

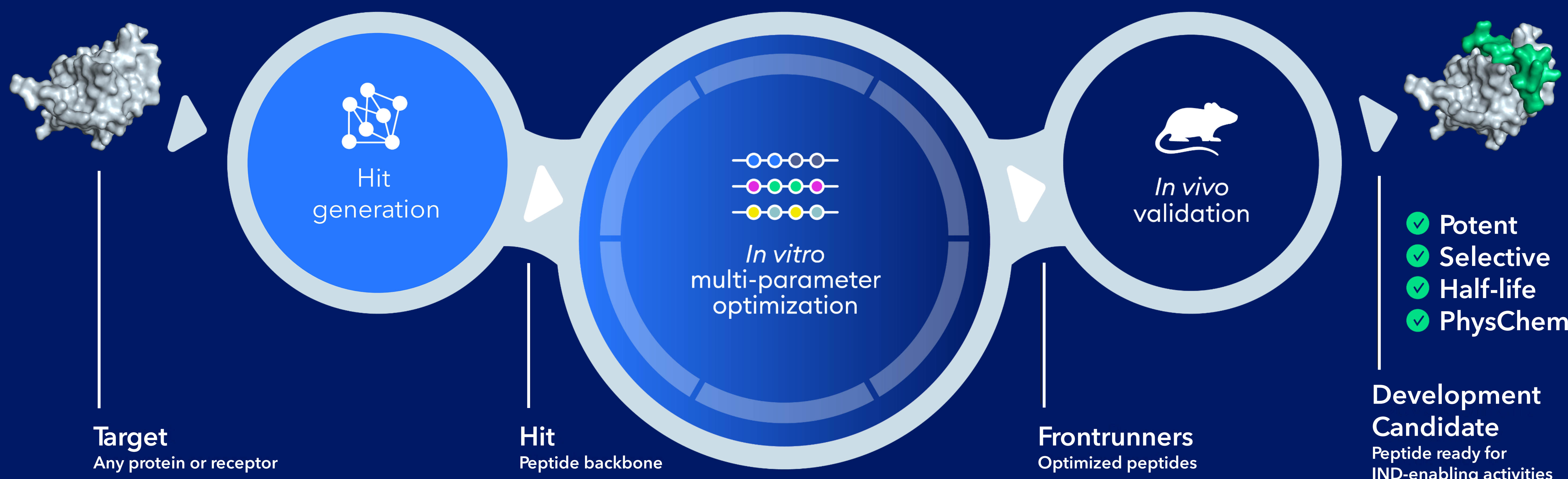
GUBox, a dual Ox1R/Ox2R peptide agonist, promotes wakefulness and reduces cataplexy in orexin/ataxin3 mice

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1 Accelerated peptide screening and drug development with streaMLine

