Scan the QR code to receive an electronic version of the poster. The QR code will expire on August 19, 2012

Malaz.AbuTarif@bms.com

Avagacestat (BMS-708163) Exposures and Study Discontinuations in Patients With Mild-to-Moderate Alzheimer's Disease

Abstract #29551 (AAIC)

Bristol-Myers Squibb

Malaz AbuTarif,[1] Stephen Kaplita,[2] Robert M. Berman,[2] Vlad Coric,[2] Kyle Baron[3]

[1]Bristol-Myers Squibb R&D, Hopewell, NJ; [2]Bristol-Myers Squibb R&D, Wallingford, CT; [3]Metrum Research Group, Tariffville, CT

ABSTRACT

Background: Avagacestat (BMS-708163) is an oral γ-secretase inhibitor designed for selective inhibition of amyloid beta (Aβ) synthesis currently in development for the treatment of mild-to-moderate and predementia Alzheimer's disease (AD). A dose-related increase in discontinuations due to adverse events (AEDCs) was observed in a 6-month study in mild-to-moderate AD (Salloway S, et al. *Alzheimer's Dementia.* 2011;7(4);S695-S696). The objective of this analysis was to assess the relationship of these AEDCs with avagacestat exposure.

Methods: Pharmacokinetic (PK) data from all available phase I and phase II studies were used to develop a population PK model for avagacestat in NONMEM. The PK model was then used to derive individual patient exposures, calculated as the average, daily steady-state concentration (Cav). The relationship between individual-level Cav and AEDCs in the 6-month, phase II study in mild-to-moderate AD (dose range: 25 to 125 mg and placebo) was investigated in WinBUGS using a logistic regression model: logit(πi) = β0+β1.(Cavi-150 ng/mL)/150 ng/mL. Noninformative prior distributions were used for logistic regression model parameters.

Results: PK data from 9 clinical studies with a total of 518 patients and 18,523 observed concentrations were utilized. A 2-compartment population PK model with first-order absorption and elimination described the data well. Population mean parameters were well estimated with a percent relative standard error less than 10% for all parameters. Interpatient variability was estimated for volume of distribution (central and peripheral: 42-47%), clearance (44%), and absorption rate constant (147%). Intrapatient variability (57%) was proportional to the observed concentrations. Exposure-AEDC modeling in the phase II study of patients with mild-to-moderate AD (N=208 patients) showed a significant increase in odds of discontinuation with increased avagacestat exposure (posterior mean odds ratio for a 150 ng/mL increase in Cav: 2.36; 95% credible interval: 1.64-3.34). The logit model was then used to simulate the expected AE-related dropout rate at intermediate doses not tested in the phase II study.

Conclusions: The exposure-AEDCs relationship, using a logistic regression approach, indicated an increase in the probability of AEDCs due to AE with increased avagacestat exposure. This relationship will be used as part of the benefit-risk assessment of different dosing regimens of avagacestat.

INTRODUCTION

- Although the underlying cause of AD remains uncertain, Aβ accumulation is hypothesized to play a central role in AD pathogenesis[1,2]
- Avagacestat is an oral γ-secretase inhibitor designed for selective inhibition of Aβ synthesis that is currently in development for the treatment of mild-to-moderate and predementia AD
- In a recent 6-month, phase II study of patients with mild-to-moderate AD treated with avagacestat, a dose-related increase in AEDCs was observed[3,4]

INTRODUCTION (continued)

- The objectives of this analysis were to assess the relationship of these AEDCs with avagacestat exposure by
  - Developing a quantitative model describing the relationship between avagacestat exposure and probability of dropout due to AE (PdropAE)
  - Estimating the PdropAEs at intermediate doses not tested clinically

METHODS

- PK data from phase I and phase II studies of avagacestat were used to develop a population PK model in NONMEM
  - This PK model was used to derive individual patient exposures, which were calculated as the average, daily Cav
- The relationship between individual-level Cav and AEDCs in the 6-month phase II study in mild-to-moderate AD was investigated using logistic regression modeling in WinBUGs
  - Logit(πi) = β0+β1.(Cavi-150 ng/mL)/150 ng/mL
  - Noninformative prior distributions were used for logistic regression parameters
  - Avagacestat dose range of 25 to 125 mg/d
- Exposure was measured as
  - Cav = $DOSE_{initial}$ (mcg)/$CL_{initial}$ (L/hr)/24hr
  - $CL_{initial}$ was taken as empirical Bayes estimate from final NONMEM run
  - For patients without PK information, individual patient covariate data were used in the population PK model to estimate the CL of a typical patient with these covariates (imputed PK estimates)
  - The logistic regression model was run with and without the imputed PK patients and the results were compared

RESULTS

- PK data from 9 clinical studies with a total of 518 patients and 18,523 observed avagacestat concentrations were utilized
- A total of 208 patients were identified in the AE data set [Table 1]

Table 1. Exploratory Data Analysis by Dose

Avagacestat Dose (mg)	Mean Cav	N_{subj}	N_{event}	$\pi^{PdropAE}$	Logit ($\pi^{PdropAE}$)
0	0.0	42	4	0.10	-2.25
25	46.2	42	4	0.10	-2.25
50	106.7	43	7	0.16	-1.64
100	262.1	41	14	0.34	-0.66
125	359.4	40	13	0.33	-0.73

Units: Dose (mg); Cav (ng/mL)

RESULTS (continued)

- A total of 42 patients in the PK data set received placebo [Table 1; Table 2]
  - For this patient cohort, the Cav values were set to zero

