AstraZeneca

Clinical Study Report Synopsis

Drug Substance	AZD0837
Study Code	D1250C00051
Edition Number	1
Date	10 November 2009

A controlled, randomised, parallel, multi centre, feasibility study of the oral direct thrombin inhibitor AZD0837, given as extended-release formulation, in the prevention of stroke and systemic embolic events in patients with atrial fibrillation, who are appropriate for but unable or unwilling to take Vitamin-K antagonist therapy

Study dates: First patient enrolled: 22 October 2007
Last patient completed: 21 October 2008

Phase of development: Therapeutic exploratory (II)

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

Study centre(s)

This study was conducted in 131 randomised patients in 6 countries in Europe (Poland, Sweden, Russia, Norway, Denmark, United Kingdom).

Publications

None at the time of writing this report.

Objectives

The primary objective of the study was to assess feasibility of conducting a study in patients with Atrial fibrillation (AF), who were appropriate for but unable or unwilling to take Vitamin-K antagonists (VKA) therapy, by evaluation of drop-out rate and compliance with treatment and study procedures.

The secondary objectives of the study were:

- to provide information on recruitment rate, expressed as number of randomised patients, in this patient population, with focus on the participating countries
- to provide dose-guiding information through evaluation of safety and tolerability of 2 dosing regimens of AZD0837 in relation to "standard therapy" according to local clinical practice (aspirin [ASA], clopidogrel or no therapy) in patients with AF, who are appropriate for but unable or unwilling to take VKA therapy, by assessment of
  - adverse events (AEs, including bleedings)
  - electrocardiogram (ECG)
  - vital signs (blood pressure [BP] and pulse)
  - laboratory values
  - physical examination
- to evaluate the pharmacokinetics (PK) of AZD0837 (pro-drug), the intermediary metabolite (AR H069927XX) and the active form (AR H067637XX) with special regard to the variability in this patient population and the relationship between systemic plasma exposure of AR H067637XX and bleeding events by evaluation of PK variables of AZD0837, AR-H069927XX and AR-H067637XX

- to evaluate the pharmacodynamic (PD) properties of AZD0837 in patients with AF who are appropriate for but unable or unwilling to take VKA therapy by evaluation of
  - level of fibrin D-dimers
  - activated partial thromboplastin time (APTT)
  - endogenous thrombin potential (ETP)
  - ecarin clotting time (ECT)
  - thrombin coagulation time (TCT).

Study design

This was a multi centre, randomised, parallel-group feasibility study. Patients with paroxysmal, persistent or permanent non-valvular AF (NVAF), who were appropriate for but unable or unwilling to take VKA therapy, were randomised into 3 parallel groups: 2 groups receiving different doses of AZD0837 once daily as oral extended release (ER) tablet formulation and one group receiving "standard therapy" according to local clinical practice. The study was open to treatment with AZD0837 versus standard therapy, but blinded to dose of AZD0837.

Target population and sample size

In determining the sample size, with 100 patients randomised to the 2 AZD0837 arms, the true, unknown drop-out rate (with 95% probability) would not exceed the observed rate with more than 7%, given that the observed drop-out rate does not exceed 25%. Assuming a similar within-subject standard deviation as D1250C00007, 50 patients in each arm of AZD0837 would provide sufficient statistical power to demonstrate a mean within-subject decrease in fibrin D-dimers of 50% after 6 weeks treatment.

131 patients were randomised to treatment and 128 patients actually received treatment/therapy. 43 patients were randomised to AZD0837 150 mg, 42 patients to AZD0837 300 mg and 45 patients to standard treatment. One patient was randomised to the AZD0837 300 mg treatment arm, but received standard therapy and 41, 41, and 46 patients subsequently received the respective treatments. For the safety population, this patient was considered to be in the standard therapy treatment group.

