

A phase 1 pharmacokinetic study of ZW800-1 for near-infrared fluorescence imaging of the urinary tract during surgery

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Introduction

The well-known near-infrared fluorophore indocyanine green is safe, clinically available, and has been used extensively. However, ICG is far from ideal due to the 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, making it an ideal candidate for NIR fluorescence imaging of the urinary tract.

Iatrogenic ureteral injury during abdominal surgery is a rare but serious complication. NIR fluorescence imaging can permit surgeons to identify anatomical structures in real-time 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 of a single dose in healthy volunteers.

Methods

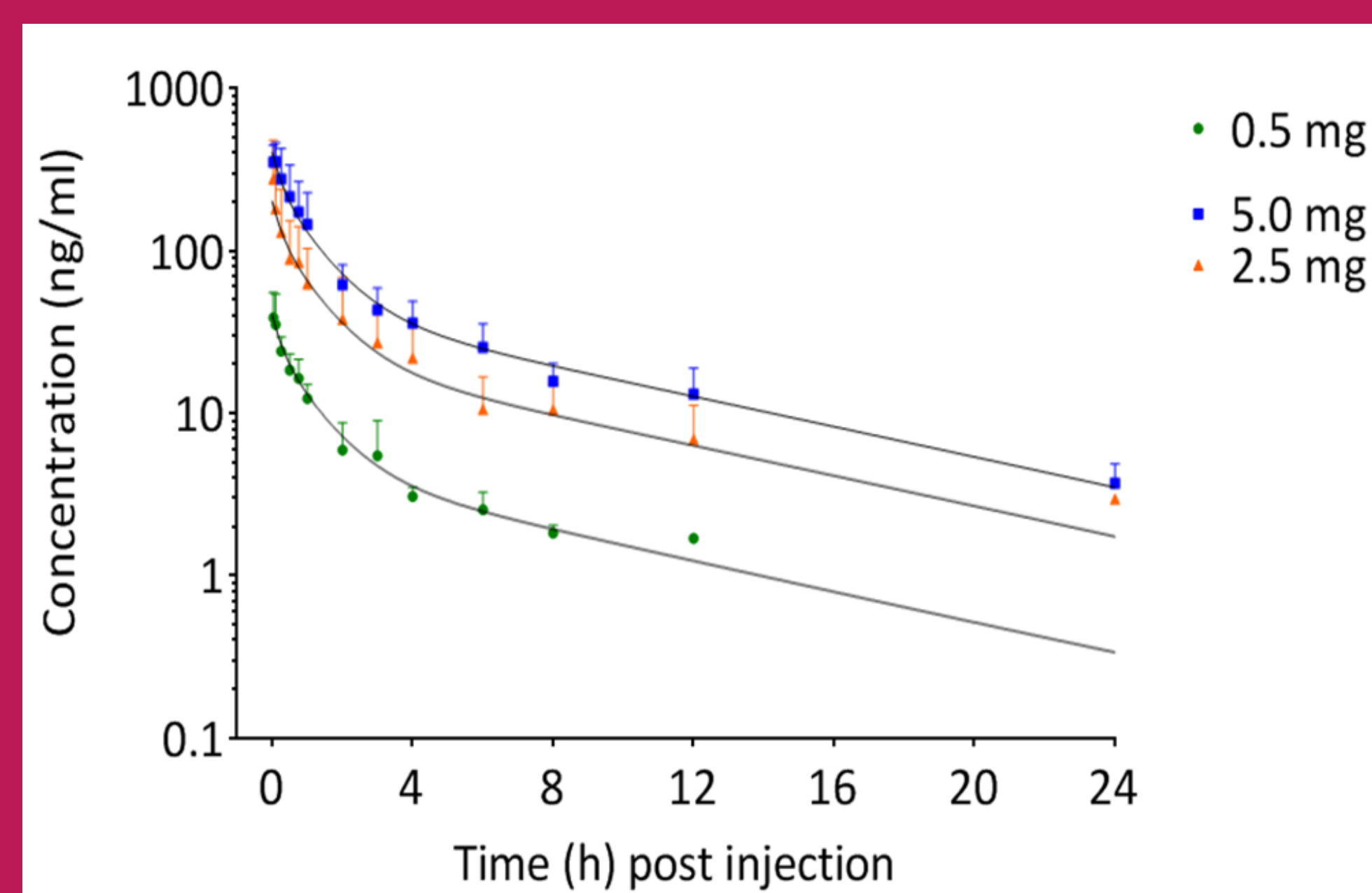
Preclinical toxicology studies in rats and dogs were conducted to characterize the safety profile of ZW800-1. A first-in-human, phase 1, single ascending dose, randomized, placebo-controlled study was performed in 16 healthy volunteers to determine the safety, tolerability and PK of ZW800-1 after intravenous (iv) injection. The doses 0.5, 2.5 and 5.0 mg ZW800-1 were investigated. Safety assessment consisted of recording AEs, 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.

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.

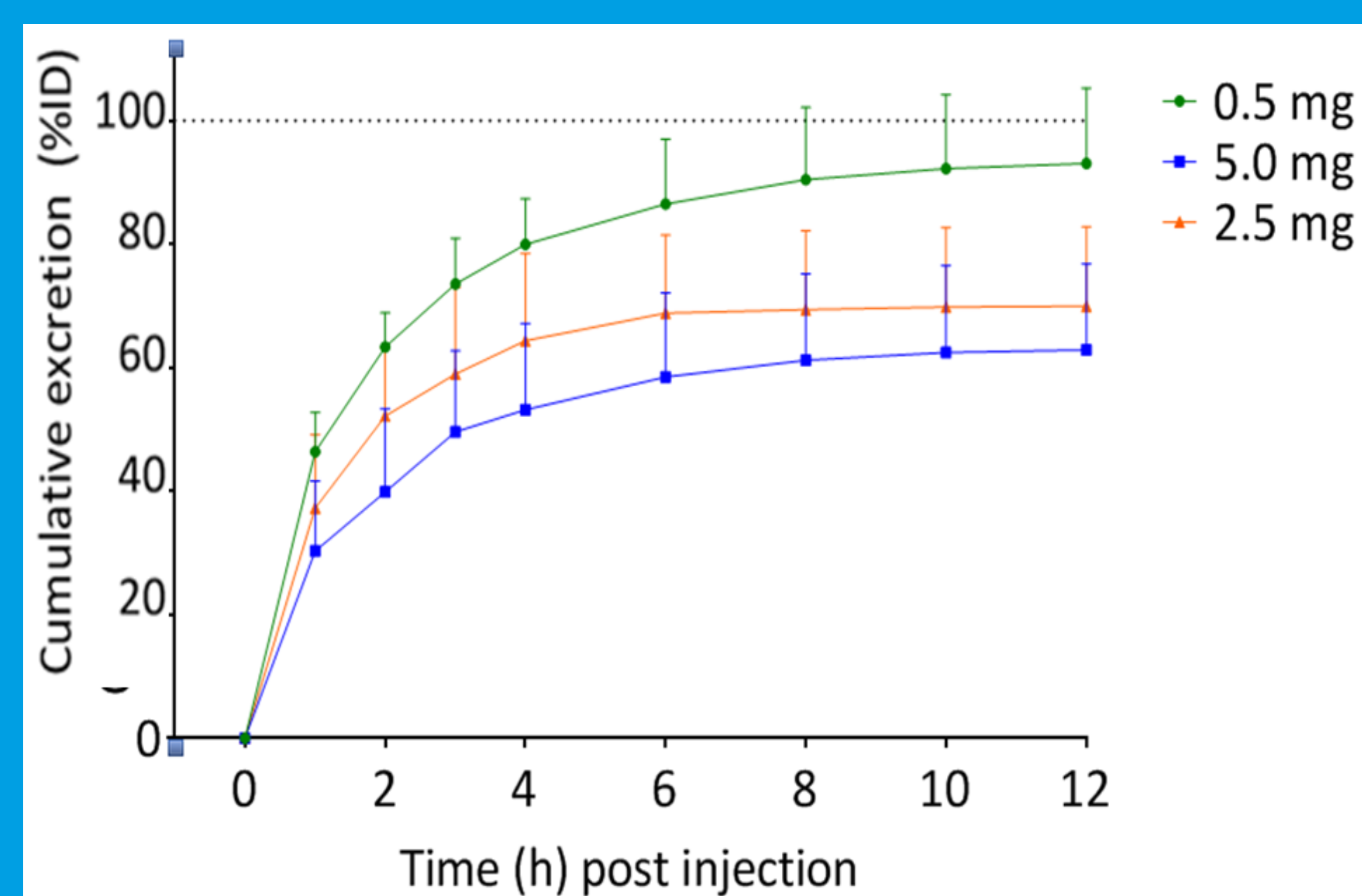
Results

Pharmacokinetics: ZW800-1 in blood



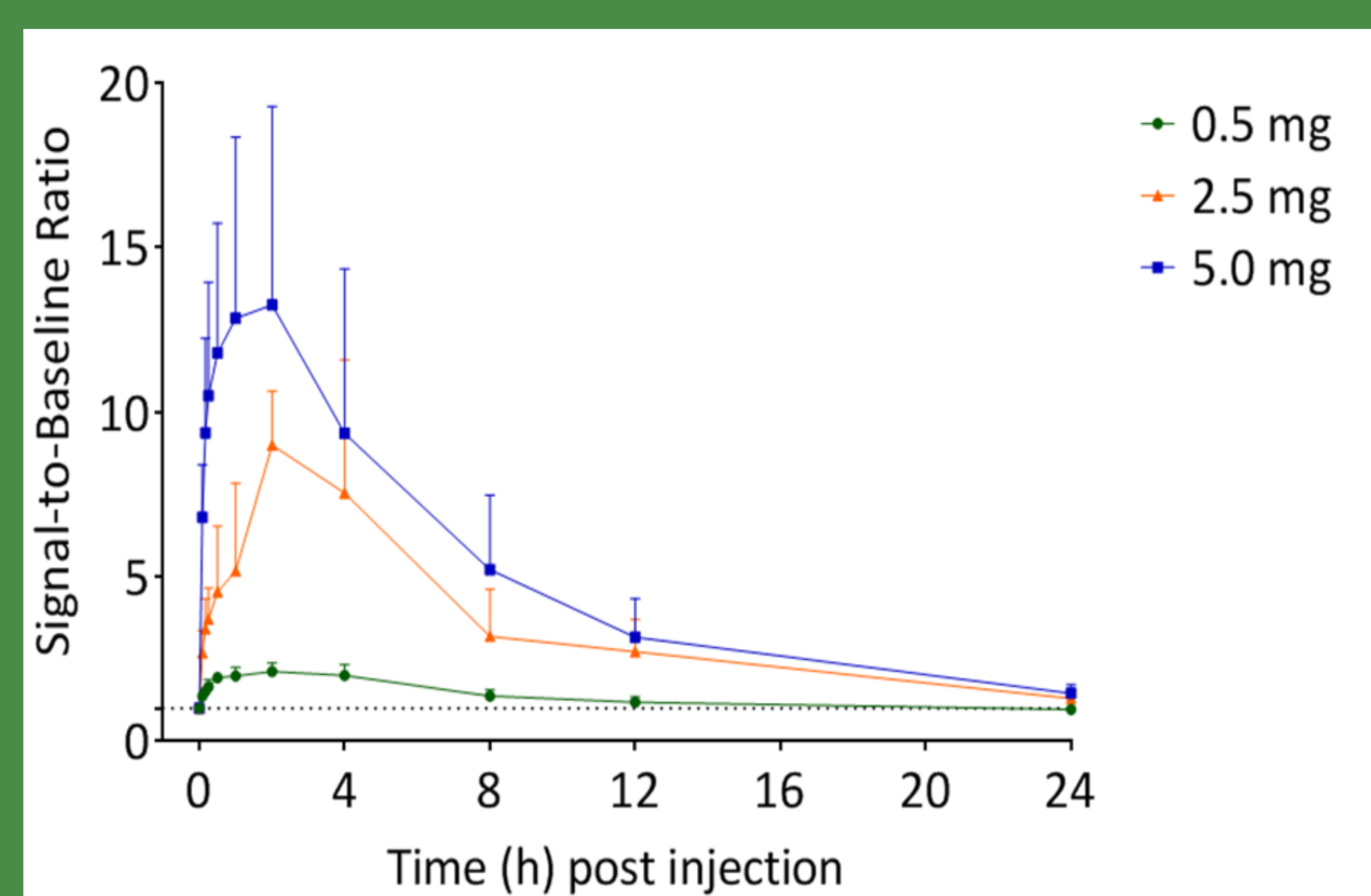
ZW800-1 concentrations were measurable for up to 24-48 hours post dose. Non-compartmental PK data analysis showed linear PK, a clearance of approximately 139 ml/min and a terminal half-life of 4 – 7 hrs.

Pharmacokinetics: ZW800-1 in urine



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.

Fluorescence of ZW800-1 in skin



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.