Table 2. Exploratory Data Analysis by Cav Quantile

Mean Cav	Cav Range	N_{subj}	N_{event}	$\pi^{PdropAE}$	Logit ($\pi^{PdropAE}$)
0	0, 0	42	4	0.10	-2.25
38	21, 53	33	3	0.09	-2.30
77	54, 109	33	3	0.09	-2.30
148	110, 189	33	7	0.21	-1.31
275	201, 321	33	12	0.36	-0.56
408	325, 658	34	13	0.38	-0.48

Units: Dose (mg); Cav (ng/mL)

- A total of 166 patients in the PK data set received avagacestat
  - However, 14 patients who received avagacestat did not have PK data available
    - For this patient cohort, the Cav values were imputed using a covariate model [Table 3]

Table 3. Patients With Imputed Exposure

Avagacestat Dose (mg)	Mean Cav	N_{subj}	$N_{elderly}$	N_{event}	Pr(event)
25	44	1	1	0	0.0
50	120	6	6	4	0.7
100	251	4	4	2	0.5
125	299	3	3	0	0.0

Units: Dose (mg); Cav (ng/mL)

- Exposure-response models were run with and without the patients with imputed exposures
- A 2-compartment population PK model with first-order absorption and elimination described the data well
  - Population mean parameters were well estimated with a percent relative standard error <10% for all parameters
  - Interpatient variability was estimated for volume of distribution (central and peripheral: 42-47%), clearance (44%), and absorption rate constant (147%)
  - Intrapatient variability (57%) was proportional to the observed concentrations
- Exposure-AEDC modeling in the phase II study of patients with mild-to-moderate AD (N=208) showed a significant increase in odds of discontinuation with increased avagacestat exposure
  - The posterior mean odds ratio for a 150-ng/mL increase in Cav was 2.36 (95% credible interval 1.64, 3.34) [Table 4]

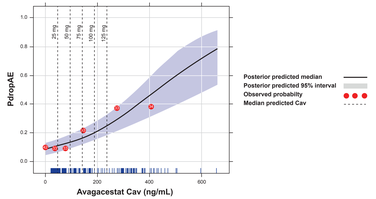
RESULTS (continued)

Table 4. Logistic Regression Results: Parameter Estimates With and Without Imputed Exposures

Parameter	Posterior Mean	RSE (%)	95% Credible Interval
Patients With Imputed Exposure			
β_0	-1.59	12.6	-1.99, -1.20
β_1	0.84	21.5	0.49, 1.21
exp(β_1)	2.36	18.4	1.64, 3.34
Excluding Patients With Imputed Exposure			
β_0	-1.75	12.8	-2.19, -1.32
β_1	0.93	20.8	0.56, 1.32
exp(β_1)	2.58	19.7	1.75, 3.74

- The observed vs predicted probability of dropouts due to AEs is presented in Figure 1

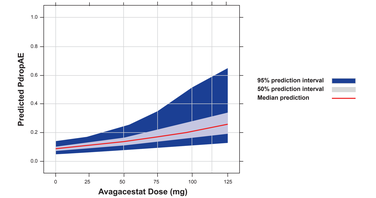
Figure 1. Posterior Predictive Check



Includes patients with imputed exposures

- The logit model was then used to simulate the expected AE-related dropout rate at intermediate doses not tested in the phase II study [Figure 2]

Figure 2. Predicted PdropAE vs Dose

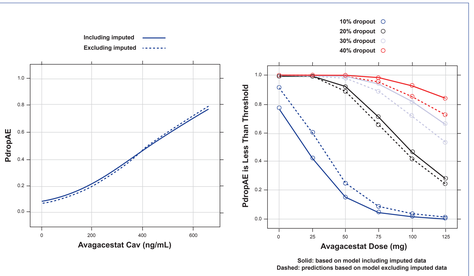


Prediction shown for elderly, 70 kg, white male patient. Includes patients with imputed exposures

RESULTS (continued)

- Modeling outcomes were compared in patients with and without imputed exposures [Table 4; Figure 3]
- Simulation from the PK/PD model provided a quantitative assessment of the likelihood that a candidate avagacestat dose will be acceptable with respect to study dropout rate [Figure 3]

Figure 3. Results With and Without Data From Imputed Patients



Predictions shown for elderly, 70 kg, white male patient

CONCLUSIONS

- The exposure-AEDCs relationship, using a logistic regression approach, indicated an increase in the probability of discontinuation due to AE with increased avagacestat exposure
- This relationship will be used as part of the benefit-risk assessment of different dosing regimens of avagacestat
- Modeling conclusions were not changed when accounting for the few patients who did not have PK measurements (no bias introduced)
- It is important to note that this study only evaluated the projected dropout rate after 6 months of treatment; rates may be higher with extended dosing

REFERENCES

1. Golde TE et al. *Neuron.* 2011;69:203-213.
2. Querfurth HW et al. *N Engl J Med.* 2010;362:329-344.
3. Salloway S et al. *Alzheimer's Dementia.* 2011;7:S695-S696.
4. Salloway S et al. Oral presentation at International Conference on Alzheimer's Disease. Paris, France. July 16-21, 2011.

ACKNOWLEDGMENTS

The authors would like to acknowledge and thank the patients, clinical site staff, and investigators who participated in the phase I and phase II clinical studies included in these analyses.

This study was funded by Bristol-Myers Squibb. Editorial and writing assistance were provided by StemScientific and funded by Bristol-Myers Squibb.