Clinical trial results:
Safety, pharmacokinetics and efficacy of AXP107-11 in combination with standard gemcitabine (Gemzar®) treatment in patients with locally advanced or metastatic, unresectable, adenocarcinoma of the pancreas, stage III-IV. A prospective, open label, multi-centre, sequential phase Ib/IIa study.

Summary

EudraCT number	2010-019214-25
Trial protocol	SE
Global end of trial date	07 December 2014

Results information

Result version number	v1 (current)
This version publication date	27 July 2017
First version publication date	27 July 2017
Summary attachment (see zip file)	AXP107-11 Clinical Study Report Synopsis (AXC001_CSR_Final 1.0_2017-05-30_synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	AXP-CT-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01182246
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Axcentua Pharmaceuticals AB
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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	07 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 December 2014
Global end of trial reached?	Yes
Global end of trial date	07 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objectives

Phase Ib
The primary objective is to determine the safety profile and MTD of AXP107-11 alone and when given in combination with gemcitabine standard therapy.
Safety will be assessed by occurrence of adverse events, abnormal changes in laboratory parameters, vital signs, ECG and relevant patient withdrawal.

Phase IIa
The primary objective is to assess the effect of a combination therapy of AXP107-11 and gemcitabine on objective response rate defined as the percentage of patients who showed complete response (CR) or partial response (PR).

Protection of trial subjects:

The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki that are consistent with International Conference on Harmonisation/Good Clinical Practice and applicable regulatory requirements. Informed consent was obtained from all patients prior to initiation of the study.

During Phase Ib, patients were hospitalised during the first 24 hours on Day -13 and Day 1 for close safety monitoring and PK sampling. The safety evaluation was based on clinical signs and symptoms and laboratory safety assessments (including complete blood count).

A study patient was withdrawn from the study treatment if, in the opinion of the Investigator, it was medically necessary (e.g. unacceptable AE), or if it was the expressed wish of the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	12
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was performed at 2 clinical sites in Stockholm, Sweden.
Consenting patients were screened for eligibility within 2 weeks prior to start of AXP107-11 treatment. Eligible patients were included in consecutive order into the initial dose-escalation part of the study (phase Ib) or directly into the maintenance part (phase IIa).

Pre-assignment

Screening details:

Male and female patients ≥ 18 years of age who were chemotherapy naive with histologically confirmed, unresectable, locally advanced or metastatic pancreatic cancer stage III-IV with a Karnofsky Performance Status (KPS) score ≥ 70 and life expectancy of more than 3 months were considered for participation.

Period 1

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

Arms

Arm title	AXP107-11 alone and when given in combination with gemcitabine

Arm description:

Phase Ib:
Four cohorts, of 3 to 7 patients each, were treated with escalating dose levels of AXP107-11 alone (2 weeks) and in combination with gemcitabine (1 week).

All patients included in the dose escalation phase were evaluated for the presence of dose limiting toxicity (DLT). Patients who did not fulfill any discontinuation criteria and who were not in disease progression were continued into the maintenance phase of the study (i.e. Phase IIa). All phase Ib patients were progressed to Phase IIa. No new patients enrolled directly into Phase IIa.

Phase IIa:
Patients started treatment with AXP107-11 alone for 2 weeks, followed by combination treatment with gemcitabine. Study treatment with the combination treatment was continued until disease progression, severe toxicity, patient withdrawal or a maximum of 6 months, whichever came first.
Follow-up:
All patients had a follow-up evaluation 28 ± 7 days after the last administration of study medication, if possible.

Arm type	Experimental
Investigational medicinal product name	AXP107-11 (4',5,7-trihydroxyisoflavone-Na-dihydrate)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Phase Ib:
In the dose escalation part of the study (phase Ib), AXP107-11 was administered once daily on the first treatment day (morning) to get a 24-hour PK profile, followed by twice daily administrations continuously throughout the treatment period. Patients were hospitalised for 24 hours on Day -13 and Day 1 for close safety monitoring and PK sampling. The patients within each dose level started treatment sequentially with at least 24 hrs between each patient, following a safety evaluation of the previous patient(s). AXP107-11 dosage was escalated as follows; 400 mg daily, 800 mg daily, 1200 mg daily and 1600 mg daily.

Phase IIa:
All 16 patients from Phase Ib continued in a modified maintenance phase (Phase IIa) in which they were treated with the dose of AXP107-11 that they received during Phase Ib; dose-escalation phase. Phase

IIa patients started treatment with AXP107-11 alone for 2 weeks, followed by combination treatment with gemcitabine.

Number of subjects in period 1	AXP107-11 alone and when given in combination with gemcitabine
Started	16
Completed	4
Not completed	12
Adverse event, non-fatal	1
Compliance issues	1
Disease Progression	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study (overall period)
Reporting group description:	
Male and female (≥ 18 years) chemotherapy naive patients with histologically confirmed, unresectable, locally advanced or metastatic pancreatic cancer stage III-IV treated with AXP107-11 alone and in combination with Gemcitabine (Gemzar®).	

