Use of Rpad, an Open-Source, Interactive, Web-Based Analysis Program, for Visualization During Model-Based Drug Development of Adipiplon, a $GABA_A$ Receptor Partial Agonist Under Investigation for the Treatment of Insomnia

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BACKGROUND

Currently available benzodiazepine and some non-benzodiazepine hypnotics indicated for the treatment of insomnia are full agonists, acting at some or all of the gamma-amino-butyric acid subtype A ($GABA_A$) receptors. Most bind with limited selectivity at recombinant receptors containing $\alpha1$, $\alpha2$, $\alpha3$, or $\alpha5$ receptor subtypes. While the efficacy of these medications has been well documented, safety concerns related to impairments in memory or psychomotor impairment persist.

Adipiplon is a $GABA_A$ receptor partial agonist with preference for $GABA_A$ receptors containing the $\alpha3$ subunit. Clinical studies confirm that this compound has sedative hypnotic effects. Unlike some other compounds where dose is limited by next day effects, as a partial agonist it may be possible to administer higher doses of this compound, achieving optimal efficacy, without the unwanted next day effects.

An ideal therapeutic for insomnia would be effective for both sleep onset and sleep maintenance, while avoiding next day residual cognitive effects and other adverse events. To achieve this therapeutic profile, drug exposure (plasma concentration) needs to 1) attain sufficient levels promptly after administration, 2) maintain sufficient levels throughout the night to maintain sleep, and 3) avoid excess exposures that may result in undesired next day effects. It is therefore important to robustly and quantitatively define 'sufficient' for each of these criteria, so consequently exposure-response (ER) relationships are being used for the adipiplon development program. The intent is to quantify a target PK profile through ER modeling to optimize the sleep cycle. This information, together with the dose-response data, will be used for informed Phase 3 dose(s) and formulation(s) selection.

To assist in communication and interpretation of the modeling 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) [1], exposes the computational facilities of the R language in dynamic web pages using a dialect of javascript [2]. Output may be customized to include text and graphics layouts to meet user specifications and needs.

METHODS

Clinical Data

Exposure-response models were developed from polysomnography (PSG) and PK data from two adipiplon dose-ranging, Phase 2b clinical trials in patients with chronic insomnia. Multiple formulations were studied in each trial to determine the best profile for rapidity of sleep onset and maintenance of sleep through the night without residual sedation the next day.

Actual results of these studies have been blinded, with the focus instead on the development and utility of the Rpad visualization tool.

Study 1 (Used for Model Development)

- randomized, double-blind, placebo-controlled, cross-over study
- determine safety and efficacy of eight different dose and formulation profiles of adipiplon compared to placebo
- 36 patients with chronic insomnia
- five treatment periods
- total doses ranged from 3 to 12 mg
- primary endpoint = wake after sleep onset (WASO)
- additional endpoints included:
  - sleep onset, as measured by latency to persistent sleep (LPS)
  - additional measures of sleep maintenance included wake time by hour (WTBH)
  - digit symbol substitution test (DSST), as measure of next day residual effect
- three nights of each treatment period in sleep lab
  - first two nights employed PSG, averaged for each assessment = objective measure of sleep parameters
  - PK testing on third night

STUDY 2 (Used for Model Qualification)

- randomized, double-blind, placebo-controlled, parallel group study
- determine safety and efficacy of five different dose and formulation profiles of adipiplon compared to placebo.
- total doses ranged from 3 to 7 mg
- primary endpoint = LPS on the first two nights of treatment
- additional endpoints included:
  - WTBH as measure of sleep maintenance
  - DSST as measure of next day residual effect
- 258 patients with chronic insomnia (~ 1/3 included in additional night for PK testing)
- study drug or placebo for approximately 14 days
- each PSG assessment = average of two nights of sleep lab

Exposure-Response Models

- separate models for LPS, WTBH and DSST
  - LPS: time required to fall asleep (onset)
  - WTBH: minutes [0-60] / hour [1-8] that patient is awake (maintenance)
  - DSST: measure of cognitive effect the next morning (residual)
- interindividual (iiv) and residual variances, as appropriate:
  - i^{th} subject
  - j^{th} observation time
  - k^{th} occasion (study visit).
- maximum likelihood estimation (NONMEM® VI, ICON Development Solutions, Ellicott City, MD)
- models / parameter estimates reproduced in R for simulations
  - variables: dose and IR fraction
  - performed to find optimal PK profile…
    - rapid onset (LPS) = increase early concentration
    - sleep maintenance (WTBH) = sufficient exposure through night
    - without residual effect (DSST) = minimize exposure next morning
- Rpad interface: visualization of these results

Model 1. Latency to Persistent Sleep (LPS) = Measure of Sleep Onset Time

$$f(t) = \frac{\ln 2 \cdot \gamma \cdot \left(\frac{t}{PRD}\right)^{\gamma}}{t} \cdot e^{-\ln 2\left(\frac{t}{PRD}\right)^{\gamma}}$$

f(t) = Weibull Probability Density
t = LPS event time; γ = shape parameter; PRD = median LPS, where:

$$PRD_{ik} = LPS_{placebo,i} \cdot \left(1 - \frac{E_{max} * Conc_{ik}}{EC_{50} + Conc_{ik}}\right)$$

Conc = adipiplon plasma concentration (ng/mL);
$LPS_{placebo}$ = median LPS following placebo treatment;
E_{max} = maximum effect on LPS (proportional);
EC_{50} = Conc required to produce 50% of Emax.

$$\text{LPS \% Reduction from Placebo}_{ik} = 100 * \frac{E_{max} * Conc_{ik}}{EC_{50} + Conc_{ik}}$$

Model 2. Wake Time by Hour (WTBH) = Measure of Sleep Maintenence

Observations (0-60 minutes / hour) were logit-transformed

$$WTBH_{pbo\cdot logit\cdot ijk} = Base - \frac{Epbo_i * kin_i * (e^{-kout_i * time_{ijk}} - e^{-kin_i * time_{ijk}})}{(kin_i - kout_i)}$$

$WTBH_{pbo\cdot logit\cdot ijk}$ = logit transformed WTBH following placebo treatment;
Base = log(59.875/60), patient assumed awake for 60 minutes prior to 'lights off';
Epbo = placebo effect;
kin = rate constant for decline in WTBH (falling asleep);
kout = rate constant for increase in WTBH (waking up).

Inclusion of drug effect:

$$WTBH_{logit\cdot ijk} = WTBH_{pbo\cdot logit\cdot ijk} - \frac{E_{max} * Conc_{ijk}}{EC_{50,ij} + Conc_{ijk}}$$

E_{max} = maximum drug effect;
Conc = adipiplon plasma concentration (ng/mL);
EC_{50} = Conc required to produce 50% of E_{max}.

Conversion back to observed scale:

$$WTBH_{ijk} = 60 * \left(\frac{WTBH_{logit,ijk}}{1 + WTBH_{logit,ijk}}\right)$$

Model 3. Digit Symbol Substitution Test (DSST) = Measure of Residual ('Next Day') Effect

$$DSST_{ik} = DSST_{0,i} \cdot (1 - SLP \cdot Conc_{ik})$$

DSST = number of correct answers;
$DSST_0$ = baseline value;
SLP = slope of the proportional effect [(ng/mL)$^{-1}$];
Conc = adipiplon plasma concentration (ng/mL).

R and Rpad

- R (www.R-project.org)
  - open source language and processing environment for statistical computing and graphics
  - similar to (and often compatible with) S language
  - over 600 add-on packages (www.cran.r-project.org), including Rpad
- Rpad (www.rpad.org/Rpad)
  - exposes computational facilities of R language
  - provides dynamic web pages using a dialect of javascript
  - output customizable to meet user specifications and needs
    - text / tables
    - graphics
    - combinations of each
  - web browser (e.g., Firefox, IE, Safari) serves as graphical user interface (GUI)
    - can be hosted on local machine, intranet or internet per user needs
    - our example runs on a local machine

Getting Started with Rpad

1. Start .Rpad File Using Javascript Dialect (Dojo, http://dojotoolkit.org/)

```
<!DOCTYPE html PUBLIC "-//W3C//DTD HTML 4.01 Transitional//EN">
<html>
<!-- by Tim Bergsma
(c) Copyright Metrum Institute 2007.
-->

<head>
<title>PK-PD viewer for adipiplon</title>
<meta http-equiv="Content-Type" content="text/html; charset=utf-8">
    <script type="text/javascript">
        rpadConfig = {
            rpadHideSource: "true"
        };
    </script>
    <script type="text/javascript" src="gui/dojo.js"></script>
    <script type="text/javascript" src="gui/Rpad.js"></script>
</head>
<body>
<h4>Dose and Formulation Visualizer</h4>
<form>
<span
contenteditable="false"><input type="button" onclick=
"javascript:rpad.calculatePage()" value="Plot"></span>
</form>
<pre dojoType="Rpad" rpadRun="init">
```

2. Available Choices for User Interactive Input Include:

- input box (HTMLinput())
- radio buttons (HTMLradio())
- check boxes (HTMLcheckbox())
- selection box (HTMLselect())

```
HTMLon()
cat("Total Dose: ")
HTMLselect("TestDose",
        c("a","b","c","d","e","f","g","h","i","j","k","l"),default="a")

cat("IR Fraction: ")
HTMLselect("IRFraction", as.character(seq(0,1,by=0.01)),default=0)

cat("Reference Total Dose: ")
HTMLselect("ReferenceDose",
        c("a","b","c","d","e","f","g","h","i","j","k","l"),default="a")

cat("Reference IR Fraction: ")
HTMLselect("RefIRFraction", as.character(seq(0,1,by=0.01)),default=1)
</pre>

<pre dojoType="Rpad" rpadRun="normal"
        rpadOutput="html">
```

a — We used Selection Boxes (HTMLselect()). Also note dummied doses (a, b, c…) IR fraction range: [0, 1]

b — Same choices repeated for "Reference."

