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Near-infrared fluorescence imaging using ZW800-1: a phase 1 study

Introduction

The well-known near-infrared (NIR) fluorophore indocyanine green is safe, clinically available, and has been used extensively. However, ICG is far from ideal due to the exclusive hepatic clearance and difficulties with conjugation to targeting moieties. Recently, the zwitterionic fluorophore ZW800-1 has been introduced. In preclinical studies, ZW800-1 exhibits low non-specific uptake and exclusive renal clearance, which makes it an ideal candidate for NIR fluorescence imaging of the urinary tract.

Iatrogenic ureteral injury during abdominal surgery is a rare but serious complication and often remains unnoticed during surgery. NIR fluorescence imaging can permit surgeons to identify in real-time anatomical structures during surgery.

Furthermore, ZW800-1 can easily be conjugated to targeting moieties. The aim of this translational study was to determine toxicity of ZW800-1 in animals, and to assess tolerability and pharmacokinetics (PK) of a single dose in healthy human volunteers.

Methods

Preclinical toxicology studies in rats and dogs were conducted to characterize the safety profile of ZW800-1.

A first-in-human, phase 1, single ascending dose, randomized, placebo-controlled study was performed in 16 healthy volunteers to determine the safety, tolerability and PK of ZW800-1 after intravenous (iv) injection.

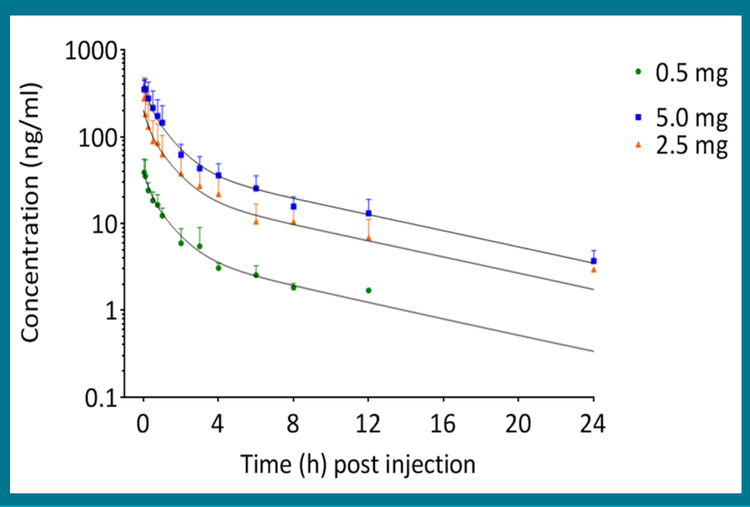
Three doses were investigated: 0.5 2.5 and 5.0 mg ZW800-1 administered as iv bolus. Safety assessment consisted of recording adverse events, clinical laboratory parameters, vital signs, ECGs, physical examination and injection site monitoring. PK of ZW800-1 were assessed by collecting blood and urine samples at defined time points up to 48 hours. NIR fluorescence imaging of the foot was performed frequently to assess the perfusion and uptake of ZW800-1 in the skin.

Results

No major toxicities were observed in the toxicology studies up to doses of 24.5 mg/kg in rats and 7.0 mg/kg in Beagle dogs. Rats were the most sensitive species and was used to determine the human equivalent dose of the no-observed-adverse-event-level which was 0.39 mg/kg (27.3 mg per 70 kg person). Pharmacology experiment suggested human doses between 0.5 – 5.0 mg.

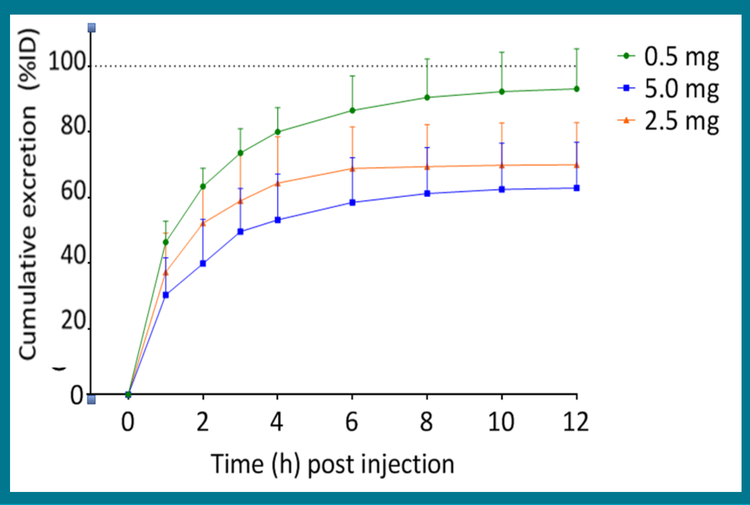
None of the healthy volunteers showed signs of acute or chronic toxicity. No significant clinical changes were seen in the volunteers after dosing.

Pharmacokinetics: ZW800-1 in blood



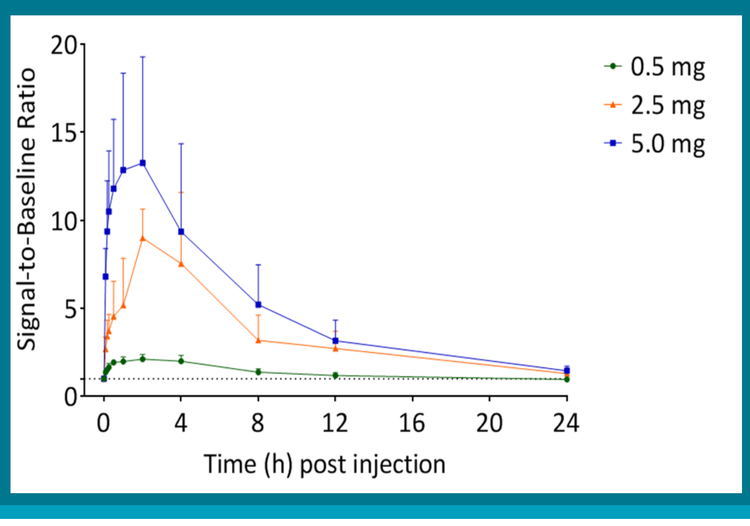
ZW800-1 concentrations were measurable for up to 24-48 hours post dose. Non-compartmental PK data analysis showed linear PK, a clearance of approximately 139 ml/min and a terminal half-life of 4 – 7 hrs.

Pharmacokinetics: ZW800-1 in urine



At 12 hours post dosing, the cumulative ZW800-1 urinary excretion was 93% (0.5 mg), 70% (2.5 mg) and 63% (5.0 mg). The majority of ZW800-1 was cleared in the first two hours post dosing.

Fluorescence of ZW800-1 in skin



The signal-to-baseline ratio in skin peaked at 2 hours and returned to baseline at 24 hours.

Conclusion

Based on the toxicology, safety and a favorable pharmacokinetic profile it is concluded that ZW800-1 may be a safe and ideal candidate for NIR fluorescence imaging of the urinary tract during surgery. A phase 2 study is designed to investigate the feasibility and optimal clinical dose of ZW800-1 to visualize the urinary tract in patients undergoing laparoscopic abdominal surgery.