Effects of Brexanolone on Resting-state and Transcranial Magnetic Stimulation Evoked Electroencephalography

A randomized, double-blind, double-dummy, 4-period crossover, placebo and active comparator-controlled study

Catherine M.K.E. de Cuba[2,3], Luke S. Watson[1], Naser Hakimi[2,3], Annika A. de Goede[2], Gabriel E. Jacobs[2,4], Aaron Koralek[1], Anne C. Smith[1], Jason Johannesen[1]*, Kemi Bankole[1], Jeff Wald[1], Patricio O'Donnell[1]*, Derek L. Buhl[1]*†, Jules A.A.C. Heuberger[2]†.

1. Sage Therapeutics, Inc., Cambridge, MA, USA , 2. Centre for Human Drug Research (CHDR), Leiden, Netherlands, 3. Leiden University Medical Centre, Leiden, The Netherlands, 4. Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands

* the author was an employee of Sage at the time the research was completed, † equal contribution

Introduction

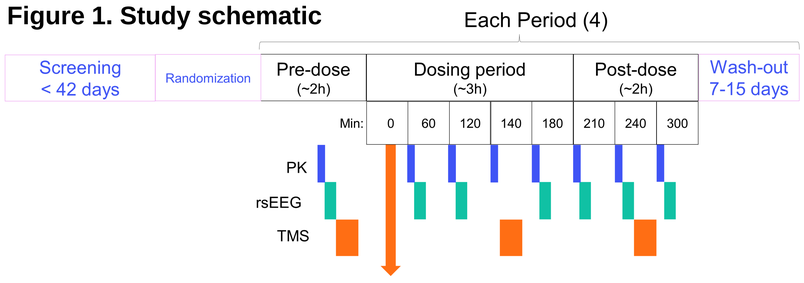
- Brexanolone (BRX), also known as SAGE-547, is a neuroactive steroid chemically identical to endogenously occurring allopregnanolone
- Neuroactive steroids have been proposed to have a novel mechanism of action (MoA) relative to other γ-aminobutyric acid chloride-gated channel receptors ($GABA_AR$) modulators, such as lorazepam
- Lorazepam is a benzodiazepine with a high affinity to all $GABA_A$Rs and acts as a positive allosteric modulator (PAM) of synaptic $GABA_A$Rs
- BRX acts as a PAM of both synaptic and extra-synaptic $GABA_A$Rs, thereby presumably enhancing phasic and tonic inhibition in the central nervous system (CNS)

We hypothesized that transcranial magnetic stimulation-evoked EEG (TMS-EEG) and resting state encephalography (rs-EEG) could:

1) Highlight differences in MoA of BRX compared to lorazepam
2) Determine a concentration-effect relationship for inducing neurocircuitry modulation by BRX

Methods

Figure 1. Study schematic



Administration of single dose:
- BRX 30 mcg/kg/h administered over 3 hours i.v. + PLC p.o.
- BRX 90 mcg/kg/h administered over 3 hours i.v. + PLC p.o.
- PLC administered over 3-hours i.v. + LOR 2 mg p.o.

BRX = brexanolone; i.v. = intravenous infusion; LOR = lorazepam; PK = pharmacokinetic assessment; PLC = placebo; p.o. = by mouth; rsEEG = resting state electroencephalogram; TMS = transcranial magnetic stimulation; y.o. = years old

TMS-EEG analysis

- Pre-dose and minute 140 and 240 post-dose
- Single and paired pulse stimulation of the dominant abductor digiti minimi motor hotspot per current guidelines[2], with paired pulses at 2, 15 and 100ms interstimulus interval (ISI)
- Analyzed in common average montage with baseline correction and a nonparametric cluster-based permutation analysis to compare the TMS-evoked potentials (TEP) between treatments
- Reported as grand averages (mean ± SEM) over all significant electrodes on the left side, and as amplitude difference in topographical distribution at the time of the cluster on the right side. The green bar represents the time window of significant differences, the thick grey bar the time window of the entire cluster (including non-significant parts), the white cross the stimulation site, and the black dots the electrode positions with the significant electrodes as red stars

Rs-EEG analysis

- Pre-dose and minute 60, 120, 180, 210, 240, 300 post-dose
- 5 minutes per eyes state per IPEG guidelines[1], spectral power was calculated per frequency band
- Mixed model for repeated measures analysis (MMRM)
- Reported in line plots of log-transformed change from baseline (μV^2) +/- standard error (SE) from the least-square means (LSM) comparisons.