Reporting group values	Overall Study (overall period)	Total	
Number of subjects	16	16	
Age categorical			
Male and female (≥ 18 years) chemotherapy naive patients with histologically confirmed, unresectable, locally advanced or metastatic pancreatic cancer stage III-IV treated with AXP107-11 alone and in combination with Gemcitabine (Gemzar®).			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	4	4	
85 years and over	0	0	
Age continuous			
Male and female (≥ 18 years) chemotherapy naive patients with histologically confirmed, unresectable, locally advanced or metastatic pancreatic cancer stage III-IV treated with AXP107-11 alone and in combination with Gemcitabine (Gemzar®).			
Units: years			
median	61		
full range (min-max)	35 to 73	-	
Gender categorical			
Male and female (≥ 18 years) chemotherapy naive patients with histologically confirmed, unresectable, locally advanced or metastatic pancreatic cancer stage III-IV treated with AXP107-11 alone and in combination with Gemcitabine (Gemzar®).			
Units: Subjects			
Female	4	4	
Male	12	12	

End points

End points reporting groups

Reporting group title	AXP107-11 alone and when given in combination with gemcitabine

Reporting group description:

Phase Ib:
Four cohorts, of 3 to 7 patients each, were treated with escalating dose levels of AXP107-11 alone (2 weeks) and in combination with gemcitabine (1 week).

All patients included in the dose escalation phase were evaluated for the presence of dose limiting toxicity (DLT). Patients who did not fulfill any discontinuation criteria and who were not in disease progression were continued into the maintenance phase of the study (i.e. Phase IIa). All phase Ib patients were progressed to Phase IIa. No new patients enrolled directly into Phase IIa.

Phase IIa:
Patients started treatment with AXP107-11 alone for 2 weeks, followed by combination treatment with gemcitabine. Study treatment with the combination treatment was continued until disease progression, severe toxicity, patient withdrawal or a maximum of 6 months, whichever came first.
Follow-up:
All patients had a follow-up evaluation 28 ± 7 days after the last administration of study medication, if possible.

Primary: Karnofsky Performance Status scale (KPS)

End point title	Karnofsky Performance Status scale (KPS)[1]

End point description:

KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks. The KPS scores range from 0 to 100. A higher score means the patient is better and able to carry out daily activities.

100-80 = Able to carry on normal activity and to work; no special care needed.
50-70 = Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.
40 -0 = Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.

End point type	Primary

End point timeframe:

Karnofsky Performance Status scale (KPS) was assessed at screening, baseline (Day -13) and thereafter weekly during the study period, including follow-up.

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 formal statistical and analytical plan was written. Descriptive data are summarised and/or listed as considered appropriate.

End point values	AXP107-11 alone and when given in combination with gemcitabine			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: performance score				
number (not applicable)				
Positive; improvement of ≥ 20 points from baseline	0			

Negative; worsening of ≥ 20 points from baseline	11			
Stable; any other result	5			

Statistical analyses

No statistical analyses for this end point

Primary: Tumor response (RECIST)

End point title	Tumor response (RECIST)[2]

End point description:

Evaluation of target and non-target lesions for:
- Complete Response (CR)
- Partial Resposnse (PR)
- Progressive Disease (PD)
- Stable Disease (SD)
- non CR/non-PD

End point type	Primary

End point timeframe:

Tumour response was evaluated at the following time points: Visit 8 (Day 1), Visit 14 (Day 29), Visit 17 (Day 50), Visit 25 (week 4 of cycle 3), Visit 33 (week 4 of cycle 5), as a confirmation of CR or PR after 4 weeks, at the follow-up.

Notes:

[2] - 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 formal statistical and analytical plan was written. Descriptive data are summarised and/or listed as considered appropriate.

End point values	AXP107-11 alone and when given in combination with gemcitabine			
Subject group type	Reporting group			
Number of subjects analysed	16			
Units: lesion size				
number (not applicable)				
Complete Response (CR)	0			
Partial Resposnse (PR)	2			
Progressive Disease (PD	7			
Stable Disease (SD)	7			
non CR/non-PD	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

AEs were to be noted during the single agent AXP107-11 treatment period (Days -13 and -6) and during cycle 1 (Days 1, 8, 15, 22, 29, 36, and 43) and during the remaining cycles on Days 1, 8, 15 and at follow-up.

Adverse event reporting additional description:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Overall Study

Reporting group description:

Male and female (≥ 18 years) chemotherapy naive patients with histologically confirmed, unresectable, locally advanced or metastatic pancreatic cancer stage III-IV treated with AXP107-11 alone and in combination with Gemcitabine (Gemzar®).

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: AEs were not summarised in tables by system organ class and preferred term.
AEs were not coded according to Medical Dictionary for Regulatory Activities (MedDRA)

Serious adverse events	Overall Study		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 16 (50.00%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	0		
General disorders and administration site conditions			
Pain	Additional description: Severe. Unlikely related to IMP. Treatment temporarily stopped.		
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain	Additional description: Severe Unlikely related to IMP. Treatment stopped.		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal obstruction	Additional description: Moderate. Unlikely related to IMP. Treatment temporarily stopped.		

subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct obstruction	Additional description: Moderate. Unlikely related to IMP. Treatment temporarily stopped.		
subjects affected / exposed	1 / 16 (6.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis	Additional description: Severe. Medical Monitor - possibly related to IMP Investigator - unlikely related to IMP		
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection	Additional description: Severe. Unlikely related to IMP. Treatment stopped.		
subjects affected / exposed	2 / 16 (12.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Overall Study		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2011	Clinical Study Protocol Amendment 1 Final dated 2011-05-10 Changes in the conduct of the study.
17 April 2012	Clinical Study Protocol Amendment 2 Final dated 2012-02-20 Final Changes in the conduct of the study, blood sampling (PK analyses).
28 May 2013	Clinical Study Protocol Amendment 3 dated 2013-03-18 Changes in conduct of the study, changes in patient information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported