

# PRECISION DOSING OF DIHYDROERGOTAMINE (DHE) BY INHALATION

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## INTRODUCTION

Dihydroergotamine (DHE, Figure 1) is a proven, effective migraine therapy, particularly when administered by the IV route. Other administration routes have inconsistent pharmacokinetic (PK) properties and administration variability, creating therapeutic variability. However, inhaled DHE delivery that closely mimics protocols for IV administration regimens may provide great benefit in migraineurs, including:

- **Rapid Onset**
- **Dosing Consistency**
- **Long Lasting Relief**
- **Reduced Recurrence**
- **Convenience of Self Administration**

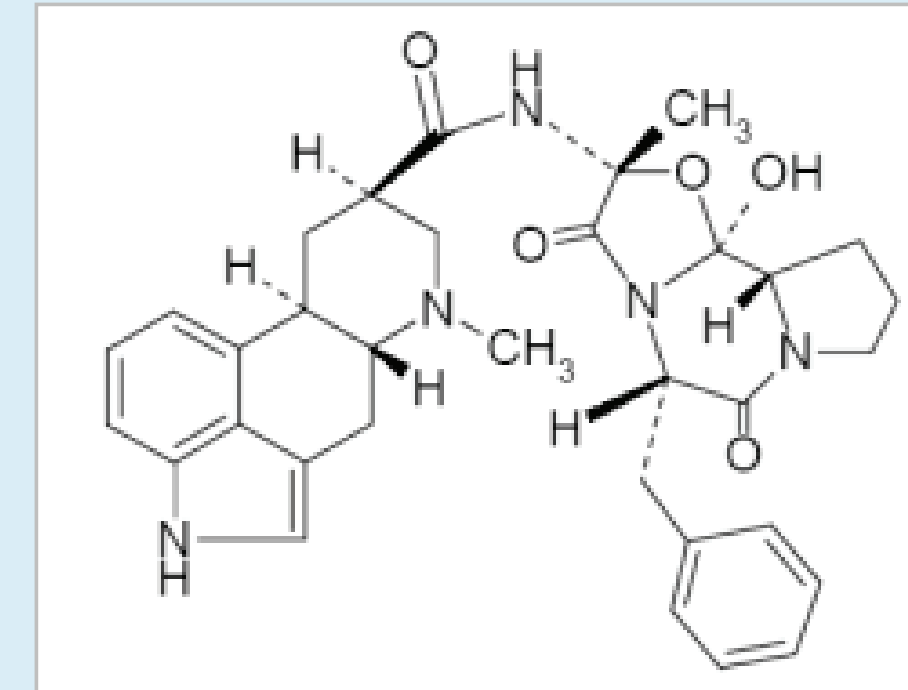


Figure 1. Chemical structure of dihydroergotamine

This work aimed to show that the Tempo™ inhaler, by automatic and precise coordination of dose administration with patient inhalation, could enable consistent inhalation dosing of inhaled DHE (MAP0004). Dose consistency and resulting pharmacokinetic response were determined via *in vitro* clinical release testing and in human clinical trial use.

## TEMPO™ INHALER

The Tempo inhaler (Figure 2,3) is designed to enable accurate and reproducible pulmonary delivery of MAP0004. The Tempo inhaler incorporates the size, ease of use, and convenience advantages associated with standard pMDIs, but overcomes their greatest limitations: inconsistent dosing, drug delivery inefficiency and the need for patients to synchronize a breath with manual triggering of the inhaler.

