Pharmacokinetics, pharmacodynamics and efficacy of OPC-61815, prodrug of tolvaptan for intravenous administration, in patients with congestive heart failure

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Background/Introduction: Tolvaptan, a vasopression V2-receptor antagonist, is effective for congestion in patients with congestive heart failure (CHF), and hyponatremia in patients with CHF and SIADH. But, this drug is not readily soluble in water and not suited for development as an injection. OPC-61815, a prodrug of tolvaptan having improved water solubility, is suitable for intravenous administration.

Purpose: The phase-II clinical study (ClinicalTrials.gov Identifier: NCT03254108) was conducted to investigate the dose for intravenous administration of OPC-61815 achieving tolvaptan exposure equivalent to that for oral administration of tolvaptan 15-mg tablet in CHF patients.

Methods: This study was a multicenter, a double-blind, randomized, active-controlled, parallel-group comparison clinical pharmacology trial. Sixty patients aged between 20 and 85 years with CHF with volume overload despite the use of conventional diuretics were randomly assigned to four treatment cohorts to receive OPC-61815 at doses of 2, 4, 8, 16 mg (i.v.) or tolvaptan at 15 mg (p.o.). Both drugs were administered once a day for 5 days. The primary endpoint was to assess the dose of OPC-61815 equivalent to tolvaptan at 15 mg using Cmax and AUC24h values after the first administration. Pharmacodynamics (urine volume, urine osmolality, serum electrolyte concentration, biomarkers), efficacy (body weight change, congestive symptoms) and safety were also evaluated.

Results: The mean Cmax and AUC of the metabolite tolvaptan increased dose-dependently following single intravenous administration of OPC-61815 at 2, 4, 8, and 16 mg. Tolvaptan exposure (Cmax and AUC24h) on Day 1 following single intravenous administration of OPC-61815 at 16 mg was the closest and similar to that following single administration of tolvaptan 15-mg tablet. OPC-61815 increased urine volume from baseline, leading to decrease in body weight and improvement of lower limb edema. The incidence of treatment-emergent adverse events was 54.2% (26/48 subjects) in the OPC-61815 2 to 16-mg, and 83.3% (10/12 subjects) in the tolvaptan 15-mg groups. No clinically relevant changes from baseline were found in laboratory parameters, vital signs, or ECG findings.

Conclusions: Tolvaptan exposure on Day 1 following single intravenous administration of OPC-61815 at 16 mg was the most similar to that following single administration of tolvaptan 15-mg tablet. There was no marked difference in tolerability between OPC-61815 at 16 mg and tolvaptan 15-mg tablet, and no clinically significant problems were observed.