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# A Phase 1 Study to Assess the Effect of Hepatic Impairment on the Pharmacokinetics, Safety, and Tolerability of Dordaviprone

Shamia L Faison [1], Joelle Batonga [1], Thangam Arumugham [2], Angela Bartkus [3], Marion E Morrison [3], Mark J Mullin [3], Timothy Tippin [3], Odin Naderer [3]

Affiliations

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## Abstract

Dordaviprone (ONC201) is a small molecule protease activator being developed for gliomas. The aim of this work was to evaluate the pharmacokinetics and safety of dordaviprone when administered to participants with moderate hepatic impairment compared to healthy matched participants. A non-randomized, open-label, single-dose study was conducted in eight participants with moderate hepatic impairment classified according to Child-Pugh criteria, and eight healthy participants matched based on age (+10 years), body mass index (BMI; +20%), and sex. Plasma concentrations of dordaviprone and the major inactive metabolite, ONC207, were determined by a validated liquid chromatography-tandem mass spectrometry method. Exposure following oral administration of 125 mg dordaviprone was increased in participants with moderate hepatic impairment relative to healthy matched participants, with the largest impact occurring on AUC. Ratios of geometric means and 90% confidence intervals (CIs) of dordaviprone exposure for $C_{max}$, $AUC_{last}$, and $AUC_{inf}$ in the moderate hepatic impairment cohort compared to the healthy matched cohort were 1.21 (0.88, 1.67), 1.50 (1.02, 2.20), and 1.55 (1.05, 2.29), respectively. Treatment-emergent adverse events were mild in nature and considered not related to dordaviprone administration. While administration of dordaviprone in participants with moderate hepatic impairment led to increased dordaviprone exposures, the anticipated increase after the recommended 625 mg dose is within exposures assessed in the thorough QT study. Therefore, no dose adjustment in patients with mild or moderate hepatic impairment is recommended.

**Keywords:** ONC201; dordaviprone; hepatic impairment; pharmacokinetics; phase 1.