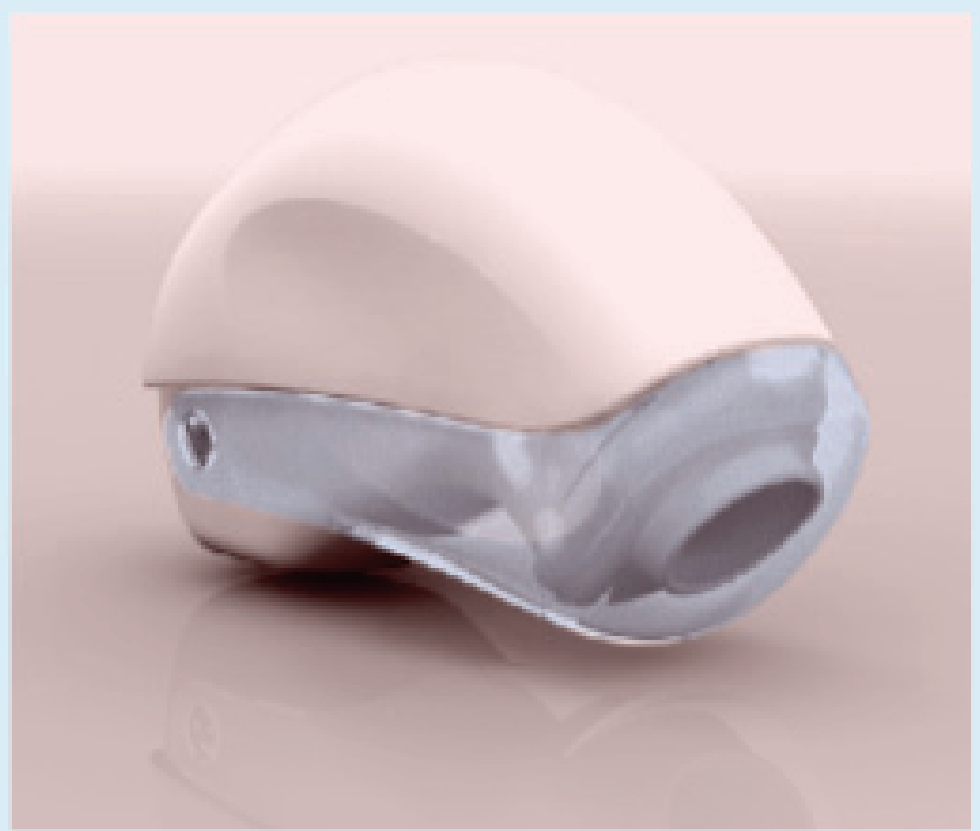


Figure 2. Appearance of the Tempo inhaler

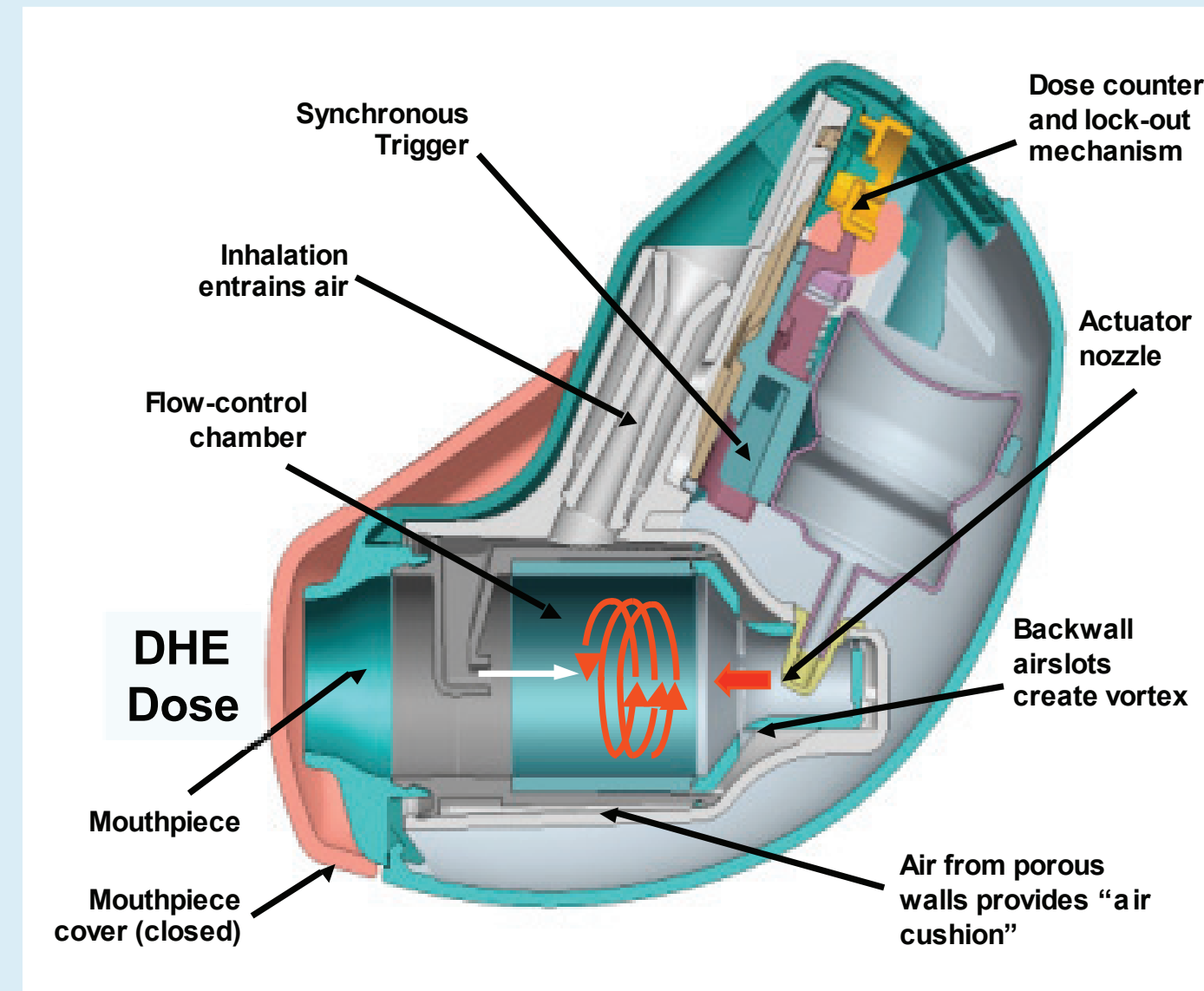


Figure 3. Cutaway plan of Tempo inhaler detailing main functional elements with mouthpiece cover in closed position

