# SAFETY PHARMACOLOGY

## *Whole Body Plethysmograph*

Plethysmography assessments are used to evaluate any potential adverse pulmonary effects as the result of preclinical safety testing and is a requirement for the development of new drug recommended by ICH Guideline S7A[1]. Whole-body plethysmography (WBP) is a non-invasive technique used to assess pulmonary function in conscious and spontaneously breathing laboratory subjects. Changes in volume, pressure and airflow can be measured to determine different respiratory parameters[1,2].

**Test System:** *Rattus norvegicus* (Sprague-Dawley).

**Number of animal per group:** 6 animals.

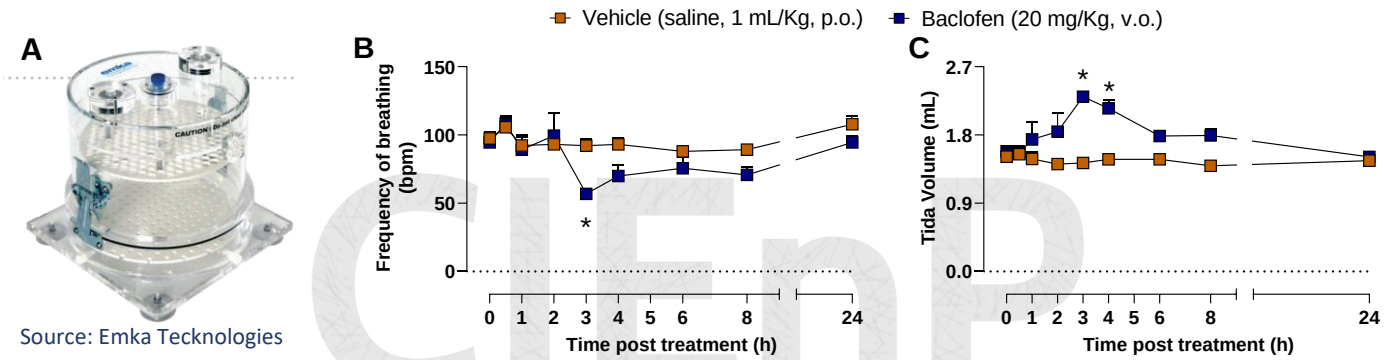
**Route of administration:** upon request.

**Treatment mode:** upon request.

**Main read-outs:** Lung function measurements such as breathing frequency and tidal volume by unrestrained whole body plethysmography.

**Alternative read-outs:** Inspiratory time, expiratory time, enhanced pause, minute volume, peak inspiratory flow and peak expiratory flow.

## *Validation Data*




Source: Emka Tecknologies

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| Parameter | Vehicle (saline, 1 mL/Kg, p.o.) | | Baclofen (20 mg/Kg, p.o.) | |
|---|---|---|---|---|
| | Baseline | 3 hours post treatment | Baseline | 3 hours post treatment |
| Frequency of breathing (bpm) | 97.46 ± 4.78 | 92.19 ± 5.11 ***-5.28%*** | 94.57 ± 2.74 | 56.87 ± 1.89[ab] ***-39.75%***[a] |
| Tidal volume (mL) | 1.51 ± 0.11 | 1.43 ± 0.05 ***-4.51%*** | 1.58 ± 0.06 | 2.30 ± 0.04[ab] ***46.39%***[a] |
| Inspiratory Time (msec) | 240.09 ± 5.44 | 253.23 ± 13.66 ***5.53%*** | 263.22 ± 4.89 | 400.18 ± 13.36[ab] ***52.07%***[a] |
| Expiratory Time (msec) | 420.04 ± 36.74 | 453.52 ± 20.69 ***9.2%*** | 432.28 ± 15.32 | 693.65 ± 27.86[ab] ***60.71%***[a] |
| Enhanced Pause (A.U.) | 0.36 ± 0.04 | 0.35 ± 0.01 ***1.21%*** | 0.35 ± 0.03 | 1.08 ± 0.16[a] ***210.92%***[a] |

Figure 1. Evaluation of safety pharmacology: (A) whole body plethysmography. Effects of Baclofen (20 mg/Kg, p.o.) on (B) frequency of breathing and (C) tidal volume in conscious rats after oral administration. Each point represents the mean ± SEM of each group. Two-way analysis of variance (ANOVA) followed by Dunnett's test were performed. *$p < 0.05$ Baclofen group compared to Vehicle group. Table (D) showing mean ± SEM values and percentage of variation from baseline to values obtained within 3 hours after treatment. [a]$p < 0.05$ Baclofen compared to Vehicle. [b]$p < 0.05$ compared to baseline data in the same group.

To avoid bias and to allow reproducibility all *in vivo* experiments follow the ARRIVE guidances[2]. Rat colony from Charles River Laboratories are breed and maintained in SPF conditions. The project includes study plan and final report. Raw data are inspected by quality assurance unity. The experimental procedures was previously approved by the CIEnP Committee on the Ethical Use of Animals.

References:

[1]ICH S7A: Safety Pharmacology Studies for Human Pharmaceuticals - S7A. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Current Step 4 version. 2000.

[2]Ewart, L et al. A multi-site comparison of in vivo safety pharmacology studies conducted to support ICH S7A & B regulatory submissions. J Pharmacol Toxicol Methods 68(1):30-43, 2013.

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