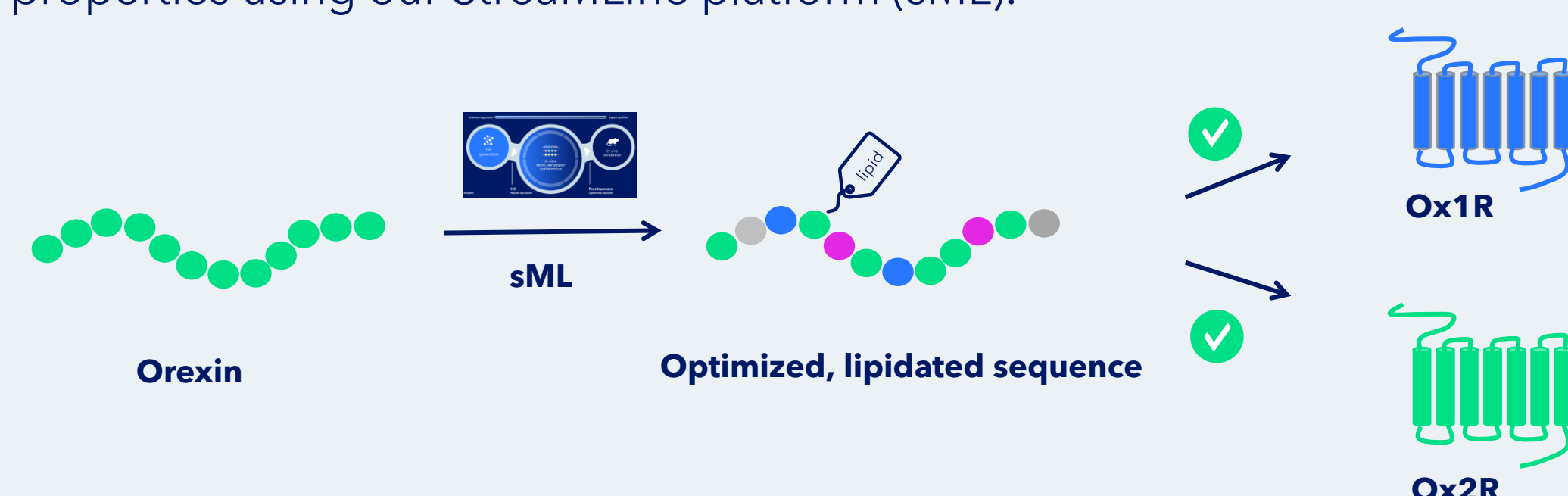
AI driven/supported Expert qualified



2 GUBox: Orexin-derived dual Ox1R/Ox2R peptide agonist to treat Narcolepsy Type 1

Aim

- + Utilize orexin analogues to activate central orexin signaling and compensate for the loss of endogenous orexin function in Narcolepsy Type 1 (NT1).