## METHODS

### (1) *In vitro* clinical release testing:

Standard pharmacopoeial (or compendial) test methods were employed to confirm:

- **Delivered Dose (DD):** dose exiting Tempo inhaler mouthpiece
- **Fine Particle Dose (FPD):** <4.7 μm, dose aimed at the deep lung and potentially available to the systemic circulation

### (2) Confirmation of inhaler firing:

Inhaler firing was confirmed by trigger test analysis, which recorded the airflow (L/min) at which the inhaler fired against a standardised inhalation flow pattern.

### (3) Clinical trial use:

Clinical trials compared the PK profile of 0.22, 0.44, 0.88 and 1.32 mg DHE delivered by the Tempo inhaler to 1.0 mg IV (3 min slow bolus) DHE 45® in healthy subjects (corresponding to 1, 2, 4 and 6 inhalations from the Tempo inhaler, respectively).

## RESULTS – *In Vitro* Testing

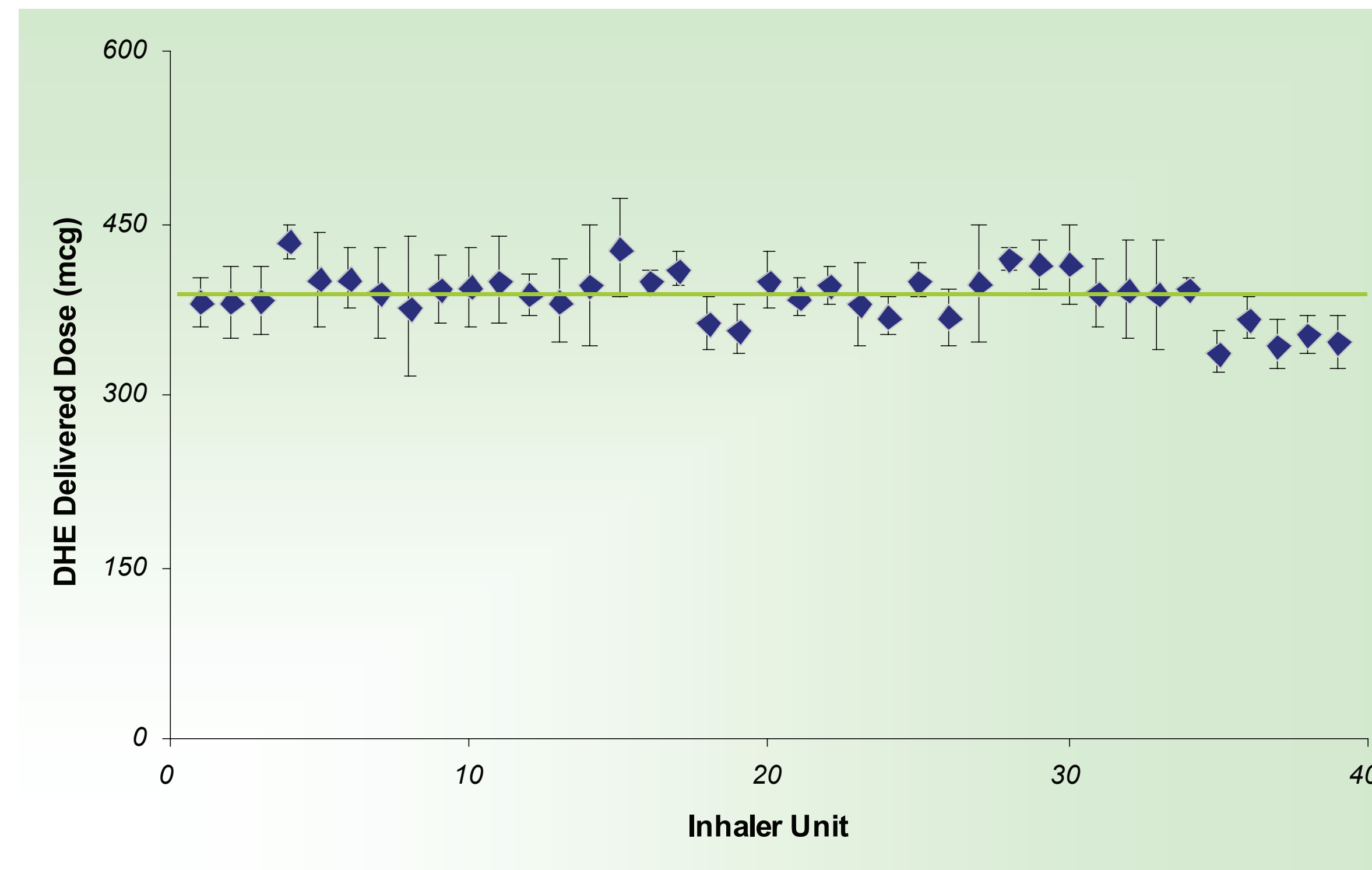


Figure 4. Delivered Dose by inhaler (n=39); DD was tested 4 times per inhaler and was tightly distributed about the mean (green line)

