Feasibility of Non-Invasive Monitoring of Respiratory, ECG and Activity Parameters in Pair-Housed Freely-Moving Adult Male Rats using a Jacketed External Telemetry System (DECRO®); A Pharmacological Validation with Baclofen.

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Jacketed monitoring for life sciences

1 INTRODUCTION

Simultaneous assessment of multiple vital functions, along with collection of standard toxicology endpoints in non-rodents using non-invasive telemetry jackets, is increasingly conducted in regulatory non-clinical studies. Equivalent solutions are lacking in rats, despite being the most common rodent species used in toxicology studies.

A Bluetooth-based telemetry jacket (DECRO solution) was developed to non-invasively record respiratory function, ECG and activity in rats.

A feasibility study was conducted in group-housed rats in environmental/husbandry conditions similar to those employed in 4-week regulatory studies.
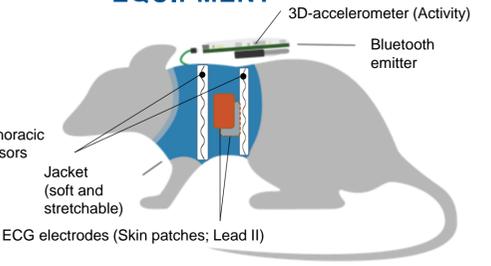
2 MATERIAL AND METHODS

ANIMALS AND TEST ARTICLES

Animals
Pair-housed, freely-moving male Wistar rats
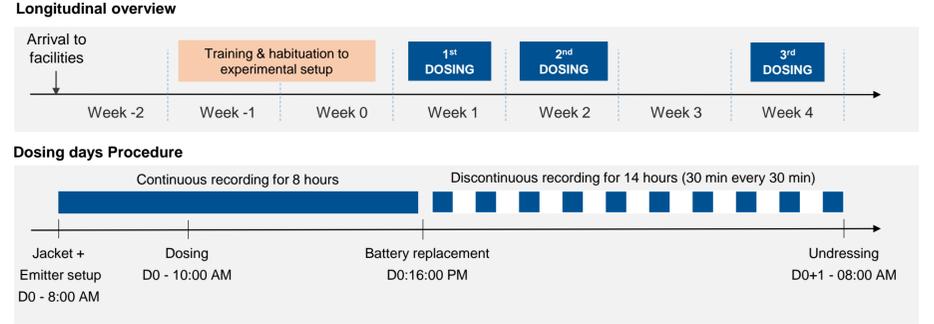Age: 9 weeks on first dosing occasion

Test materials
Vehicle control (n=4)
R(+)-Baclofen (15 mg/kg; n=4)

Gavage dosing

EQUIPMENT

3D-accelerometer (Activity)
Bluetooth emitter
Abdominal/Thoracic inductive sensors (Respiration)
Jacket (soft and stretchable)
ECG electrodes (Skin patches; Lead II)

EXPERIMENTAL DESIGN

Longitudinal overview

Arrival to facilities — Training & habituation to experimental setup — 1st DOSING — 2nd DOSING — 3rd DOSING

Week -2 | Week -1 | Week 0 | Week 1 | Week 2 | Week 3 | Week 4

Dosing days Procedure

Continuous recording for 8 hours | Discontinuous recording for 14 hours (30 min every 30 min)

Jacket + Emitter setup D0 - 8:00 AM
Dosing D0 - 10:00 AM
Battery replacement D0:16:00 PM
Undressing D0+1 - 08:00 AM

PARAMETERS AND DATA ANALYSIS

- Proprietary software DECRO 1.0.0
- 10-minute averages of good quality, continuously or intermittently acquired telemetry signals (-2h to +24h)
- Recorded parameters: heart rate, respiratory rate, inspiratory/expiratory times, tidal/minute volumes, activity level (10-minute averages)

STATISTICS

- Two-way (time and dose) repeated measures ANOVA
- If significant time-by-dose interaction, vehicle *vs* baclofen comparisons at each time-point
- If no interaction, global dose effect (vehicle *vs* baclofen) averaged over all time-points
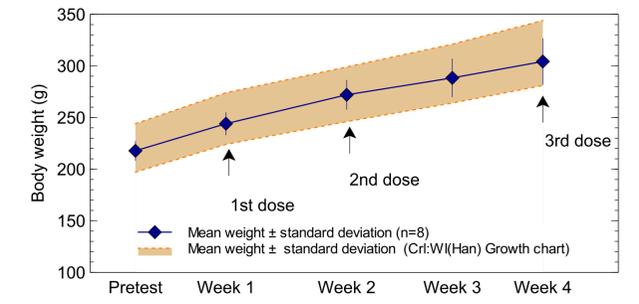
4 DISCUSSION

- DECRO® external telemetry jacket was very well tolerated when worn for 24 hours on several occasions by pair-housed, growing rats
- The quality of the respiratory, ECG and accelerometry signals permitted to robustly analyze the effects of baclofen on these vital functions
- Baclofen (15 mg/kg, *p.o.*) exerted the expected depressant effects on respiration (lower respiratory rate/higher inspiratory time) and on the level of activity. Baclofen effects generally resumed by 3.5 to 6 hours postdose
- To our knowledge, this study revealed a novel finding: **the sustained and reproducible baclofen-induced increase in heart rate in freely-moving, conscious rats.**
- The tachycardic effects of baclofen occurred while the activity level was very low. This finding supports:
  - An intrinsic pharmacological effect of baclofen on cardiac function
  - The interest of assessing the animal's activity when testing new compounds

5 CONCLUSION

This study demonstrates the feasibility of non-invasive and longitudinal assessment of vital physiological functions using the DECRO telemetry jacketed solution in socially-housed, freely-moving rats, in both safety pharmacology and toxicology experimental conditions.