- + How? Engineering highly potent dual orexin receptor (OxR) 1 and OxR2 agonists from orexin backbone with optimized pharmacokinetic (PK) and physiochemical properties using our StreaMLine platform (sML).



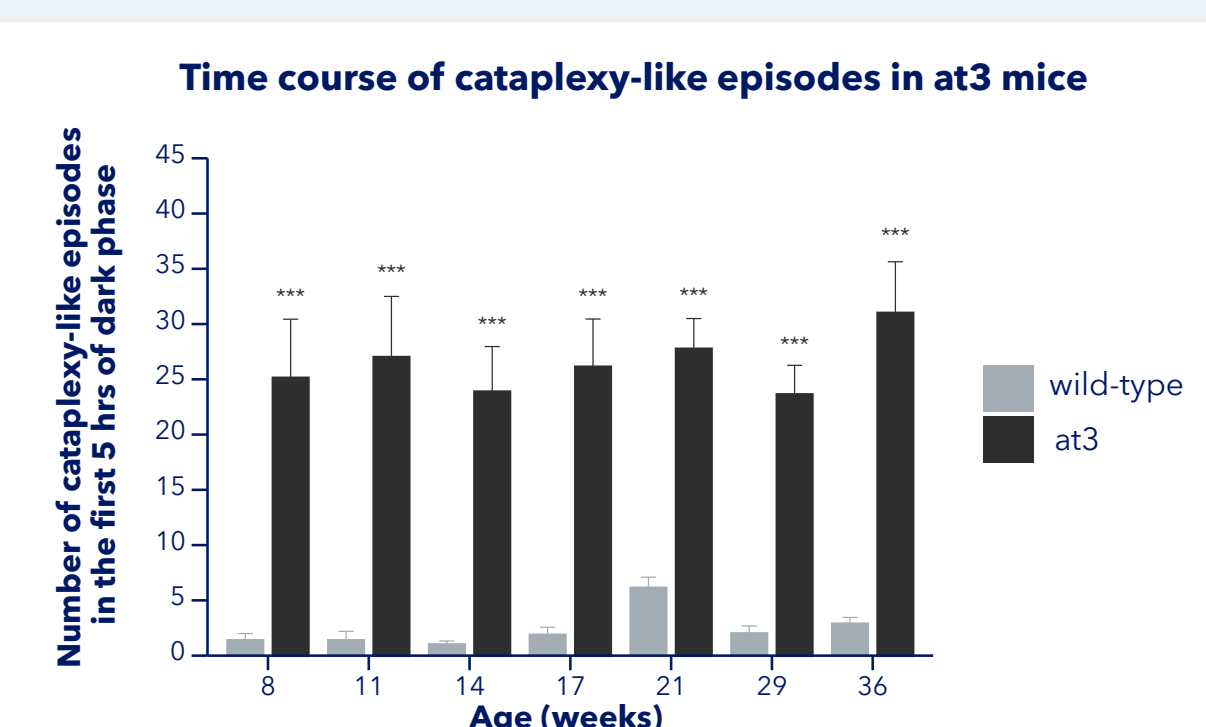
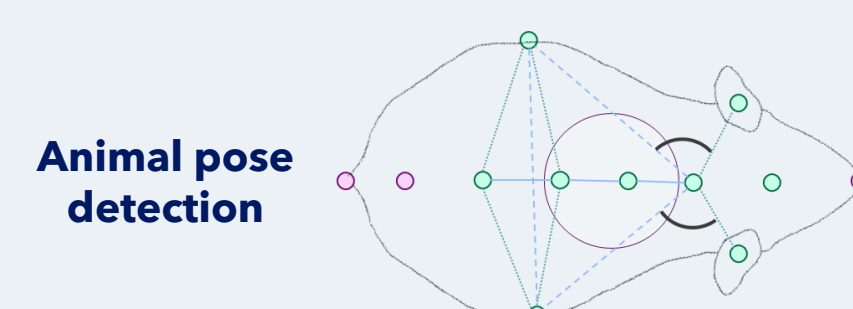
3 In vivo validation using PURPOSE: AI-based behavioral monitoring platform