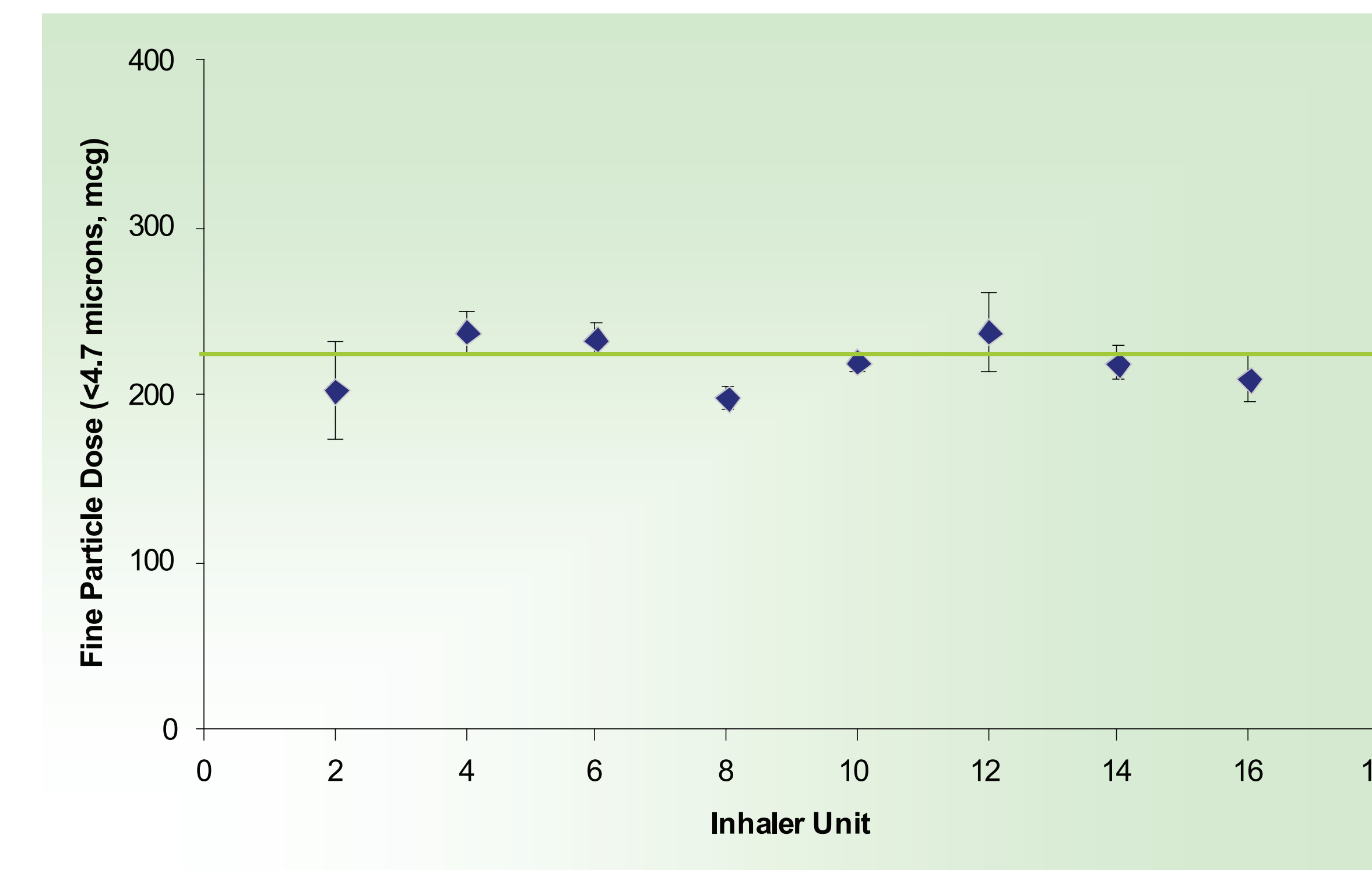


Figure 5. FPD by inhaler (n=8); FPD was tested 3 times per inhaler and was tightly distributed about the mean FPD (green line)

