

Model-based meta-analysis of γ -secretase inhibitor data: Has A β production inhibition been adequately tested as therapeutic approach in mild AD?

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Background

- The amyloid beta peptide (A β) plays a pivotal role in Alzheimer's disease (AD) pathogenesis. The A β peptide is generated from Amyloid precursor protein, APP, via the sequential cleavages by β - and γ -secretase.
- γ -secretase inhibitors (GSIs) have reached late stage clinical trials, of which none has resulted in significant improvement for the patients.
- GSIs have a complex impact on A β levels which makes it difficult to interpret their net impact on CNS A β levels.

Objectives and Approach

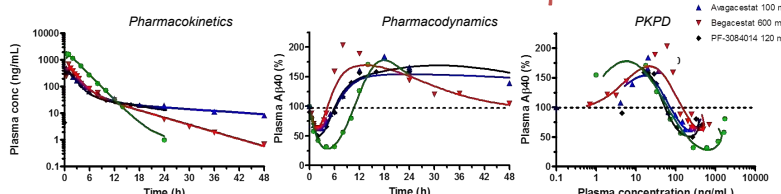
- To get a better understanding on what effect clinical GSIs have had on brain A β levels in clinical trials by performing a quantitative meta pharmacokinetic-pharmacodynamic (PKPD) analysis on A β biomarkers from published GSI clinical trials.
- To investigate if preclinical data on GSI pharmacology could be used to predict CNS and plasma A β production in man.

Data sources & Methods

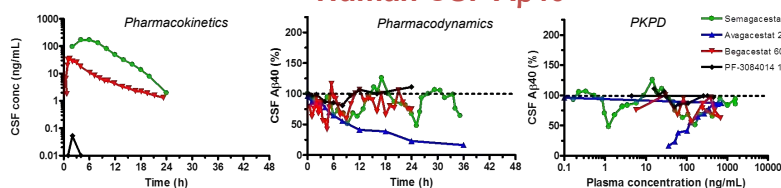
- Time course of (pre)clinical data on A β biomarkers and drug exposure were digitized from the public domain (see refs) for Semagacestat, Avagacestat, Begacestat, PF3084014. Additional preclinical A β inhibition data was generated in house.
- A model-based meta PKPD analysis was undertaken with mean time-concentration-effect observations using a descriptive modeling approach using a composite E_{max} model, combined with a turnover model to describe the biphasic effects. Systems parameters were kept constant between compounds, whereas the drug parameters were allowed to differ.
- From the population parameter estimates, the exposure giving 50% inhibition from baseline (IC₅₀) was derived and used for interspecies comparison.

Results: Human Analysis

Human Plasma A β 40



Human CSF A β 40



- Bi-phasic effects in plasma A β were observed for all compounds, which resulted in averaged increase over time, rather than the anticipated decrease (Table 1).
- No significant effects on CSF A β levels for Semagacestat, Begacestat, PF3084014 were observed for clinically relevant doses, whereas 200 mg Avagacestat seem to reduce CSF A β 40 levels after single dose (placebo baseline drift).
- Avagacestat doses below 100 mg are being used in continued clinical testing and seem not to reduce A β 40 (see figure 2 and ref 11).

Table 1. Prediction of the average plasma A β 40 effect over 24h after single dose of GSI tested in long term clinical trials.

Compound	Single dose	Mean effect 0-24 h	Ref.
Semagacestat (LY450139)	140 mg	+17%	3
Avagacestat (BMS708163)	200 mg	+26%	1

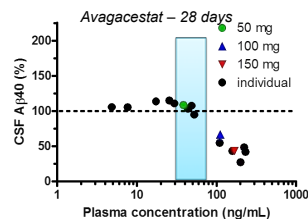
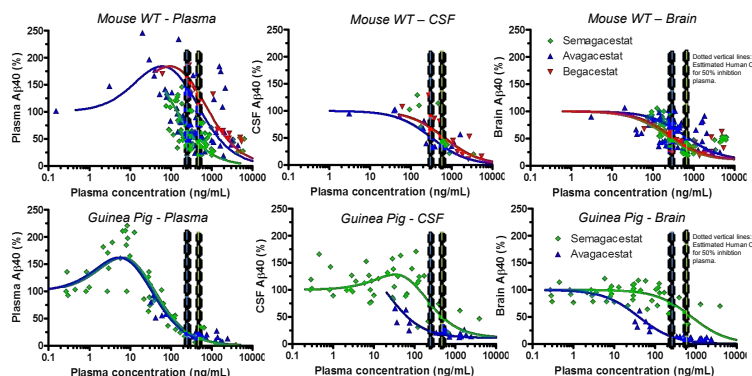


Figure 2. CSF A β 40 response after 28 days (ref 6)

Results: Mouse and Guinea Pig analysis



- Bi-phasic effects in plasma A β 40 in mouse and guinea pig were observed for all GSIs similar to the clinical observations.
- A tendency to bi-phasic effect for semagacestat was seen in CSF in GP, but no bi-phasic effects were observed in brain for any compound.

Table 2. Unbound plasma concentration estimates (nM) giving 50% inhibition (IC₅₀) of A β 40 levels in human, mouse and GP from the population PKPD analysis

Compound	A β 40	Human	Mouse WT	Guinea-Pig
Semagacestat	plasma	1167	925	294
	CSF	-	1572	1244
	brain	-	665	2057
Avagacestat	plasma	10	47	1.5
	CSF	-	10	1.0
	brain	-	24	0.6

Can preclinical data predict human observations?

- Time course of A β is determined by the dynamics of A β (turnover), the pharmacokinetics and the unbound potency and brain/plasma ratio.
- Human predictions on plasma A β 40 were made based on mouse and GP *in vivo* potency estimates with observed human PK and human A β turnover estimates.
- The mouse predicts the plasma A β 40 effect within a 3-fold range, whereas GP seems to overpredict.
- Both mouse & GP would predict small CNS effects for clinically used doses of Semagacestat assuming brain/plasma ratio is similar between species (mean reduction of 10-25% reduction from baseline).

Figure 4. Prediction of human Plasma, CSF and Brain A β 40 for 100 mg Semagacestat based on mouse data analysis, superimposed on clinical observations. Average effect for plasma, CSF and brain is +10, -15, -25% change from baseline over a 24h interval.

Conclusions

- The observed inhibition on CNS A β production in clinical trials conducted so far has been very limited both in size and duration.
- The limited information on clinical CSF A β levels does not indicate a significant reduction in A β levels at intended therapeutic doses. Variability in observations and change in placebo might mask modest CSF effects.
- We see similar (qualitative) but not identical (quantitative) A β effects between man, mouse and guinea pig.
- Comparing clinical plasma and CSF data with animal plasma, CSF and brain A β data in response to the same GSIs, suggests that biphasic plasma effects with no net lowering over 24 h could have been predicted from *in vivo* results and that modest inhibition of CNS A β levels were expected (10-25% reduction in brain A β 40 for Semagacestat).
- More efficacious A β production targeting drugs that lower A β substantially over the dosing interval period should be tested in clinical trials to prove or disprove whether these drug targets are efficacious in mild AD.

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