Development and Application of a Semi-Mechanistic Model for Modulation of Amyloid-β in Cerebrospinal Fluid after Inhibition of γ-secretase

Huub J Kleijn[1], Jeremy Hing[2], Jing Su[3], Rik de Greef[1], Greg Winchell[4], Laura B Rosen[3], Julie A Stone[4]

[1]Merck Research Laboratories, MSD, Oss, The Netherlands; [2]Merck Research Laboratories, Rahway, NJ, USA; [3]Merck Research Laboratories, Upper Gwynedd, PA, USA; [4]Merck Research Laboratories, West Point, PA, USA

Background and Objectives

Alzheimer Disease (AD) is a chronic neurodegenerative disease characterized by brain atrophy, loss of neurons and loss of synaptic function secondary to amyloid plaque and neurofibrillary tangle formation [1]. Amyloid-β, the major constituent of amyloid plaque, is generated by γ-secretase. The γ-secretase inhibitor MK-0752 is being developed as a disease-modifying agent for AD. Target modulation by MK-0752 can be characterized by assessment of amyloid-β in cerebrospinal fluid (CSF) as amyloid-β in CSF likely reflects amyloid-β produced in the brain and subsequently distributed into CSF. CSF amyloid-b is thought to be a better target engagement marker of brain tissue activity than plasma amyloid-β which likely also reflects peripheral (non-CNS) production sources. One of the challenges that has emerged in interpretation of CSF amyloid-β data is the presence of an upward baseline drift phenomena that is present to varying degrees across individuals and studies.

The aim of the present analysis was to establish the relation between drug exposure and amyloid-β modulation in presumed brain as reflected in CSF amyloid-β data (with appropriate drift correction) to enable optimization of drug development strategies and benchmarking across drugs targeted for AD.

Methods

Study design and participants

- Subjects: healthy volunteers, n=47
- Treatment: placebo or MK-0752 (110, 300, 500, 750 or 1000 mg)
- Assessments: frequent blood (0-96 h) and CSF sampling (indwelling catheter at lumbar region, 0 – 30 h)
- Pharmacokinetics: MK-0752 concentrations in plasma and CSF (Fig 1)
- Biomarker: CSF amyloid-β (Fig 2)
- NONMEM VII, FOCE
- PK CSF: link models (log-normal between subject variability and additive residual error model)
- Biomarker: direct and indirect effect models combined with transit models; time dependent models to account for baseline drift (log-normal between subject variability and additive residual error model)
- Simulations including parameter uncertainty based on the covariance matrix from NONMEM (n=1000 / dose) for quantification of CSF amyloid-β effects at steady state

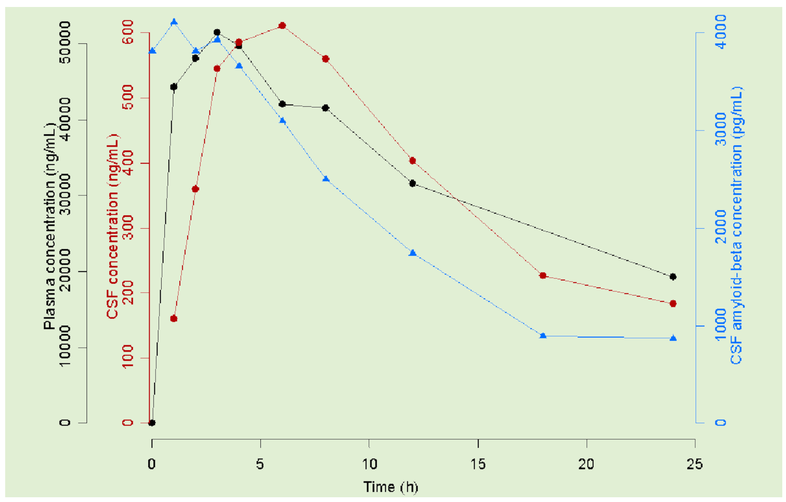

Figure 1. PK profiles in plasma and CSF and CSF amyloid-β profile (median profiles of 1000 mg dose group)

