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ORIGINAL ARTICLE

# A first-in-man phase I tolerability and pharmacokinetic study of the cyclin-dependent kinase-inhibitor AZD5438 in healthy male volunteers

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**Abstract** AZD5438 is a novel cyclin-dependent kinase inhibitor with preclinical pharmacodynamic (PD) activity against a range of human tumour xenografts. A first-in-man tolerability and pharmacokinetic (PK) study involving single ascending doses of AZD5438 was conducted in healthy male volunteers. Single oral doses ranging from 5 to 160 mg were studied in 23 subjects. Dose-limiting nausea and vomiting occurred at 160 mg in the absence of prophylactic anti-emetics. The maximum tolerated dose (the dose at which no dose limiting toxicities occurred) was 80 mg, and the maximum well-tolerated dose was deemed to be 60 mg, which was associated with grade1 nausea but no vomiting. $T_{max}$ occurred between 0.5–3.0 hours with a relatively short plasma half-life of 1–3 h. The coefficient of variation of exposures within a dose level ranged from 22–71% (AUC) to 16–63% ($C_{max}$), and exposure increased with increasing dose across the doses studied. <1% of the parent compound was excreted in the urine, suggesting metabolism as the major clearance mechanism. The maximum well-tolerated dose and a number of doses below this level will be taken forward into a PD study using normal tissue biomarkers in humans to determine proof of AZD5438's action on the cell cycle. The pharmacokinetic profile of AZD5438 determined within this study will be used to guide the time-points for PD analysis within the planned PD study.

**Keywords** Cell cycle · AZD5438 · CDK · Pharmacokinetics · Tolerability

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**Abbreviations**

| | |
|---|---|
| CPU | Clinical pharmacology unit |
| UK | United Kingdom |
| mg | Milligram |
| kg | Kilogram |
| mL | Millilitre |
| DLT | Dose limiting toxicity |
| SMC | Safety monitoring committee |
| MWTD | Maximum well-tolerated dose |

## Introduction

Normal cell division is regulated by many signals integrated together into the cell cycle. Two dominant groups of molecules, cyclins and their associated

cyclin-dependent kinases (CDKs), control these signals. Genetic and immunohistochemical profiling of tumour tissues has identified several components of the CDK signalling pathway that are altered in cancer [5–7, 9, 10, 13]. Cyclins and phosphatases that activate the CDKs may be amplified and/or over-expressed in tumours, and the concomitant inhibitor proteins may be reduced in amount or activity.

The development of inhibitors that target key CDKs as the focus of therapeutic strategies for the treatment of a wide range of tumours has been aggressively pursued for a number of years [1, 3]. The "first generation" agents such as Alvocidib (flavopiridol; Aventis-NCI) and seliciclib (CYC-202, (*R*)-Roscovitine; Cyclacel) have, despite initial promise pre-clinically, tended to lack clinical efficacy [3, 4, 11]. AstraZeneca has recently developed the small-molecule CDK-inhibitor, AZD5438 (Fig. 1), for use in the clinic as an anti-tumour agent [14].

Preclinical pharmacology of AZD5438 (Byth et al, manuscript in preparation) has shown that the molecule in vitro behaves as a potent inhibitor of the human cyclin E/CDK2 complex ($IC_{50}$ 0.006 μM), the cyclin B1/CDK1 complex ($IC_{50}$ 0.016 μM), and the cyclin A/CDK2 complex ($IC_{50}$ 0.045 μM). In vivo experiments (Wilkinson et al., manuscript in preparation) have shown 40–95% growth inhibition across a wide range of human tumour xenografts, with a clear dose-response to compound. Tumour volume effects in both rat and mouse xenograft models were closely associated with duration of exposure above a threshold free drug level, in addition to pharmacodynamic evidence of inhibition of phosphorylation of cellular substrates of CDK2 in the tumours, and effects on progression of cells through the cell cycle.

We conducted a first-in-man study to address the tolerability and pharmacokinetics of ascending single oral doses of AZD5438 in healthy male volunteers.

