Model-based Analysis to Support Strategic Decision Making: A Case Study from the Development of a 5HT6 Antagonist for the Treatment of Alzheimer's Disease

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BACKGROUND

SAM-531 (PF-05212377) is a potent and selective 5-HT6 antagonist being developed for symptomatic therapy for mild-to-moderate Alzheimer's Disease patients. As part of a phase 2b study protocol (NCT00895895) for SAM-531, a 24 week interim analysis was conducted. Pre-specified interim analyses included a model-based dose-response analysis to support the futility assessment and (in the event of non-futility), dose selection.

Decision criteria for futility and dose selection were formulated in terms of the following endpoints: ADAS-cog, NPI, DAD, and discontinuation. **In this poster we focus exclusively on the ADAS-cog analysis.** The case for model-based analysis of the ADAS-cog endpoint is particularly compelling, since:

- The considerable variability associated with the endpoint entails substantial inferential uncertainty, even for relatively large trials, when analyzed in isolation.
- The public availability of multiple sources of ADAS-cog data presents an opportunity to improve estimation by leveraging historical information.

OBJECTIVE

The objectives of the model-based dose-response interim analysis were:

- To inform the selection of either one dose level or two dose levels for further study in Phase 3.
- To provide an assessment of the likelihood that target criteria for symptomatic monotherapy (including a 4 point difference from placebo for the ADAS-cog) are satisfied at the selected dose(s).
- To compare the longitudinal effect profile of SAM-531 to that of donepezil 10 mg QD.

METHODS

STUDY DESIGN

Study NCT0089589 is a 52-week, 2-period, multicenter, randomized, double-blind, donepezil referenced, placebo-controlled, efficacy and safety study of 3 dosage levels of SAM-531 in outpatients with mild-to-moderate Alzheimer Disease. Approximately 460 patients were randomly assigned to receive placebo, donepezil, or 1 of 3 dosage levels of SAM-531 (1.5, 3.0, or 5.0 mg/day) for 24 weeks (treatment period I). After 24 weeks of treatment, patients who received placebo in period I were assigned to receive SAM-531 5 mg/day for the remaining 28 weeks of the study (treatment period II).
The 24-week endpoint was pre-specified to be analyzed without waiting for the completion of the 52-week study as soon as 100% of the total number of patients had been randomly assigned and had reached the 24-week visit or discontinued early.

DATA

In addition to the primary (24 week) efficacy data set, data from a Phase 2a study (NCT00481520) were used in the analysis to support estimation of the dose-response. Additionally, an extensive supplementary data set was leveraged in the analysis in order to support the estimation of anciallary (non-drug-effect) parameters, including those parameters describing the placebo time-course and variance components. The supplementary data sources consisted of:

- The meta-data set assembled and analyzed by Ito et al.[1] These data consist of summary means by treatment arm for 52 clinical trials of acetylcholinesterase inhibitors in patients with mild to moderate Alzheimer's Disease, and represent approximately 19,972 patients.
- Individual patient longitudinal data from:
  - The Alzheimer's Disease cohort of the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI).
  - The CAMD database of patient-level data from placebo arms in randomized trials.
  - A phase 2, 12 week, randomized, double-blind, placebo-controlled, study evaluating the safety and efficacy of three fixed doses of oral CP-457,920 (30 mg QD, 60 mg BID and 120 mg BID) and donepezil. (This was used only as an additional source of patient-level placebo and donepezil data.)

METHODS

MODEL

For the analysis of the ADAS-cog endpoint, a previously developed longitudinal dose-response model was employed[2]. This model describes the progression of ADAS-cog scores in the mild-to-moderate Alzheimer's Disease population as parametric function of baseline MMSE, time since randomization, and dose-level for the randomized intervention. Key elements of the validation of this model have been presented previously (http://metrumrg.com/images/stories/publications/ascpt-ves.pdf).

$$\log\left[\frac{\theta_{ipk}}{1-\theta_{ipk}}\right] = \eta_{pk} + \alpha_{pk} t_{ipk} + g^{\mathrm{PBO}}(t_{ipk}) + g^{\mathrm{DRG}}(t_{ipk}, d_{pk}), \quad (1)$$

where

- The indices ipk refer to the the i^{th} assessment for patient p in study k.
- θ_{ipk} is the patient-level conditional expectation for the normalized ADAS-cog score (the original 0–70 scale is normalized to a 0–1 scale by dividing by seventy). The logit transformation is applied to the θ values in order to constrain the predictive distribution to the range 0–1 (or 0–70 after reverse normalization).
- η_{pk} is the baseline intercept (on the logit scale).
- α_{pk} is the rate of natural progression (on the logit scale).
- $g^{\mathrm{PBO}}(t_{ipk})$ is the incremental effect (above and beyond the natural state) of placebo at time t_{ipk} (on the logit scale).
- $g^{\mathrm{DRG}}(t_{ipk}, d_{pk})$ is the incremental effect (above and beyond the the natural state and the effect of placebo, on the logit scale) of drug at normalized dose d_{pk} (normalized doses are obtained by dividing nominal doses by drug-specific reference doses) at time t_{ipk}.

The η_{pk} and α_{pk} are modeled as random effects whose expected values vary linearly with baseline MMSE.

$$\eta_{pk} \sim \mathrm{N}\left(\mu_{\eta,k} + \lambda_\eta (BMMSE_{pk} - 21),\, \sigma^2_{\eta,k}\right) \quad (2)$$
$$\alpha_{pk} \sim \mathrm{N}\left(\mu_{\alpha,k} + \lambda_\alpha (BMMSE_{pk} - 21),\, \sigma^2_{\alpha,k}\right), \quad (3)$$

Additionally, study-level variation beyond that explained by covariates and inter-subject variation is accommodated by introducing study-level random effects:

$$\mu_{\eta,k} \sim \mathrm{N}\left(\nu_\eta,\, \psi^2_\eta\right) \quad (4)$$
$$\mu_{\alpha,k} \sim \mathrm{N}\left(\nu_\alpha,\, \psi^2_\alpha\right) \quad (5)$$

The basic model structure described above has already been shown to successfully characterize a wide range of historical data, including ADNI as well as placebo arms and acetylcholinesterase inhibitor arms in randomized interventional trials. However, the model term of primary interest for our present purposes is the $g^{\mathrm{DRG}}(t_{ip}, d_p)$ term for SAM-531, for which the Phase 2b interim data will be the first substantive source of information. We therefore proceed with the same parametric form as has been used for other symptomatic agents:

$$g^{\mathrm{DRG}}(t_{ipk}, d_p) = (d_{pk})^\gamma \frac{E_\Delta t_{ipk}}{ET_{50} + t_{ipk}}. \quad (6)$$

The dose term allows for concave or convex dose-response relationships as well as linear dose-response (if $\gamma = 1$), and the longitudinal term allows for a monotonic increase toward a horizontal asymptote E_Δ as time goes to infinity, consistent with typical assumptions for symptomatic agents.
The effect on the original scale at a given dose level d is then equal to the following difference in expected values:

$$f^{\mathrm{DRG,\ ADAS}}(24, d) = 70 \times \left(E[\mathrm{inv.logit}(\eta_{pk} + \alpha_{pk} \times 24 + g^{\mathrm{PBO}}(24) + g^{\mathrm{DRG}}(24, d))] - E[\mathrm{inv.logit}(\eta_{pk} + \alpha_{pk} \times 24 + g^{\mathrm{PBO}}(24))]\right), \quad (7)$$

where the inverse logit function, $\mathrm{inv.logit(x)} = 1/(1+\exp(-x))$ is applied in order to convert predicted values back to the original scale.

METHODS

COMPUTATION

A Bayesian implementation of the model was fitted via Markov Chain Monte Carlo (MCMC) simulation in the WinBUGS (version 1.4.3) software. Three independent MCMC chains of length 15,000 were simulated, resulting in 500 posterior samples each after burn-in (2,500) and thinning (1 per 25), combining to a total of 1,500 posterior samples for inference.

MODEL EVALUATION

Posterior predictive checks [3] were used to assess the agreement of observed trial statistics with trial statistics simulated from the model (see Figures 1 and 2).

MODEL SUMMARY AND INFERENCE

Drug effects were estimated via population simulation: for each treatment regimen, 10,000 patients were simulated from the fitted model (this was done separately for each posterior sample), and the mean of the simulated patients was taken as an approximation to the expected response.

DECISION CRITERIA FOR ADVANCEMENT

Pre-specified decision criteria required the following conditions to be met to support further development of the drug.

- P(drug effect > 0) $\geq$ 90%
- P(drug effect > 4) $\geq$ 25%

RESULTS

MODEL EVALUATION

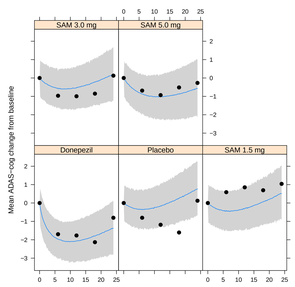

Figure 1: Posterior predictive check to ensure that observed data are consistent with data simulated from the model. Points represent observed data, blue lines represent model-based point estimates (posterior medians) of expected values, and shaded regions represent 90% posterior prediction intervals, incorporating parameter uncertainty.

Key observations based on posterior predictive checks (Figures 1 and 2) include:

- The model predicted placebo response was higher (worse) than the observed trend. Observed placebo means were nonetheless generally contained in the model 90% prediction intervals (with the exception of the mean for the 18 week visit).
- The observed trend for the donepezil arm was highly consistent with the model prediction.
- The longitudinal trends for the SAM-531 3.0 mg arm and the SAM-531 5.0 mg arm were consistent with model predictions. The trend in the 1.5 mg arm departed from the model prediction but was still contained in the model 90% prediction interval.
- The dose-response trend for SAM-531 at 24 weeks was consistent with the range of expectation reflected by the model 90% prediciton intervals.

RESULTS

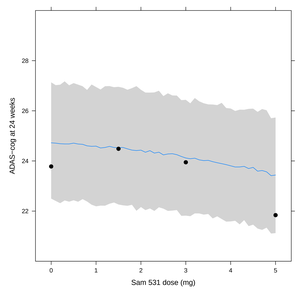

Figure 2: Posterior predictive check for shape of dose-response. Interpretation of points, lines and shading is as in Figure 1. The departure of the model based prediction (blue line) from the observed data reflects the use of the supplementary data in model fitting.

MODEL SUMMARY

- Based on the fitted model, the estimated treatment effect of SAM-531 is 1.26 points (placebo adjusted) at 24 weeks for the 5 mg dose group. The estimated probability of that this effect exceeds zero is 98%, however the probability that it exceeds 4 points was effectively 0% (the upper bound of the 90% confidence interval is approximately 2.3 points.)
- The model-based estimate of the effect of donepezil 10 mg at 24 weeks was 2.06 points (placebo adjusted).
- The onset of effect of donepezil 10 mg (characterised by the time to 50% of the full effect) was approximately 2 weeks and was faster than that for SAM-531 5.0 mg . A nearly maximal effect for donepezil was apparent after 4-5 weeks of treatment while the effect for 5.0 mg SAM-531 did not appear to be nearly maximal even after 24 weeks of treatment.

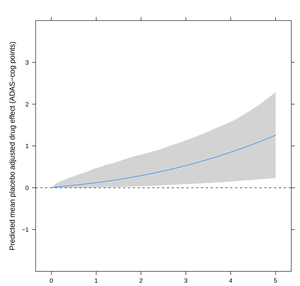

Figure 3: Estimated placebo-adjusted effect at week 24 with 90% credible interval, as a function of dose.

RESULTS

Treatment	Estimated Difference from Placebo			P(Effect > 0) (%)	P(Effect > 4) (%)
	Point Est.	5% Lower Bound	95% Upper Bound		
SAM-531 1.5mg	0.20	0.02	0.63	98	0
SAM-531 3.0mg	0.53	0.09	1.14	98	0
SAM-531 5.0mg	1.26	0.23	2.29	98	0
donep 10mg	2.06	1.79	2.35		

Table 1: Estimated placebo-adjusted effects, probability of a positive drug effect, and probability of effect exceeding a four point difference versus placebo.

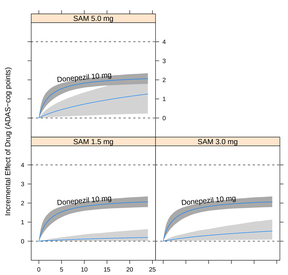

Figure 4: Estimated placebo-adjusted effect with 90% credible interval, as a function of time.

DISCUSSION

- Our model-based analysis of the donepezil and placebo arms indicates that observed trends for both arms were within the range of expectation for a study of this size. Therefore, notwithstanding the unusual trend for the placebo arm, the study should not be considered a "failed trial".
- Because the use of historical control data entails a predicted placebo response that is higher (worse) than observed, our analysis resulted in a more optimistic assessment of drug effects than would be expected from non-model-based analyses. Despite this optimistic perspective, the pre-specified advancement criteria for the compound were clearly not satisfied.
- The small effect size and slow onset of effect may be attributed to the low 5HT6 receptor occupancy (RO) which has been estimated from human PET data to be less than 30 percent after multiple 5 mg QD doses.

CONCLUSIONS

- The estimated magnitude of effect is not sufficient at any practical clinical dose to warrant further development of SAM-531 at this time.
- The moderate evidence of non-zero (positive) dose response may provide some additional rationale for 5HT6 as a target in Alzheimer's Disease.

When viewed as a case-study, the following conclusion is also warranted:

- Model-based analysis leveraging historical data may be used to put anomalous results in context, improve the precision of inferences, and increase confidence in decision making.

REFERENCES

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[2] Rogers, J., Polhamus, D., Gillespie, W., Ito, K. and Romero, K. Beta Regression Meta-Analysis Using a Combination of Patient-level and Summary-level Data, with Application to Alzheimer's Disease. *J Pharmacokinet Pharmacodyn (accepted in April)* (2012).

[3] Gelman, A., Carlin, J.B., Stern, H.S. and Rubin, D.B. *Bayesian data analysis* (Chapman & Hall/CRC, New York, 2004).