Longitudinal Analysis of the Individual Placebo Response from Double-blind Clinical Studies using the MATRICS Consensus Cognitive Battery (MCCB) in Cognitive Impairment Associated with Schizophrenia (CIAS)

Timothy Nicholas[1], Vicki Davis[2], Francois Gaudreault[1], Brendon Binneman[1] , Nicholas Demartinis[1] ,Jessica Y Mancuso[1] , Danny Chen[1], Alexandra Atkins[2], Ilise Lombardo[3], Richard Keefe[2,4]

1: Pfizer Inc. USA; 2: NeuroCog Trials Durham, NC USA; 3: Axovant Sciences Inc. New York, NY; 4:Duke University, Durham, NC.

Introduction

Background & Objectives

The MATRICS Consensus Cognitive Battery (MCCB) was developed to provide an assessment of cognitive impairment and measure change in clinical trials for Cognitive Impairment Associated with Schizophrenia (CIAS). While pivotal trials are expected to be 24 weeks in duration to characterize the benefit risk of an investigational product to treat (CIAS), earlier clinical studies such as proof of concept (POC) or dose-ranging trials may be of shorter duration. It is therefore important to understand the natural history progression and variability of the MCCB over relatively brief periods of time in order to more confidently design and power early-stage clinical trials. These data will assist in informing early development decision-making in drug development for CIAS. The objective of this analysis was to characterize the time course of the MCCB in placebo subjects with CIAS.

Methods

Data

The individual-level data in the placebo arm from 8 randomized, double-blind clinical studies were combined into a single dataset consisting of 514 subjects (n=1773 total observations). Sampling times on MCCB ranged from 4 to 24 weeks. Median age of the combined dataset was 45 years old and ranged from 18 to 65 years. Median baseline MCCB composite score was 27.0 units.

Model

A nonlinear mixed effects model for the time course of the MCCB composite T-score was constructed using R software (v3.1.1). The time to maximal placebo (PBO_{max}) effect was characterized by an exponential rate constant (Eq.1). An ET_{50} model structure (Eq.2) was also explored. The effects of baseline MCCB composite score, age and gender on PBO_{max} were assessed. In addition, the effect of having a screening MCCB assessment prior to baseline was explored as a binary covariate on the magnitude of placebo effect. Model fit and inclusion of covariates was determined using likelihood ratio tests and goodness of fit diagnostics. Inter-individual level random effects on PBO_{max} were nested within study level random effects. Random effects were modeled as additive given the nature of the scale.

Base model structures are shown in the following equations:

Eq.1 $$Observation = PBO_{max} * \left(1 - e^{-k*t}\right)$$

Eq.2 $$Observation = PBOmax * \left(\frac{t^{\gamma}}{ET50^{\gamma} + t^{\gamma}}\right)$$

Results

Table 1. Study Level Observations and Demographics

Study No.	Week	MCCB (mean)	MCCB (SD)	N Obs	N Screen	Age (mean)	Baseline (mean)	% Female
1	0	0.00	0.00	72	72	42.3	29.0	24%
1	6	1.74	4.47	65	65	42.2	28.5	23%
1	12	1.72	4.70	60	60	42.5	28.8	25%
2	0	0.00	0.00	50	50	42.9	29.4	18%
2	6	0.63	4.65	43	43	42.7	30.1	19%
2	12	0.88	5.46	41	41	43.3	29.9	20%
3	0	0.00	0.00	67	67	43.3	25.5	28%
3	6	0.83	4.80	59	59	43.1	25.2	29%
3	12	0.68	5.25	56	56	43.3	25.6	27%
4	0	0.00	0.00	136	136	41.4	26.6	43%
4	6	2.50	5.00	114	114	41.5	26.2	44%
4	12	2.44	5.13	110	110	41.7	26.0	42%
4	18	4.27	5.59	101	101	41.6	25.9	41%
4	24	4.76	6.30	96	96	42.3	26.3	43%
5	0	0.00	0.00	111	0	42.9	27.5	41%
5	8	2.07	5.21	111	0	42.9	27.5	41%
5	16	3.46	5.42	93	0	43.1	28.3	43%
6	0	0.00	0.00	52	0	42.5	30.9	33%
6	6	1.61	5.41	44	0	43.1	31.0	30%
6	12	1.85	8.47	39	0	43.1	30.3	31%
7	0	0.00	0.00	75	0	42.5	23.3	23%
7	9	1.93	5.46	55	0	40.9	24.2	18%
7	17	2.48	6.30	50	0	41.4	24.9	14%
8	0	0.00	0.00	15	0	41.5	27.5	13%
8	4	2.91	3.02	11	0	40.5	26.9	18%

Baseline MCCB composite score, age, and gender relationships were compared graphically (see figures below) prior to being assessed as covariates in the model. No correlations were observed.

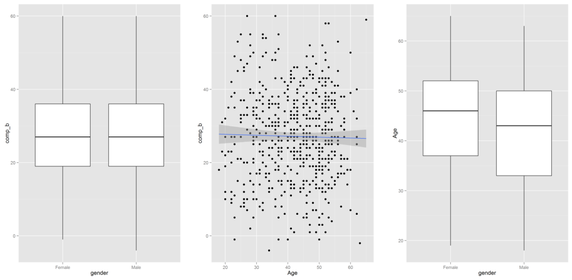


Table 2. Base Model Comparison

Model Name	AIC	BIC	Log-Likelihood	PBO (units)	'rate'	Time to Steady State
Base (Eq.1) m1.1	9851.052	9884.065	-4919.526	1.97	7.4 week $^{-1}$	0.7 week
Base (Eq.2) et50m1.0	9853.884	9886.897	-4920.942	1.98	0.0981 week	1 week

Base (Eq.2) et50m1.0 was estimated with γ=1 as limited data in the early portion of the time curve prevented estimation of γ.

Model m1.1 had a nominally lower AIC, and similar goodness of fit diagnostics (not shown), as compared to model et50m1.0. Therefore model m1.1 was used as the base structural model for further assessment.

Table 3. Covariate Model Building

Model Name	Model Specific	Df	AIC	BIC	logLik	Test	L.Ratio
m1.1	Base model	6	9851.052	9884.065	-4919.52	NA	
m2.1	Baseline	7	9748.825	9787.340	-4867.41	m1.1 - m2.1	104
m3.1	Screening	7	12720.559	12759.074	-6353.28	m1.1 - m3.1	-2868
m4.1	Age	7	9848.027	9886.543	-4917.01	m1.1 - m4.1	5.02
m5.1	Gender	7	10301.235	10339.75	-5143.61	m1.1 - m5.1	-448.18
m7.1	Baseline + Age	8	9734.764	9778.782	-4859.38	m2.1 - m7.1	16.06

Both baseline and age had a significant improvement in model fit leading to the final model (Eq.3) which included both covariates.

Final model structure:

Eq.3 $$Observation_{i,j,k} = PBO_{maxj} * (1 - e^{-rate*t_k}) * \left(\frac{Baseline_j}{meanBaseline}\right)^{\gamma 1} * \left(\frac{Age_j}{meanAge}\right)^{\gamma 2} + \eta_i + \eta_{i,j} + \varepsilon_{i,j}$$

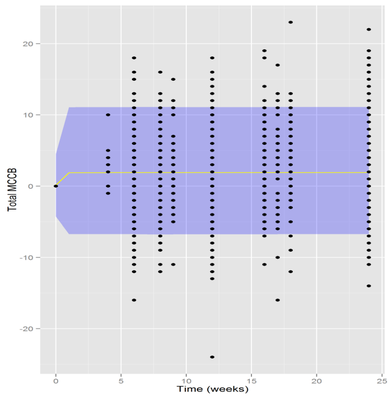
For study i, individual j, and time k.

The final model parameter estimates are shown in Table 4. Describing a rapid increase from baseline to a plateau.

Table 4. Final Model (m7.1) Parameter Estimates

Parameter	Value	SE
PBO_{max}	1.80 units	0.279
ln(rate)	1.98 weeks^{-1}	0.371
Baseline	-0.331	0.0957
Age	-0.632	0.158

A visual predictive check (VPC) is displayed on the right. The blue shaded region captures the model simulated 90% prediction interval, the yellow line is the median, and the black points are the observed data.



Discussions

The maximal placebo effect (PBO_{max}) was estimated to be 1.80 (SE=0.279) units (which is similar to previous reports[1,2]). Baseline MCCB and age were found to be significant covariates in the model. Gender was not a significant covariate in the model. The effect of having a screening MCCB assessment prior to baseline failed to improve the model fit. Given the minimal data in the early portion of the time curve to inform the parameter estimation, the rate constant has a fair amount of uncertainty associated with the estimate. The exponential rate constant was estimated to be 7.2 (95% CI: 3.5, 15) weeks^{-1}, and the corresponding time to the steady state maximal placebo effect ranges from 0.3 to 1.4 weeks. This estimate of time to steady state is very rapid, is influenced by the curve equation, and may suggest a threshold type effect. Additional data in the early phase of the time course would be required to further refine the early portion of the curve.

Conclusions

A non-linear model based on individual-level data was generated to characterize the MCCB time course in placebo subjects with CIAS. Both baseline MCCB and age were found to be significant on the maximal placebo effect. Though the 95% CI for the placebo rate constant was wide, the output of the model suggests a relatively rapid time to the steady state maximal placebo effect. While it is recognized that different mechanisms of action may have different time course of effect, ensuring a comprehensive understanding of the MCCB placebo time course will enable early decision-making in drug development for CIAS.

Selected References

1. Gaudreault F, Tan B, Liu J, Chen D. Model-Based Meta-Analysis of Longitudinal MATRICS Consensus Cognitive Battery (MCCB) for Cognitive Impairment Associated with Schizophrenia (CIAS). 2014 J Pharmacokinet Pharmacodyn v41 s87-s88

2. Umbricht D, Keefe R, Murray S, Lowe D, Porter R, Garibaldi G, Santarelli L. A randomized, placebo-controlled study investigating the nicotinic α7 agonist, RG3487, for cognitive deficits in schizophrenia. Neuropsychopharmacology, 2014; 39(7): 1568-1577. (*PMCID: PMC4023143*).

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