For inclusion in the study patients had to fulfil all of the following criteria:

- Paroxysmal, persistent or permanent NVAF verified by at least 2 ECGs in the last year separated by at least one week

- In addition to AF, the patient had the following risk-factors:

  Either one of the following risk-factors was sufficient for inclusion (high-risk patient):

  – Previous cerebral ischaemic attack (stroke or transient ischaemic attack [TIA], >30 days prior to randomisation)

  – Previous systemic embolism

  or at least one of the following risk-factors was needed for inclusion (1 risk-factor = moderate risk patient, 2 or more risk-factors = high-risk patient):

  – Age ≥75 years

  – Symptomatic congestive heart failure

  – Impaired left ventricular systolic function

  – Diabetes mellitus

  – Hypertension requiring anti-hypertensive treatment

- In addition, to AF the patient was to be appropriate for, but unable or unwilling to take, VKA therapy by fulfilling at least one of the following criteria:

  – In hospital records, documented inability to keep prothrombin complex international normalised ratio (INR) levels within 2.0 to 3.0 during a continuous and recent period of at least 3 months, leading to the conclusion that VKA therapy did not offer an adequate level of benefit vs risk in the specific patient.

  – Permanent cessation or refusal by the patient to take VKA therapy due to reasons specified in hospital records present, recorded no later than one month before start of the study.

  – Refusal to participate in study D1250C00008 due to the possibility of being randomised to VKA treatment. For VKA naïve patients, this must have been stated in the hospital records at least 1 week in advance of enrolment in the study.

  – Treating physician's assessment that VKA is inappropriate for this patient recorded no later than one month before start of this study.

  – Allergic reactions to VKA as documented in hospital records.

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

Investigational product or test drug	Dosage form, strength, dosing schedule, and route of administration	Manufacturer	Batch number[a]
AZD0837	Extended-release tablets 150 mg (as AZD0837 besylate 198 mg), oral	AstraZeneca, Sweden	H1825-02-01-03
Placebo	Extended-release tablets 150 mg placebo, oral	AstraZeneca, Sweden	H1876-01-01-01

In the patients randomised to treatment with AZD0837 concomitant therapy with ASA was not recommended. However, if judged absolutely necessary by the local investigator, an ASA dose ≤100 mg once daily was acceptable. Combination therapy with AZD0837 and clopidogrel was not allowed.

In the patients randomised to standard therapy, according to local clinical practice the following alternatives were available:

- ASA 75 to 325 mg once daily
- No treatment
- Clopidogrel 75 mg once daily.

Commercially available ASA and clopidogrel were prescribed by the investigator.

Duration of treatment

The study treatment was administered for a flexible period (1 to 6 months) depending on when the patient was recruited into the study.

Criteria for evaluation - efficacy and pharmacokinetics (main variables)

Primary outcome variables:

The primary variables in this study were:

- Drop-out
  - defined as premature discontinuation of study drug, due to any reason
  - defined as premature discontinuation of study, due to any reason

- Compliance
  - for AZD0837 patients: with regards to study drug, defined as how large a percentage of the amount of study drug specified by the protocol that a patient has actually taken
  - for all patients: with regards to study visits, defined as how large a fraction of the visits stipulated by the study protocol that the patient attended

Secondary outcome variables:

- Patient recruitment rate defined as number of randomised patients.

Pharmacokinetic

- PK variables of AZD0837, AR-H069927XX and AR-H067637XX.

Pharmacodynamic

- Fibrin D-dimer, for all patients
- APTT for all patients at Visit 2, remaining visits only for patients on AZD0837
- ETP, for all patients
- ECT for patients on AZD0837
- TCT for patients on AZD0837.

Criteria for evaluation - safety (main variables)

Adverse events (AEs), bleeding events, laboratory values, physical examination, ECG and vital signs.

Statistical methods

Drop-out rates were presented descriptively as number of patients (%) with a one-sided upper bound 95% confidence interval as well as cumulative drop-out rates (per patient year) with 95% one-sided, upper bound confidence limits, using Kaplan-Meier estimates of time (days) to drop-out. Compliance was presented descriptively as well as mean values with 95% confidence intervals.

Safety data were presented descriptively as treated by treatment arm.

PK and PD data were presented descriptively for applicable treatment arms and for AZD0837 arms. A particular focus of the PD analysis was on patients who were naïve with respect to anticoagulants (VKA and/or unfractionated heparin/low-molecular-weight heparin).

Subject population

The analysis sets and the number of patients in each analysis set are summarised in the table below.