c — An element with dojoType 'Rpad' contains inline R code. Allows user to include R code in .Rpad file

3. Model Calculations

- Within .Rpad file and/or source an existing R script
- Selections = Input Variables ("*TestDose*" and "*IRFraction*")

```
sigmoidEmax <- function(x,e0,emax,ex50,gamma){
            xg = x^gamma
            e0 + emax*xg/(ex50^gamma+xg)}

simMedianLPS <- function(conc,iiv=F) {
            theta = c(##,##,##,##)
            omega = ##
            if(iiv)
                        eta = rnorm(n,0,sqrt(omega))
            else
                        eta = 0
            base = theta[1]*exp(eta)
            emax = logit.inv(theta[2])
            base*(1-sigmoidEmax(conc,0,emax,theta[3],theta[4])) }

release <- expand.grid(dose=TestDose,IRFraction=IRFraction)
releaseSLPS <- simMedianLPS(release$conc,iiv=F)
```

a — Parameter estimates for fixed and random effects
Option to include interindividual variability (or could include code for parameter uncertainty)

b — "conc" from PK simulation (not shown) based on TestDose and IRFraction

4. Code for Table and Graphs

```
table2 <- table1[,c("LPSperc","WTBHperc","DSSTperc")]

HTMLon()
cat("Summary of Responses (% changes) Relative to Reference and Placebo")
HTMLoff()

HTMLon()
Html(cbind(attr(table2,"vname"), rownames(table2),
            as.matrix(format(as.data.frame(unclass(table2),
            row.names = 1:NROW(table2))))))
HTMLoff()

plt1 <- xyplot(conc~time, ylab="adipiplon conc", xlab="time after dose",
  data=conc,auto.key=T, groups=form, panel=panel.superpose,
  type="l", scales=list(y=list(…)) )

plt2 <- xyplot(delta~as.double(grps), groups=form, data=wake,type="b",
  ylab="Waketime by hour change from placebo (min)",
  xlab="Hour after 'lights out'", auto.key=T,
  scales=list(y=list(…)) )
```

a — Table 1 constructed separately (not shown) to contain % differences: Test vs. Reference and Test vs. Placebo. WTBHperc = sum of WTBH % for sleep maintenance hours of interest

b — Figures: Concentration-time and WTBH improvement vs. placebo for each hour

5. Visual Layout for Graphs

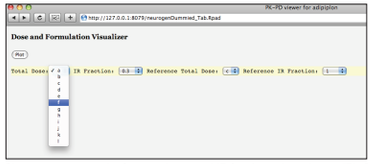
```
HTMLon()

newgraph(width=9,height=6)
print(plt1,split=c(1,1,3,2),more=TRUE)
print(plt2,split=c(2,1,3,2),more=FALSE)

showgraph()
HTMLoff()
```

Using Rpad from R

- install Rpad library from CRAN using Package Installer
- change to appropriate working directory: > setwd("~/project/Neurogen/visualizer")
- load Rpad library: >library(Rpad)
- launch: >Rpad()
- default browser window will open
- choose desired Rpad project = corresponds to .Rpad file name
- from selection boxes:
  - choose total dose and fraction of dose as IR for the test and the reference
- choose "Plot"

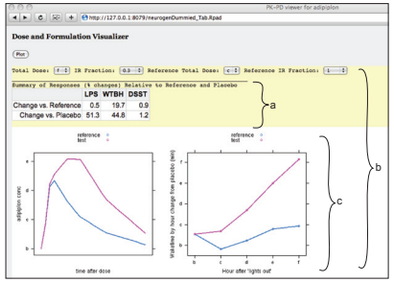
RESULTS

Figure 1. RPad Screen Capture



Choose your test and reference doses and IR fractions, then choose "Plot"

Figure 2. Table and Graphs: 'Instant' Comparisons



a — Table of % Differences: Test vs. Reference and Test vs. Placebo

b — Fully customizable… tables and figures can be suited to display any calculations or figures of interest. If you can make it in R, you can show it in Rpad!

c — Figures: Concentration-time (left) and WTBH improvement vs. placebo for each hour (right)

SUMMARY

- Modeling & simulation of adipiplon exposure-response relationships has enabled informed decisions regarding dose and formulation development
- Rpad, an open-source (GNU GPL) software tool, provided interactive visualization of adipiplon modeling and simulation results
- This Rpad implementation facilitated discussions and decision making and exemplified the concept of model-based drug development described in the FDA's 'Critical Path' initiative [3]
- 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

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