# Clinical trial results:
# A Phase Ib/IIa study of combination therapy with Gemcitabine and Atu027 in subjects with locally advanced or metastatic pancreatic adenocarcinoma

## Summary

| | |
|---|---|
| EudraCT number | 2012-004429-26 |
| Trial protocol | DE |
| Global end of trial date | 05 January 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 16 September 2017 |
| First version publication date | 16 September 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | Atu027-I-02 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Silence Therpeutics GmbH |
| Sponsor organisation address | Robert-Rössle-Str. 10, Berlin, Germany, 13125 |
| Public contact | Mike Khan, PhD, Silence Therapeutics GmbH<br>Robert-Rössle-Str. 10,<br>13125 Berlin, +49 30 9489 2800, |
| Scientific contact | Mike Khan, PhD, Silence Therapeutics GmbH<br>Robert-Rössle-Str. 10,<br>13125 Berlin, +49 30 9489 2800, |

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 | 08 February 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 January 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 January 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objectives of this study were to evaluate the safety and pharmacokinetics of Atu027 when used in combination with gemcitabine in subjects with locally advanced or metastatic pancreatic adenocarcinoma.

Protection of trial subjects:

A lead-in safety period was installed for this study enrolling three subjects with non-pancreatic cancer for whom conventional treatment options had failed. Subjects of this safety cohort were to be treated in a 28-day cycle with Atu027 twice weekly for four weeks and gemcitabine once weekly for the first three weeks. Subjects of the safety cohort were included consecutively at 2-week intervals. If one of the subjects in the safety cohort experienced an unacceptable toxicity, the safety cohort was to be expanded to six subjects. If one of these additional three subjects experienced an unacceptable toxicity, the study was to be stopped. After all subjects finished one 28-day cycle, safety data were to be reviewed by a data safety monitoring board (DSMB). If no safety concerns were observed, subjects with locally advanced or metastatic pancreatic adenocarcinoma were to be enrolled into the treatment period and subjects of the safety cohort were to be given the opportunity to get further treatment with Atu027. In case of intolerable side effects that were judged by the investigator to be detrimental to the subject's well-being, during the treatment period, treatment was to be stopped. These subjects were not to be withdrawn from the study (End of Treatment and Follow-up visits were performed).

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 27 March 2013 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 1 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Germany: 23 |
| Worldwide total number of subjects | 23 |
| EEA total number of subjects | 23 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| wk | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 9 |
| From 65 to 84 years | 14 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The recruitment started on 27-Mar-2013 with the first patient of the safety cohort and ended on 08-Jul-2014 with the last patient included in the treatment period.

### Pre-assignment

Screening details:

26 subjects with locally advanced or metastatic pancreatic adenocarcinoma were screened for the treatment period, out of which two were screening failures, and 24 subjects got randomised for treatment. One subject was a screening failure post randomisation, therefore, 23 subjects received treatment.

### Period 1

| | |
|---|---|
| Period 1 title | Treatment cohort |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | Arm 1: Atu027 once weekly |

Arm description:

Arm 1 of the treament period received 0.253 mg/kg Atu027 administered i.v. and gemcitabine 1,000 mg/m² (doses could have been reduced based on toxicity) once weekly for three consecutive weeks in 28-day treatment cycles.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Atu027 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Treatments were administered in 28-day treatment cycles: 0.253 mg/kg Atu027 were administered i.v. once weekly for three consecutive weeks.
The Atu027 dose for the first treatment of Cycle 1 was calculated with the body weight measured at Baseline. At least at the beginning of each following cycle, the dose was adjusted if there was a change in body weight of 10% or greater compared to the latest weight used for dose calculation.

| | |
|---|---|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Treatments were administered in 28-day treatment cycles: gemcitabine 1,000 mg/m² (doses could have been reduced based on toxicity) was administered once weekly for three consecutive weeks.
The gemcitabine dose for Cycle 1 was calculated with Dubois formula with the body surface area evaluated at Baseline. Gemcitabine was given at 1,000 mg/m² by 30-minute i.v. infusion. Dosage modifications at each cycle or within a cycle were applied based upon the actual body weight or on the grade of toxicity experienced by the subject and were done according to the SmPC.