## Subjects and methods

### Preclinical toxicology

Toxicology studies up to 1 month in duration have been conducted in rats and dogs, in addition to conventional genetic toxicology and safety pharmacology studies. In rats (five per sex per group), 67 μmol/kg/day over 15 days was not tolerated with two mortalities at day 5 and significant reduction in food consumption in the other animals prior to termination. Rats dosed at 40 μmol/kg/day demonstrated a 20–40% reduction in food intake but no change in body weight during the 15 day study. The major histological findings at 40 and 67 μmol/kg/day were of increased apoptosis and necrosis in the bone marrow and lymphoreticular system, irritation of the gastrointestinal tract and inflammation of the synovial joints and tendons. Dosing up to 30 μmol/kg/day for 1 month produced no clear treatment related changes during the live phase and only splenic extramedullary hemopoesis histologically. These changes were reversible during a 1 month recovery period. Adverse events at 26.9 μmol/kg/day for 1 month in dogs were emesis, decreased appetite and weight loss. There were minor changes in haematological and liver function parameters, and histopathological changes in the adrenal gland, thymus, liver, small intestine and stomach all of which showed evidence of reversibility during a 1 month recovery period. There was no genetic toxicological liability from either in vivo (rat micronucleus assay) or in vitro (Ames test and mouse lymphoma assay) studies.

With appropriate safety scaling (http://www.fda.gov/cber/gdlns/dose.htm), these preclinical studies suggested that dosing of AZD5438 to healthy human volunteer subjects would be permissible. To maximise the safety margins within the healthy volunteer study, however, a free drug $C_{max}$ of 100 ng/ml AZD5438 (based on an estimated human plasma protein binding of 85.8%), was set as a predefined PK stopping limit in the healthy volunteer study based on the level below which serious symptomatic preclinical toxicities did not occur. This predefined upper limit of free drug exposure was within the range at which pharmacodynamic activity of AZD5438 was noted during preclinical in vitro and in vivo studies (Byth et al., Wilkinson et al., manuscripts in preparation).

### Study overview and healthy volunteer recruitment

A randomised, placebo-controlled, double blind healthy volunteer study was conducted in the United Kingdom (UK) in full accordance with the Declaration of Helsinki and the International Committee on Harmonisation's guidelines on Good Clinical Practice. Subjects gave their written informed consent prior to any study procedure being performed. All study protocols, amendments and informed consent forms were approved in writing by an independent ethics committee.

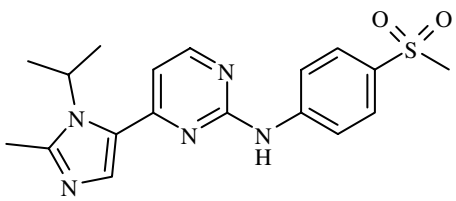


**Fig. 1** Structure of AZD5438

Study specific inclusion criteria included a body mass index between 18 and 30 kg/m$^2$, normal medical history, physical examination, routine blood tests and resting 12 lead ECG, as well as negative screens for serum Hepatitis B sAg, Anti-Hepatitis C antibody and anti-HIV antibody. Specific exclusion criteria included the use of any prescribed, non-prescribed or herbal medications (with the exception of paracetamol within the recommended daily dosage) within 3 weeks of the first dose of study drug, or receipt of another new chemical entity during the preceding 4 months. Study specific restrictions included abstinence from consuming grapefruit, liquorice, cruciferous vegetables, alcohol or high caffeine-containing foods/drinks for 24–72 h before and after each dose of study drug, and abstinence from any concomitant medication or therapy (except paracetamol), unless deemed necessary by the study physician.

## Drug supply and administration

AZD5438 was supplied by AstraZeneca Investigational Products (Macclesfield, UK) in 2.5, 20 and 100 mg tablets, with matching placebos. AZD5438/placebo tablet(s) were administered orally in the semi-recumbent position with 240 ml of still mineral water.

## Safety, tolerability and pharmacokinetics

The study was designed as an alternating-panel, rotating placebo design using three cohorts of eight volunteers. On study days, within each cohort, six volunteers were randomised to receive the same single fixed oral dose of AZD5438 and two randomised to placebo. Volunteers were resident for at least 48 h after dosing. Heart rate, blood pressure and ECGs (three per time point) were performed pre-dose and 1, 3, 8, 24, 48 and 72 h post-dosing. Adverse event reporting and blood samples for AZD5438 pharmacokinetic (PK) analysis were collected pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 120, 144 and 240 h post-dosing. A different cohort attended the Clinical Pharmacology Unit (CPU) to receive AZD5438 at the next dose level (or placebo) each week. Cohorts underwent a minimum 3-week washout period before repeat dosing. Venous blood samples (1.2 ml) for PK analysis were collected into tubes containing lithium heparin anticoagulant, labelled, mixed and then centrifuged at 1,500*g* for 10 min. Plasma was decanted and transferred to individually labelled tubes and stored at −80°C, within 30 min of collection, until analysis. Following the analysis of PK data from the earlier dose levels, PK samples were not taken beyond 24 h post-dosing at the last two dose levels tested (160 and 60 mg). Immediately before dosing the bladder was voided (pre-dose sample), thereafter all urine passed was collected into a single container until 24 h post-dose. During collection the bulk sample was stored at 4°C. At the end of the collection period, following mixing, sub-samples of 20 ml of both the pre- and post-dose urine were transferred to clean labelled tubes and stored at −80°C until analysis. AZD5438 drug concentrations in plasma (AstraZeneca DMPK, Alderley Park, Cheshire, UK) and urine (CentreLabs Clinical Research, Alconbury, Cambridgeshire, UK) were determined by high-performance liquid chromatography with tandem mass-spectrometric detection.

From allometric scaling methods based on body surface area, the human equivalent of the minimal-effect dose level from rat and dog 14-day exposure studies was 30 and 40 mg/m$^2$, respectively. Utilising a tenfold safety-scaling factor, the starting dose of AZD5438 in humans was calculated at between 4.8 and 6.4 mg, with 5 mg chosen in practice. Initial planned dose escalations were to be 10, 20, 40, 80, 160, 300, 600 and 1,000 mg, pending emerging safety, tolerability and pharmacokinetic data.

Any adverse events reported by the subjects were graded according to the National Cancer Institute Common Terminology Criteria (CTC) Version 3, March 2003 and followed up until resolution, or until the investigator considered the event would not improve, or for 30 days if not considered treatment related. Supportive interventions to ameliorate toxicities were permitted, but prophylactic measures were not. A safety monitoring committee (SMC) reviewed all available exposure, safety and tolerability data before making a decision on each dose escalation. Unblinding was only to occur in the event that this information was critical for managing adverse events. Dose escalation was not to proceed if any of the following occurred: Escalation would produce an estimated mean free drug $C_{max}$ of $\geq$100 ng/ml; $\geq$2 volunteers administered AZD5438 in any cohort experienced either a pre-specified dose limiting toxicity (DLT), or an increase in QTc interval from baseline of >60 ms, or an absolute value >500 ms with no corresponding change in placebo-treated volunteers; or in the view of the SMC there was any other unacceptable toxicity.

Pre-specified DLTs were based on the preclinical toxicity profile of AZD5438 and on the toxicities seen with other CDK inhibitors in the clinic, notably gastrointestinal disturbance and myelosuppression. The pre-specified DLTs were maximum observed CTC grades $\geq$2 for nausea, vomiting or diarrhoea; Hb < 115 or reduction in baseline >20 g/l; white cell count

$<3.0 \times 10^9$/l; neutrophil count $< 1.5 \times 10^9$/l or platelet count $<100 \times 10^9$/l; increase in AST, ALT or alkaline phosphatase ≥3 times the upper limit of normal (ULN) or increase in bilirubin of ≥1.5 times the ULN on ≥2 occasions following a single dose of AZD5438; consistent increase in AST, ALT or ALP ≥2 times the ULN (1.5 times ULN for bilirubin) at two dose levels.

Safety, tolerability and pharmacokinetic data were summarised for each dose level. Pharmacokinetic parameters were assessed using standard non-compartmental analysis. No formal statistical analyses were undertaken.

## Results

In total, 23 volunteers with a mean age of 35.4 years (range 20–47) and a mean height and weight of 178.7 cm (range 164–192) and 81.3 kg (range 61–105), respectively were randomised and treated (cohort 1 $n = 8$, cohort 2 $n = 8$, cohort 3 $n = 7$). Eight subjects were initially enrolled into cohort 3, however one patient could not attend the scheduled visits. There were no major protocol deviations.