References

1. Jobert, M. et al. Guidelines for the recording and evaluation of pharmaco-eeg data in man: The international pharmaco-EEG society (IPEG): The IPEG pharmaco-EEG guideline committee. Neuropsychobiology vol. 66 Preprint at https://doi.org/10.1159/000343478 (2012).
2. Rossi, S. et al. Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines. Clinical Neurophysiology vol. 132 Preprint at https://doi.org/10.1016/j.clinph.2020.10.003 (2021).

- Funding: This study was funded by Sage Therapeutics
- Acknowledgements: We thank the participants for helping us reimagine brain health. We thank the clinical trial investigators and their staff. This study was sponsored by Sage Therapeutics, Inc.
- Disclosures: Luke Watson, Aaron Koralek, Anne Smith, Jason Johannesen, Kemi Bankole and Jeff Wald are employees of Sage Therapeutics, Inc., and may own stock. Patricio O'Donnell and Derek Buhl are former employees of Sage Therapeutics, Inc., and may own stock and/or stock options in the company.

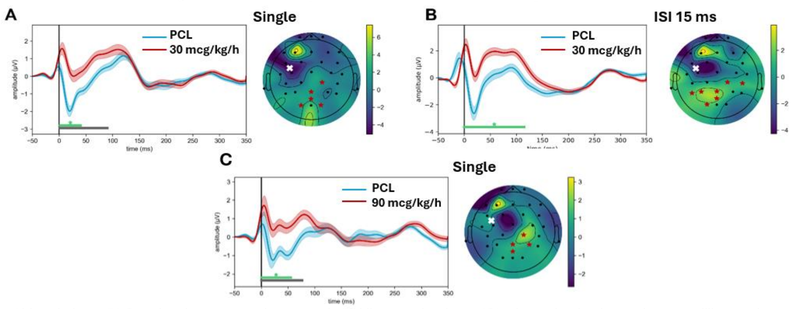
American College of Neuropsychopharmacology, Arizona, Monday 9th of December 2024: Contact: kdcuba@chdr.nl

Results

TMS-EEG

- Modulation of specific TEP components and topographical location of clusters differentiate between BRX and lorazepam's effects

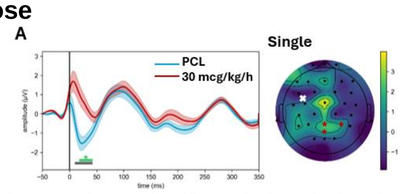
Figure 2. BRX 30mcg/kg/h (A+B) and BRX 90mcg/kg/h (C) modulate early TEP components 2,5 hours post-dose



Abbreviations: PLC = placebo; mcg = microgram; kg = kilogram; h = hour; ISI = interstimulus interval; ms = milliseconds

- Both BRX 30mcg/kg/h (2A+2B) and BRX 90mcg/kg/h (2C) significantly increased early TEP responses over the first 100ms at the contralateral centroparietal region for single and paired pulse (ISI 15 ms) relative to placebo, including the N45 and P60 components

