

Pharmacokinetics and dosimetry of lutetium Lu 177 zadavotide guraxetan in patients with metastatic castration-resistant prostate cancer (mCRPC): Results from the ECLIPSE sub-study.

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Background: ECLIPSE (NCT05204927) is an ongoing confirmatory, pivotal, randomized, open-label, multicenter Phase 3 trial, evaluating efficacy and safety of Lutetium Lu 177 zadavotide guraxetan (a proprietary formulation of ^{177}Lu -PSMA-I&T) compared with androgen receptor pathway inhibitors (ARPI) switch in patients with mCRPC who have not previously received taxane-based chemotherapy for mCRPC. The ECLIPSE sub-study evaluated PK and radiation dosimetry of Lutetium Lu 177 zadavotide guraxetan in a subset of patients. **Methods:** Biodistribution, PK and radiation dosimetry were assessed in a subset of 26 patients (not randomized to the main ECLIPSE trial). Eligible patients received a target of $7.4 \pm 10\%$ GBq of Lutetium Lu 177 zadavotide guraxetan at the beginning of each 6-week cycle for up to 6 doses. Single photon emission computed tomography/computed tomography (SPECT/CT) imaging was performed 4, 24, 48, and 168h post-administration of Cycle 1. PK plasma samples were collected at the same time points and measured for activity. A subset of patients (16/26) also underwent SPECT/CT imaging and PK sampling at the same timepoints after Cycle 3. Organ Level Internal Dose Assessment (OLINDA 2.2.3) was used to compute organ and whole body absorbed radiation doses for each patient. **Results:** Physiologic uptake of Lutetium Lu 177 zadavotide guraxetan was predominantly observed in the kidneys (0.41 ± 0.15 Gy/GBq), bladder (0.41 ± 0.05 Gy/GBq), salivary glands and lacrimal glands (0.19 ± 0.16 and 0.40 ± 0.36 Gy/GBq, respectively) and some parts of the gastrointestinal (GI) tract (left colon, 0.47 ± 0.31 Gy/GBq and rectum, 0.44 ± 0.30 Gy/GBq). Extrapolated to a cumulative activity of 44.4 GBq over 6 cycles, the absorbed doses were estimated at 18.2 Gy for the kidneys, 8.44 Gy for the salivary glands, and 17.8 Gy for the lacrimal glands, allowing for an increase in the maximum number of cycles to 6 in the ECLIPSE trial. Plasma concentration decreased over time with a similar profile in all patients, initially with a faster decline (mean distribution $t_{1/2}$ was 1.89 ± 0.34 hours) followed by a slower, prolonged decrease. The mean elimination $t_{1/2}$ was 14.70 ± 10.10 hours. The clearance values (13.06 ± 16.50 L/h) indicate a rapid clearance of most of the injected dose from the body with renal excretion as the primary route. **Conclusions:** These results demonstrate that Lutetium Lu 177 zadavotide guraxetan exhibits predictable physiologic uptake patterns, with the highest absorbed doses observed in the kidneys. The PK profile indicates a biphasic clearance with a rapid initial distribution phase followed by slower elimination, supporting suitability of Lutetium Lu 177 zadavotide guraxetan for therapeutic use with acceptable organ-specific radiation exposure in patients with mCRPC not previously treated with taxane-based chemotherapy for mCRPC. Clinical trial information: NCT05204927. Research Sponsor: Curium.