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A phase 1, randomized, crossover trial to assess the effect of itraconazole on the pharmacokinetics of dordaviprone in healthy adults

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Abstract

Aims: Dordaviprone (ONC201) is a novel, small molecule with antitumor efficacy in gliomas. The aim of this work was to evaluate the pharmacokinetics and safety of dordaviprone when given alone and when coadministered with a strong cytochrome P450 (CYP)3A4 inhibitor, itraconazole.

Methods: In vitro human liver microsomes and recombinant human CYP enzyme assays were used to assess CYP-mediated metabolism of dordaviprone. The clinical study was conducted in 18 healthy male and female participants as part of a larger 3 period open-label, randomized, crossover bioequivalence and drug-drug interaction evaluation. Dordaviprone and metabolite ONC207 plasma concentrations were determined by validated liquid chromatography-tandem mass spectrometry methods.

Results: In vitro assessments of CYP-mediated dordaviprone metabolism indicated that CYP3A4 was the major CYP involved in the oxidation of dordaviprone. Accordingly, concomitant administration of dordaviprone with itraconazole significantly increased dordaviprone plasma maximum plasma concentration and area under the plasma concentration-time curve by 1.9 and 4.5-fold, respectively, compared to dordaviprone alone. Treatment-emergent adverse events were reported by 1 (5.6%) participant after receiving dordaviprone alone, and by 4 (22.2%) participants after receiving dordaviprone with itraconazole.

Conclusion: Concomitant administration of dordaviprone with itraconazole significantly increased dordaviprone exposure confirming CYP3A4 is a major clearance pathway for dordaviprone. While dordaviprone was generally well tolerated when administered as a single 125-mg dose with concomitant itraconazole, dose adjustment in patients receiving 625 mg dordaviprone with strong CYP3A4 inhibitors is warranted.

Keywords: drug–drug interaction; pharmacokinetics; phase 1.