Orexin/ataxin3 (at3) mouse model

- + Orexin/Ataxin3 (at3) mouse model display progressive loss of orexin neurons leading to altered sleep-wake patterns and cataplexy-like episodes.

PURPOSE platform

- + 24hrs recording of individual at3 mice.
- + ML algorithm distinguishes cataplexy from sleep and intermediate activity by classifying active/inactive periods.
- + Unbiased sleep-wake quantification reveals a clear narcolepsy-cataplexy phenotype, characterized by severe inactivity (data not shown) and the presence of cataplexy-like episodes during the dark (active) phase across different ages in at3 mice.



Robust quantification of cataplexy in at3 mice

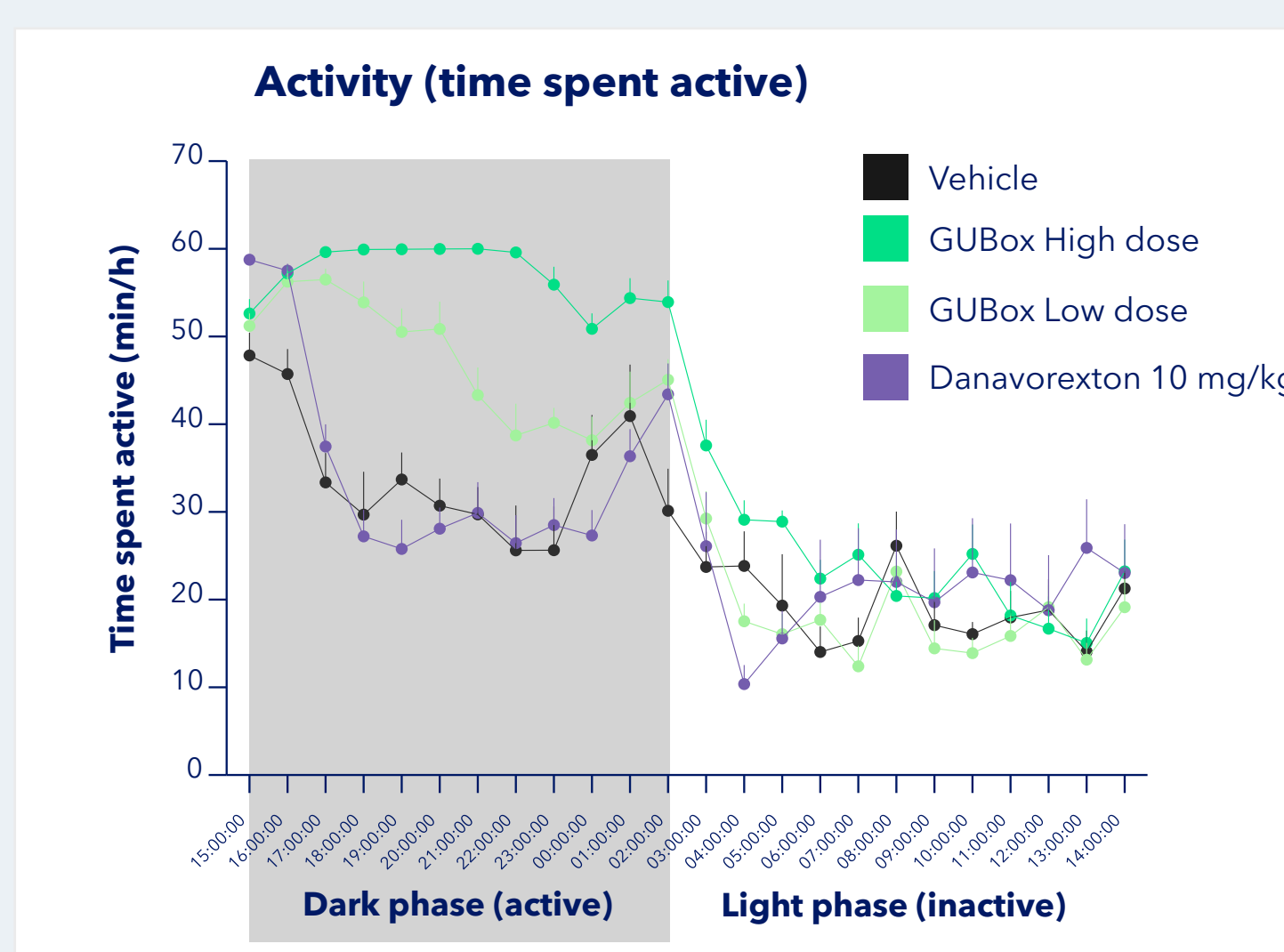
4 Wake-promoting and anti-cataplexy effects of GUBox

