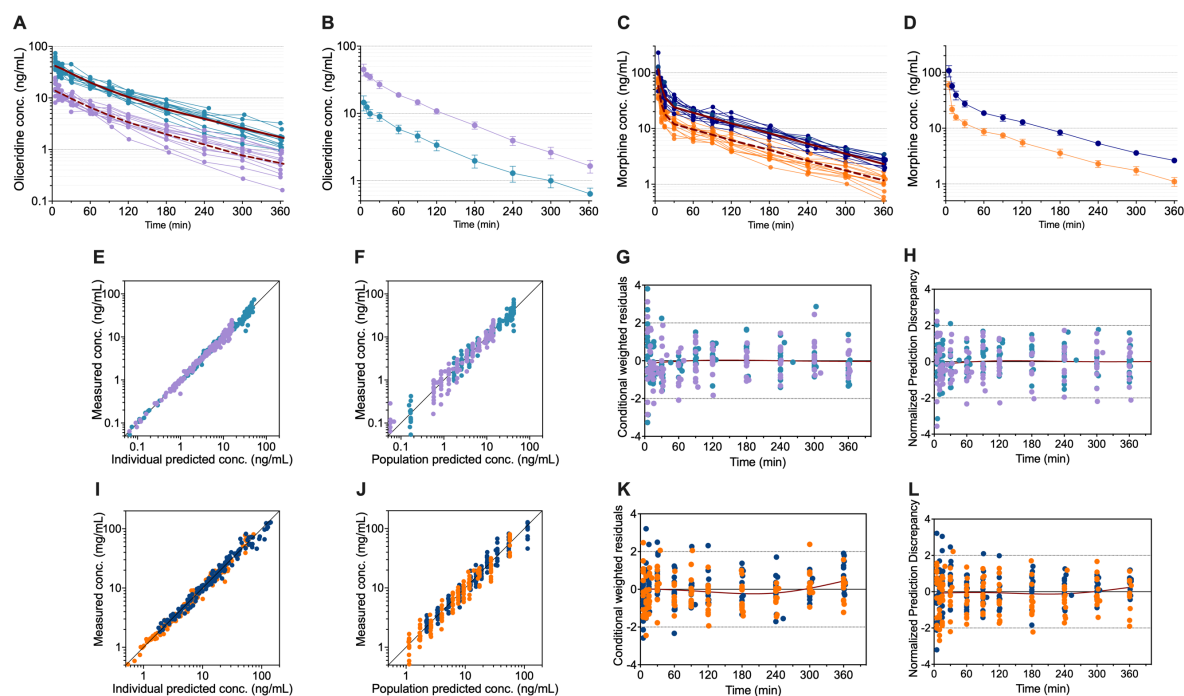Supplemental document 3 to:

Neurocognitive effect of biased μ-opioid receptor agonist oliceridine, a utility function analysis and comparison with morphine
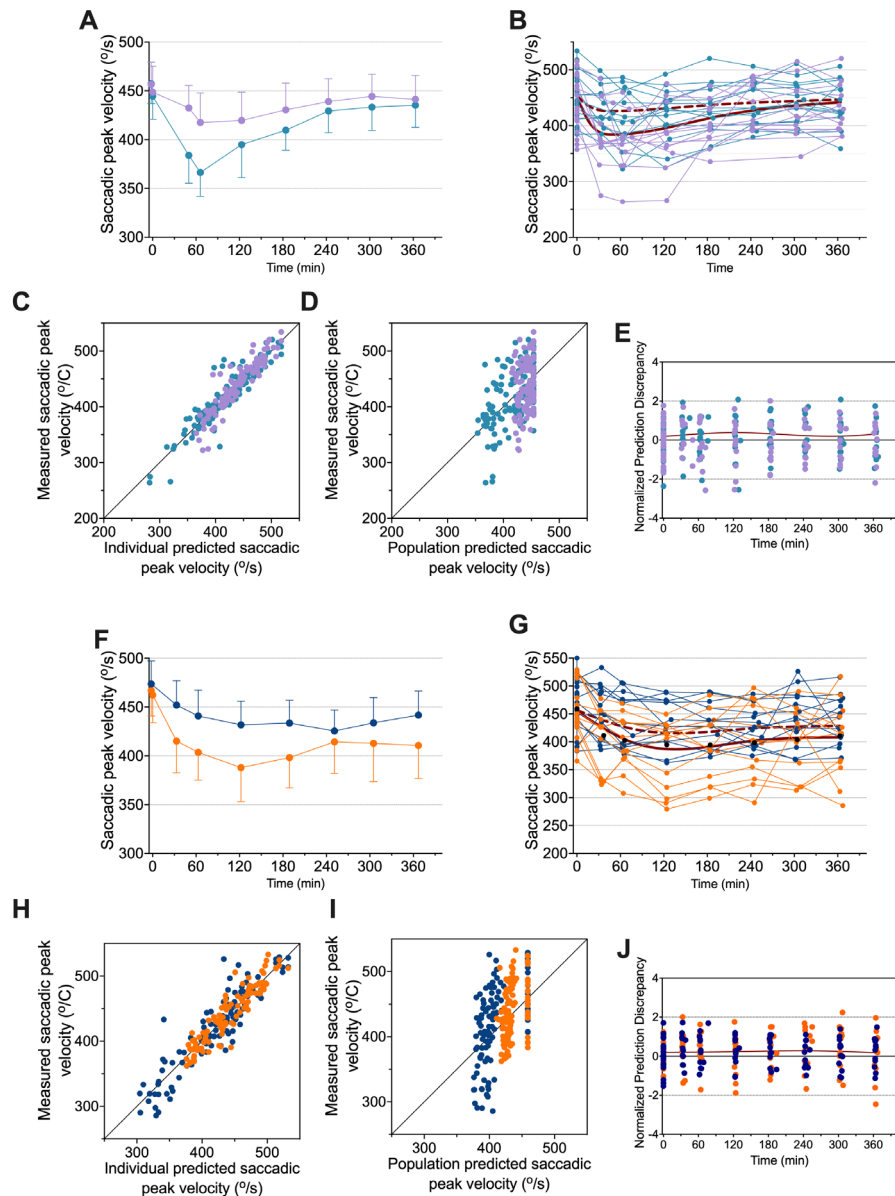
Laurence Moss MD,[1] Hemme Hijma PhD,[1] Mark Demitrack MD,[2] Jessica Kim MSc,[2] Geert Jan Groeneveld MD PhD,[1,3] Monique van Velzen PhD,[3] Marieke Niesters MD PhD,[3] Albert Dahan MD PhD,[3,4] Erik Olofsen PhD[3]

1. Centre for Human Drug Research, Leiden, the Netherlands; 2. Trevena Inc., Chesterbrook, Pennsylvania, USA; 3. Department of Anesthesiology, Leiden University Medical Center, Leiden, the Netherlands; 4. PainLess Foundation, Leiden, the Netherlands

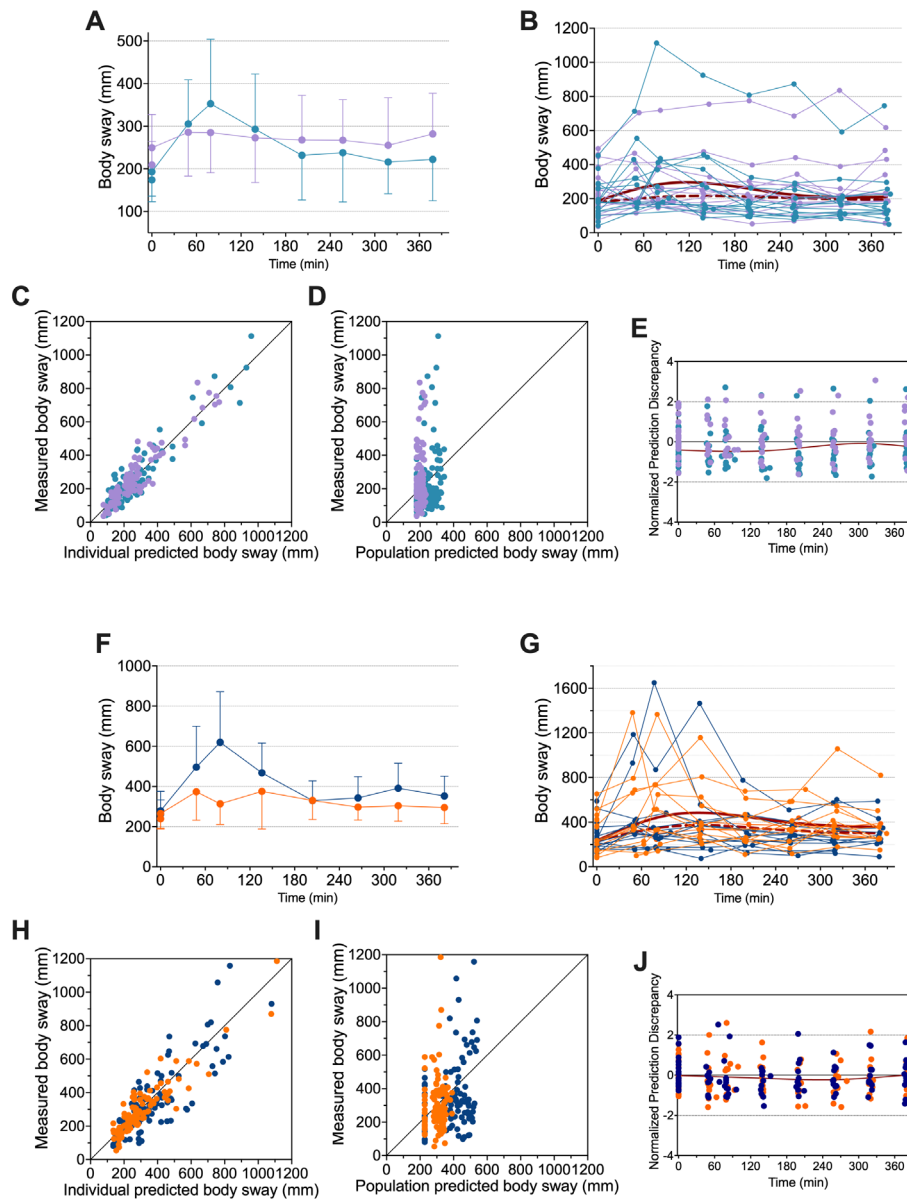**Pharmacodynamic-pharmacokinetic analysis: supplemental Figures 1-4**

Supplemental Figure 1. Pharmacokinetic data and goodness of fit plots. A. Individual plasma concentrations in subjects receiving 1 mg or 3 mg intravenous oliceridine. Red lines are the population fits for 1 mg (broken line) and 3 mg oliceridine (continuous line). **B.** Average plasma concentrations ± 95% confidence intervals for 1 mg and 3 mg intravenous oliceridine. **C.** Individual plasma concentrations in subjects receiving 5 mg or 10 mg intravenous morphine. Red lines are the population fits for 5 mg (broken line) and 10 mg morphine (continuous line). **D.