant antiviral activity against SARS-CoV-2. The HIV protease is a dimeric aspartic protease and DRV binds at its active site.[6] The crystal coordinates of the compound binding to HIV protease are deposited in the Protein Data Bank (PDB-code 1T3R). The crystal structure of HIV protease with DRV reveals a tight extensive hydrogen bonding network, explaining the high potency of DRV against HIV, where it has been demonstrated over many years to be a safe and effective therapy. Researchers at Shanghai Tech University have resolved a high-resolution crystal structure of the SARS-CoV-2 main 3C-like (3CL) protease, a cysteine protease (PDB-code 6LU7). Janssen did an *in-silico* docking experiment of DRV in this crystal structure of SARS-CoV-2 protease and found several docking poses. However, all these poses showed very few interactions of DRV with the catalytic center in the active site of the protease, unlike the many strong interactions observed for DRV bound to HIV protease. These results are consistent with the much lower in vitro activity of DRV against SARS-CoV-2 as compared to HIV.

De Meyer et al (2020)[1] evaluated the in vitro antiviral activity of DRV against a clinical isolate from a patient infected with SARS-CoV-2. DRV showed no activity against SARS-CoV-2 at clinically relevant concentrations. These data do not support the use of DRV for treatment of COVID-19.

- SARS-CoV-2 was isolated from human samples and cultured in Caco-2 cells. Remdesivir (GS-5734) was used as a positive control. DRV and remdesivir were added in 4-fold dilutions to a concentration range of 0.02 µM to 100 µM. Cells were

then incubated for 48 hours before the cytopathogenic effect (CPE) was visually scored by two independent laboratory technicians. Evaluation of CPE was also done using a 3-(4,5-dimetiltiazol-2-il)-2,5-difeniltetrazolio (MTT; Sigma-Aldrich) method.

- DRV did not demonstrate any inhibition of SARS-CoV-2 induced CPE (EC_{50}>100 µM) while remdesivir demonstrated strong antiviral activity against SARS-CoV-2 with an EC_{50} of 0.11 µM based on visual scoring of inhibition of CPE. Similar results were obtained using the MTT method (EC_{50} = 0.38 µM).
- No cytotoxicity of DRV or remdesivir was observed on Caco-2 cells with CC_{50} values >100 µM. The selectivity index (CC_{50} / EC_{50}) for DRV could not be calculated due to the lack of antiviral activity. In contrast, remdesivir had a selectivity index of >900 by visual CPE scoring and >260 by the MTT method.

Ellinger et al (2020)[2] conducted an in vitro screening of 5632 compounds to identify possible candidates for clinical studies against SARS-CoV-2. Compounds were screened for their inhibition of viral induced cytotoxicity using the human epithelial colorectal adenocarcinoma cell line Caco-2 and a SARS-CoV-2 isolate obtained from an individual originally exposed to the virus in the Wuhan region of China. Primary screening was performed at 10 µM compound concentration, at a virus multiplicity of infection (MOI) of 0.01 and a virus incubation period of 48 h, to ensure multiple viral replication cycles. DRV was noted to be inactive against SARS-CoV-2 during the primary screening phase.

CLINICAL DATA

A single-center, open-label, randomized, controlled trial was conducted at Shanghai Public Health Clinical Center to evaluate the fixed-dose combination product DRV 800 mg/COBI 150 mg for treatment of patients with laboratory-confirmed COVID-19 (n=30).[3] The primary endpoint (viral clearance rate at day 7 after randomization) showed that DRV/COBI was not effective (NCT04252274).

LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, and DERWENT® (and/or other resources, including internal databases) pertaining to this topic was conducted on 03 May 2023. Prospective, randomized, controlled clinical trials were summarized.

REFERENCES

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