Clinical Study Report Synopsis

Drug Substance	AZD7325
Study Code	D1140C00008
Date	10 March 2010

A Single-Centre, Single-Dose, Double-Blind, Randomized, Placebo- and Active-Controlled Crossover Study to Evaluate the Abuse Potential of AZD7325 in Healthy Recreational CNS Depressant Users

Study dates:	First volunteer enrolled: 22 May 2009 Last volunteer last visit: 8 September 2009
Phase of development:	Clinical pharmacology (I)

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

An abbreviated (synopsis-only) clinical study report was considered to be appropriate for this Phase I study because AstraZeneca has discontinued the AZD7325 development program.

Study center

This study was conducted at a single center in Toronto, Canada.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Primary and secondary objectives and outcome variables

Objective	Outcome variable(s)
Primary	
To evaluate the abuse potential of AZD7325 compared to lorazepam in healthy recreational CNS depressant users.	Drug Liking VAS E_{max}
Secondary	
To evaluate the abuse potential of lorazepam compared to placebo in healthy recreational CNS depressant users to confirm study validity.	Drug Liking VAS and secondary VAS items (Overall Drug Liking, Take Drug Again, Good Effects, High, Bad Effects, Alertness/Drowsiness, Any Effects, Attention span, Performance), SDV, ARCI scales: euphoria (MBG scale), dysphoria (LSD scale), and sedation (PCAG scale)
To evaluate the abuse potential of AZD7325 compared to lorazepam in healthy recreational CNS depressant users.	Secondary VAS items, SDV, ARCI scales
To evaluate the abuse potential of AZD7325 compared to placebo in healthy recreational CNS depressant users.	VAS items, SDV, ARCI scales
To evaluate the psychomotor and cognitive effects of AZD7325 compared to lorazepam and placebo in healthy recreational CNS depressant users and to confirm the psychomotor and cognitive effects of lorazepam compared to placebo.	DA test, CRT test, and HVLT-R
To evaluate the safety and tolerability of single doses of AZD7325 in healthy recreational CNS depressant users.	AEs, laboratory variables, vital signs (blood pressure, pulse, body temperature), ECG (heart rate, P and QRS durations, PR, QT and QT intervals)
To evaluate proportions of subjects with suicidal behavior and suicidal ideation occurrences after baseline up to final follow-up	C-SSRS

AE Adverse event; ARCI Addiction Research Center Inventory; C-SSRS Columbia Suicide Severity Rating Scale; CNS Central nervous system; CRT Choice Reaction Time; DA Divided Attention; E_{max} Maximum effect; ECG Electrocardiogram; HVLT-R Hopkins Verbal Learning Test—Revised; LSD Lysergic Acid Diethylamide; MBG Morphine Benzedrine Group; PCAG Pentobarbital Chlorpromazine Alcohol Group; SDV Subjective Drug Value; VAS Visual analogue scale.

Study design

This was a randomized, double-blind, placebo- and active-controlled crossover study. Each healthy volunteer participated in a medical screening visit, a qualification phase, 7 treatment periods, and an end-of-study visit. During each treatment period, subjects received a single oral dose of 1 of the following treatments: Placebo, Lorazepam 1.5 mg, Lorazepam 3 mg, Lorazepam 6 mg, AZD7325 10 mg, AZD7325 40 mg, or AZD7325 80 mg.

Target subject population and sample size

A total of 35 healthy volunteer recreational CNS depressant users, aged 18 to 55 years of age, inclusive, were to be enrolled in the treatment phase to ensure that at least 28 volunteers completed the study (≥1 volunteer per treatment sequence). Recreational CNS depressant use was defined as ≥10 lifetime occasions of non-medical use of drugs with depressant/sedative properties (eg, benzodiazepines, barbiturates, gamma-hydroxy butyrate [GHB], flunitrazepam, zopiclone, zolpidem, cannabis), and ≥1 non-medical use in the year prior to screening.

As determined by a paired t-test with a 2-sided significance level of 0.05, a sample size of 28 volunteers would have at least 90% power to detect a 10 point difference in Drug Liking VAS E_{max} using an estimated standard deviation (SD) of 14.8 (pooled between volunteer SD from placebo, alprazolam 1.5 mg and alprazolam 3 mg data from unpublished studies performed at the investigational site). The study was also adequately powered to ensure study validity (eg, lorazepam versus placebo contrasts): As determined by a paired t-test with a 2-sided significance level of 0.05, a sample size of 28 volunteers would have greater than 99% power to detect a difference between lorazepam and placebo, based on an estimated effect size of 1.7 (based on pooled alprazolam 1.5 mg data [≈3 mg lorazepam] for Drug Liking VAS).

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

AZD7325 was dosed as 10 mg (batch #F13583), and 40 mg (batch #F13721) capsules. Lorazepam (OHM Labs) was dosed as 0.5 mg (batch #F13536), 1 mg (batch #F13537), and 2 mg (batch #F13538) tablets that were overencapsulated by AstraZeneca. Matching placebo capsules for AZD7325 (batch #F13586) and lorazepam (batch #F13324) were supplied by AstraZeneca.

Duration of treatment

Seven single-dose treatment periods, separated by washout periods of 7 to 21 days.

Statistical methods

Primary and secondary pharmacodynamic (PD) variables were analyzed using a mixed-effect model for a crossover study. The model included treatment, period, treatment sequence, and first-order carryover effect as fixed effects; baseline (pre-dose) measurement as covariables where applicable; and volunteers nested within treatment sequence as random effect. Multiple contrasts were performed to compare primary and secondary outcome variables for AZD7325 against lorazepam and placebo. Significant period and sequence effects were observed for

some endpoints, including Drug Liking VAS E_{max} (p=0.002 and 0.036) and were therefore included in the analysis model, where appropriate. Assumptions for normality of data and homogeneity of variance test were met and therefore no non-parametric analysis was performed. The safety data were summarized using descriptive statistics.

Subject population

As shown in Table S 2, of the 35 randomized subjects, 28 completed the study and were included in the PD analysis. These healthy volunteers were predominantly White males and had a mean age of 34.4 years.

Table S 2 Subject disposition and demographics

Disposition			
n (%) randomized		35	(100.0%)
n (%) of subjects who:	Completed	28	(80.0%)
	Discontinued:	7	(20.0%)
	- Adverse event	4	(11.4%)
	- Voluntary discontinuation	1	(2.9%)
	- Other reason[a]	2	(5.7%)
n (%) included in the safety analysis[b]		35	(100.0%)
n (%) included in the pharmacodynamic analysis[c]		28	(80.0%)
Demographic characteristics (safety analysis set)			
Gender, n (%):	Male	29	(82.9%)
	Female	6	(17.1%)
Age (years):	Mean (SD)	34.4	(9.49)
	Range	19	to 52
Race, n (%):	White	20	(57.1%)
	Black/African American	10	(28.6%)
	Asian	3	(8.6%)
	American Indian/Alaska native	1	(2.9%)
	Other	1	(2.9%)
BMI (kg/m^2)	Mean (SD)	25.2	(2.99)
	Range	19	to 31

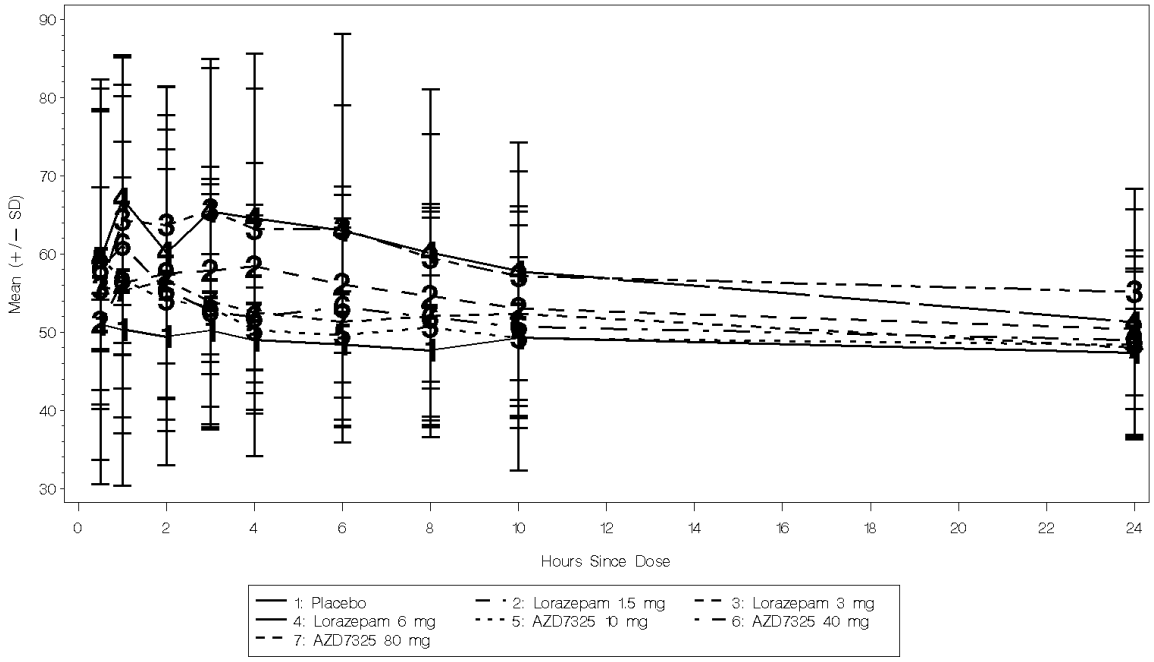
[a] Two volunteers were considered unreliable and were discontinued.
[b] Number of subjects who took ≥1 dose of study treatment.
[c] Number of subjects who completed all 7 treatment periods.
BMI Body mass index; n Number of healthy volunteers meeting criterion; SD standard deviation.

