(VAL-413) Orotecan® (Oral irinotecan HCl)

Background: Irinotecan in Pediatric Oncology

Intravenous Irinotecan (IV):
Irinotecan (IV) is a chemotherapy agent commonly used alone or in combination with other treatments for the management of adult and pediatric solid tumors. In pediatric cancers these include, but are not limited to:

Ewing sarcoma – Neuroblastoma – Rhabdomyosarcoma – Hepatoblastoma - Medulloblastoma

IV administration via infusion, while effective, often requires protracted daily in-patient infusion treatments, contributing to patient burden and logistical challenges for families.

IV irinotecan given orally has been established as an effective alternative to intravenous treatment; however, poor palatability of the IV product has significantly limited clinical adoption of this practice.

Orotecan® (Oral Irinotecan HCl) A Patient-Centered Innovation

Overview:
Orotecan® is a novel oral formulation of irinotecan hydrochloride developed to improve treatment experience for pediatric patients. It provides a more convenient, at-home alternative to traditional IV administration, aiming to minimize the physical, emotional, and logistical burden of frequent hospital visits.

Key Benefits:

- **Reduced Hospital Time:** IV regimens can consume 30–50% of treatment time in hospital settings.
- **At-Home Convenience:** Allows treatment continuity with fewer disruptions to daily routines.
- **Improved Quality of Life:** Minimizes emotional and physical toll associated with hospital-based care.
- **Enhanced Compliance & Cost Savings:** Home-based care may improve adherence to therapy and reduce healthcare resource demands.

Clinical Development – Lead-in-Trial:

Orotecan® is currently undergoing a multicenter Phase 1/2a clinical trial to assess its safety, tolerability, and pharmacokinetics when administered alongside oral temozolomide. The study targets 20 pediatric patients aged 1 to 30 years with recurrent solid tumors, including Ewing sarcoma, neuroblastoma, rhabdomyosarcoma, hepatoblastoma, and medulloblastoma.

Study Endpoints:

- Characterize pharmacokinetics of **Orotecan®** vs. unformulated irinotecan (p.o.)
- Confirm improved tolerability
- Tumor response (RECIST v1.1)
- Safety and tolerability (CTCAE v5.0)

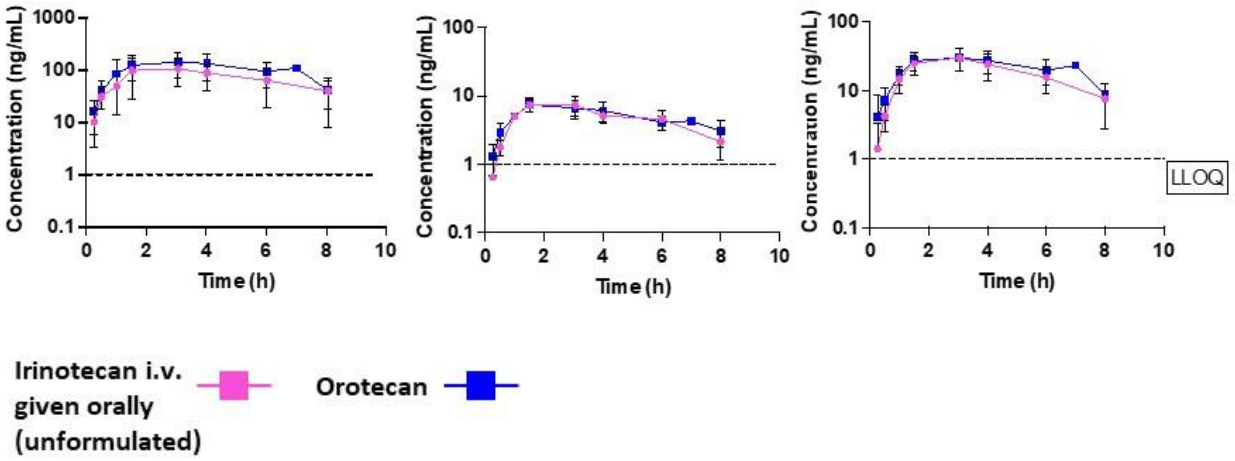
Clinical Trial:

Orotecan® is currently being studied in a Phase 1-2 clinical trial enrolling at nine clinical sites in the United States. (ClinicalTrials.gov ID: NCT04337177)

- Duke University Children's Hospital
- Cincinnati Children's Hospital Medical Center
- Sarah Cannon Research Institute
- University of North Carolina
- UCSF Medical Center
- Atrium Health, Levine Children's Hospital
- Children's National Hospital
- Phoenix Children's Hospital
- Riley Hospital for Children

Interim Study Results:

Presented at the American Association for Cancer Research (AACR) annual meeting in April 2025 indicated that **Orotecan®** was well-tolerated, with no dose-limiting toxicities observed at the 90 mg/m^2/day dose level. Pharmacokinetic analyses demonstrated that the oral formulation achieved plasma levels of irinotecan and its active metabolite SN-38 comparable to those observed with IV administration.



- Patients have been treated for up to 13 cycles (9months) at home.
- Well-tolerated up to 90 mg/m^2/day with no dose-limiting toxicities
- Achieved plasma levels of irinotecan and SN-38 comparable to IV administration
- Some patients have received treatment at home for up to 13 cycles (9 months)

Clinical Development Strategy:

- **Orotecan®** is positioned to enter pivotal registration-directed trials for recurrent pediatric cancers. The FDA has provided guidance that a single-arm trial with response endpoints would be suitable to support accelerated approval for **Orotecan®.**

Market Opportunity:

- Pediatric cancers represent orphan cancer indications.
- Feedback from oncologists suggests strong potential for **Orotecan®** adoption in adult patients, indicating a substantial market opportunity