** Average plasma concentrations ± 95% confidence intervals for 5 mg and 10 mg intravenous oliceridine. Individual predicted concentrations *versus* measured concentrations for oliceridine (**E**) and morphine (**I**). Population predicted concentrations *versus* measured concentrations for oliceridine (**F**) and morphine (**J**). Conditional weighted residuals *versus* time for oliceridine (**G**) and morphine (**K**). Normalized prediction discrepancy for oliceridine (**H**) and morphine (**L**). Purple symbols: 1 mg intravenous oliceridine, green/blue symbols: 3 mg intravenous oliceridine, orange symbols: 5 mg intravenous morphine, dark blue symbols: 10 mg intravenous morphine.
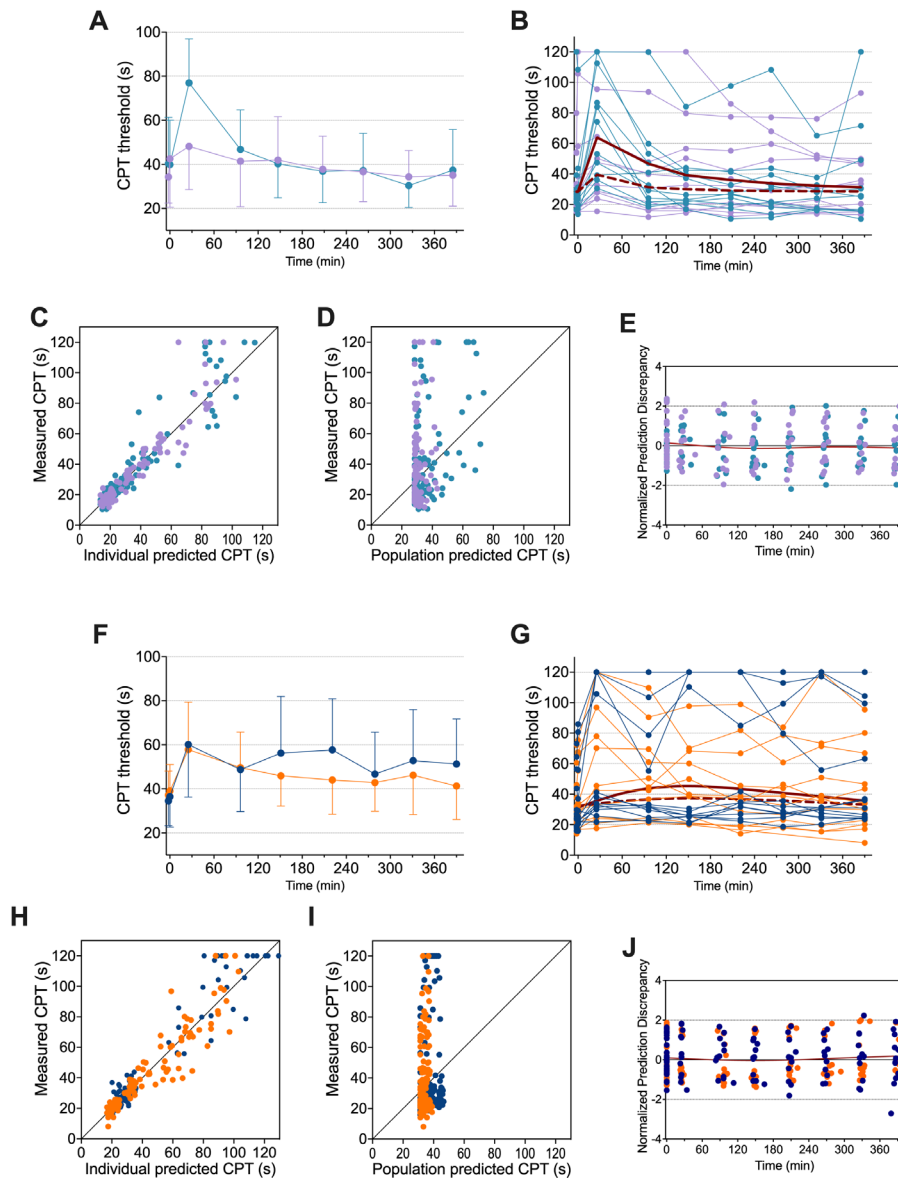
Supplemental Figure 2. Saccadic peak velocity data and goodness-of-fit plots. **A-E. Oliceridine.** Mean ± 95% confidence interval (**A**) and individual data (**B**) following 1 and 3 mg intravenous oliceridine. The red lines are the population fits for 1 mg (broken line) and 3 mg (continuous line) oliceridine. **C.** Individual predicted data *versus* measured data. **D.** Population predicted data *versus* measured data. **E.** Normalized prediction error *versus* measured data with a smooth curve plotted through the data (red line). Purple symbols: 1 mg intravenous oliceridine, green/blue symbols: 3 mg intravenous oliceridine. **F-J**. **Morphine.