Table S1 Analysis sets

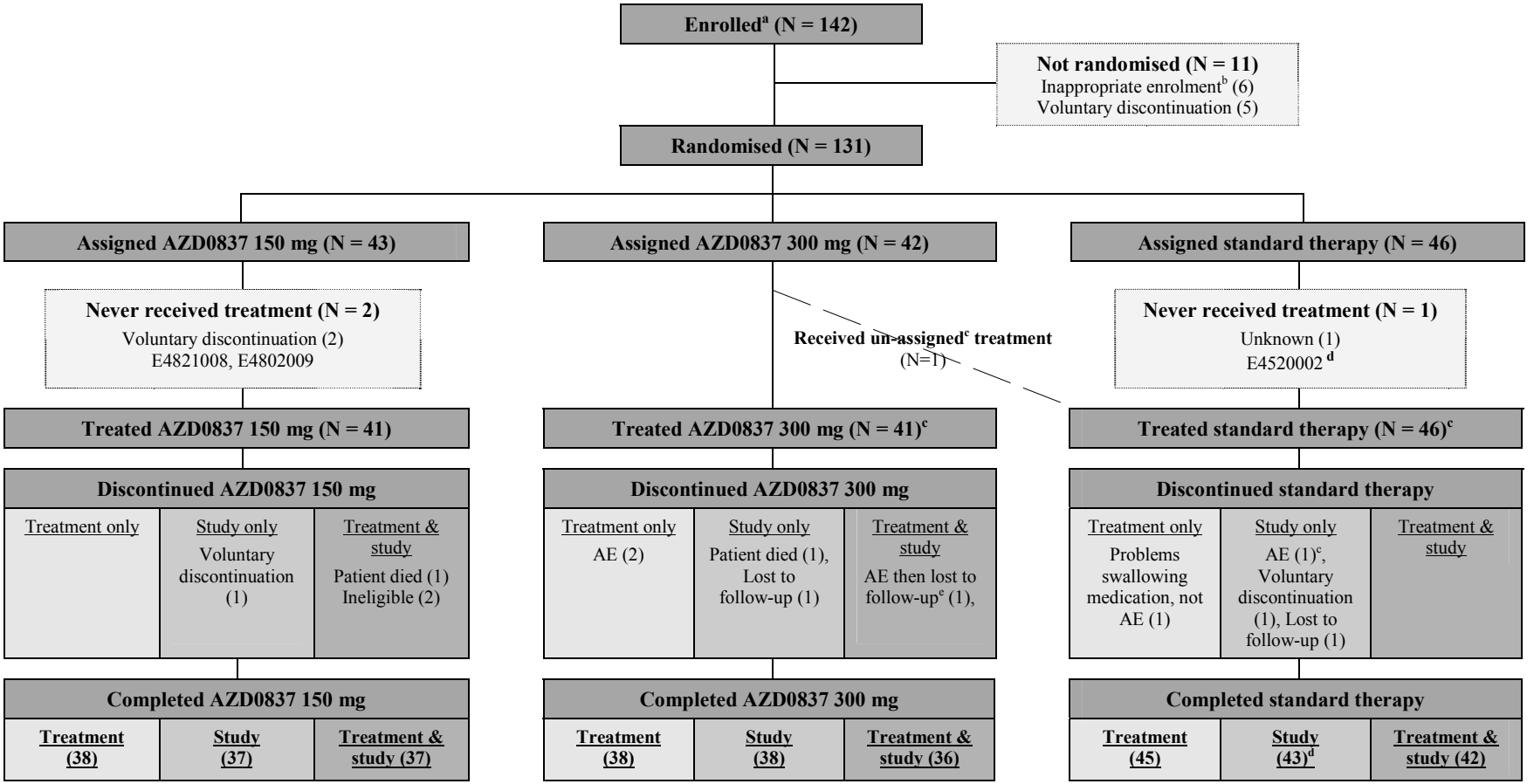
	Number (%) patients		
	AZD0837 150 mg	**AZD0837 300 mg**	**Standard Therapy**
Full analysis set (ie as randomised)	41 (100.0)	42 (100.0)	45 (100.0)
Safety analysis set (ie as treated)	41 (100.0)	41 (97.6)	46 (102.2)
Pharmacokinetic analysis set (ie as treated)[a]	40 (97.6)	39 (92.9)	0

[a] In addition to patient E4520004 who receive the wrong treatment, patients were excluded from the pharmacokinetic analysis set due to poor compliance with study treatment.

Patient E4520004 received standard therapy instead of the assigned study treatment (AZD0837 300mg).
Percentages are based on the number of patients assigned to each treatment group.

The disposition of the healthy patients in this study is summarised in the figure below.

Figure S1 Disposition (All enrolled population, as treated)



[a] Enrolment refers to the signing of the informed consent form.
[b] Three of which were not randomised for "other reasons"; however, inspection of these reasons indicates that the reasons represented failure to meet the eligibility criteria.
[c] This figure presents patients as treated.
[d] Patient E4520002, was reported to have completed the study but in fact the patient discontinued the study after randomisation, but prior to receiving any study treatment. Because of this error, the reason for the withdrawal from the study was undocumented. Since this tabulation is provided on an "as treated" basis, this untreated patient is not considered as a study completer.
[e] One patient stopped treatment due to an AE but stayed in the study before being subsequently lost to follow-up.

AE adverse event; DAE Premature discontinuation of study treatment due to an AE.

The demographic and baseline characteristics (including specific cardiovascular history) of the patients recruited into this study suggest that it is feasible to conduct clinical studies in patients with AF, who are unable or unwilling to take VKA.

Inspection of the status of the patients' VKA experience is informative for future studies: 62% of patients were recruited with permanent cessation or refusal by the patient to take VKA therapy and/or 21% patients with the physician's assessment that VKA was inappropriate. The recruitment of around 40% of patients who were VKA-naïve reflects the unwillingness of many patients and physicians to utilise VKA therapy. Also 24% of patients were recruited with a documented inability to keep INR levels within 2.0 to 3.0 over a 3-month period and 2% due to allergic reactions to VKA.

Summary of efficacy results

The drop-out rate was lower than estimated in the sample size calculation; however, it should be borne in mind that the median duration of treatment was around 6 weeks.

Given the low number of patients in the study and the variable treatment duration (4 weeks to 6 months), the drop-out rate was broadly comparable across all groups. Data did not suggest any bias with regard to patient management arising from the open-label study design.

Table S2 Drop-out rate (full analysis set)

	Number (%) patients		
	AZD0837 150 mg (N=41)	**AZD0837 300 mg (N=42)[a]**	**Standard Therapy (N=45)**
Number of patients dropping out	4 (9.8%)	6 (14.3%)	3 (6.7%)
Upper bound 95% of the one-sided confidence interval	21.0%	26.3%	16.3%
Mean duration of participation in patient years	0.217	0.200	0.218
Cumulative rate per patient year	0.45	0.71	0.31
95% confidence interval	0.12, 1.15	0.26, 1.55	0.06, 0.89
Time at risk of drop-out (patient years)	8.90	8.41	9.83
Number of patients dropping out with premature discontinuation of study drug	3 (7.3%)	3 (7.1%)	1 (2.2%)
Number of patients dropping out with premature discontinuation of study	4 (9.8%)	4 (9.5%)	2 (4.4%)

[a] Patient E4520004 received standard therapy instead of the assigned study treatment (AZD0837 300mg).
A patient year is determined by summing the number of days from randomisation to day of drop-out or censoring and dividing by 365.25 days to convert to proportion of a year.
The cumulative proportion of drop-outs per patient year was determined by totalling the number of patient who dropped out and dividing by the sum of patient year across all patients.

Overall compliance with study treatment and study visits was acceptable. The overall mean (± SD) compliance with study treatment was 96.95% ± 16.503 for 150 mg AZD0837 and 99.82% ± 11.383 for 300 mg AZD0837. The overall mean (± SD) compliance with study visits was 93.3% ± 15.01 for the 150 mg AZD0837 group, 95.6% ± 10.45 for the 300 mg AZD0837 group and 97.5% ± 6.80 for the standard therapy group. Generally compliance with assessments was acceptable; however, for certain assessments the compliance was poor. In all groups, the week 4 urinalysis compliance was low and very few faecal examinations were performed after week 2. The overall compliance with PK/PD assessments was low at week 8. **Note:** Several patients finished treatment at week 8. Unfortunately, although the expectation was that the PK/PD assessments would be performed for these patients (as true week 8 assessments), in practice these were omitted and not performed in addition to the termination visit (Visit 11) assessments. Given the compliance with the other specified assessments, this observation was likely not owing to the patients' unwillingness. Compliance with PK/PD was good when the termination visit did not occur at week 8.

A total of 128 study sites were approached with respect to participating in this study. The majority of patients were identified in the early month(s) of each countries period of recruitment. With the exception of "permanent cessation or refusal by the patient to take VKA therapy" and the "treating physician's assessment that VKA was inappropriate" the available patient pools were exhausted in the initial month(s).

Summary of pharmacokinetic results

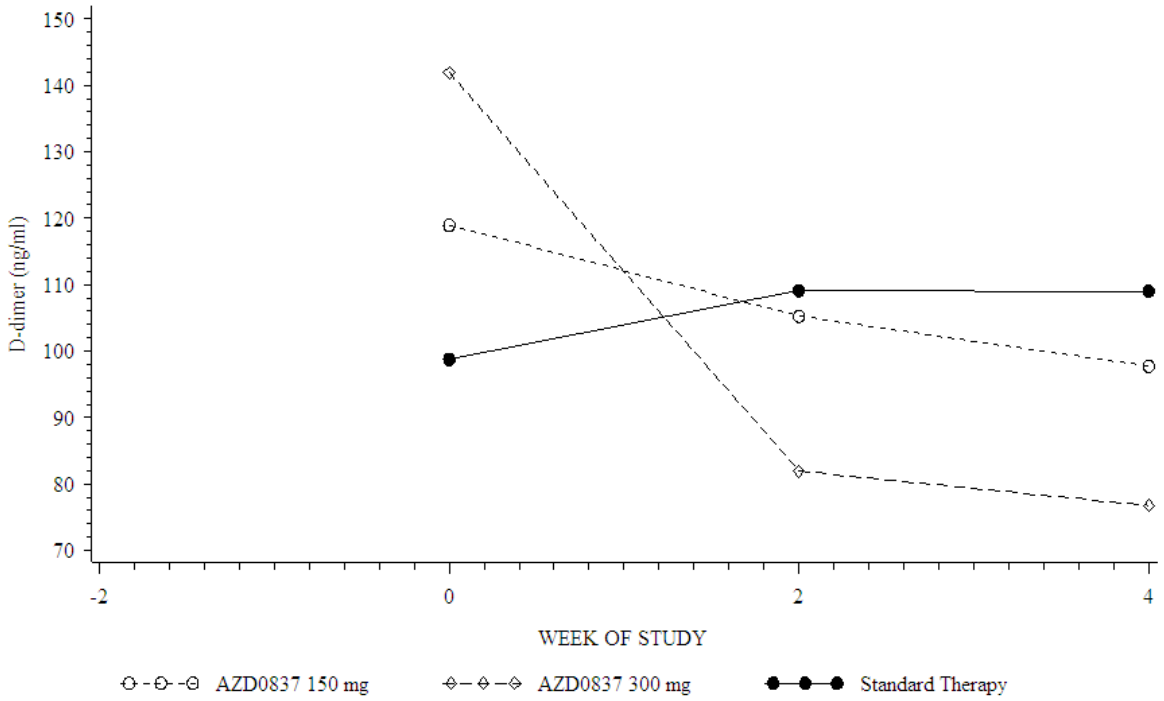
Pharmacokinetic data compared well with previous studies. For the active metabolite (AR-H067637XX), inter-patient variability (expressed as CV for 150 mg and 300 mg) was 60% and 45% at week 2, 49% and 39% at week 4, and 45% and 36% at week 8. It should be noted that although the PK samples were collected just before tablet intake in the morning, the actual time after administration of the last previous dose varied and will contribute to the inter-patient variability for the plasma concentrations. Compliance with PK sampling was low in patients who finished study treatment at week 8.

Bleeding events were recorded in 5 patients in the AZD0837 300 mg treatment group and none in 150 mg). It was not possible to assess any relation between PK data and bleeding events as there are so few observations and many factors contribute to bleeding tendency. Although, the plasma levels did not appear to be markedly raised with the clinically relevant minor bleed and were rather average in the case of the minimal bleeding events.

Summary of pharmacodynamic results

There was a stable decrease in fibrin D-dimer in both AZD0837 treatment groups. The decrease was larger in the 300 mg AZD0837 treatment group.

