Verubecestat Pharmacokinetic and Exposure-Response Results From APECS, a Phase 3 Trial in Prodromal Alzheimer's Disease

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INTRODUCTION

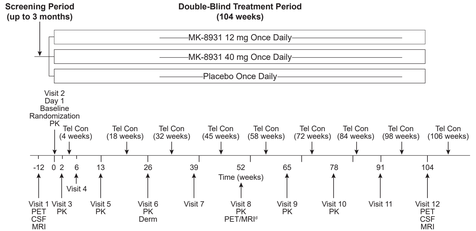
- The BACE inhibitor verubecestat (MK-8931) demonstrated cognitive and functional decline relative to placebo in a 2-year Phase 3 trial of individuals with prodromal AD (APECS; NCT01953601), along with reductions in brain volume and amyloid plaque. Disease progression modeling has demonstrated a lack of dose or exposure dependency in the clinical cognition and function endpoints (see Poster# P1-044)
- In this analysis, pharmacokinetic (PK), safety, and biomarker data from the trial were examined to characterize target engagement and biomarker exposure-response

METHODS

The exposure-response (ER) analysis included data from the APECS Phase 3 trial in patients with prodromal AD (NCT01953601)

- Participants had amnestic mild cognitive impairment and were positive for an AD biomarker
- Participants received daily doses of verubecestat 12 mg or 40 mg or placebo and were treated for 104 weeks
- The FAS dataset consisted of 1,420 participants

Trial Design



Data Sources

Secondary outcome measures for the effects of verubecestat in APECS:

- Brain volumetric measures (including whole brain volume) were assessed using MRI
- The amount of cortical amyloid deposition was measured using positron emission tomography (PET) and [^{18}F]flutemetamol as the amyloid imaging PET ligand
- Plasma and/or dried-blood-spot samples were collected during 4-7 visits for determination of verubecestat concentrations (4,050 samples from 963 participants)

vMRI and PET Amyloid Exposure-Response Modeling

- The relationship between biomarker response (expressed as change from baseline) and verubecestat exposure was evaluated
- An Emax function was applied to fit the data

$$\text{Change from baseline} = Placebo\ CfB + \frac{Emax}{EC50+AUC}$$

- NONMEM 7.2 and R version 3.5.1 were used for analysis. Model fit was evaluated by ΔAIC (Akaike information criterion) and goodness-of-fit plots

Safety Exposure-Response Models

- Select adverse event (AE) terms or groupings of terms were identified for analysis based on an imbalance in incidence rates in verubecestat arms vs placebo
- SAS software 9.4 was used for analysis
- Test for exposure-response
  - Keep active treated subjects only
  - Fit a linear logistic regression model to data
  - Determine *P* value for non-zero slope for time-weighted AUC
  - *P* value <0.05 defines statistically significant E-R

RESULTS – POPULATION PK

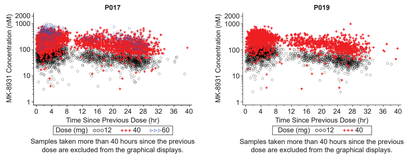
Consistency of APECS PK With Expectation

- PK obtained in most APECS subjects in verubecestat arms (n=963)
- PK consistent with a previous Phase 3 trial in patients with mild to moderate AD (EPOCH) and Phase 1 results
- PK exposures were previously associated with 67% and 84% average inhibition of CSF Aβ40 at the 12 and 40 mg doses, respectively[1]

Exposure Measure	Statistic	12 mg		40 mg	
		EPOCH	APECS	EPOCH	APECS
$AUC_{0\text{-}24hr}$ (μM.hr)	Mean (SD)	1.46 (0.31)	1.46 (0.30)	4.83 (1.01)	4.83 (1.00)
	Median	1.43	1.43	4.71	4.77
	Min, Max	0.54, 2.58	0.51, 3.36	1.94, 9.85	1.63, 9.16
	n	686	483	680	480
C_{max} (nM)	Mean (SD)	79.10 (17.02)	78.96 (16.41)	262.55 (54.85)	263.18 (54.55)
	Median	77.51	77.59	257.36	258.50
	Min, Max	28.25, 137.43	28.76, 167.03	113.36, 486.33	98.82, 472.81
	n	686	483	680	480
C_{trough} (nM)	Mean (SD)	42.15 (10.00)	42.02 (9.85)	138.08 (33.27)	137.73 (32.29)
	Median	41.26	40.50	134.50	136.67
	Min, Max	16.74, 84.58	12.41, 112.69	35.55, 335.12	37.30, 294.73
	n	686	483	680	480

hr, hour; n, number of patients; nM, nanomolar; Min, minimum; Max, maximum; SD, standard deviation; μM, micromolar

Concentration-Time EPOCH and APECS PK Data – Truncated to Time Since Last Dose <40 hr



Samples taken more than 40 hours since the previous dose are excluded from the graphical displays.

RESULTS – SAFETY

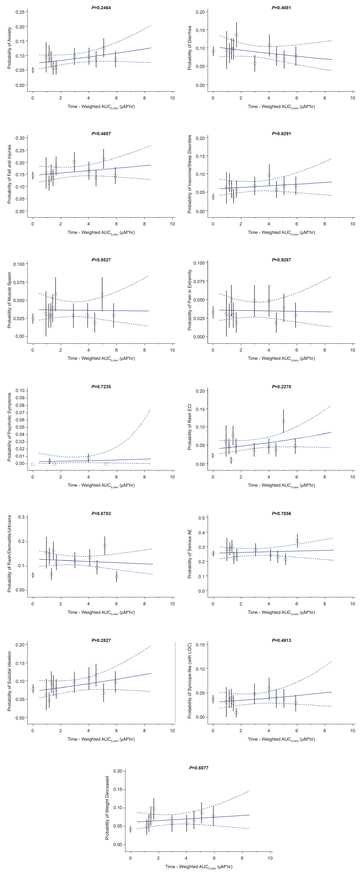
Safety Exposure-Response

- No statistically significant exposure dependency for occurrence of any AE tested
  - Flat relationship contained within the uncertainty bounds in each case
- Suggests the AE profile is similar across exposures from 12 and 40 mg