| | |
|---|---|
| **Arm title** | Arm 2: Atu027 twice weekly |

Arm description:

Arm 2 of the treatment period received 0.253 mg/kg Atu027 administered i.v. twice weekly for four consecutive weeks and gemcitabine 1,000 mg/m² (doses could have been reduced based on toxicity) once weekly for three consecutive weeks in 28-day treatment cycles. Each combination cycle was

followed by a gemcitabine-monotherapy cycle.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Atu027 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Treatments were administered in 28-day treatment cycles: 0.253 mg/kg Atu027 were administered i.v. twice weekly for four consecutive weeks followed by a 28-day cycle with no Atu027 treatment.
The Atu027 dose for the first treatment of Cycle 1 was calculated with the body weight measured at Baseline. At least at the beginning of each following cycle, the dose was adjusted if there was a change in body weight of 10% or greater compared to the latest weight used for dose calculation.

| | |
|---|---|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Treatments were administered in 28-day treatment cycles: gemcitabine 1,000 mg/m² (doses could have been reduced based on toxicity) was administered once weekly for three consecutive weeks. Each combination cycle was followed by a gemcitabine-monotherapy cycle.
The gemcitabine dose for Cycle 1 was calculated with Dubois formula with the body surface area evaluated at Baseline. Gemcitabine was given at 1,000 mg/m² by 30-minute i.v. infusion. Dosage modifications with each cycle or within a cycle were applied based upon the actual body weight or on the grade of toxicity experienced by the subject and were done according to the SmPC.

| | |
|---|---|
| **Arm title** | Total |

Arm description:

All patients of Arm 1 and all patients of Arm 2 who received Atu027 and gemcitabine.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Atu027 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Treatments were administered in 28-day treatment cycles: 0.253 mg/kg Atu027 were administered i.v. once weekly for three consecutive weeks or twice weekly for four consecutive weeks followed by 4 weeks of no Atu027 treatment.
The Atu027 dose for the first treatment of Cycle 1 was calculated with the body weight measured at Baseline. At least at the beginning of each following cycle, the dose was adjusted if there was a change in body weight of 10% or greater compared to the latest weight used for dose calculation.

| | |
|---|---|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Treatments were administered in 28-day treatment cycles: gemcitabine1,000 mg/m² (doses could have been reduced based on toxicity) was administered once weekly for three consecutive weeks. For patients receiving Atu027 twice weekly, each combination cycle was followed by a gemcitabine-monotherapy cycle.
The gemcitabine dose for Cycle 1 was calculated with Dubois formula with the body surface area evaluated at Baseline. Gemcitabine was given at 1,000 mg/m² by 30-minute i.v. infusion. Dosage modifications at each cycle or within a cycle were applied based upon the actual body weight or on the

grade of toxicity experienced by the subject and were done according to the SmPC.

| **Number of subjects in period 1** | Arm 1: Atu027 once weekly | Arm 2: Atu027 twice weekly | Total |
|---|---|---|---|
| Started | 11 | 12 | 23 |
| Completed | 6 | 7 | 13 |
| Not completed | 5 | 5 | 10 |
| Consent withdrawn by subject | 2 | - | 2 |
| Death | 3 | 3 | 6 |
| Lost to follow-up | - | 2 | 2 |

| **Period 2** | |
|---|---|
| Period 2 title | Follow-up period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

**Arms**

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Arm 1: Atu027 once weekly FU |

Arm description:

Follow up of Arm 1 for safety for a further year without study medication.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| | |
|---|---|
| **Arm title** | Arm 2: Atu027 twice weekly FU |

Arm description:

Follow up of Arm 2 for safety for a further year without study medication.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 2** | Arm 1: Atu027 once weekly FU | Arm 2: Atu027 twice weekly FU |
|---|---|---|
| Started | 6 | 7 |
| Completed | 1 | 1 |
| Not completed | 5 | 6 |
| Consent withdrawn by subject | 1 | 1 |
| Death | 4 | 5 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Treatment cohort |

Reporting group description:

23 subjects were randomised to two treatment arms and received either Atu027 once weekly and Gemcitabine once weekly, or Atu027 twice weekly and Gemcitagine once weekly.

| Reporting group values | Treatment cohort | Total | |
|---|---|---|---|
| Number of subjects | 23 | 23 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 9 | 9 | |
| From 65-84 years | 14 | 14 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 14 | 14 | |
| Male | 9 | 9 | |
| ECOG performance status<br>Units: Subjects | | | |
| ECOG 0 | 7 | 7 | |
| ECOG 1 | 16 | 16 | |

| Subject analysis sets | |
|---|---|
| Subject analysis set title | PK analysis set - Atu027 once weekly |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

4 subjects of Arm 1 who received Atu027 once weekly.

| Subject analysis set title | PK analysis set - Atu027 twice weekly |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

3 subjects of the safety cohort plus 4 subjects of Arm 2 who all received Atu027 twice weekly.

| Reporting group values | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | |
|---|---|---|---|
| Number of subjects | 4 | 7 | |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 2 | 2 | |
| From 65-84 years | 2 | 5 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 5 | |
| Male | 2 | 2 | |

| ECOG performance status<br>Units: Subjects | | | |
|---|---|---|---|
| ECOG 0<br>ECOG 1 | | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Arm 1: Atu027 once weekly |

Reporting group description:

Arm 1 of the treament period received 0.253 mg/kg Atu027 administered i.v. and gemcitabine 1,000 mg/m² (doses could have been reduced based on toxicity) once weekly for three consecutive weeks in 28-day treatment cycles.

| | |
|---|---|
| Reporting group title | Arm 2: Atu027 twice weekly |

Reporting group description:

Arm 2 of the treatment period received 0.253 mg/kg Atu027 administered i.v. twice weekly for four consecutive weeks and gemcitabine 1,000 mg/m² (doses could have been reduced based on toxicity) once weekly for three consecutive weeks in 28-day treatment cycles. Each combination cycle was followed by a gemcitabine-monotherapy cycle.

| | |
|---|---|
| Reporting group title | Total |

Reporting group description:

All patients of Arm 1 and all patients of Arm 2 who received Atu027 and gemcitabine.

| | |
|---|---|
| Reporting group title | Arm 1: Atu027 once weekly FU |

Reporting group description:

Follow up of Arm 1 for safety for a further year without study medication.

| | |
|---|---|
| Reporting group title | Arm 2: Atu027 twice weekly FU |

Reporting group description:

Follow up of Arm 2 for safety for a further year without study medication.

| | |
|---|---|
| Subject analysis set title | PK analysis set - Atu027 once weekly |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

4 subjects of Arm 1 who received Atu027 once weekly.

| | |
|---|---|
| Subject analysis set title | PK analysis set - Atu027 twice weekly |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

3 subjects of the safety cohort plus 4 subjects of Arm 2 who all received Atu027 twice weekly.

### Primary: PK Atu027siRNA - Cmax

| | |
|---|---|
| End point title | PK Atu027siRNA - Cmax[1] |

End point description:

The maximum serum concentration that Atu027siRNA achieved after it has been administrated and before administration of the next dose.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Cycle 1

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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| End point values | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[2] | 7 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Atu027 First Administration | 142.33 (± 10.7) | 130.44 (± 32.1) | | |
| Atu027 Sixth Administration | 146.27 (± 35.2) | 152.16 (± 32.6) | | |

Notes:

[2] - 1st Admin: samples of 4 subjects were available. 6th Admin: samples of 2 subjects were available.