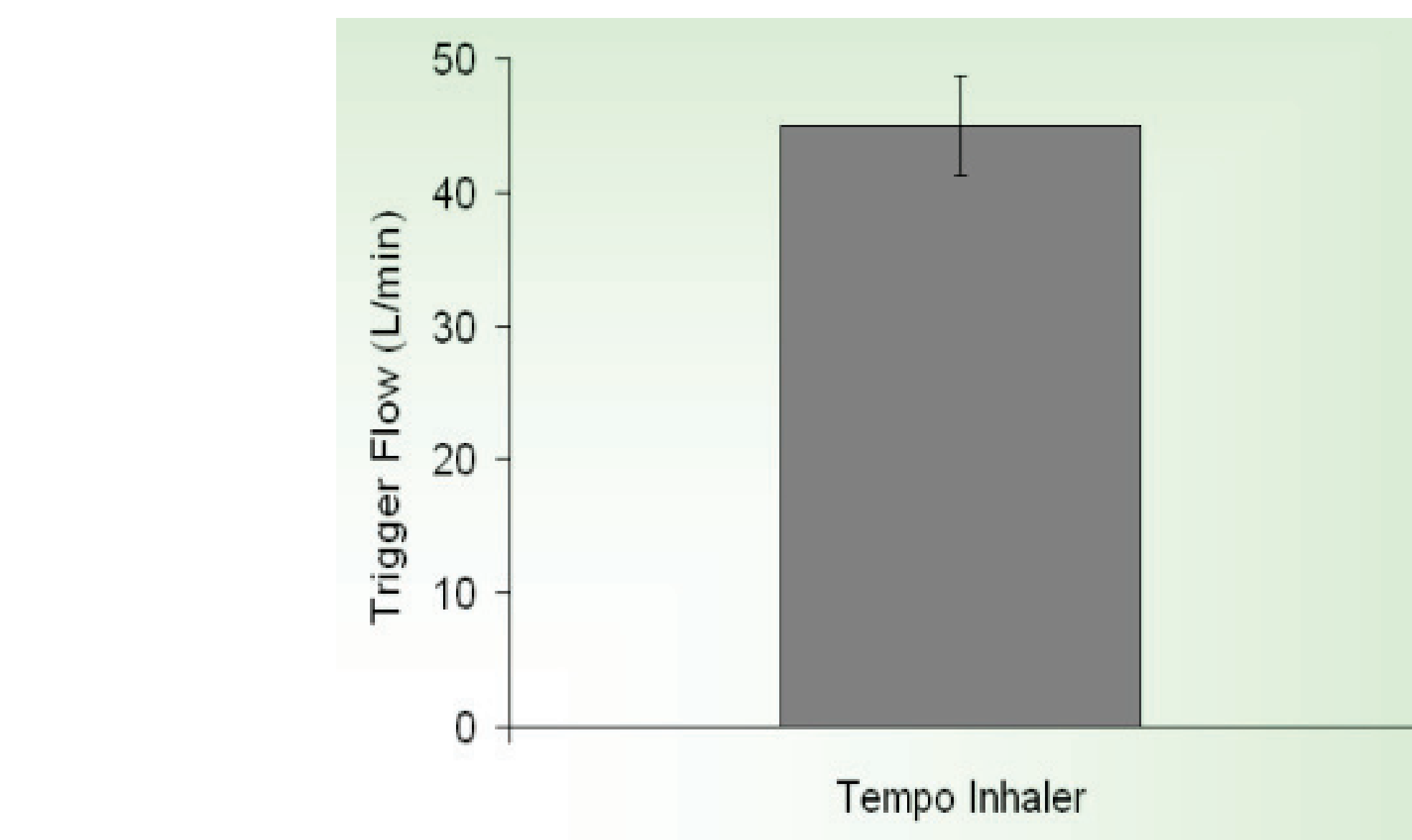


Figure 6. Trigger flow consistency (n=39 inhalers); inhalers fired at approximately 45 L/min