** Mean ± 95% confidence interval (**A**) and individual data (**B**) following 5 and 10 mg intravenous morphine. The red lines are the population fits for 5 mg (broken line) and 10 mg (continuous line) morphine. **C.** Individual predicted data *versus* measured data. **D.** Population predicted data *versus* measured data. **E.** Normalized prediction error *versus* measured data with a smooth curve plotted through the data (red line). Orange symbols: 5 mg intravenous morphine, dark blue symbols: 10 mg intravenous morphine.

Supplemental Figure 3. Body sway data and goodness-of-fit plots. **A-E. Oliceridine.** Mean ± 95% confidence interval (**A**) and individual data (**B**) following 1 and 3 mg intravenous oliceridine. The red lines are the population fits for 1 mg (broken line) and 3 mg (continuous line) oliceridine. **C.** Individual predicted data *versus* measured data. **D.** Population predicted data *versus* measured data. **E.** Normalized prediction error *versus* measured data with a smooth curve plotted through the data (red line). Purple symbols: 1 mg intravenous oliceridine, green/blue symbols: 3 mg intravenous oliceridine. **F-J**. **Morphine.** Mean ± 95% confidence interval (**A**) and individual data (**B**) following 5 and 10 mg intravenous morphine. The red lines are the population fits for 5 mg (broken line) and 10 mg (continuous line) morphine. **C.** Individual predicted data *versus* measured data. **D.** Population predicted data *versus* measured data. **E.** Normalized prediction error *versus* measured data with a smooth curve plotted through the data (red line). Orange symbols: 5 mg intravenous morphine, dark blue symbols: 10 mg intravenous morphine.

Supplemental Figure 4. Cold pressor test tolerance threshold data and goodness-of-fit plots. **A-E. Oliceridine.** Mean ± 95% confidence interval (**A**) and individual data (**B**) following 1 and 3 mg intravenous oliceridine. The red lines are the population fits for 1 mg (broken line) and 3 mg (continuous line) oliceridine. **C.** Individual predicted data *versus* measured data. **D.** Population predicted data *versus* measured data. **E.** Normalized prediction error *versus* measured data with a smooth curve plotted through the data (red line). Purple symbols: 1 mg intravenous oliceridine, green/blue symbols: 3 mg intravenous oliceridine. **F-J**. **Morphine.** Mean ± 95% confidence interval (**A**) and individual data (**B**) following 5 and 10 mg intravenous morphine. The red lines are the population fits for 5 mg (broken line) and 10 mg (continuous line) morphine. **C.** Individual predicted data *versus* measured data. **D.** Population predicted data *versus* measured data. **E.** Normalized prediction error *versus* measured data with a smooth curve plotted through the data (red line). Orange symbols: 5 mg intravenous morphine, dark blue symbols: 10 mg intravenous morphine. CPT cold pressor test.