Summary of pharmacodynamic results

Mean scores over time for the Drug Liking VAS are shown in Figure S 1. Mean Drug Liking VAS scores for placebo remained near neutral (50) for the duration of the timecourse. Lorazepam 3 and 6 mg increased Drug Liking VAS scores, with an onset and peak between 0.5 and 3 hours postdose, and the scores remained in the liking range of the scale until at least 10 hours postdose. AZD7325 also increased Drug Liking VAS scores, with an onset and peak within approximately 0.5 to 2 hours postdose--these increases were relatively transient, lasting

approximately 2 to 3 hours. Drug Liking VAS scores for AZD7325 were approximately intermediate between those of placebo and the 2 highest doses of lorazepam (3 mg and 6 mg), and were more similar in peak magnitude to those of lorazepam 1.5 mg.

Figure S 1 Mean scores (±SD) over time for Drug Liking VAS (pharmacodynamic analysis set)



Scale: Drug Liking VAS item: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral (no drug effect) point.
SD Standard deviation; VAS Visual analogue scale.

ANOVA results indicate a significant overall treatment effect ($p<0.001$). To address the primary objective, AZD7325 Drug Liking E_{max} values were compared to those of lorazepam (Table S 3). The dose-level comparisons were of primary interest for this objective (ie, low dose versus low dose, mid-dose versus mid-dose, etc). While AZD7325 10 mg was not significantly different from lorazepam 1.5 mg, both AZD7325 40 and 80 mg had significantly lower Drug Liking E_{max} values compared to lorazepam 3 mg and 6 mg, respectively. The additional contrasts of AZD7325 compared to lorazepam demonstrated that all 3 AZD7325 doses had significantly lower Drug Liking VAS E_{max} values than lorazepam 3 mg and 6 mg. AZD7325 40 mg E_{max} was significantly greater than lorazepam 1.5 mg E_{max}, while AZD7325 80 mg E_{max} was not significantly different from lorazepam 1.5 mg E_{max}.

The Drug Liking VAS E_{max} values for all 3 doses of lorazepam were significantly greater than the E_{max} for placebo, thereby confirming the validity of the study and sensitivity of the Drug Liking VAS E_{max} endpoint to the effects of the positive comparator. E_{max} values for all 3 doses of AZD7325 were also significantly greater than the E_{max} for placebo.

Table S 3 ANOVA[a] results for Drug Liking VAS[b] E_{max} (maximum liking) (pharmacodynamic analysis set)

Pairwise comparison	LS mean differences (SE)	95% CI (lower, upper)	p-value	Adjusted p-value[c]
Lorazepam vs placebo (study validity)				
LPM 1.5 mg–placebo	7.3 (3.41)	0.5, 14.0	**0.035**	**0.041**
LPM 3 mg–placebo	23.4 (3.41)	16.7, 30.2	**<0.001**	**<0.001**
LPM 6 mg–placebo	23.1 (3.42)	16.3, 29.9	**<0.001**	**<0.001**
AZD7325 vs lorazepam (primary contrasts)				
AZD 10 mg–LPM 1.5 mg	0.0 (3.41)	-6.7, 6.8	0.997	0.997
AZD 40 mg–LPM 3 mg	-8.7 (3.40)	-15.4, -2.0	**0.012**	**0.019**
AZD 80 mg–LPM 6 mg	-9.7 (3.42)	-16.5, -3.0	**0.005**	**0.009**
AZD7325 vs placebo				
AZD 10 mg–placebo	7.3 (3.43)	0.5, 14.1	**0.035**	**0.041**
AZD 40 mg–placebo	14.7 (3.41)	8.0, 21.5	**<0.001**	**<0.001**
AZD 80 mg–placebo	13.4 (3.42)	6.6, 20.1	**<0.001**	**<0.001**
AZD7325 vs lorazepam (additional contrasts)				
AZD 10 mg–LPM 3 mg	-16.1 (3.41)	-22.9, -9.4	**<0.001**	**<0.001**
AZD 10 mg–LPM 6 mg	-15.8 (3.40)	-22.5, -9.1	**<0.001**	**<0.001**
AZD 40 mg–LPM 1.5 mg	7.5 (3.42)	0.7, 14.2	**0.030**	**0.041**
AZD 40 mg–LPM 6 mg	-8.4 (3.41)	-15.1, -1.6	**0.015**	**0.023**
AZD 80 mg–LPM 1.5 mg	6.1 (3.40)	-0.6, 12.8	0.076	0.081
AZD 80 mg–LPM 3 mg	-10.1 (3.41)	-16.8, -3.3	**0.004**	**0.008**

[a] Sources of variation: Overall treatment effect was $p<0.001$. Period and sequence effects were also significant ($p\leq0.036$).

[b] Drug Liking VAS item: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral (no drug effect) point.

[c] p-values were adjusted using the Benjamini and Hochberg procedure to account for the effect of multiple treatment comparisons.

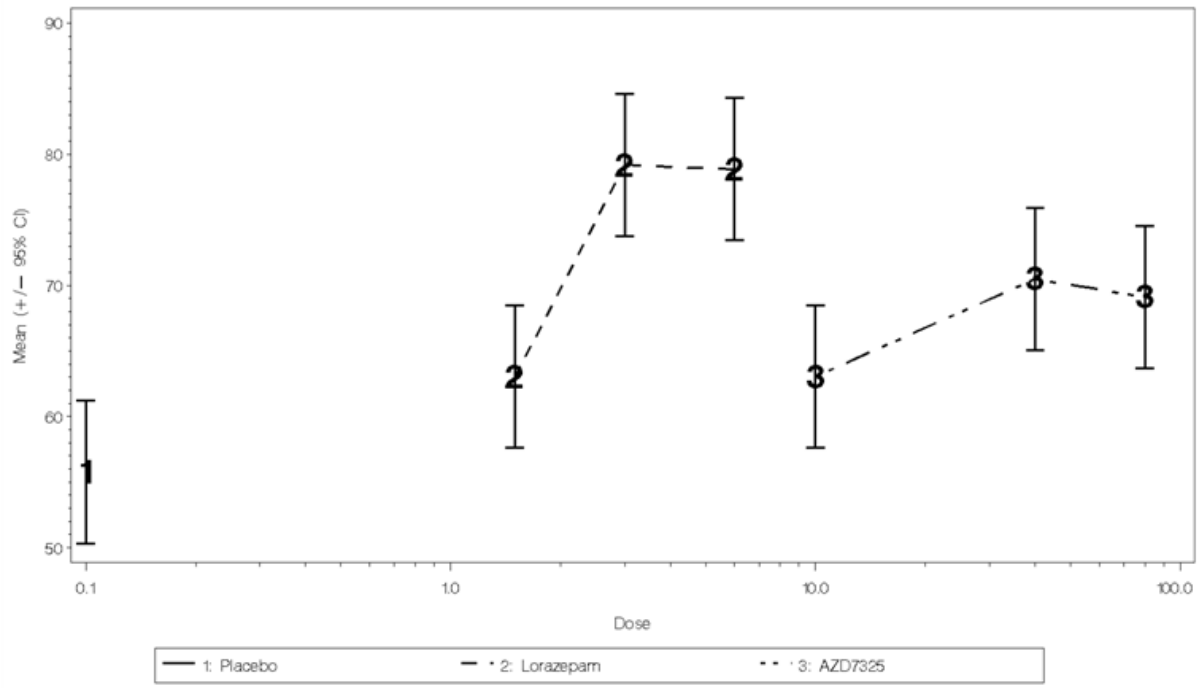
ANOVA Analysis of variance; AZD AZD7325; CI Confidence interval; E_{max} Maximum effect; LPM Lorazepam; LS Least squares; SE Standard error; VAS Visual analogue scale.

The secondary outcome measures showed a pattern of effects generally consistent with the primary endpoint and the more transient effects of AZD7325. Many of the significant differences between lorazepam and AZD7325 were observed in the time-weighted mean (TW_{mean}) values (eg, mean effect over timecourse). The results suggest a lower overall effect of AZD7325, which was supported by the lower effects of AZD7325 on the global/reflective measures (end of day/next-day measures of balance of effects, eg, Overall Drug Liking VAS). Although negative effects ('at this moment') were not noticeably different between AZD7325 and lorazepam, the lower E_{min} values on the Drug Liking VAS associated with AZD7325 suggest that, on balance, it was more 'disliked' than lorazepam.

AZD7325 did not significantly impair cognitive or psychomotor performance in this study, even at doses up to 8-times the proposed therapeutic dose (10 mg). In contrast, lorazepam showed significant and dose-related impairment on most cognitive and psychomotor endpoints. Subjects did report significant subjective sedation with AZD7325 with peak effects similar to that of lorazepam (although with a different timecourse). In addition, subjects perceived that their performance/attention was decreased with AZD7325, although there was no evidence of impairment in performance or attention on the objective performance measures. On manual tracking variables (furthest diagonal distance, percentage over road and RMS distance), there were clear dose-related decreases in performance with lorazepam, while AZD7325 showed little or no effect on these variables.

The dose-effect relationship for AZD7325 appeared to be shallower than for lorazepam on the primary endpoint (see Figure S 2). These results also indicate that for both lorazepam and AZD7325, the full range of doses with potential for abuse was adequately explored.

Figure S 2 Log dose effect graph for Drug Liking VAS E_{max} (pharmacodynamic analysis set)



Drug Liking VAS item: "At this moment, my liking for this drug is", where values can range from 0 (strong disliking) to 100 (strong liking) and 50 is the neutral (no drug effect) point.
CI Confidence interval; E_{max} Maximum effect; VAS Visual analogue scale.

The dose-effect relationships with the balance effects and some of the positive effects variables were consistent with those of the primary endpoint. For other variables, in particular High VAS, ARCI PCAG, and Any Effects VAS, the dose-effect relationships were similar between lorazepam and AZD7325. The comparable responses on the Any Effects VAS

confirm that adequately high AZD7325 doses were used in the study, and further support the hypothesis that AZD7325 has intrinsically different abuse potential than lorazepam, since for a similar degree of 'any effects', AZD7325 was less 'liked'.

Overall, AZD7325 showed significant abuse potential compared to placebo, but less than that of lorazepam. Maximum drug liking and other abuse-related positive/balance effects for AZD7325 were observed at doses 4- and 8-fold higher than the proposed therapeutic dose and were generally lower than the maximum effects observed for lorazepam. The effects of AZD7325 10 mg were minimal.

Summary of safety results

There were no deaths or other serious adverse events in the study. Four healthy volunteers discontinued due to AEs: 1 due to mild elevated AST and ALT following a 10 mg dose of AZD7325, 1 due to mild visual impairment following a 40 mg dose of AZD7325, 1 due to moderate otitis external (treatment listed as 'missing'), and 1 due to mild arrhythmia following a 1.5 mg dose of lorazepam. The proportion (n/N [%]) of volunteers for whom AEs were reported following each treatment was as follows: 12/34 (35.3%) for placebo, 22/32 (68.8%) for lorazepam 1.5 mg, 28/31 (90.3%) for lorazepam 3 mg, 29/29 (100.0%) for lorazepam 6 mg, 17/30 (56.7%) for AZD7325 10 mg, 26/32 (81.3%) for AZD7325 40 mg, and 27/33 (81.8%) for AZD7325 80 mg. The individual AEs with the highest incidence were somnolence (15% for placebo, 60% to 97% for lorazepam, and 20% to 34% for AZD7325), euphoric mood (0% for placebo, 7% to 10% for lorazepam, and 27% to 44% for AZD7325), and dizziness (0% for placebo, 3% to 7% for lorazepam, and 10% to 21% for AZD7325).

There were no reports of suicidal behavior or ideation during the study, nor any clinically relevant treatment-related changes or trends in any laboratory, vital signs, or ECG variables.