Clinical Study Report Synopsis

Drug Substance	AZD3480 (TC-1734)
Study Code	TC-1734-226-CRD-005
Edition Number	1
Date	01 July 2010

An Exploratory Trial of AZD3480 (TC-1734) for the Treatment of Adult Attention-Deficit/Hyperactivity Disorder (ADHD)

Study dates: First subject enrolled: 27 June 2008
Last subject last visit: 09 July 2009

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre

Clinical Neuroscience Research Unit
Mental Health Services
Fletcher Allen HealthCare
Burlington, VT (USA)

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
to evaluate the effects of 2 weeks of AZD3480 on the symptoms of ADHD as measured by the CAARS-INV total ADHD symptom score (sum of Inattention and Hyperactivity/Impulsivity scores).	CAARS-INV total ADHD symptom score (sum of Inattention and Hyperactivity/Impulsivity scores).	Efficacy
Secondary	**Secondary**	
to evaluate the safety of AZD3480 in this patient population	Adverse events, standard clinical laboratory safety assessments (chemistry and haematology),vital signs, ECG and physical examinations	Safety
to evaluate the effects of 2 weeks of AZD3480 compared to placebo on cognitive performance measured by the CDR and the CNRU cognitive testing batteries	CDR: power of attention, continuity of attention, quality of working memory, quality of episodic secondary memory and speed of memory CNRU: Stop Signal Task, Two choice task, High-Low Imagery Task (Immediate and Delayed Recall), n-back task, Balloon Analogue Risk Task	Efficacy
to evaluate the effects of 2 weeks of AZD3480 compared to placebo on self-reported ADHD symptoms as measured by the CAARS-S	CAARS-S	PRO
to evaluate pharmacokinetics of AZD3480 during each treatment period, for correlations with efficacy measures.	AZD3480 exposure	PK

The following efficacy outcome was also reported

- Clinical Global Impressions (CGI): illness severity, global improvement (change), and efficacy index

The following PRO outcomes were also reported

- Profile of Mood States (POMS)
- Symptom Check List – 90 (SCL-90)

Study design

This was a randomized 3-way cross-over placebo-controlled trial with 3 treatment periods, each of which was 2 weeks in duration.

Target subject population and sample size

In the 3 treatment periods, either AZD3480 [5 mg/day, or 50 mg/day] or placebo was administered to 24 non-smoking adults with DSM-IV confirmed ADHD. All CYP2D6 slow metabolizers were excluded from the study.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

- TC-1734-226 (AZD3480) capsule hard, 5 mg (benzoate salt); batch number: H1895-01-01-01
- TC-1734-226 (AZD3480) capsule hard, 50 mg (benzoate salt); batch number: H1813-02-01-01
- Placebo capsule; batch number: H1814-01-01-02

Duration of treatment

There were 3 treatment periods, each of which was 2 weeks in duration. There was a three week washout between each treatment period to minimize drug carryover effects.

Statistical methods

The primary objective of this study was to determine the effect of AZD3480 in adults with ADHD. The primary comparison was the CAARS-INV total score following 2 weeks of placebo treatment compared to two weeks of each drug treatment (5 and 50 mg). Baseline differences prior to each drug treatment were analyzed and covaried. Examination of possible carryover effects of treatment through washout was examined by comparing the end of washout assessments with the pre-treatment assessments (e.g., CAARS, CDR, CNRU).

The results from the CDR test battery will be reported separately from the CSR.

Subject population

The study was stopped when 24 subjects (the planned sample size) completed the study. As a consequence, the study population includes 30 randomized subjects, 24 “completers”, 3 drop-outs and 3 subjects who were still active participants when the study was stopped. A completer was defined as a subject who completed at least 2 double-blind treatment periods

where one of those treatments was placebo. There was 1 subject who completed 2 of 3 double-blind periods and was therefore defined as a completer. The three subjects who were still enrolled at the time the blind was broken were intentionally over-enrolled to ensure efficient completion of 24 subjects in case of study drop-outs. Because of the requirement to initiate data analysis after 24 completed subjects, efficacy data (including clinician ratings, subject ratings, and cognitive testing) from these final 3 subjects were not analyzed. However, these subjects were included in the demographics, safety and adverse event analyses in this report.

Demographics data for the 30 randomized subjects and 24 completed subjects is summarized in Table 1.

Table 1: Sample Characteristics – mean (standard deviation)

	Gender	Age	Education (16 = BA)	FSIQ	CAARS-Total Sxs	CGI-Illness Severity
Total (n=30)	Male 21 Female 9	44.33 (12.97)	15.96 (1.77)	117.00 (10.09)	41.03 (6.16)	4.97 (0.67)
Completers (n=24)	Male 18 Female 6	44.25 (11.88)	16.30 (1.55)	116.25 (10.51)	41.21 (6.37)	4.96 (0.75)

Of the 30 subjects, 20 had been previously diagnosed with ADHD, and 10 were newly diagnosed at screening. All subjects met DSM-IV criteria for ADHD (by K-SADS-PL) with 1 subject identified as Primarily Hyperactive –Impulsive Type, 9 identified as Primarily Inattentive Type, and the remaining 20 subjects identified as Combined Type. See Appendix C for the subject data listings.

All 30 randomized subjects were categorized as Rapid CYP2D6 metabolizers, defined as having $\geq$ 1.0 functional CYP2D6 alleles (vs. $\geq$ 1.5 functional CYP2D6 alleles per Study Protocol) and not taking any moderate or strong CYP2D6 inhibitor.

Summary of efficacy results

Primany Outcome Measure: Connors Adult ADHD Rating Scale – Investigator (CAARS-INV) Total Symptoms Scale

There was a significant ($F(2,23)=5.15$, $p<0.05$), overall dose effect for the 50 mg dose, compared to placebo, when the baseline visit is included in the a statistical model. The 50 mg dose was associated with a significant ($p<.0001$) effect compared to placebo, after 2 weeks of treatment. The 5 mg dose did not show a significant overall effect compared to placebo (0=0.307), and it was not associated with significant effects after week 1 (p=0.909) or week 2 (p=0.077) of treatment .

There was a significant [$F(4,23)=4.13$, $p<.05$] Dose X Week interaction on the Total ADHD Symptoms Scale score compared to baseline visit., when visit is included in the statistical model. The 50 mg treatment was associated with significant ($p<.01$) reduction in scores after

both 1 and 2 weeks of treatment. The 5 mg dose was associated with a significant ($p<.05$) decline in Total ADHD Symptom score after two weeks of treatment. Scores during placebo treatment were not significantly different by week and Pre scores were not significantly different from each other (across drug conditions).

Secondary Outcome Measures

There was a trend toward beneficial effect of the 50 mg dose of AZD3480 on the Improvement Index of the CGI.

The 50 mg dose was associated with statistically significant improvement in a laboratory measure of impulsivity, the Stop Signal Task.

Analyses of secondary endpoints indicate that the 50 mg dose of AZD3480 has beneficial effects on working memory (with a trend towards this effect at the 5 mg dose) and that both doses of AZD3480 improve recognition memory. There were no clear effects of either dose of AZD3480 on risk taking or delay aversion in this study. Self-report data on the CAARS-S found beneficial effects at 2 weeks of treatment for the 5mg dose of AZD3480. These results are consistent with the CAARS-INV reports at this dose and reflect improvement in ADHD symptoms and mood. The 50 mg dose was not consistently associated with changes in self reported symptoms on the CAARS-S.

Summary of safety results

AZD3480 was very well tolerated in this study with the frequency, type, and severity of adverse events during the 5 and 50 mg treatment periods no different from those reported during placebo. There were no significant, drug-related effects on systolic blood pressure or respiration rate. There were several statistically significant changes in vital sign measures associated with the 5 mg dose of AZD3480. However, the clinical relevance of these effects as well as their physiological basis is uncertain.