Figure S2 **Fibrin D-dimer: median values by treatment over time, all patients (full analysis set)**

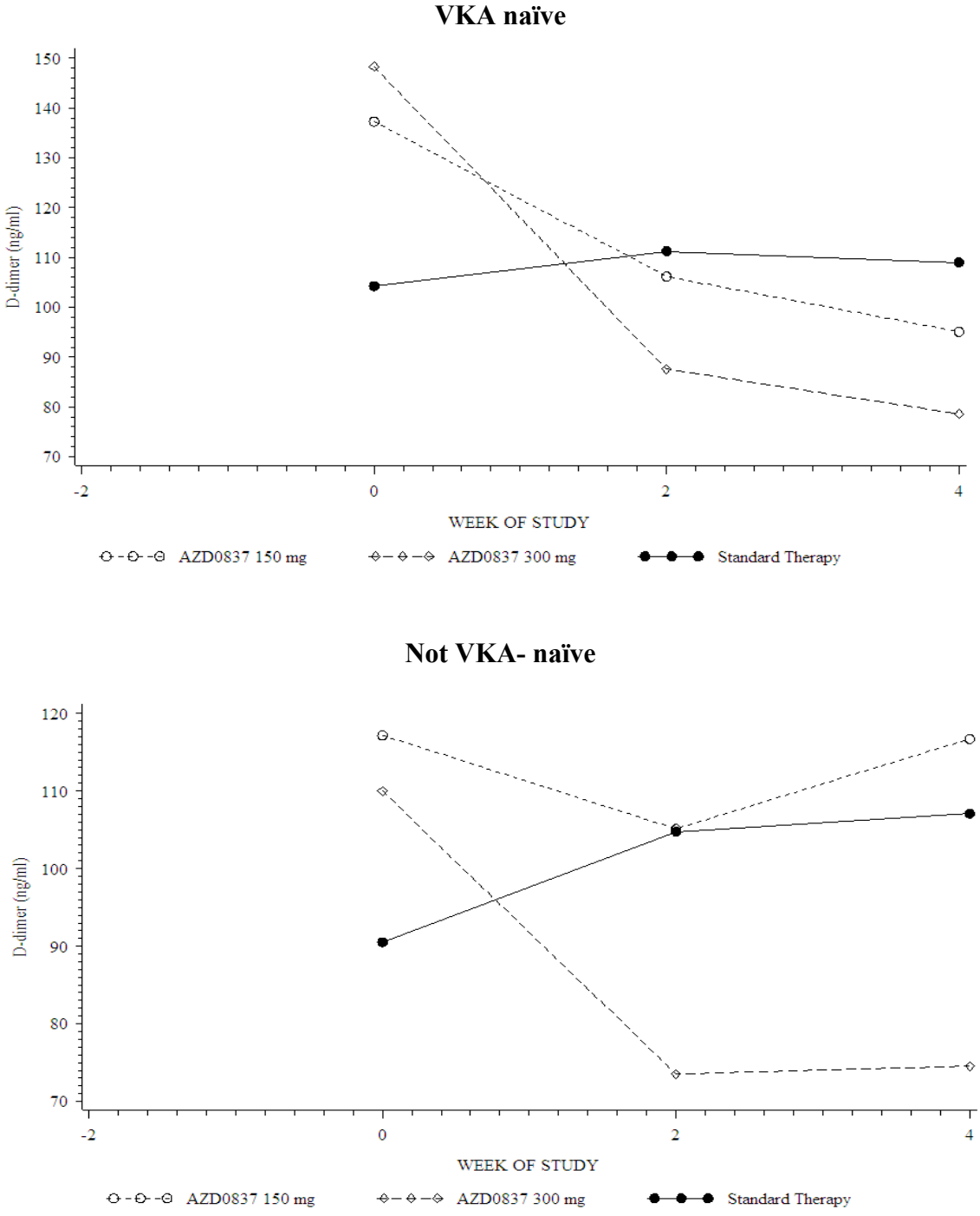


Note: Patient numbers were low after week 4, so trends cannot be reliably interpreted beyond this time point.
Note: Standard therapy was according to local clinical practice, using the following available alternatives: acetylsalicylic acid (75 to 325 mg once daily), no treatment, or clopidogrel (75 mg once daily).

A similar pattern of findings was observed in the sub-group of patients who were naïve to VKA treatment; however, the 300 mg AZD0837 treatment group showed a clear response in the patients who were not naïve to VKA treatment while the response was less clear in the 150 mg AZD0837 treatment group (Figure S3).

The observed mean decrease in fibrin D-dimers within patients in the 300 mg AZD0837 (all patients combined) group was comparable to that observed Lip et al 1996 (around 50%).

Figure S3 **Fibrin D-dimer: median values by treatment over time, by VKA status (full analysis set)**



Note: Patient numbers were low after week 4, so trends cannot be reliably interpreted beyond this time point.
Note: Standard therapy was according to local clinical practice, using the following available alternatives: acetylsalicylic acid (75 to 325 mg once daily), no treatment, or clopidogrel (75 mg once daily).
Note: Naïve means that the patient had never received VKA therapy in the past.

There was a stable prolongation of APTT in both AZD0837 treatment groups. The response was larger in the 300 mg AZD0837 treatment group. A similar pattern of findings was observed in the sub-group of patients who were naïve to VKA treatment; however, the difference in the size of the response was less marked in the patients who were not naïve to VKA treatment.

There was a stable decrease in ETP and prolongation of ECT and TCT in both AZD0837 treatment groups. The response was larger in the 300 mg AZD0837 treatment group

Summary of safety results

Both the low patient numbers and the variable (and often short) treatment duration need to be borne in mind when interpreting the safety data,. However, in this study, AZD0837 in doses of 150 mg and 300 mg od appeared well tolerated when compared to standard treatment (for 1 to 6 months treatment).

Table S3 Number (%) of patients who had an adverse event in any category (safety population)

	Number of patients		
	AZD0837 150 mg (N = 41)	**AZD0837 300 mg (N = 41)**	**Standard Therapy (N = 46)**
On-treatment AEs			
Number of patients			
Any AE	15	16	20
Any AE with outcome of death	1	0	0
Any SAE (including those with an outcome of death)	2	3	2
DAE	1[a]	3	0
Number of AEs			
Any AE	34	24	45
Any AE with outcome of death[a]	1	0	0
Any SAE (including those with an outcome of death)[d]	2	3	2
DAE	1[a]	3	0
Off-treatment AEs			
Number of patients			
Any AE	10	14	15
Any AE with outcome of death	0	1	0
Any SAE (including those with an outcome of death)	0	5	1

Table S3 Number (%) of patients who had an adverse event in any category (safety population)

	Number of patients		
	AZD0837 150 mg (N = 41)	**AZD0837 300 mg (N = 41)**	**Standard Therapy (N = 46)**
Number of AEs			
Any AE	17	19	23
Any AE with outcome of death	0	1	0
Any SAE (including those with an outcome of death)	0	5	1

[a] The investigator indicated a DAE for Patient E4820009; however, since treatment was stopped due to the patient's death, but there was no active decision on the part of the investigator so this was not a DAE.

Patients with multiple events in the same category are counted only once in that category. Multiple events in the same category are counted multiple times in that category.

AE adverse events; DAE premature discontinuation of study treatment due to an AE; SAE serious adverse events.

Two patients died during the study: one on-treatment with 150 mg AZD0837 (renal failure) and one off-treatment in the 300 mg AZD0837 group (cardiac arrest). The decline in renal function started prior to treatment, with death being on Study Day 3. The cardiac arrest occurred around 2 weeks after the last intake of study medication.

The numbers of AEs and SAEs during the treatment period were similar in all treatment groups. Excluding the erroneous reporting of the renal failure leading to death as a DAE in the 150 mg group, DAEs were only seen in the AZD0837 300 mg group; however, overall there were too few patients to draw conclusions.

The rate of bleeding events was low, and all bleeding events (including the single minor bleed) were self-limiting and resolved without treatment.

There were no apparent differences in the overall frequency of AEs between the dosing regimens. The most commonly reported AE in AZD0837 patients was bronchitis followed by nausea, upper respiratory tract infection and epistaxis. The number of patients with AEs was low and similar in all treatment groups. AEs of cardiac origin were infrequent in all treatment groups, and there were similar findings in all treatment groups regarding GI disorders.

The overall assessment of safety laboratory values, vital signs, ECGs or physical examinations evaluating both mean changes and individual findings did not raise any safety concerns.

Considering data up to and including week 4, the mean creatinine values were similar in the 150 mg AZD0837 and standard therapy treatment groups; with values at weeks 2 and 4 being only slightly higher in the 300 mg AZD0837 group. Thus, in line with previous studies with AZD0837, data indicate that mean s-creatinine can be reversibly increased on AZD0837 treatment. However, cystatin C data indicate that glomerular filtration rate was not affected.

No patient had both ALT ≥ 3xULN and bilirubin ≥ 2xULN (at any time). No patient had ALT ≥ 3xULN on treatment, two patients had single values at baseline which decreased on randomised treatment (one 300 mg AZD0837, one standard therapy) and one patient who at follow-up after standard treatment had a single value of ALT ≥ 3xULN.