## RESULTS – *Clinical Trial Use*

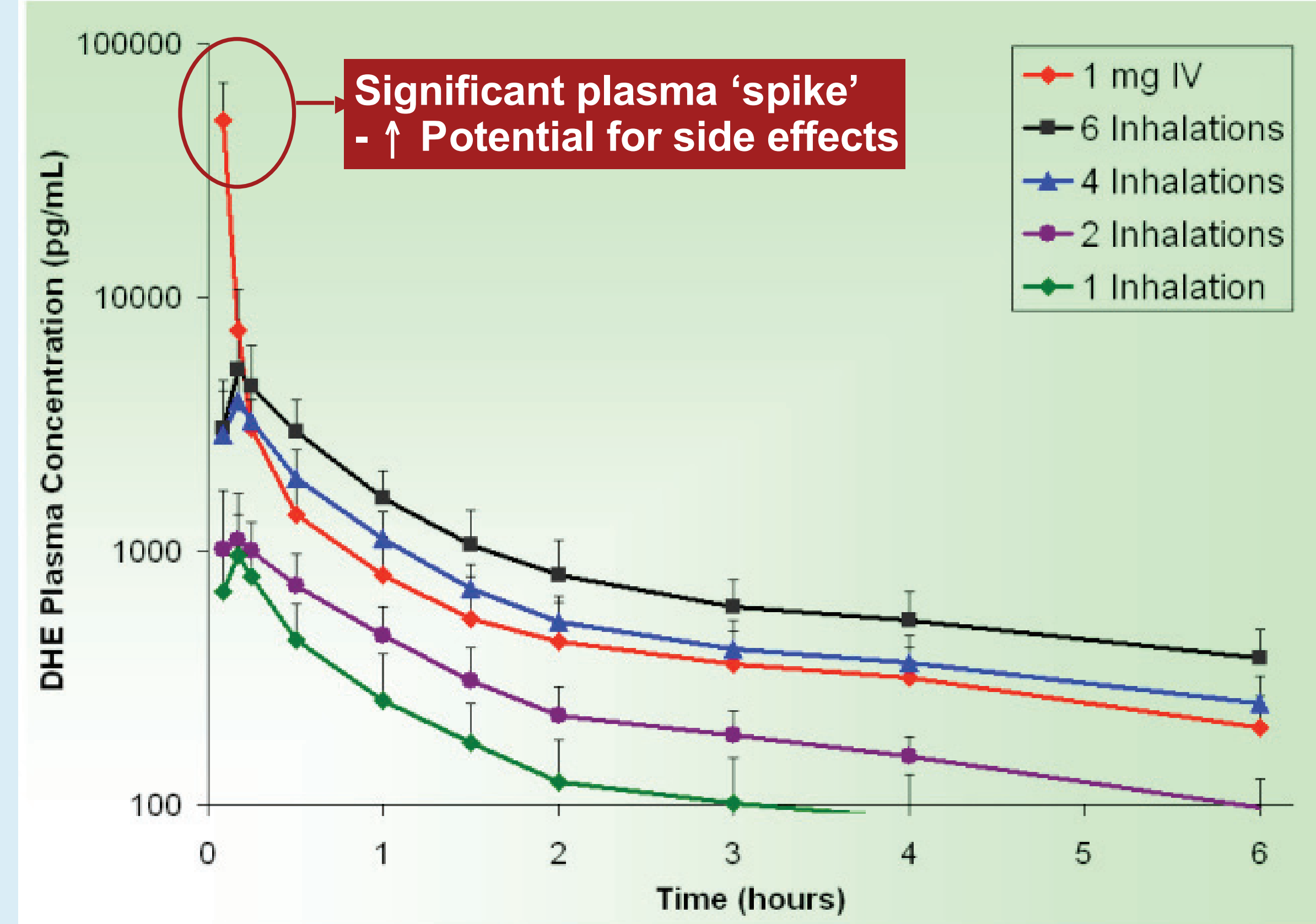


Figure 7. Pharmacokinetic plasma profiles following MAP0004 and IV administration (subjects – 6 inhalations: n=12; 4 inhalations: n=12; 2 inhalations: n=6; 1 inhalation: n=6; IV: n=16)