Linear Logistic Regression Models of Time-Weighted AUC by Adverse Event

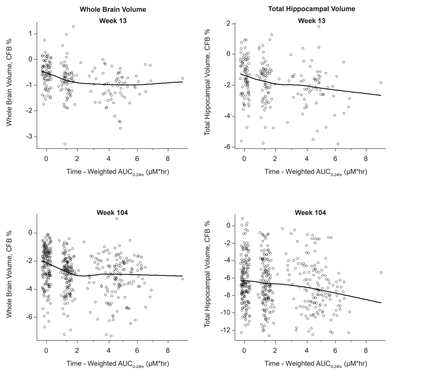
Adverse Event	N	Estimate	Standard Error	Odds Ratio	95% CI for Odds Ratio Lower Bound	95% CI for Odds Ratio Upper Bound	*P* Value
Rash ECI	963	0.0948	0.0785	1.099	0.943	1.282	0.2270
Anxiety	963	0.0724	0.0624	1.075	0.951	1.215	0.2464
Suicidal ideation	963	0.0678	0.0632	1.070	0.946	1.211	0.2827
Diarrhea	963	-0.0535	0.0647	0.948	0.835	1.076	0.4081
Fall and injuries	963	0.0361	0.0489	1.037	0.942	1.141	0.4607
Syncope-like (with LOC)	963	0.0646	0.0939	1.067	0.887	1.282	0.4913
Weight decreased	963	0.0367	0.0714	1.037	0.902	1.193	0.6077
Insomnia	963	0.0350	0.0725	1.036	0.898	1.194	0.6291
Rash/dermatitis/urticaria	963	-0.0233	0.0556	0.977	0.876	1.089	0.6753
Psychotic symptoms	963	0.0972	0.2748	1.102	0.643	1.889	0.7235
Serious AE	963	0.0128	0.0411	1.013	0.935	1.098	0.7556
Pain in extremity	963	-0.0088	0.0985	0.991	0.817	1.202	0.9287
Muscle spasm	963	-0.0058	0.0971	0.994	0.822	1.203	0.9527

Observed Proportion of Each AE With Logistic Regression Models Overlay

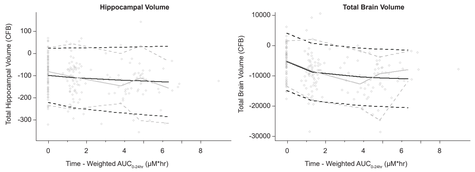


Lines - represent the model-based predicted probability of the AE and associated 90% CI
Circles - represent the median exposure and associated observed probabilities in the patients binned by deciles of exposure
Bars (around the circles) - represent 1 standard error of the observed proportions

RESULTS – BIOMARKER EXPOSURE-RESPONSE MODELS



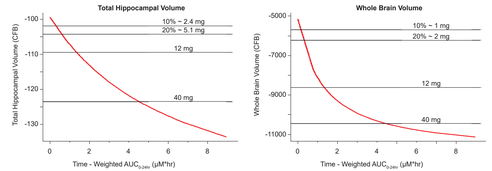
vMRI Exposure-Response Models



Model Parameter	Hippocampal		Total Brain	
	Estimate	RSE(%)	Estimate	RSE(%)
Change from baseline with no exposure (placebo)	-99.4	8	-5160	11
Emax – maximum change from baseline	-59.6	152	-6810	29
EC50 – exposure at which 50% of maximum effect is achieved (μM.hr)	6.7	249	1.3	88

- Time course of vMRI drug effects indicates that these occurred early in study. Therefore, focused ER work on W13 data
- Exposure response evident for hippocampal and total brain volume loss at W13
- E-R models developed for each (illustrated in figures overlaying observed data)
- Used to predict doses with less vMRI loss (10% and 20% of the 40 mg effect)

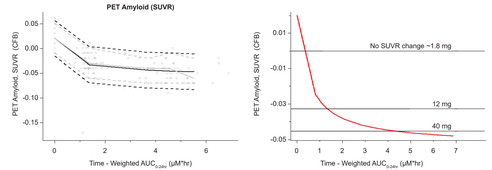
vMRI Exposure-Response



RESULTS – MODELING PET AMYLOID LOAD

- PET amyloid (SUVR) data from Week 104 demonstrated a strong exposure dependency (EC50 = 0.5 μM.hr) consistent with reduced plaque with treatment compared to gain in plaque on placebo
- Exposure-response models developed (illustrated in figure overlaying observed data)
- A dose of 1.8 mg (~27% inhibition of CSF Aβ40) was predicted to correspond to stable plaque levels

PET Amyloid Exposure-Response Model



Model Parameter	Estimate	RSE(%)
Change from baseline with no exposure (placebo)	0.0201	11
Emax – maximum change from baseline	-0.0732	9
EC50 – exposure at which 50% of maximum effect is achieved (μM.hr)	0.518	48

CONCLUSIONS

- The PK results indicate that APECS-tested drug exposures correspond to 67% and 84% inhibition of CSF Aβ40 at the 12 and 40 mg doses
- Exposure dependency in both treatment-related brain volume loss and reduction in amyloid plaque load was identified in the APECS data
- However, these differences in biomarkers were not associated with exposure dependency in cognition, function, or safety outcomes

Reference

1. Kennedy ME, et al. *Sci Transl Med.* 2016;8(363):363ra150.

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