Dose escalations occurred as planned with the top dose of AZD5438 investigated being 160 mg (cohort 3), at which two volunteers experienced gastrointestinal DLTs (nausea, vomiting and abdominal pain) (Fig. 2**)**. An additional lower dose level (60 mg) was subsequently explored in cohort 1 to better define the threshold for symptomatic toxicity. From cohort 1, two volunteers were discontinued following the 40 mg dosing day. In one instance this was due to a marginally decreased white blood cell/neutrophil count with nadirs of $2.83 \times 10^9$/l and $1.49 \times 10^9$/l, respectively noted 10 days after dosing with 40 mg AZD5438. The neutrophil count had fully recovered within 5 days and the white blood cell count had almost fully recovered ($3.47 \times 10^9$/l) by the same stage with full recovery of both counts noted by 26 days post-dosing. In the other instance, discontinuation was due to an ear infection in a volunteer dosed with placebo. In total 20 of the 23

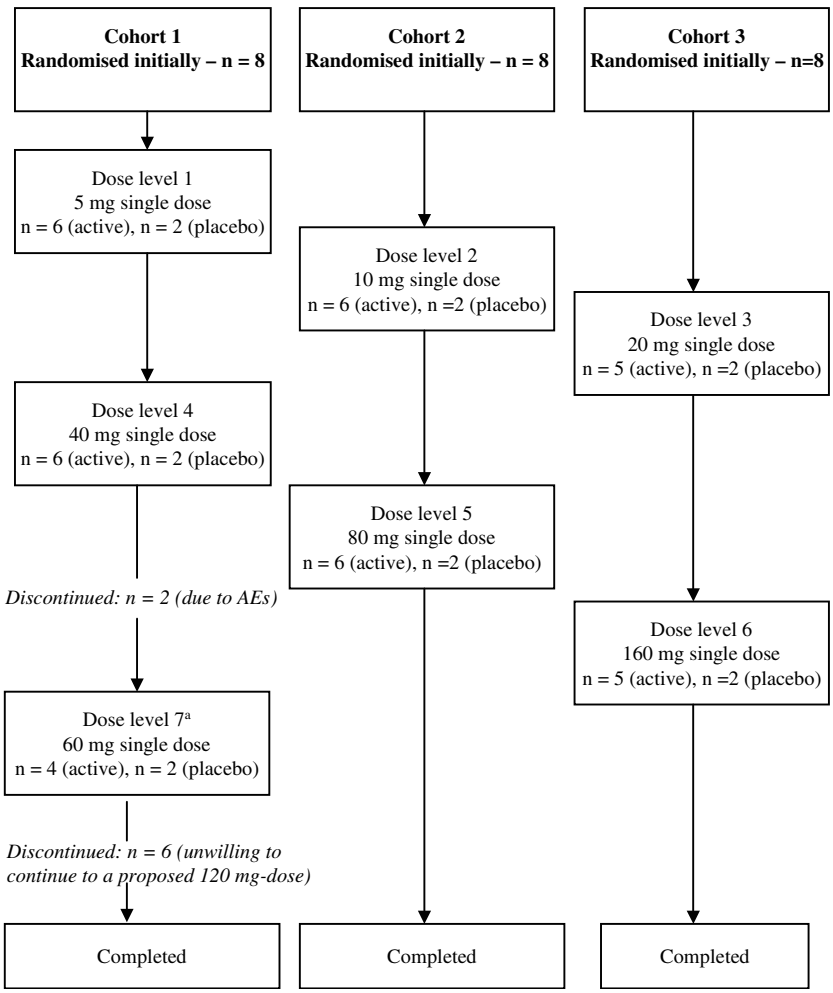


**Fig. 2** Flow chart showing volunteer disposition during study. In all cases *n* refers to the number of subjects

volunteers experienced adverse events, with the majority being reported by only a single volunteer and at CTC grade 1. In the opinion of the investigators, prior to unblinding, 17 of the volunteers experienced adverse events that had a reasonable possibility of being related to AZD5438. Full details of the adverse events considered possibly drug-related experienced by the volunteers are shown in Table 1. The most common toxicities occurred within the gastrointestinal system and were nausea, vomiting and diarrhoea. The maximum tolerated dose (the dose at which no DLTs occurred) was 80 mg, and the MWTD was deemed to be 60 mg, which was associated with grade 1 nausea but no vomiting.