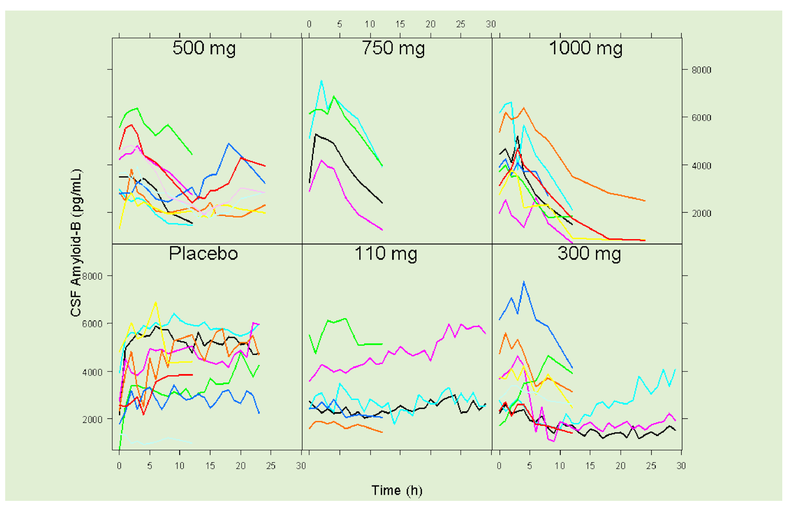

Figure 2. Individual observed CSF amyloid-β profiles

Results

CSF PK model

- The relation between MK-0752 concentrations in plasma and CSF was described with an extended link model connecting a CSF compartment via a transit compartment to the central plasma compartment (Table 1, Fig 3).
- Observed MK-0752 plasma concentrations, instead of model-predicted plasma concentrations, as driver for CSF concentrations resulted in more precise estimates and reduced inter-individual variability (data not shown).

Table 1. Parameter estimates

Parameters	Estimates	SE (95% CI)	IIV (%)
CSF PK model			
MTT_{csf} (h^{-1})	1.94	1.71 – 2.24	32
f_{brain}	0.0129	0.012 – 0.0138	20
CSF Amyloid-β model			
E_{MAX}	0.862	0.670 – 0.950	
IC_{50} (ng/mL)	80.6	63.7 – 102	
n	2.32	1.35 – 3.29	
Baseline (pg/mL)	3170	2747 – 3593	42
$MTT_{Aβ,csf}$ (h)	8.28	7.42 – 9.36	22
Et_{MAX} (pg/mL)	1080	406 – 1745	84
It_{50} (h)	3.45	0 – 8.7	179
n_t	0.923	0.48 – 1.37	

[1]: MTT, mean transit time; fbrain, brain available fraction; SE, standard error; IIV, interindividual variability (log-normal) expressed as CV%

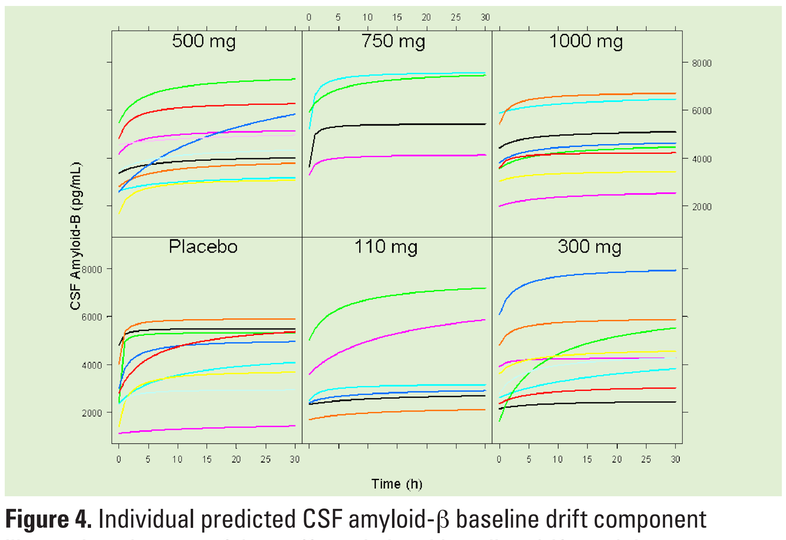

Figure 4. Individual predicted CSF amyloid-β baseline drift component illustrating absence of drug effects in local baseline drift model

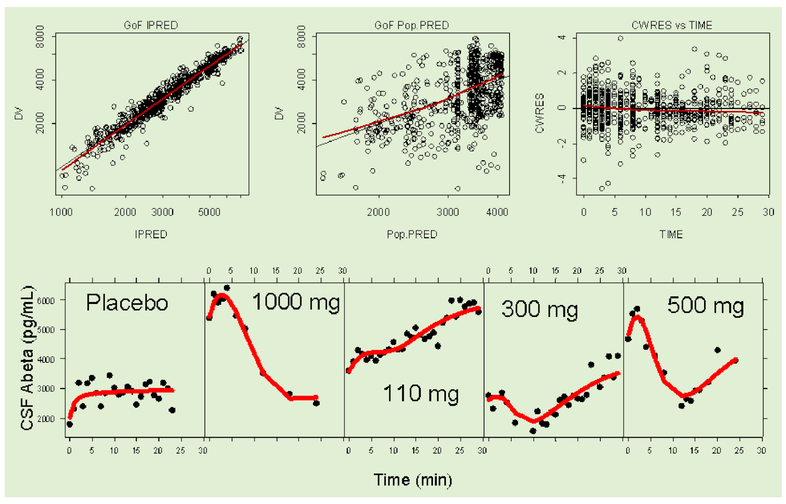

Figure 5. Goodness of fit and examples of individual model fits of CSF amyloid-β profiles