## Statistical analyses

No statistical analyses for this end point

## Primary: PK Atu027siRNA - tmax

| End point title | PK Atu027siRNA - tmax[3] |
|---|---|

End point description:

The time taken to reach the maximum concentration of Atu027siRNA.

| End point type | Primary |
|---|---|

End point timeframe:

Cycle 1

Notes:

[3] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| End point values | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[4] | 7 | | |
| Units: hour | | | | |
| median (full range (min-max)) | | | | |
| Atu027 First Administration | 4.25 (4 to 4.5) | 4 (1 to 4.5) | | |
| Atu027 Sixth Administration | 4 (4 to 4) | 4 (2 to 4.5) | | |

Notes:

[4] - 1st (6th) Admin: samples of 4 (2) subjects were available. Infusion took place over 4 hours.

## Statistical analyses

No statistical analyses for this end point

## Primary: PK Atu027siRNA - AUClast

| End point title | PK Atu027siRNA - AUClast[5] |
|---|---|

End point description:

Area under the plasma concentration time curve from zero to the time of last measurable conentration for Atu027siRNA.

| End point type | Primary |
|---|---|

End point timeframe:

Cycle 1

Notes:

[5] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| **End point values** | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[6] | 7 | | |
| Units: ng x h/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Atu027 First adeministration | 902.4 (± 42.9) | 801.7 (± 27.6) | | |
| Atu027 Sixth Administration | 1297.9 (± 33.6) | 1037.4 (± 31.9) | | |

Notes:

[6] - 1st Admin: samples of 4 subjects were available. 6th Admin: samples of 2 subjects were available.

## Statistical analyses

No statistical analyses for this end point

## Primary: PK AtuFect01 - Cmax

| End point title | PK AtuFect01 - Cmax[7] |
|---|---|

End point description:

The maximum serum concentration that AtuFect01 achieved after it has been administrated and before administration of the next dose.

| End point type | Primary |
|---|---|

End point timeframe:

Cycle 1

Notes:

[7] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| **End point values** | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[8] | 7 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Atu027 First Administration | 6824 (± 15.4) | 6775.1 (± 13.6) | | |
| Atu027 Sixth Administration | 6841.8 (± 21.2) | 9990.9 (± 13.2) | | |

Notes:

[8] - 1st Admin: samples of 4 subjects were available. 6th Admin: samples of 2 subjects were available.

## Statistical analyses

No statistical analyses for this end point

## Primary: PK AtuFect01 - tmax

| End point title | PK AtuFect01 - tmax[9] |
|---|---|

End point description:

The time taken to reach the maximum concentration of AtuFect01.

| End point type | Primary |
|---|---|

End point timeframe:

Cycle 1

Notes:

[9] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| End point values | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[10] | 7 | | |
| Units: hour | | | | |
| median (full range (min-max)) | | | | |
| Atu027 First Administration | 6.2 (4.5 to 8) | 6 (4.5 to 8) | | |
| Atu027 Sixth Administration | 6.9 (6 to 7.8) | 4.5 (4.5 to 8) | | |

Notes:

[10] - 1st Admin: samples of 4 subjects were available. 6th Admin: samples of 2 subjects were available.

### Statistical analyses

No statistical analyses for this end point

## Primary: PK AtuFect01 - AUClast

| End point title | PK AtuFect01 - AUClast[11] |
|---|---|

End point description:

Area under the plasma concentration time curve from zero to the time of last measurable conentration for AtuFect01.

| End point type | Primary |
|---|---|

End point timeframe:

Cycle 1

Notes:

[11] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| End point values | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[12] | 7 | | |
| Units: h x ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Atu027 First Administration | 116200 (± 20.8) | 123375 (± 12.9) | | |

| | | | | |
|---|---|---|---|---|
| Atu027 Sixth Administration | 120551 (± 27.7) | 182571 (± 19) | | |

Notes:

[12] - 1st Admin: samples of 4 subjects were available. 6th Admin: samples of 2 subjects were available.