There was no evidence of myelosuppression over the 5–160 mg dose range, beyond the single volunteer with the marginally low white cell count at the 40 mg dose level already described. Furthermore, there were no clinically important findings relating to other safety laboratory parameters, physical examination, vital signs or ECG parameters, with the exception of discernible but non-clinically significant QTc increases (Bazett's correction) at the non-tolerated 160 mg dose level. No volunteer had a QTc interval >500 ms or an

**Table 1** Timing of onset, duration and maximum CTC grade of adverse events considered to be drug-related (prior to unblinding) by dose

| AZD5438 dose | Volunteer identifier | Adverse event | Maximum CTC grade | Onset post-dose | Duration |
|---|---|---|---|---|---|
| Placebo ($n$ = 14) | H (60 mg) | Headache | 1 | 52 h 55 min | 10 h |
| | I (60 mg) | Dizziness | 1 | 1 h 10 min | 5 min |
| | | Headache | 1 | 1 h 10 min | 5 min |
| | B (160 mg) | Headache | 1 | 35 days | 3 h |
| 5 mg ($n$ = 6) | A | Pruritic rash | 2 | 10 h 50 min | 12 h |
| 20 mg ($n$ = 5) | B | Erythematous rash | 1 | 3 h 6 min | 14 min |
| 40 mg ($n$ = 6) | C | Leucopenia/neutropenia | 2 | 10 days | 26 days |
| | D | Nausea | 1 | 59 min | 1 h 4 min |
| | E | Nausea | 1 | 55 min | 2 h 10 min |
| 60 mg ($n$ = 4) | F | Nausea | 1 | 1 h 45 min | 20 min |
| | D | Dizziness | 1 | 1 h 26 min | 10 min |
| | | Nausea | 1 | 1 h 15 min | 55 min |
| | E | Nausea | 1 | 1 h 15 min | 30 min |
| | | Dyspepsia | 1 | 23 h 45 min | <24 h |
| | G | Nausea | 1 | 1 h 5 min | 2 h 45 min |
| 80 mg ($n$ = 6) | J | Headache | 1 | 1 h 27 min | 3 h 13 min |
| | | Vomiting | 1 | 2 h 20 min | 5 min |
| | | Nausea | 1 | 1 h 14 min | 3 h 11 min |
| | K | Vomiting | 2 | 1 h 10 min | 2 h 10 min |
| | | Nausea | 1 | 1 h 10 min | 3 h 20 min |
| | L | Nausea | 1 | 45 min | 1 h 30 min |
| | | Vomiting | 1 | 1 h 35 min | 10 min |
| | M | Nausea | 1 | 2 h | 4 h 2 min |
| | N | Vomiting | 2 | 1 h 33 min | 7 min |
| | | Nausea | 1 | 55 min | 3 h 5 min |
| 160 mg ($n$=5) | O | Nausea | 1 | 1 h 10 min | 3 h 15 min |
| | | Diarrhoea | 1 | 2 h 22 min | 7 h 33 min |
| | P | Nausea | 2 | 1 h 4 min | 4 h 26 min |
| | | Vomiting | 3 | 1 h 4 min | 2 h 46 min |
| | Q | Vomiting | 1 | 2 h 2 min | 8 min |
| | | Nausea | 1 | 50 min | 3 h 20 min |
| | | Abdominal pain | 1 | 1 h 40 min | 10 min |
| | | Diarrhoea | 1 | 1 h 40 min | <24 h |
| | R | Nausea | 1 | 1 h 10 min | 2 h 50 min |
| | | Vomiting | 2 | 1 h 10 min | 1 h 36 min |
| | S | Diarrhoea | 1 | 1 h 10 min | <24 h |
| | | Nausea | 2 | 43 min | 12 h 52 min |
| | | Vomiting | 2 | 4 h 18 min | 4 h 17 min |
| | | Abdominal pain | 2 | 4 h 18 min | 8 h 17 min |
| | | Dizziness | 1 | 1 h 22 min | 8 h 13 min |

No subjects at 10 mg AZD5438 experienced adverse events considered possibly drug-related

$n$ number of subjects receiving placebo or AZD5438

increase in QTc interval from baseline >60 ms at any dose. Up to 80 mg no clinically important mean increases in QTc from baseline were seen with AZD5438 (any mean increases were <10 ms). However, at 160 mg mean increases in the dose cohort up to 30.4 ms were seen with AZD5438.