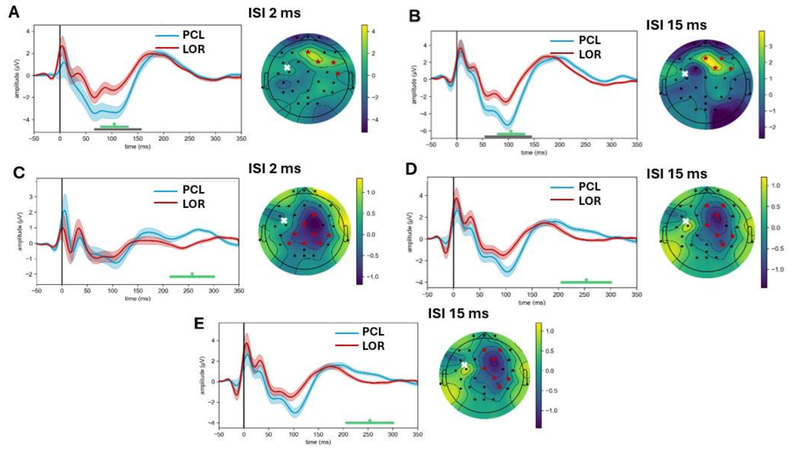
Figure 3. BRX 30mcg/kg/h (A) modulates early TEP component 4 hours post-dose



Abbreviations: PLC = placebo; mcg = microgram; kg = kilogram; h = hour; ISI = interstimulus interval; ms = milliseconds

- BRX 30mcg/kg/h (3A) significantly increased the early P30 TEP component at the contralateral centroparietal region for single pulse, relative to placebo

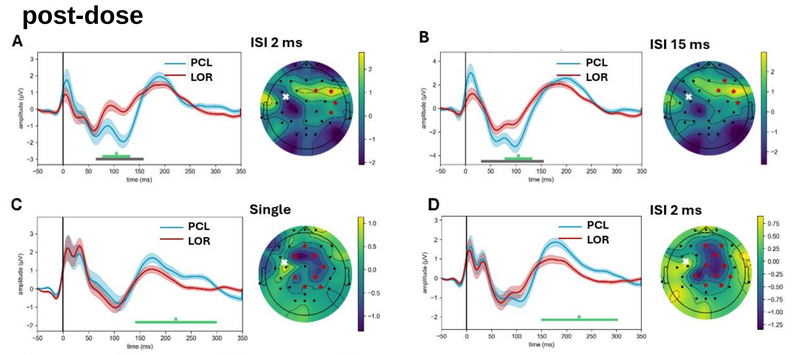
Figure 4. Lorazepam modulates late TEP components 2,5 hours post-dose



Abbreviations: PLC = placebo; LOR = lorazepam; ISI = interstimulus interval; ms = milliseconds

- Lorazepam reduced the late N100 TEP component in the contralateral frontocentral region for paired pulse ISI 2 (4A) & 15 ms (4B) and late TEP response between 200-300 msec including the P180 TEP component in the contralateral centroparietal region for paired pulse at ISI 2 (4C) and 15 ms (4D+4E), relative to placebo

Figure 5. Lorazepam modulates late TEP components 4 hours post-dose



Abbreviations: PLC = placebo; LOR = lorazepam; ISI = interstimulus interval; ms = milliseconds

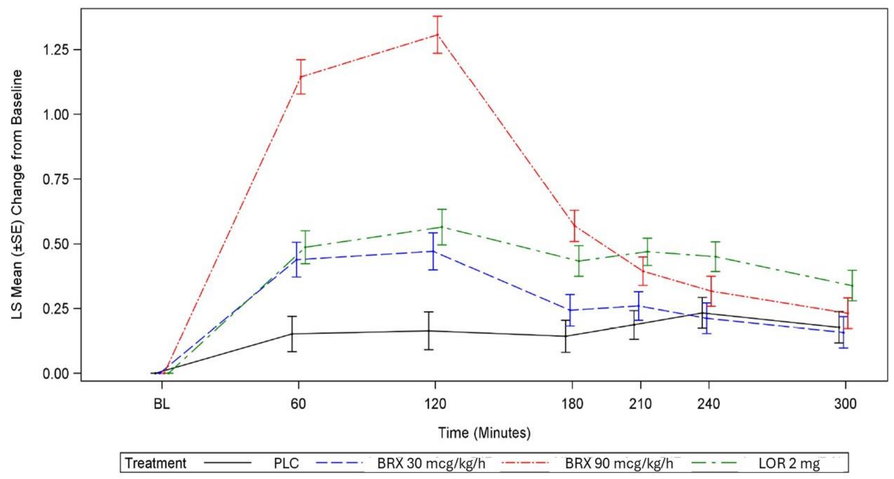
- Lorazepam reduced the late N100 TEP component in the contralateral frontocentral region for paired pulse ISI 2 (5A) & 15 ms (5B) and late TEP response between 150-300 msec including the P180 TEP component in the contralateral centroparietal region for single (5C) and paired pulse at ISI 2 ms (5D), relative to placebo