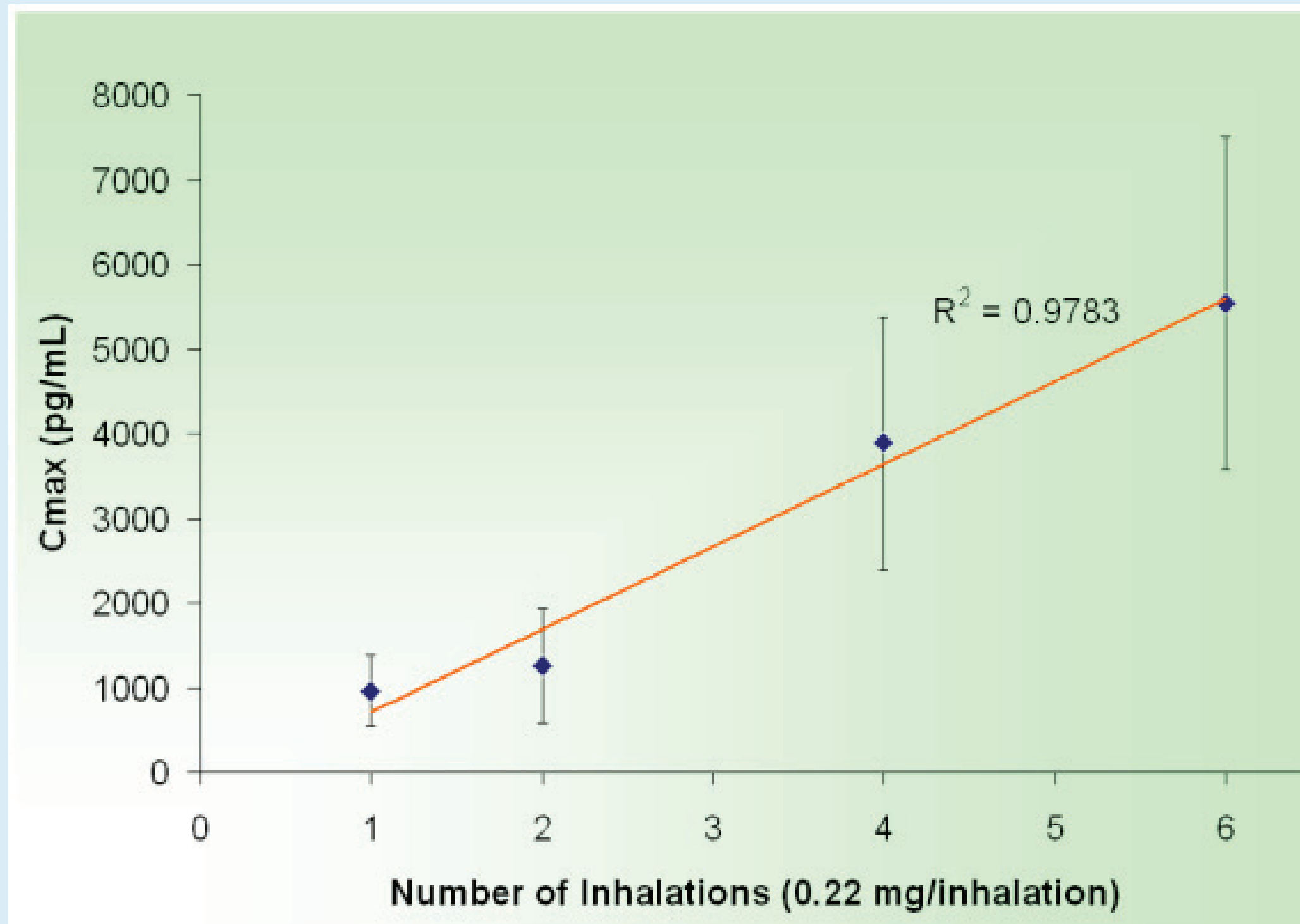


Figure 8. C<sub>max</sub> vs. Number of inhalations. Dose proportionality was confirmed by a positive correlation

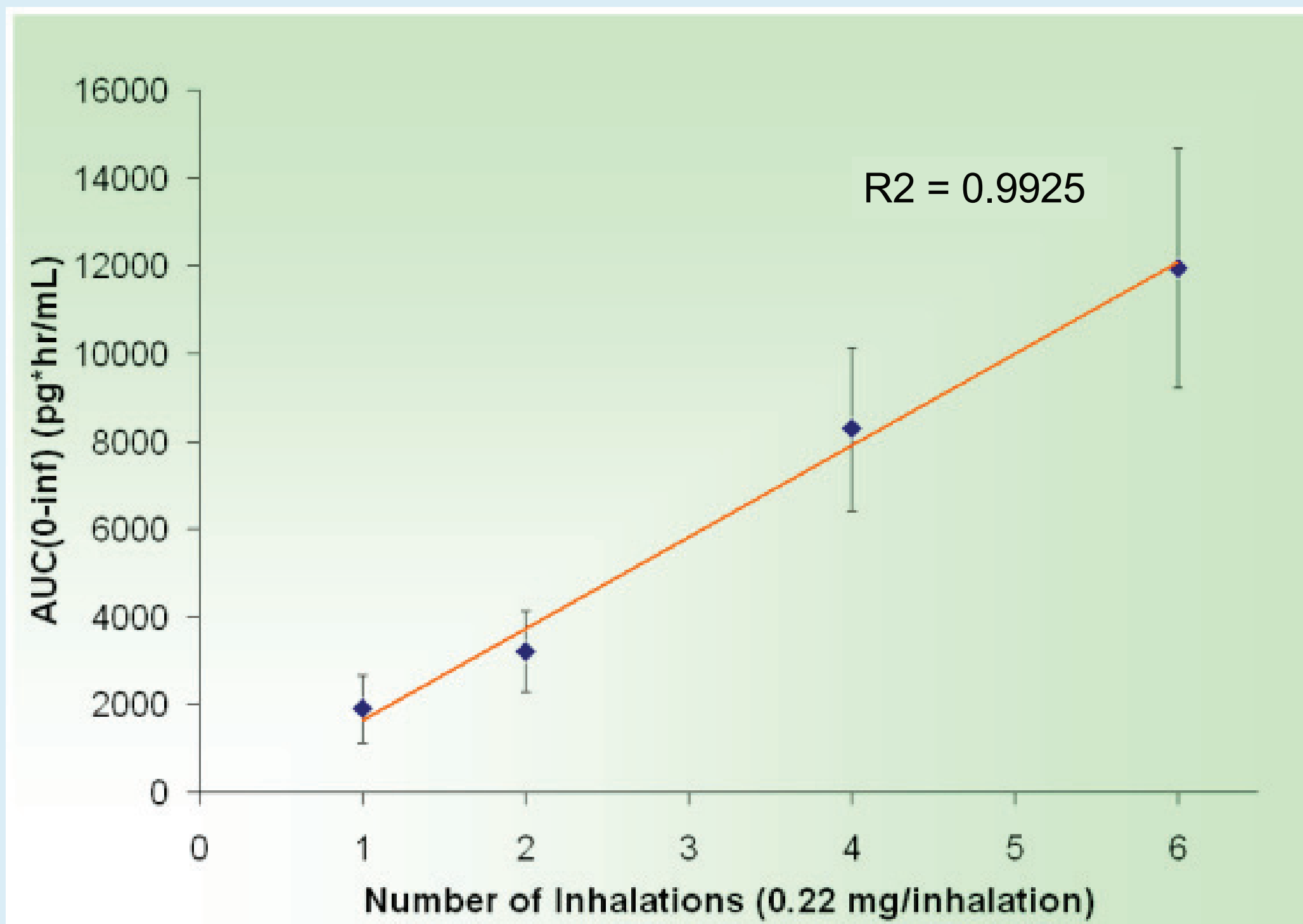


Figure 9. AUC vs. Number of inhalations. Dose proportionality was confirmed by a positive correlation