3 RESULTS / KEY OUTCOMES

HEALTH STATUS AND WELL-BEING 👍

1st dose | 2nd dose | 3rd dose

Mean weight ± standard deviation (n=8)
Mean weight ± standard deviation (Crl:WI(Han) Growth chart)

Pretest | Week 1 | Week 2 | Week 3 | Week 4
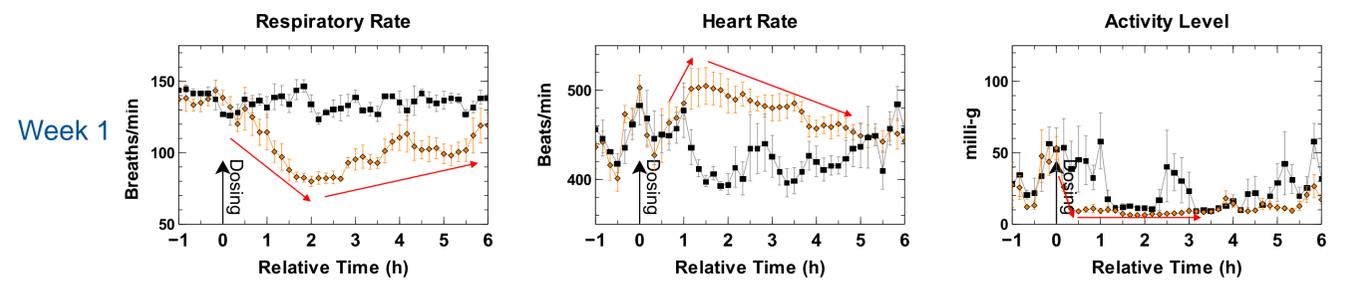
JACKET TOLERABILITY 👍

- No general and local clinical signs with repeated/intermittent jacket wearing
- Normal rat growth with repeated/intermittent jacket wearing and baclofen administration
- Expression of normal behavioral repertoire and social interactions

DATA ACQUISITION AND QUALITY 👍

- Social housing did not preclude to record a high load of good to excellent quality signal (> 95%)
- Signal filtering was done mostly based on exclusion of non-physiological values
- Markers for respiratory/ECG cycle identification were properly placed with the automated algorithm

ECG

Respiration

Predose

2 h post-Baclofen
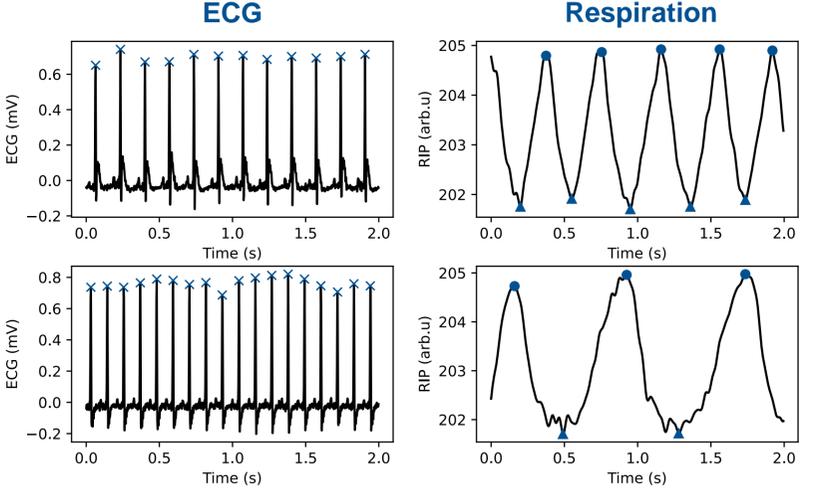
EFFECTS OF BACLOFEN EVALUATED WITH DECRO JACKET 👍

Respiratory Rate | **Heart Rate** | **Activity Level**

Week 1

	Heart Rate	Respiratory Rate	Inspiratory Time	Expiratory Time	Tidal Volume	Minute Volume	Activity Level	Statistical Significance
Wk 1: acute assessment ("ICH S7A") / Week 1	↗↗	↘↘	↘↘	↗	↔↔	↘	↘↘	1/1.5h to 4.5/6h
Wks 2 and 4: longitudinal assessment ("ICH M3(R2)") / Week 2	↗	↘	↘	↔↔	↗	↔↔	↘	1/2h to 3.5/6h
Week 4	↗	↘	↘	↔↔	↔↔	↔↔	↔↔	1h to 6h