# Clinical trial results:
# A Cancer Research UK Phase I/IIa trial of AT9283 (a selective inhibitor of aurora kinases) given over 72 hours every 21 days via intravenous infusion in children and adolescents aged 6 months to 18 years with relapsed and refractory acute leukaemia.

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

| | |
|---|---|
| EudraCT number | 2009-016952-36 |
| Trial protocol | GB |
| Global end of trial date | 01 July 2014 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 05 June 2016 |
| First version publication date | 24 July 2015 |
| Version creation reason | • Correction of full data set<br>Data reviewed and corrected following EudraCT system downtime (July 2015 to January 2016). |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CR0708-12 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01431664 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Cancer Research UK |
| Sponsor organisation address | 407 St John Street, London, United Kingdom, EC1V 4AD |
| Public contact | Centre for Drug Development, Cancer Research UK, +44 02072420200, regquery@cancer.org.uk |
| Scientific contact | Centre for Drug Development, Cancer Research UK, +44 02072420200, regquery@cancer.org.uk |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 04 December 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 July 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 July 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

To recommend a dose of AT9283 for Phase II evaluation in paediatric patients with acute leukaemia.

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 14 September 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Worldwide total number of subjects | 7 |
| EEA total number of subjects | 7 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 2 |
| Children (2-11 years) | 3 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 1 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Study participants were enrolled from 14 September 2011 to 01 July 2014 in 4 clinical study centres in the UK.

### Pre-assignment

Screening details:

Patients were male or female aged 6 months to 18 years old, who had morphologically proven acute leukaemia (relapsed and refractory disease) with Karnofsky/Lansky play performance score of at least 50 and a life expectancy of at least 8 weeks.

### Period 1

| | |
|---|---|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Cohort 1 (9.0 mg/m2/day) |

Arm description:

AT9283 9.0 mg/m2/day dose level.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | AT9283 |
| Investigational medicinal product code | AT9283 |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered as a 72 hour intravenous infusion every 21 days (one treatment cycle).

| | |
|---|---|
| **Arm title** | Cohort 2 (14.5 mg/m2/day) |

Arm description:

AT9283 14.5 mg/m2/day dose level.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | AT9283 |
| Investigational medicinal product code | AT9283 |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered as a 72 hour intravenous infusion every 21 days (one treatment cycle).

| | |
|---|---|
| **Arm title** | Cohort 3 (23.0 mg/m2/day) |

Arm description:

AT9283 23.0 mg/m2/day dose level.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | AT9283 |
| Investigational medicinal product code | AT9283 |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered as a 72 hour intravenous infusion every 21 days (one treatment cycle).

| **Number of subjects in period 1** | Cohort 1 (9.0 mg/m2/day) | Cohort 2 (14.5 mg/m2/day) | Cohort 3 (23.0 mg/m2/day) |
|---|---|---|---|
| Started | 3 | 3 | 1 |
| Completed | 3 | 3 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1 (9.0 mg/m2/day) |
| Reporting group description:<br>AT9283 9.0 mg/m2/day dose level. | |
| Reporting group title | Cohort 2 (14.5 mg/m2/day) |
| Reporting group description:<br>AT9283 14.5 mg/m2/day dose level. | |
| Reporting group title | Cohort 3 (23.0 mg/m2/day) |
| Reporting group description:<br>AT9283 23.0 mg/m2/day dose level. | |

| Reporting group values | Cohort 1 (9.0 mg/m2/day) | Cohort 2 (14.5 mg/m2/day) | Cohort 3 (23.0 mg/m2/day) |
|---|---|---|---|
| Number of subjects | 3 | 3 | 1 |
| Age categorical<br>Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 1 | 1 | 0 |
| Children (2-11 years) | 1 | 1 | 1 |
| Adolescents (12-17 years) | 0 | 1 | 0 |
| Adults (18-64 years) | 1 | 0 | 0 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 1 | 0 | 1 |
| Male | 2 | 3 | 0 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 7 | | |
| Age categorical<br>Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 2 | | |
| Children (2-11 years) | 3 | | |
| Adolescents (12-17 years) | 1 | | |
| Adults (18-64 years) | 1 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | | |
| Male | 5 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Cohort 1 (9.0 mg/m2/day) |
| Reporting group description: AT9283 9.0 mg/m2/day dose level. | |
| Reporting group title | Cohort 2 (14.5 mg/m2/day) |
| Reporting group description: AT9283 14.5 mg/m2/day dose level. | |
| Reporting group title | Cohort 3 (23.0 mg/m2/day) |
| Reporting group description: AT9283 23.0 mg/m2/day dose level. | |
| Subject analysis set title | All treated patients |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All enrolled and eligible patients who received at least one dose of AT9283. | |