## DISCUSSION

### *In vitro* Clinical Release Testing

DD was highly consistent for all inhalers tested (Figure 4) and averaged 0.39 ± 0.02 mg (n=39, RSD = 5.1%), which complied with international testing standards (FDA, USP, Ph. Eur).

FPD consistency is driven by both the Tempo inhaler performance and the DHE drug formulation. These characteristics were optimised during development to ensure maximal deposition of drug into the deep lung where drug is rapidly absorbed into the blood stream. Consistent FPD *in vitro* was predicted to positively correlate with consistent PK in humans. Figure 5 shows the FPD data from 8 inhalers, which showed tight control of dosing around a mean of 0.22 ± 0.02 mg (RSD = 9.1%) per actuation.

Trigger flow data in Figure 6 indicate the airflow at which inhalers fired, when tested against a simulated inhalation profile. This test confirms that the inhalers fired successfully against a simulated patient inhalation. Trigger flow was reproducible and inhalers fired at a mean airflow of 45 ± 3.7 L/min (RSD = 8.2%).

### Clinical Trial Use

Clinical trial evaluation (Figure 7) in a Phase 1 trial<sup>1</sup> showed MAP0004 achieved a rapid T<sub>max</sub>, only slightly longer than for IV dosing: 10 min for MAP0004 vs. 5 min for IV 1.0 mg. These results are also significantly faster than for 1.0 mg nasal DHE administration, which exhibits T<sub>max</sub> at ~54 min<sup>2</sup>.

C<sub>max</sub> for IV was at least 17 times greater than for any inhaled dose studied. For instance, C<sub>max</sub> for 4 inhalations was 2874 pg/mL compared to 49473 pg/mL for IV. The greatly reduced peak plasma concentration via MAP0004 inhalation appeared to correlate with a lower incidence of adverse effects compared to IV administration, such as nausea (8% MAP0004 vs. 63% IV), dizziness (22% MAP0004 vs. 44% IV) and paresthesia (0% MAP0004 vs. 31% IV).

C<sub>max</sub> was linear with inhaled MAP0004 dose (Figure 8, R<sup>2</sup>=0.9783). Following 2 inhalations (0.44 mg FPD), C<sub>max</sub> was 1101 pg/mL. As a comparison, 1.0 mg nasally administered DHE<sup>2</sup>, achieved a similar C<sub>max</sub> at 1000 pg/mL, but occurred ~44 min later than the inhaled route. AUCs for inhaled also correlated linearly (Figure 9, R<sup>2</sup>=0.9925), indicating excellent dose proportionality.

In a Phase 2 trial<sup>3</sup>, MAP0004 pharmacokinetics were associated with early superior pain relief vs. placebo at 10 min (27% for MAP0004 (n=47) vs. 0% for placebo (n=16), p<0.028).

It is evident that MAP0004 rapidly achieves therapeutic plasma concentrations that are proportional to dose and are insufficient to precipitate adverse effects. Dose consistency is also required to ensure these positive aspects of MAP0004. Table 1 shows %RSD for C<sub>max</sub> and AUC, clearly showing that MAP0004 was as consistent as IV administration. This consistency is driven by dosing from the Tempo inhaler, as confirmed with *in vitro* testing.

PK Parameter	%RSD: 4 inhalations (n=12)	%RSD: IV (n=12)
AUC	22	30
C <sub>max</sub>	39	39

Table 1. Comparison of %RSD values for AUC and C<sub>max</sub> for two delivery routes

## CONCLUSIONS

This work establishes that precision dosing of MAP0004 is achieved, as confirmed by excellent dose proportionality and low variability that was essentially equivalent to IV dosing.

MAP0004 consistently and rapidly reached therapeutic plasma concentrations at 10 min and was associated with both efficacy (superior pain relief vs. placebo) and an enhanced safety profile (significant reduction in adverse effects vs. IV dosing).

### References:

1. Shrewsbury S et al. Comparative clinical PK of DHE via a novel system (Tempo™ Inhaler). Headache 2007; 47 (5): 754
2. Humbert H et al. Human pharmacokinetics of dihydroergotamine administered by nasal spray. Clin Pharmacol Ther 1996; 60(3):265-275
3. Aurora S et al. Rapid and sustained clinical efficacy and safety of inhaled DHE via (Tempo™ Inhaler). American Headache Society 2007