## Statistical analyses

No statistical analyses for this end point

## Primary: PK Lipid DPyPE - Cmax

| End point title | PK Lipid DPyPE - Cmax[13] |
|---|---|

End point description:

The maximum serum concentration that Lipid DPyPE achieved after it has been administrated and before administration of the next dose.

| End point type | Primary |
|---|---|

End point timeframe:

Cycle 1

Notes:

[13] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| End point values | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[14] | 7 | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Atu027 First Administration | 5848.1 (± 12.9) | 5521.5 (± 17.1) | | |
| Atu027 Sixth Administration | 5347.7 (± 16.1) | 7675 (± 20.7) | | |

Notes:

[14] - 1st Admin: samples of 4 subjects were available. 6th Admin: samples of 2 subjects were available.

## Statistical analyses

No statistical analyses for this end point

## Primary: PK Lipid DPyPE - tmax

| End point title | PK Lipid DPyPE - tmax[15] |
|---|---|

End point description:

The time taken to reach the maximum concentration of Lipid DPyPE.

| End point type | Primary |
|---|---|

End point timeframe:

Cycle 1

Notes:

[15] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| End point values | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[16] | 7 | | |
| Units: hour | | | | |
| median (full range (min-max)) | | | | |
| Atu027 First Administration | 4.5 (4 to 8) | 4.5 (4 to 8) | | |
| Atu027 Sixth Administration | 7.9 (7.8 to 8) | 4.5 (4.5 to 7.6) | | |

Notes:

[16] - 1st Admin: samples of 4 subjects were available. 6th Admin: samples of 2 subjects were available.

### Statistical analyses

No statistical analyses for this end point

## Primary: PK Lipid DPyPE - AUClast

| End point title | PK Lipid DPyPE - AUClast[17] |
|---|---|

End point description:

Area under the plasma concentration time curve from zero to the time of last measurable conentration for Lipid DPyPE.

| End point type | Primary |
|---|---|

End point timeframe:

Cycle 1

Notes:

[17] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| End point values | PK analysis set - Atu027 once weekly | PK analysis set - Atu027 twice weekly | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 4[18] | 7 | | |
| Units: h x ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| Atu027 First Administration | 95237 (± 12.7) | 98685 (± 15.3) | | |
| Atu027 Sixth Administration | 93996 (± 21.1) | 136133 (± 19.5) | | |

Notes:

[18] - 1st Admin: samples of 4 subjects were available. 6th Admin: samples of 2 subjects were available.

### Statistical analyses

No statistical analyses for this end point

## Primary: Number of adverse events

| End point title | Number of adverse events[19] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Adverse events were reported from Baseline until 5 weeks after end of treatment or premature termination.

Notes:

[19] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| **End point values** | Arm 1: Atu027 once weekly | Arm 2: Atu027 twice weekly | Total | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 12 | 23 | |
| Units: adverse events | 116 | 147 | 263 | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with adverse events

| End point title | Number of subjects with adverse events[20] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Adverse events were reported from Baseline until 5 weeks after end of treatment or premature termination.

Notes:

[20] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| **End point values** | Arm 1: Atu027 once weekly | Arm 2: Atu027 twice weekly | Total | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 12 | 23 | |
| Units: subject | 11 | 11 | 22 | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of adverse events related to Atu027

| End point title | Number of adverse events related to Atu027[21] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Adverse events were reported from Baseline until 5 weeks after end of treatment or premature termination.

Notes:

[21] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| **End point values** | Arm 1: Atu027 once weekly | Arm 2: Atu027 twice weekly | Total | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 12 | 23 | |
| Units: adverse events | 25 | 24 | 49 | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with adverse events related to Atu027

| End point title | Number of subjects with adverse events related to Atu027[22] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Adverse events were reported from Baseline until 5 weeks after end of treatment or premature termination.

Notes:

[22] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| **End point values** | Arm 1: Atu027 once weekly | Arm 2: Atu027 twice weekly | Total | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 12 | 23 | |
| Units: subject | 5 | 7 | 12 | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of serious adverse events

| End point title | Number of serious adverse events[23] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Adverse events were reported from Baseline until 5 weeks after end of treatment or premature termination.

Notes:

[23] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| **End point values** | Arm 1: Atu027 once weekly | Arm 2: Atu027 twice weekly | Total | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 12 | 23 | |
| Units: adverse events | 13 | 10 | 23 | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of subjects with serious adverse events

| End point title | Number of subjects with serious adverse events[24] |
|---|---|

End point description:

| End point type | Primary |
|---|---|

End point timeframe:

Adverse events were reported from Baseline until 5 weeks after end of treatment or premature termination.

Notes:

[24] - 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: No statistical analyses was planned for this Phase Ib/IIa clinical study.

| **End point values** | Arm 1: Atu027 once weekly | Arm 2: Atu027 twice weekly | Total | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 11 | 12 | 23 | |
| Units: subject | 9 | 7 | 16 | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from Baseline until 5 weeks after end of treatment or premature termination.

| | |
|---|---|
| Assessment type | Non-systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety period |

Reporting group description:

The three subjects of the safety cohort with non-pancreatic cancer and for whom conventional treatment options had failed were treated for one 28-day treatment cycle with 0.253 mg/kg Atu027 i.v. twice weekly for four weeks and gemcitabine 1,000 mg/m2 (doses could have been reduced based on toxicity) once weekly for the first three weeks.

| | |
|---|---|
| Reporting group title | Treatment period: Arm 1: Atu027 once weekly |

Reporting group description:

Arm 1 of the treament period received 0.253 mg/kg Atu027 administered i.v. and gemcitabine 1,000 mg/m² (doses could have been reduced based on toxicity) once weekly for three consecutive weeks in 28-day treatment cycles.

| | |
|---|---|
| Reporting group title | Treatment period: Arm 2: Atu027 twice weekly |

Reporting group description:

Arm 2 of the treatment period received 0.253 mg/kg Atu027 administered i.v. twice weekly for four consecutive weeks and gemcitabine 1,000 mg/m² (doses could have been reduced based on toxicity) once weekly for three consecutive weeks in 28-day treatment cycles. Each combination cycle was followed by a gemcitabine-monotherapy cycle.

| **Serious adverse events** | Safety period | Treatment period: Arm 1: Atu027 once weekly | Treatment period: Arm 2: Atu027 twice weekly |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 9 / 11 (81.82%) | 7 / 12 (58.33%) |
| number of deaths (all causes) | 0 | 3 | 3 |
| number of deaths resulting from adverse events | | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 11 (27.27%) | 2 / 12 (16.67%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| Tumour pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Concussion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Device occlusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Extravasation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| multi-organ failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Ileus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Biliary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Safety period | Treatment period: Arm 1: Atu027 once weekly | Treatment period: Arm 2: Atu027 twice weekly |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 3 (100.00%) | 11 / 11 (100.00%) | 11 / 12 (91.67%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vasculitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 5 / 11 (45.45%) | 5 / 12 (41.67%) |
| occurrences (all) | 2 | 7 | 7 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 2 / 11 (18.18%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 3 | 5 |
| Chest pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Chills | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injection site reaction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Localised oedema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 11 (27.27%) | 5 / 12 (41.67%) |
| occurrences (all) | 0 | 4 | 7 |
| Pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|---|---|---|
| Cough | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 2 | 2 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Apathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Emotional distress | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Panic attack | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 11 (27.27%) | 4 / 12 (33.33%) |
| occurrences (all) | 1 | 8 | 7 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 11 (9.09%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 2 | 2 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 11 (27.27%) | 8 / 12 (66.67%) |
| occurrences (all) | 1 | 7 | 13 |
| Alanine aminotransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 3 / 12 (25.00%) |
| occurrences (all) | 0 | 2 | 3 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 3 | 2 |
| Protein total decreased | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| White blood cell count increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 2 |
| Laceration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skull fracture | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Syncope | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood and lymphatic system disorders | | | |