### Primary: Recommended Dose of AT9283 for Phase IIb Evaluation

| | |
|---|---|
| End point title | Recommended Dose of AT9283 for Phase IIb Evaluation[1] |
| End point description: The biologically active dose of AT9283 and maximal dose of AT9283 at which no more than one out of up to six patients at that dose level experienced a probably or highly probably drug related dose limiting toxicity (DLT) during the first cycle of AT9283. | |
| End point type | Primary |
| End point timeframe: First cycle of AT9283 administration. | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: All safety data were presented in a descriptive fashion, with adverse events reported for each dose level and presented by adverse event term by the worst grade observed.

| End point values | All treated patients | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 7 | | | |
| Units: mg/m2/day | | | | |
| Maximum administered dose | 23 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety

| | |
|---|---|
| End point title | Safety |
| End point description: The causality and severity grading of each adverse event (AE), according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE),Version 4.02. All AEs with a causality of possibly, probably or highly probably related to AT9283 were considered to indicate relatedness. | |

| End point type | Secondary |
|---|---|

End point timeframe:

From patient consent to 28 days post last dose of AT9283.

| **End point values** | All treated patients | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 7 | | | |
| Units: No. of AEs | | | | |
| All AEs | 97 | | | |
| Related AEs | 29 | | | |
| DLTs | 0 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Response

| End point title | Response |
|---|---|

End point description:

Patients' disease was measured and characterised according to the following disease response criteria:
Complete remission (CR) - absolute neutrophil count (ANC) ≥1.0x10^9/L; platelet count ≥100x10^9/L; bone marrow <5% blasts.
Complete remission with incomplete bone marrow recovery (CRi) - ANC ≥0.75x10^9/L; platelet count ≥75x10^9/L; bone marrow <5% blasts.
Partial remission (PR) - ANC ≥0.75x10^9/L; platelet count ≥75x10^9/L; bone marrow <25% blasts.
and disease progression (PD).

| End point type | Secondary |
|---|---|

End point timeframe:

From baseline until after 6 cycles.

| **End point values** | All treated patients | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 7 | | | |
| Units: Number of subjects with a response | | | | |
| CR | 0 | | | |
| CRi | 0 | | | |
| PR | 0 | | | |
| PD | 7 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: AT9283 Pharmacokinetic Profile

| End point title | AT9283 Pharmacokinetic Profile |
|---|---|

End point description:

Pharmacokinetic (PK) parameters: maximum concentration (Cmax), area under the time-concentration curve (AUC), half-life, clearance (Cl) and steady state volume of distribution (Vss).

| End point type | Secondary |
|---|---|

End point timeframe:

Pre-treatment Day 1 through to Day 4 of Cycle 1.

| End point values | Cohort 1 (9.0 mg/m2/day) | Cohort 2 (14.5 mg/m2/day) | Cohort 3 (23.0 mg/m2/day) | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 3 | 3 | 1 | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cmax (ng/mL) | 21.9 (± 16.9) | 37.5 (± 11.4) | 46 (± 0) | |
| AUC (ng/mL. hr) | 990 (± 514) | 2268 (± 929) | 2766 (± 0) | |
| Half-life (hr) | 5.3 (± 0.9) | 5.3 (± 1.1) | 5.3 (± 0) | |
| Cl (L/hr) | 25.7 (± 12.8) | 23.1 (± 26) | 18.4 (± 0) | |
| Vss (L) | 197 (± 125) | 180 (± 215) | 141.7 (± 0) | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events:<br>From patient consent to 28 days post last dose of AT9283. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | NCI-CTCAE |
| Dictionary version | 4.02 |

| Reporting groups | |
|---|---|
| Reporting group title | Cohort 1 (9.0 mg/m2/day) |
| Reporting group description:<br>AT9283 9.0 mg/m2/day dose level. | |
| Reporting group title | All treatment cohorts |
| Reporting group description:<br>All patients treated at the range of AT9283 dose levels administered. | |
| Reporting group title | Cohort 3 (23.0 mg/m2/day) |
| Reporting group description:<br>AT9283 23.0 mg/m2/day dose level. | |
| Reporting group title | Cohort 2 (14.5 mg/m2/day) |
| Reporting group description:<br>AT9283 14.5 mg/m2/day dose level. | |

