

CIBIC+ at Week 24 LOCF in Study AZ3100603

| Treatment | Week 24 LOCF (SE) | Difference from Placebo (95% CI) |
|----------------|-------------------|----------------------------------|
| Placebo | 3.94 (0.11) | |
| 35mg SB-742457 | 3.63 (0.11) | -0.31 (-0.62,-0.00); p=0.047 |

Week 24 CIBIC+ score: 4 indicates no change, <4 indicates improvement and >4 indicates worsening

ADAS-cog at Week 24 LOCF in Study AZ3100603

| Treatment | Change from Baseline (SE) | Difference from Placebo (95% CI) |
|----------------|---------------------------|----------------------------------|
| Placebo | -0.25 (0.59) | |
| 35mg SB-742457 | -1.53 (0.61) | -1.28 (-2.96,0.40); p=0.135 |

ADAS-cog in Subjects With MMSE Less Than or Equal to 18 at Week 24 LOCF in Study AZ3100603

| Treatment | Change from Baseline (SE) | Difference from Placebo (95% CI) |
|----------------|---------------------------|----------------------------------|
| Placebo | 3.62 (1.17) | |
| 35mg SB-742457 | 1.89 (1.09) | -1.73 (-4.66,1.20); p=0.246 |

ADAS-cog in Subjects With MMSE Greater Than 18 at Week 24 LOCF in Study AZ3100603

| Treatment | Change from Baseline (SE) | Difference from Placebo (95% CI) |
|----------------|---------------------------|----------------------------------|
| Placebo | -2.34 (0.73) | |
| 35mg SB-742457 | -2.77 (0.78) | -0.42 (-2.45,1.60); p=0.680 |

Conclusions: Treatment with SB-742457 35 mg/day for 24 weeks significantly improved global functioning compared with placebo in subjects with mild-to-moderate AD. SB-742457 was well tolerated. Further investigation into the effects of SB-742457 in patients with AD is required.

O3-04-07 TAU AGGREGATION INHIBITOR (TAI) THERAPY WITH REMBER™ ARRESTS DISEASE PROGRESSION IN MILD AND MODERATE ALZHEIMER'S DISEASE OVER 50 WEEKS

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Background: Neurofibrillary degeneration is correlated with clinical dementia. Methylthionium chloride (MTC, rember™) dissolves Tau polymers (Paired Helical Filaments) isolated from AD brain, and prevents Tau aggregation in cell models at the nanomolar range (0.15 - 0.58 μM). MTC has efficacy in Tau transgenic animal models, reversing cognitive and other behavioural defects, and reversing Tau pathology in the brain. **Methods:** An exploratory, dose-range finding, parallel design, double-blind, randomised, placebo-controlled trial of rember™ monotherapy was conducted in 332 subjects meeting DSM-IV and NINCDS-ADRDA for probable AD in UK and Singapore. The primary objective was to investigate the effects of oral MTC at 30, 60 and 100 mg three times per day, compared with placebo, on cognitive function (ADAS-cog) in patients with mild or moderate AD stratified by CDR. The 100mg dose was found to have a formulation defect limiting release of the therapeutic form of MTC. Secondary outcomes included MMSE, CDRsb, CGIC, ADFACS and NPI. Nested studies of SPECT- and PET-scan outcomes at 6 months are reported separately. **Results:** In the prespecified analysis at 24 weeks, rember™ produced a significant improvement relative to placebo of -5.4 ADAS-cog units in CDR-moderate subjects at the 60mg dose. There was no placebo decline in CDR-mild AD over the first 24 weeks preventing initial efficacy analysis, although efficacy was demonstrated in mild AD by the SPECT-scan outcomes. rember™ stabilised the progression of AD over 50 weeks

in both mild and moderate AD. The overall effect size was -6.8 ADAS-cog units vs. decline of 7.8 units in the placebo/comparator arm, with significant efficacy demonstrated separately in mild and moderate subgroups. rember™ efficacy was confirmed on all secondary outcomes. The rember™ efficacy analysis met new EMEA guidelines for disease-modifying therapy by slope analysis and two-time-point analysis, supported by SPECT and PET evidence of efficacy in brain regions strongly affected by Tau pathology. **Conclusions:** This represents the first evidence that TAI monotherapy with rember™ is a viable disease-modifying treatment for mild and moderate AD which may also have preventative application at preclinical Braak stages of AD.

O3-04-08 NO SECULAR TREND AND HIGH VARIABILITY FOR ADAS-COG CHANGE AMONG PLACEBO GROUPS FROM CLINICAL TRIALS

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Background: Efficacy trials for AD drugs depend on the placebo group worsening on the ADAS-cog. Failure of the placebo group to worsen decreases the likelihood that an otherwise effective drug can be recognized as effective. Experts worry that patients may show less worsening than they had in earlier trials, that the ADAS-cog might not be what it once was, and cholinesterase inhibitors are to blame. **Methods:** We searched published and unpublished sources for 6 months or longer randomized, double-blind, placebo-controlled trials for AD. We extracted information about trial size, countries, number of sites, treatment allocation ratios, enrolment dates, age, gender, ADAS-cog and MMSE scores. We combined summary data from individual trials using weighted statistics and standard meta-analysis methods. **Results:** We found 103 trials between 1991 and 2005 and obtained information from 87. Mean age per trial was 73 years (SD=3.0); 58% were female. Mean pre-treatment MMSE and ADAS-cog scores were 19.3 (range, 13.2-26.8) and 24.9 (12.8-39.5), respectively. Mean placebo group changes at 6- and 12- months for the MMSE were -0.73 (SD = 0.94) and -2.77 (SD=0.94), and for the ADAS-cog were 1.44 (SD=1.58) and 4.13 (SD=2.39), respectively, and varied widely among trials. There were no changes in baseline characteristics or cognitive change scores across the 15-year time period of the trials. Smaller placebo groups were associated with more variable change, larger variances, and less likelihood of worsening. Placebo sample sizes <100 had a 37% chance of not showing significant change, and samples >200 all showed significant worsening at 6-months. In 12-month studies 95% of placebo sample sizes >100 showed significant decline. Less worsening was associated with trials with non-English speaking sites; less variance with more frequent assessments. Cholinesterase inhibitors use was not associated with less decline. **Conclusions:** The most reliable approach to maximize likelihood for demonstrating efficacy is to have placebo sizes greater than 200, use the ADAS-cog at least 4 times and in English. Individual patient data should be provided by sponsors for independent, unbiased analyses. Effective drugs may not have been recognized and ineffective drugs misrecognized.

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ORAL

O3-05

THERAPEUTIC STRATEGIES 1

O3-05-01 A NOVEL APPROACH TO SCREENING INHIBITORS OF AMYLOID FORMATION

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