

# Near-infrared fluorescence imaging with cRGD-ZW800-1

The cornerstone of curative treatment of colorectal carcinoma remains resection of the tumor and regional lymph nodes. Discriminating between malignant and benign tissue can be challenging, especially after neoadjuvant treatment. Hence, strategies are being explored to overcome this. As almost all solid tumors depend on neoangiogenesis for sufficient blood supply and tumor growth, this may a target for clear tumor demarcation. cRGD is a peptide targeting integrins associated with neoangiogenesis. cRGD was conjugated to the near-infrared (NIR) fluorophore ZW800-1 and demonstrated in preclinical studies to visualize tumors using NIR fluorescence imaging

*K.S. de Valk*<sup>1,2</sup>, *H.J.M. Handgraaf*<sup>2</sup>, *M.M. Deken*<sup>1,2</sup>, *B.G. Sibinga Mulder*<sup>2</sup>, *M. van Esdonk*<sup>1</sup>, *A.R.P.M. Valentijn*<sup>2</sup>, *J.V. Frangioni*<sup>3</sup>, *A.L. Vahrmeijer*<sup>2</sup>, *J. Burggraaf*<sup>1,2</sup>.

<sup>1</sup> Centre for Human Drug Research, the Netherlands  
<sup>2</sup> Leiden University Medical Center, the Netherlands  
<sup>3</sup> Curadel, United States of America

## Aim

To determine the safety, tolerability and pharmacokinetics of an intravenous injection of cRGD-ZW800-1 in healthy volunteers. The data from the healthy volunteer study will be used to design a phase 2 study to investigate the feasibility of cRGD-ZW800-1 during surgery and determine the optimal dose.

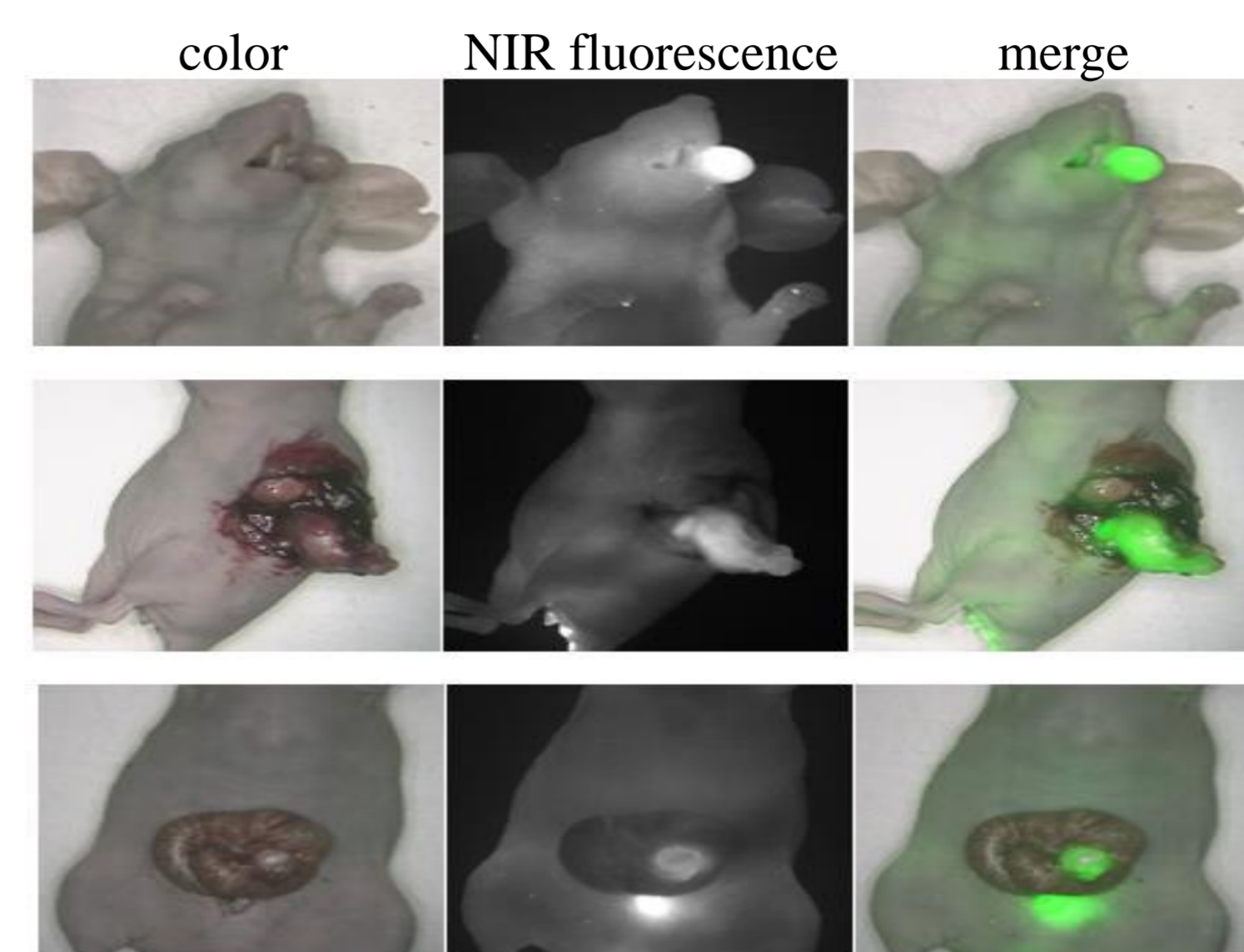
## Conclusion

Based on the distinctive integrin binding, absence of safety signals and predictable PK, cRGD-ZW800-1 appears to be a suitable imaging agent to visualize clinically colorectal cancer in real-time during surgery. A phase 2 study is designed to evaluate the diagnostic value of NIR fluorescence imaging using cRGD-ZW800-1 in patients with primary colorectal cancer.

## Results

### Preclinical studies:

Three tumor mice models were investigated (head-and-neck, pancreas- and colorectal tumor model). Tumors were visible in mice from 0.25 nmol; the optimal dose was 10 nmol (human equivalent dose: 63 micrograms). cRGD-ZW800-1 up to 15 mg/kg was well-tolerated in rats. The human equivalent dose of the no-observed-adverse-effect-level was 0.81 mg/kg



### First-in-human study:

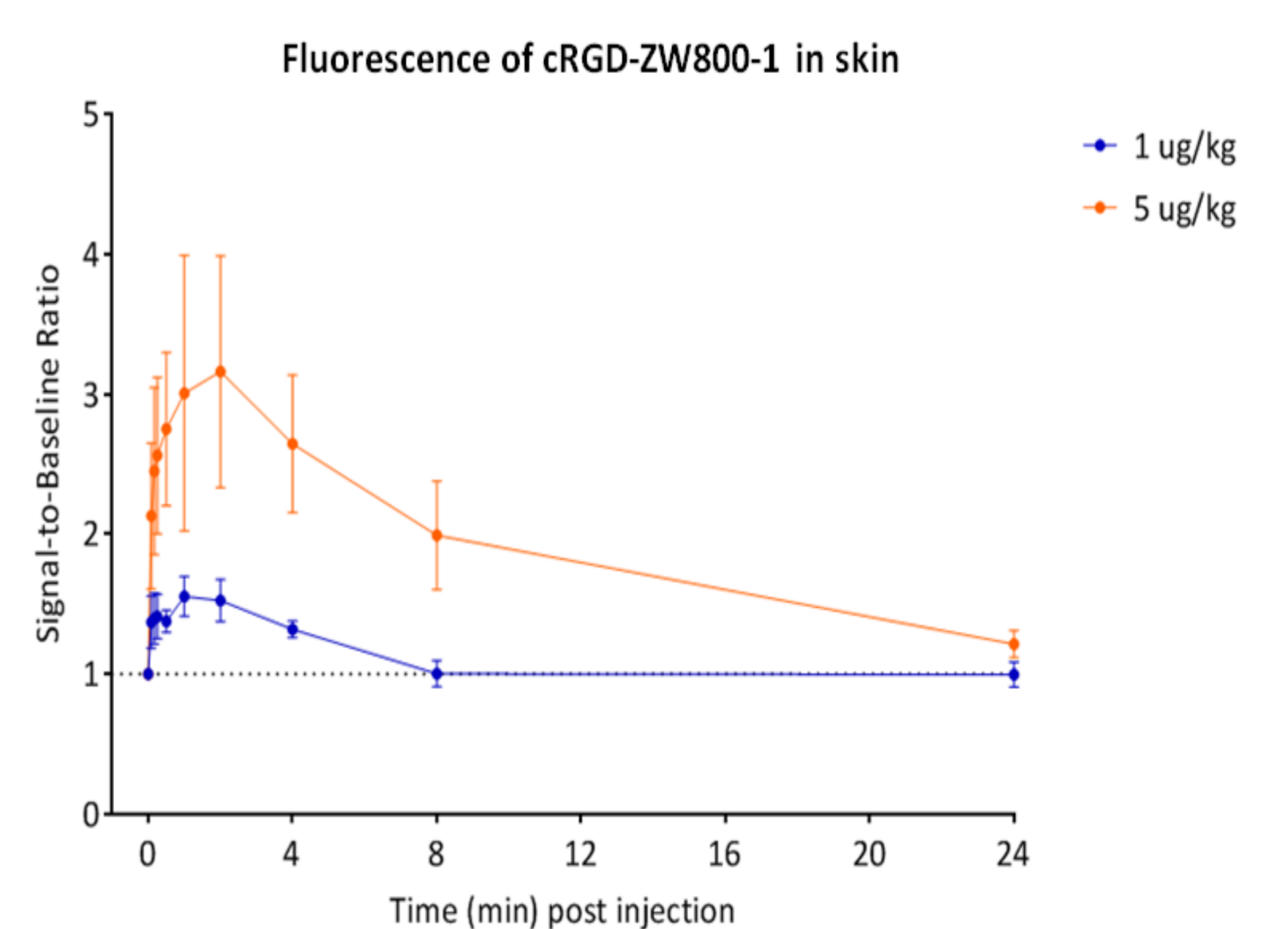
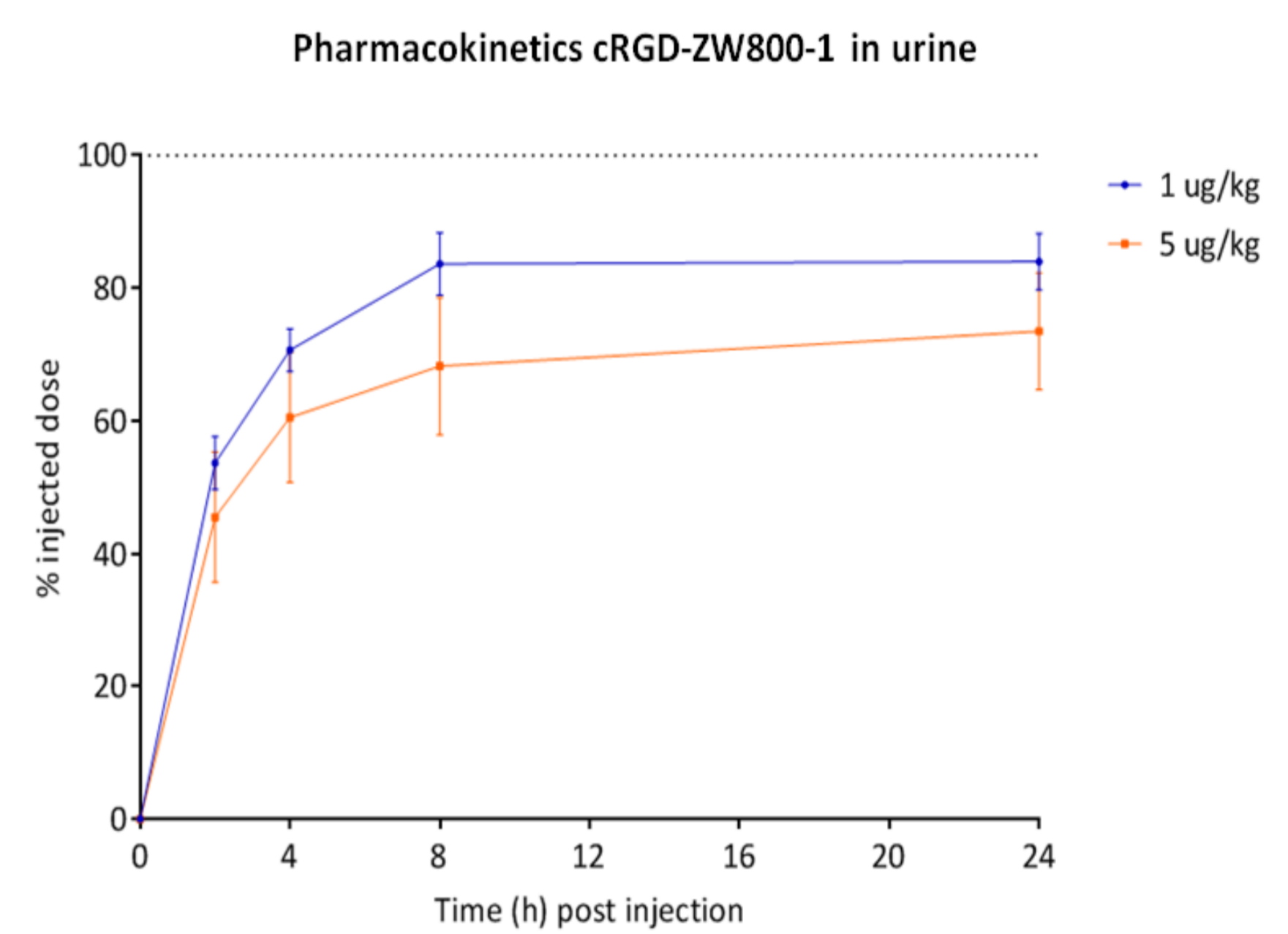
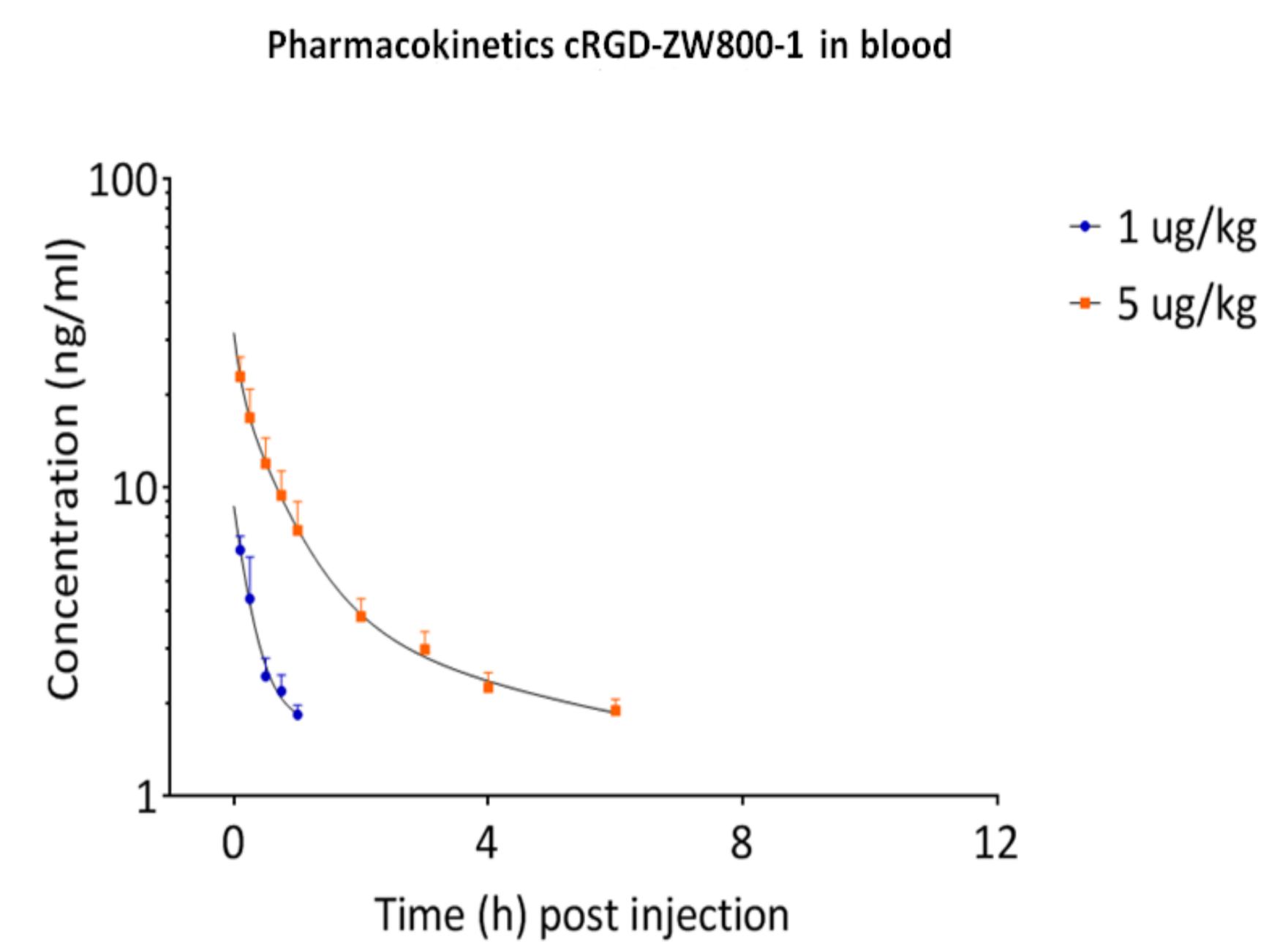
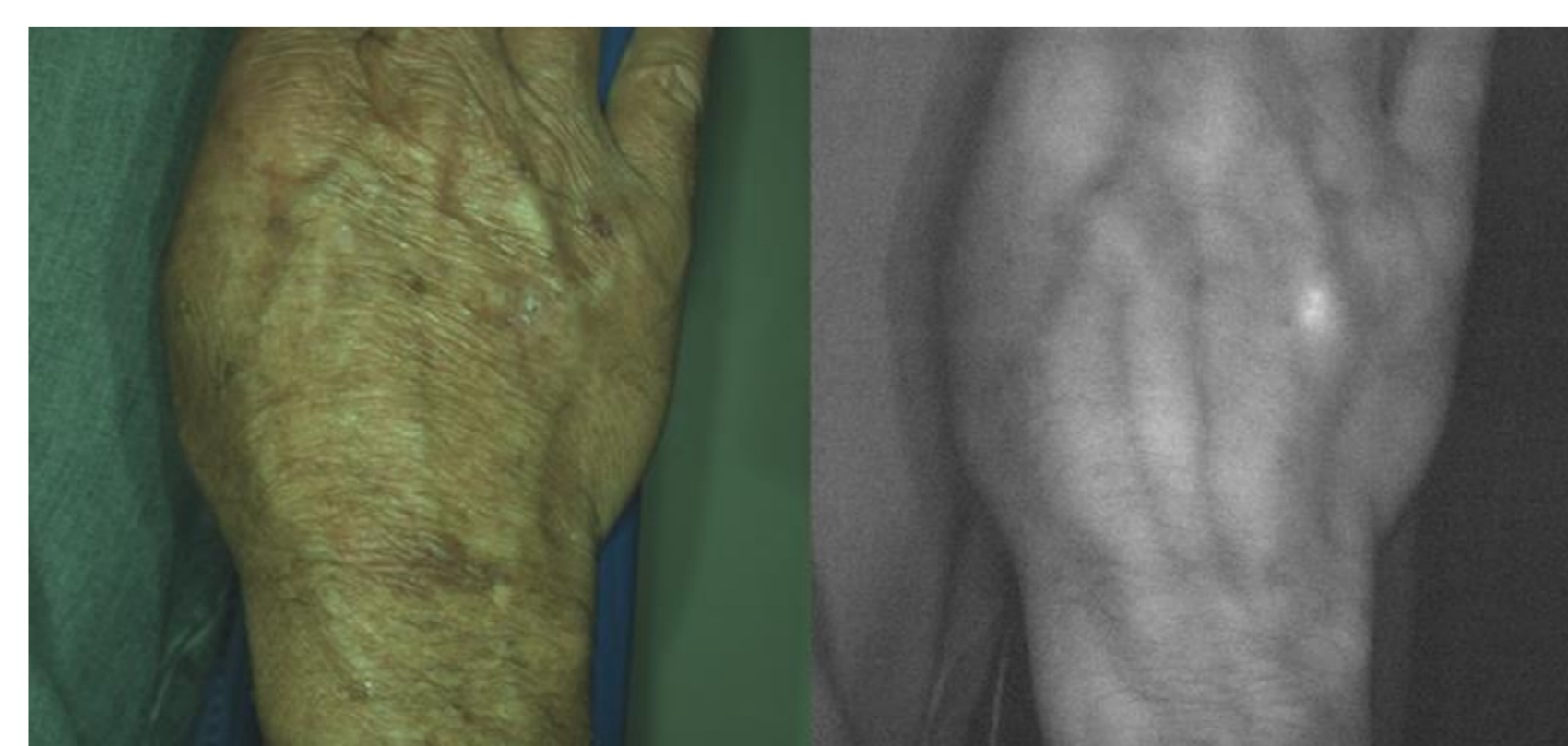
A phase 1, randomized, placebo-controlled, single ascending dose study was performed in 11 healthy volunteers to determine the safety, tolerability and pharmacokinetics of 0.001 mg/kg (microdose) and 0.005 mg/kg cRGD-ZW800-1 intravenous injection.

None of the healthy volunteers showed signs of toxicity or significant clinical changes after dosing. cRGD-ZW800-1 blood concentrations were measurable up to 1 hour post dose in the 0.001 mg/kg group and up to 6 hours in the 0.005 mg/kg group.

The mean cumulative renal excretion of cRGD-ZW800-1 was 83% (0.001 mg/kg) and 68% (0.005 mg/kg) at 8 hours post dosing. Skin fluorescence peaked at 1 hour post dosing and returned back to baseline within 24 hours.

### Additional finding:

One healthy volunteer had a recent wound with a scab on the hand present at time of cRGD-ZW800-1 injection. The lesion became fluorescent within 15 min after dosing and remained above background for 24 hours.



**LU** Leiden University  
**MC** Medical Center

**CHDR**  
Centre for Human Drug Research