

**Title:** Use of Rpad, an open-source, interactive, web-based analysis program, for visualization during model-based drug development of adiplon, a GABA<sub>A</sub> receptor partial agonist under investigation for the treatment of insomnia.

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**Objectives:** To implement an open-source (GNU GPL) software tool as a means of providing interactive visualization of adiplon (formerly NG2-73) modeling and simulation results.

**Methods:** A series of exposure-response models had been developed to describe the onset, duration, and residual (next day) effects of adiplon, a GABA<sub>A</sub> receptor partial agonist currently under investigation for the treatment of insomnia. Maximizing sleep onset and duration (maintenance) while minimizing next day residual effect required consideration of potential trade-offs between total dose, oral absorption rate and systemic elimination rate, where the first two of these variables can be optimized through dosage and formulation adjustments. Formulation variables included the potential for a combination of immediate- (IR) and controlled-release (CR) rates. Predicted concentration-time profiles from ranges of IR and CR doses were used within the exposure-response models to predict optimal targets for the onset, duration and residual effects. To assist in communication and interpretation of these results, an interactive visualization tool was developed using the open-source (GNU GPL) software tool Rpad (<http://www.rpad.org/Rpad>). Rpad, available as a library package for R (R Development Core Team; [www.r-project.org](http://www.r-project.org)), exposes the computational facilities of the R language in dynamic web pages using a dialect of javascript. [1]. Output may be customized to include text and graphics layouts to meet user specifications and needs.

**Results:** The modeling predicted that an existing CR formulation, with an additional IR dose, would be expected to provide for improved sleep onset and maintenance without a residual effect relative to placebo. Exposure-response models for adiplon, originally developed in NONMEM (Icon Development Solutions, Ellicott City, Maryland, USA), were regenerated within R and included components to allow for stochastic simulations (e.g., parameter uncertainty, interindividual variability) based on pseudo-random sampling from a multivariate-normal variance-covariance matrix. The Rpad visualizer was developed with interactive choices of total dose and relative fraction of IR and MR doses. These same choices were provided for a reference or comparator formulation. Output generated by the visualizer included graphical representations of the predicted concentration-time profiles and efficacy measures: latency to persistent sleep (LPS, sleep onset), wake time by hour (WTBH, sleep maintenance) and digit symbol substitution test (DSST, residual effect), as well as textual summaries of the simulation results. This tool allowed the development team and management to explore the expected impact of variations to the proposed doses and formulations, enabling selection of doses for phase 3 development.

**Conclusions:** An implementation of Rpad, an open-source (GNU GPL) software tool, provided interactive visualization of adiplon modeling and simulation results. The tool facilitated discussions and decision making and exemplified the concept of model-based drug development described in the FDA's 'Critical Path' initiative [2]. Overall, the relative ease of development, and flexibility for displaying results, make the freely available Rpad a suitable platform for visualization and communication of modeling and simulation results.

#### References:

[1] Short T.A. Rpad: open source in action. Power Engineering Society General Meeting, 2006. 2006. ISBN: 1-4244-0493-2

[2] US Department of Health and Human Services, Food and Drug Administration. Innovation or stagnation? Challenge and opportunity on the critical path to new medical products, <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>.