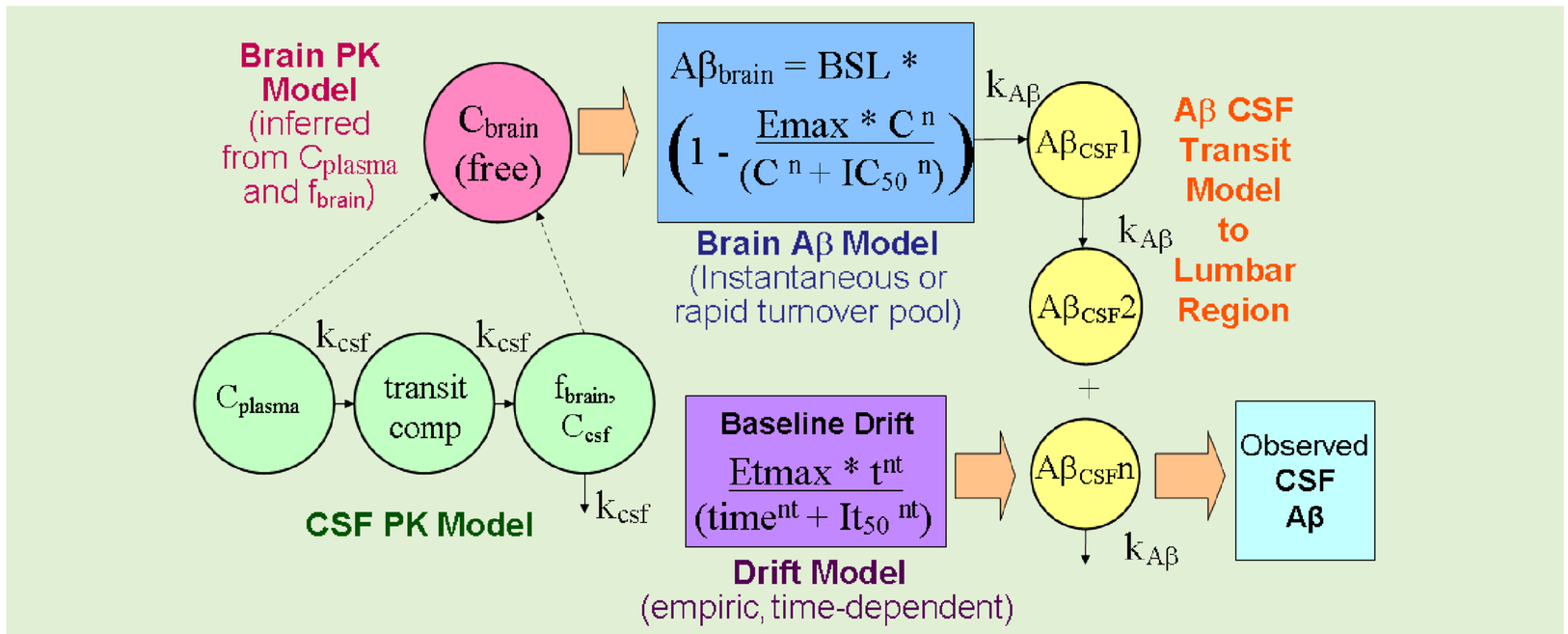

Figure 3. PKPD model framework for interpretation of CSF amyloid-β modulation

CSF amyloid-β model

- For modulation of amyloid-β in brain, plasma concentrations scaled by the individually estimated brain bioavailable fraction, were used as driver. Evidence for fast brain entry was based on preclinical experiments.
- Time-lag in CSF amyloid-β response was due in part to slow transport within CSF but attempts to discriminate between amyloid-β turnover and delay by CSF flow were not successful.
- Interpretation of CSF amyloid-β data was hampered by substantial baseline drift. Baseline drift, modeled with an Emax like baseline function with time, could be separated from drug effects (Fig 4).
- A mechanistic model combining a sigmoid Emax direct effect model for modulation of brain Aβ production with a set of four transit compartments accounting for transport to lumbar CSF sampling site and an additive, independent drift component best described the CSF amyloid-β profiles (Fig 5).

Simulations

- The dose-response relation for percentage change of CSF amyloid-β exposure at steady state is illustrated in Fig 6 and indicates that the drug effects were precisely characterized.

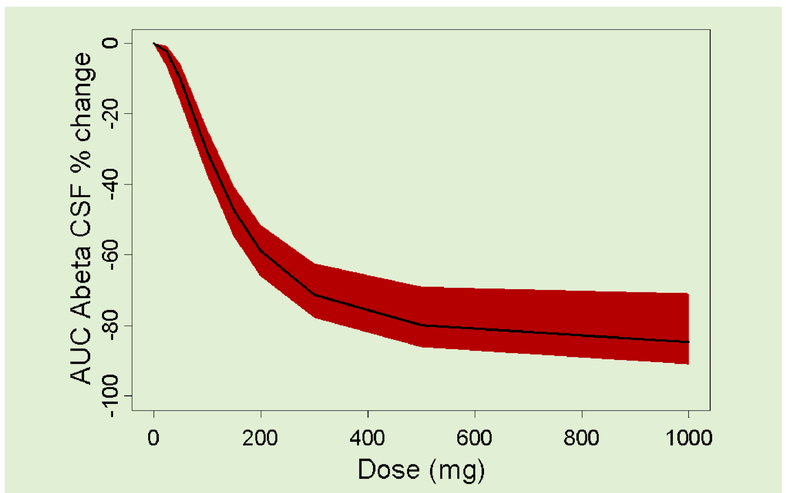

Figure 6. Simulated drug effects on CSF amyloid-β at steady state (median and 90% confidence interval)

Conclusions

- **A model structure was established allowing estimation of drug effect parameters on CSF amyloid-β modulation in the presence of baseline drift.**
- **The time course of CSF amyloid-β following placebo and MK-0752 treatment was well characterized.**
- **The semi-mechanistic approach will enable inference on brain Amyloid-β modulation profile and exploration of CSF amyloid-β modulation in the disease state, e.g. in presence of a plaque pool.**

References: [1 Katzman R. Alzheimer's disease is a degenerative disorder. Neurobiol Aging 1989;10:581-582.
[2] L.B. Rosen, J.A. Stone, et al. The Gamma Secretase Inhibitor MK-0752 Acutely and Significantly Reduces CSF Aβ40 Concentrations in Humans. Oral presentation at 10th International Conference on Alzheimer's Disease and Related Disorders (July 16-20, 2006, Madrid, Spain)

MSD

1121001