Methods

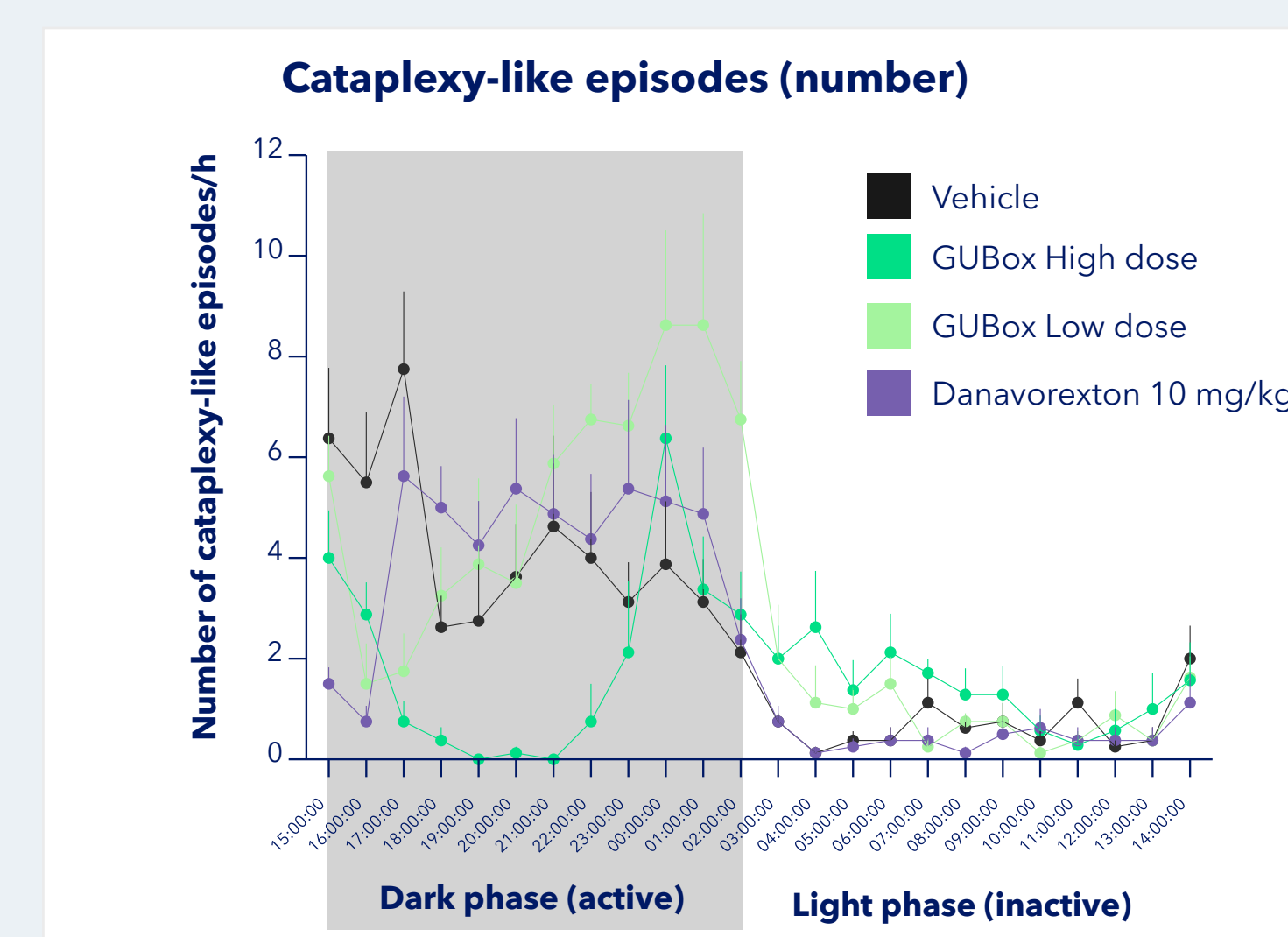
Chow-fed male at3 mice (~25 weeks of age, n=8/group) received a subcutaneous (SC) dose of GUBox, danavorexton (TAK-925, small molecule Ox2R-selective agonist), or vehicle. Automated 24 hrs real-time recording and analysis of activity/wakefulness and cataplexy-like episodes was performed using PURPOSE (starting at 15.00). Parallel plasma exposure analysis was performed in wild-type littermate controls.

Results

GUBox dose-dependently increased wakefulness time and decreased the number and duration of cataplexy-like episodes in narcoleptic mice. GUBox demonstrated prolonged benefits on both wakefulness time and cataplexy (up to 12h post-dosing) compared to danavorexton (up to 3h post-dosing). The differential efficacy profiles were supported by extended systemic exposure of GUBox compared to danavorexton (data not shown).



GUBox and danavorexton both enhance wakefulness, with GUBox demonstrating a markedly extended duration of action compared to danavorexton



GUBox decreased cataplexy-like episodes longer than danavorexton, demonstrating a more sustained effect

5 Conclusion

GUBox is a highly potent dual OxR1/OxR2 peptide agonist developed via Gubra's sML platform. We report superior wake-promoting and anti-cataplexy effects of GUBox, as compared to danavorexton, in narcoleptic mice. Collectively, our findings support the therapeutic potential of GUBox for the treatment of NT1.

GUBox:

- + Highly potent dual OxR1/OxR2 peptide agonist
- + Excellent physical and chemical stability
- + PK supports once-daily SC dosing in humans
- + Improves narcolepsy-like behavioural phenotypes in at3 mice



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