| Serious adverse events | Cohort 1 (9.0 mg/m2/day) | All treatment cohorts | Cohort 3 (23.0 mg/m2/day) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 5 / 7 (71.43%) | 1 / 1 (100.00%) |
| number of deaths (all causes) | 0 | 1 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 7 (42.86%) | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders - other, specify | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death NOS | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 1 / 1 (100.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Cohort 2 (14.5 mg/m2/day) | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders - other, specify | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Death NOS | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Cohort 1 (9.0 mg/m2/day) | All treatment cohorts | Cohort 3 (23.0 mg/m2/day) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 7 / 7 (100.00%) | 1 / 1 (100.00%) |
| General disorders and administration site conditions | | | |
| Facial oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oedema limbs | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fever | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Flu like symptoms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| General disorders and administration site conditions - other, specify | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 7 (28.57%) | 1 / 1 (100.00%) |
| occurrences (all) | 2 | 3 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Confusion | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Psychiatric disorders - other, specify | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Restlessness | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Investigations - other, specify | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 4 / 7 (57.14%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Weight gain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| White blood cell decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 3 (66.67%) | 3 / 7 (42.86%) | 0 / 1 (0.00%) |
| occurrences (all) | 3 | 4 | 0 |
| Injury, poisoning and procedural complications | | | |
| Injury, poisoning and procedural complications - other, specify | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Nervous system disorders | | | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 4 / 7 (57.14%) | 1 / 1 (100.00%) |
| occurrences (all) | 3 | 7 | 1 |
| Blood and lymphatic system disorders - other, specify | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Gastrointestinal disorders - other, specify | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Mucositis oral | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 1 / 1 (100.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 7 (42.86%) | 1 / 1 (100.00%) |
| occurrences (all) | 0 | 4 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 1 / 1 (100.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Infections and infestations | | | |
| Infections and infestations - other, specify | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Upper respiratory infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Wound infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 7 (14.29%) | 0 / 1 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 2 / 7 (28.57%) | 0 / 1 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |

| **Non-serious adverse events** | Cohort 2 (14.5 mg/m2/day) | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | | |
| General disorders and administration site conditions | | | |
| Facial oedema | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Oedema limbs | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Fever | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Flu like symptoms | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions - other, specify | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Confusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders - other, specify | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|---|---|---|
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Investigations - other, specify<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | | |
| Neutrophil count decreased<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | | |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all) | 3 / 3 (100.00%)<br>4 | | |
| Weight gain<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| White blood cell decreased<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | | |
| Injury, poisoning and procedural complications<br>Injury, poisoning and procedural complications - other, specify<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Nervous system disorders<br>Lethargy<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Somnolence<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>3 | | |

| | | | |
|---|---|---|---|
| Blood and lymphatic system disorders - other, specify<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | | |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastrointestinal disorders - other, specify<br>subjects affected / exposed<br>occurrences (all)<br><br>Mucositis oral<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>1 / 3 (33.33%)<br>1<br><br>0 / 3 (0.00%)<br>0<br><br>0 / 3 (0.00%)<br>0<br><br>2 / 3 (66.67%)<br>3 | | |
| Skin and subcutaneous tissue disorders<br>Dry skin<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1<br><br>0 / 3 (0.00%)<br>0 | | |

| | | | |
|---|---|---|---|
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Bone pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Infections and infestations - other, specify | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | | |
| occurrences (all) | 2 | | |
| Upper respiratory infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | | |
| occurrences (all) | 1 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | | |
| occurrences (all) | 0 | | |

| | | | |
|---|---|---|---|
| Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all) | 0 / 3 (0.00%)<br>0 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 03 August 2011 | Reduction in the starting and escalated doses of AT9283, addition of skin biopsy and notification of a change to the Sponsor's contact details. |
| 20 June 2012 | Change to the AT9283 dose levels explored in the study (starting dose and escalated dose). |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early termination of the trial due to poor recruitment, attributed to a lack of patients and new competing studies meant that only a small number of patients were administered AT9283 (across a total of three dose levels).

Notes: