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A Phase I, Randomised, Open-label, 2-Way Crossover Study to Assess the Effect of ZD1839 (IRESSA™) on the Anticoagulant Properties and Pharmacokinetics of Warfarin in Healthy Male Subjects

Principal investigator

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Study centre

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Study dates		**Phase of development**
First volunteer enrolled	23 July 2003	Clinical pharmacology (I)
Last volunteer completed	12 September 2003	
Date of premature study termination	23 August 2003	

Study design and objectives

According to the protocolled design, this was to be a randomised, open-label, single-centre, 2-way crossover Phase I study consisting of 2 treatment periods (A and B). In Period A, volunteers were to be randomised to receive either:

- ZD1839 250 mg as a single daily oral dose for 15 consecutive days, with a single dose of 20 mg warfarin sodium co-administered on Day 9
- single oral dose of 20 mg warfarin sodium on Day 9

In Period B, after a minimum washout of 21 days, volunteers were to be crossed over to the treatment not received in Period A. However, this study was terminated before Period B, because of tolerability issues.

The objectives of this study are given in Table S1, along with their associated variables.

Table S1 Objectives of the study, and related variables

Objectives	Variables
Primary	**Primary**
To assess the effect of steady-state concentrations of ZD1839 on the anti-coagulant properties of warfarin	**Primary variables:** International Normalized Ratio (INR) following the warfarin dose, summarised by maximum INR (INR_{max}) and area under INR-time curve from 0 to 168 h ($AUC_{(0–168)}$)
	Supportive 'secondary' variables, determined after the warfarin dose: Time to INR_{max} (INR t_{max}) aPTT, summarised by $aPTT_{max}$, aPTT t_{max}, and aPTT $AUC_{(0-168)}$. Concentrations of Factor VII, summarised by Factor VII_{max}, Factor VII t_{max}, and Factor VII $AUC_{(0-168)}$
Secondary	**Secondary**
To assess the effect of steady state concentrations of ZD1839 on the pharmacokinetic properties of warfarin	R- and S-warfarin C_{max}, $t_{max,}$ AUC, $AUC_{(0-t)}$, $t_{½}$, λ_z and CL/f Free (ie, unbound) R- and S-warfarin plasma concentrations at 1, 2, 3, and 5 h post-dose
To confirm the attainment of steady-state plasma levels of ZD1839 on Study Day 8	Trough levels ($C_{ss,min}$) of ZD1839 throughout the ZD1839 dosing period
To assess any effect of steady state dosing with 250 mg of ZD1839 on clotting parameters in man	INR, aPTT, Factor VII, and Vitamin K levels in the presence and absence of steady state ZD1839 on Day 8 of each dosing period
To assess the steady state pharmacokinetics of ZD1839 in healthy subjects	ZD1839 $C_{ss,max}$, ZD1839 t_{max}, and ZD1839 AUC_{ss} on Day 9
To assess the tolerability of multiple dosing of ZD1839 in healthy subjects	Adverse events, blood pressure and heart rate, 12-lead electrocardiogram, clinical chemistry, haematology and urinalysis

aPTT Activated partial prothrombin time.
$AUC_{(0-168)}$ Area under the response-time curve from 0 to 168 h.
t_{max} Time to reach peak or maximum concentration or maximum response following drug administration.

Target subject population and sample size

Eighteen healthy male volunteers aged between 18 and 60 years. The sample size was based on the numbers required for the planned statistical analysis of the primary variables.
Key inclusion criterion: INR, Factor VII, and aPTT within normal reference ranges.
Key exclusion criteria: receipt of aspirin or drugs known to affect the clotting mechanism ≤2 weeks before study start; receipt of drugs (given for ≥1 month) known to be associated with interstitial lung disease (ILD) within 6 months before study start; definite or suspected personal or family history of significant adverse drug reactions, or hypersensitivity to drugs with similar chemical structure to ZD1839, or warfarin or related anticoagulants; donation or receipt of blood products ≤3 months before screening; currently receiving or taken in past 4 weeks, any treatment that modifies gastric pH; treatment within previous 6 weeks with drugs known to induce or inhibit CYP450 isoenzymes involved in warfarin metabolism; treatment within previous 6 weeks with drugs known to inhibit or induce CYP3A4; poor CYP2C9 metabolisers; personal or family history of actual or suspected bleeding disorder; evidence of faecal occult blood at screening; vegetarians or vegans; previous history of gastrointestinal bleeding or peptic ulceration, or history of significant dyspepsia within past 2 years; previous history of idiopathic pulmonary fibrosis, sarcoidosis, cryptogenic or extrinsic allergic alveolitis, childhood asthma, or connective tissue disorders; resting ECG with QTc interval

>440 msec; history of thrombosis; volunteers who had travelled from the Far East or Toronto (Canada) ≤2 weeks before screening or who had been in contact with a person with viral pneumonia ≤2 weeks before screening.

Study treatment: dosage, mode of administration, and batch number

ZD1839 250 mg was given as 1 x 250 mg tablet (formulation number F12653; batch number P/4005/03); warfarin sodium was given as a single 20 mg oral dose (4 x 5 mg tablets).

Duration of treatment

Each volunteer was to receive a total of 15 single oral doses of ZD1839 250 mg and 2 single oral doses of warfarin sodium 20 mg, and was to be involved in the study for ~9 weeks. Volunteers on the 'ZD1839 + warfarin' arm were to remain resident in the GDRU from the morning before the first ZD1839 dose (ie, Day –1) until Day 17 (48 h after the last dose of ZD1839). Volunteers on the 'warfarin only' arm were to remain in the GDRU from the morning before their full pharmacodynamic screen (Day 7) until Day 12 (72 h after the warfarin dose).

Statistical methods

This study was terminated early; therefore no formal statistical analysis was performed.

Study population

Eighteen healthy male volunteers (mean age 26.3 years [range: 18 to 42 years], mean weight 76.6 kg [range: 63 to 89 kg]) were recruited. One volunteer was Black, 17 were Caucasian.

Owing to a misinterpretation of the study protocol, volunteers were not allocated to study treatment according to a random scheme. Instead, for Period A, the first 9 volunteers that were enrolled were allocated to ZD1839 + warfarin, and the following 9 were allocated to warfarin alone. However, an agreement was made between AstraZeneca and GRDU to continue with the study using GRDU's interpretation of allocation to treatment. The study was terminated prematurely because of tolerability issues with multiple dosing of ZD1839 250 mg, in accordance with the stopping criteria specified in the protocol; therefore, the study did not proceed to Period B.

Summary of pharmacodynamic results

As a consequence of the early termination of this study, the 2 treatments (ie, warfarin alone and warfarin + ZD1839) were given to separate groups of volunteers, and hence a meaningful comparison of the pharmacokinetic and pharmacodynamic data between the 2 treatment groups was not possible, particularly given the previously recognised wide inter-individual variations in pharmacodynamic effects associated with warfarin treatment.

Summary of pharmacokinetic results

Evaluation of the C_{min} data for the 7 volunteers who received ZD1839 250 mg to at least Day 9 showed that steady state exposure was achieved within 8 days of starting dosing. The

inter-individual variability in measures of steady state exposures seen in this study was consistent with the variability seen previously for ZD1839 in both healthy volunteers and cancer patients. The steady state plasma pharmacokinetic parameters of ZD1839 on Day 9 are summarised in Table S2.

Table S2 Steady state plasma pharmacokinetic parameters of ZD1839 (Day 9)

Parameter (units)	Summary statistic	ZD1839 250 mg + warfarin 20 mg (n=7)
AUC_{ss} (ng.h/mL)	Geometric mean (CV %)	5680 (64.22)
$C_{ss,max}$ (ng/mL)	Geometric mean (CV %)	349.6 (49.70)
$C_{ss,min}$ (ng/mL)	Geometric mean (CV %)	141.6 (101.2)
t_{max} (h)	Median (range)	5 (1 to 7)

AUC_{ss} Area under the plasma concentration-time curve from time zero to infinity during the dosing interval.
$C_{ss,max}$ Maximum steady state plasma concentration during the dosing interval.
$C_{ss,min}$ Minimum steady state plasma concentration during the dosing interval.
n Number of observations.
t_{max} Time of maximum plasma concentration.

Informal comparison of the data from this study with that from an earlier multiple-dose study (1839IL/0034) in which healthy volunteers were given ZD1839 100 mg once daily (twice on Day 1) for 14 consecutive days, showed that the steady state exposure achieved was ~6-fold higher in the present study, despite an increase in dose of only 2.5-fold. Furthermore, comparison of the gmean AUC_{ss} achieved in these volunteers with the gmean AUC (2583 ng.h/mL) following a single 250 mg dose to healthy volunteers in previous studies, suggests that the steady state exposures achieved following the 250 mg dose are greater than might be expected on the basis of the single-dose pharmacokinetics of ZD1839 and assuming time-independent pharmacokinetics.

Monitoring of the study drug supply confirmed that the protocolled dosing regimen was adhered to. In addition, the bioanalytical data were re-examined to confirm the plasma concentrations reported, and the pharmacokinetic data previously obtained for ZD1839 in man do not suggest any time dependency in the pharmacokinetics. Comparison of individual AUC_{ss} values shows that (except for Volunteer 007 with AUC_{ss} of 10800 ng.h/mL), they were all within the range of single-dose AUCs seen previously at 250 mg (348 to 9470 ng.h/mL); thus, this apparent discrepancy may be a function of the small number of observations in the context of the known variability in the pharmacokinetics of ZD1839. The $C_{max,ss}$ and AUC_{ss} values in these volunteers were similar to those determined previously in cancer patients following multiple dosing with ZD1839 225 mg.

Summary of safety results

Sixteen volunteers received 1 dose of warfarin 20 mg. Nine volunteers received ZD1839 250 mg once daily for up to 12 days; total exposure to ZD1839 ranged from 1500 to 3000 mg.

The numbers of volunteers with adverse events in each category following exposure to study treatment are summarised in Table S3. In total, 89 adverse events were reported by the 9 volunteers allocated to ZD1839 + warfarin in Period A. All of these events were CTC grade 1 or 2, and the majority resolved. Three volunteers had adverse events with an outcome of 'still present' at the end of the study, these were: pruritus, rash and acneiform dermatitis (1 volunteer), acneiform dermatitis (1 volunteer), weight decreased and decreased appetite (1 volunteer). Many of the adverse events were of short duration (<48 h). Those events with the longest duration tended to be rash, dermatitis, and similar dermatological conditions, as well as abdominal pain, flatulence, and diarrhoea.

A total of 11 adverse events was reported by the separate group of 9 volunteers who were allocated to warfarin only in Period A. All of these events were CTC grade 1 or 2, and all except 1 had an outcome of 'no longer present' at the end of the study.

Table S3 Number of volunteers with adverse events in each category

Category of adverse event[a]	Number of volunteers		
	ZD1839 250 mg[b] (n=9)	Warfarin 20 mg + ZD1839 250 mg[b] (n=7)	Warfarin 20 mg[c] (n=9)
All adverse events	8	7	5
All serious adverse events other than death	0	0	0
Discontinuations due to adverse events[d]	3	3	0
Deaths	0	0	0

[a] A volunteer may have had adverse events in >1 category.
[b] The 'ZD1839' and 'ZD1839 + warfarin groups are not mutually exclusive.
[c] The 'warfarin only' treatment group consists of a separate group of 9 volunteers.
[d] Volunteers summarised according to treatment they were receiving at the time the adverse event began, not the treatment they were receiving at the time of discontinuation.

The most commonly reported adverse events in this study were gastrointestinal disorders (in particular, diarrhoea), skin and subcutaneous tissue disorders (particularly rash and acneiform dermatitis), epistaxis, and headache. Diarrhoea, rash, and epistaxis have been reported previously in association with ZD1839. No deaths, serious adverse events, or other significant adverse events were reported, and there were no unexpected adverse events. Six volunteers discontinued from the study because of adverse events: 4 experienced rash, 1 had diarrhoea, and 1 had diarrhoea and epistaxis. Although these events were not considered to represent a risk to the safety of the volunteers, they suggest that ZD1839 250 mg was not well tolerated when given as multiple doses. There were no clinically significant findings related to haematology, clinical chemistry, urinalysis, ECG, blood pressure, or heart rate during the course of this study.

Conclusions

- Premature termination of this study precluded any meaningful evaluation of the effect of steady state levels of ZD1839 on the anticoagulant properties and pharmacokinetic properties of warfarin.

- Evaluation of the C_{min} data for the 7 volunteers who received ZD1839 250 mg to at least Day 9 showed that steady state exposure was achieved within 8 days of starting dosing.

- Based on gmean exposure, the ZD1839 steady state exposure observed in the volunteers in this study was higher than would be expected for a 250 mg once-daily dose. No pharmacokinetic, bioanalytical, drug supply, or drug administration explanation can be found to explain this observation, and individual subject AUC_{ss} values, though high, lay within the range expected from previous studies.

- ZD1839 250 mg was not well tolerated when given as multiple oral doses to healthy male volunteers; however there were no safety concerns.