| | | | |
|---|---|---|---|
| Anaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 11 (27.27%) | 6 / 12 (50.00%) |
| occurrences (all) | 1 | 4 | 8 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemorrhagic anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 2 | 1 |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Thrombocytosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Ear and labyrinth disorders | | | |
| Hearing impaired | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Vertigo | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vestibular disorder | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Ascites | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 2 | 1 |
| Abdominal hernia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Constipation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Faecal vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Ileus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Impaired gastric emptying | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Melaena | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|---|---|---|---|
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 5 / 11 (45.45%) | 7 / 12 (58.33%) |
| occurrences (all) | 0 | 5 | 8 |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 3 / 11 (27.27%) | 5 / 12 (41.67%) |
| occurrences (all) | 0 | 3 | 5 |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Erythema | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Endocrine disorders | | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 11 (0.00%) | 3 / 12 (25.00%) |
| occurrences (all) | 1 | 0 | 3 |
| Device related infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mucosal infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Postoperative wound infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Prostate infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 11 (9.09%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |

| | | | |
|---|---|---|---|
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 11 (9.09%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 3 / 12 (25.00%) |
| occurrences (all) | 0 | 2 | 3 |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 11 (18.18%) | 3 / 12 (25.00%) |
| occurrences (all) | 0 | 4 | 4 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 11 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 13 February 2013 | The following changes were introduced before subject enrolment:<br>• The inclusion and exclusion criteria for the safety period were adapted to those for the main part except for those referring to the primary indication.<br>• The criteria for subject withdrawal were revised.<br>• Expected toxicities under treatment with gemcitabine and Atu027 and the management of toxicities attributable to gemcitabine or Atu027 were included. Increased blood lipase and fatigue were the most common Atu027-related adverse events in the phase I study. In this study these were expected due to the underlying disease. However, grade 3 fatigue and a severe increase in lipase values were considered unacceptable and dosing with Atu027 was to be adjusted. Lipase values were to be monitored closely.<br>• Information on the calculation of doses of gemcitabine and Atu027 was added.<br>• The measurement of blood urea nitrogen was deleted because separate urea and creatinine measurements were assumed to be sufficient for the evaluation of renal function.<br>• Disease response was to be evaluated based on the clinical judgment of the investigator at the end of treatment/premature termination (EOT/PT) visit, 5 weeks after EOT/PT, and during the 1-year follow up.<br>• A time window for the EoT/PT visit was included.<br>• Concomitant medications were only to be documented until the EoT/PT visit instead of up to FU Visit 1.<br>• Further corrections and adaptations for consistency were made. |
| 27 August 2013 | • Introduction of an electronic SAE reporting system.<br>• Deletion of study visits: in Arm 2, visits at Days 1, 8, 15, 22, and 25 in cycles in which only gemcitabine was administered were deleted. All safety assessments initially planned to be performed at Day 1 were therefore rescheduled to Day 4.<br>• Formal change: corrections of the RECIST Version (an incorrect version was erroneously referenced in protocol version 2.0). |
| 12 May 2014 | • The name of the company was changed to Silence Therapeutics GmbH. All references were adjusted accordingly.<br>• Exclusion criterion #2 was changed from haemoglobin A1c (HbA1c) > or = 7% to haemoglobinA1c (HbA1c) > or = 8% to allow more subjects to be treated with Atu027. The lower value was still considered prudent to avoid any suitable subject being unnecessarily denied therapy.<br>• A footnote was added stating that for the 12-lead ECG at Baseline, data from the subject's medical record (within the last 7 days) may be used.<br>• Clarified that the safety laboratory is to be done within 24 hours before the start of gemcitabine/Atu027.<br>• Clarified that the investigator could make the dose adjustment for Atu027 earlier on his own discretion (during the cycle or in case the weight changed less than 10 %). This change was done to clarify that the dose can always be adjusted to the actual weight.<br>• Clarified that the dose of gemcitabine was added stating that the dose should be adjusted to the actual body weight. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported