

A drug development tool for trial simulation in prodromal Alzheimer's patient using the Clinical Dementia Rating scale Sum Of Boxes score (CDR-SOB)



Sylvie Retout¹, Isabelle Delor², Ronald Gieschke¹, Philippe Jacqmin², Jean-Eric Charoin¹ for Alzheimer's Disease Neuroimaging Initiative.

(1) Pharma Research and Early Development, Clinical Pharmacology, F. Hoffmann-La Roche AG, Basel, Switzerland
(2) SGS-Exprimo, Mechelen, Belgium

Introduction

- Population Alzheimer's disease (AD) progression models have been developed using the Alzheimer's Disease Assessment Scale — cognitive subscale (ADAS-cog) scores to describe the dementia stage of the disease [1-2]. However, those models cannot be used in the context of drug development projects focusing on earlier stages of the disease such as with prodromal or mild cognitive impairment (MCI) patients, and for which endpoint is assessed by CDR-SOB scores.

Objectives

- To support the development of an AD progression model based on CDR-SOB scores and to demonstrate, by simulation, the usefulness of such a model for clinical trial optimisation.

Alzheimer's Disease Model

- An AD progression population model was developed [3] using the CDR-SOB scores from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [4]. The model assumes that patients shared the same disease trajectory (DT) but entered the study at different stages of the disease. The disease progression can then be described by a differential equation:
- $$\frac{\partial CDR(t)}{\partial t} = (RATE + CDR(t) \times ALP) \times \frac{T^{30}}{(DOT^{30} + T^{30})}$$
- When time equals the disease onset time (DOT), an increase in the CDR-SOB score is triggered, depending on a disease rate (RATE) continuously adjusted to the subjects' velocity by an additive term ($CDR(t) \times ALP$) (i.e. exponential term after integration). The model also integrates the influences of three covariates on the score time course: CDR-SOB at study entry and ADAS-COG score at study entry on DOT as well as MMSE (Mini Mental State Examination) on ALP.
 - Last the model enabled during the modeling step to identify two main disease trajectories especially in MCI subjects, with either fast or slow progressing subjects. A GAM analysis demonstrated that those subpopulations are best identified using three major covariates: CDR-SOB at study entry, Functional Assessment Questionnaire (FAQ) and estimated individual hippocampal volume atrophy of the patient (RHPNM)

For more details on AD model development, please refer to Poster I-04 by Delor I et al (PAGE 2013).

Clinical trial investigation

Criteria selection

- We first use the AD model to investigate the impact of different patients selection criteria on the placebo time course of AD. To do that we focus on MCI subpopulation and define 3 different selection criteria (SCRIT) as described in Table 1. Those criteria were selected in order to increase the chance to recruit fast progressing MCI patients.
- For each selection criteria, we simulate the median as well as the 80% prediction interval of the score time course for a 5 years period with evaluation every 6 months. Those simulations are performed via the implementation of the AD model in Simulo (a Java-R based software) and using one replicate of 5000 patients. The covariates are randomly bootstrapped with replacement from the ADNI database to keep the correlation.

Table 1. Description of the 3 different selection criteria

	SCRIT1	SCRIT2	SCRIT3
Selection criteria	MCI patients as defined by ADNI	MCI patients as defined by ADNI AND CDR-SOB at study entry ≥ 1.5	MCI patients as defined by ADNI AND CDR-SOB at study entry ≥ 1.5 AND Estimated hippocampal volume atrophy (RHPNM) < 0.9 AND FAQ at study entry ≥ 3
Percentage of MCI patients in the ADNI database	100%	60%	24%

Treatment effect implementation

- We then investigate the impact of different dose effects on the CDR-SOB time course. To do that, we consider two types of drug effect, either inhibiting all components (μ_1) or only the ALP term (μ_2) such as expressed in the equation below:

$$\frac{\partial CDR(t)}{\partial t} = (RATE + CDR(t) \times ALP \times (1 - \mu_2)) \times \frac{T^{30}}{(DOT^{30} + T^{30})} \times (1 - \mu_1)$$

- We focus on a whole inhibition of either 30% or 50% of the system by the drug ($\mu_1 = 0.3$) or ($\mu_1 = 0.5$) or on a partial inhibition with ($\mu_2 = 0.7$)

Power to detect a treatment effect

- Last we consider a clinical trial involving 240 patients divided into two groups, one receiving an active treatment (N=120) and one under placebo (N=120). For each case of selection criteria and each type of treatment effect implementation, we investigate the power to detect a at least 1.5 difference on the change from baseline scores between the two groups. This investigation is performed at different time points (1.5, 2, 2.5, 3, 3.5, 4 years) using a Wilcoxon test on each of the 1000 generated trial replicates.

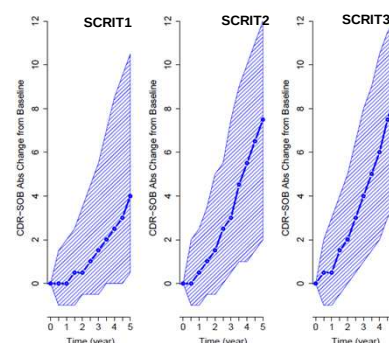
References

- [1] Ito, K. et al. *Alzheimers Dement.* (2010) 6: 39-53
[2] Samtani, M.N. et al. *J. Clin. Pharmacol.* (2012) 52: 629-644
[3] Delor, I. et al. *Abstr PAGE 22* (2013)
[4] http://www.loni.ucla.edu/fda_Aoqin.jsp?project=ADNI

Results

Criteria selection

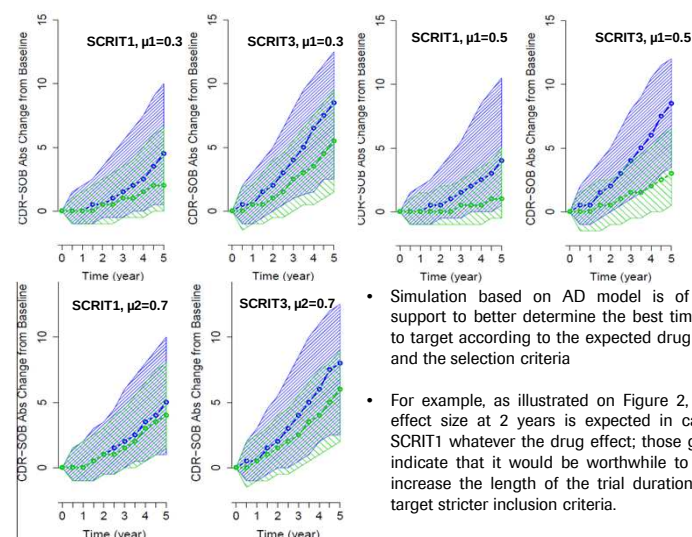
Figure 1. Median and 80% prediction interval of the CDR_SOB time course according to the criteria selection for patient recruitment



- Clear impact of the selection criteria on the time course of the CDR-SOB score
 - Faster progressing patient population with less variability selected as the constraints become stricter
- ⇒ Need to be balanced in practice with the higher screening number of patients to be performed to target a given number of patients in that specific population

Treatment effect implementation

Figure 2. Median and 80% prediction interval of the absolute change from baseline CDR_SOB time course according to the criteria selection and the treatment effect. Blue curves corresponds to a placebo group whereas green curves correspond to a treatment group.



- Simulation based on AD model is of great support to better determine the best timepoint to target according to the expected drug effect and the selection criteria
- For example, as illustrated on Figure 2, a low effect size at 2 years is expected in case of SCRIT1 whatever the drug effect; those graphs indicate that it would be worthwhile to either increase the length of the trial duration or to target stricter inclusion criteria.

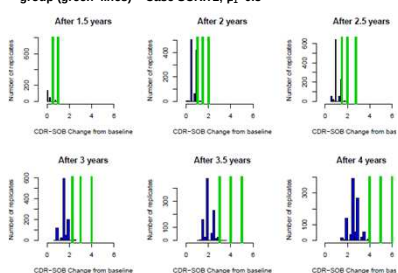
Power to detect a treatment effect

- The distributions of the 1000 estimated medians for SCRIT2 with $\mu_1=0.3$ are represented on Figure 3 per time points, with some strong overlay between placebo and treatment group up to 3.5 years. This correlates with the estimated powers close or lower than 50% during that period (Table 2).
- Strong impact of the selection criteria on power to detect a treatment effect with impressive increase between SCRIT1 and SCRIT3. But again, needs to be balanced with the difficulty to recruit such population.
- Balance between the number of subjects and trial length not shown but plays also a major role to achieve a given power.

Table 2. Power to detect a treatment effect according to selection criteria and treatment effect

	Timepoint (y)	SCRIT1	SCRIT2	SCRIT3
$\mu_1=0.3$	1.5	0	0	0.2
	2	0	0.2	4.2
	2.5	0.3	5.5	33.2
	3	3.7	25.1	71.5
	3.5	14	51.8	94
$\mu_1=0.5$	4	32.8	73.9	98.6
	1.5	0	0.3	9.4
	2	1.3	19.0	71.7
	2.5	18.8	70.7	98.5
	3	60.8	94.3	100
	3.5	88.6	99.3	100
	4	97.4	99.9	100

Figure 3. Histograms of the medians in the treatment group computed on the 1000 replicates per time points (blue). Overlay with 5th, 50th and 95th percentiles of the medians in the placebo group (green lines) – Case SCRIT2, $\mu_1=0.3$



Conclusion

- AD model allows a good understanding and quantification of the CDR-SOB time course taking into account the impact of inclusion criteria/disease severity on treatment effect and required trial length.
- Great support to clinical trial planification by determining how and when enough effect size should be achieved for differentiation.
- Can also support the estimation of the real drug effect by longitudinal analysis integrating the natural disease history once data collected at the end of the trial.