Following single oral doses, quantifiable plasma concentrations were detectable at all dose levels indicating human oral bioavailability. Absorption was rapid with $t_{max}$ occurring 0.5–3 h post-dosing, independently of dose. After attainment of the $C_{max}$, concentrations fell rapidly to, or below, the limit of quantification of the assay (0.501 ng/ml) 12–24 h post-dosing. The half-life of 1–3 h was also largely dose-independent. Individual exposures ($C_{max}$ and AUC) increased with increasing dose. The coefficient of variation of exposures within a dose level ranged from 22–71% (AUC) to 16–63% ($C_{max}$). Summary pharmacokinetic data are presented in Table 2. The geometric mean plasma concentration–time profiles of AZD5438 are shown in Fig. 3. At all dose levels the mean percentage of the dose excreted unchanged in the urine was low (range 0.551–0.956%) indicating limited renal excretion of the parent compound and appeared to be dose-independent.

## Discussion

AZD5438 is a novel CDK inhibitor. It has preclinical evidence of activity against cyclin E/CDK2, cyclin B1/CDK1 and cyclin A/CDK2 complexes in vitro and evidence of xenograft growth inhibition and reduction in phosphorylation of pRb, the cellular substrate of CDK2, in vivo (Byth et al., Wilkinson et al., manuscripts in preparation).

It is orally bioavailable in man (Table 2; Fig. 3), with a rapid $T_{max}$ and a relatively short plasma $t_{1/2}$ following single oral dosing. Parameters of exposure increased with dose and across the dose range studied, although there was a trend towards a slightly greater than proportional increase in exposure, there was no evidence to conclude significant non-linearity. Total apparent drug clearance (CL/F) showed a trend towards a slight decrease with increasing dose which could be a consequence of a true change in clearance or of a change in the bioavailability of the oral formulation as adminsitered dose increased. Clearance is most likely to occur predominantly through metabolism. Urinary excretion of the unchanged compound was <1%. In the absence of prophylactic supportive measures, tolerability was

**Table 2** Plasma pharmacokinetic parameters of AZD5438 following single oral doses

| Parameters (units) | Statistic | AZD5438 dose (mg) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 20 | 40 | 60 | 80 | 160 |
| $C_{max}$ (ng/ml) | gmean | 7.893 | 29.08 | 52.56 | 121.4 | 300.7 | 292.5 | 608.8 |
| | (CV%) | (48.68) | (22.71) | (62.63) | (37.75) | (22.31) | (45.80) | (15.89) |
| | *n* | 6 | 6 | 5 | 6 | 4 | 6 | 5 |
| $t_{max}$ (h) | Median | 1.75 | 1.50 | 1.00 | 1.50 | 1.50 | 1.25 | 1.00 |
| | (Range) | (1.00–3.00) | (0.50–2.00) | (0.50–1.50) | (1.00–3.00) | (1.00–3.00) | (1.00–2.00) | (0.50–1.50) |
| | *n* | 6 | 6 | 5 | 6 | 4 | 6 | 5 |
| $AUC_{(0\text{-}t)}$ (ng h/ml) | gmean | 22.86 | 76.05 | 146.1 | 336.4 | 961.2 | 911.5 | 2,418 |
| | (CV%) | (62.79) | (34.09) | (55.24) | (40.27) | (21.81) | (71.48) | (51.23) |
| | *n* | 6 | 6 | 5 | 6 | 4 | 6 | 5 |
| AUC (ng h/ml) | gmean | 27.69 | 78.33 | 149.0 | 342.0 | 971.2 | 915.8 | 2,422 |
| | (CV%) | (59.28) | (34.40) | (54.85) | (41.07) | (21.67) | (71.21) | (51.23) |
| | *n* | 5 | 6 | 5 | 6 | 4 | 6 | 5 |
| $t_{½}$ (h) | Mean[a] | 1.741 | 1.640 | 1.806 | 1.810 | 2.057 | 2.080 | 2.196 |
| | (SD) | (0.294) | (0.426) | (0.281) | (0.258) | (0.627) | (0.619) | (0.492) |
| | *n* | 5 | 6 | 5 | 6 | 4 | 6 | 5 |
| CL/F (L/h) | gmean | 180.6 | 127.7 | 134.2 | 116.9 | 61.78 | 87.35 | 66.06 |
| | (CV%) | (59.28) | (34.40) | (54.85) | (41.07) | (21.67) | (71.21) | (51.23) |
| | *n* | 5 | 6 | 5 | 6 | 4 | 6 | 5 |
| $V_{ss}/F$ (L) | Mean[a] | 737.3 | 393.5 | 451.4 | 413.1 | 231.7 | 338.3 | 260.9 |
| | (SD) | (387.1) | (77.48) | (170.4) | (158.9) | (15.71) | (147.1) | (34.31) |
| | *n* | 5 | 6 | 5 | 6 | 4 | 6 | 5 |