Results

rs-EEG

- We only reported statistically significant effects that are consistently present with regards to frequency, location, timepoint and eye state because numerous statistically significant effects were observed
- Alpha-, delta-, and gamma-power also demonstrated unique modulation by BRX relative to both placebo and lorazepam
- Safety, PK and TMS-EMG data are presented on a separated poster by Watson et al.

Figure 6. rs-EEG beta-power is a strong biomarker for BRX modulation, demonstrating dose-dependent effects

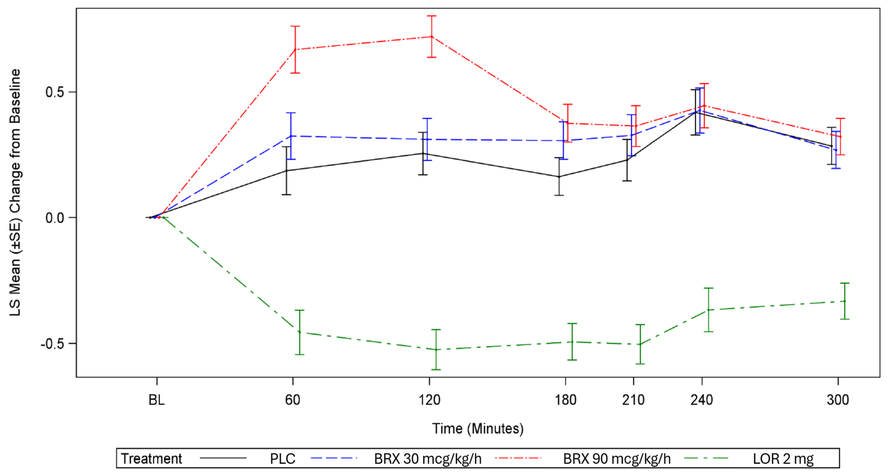


P-values are derived from least-square means comparisons between conditions using a MMRM analysis.

Abbreviations: LS = least squares; SE = standard error; PLC= placebo, BRX=brexanolone, LOR=lorazepam.

- Beta-power at the Fz-Cz electrodes with eyes closed (μV^2) was significantly increased in both BRX 30 mcg/kg/h (p=0.0108) and BRX 90 mcg/kg/h (p<0.0001) relative to placebo
- Beta-power at the Fz-Cz electrodes with eyes closed (μV^2) was significantly increased in lorazepam p<0.0001 relative to placebo

Figure 7. rs-EEG theta-power differentiates between BRX and lorazepam



P-values are derived from least-square means comparisons between conditions using a MMRM analysis.

Abbreviations: LS = least squares; SE = standard error; PLC= placebo, BRX=brexanolone, LOR=lorazepam.

- Theta-power at the Fz-Cz electrodes with eyes closed (μV^2) was significantly increased in BRX 30mcg/kg/h (p<0.0001) and BRX 90mcg/kg/h (p<0.0001) relative to lorazepam
- Theta-power at the Fz-Cz electrodes with eyes closed (μV^2) was significantly decreased in lorazepam (p<0.0001) relative to placebo

Conclusions

- We demonstrated that BRX has a distinct pharmacodynamic TMS-EEG and rs-EEG profile compared to lorazepam in healthy male volunteers, and together with the TMS-EMG findings presented by Watson et al., this supports differential putative MoAs for the GABAergic neuroactive steroid BRX compared to the non-selective $GABA_A$ benzodiazepines
- We demonstrated a concentration-effect relationship for inducing neurocircuitry modulation by BRX
- Together, these findings illustrate the potential value of TMS-EMG-EEG and rs-EEG as pharmacodynamic biomarkers in early CNS drug development with novel GABAergic modulators