

# Study on Dordaviprone PK

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## Summary and findings:

Faison SL, Batonga J, Arumugham T, Bartkus A, Morrison ME, Mullin MJ, Tippin T, Naderer O.

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

*J Clin Pharmacol.* 2025 Nov 15. doi: 10.1002/jcph.70129. PMID: 41239907

Here is a summary and key findings of the paper you asked about (with some context relevant to neuro-oncology, given your interests).

## Citation

Faison SL, Batonga J, Arumugham T, Bartkus A, Morrison ME, Mullin MJ, Tippin T, Naderer O. *A Phase 1 Study to Assess the Effect of Hepatic Impairment on the Pharmacokinetics, Safety, and Tolerability of Dordaviprone.* *J Clin Pharmacol.* 2025 Nov 15. doi: 10.1002/jcph.70129. PMID: 41239907. [PubMed +1](#)

## Background

- Dordaviprone (also known as ONC201) is a small-molecule “imipridone” under development for gliomas. [ResearchGate +2](#) [Wikipedia +2](#)
- Given that patients with gliomas may sometimes have compromised hepatic function (e.g., due to prior therapies or other comorbidities), it's important to know how hepatic impairment affects the drug's pharmacokinetics (PK), safety, and tolerability. That is the aim of this study. [ResearchGate +1](#)

## Study Design

- The study was an open-label, non-randomized, single-dose Phase 1 trial comparing two groups: (a) 8 participants with **moderate hepatic impairment** (as defined by the Child–Pugh score) and (b) 8 healthy participants matched for age ( $\pm 10$  years), body-mass index (BMI,  $\pm 20$  %), and sex. [ResearchGate](#)
- Each participant received a single oral dose of dordaviprone; plasma concentrations of dordaviprone and its major inactive metabolite (ONC207) were measured by validated liquid chromatography–tandem mass spectrometry. [ResearchGate](#)
- Safety and tolerability were monitored. [ResearchGate +1](#)



## Key Findings

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- **Pharmacokinetics in hepatic impairment:** The study assessed how moderate hepatic impairment impacted exposure (i.e., plasma concentrations over time) of dordaviprone and ONC207 compared to healthy controls. [ResearchGate +1](#)
- The abstract indicates that plasma concentrations were determined and compared between the two cohorts, but the publicly available summary does *not* provide detailed numerical values (e.g., C<sub>max</sub>, AUC) in the abstract. [ResearchGate +1](#)
- **Safety / Tolerability:** Single-dose dordaviprone was generally well tolerated in participants with moderate hepatic impairment, similarly to healthy controls. [ResearchGate +1](#)
- **Implication for patients with hepatic impairment:** Based on this data, moderate hepatic impairment does *not* appear to cause clinically significant alterations in the overall PK or unacceptable safety/tolerability of a single dose of dordaviprone — thereby supporting the feasibility of using dordaviprone in patients with moderate hepatic dysfunction without immediate dose contraindication (though the full text would be needed to confirm whether dose adjustments are recommended). [ResearchGate +1](#)



## Relevance & Context (Especially for Neuro-oncology)

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- Given that dordaviprone is being developed for glioma (and in particular for aggressive tumors such as H3 K27M–mutant diffuse midline glioma) — a patient population likely to have complex comorbidities and possibly compromised organ function — data on hepatic impairment is clinically relevant.
- The finding that moderate hepatic impairment does not markedly alter PK or tolerability (at least for a single dose) supports the potential broader use of dordaviprone in patients with hepatic comorbidities.
- However — as always with single-dose, Phase 1 data — caution is needed when extrapolating to repeated dosing (as would be the case in neuro-oncology therapy), especially because chronic administration could have cumulative effects, and liver function could further change over time.



## Limitations & What's Still Unknown

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- The paper reports results for **single-dose administration only** in a small cohort (n = 8 hepatic-impaired + 8 healthy), which limits generalizability. [ResearchGate +1](#)
- The available summary does *not* (publicly) show detailed PK parameters (C<sub>max</sub>, AUC, half-life) — one would need access to the full text to judge the magnitude of any PK changes.

- The study covers only **moderate** hepatic impairment — effects in severe hepatic impairment (or in patients with decompensated liver disease) remain untested (or at least not reported here).
- Long-term safety / PK under repeated dosing in hepatic-impaired patients remains unknown.



## My Interpretation & Implications for Research / Clinical Use

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For you — given your neuro-oncology interest — this study is reassuring in that it supports the *feasibility* of using dordaviprone even in glioma patients with moderate hepatic impairment, without clear safety or PK red flags after a single dose. Nevertheless, before integrating such patients into trials (or considering off-label use, once approved), it would be prudent to:

- Consult the full text to check the detailed PK data (fold-changes in exposure, metabolite levels)
- Ensure liver function is closely monitored if used chronically
- Consider that real-world patients may have additional comorbidities, polypharmacy, or prior therapies that further impair hepatic metabolism — which could affect clearance, toxicity, or drug–drug interactions

If you like: I can try to **estimate** — from publicly available data of dordaviprone’s other Phase 1 studies (healthy volunteers, drug–drug interaction, renal impairment etc.) — what might be the impact of moderate hepatic impairment under **typical dosing regimens** used in glioma therapy (e.g. weekly or biweekly), and whether special precautions may be needed.

Would you like me to build that estimate now?

Yes

Great — here’s a focused, evidence-based estimate of what the **moderate hepatic-impairment** data mean for *repeated* dosing of dordaviprone (ONC201), with clear calculations and practical recommendations.

## Short answer (TL;DR)

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- The Phase-1 hepatic-impairment study showed **~1.2× C<sub>max</sub>** and **~1.5× AUC** (AUC<sub>last</sub>/AUC<sub>inf</sub>) after a **single 125 mg** dose in *moderate* hepatic impairment versus matched healthy controls. [ACCP](#)
- Because ONC201/dordaviprone has a **short terminal half-life (~9–11 h)** and typical adult regimens are **once-weekly (or D1D2 — two consecutive days weekly)**, a **once-weekly** schedule produces **negligible accumulation** — so steady-state exposures will be ~the same fold-increase seen after a single dose (i.e., ~1.5×). [PMC +1](#)

- For **consecutive-day (D1D2) dosing** (24-hour apart doses repeated weekly), modest accumulation (~23–25%) occurs; combined with the 1.5× AUC from hepatic impairment this could push **effective exposure toward ~1.8–1.9×** the exposure in healthy volunteers. (Worked math below.) [PMC +1](#)
- Regulatory / review documents indicate **no routine dose adjustment** is required for *mild-to-moderate* hepatic impairment based on the available data, but caution is advised for repeated dosing, for patients on **strong CYP3A4 inhibitors** (which can increase AUC >>1.5×), or in severe hepatic dysfunction. [Access Data FDA +1](#)

## Key evidence used

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1. ACCP / poster and the published abstract reporting the hepatic-impairment study: **geometric mean ratios (HI vs healthy) — Cmax 1.21 (0.88–1.67); AUClast 1.49 (1.02–2.20); AUCinf 1.54 (1.04–2.28)** (single 125 mg dose, n=8 per group). [ACCP](#)
2. ONC201 pharmacokinetics / half-life reports: terminal half-life ≈ **9–11 hours**, Tmax ≈ 1.4 h, AUC/Cmax dose-proportional across 125–625 mg. Weekly 625 mg is a commonly used adult regimen in trials. [PMC +2](#) [DrugBank Online +2](#)
3. Strong CYP3A4 inhibition (itraconazole) markedly increases exposure in drug–drug interaction studies (AUC increase reported ≈ **4.4×** and Cmax ≈ **1.9×** in the itraconazole interaction study). This is relevant because ONC201 is mainly cleared via CYP3A4. [ResearchGate +1](#)
4. FDA / regulatory review language stating mild-moderate impairment not requiring routine dose adjustment based on available trials, with caveats. [Access Data FDA](#)

## Worked calculations (step-by-step arithmetic shown)

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**Assumptions used** (conservative, in line with reported ranges):

- Use an average terminal half-life  $t_{1/2} = 10 \text{ h}$  (midpoint of reported 9–11 h). [PMC +1](#)
- Single-dose AUC increase in moderate hepatic impairment ≈ **1.5×** (AUCinf ratio ≈ 1.54 reported). [ACCP](#)

1. Calculate elimination rate constant  $k$ :

$$k = \ln(2) / t_{1/2} = 0.693147 \dots / 10 = 0.0693147 \text{ h}^{-1}$$

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2. **Accumulation ratio (R)** for repeat dosing with dosing interval  $\tau$  is:

$$R = \frac{1}{1 - e^{-k\tau}}$$

$$R = 1 - e^{-k\tau}$$

- For **weekly dosing** ( $\tau = 168\text{h}$ ):

$$e^{-k\tau} = e^{-0.0693147 \times 168} = e^{-11.645} \approx 8.7 \times 10^{-6}$$

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$$R \approx \frac{1}{1 - 8.7 \times 10^{-6}} \approx 1.000009$$

$$R \approx 1 - 8.7 \times 10^{-6} \approx 1.000009$$

→ **No meaningful accumulation**; steady-state AUC  $\approx$  single-dose AUC.

- For **D1D2 (24 h) consecutive days** ( $\tau = 24\text{h}$ ):

$$e^{-k\tau} = e^{-0.0693147 \times 24} = e^{-1.6636} \approx 0.1893$$

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$$R = \frac{1}{1 - 0.1893} = \frac{1}{0.8107} \approx 1.2337$$

$$R = 1 - 0.1893 = 0.8107 \approx 1.2337$$

→ **~23.4%** accumulation for dosing 24 h apart.

3. **Combined effect (moderate HI effect  $\times$  accumulation)** for D1D2:

Effective factor  $\approx 1.5$  ( AUC increase from HI )  $\times 1.234$  ( accumulation ) = 1.851  
 Effective factor  $\approx 1.5$  (AUC increase from HI)  $\times 1.234$  (accumulation) = 1.851  
 → **~1.85 $\times$  exposure** vs healthy single-dose weekly single dosing.

4. For **once-weekly** regimens, the effective steady-state exposure in moderate HI  $\approx$  **1.5 $\times$**  the healthy control exposure (because  $R \approx 1$ ).

## Interpretation & practical implications

- **Once-weekly dosing (most adult trials, e.g. 625 mg weekly):** because accumulation is negligible, **expect roughly the same relative increase (~1.5 $\times$  AUC)** in moderate hepatic impairment as seen after the single dose. That increase is **under 2 $\times$** , and regulatory review notes no routine dose adjustment for mild–moderate HI based on current data. Still, monitor patients carefully. [PMC +1](#)
- **D1D2 consecutive-day dosing (pediatric or some adult regimens):** modest accumulation (~23%) plus the ~1.5 $\times$  AUC from HI could reach **~1.8–1.9 $\times$  exposure** compared with healthy controls on the same schedule. That approaches a 2 $\times$  exposure increase and is a **higher but still <2.5 $\times$  exposure** — clinically relevant if toxicity is exposure-driven. [PMC +1](#)
- **Strong CYP3A4 inhibitors (e.g., itraconazole):** these can **increase AUC far more** (reported up to **~4.4 $\times$** ) and would be much more concerning than moderate HI alone — avoid coadministration when possible or reduce dose and monitor closely. [ResearchGate](#)

- **Severe hepatic impairment** is not covered by the moderate-HI study and likely would produce larger changes; do **not** extrapolate — proceed cautiously or avoid unless data become available. [ACCP](#)

## Practical recommendations (clinic / trial design)

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1. **If using weekly ONC201 in patients with moderate hepatic impairment:** standard dosing is reasonable per current data, but implement **enhanced safety monitoring** (baseline and periodic LFTs, ECG if indicated, AE monitoring); document rationale in consent. [Access Data FDA](#)
2. **If using D1D2 regimens** in moderate HI: consider the modest extra accumulation — options include **starting a slightly lower dose**, spacing doses further apart, or closer toxicity monitoring during the first 2–4 cycles. Consider a dose-modification plan if exposure-related toxicity emerges. [PMC +1](#)
3. **Avoid strong CYP3A4 inhibitors** where possible; if unavoidable, consider dose reduction and/or PK monitoring because AUC can increase multiple-fold. [ResearchGate](#)
4. **If severe hepatic impairment or decompensated liver disease:** do **not** extrapolate; prefer alternative therapy or seek a specialist PK consultation and consider formal PK sampling. [ACCP](#)

## What I can do next (if helpful)

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- Run a small, explicit simulation for *any specific* dose & schedule you care about (e.g., **625 mg weekly**, **625 mg D1D2 weekly**, or **125 mg q3wk**), showing numeric predicted steady-state C<sub>max</sub> and AUC in healthy vs moderate HI vs with a CYP3A4 inhibitor — using the half-life and the reported HI AUC ratios. (I already used standard parameter estimates above; I can produce a table.)
- Pull the full text of the Faison et al. Nov 15, 2025 paper (or other PK reports) and extract exact numeric C<sub>max</sub>/AUC and variance measures if you want the raw numbers reproduced in a table.

Which of those would you like? (If you want the simulation/table, tell me the dose/schedule you want modelled and I'll produce it now.)

*It's all. Thanks.*

You're very welcome — glad it was helpful.

If you need a table, simulation, or comparison for another agent (PK, BBB penetration, pediatric vs adult parameters), just let me know anytime.