Evidence of Efficacy for TC-1734 (AZD3480) in the Treatment of Cognitive Impairment in Older Subjects

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Introduction

Numerous pre-clinical animal models indicated TC-1734 (AZD3480) had a beneficial effect on cognition (1). Early work in man likewise provided evidence TC-1734 (AZD3480) might have a beneficial effect on cognition, especially attention and episodic memory (2). The present study assessed the efficacy of TC-1734 (AZD3480) in an older population with subjective and objectively defined Age Associated Memory Impairment (AAMI).

Methodology

Volunteers aged 50-80 years with subjective memory impairment and who scored at least 1 standard deviation below that seen in healthy young adults on the Wechsler Memory Scale – Revised, Paired Associate Learning Test, were randomized into a double blind fixed dose, placebo controlled, parallel group study. Subjects did not meet criteria for MCI. Treatment was for 16 weeks and subjects received 25 mg, 50 mg TC-1734 (AZD3480) or placebo. Routine safety measures were taken. Cognitive performance was assessed using the Cognitive Drug Research (CDR) computerized test battery on day -1 and at weeks 8 and 16. Analysis was undertaken with the Intent To Treat population (ITT n=193) and the Per Protocol population (PP n=168) looking at between-group comparisons of change from baseline to week 8 and baseline to week 16 using a Mixed Model Analysis of Covariance. A Subject Global Impression (SGI) rating scale was used to assess self-rated overall cognitive performance. The three primary outcome measures, Power of Attention (POA), Quality of Episodic Memory (QEM) – both from the CDR test battery - and the SGI were tested in a hierarchical manner, the next variable only being tested if the preceding one was positive in order to preserve alpha at the 0.05 level.

Safety & Tolerability

There were 115 AEs on placebo, 106 on 25mg and 134 on 50mg TC-1734 (AZD3480). There were 5 reported SAEs, two on drug and three on placebo, plus one pelvic fracture. The most frequent AEs are given in Table 3.

No effect of clinical significance was seen on hematology, biochemistry or urinary measures. Likewise vital signs and ECGs were not effected by the medication.

Efficacy

Results for the primary outcome measures are given in Table 4. As can be seen, 50mg TC-1734 (AZD3480) was superior compared to placebo on all 3 measures. This was true in both the ITT and PP populations. In both analyses only Power of Attention was positive for 25mg TC-1734 (AZD3480).
Results from week 8 and 16 are given for Power of Attention (Figure 1), Episodic Memory (Figure 2) and SGI (Figure 3). Superiority for 50mg TC-1734 (AZD3480) was seen at both week 8 and week 16 on the CDR variables and at week 16 on the SGI.

Demographics

Patient disposition is given in Table 1 and baseline characteristics in Table 2.

Table 1
Patient Disposition: Pre-screened= 373
Screened=224

	Placebo	TC-25mg	TC-50mg	Total
Randomized	66	59	68	193
Completed	58	53	57	168
Dropout AE	3	4	4	11

Table 2: Baseline Characteristics

	Placebo	TC-25mg	TC-50
Age (years) M:F	65.3 31:35	64.8 19:40	65.3 36:32
WMS-R PAL	15.8	15.8	15.7

Table 3: Most Frequent Adverse Event by Treatment Group

Type	Placebo	TC-25mg	TC-50mg
Dizziness	9	4	8
Headache	2	5	5
URTI	1	3	5
Head Cold	1	4	4
Diarrhea	4	3	4
Back Pain	5	2	3

Table 4: Primary Efficacy Analysis – Change from Baseline to Week 16- ITT Population

Efficacy Measure	TC-1734 (AZD3480) 25mg	TC-1734 (AZD3480) 50mg
Power of Attention	0.0251**	0.0135**
Quality of Episodic Memory	0.8122	0.0285**
SGI-Overall Cognitive Impression	0.6363	0.0146**

**p<0.05

Figure 1: CDR – Power of Attention
ITT Population

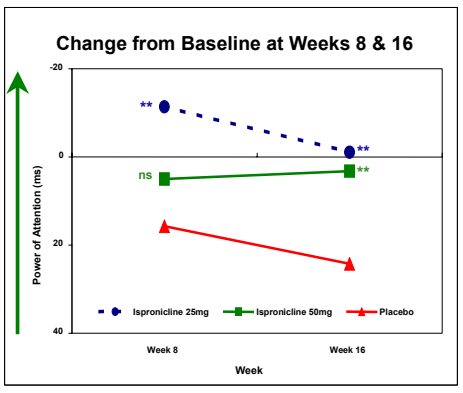


Figure 2: CDR - Quality of Episodic Memory
ITT Population

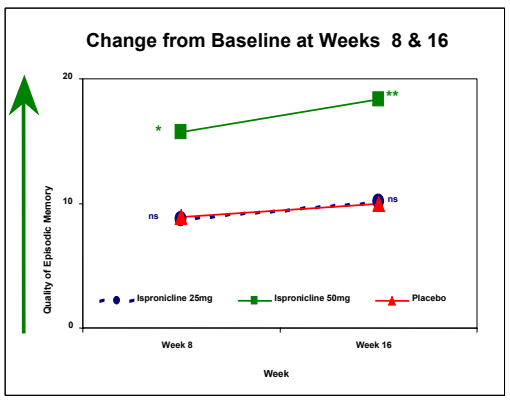
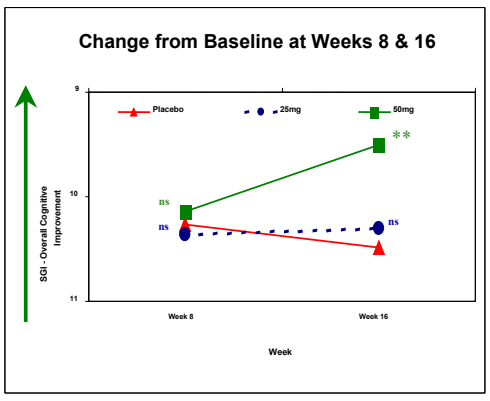


Figure 3: SGI - Overall Cognitive Impression
ITT Population



NS= not significant, **p<0.05

Discussion

In this study both objective measures (CDR) and a subjective rating scale (SGI) were superior on 50mg TC-1734 (AZD3480). Alignment on these measures at the higher dose indicates a potentially robust drug effect with 25mg being a possible minimal effective dose. Further work will be undertaken to assess this and whether TC-1734 (AZD3480) has benefit in treating patients with Alzheimer's disease.

Conclusion

TC-1734 (AZD3480) had an acceptable safety profile and was well tolerated. 50mg TC-1734 (AZD3480) has a beneficial effect on cognition in subjects with AAMI. This effect was seen at week 8 and week 16 but was less marked on 25mg TC-1734 (AZD3480).

References

1. Gatto, G, et al (2004). TC-1734. An orally active neuronal nicotinic acetylcholine receptor modulator with antidepressant, neuroprotective and long lasting cognitive effects. CNS Drug Review Vol 10, No. 2 p147-166
2. Dunbar, G and Kuchibhatla R (2006). Cognitive enhancement in man with ispronicline (TC-1734) a nicotinic partial agonist. Journal Molecular Neuroscience: in press