AUC: area under the plasma concentration–time curve from zero to infinity, $AUC_{(0\text{-}t)}$: area under the plasma concentration–time curve from zero to the time of the last quantifiable concentration, CL/F: total apparent drug clearance, $C_{max}$: maximum plasma drug concentration, CV%: coefficient of variation expressed as a percent of the gmean, gmean: geometric mean, *n*: number of observations, SD: standard deviation, $t_{½}$: terminal half-life, $t_{max}$: time to $C_{max}$, $V_{ss}/F$: apparent volume of distribution at steady-state

[a] Arithmetic mean (arithmetic mean and SD calculated using untransformed data)

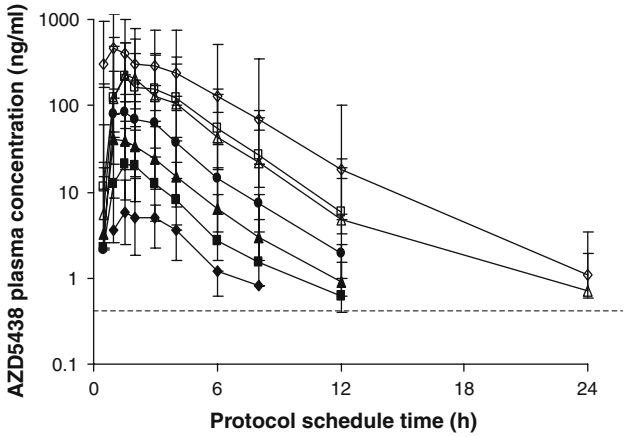


**Fig. 3** Pharmacokinetic profile following oral administration of AZD5438. Plasma concentrations of AZD5438 were determined before dosing and up to 24 h following single oral administrations of AZD5438 at 5 (*filled diamond*), 10 (*filled square*), 20 (*filled triangle*), 40 (*filled circle*); 60 (*open square*);80 (*open triangle*) and 160 mg (*open diamond*). Limit of quantification was 0.501 ng/ml (shown by *dotted line*). *Each point* represents the mean (± standard deviation) plasma concentration at each time point. Geometric mean values were not calculated where more than 50% of values were not quantifiable

limited by gastro-intestinal side-effects, with 80 mg being the maximum tolerated dose and 60 mg being the maximum well-tolerated dose achieved (Table 1). The side-effect profiles of other cell cycle inhibitors trialled in cancer patients, the majority of which have been administered intravenously, have often been dominated by gastrointestinal toxicity and myelosuppression suggesting that, some or all of these may represent class effects [1–4, 12].

The timing of the peak side-effects with AZD5438 fitted with the symptoms being $C_{max}$ related in terms of both onset and offset (Tables 1, 2; Fig. 3). Of note, the estimated free drug $C_{max}$ of AZD5438 at the non-tolerated 160 mg, was 87.2 ng/ml (based on an estimated human plasma protein binding of 85.8%), close to the predefined PK stopping limit of 100 ng/ml derived from preclinical toxicokinetic data.

Although there were discernible QTc effects with AZD5438 at the 160 mg dose, these did not reach clinical significance and the impact of autonomic effects on the QTc interval secondary to any gastrointestinal symptoms occurring in the volunteers at the time cannot be excluded.

The described approach of utilising healthy volunteers unencumbered by the cancer disease process, its complications or its treatment allowed a human pharmacokinetic profile for AZD5438, along with tolerability data, to be generated within a short number of months. Following the determination of pharmacokinetic and tolerability data on AZD5438 in man for the first time, this information will be used to determine the doses employed and the timing of the assessments made within a subsequent pharmacodynamic study in healthy volunteers in order to establish proof of AZD5438's action on a downstream biomarker of CDK-inhibition within normal tissues.

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