



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
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Silence Therapeutics GmbH
Sponsor organisation address	Robert-Rössle-Str. 10, Berlin, Germany, 13125
Public contact	Mike Khan, PhD, Silence Therapeutics GmbH Robert-Rössle-Str. 10, 13125 Berlin, +49 30 9489 2800,
Scientific contact	Mike Khan, PhD, Silence Therapeutics GmbH Robert-Rössle-Str. 10, 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 treatment 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
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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-monootherapy 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-monootherapy 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
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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: gemcitabine 1,000 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-monootherapy 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
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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 Gemcitabine once weekly.

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

Subject analysis sets

Subject analysis set title	PK analysis set - Atu027 once weekly
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Subject analysis set type	Safety analysis
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Subject analysis set description:

4 subjects of Arm 1 who received Atu027 once weekly.

Subject analysis set title	PK analysis set - Atu027 twice weekly
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Subject analysis set type	Safety analysis
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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			
Units: Subjects			
Adults (18-64 years)	2	2	
From 65-84 years	2	5	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	2	5	
Male	2	2	

ECOG performance status			
Units: Subjects			
ECOG 0			
ECOG 1			

End points

End points reporting groups

Reporting group title	Arm 1: Atu027 once weekly
Reporting group description: Arm 1 of the treatment period received 0.253 mg/kg Atu027 administered i.v. and gemcitabine 1,000 mg/m ² (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/m ² (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 administered 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]
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End point description:

The time taken to reach the maximum concentration of Atu027siRNA.

End point type	Primary
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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]
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End point description:

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

End point type	Primary
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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 administration	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 - Atufect01 once weekly	PK analysis set - Atufect01 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))				
Atufect01 First Administration	6.2 (4.5 to 8)	6 (4.5 to 8)		
Atufect01 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 concentration 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 - Atufect01 once weekly	PK analysis set - Atufect01 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)				
Atufect01 First Administration	116200 (± 20.8)	123375 (± 12.9)		

Atu027 Sixth Administration	120551 (\pm 27.7)	182571 (\pm 19)		
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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]
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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
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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 (\pm 12.9)	5521.5 (\pm 17.1)		
Atu027 Sixth Administration	5347.7 (\pm 16.1)	7675 (\pm 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]
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End point description:

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

End point type	Primary
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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]
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End point description:

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

End point type	Primary
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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]
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End point description:

End point type	Primary
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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]
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End point description:

End point type	Primary
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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]
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End point description:

End point type	Primary
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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]
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End point description:

End point type	Primary
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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]
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End point description:

End point type	Primary
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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]
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End point description:

End point type	Primary
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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
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Dictionary used

Dictionary name	MedDRA
Dictionary version	16

Reporting groups

Reporting group title	Safety period
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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
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Reporting group description:

Arm 1 of the treatment 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
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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 occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 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 occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	2 / 11 (18.18%) 2	2 / 12 (16.67%) 2
Pulmonary embolism subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Apathy subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Emotional distress subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Panic attack subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Investigations			
Neutrophil count decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	3 / 11 (27.27%) 8	4 / 12 (33.33%) 7
White blood cell count decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 11 (9.09%) 2	2 / 12 (16.67%) 2
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	3 / 11 (27.27%) 7	8 / 12 (66.67%) 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 occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	1 / 12 (8.33%) 2
Laceration			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Rib fracture			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Skull fracture			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Cardiac failure			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Sinus tachycardia			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Nervous system disorders			
Dizziness			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Peripheral sensory neuropathy			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Syncope			
subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 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 occurrences (all)	0 / 3 (0.00%) 0	5 / 11 (45.45%) 5	7 / 12 (58.33%) 8
Stomatitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	3 / 11 (27.27%) 3	5 / 12 (41.67%) 5
Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Erythema subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Pruritus subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 11 (0.00%) 0	1 / 12 (8.33%) 1
Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Renal and urinary disorders Cystitis noninfective subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 0
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 11 (9.09%) 1	0 / 12 (0.00%) 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	<p>The following changes were introduced before subject enrolment:</p> <ul style="list-style-type: none">• 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.• The criteria for subject withdrawal were revised.• 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.• Information on the calculation of doses of gemcitabine and Atu027 was added.• 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.• 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.• A time window for the EoT/PT visit was included.• Concomitant medications were only to be documented until the EoT/PT visit instead of up to FU Visit 1.• Further corrections and adaptations for consistency were made.
27 August 2013	<ul style="list-style-type: none">• Introduction of an electronic SAE reporting system.• 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.• Formal change: corrections of the RECIST Version (an incorrect version was erroneously referenced in protocol version 2.0).
12 May 2014	<ul style="list-style-type: none">• The name of the company was changed to Silence Therapeutics GmbH. All references were adjusted accordingly.• 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.• 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.• Clarified that the safety laboratory is to be done within 24 hours before the start of gemcitabine/Atu027.• 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.• 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