CLINICAL STUDY REPORT

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.

Sponsor Study Code:	AXP107-11
EudraCT Number:	2010-019214-25
Report Version and Date:	Final Version 1.0, 2017-05-30
Phase:	Phase Ib/IIa
Test Product:	AXP107-11 in escalating doses (Phase Ib) followed by treatment with maintenance dose (phase IIa) in combination with gemcitabine standard therapy.
Proposed Indication:	Pancreatic cancer stage III/IV
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First Patient First Visit:	2010-11-03
First Patient First Dose:	2010-11-16
Last Patient Last Visit:	2014-09-23
Last Collection of Survival Data:	2014-12-07

1 SIGNATURES

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.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Principal Investigator:

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Date

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Axcentua Pharmaceuticals AB

17 06 02
Date

Biostatistician:

Ronny Westberg
RW Clinical Trials AB

June 1, 2017
Date

2 SYNOPSIS

Name of Sponsor/Company:

Axcentua Pharmaceuticals AB

Name of Finished Product:

AXP107-11

Name of Active Ingredient:

4',5,7-trihydroxyisoflavone-Na-dihydrate

Study Title:

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.

Coordinating Investigator:

Matthias Löhr, MD, PhD, Professor.

Study Centres:

Site 1: Dept. of Clinical Science, Intervention and Technology, Div. of surgery, Karolinska University Hospital, Huddinge, Sweden.
Site 2: Radiumhemmet, Sektionen för Gastrointestinal, Urologisk och Neuroendokrin Cancer, Onkologiska kliniken, Karolinska University Hospital, Solna, Sweden.

Publication based on the study (reference):

Löhr J-M, Karimi M., Omazic B., Kartalis N., Verbeke C.S., Berkenstam A., Frödin J-E. A phase I dose escalation trial of AXP107-11, a novel multi-component crystalline form of genistein, in combination with gemcitabine in chemotherapy-naive patients with unresectable pancreatic cancer. Pancreatology 2016 Jul-Aug;16(4):640-645.

Studied period (years):	**Phase of development:**
First patient first Visit: 2010-11-03 First patient first dose: 2010-11-16 Last patient last Visit: 2014-09-23 Last collection of survival data: 2014-12-07	Phase Ib/IIa

Objectives:

Primary objective:

Phase Ib

- The primary objective was to determine the safety profile and the maximum tolerated dose (MTD) of AXP107-11 alone and when given in combination with gemcitabine standard therapy.
  Safety was assessed by occurrence of adverse events (AEs), abnormal changes in laboratory parameters, vital signs, electrocardiogram (ECG) and relevant patient withdrawal.

Phase IIa

- The primary objective was 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).

Secondary objectives

Phase Ib

Determined the pharmacokinetic (PK) profile of escalating doses of AXP107-11.

Phase IIa

- To assess the safety and tolerability of a combination therapy of AXP107-11 and gemcitabine. Safety was assessed by occurrence of AEs, abnormal changes in laboratory parameters, vital signs, ECG, relevant patient withdrawal and percentage of patients having reduction, omission or discontinuation of any study medication.

- To assess the effect of a combination therapy of AXP107-11 and gemcitabine on overall survival (OS).
- To assess the effect of a combination therapy of AXP107-11 and gemcitabine on overall survival rate at 6 months after start of combination therapy.
- To assess the effect of a combination therapy of AXP107-11 and gemcitabine on time to progression according to response evaluation criteria in solid tumours (RECIST).
- To assess the effect of a combination therapy of AXP107-11 and gemcitabine on palliation, defined as the percentage of patients who showed CR, PR or stable disease (SD) according to RECIST.
- To assess the effect of a combination therapy of AXP107-11 and gemcitabine on clinical benefit response (CBR), a composite of measurements of pain (pain intensity and analgesics consumption), Karnofsky performance status and weight.
- To assess the effect of combination therapy of AXP107-11 and gemcitabine on the tumour mass and permeability using computed tomography (CT) and F-18 fluorodeoxyglucose positron emission tomography, respectively.
- To assess the effect of a combination therapy of AXP107-11 and gemcitabine on symptom distress score as measured by the Edmonton Symptom Assessment System (ESAS).
- To assess the effect of a combination therapy of AXP107-11 and gemcitabine on quality of life as assessed by the EORTC QLQ-C30 questionnaire and the PAN26 module.

Study design:

This was a prospective, open label, multi-centre, sequential phase Ib/IIa study.

Consenting patients were screened for eligibility within 2 weeks prior to start of study treatment. Eligible patients were included in consecutive order in the initial dose-escalation part of the study (phase Ib) or directly into the maintenance part (phase IIa).

Phase Ib; dose-escalation

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). Patients within each dose level started treatment with AXP107-11 sequentially with at least 24 h between each patient, following a safety evaluation of the previous patient(s). A dose escalation of AXP107-11 was performed following a careful safety evaluation on Day 8, until the highest dose level had been evaluated or an MTD had been defined.

All patients included in the dose escalation phase were evaluated for the presence of dose limiting toxicity (DLT) on Day 8. Patients who did not fulfil any discontinuation criteria and who were not in disease progression were continued into the maintenance phase of the study. These patients continued AXP107-11 treatment on the dose level initiated together with gemcitabine, continuing the 7-week cycle, followed by 3-week cycles until the end of the 6-month treatment period.

Phase IIa; maintenance phase

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.
The first 7-week cycle included 17 Visits to the clinic and the following 3-week cycles included 4 Visits/cycle.

Follow up

All patients had a follow-up evaluation 28 ± 7 days after the last administration of study medication, if possible. Each patient was also followed up long-term for survival and progression of their disease. All patients were also scheduled to visit the clinic according to normal clinical practice, which means that the patient visited the clinic approximately once a week.
Patients with an ongoing CR, PR or SD at the 28-day post-treatment evaluation visit, continued to be followed long-term at 12-week intervals (± 1 week) until disease progression, death, or initiation of another therapy.
Long-term follow-up of patients who had discontinued due to disease progression or due to any other discontinuation criteria was performed by weekly telephone calls by the study nurse to collect data regarding survival status and general health

For patients with documented tumour response (CR, PR) or SD and no intolerable toxicity after 6 months' combination treatment, AXP107-11 treatment was continued during the long-term follow-up, after approval by Axcentua Pharmaceuticals AB. These patients continued to be followed at long-term follow-up visits every 12 weeks (± 1 week).

The end of study was defined as 6 months after the last patient started combined treatment or after the last patient had deceased (whatever applied first).

Each patient was involved in the study for a maximum of 8 months with a long-term follow-up until death and/or disease progression.

Number of patients (planned and analysed):

	Total
No. planned:	Phase Ib = 24 patients, Phase IIa = 20 patients
No. included and treated:	16 patient in total (the patients were included in phase Ib and phase IIa [modified])
Males/females:	12/4
Median age:	61 (range 35-73)
No. analysed:	16
No. completed:	4

Diagnosis and main criteria for inclusion:

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.

Test product, dose and mode of administration, batch number:

Phase Ib

AXP107-11 (4',5,7-trihydroxyisoflavone-Na-dihydrate) 100-mg capsules were ingested orally once daily on the first treatment day, followed by twice daily administrations continuously throughout the study period. AXP107-11 was administered during 14 days prior to initiation of gemcitabine treatment. A maximum of 4 dose levels between 400 mg/day and 1600 mg/day were to be tested. The following doses were administered; 400 mg/day, 800 mg/day, 1200 mg/day and 1600 mg/day. The MTD was defined as the dose level at which at least 3 out of 6 patients experienced a DLT. The MTD was not reached.

Phase IIa (modified compared to the clinical study protocol)

The recommended dose of AXP107-11 used in the IIa part of the study (maintenance dose) was dose level 4 (1600 mg/day) or 80% of the MTD defined in phase Ib, rounded up/down to the nearest 100 mg. AXP107-11 was administered in combination with gemcitabine until disease progression, severe toxicity, patient withdrawal or during a maximum of 6 months, whichever came first.

Contrary to the plan outlined in the clinical study protocol, all patients from Phase Ib continued in a modified maintenance phase in which they were treated with the dose of AXP107-11 that they received during Phase Ib (dose levels between 400 mg/day and 1600 mg/day).

Gemcitabine (Gemzar®) was administrated by i.v. infusion, 1000 mg/m² over 30 min, once weekly. Gemcitabine was given starting with a 7-week cycle (dosing Days 1, 8, 15, 22, 29, 36 and 43) followed by repeated 3-weeks cycles (dosing Days 1, 8 and 15 of each treatment cycle). Each cycle was followed by 1 gemcitabine-free week.

All treatments and assessments planned for Phase IIa were performed with the exception of: PET examinations and CBR evaluation.

No new patients were included.

The following batches of AXP107-11 were used in the study: C10024A, C10024B, C11001A, C11001B, C11015A and C11015B.

Reference product, dose and mode of administration, batch number:

Not applicable.

Duration of treatment:

AXP107-11 was taken once daily the first day, followed by twice daily for 6 month. For patients with documented tumour response (CR, PR) or SD and no intolerable toxicity after 6 months' combination treatment, AXP107-11 treatment was continued during the long-term follow-up, after approval by Axcentua Pharmaceuticals AB.

Safety Assessments:

Safety was assessed by physical examination, weight, vital signs (blood pressure, heart rate, respiratory rate, temperature), ECG, clinical laboratory tests in blood (clinical chemistry, haematology) and urine, AE reporting and DLT.

Pharmacokinetic assessments:

The following pharmacokinetic (PK) parameters were determined:
Time before the start of absorption (t_{lag} [h])
Time of peak plasma concentration of AXP107-11 (T_{max} [h])
Peak plasma concentration of AXP107-11 (C_{max} [ng/mL])
Terminal phase elimination rate constant (K_{el})
Half-life associated with the terminal rate constant ($t_{1/2}$ [h])
Area under the plasma concentration time curve from 0 to infinity ($AUC_{0-\infty}$ [ng/h/mL])
Area under the concentration-time curve from time 0 to the time point (AUC [0-t_n] [ng/h/mL])
Percentage of AUC obtained by extrapolation (AUC[t_n-∞] [%])
Apparent volume of distribution during terminal phase (Vd/F [L])
Apparent total body clearance of drug from plasma (CL/F [mL/min])

Blood samples for analysis of PK parameters were collected during phase Ib:
• Day -13: pre-dose, 30 min, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose. After 2012-04-17 (Amendment 2), the time points for sampling were changes to: Day -13: pre-dose, 30 min, 45 min, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours post-dose.
• Days 1, 8 and 15: single samples for determination of plasma concentration of AXP107-11 before the gemcitabine infusion and at the individual max plasma concentration (T_{max}).

Efficacy Assessments:

Efficacy were assessed by Karnofsky performance status scale (KPS), clinical benefit response (CBR) according to a modified Burris scheme, tumour response (RECIST), tumour marker CA 19-9 (for confirmation of tumour response), exploratory biomarkers, tumour permeability measurements using positron emission tomography (PET), quality of life by EORTC QLQ-C30 questionnaire and PAN26 module, symptom severity assessment using the Edmonton Symptom Assessment System (ESAS), and survival status.

Statistical methods:

Descriptive data were summarized and/or listed as considered appropriate. Kaplan Meier curves were created to estimate time-to-event variables (e.g. time to progression, overall survival). The Pearson X^2-test or Fisher's exact test were used to compare proportions when appropriate. Time to progression and overall survival were calculated from the date of the first AXP107-11 dose given until the date of documented PD and death, respectively. Response duration was calculated from the date of the first documentation of response until the PD date. The Medlog System package, version 2013-6 (Analysis Corporation) was used for computerizing study data and for performing statistical analyses.

CBR was not evaluated. ESAS, EORTC QLQ-30 and PAN 26 data were listed.

SUMMARY OF RESULTS

SAFETY RESULTS:

Primary objective

- The study included 16 patients, of which 4 completed the study. All other patients were withdrawn and died due to disease progression. The 4 patients that completed the study died eventually due to disease progression.
- No toxic events were noted during the 2 weeks of AXP107-11 monotherapy and the drug did not seem to increase the toxicity when combined with gemcitabine.
- DLTs were observed in 7 patients. Seven patients had grade 3 non-haematological toxicities (cholangitis, allergy to contrast, fatigue/nausea, infection, vomiting, abdominal pain and pancreatitis). One patient reported a grade 4 haematological toxicity (neutropenia). This event was assessed as unrelated to AXP107-11 and did therefore not fulfil the DLT criteria. The events were distributed among the dose levels.
- Eight patients reported in total 10 SAEs of which 2 were assessed as related to the IMP by the investigator (cholecystitis and pancreatitis).
- Three SAEs from 2 patients (cholecystitis and pancreatitis) were reported as SUSAR.
- The MTD was not reached in the study. Due to concerns expressed by the patients related to a high capsule burden it was decided to stop the dose escalation at 1600 mg/day.
- A total of 13 patients (81%) reported AEs. Most patient reported unique AEs. A few AEs were reported more than once, for example neutropenia (3 patients) and cholecystitis (2 patients).
- Six patients reported AEs of severe intensity all of which were assessed as unlikely related to treatment with IMP. One patient reported a life-threatening AE (sepsis) also assessed as unlikely related to treatment with IMP.

EFFICACY RESULTS:

Primary objective

- No patients had a complete response but in 2 patients, partial responses (13%) were noted. The response was noted on the liver metastases and the pancreatic tumour and on the liver and lymph node metastases, respectively. A response duration of 7.1 months was noted in 1 patient, whose liver metastases responded fairly well to the treatment.

Secondary objectives

- Palliation, defined as CR, PR or SD, occurred in 9 of 16 patients (56%).
- In 7 patients, the disease was classified as stable, which meant a progression free period of at least 10 weeks.
- At progression, the most common progression site was the liver, 13 patients had progression observed in the liver. Other tumour progression sites found were the lymph nodes (3 patients), pancreas (2), bone (2), carcinos (1), peritoneal carcinos (1), omentum (1), and ascites (1).
- The median progression-free survival (PFS) was 2.6 months and the median overall survival (mOS) was 4.9 months. The outcome for women appeared considerably poorer than for the men: their PFS was 2.1 months *versus* 4.4 months in men and the women's mOS was 2.3 months *versus* 6.3 months in men.
- The overall survival appeared slightly better for patients without non-target lesions (mOS 6.3 months) compared to the patients who had non-target lesions (mOS 4.4 months).
- Seven patients (44%) survived longer than 6 months, and 3 patients (19%) were still alive at the 1-year follow-up.
- The survival appeared slightly better for the patients who had a Karnofsky index ≥90 at the start of the study (although only 2 patients had a Karnofsky index lower than 90).
- Several of the patients gained in weight above their weight at inclusion for short periods of time but no patient reached the positive criterion of: ≥ 7% increase from baseline, sustained for ≥ 4 weeks. The

majority of patients decreased in weight during the study (10 patients), and 6 patients more or less kept their weight during the study.

- A majority of the patients had decreased in weight already the last 3 months before inclusion into the study. The overall survival was to some extent better for the patients who had lost ≥5 kg, with a median overall survival of 6.8 months, compared to 3.6 months for the patients who lost <5 kg.
- Patients with lower C-reactive protein (CRP) levels at inclusion had a slightly longer time to tumour progression, median time to progression was 4.5 months compared to 1.9 months for the patients with higher CRP levels at inclusion.
- All patients had elevated S-CA 19-9 levels at the inclusion of the study. A drop of 50% or more in S-CA 19-9 was recorded in 8 patients during the treatment period. The overall survival was slightly better for the patients with higher S-CA 19-9 levels at the entrance of the study.
- *Data for Symptom distress score as measured by the Edmonton Symptom Assessment System (ESAS) after combination therapy with AXP107-11 and gemcitabine were only listed.*
- *Data for Quality of life as assessed by the EORTC QLQ-C30 questionnaire and the PAN26 module after combination therapy with AXP107-11 and gemcitabine were only listed.*

PHARMACOKINETICS:

- Sixteen patients were administered capsules containing AXP107-11 in the dose-cohorts: 200, 400, 600 and 800 mg, and the pharmacokinetics were evaluated after a single dose. The pre-dose samples showed no detectable concentrations of AXP107-11, and the post-dose plasma concentrations were detectable in samples from all patients.
- The absorption of AXP107-11 was rather rapid, generally the t_{lag} was between 0-45 min post-dose. The maximal plasma concentration, C_{max}, of AXP107-11 was reached between 1 to 3 hours post-dose (t_{max}), thereafter the concentration decreased rather rapidly with a multi-compartmental elimination curve.
- On average, the C_{max} increased from 181 to 291 µg/L (1.6 fold) and the corresponding $AUC_{0\text{-}12h}$ increased from 331 to 629 hr* µg/L (1.9-fold) after administering 400 or 800 mg AXP107-11. The increase in exposure indicated approximate dose proportionality after single dosing of AXP107-11 in the dose interval 400-800 mg.

OVERALL CONCLUSIONS:

The study included 16 patients, of which 4 completed the study. All other patients were withdrawn and died due to disease progression. The 4 patients that completed the study died eventually due to progressive disease.

Conclusions Phase Ib

Primary objective:

- The safety profile indicated that administration up to 1600 mg AXP107-11/day was safe, no toxic events were noted during the 2 weeks of monotherapy with AXP107-11 and the drug did not seem to increase the toxicity when combined with gemcitabine. The MTD was not reached. The dose escalation was stopped at 8 relatively large capsules twice daily (1600 mg/day) due to patient concerns.
- DLTs were observed in 7 patients. Seven patients had grade 3 non-haematological toxicities (cholangitis, allergy to contrast, fatigue/nausea, infection, vomiting, abdominal pain and pancreatitis). One patient reported a grade 4 haematological toxicity (neutropenia). This event was assessed as unrelated to AXP107-11 and did therefore not fulfil the DLT criteria. The events were distributed among the dose levels.
- Eight patients reported in total 10 SAEs of which 2 were assessed as related to the IMP by the investigator and reported as SUSARs (cholecystitis and pancreatitis).

Secondary objective:

- There was approximate dose proportionality after single dosing of AXP107-11 in the dose interval 400-800 mg. AXP107-11 was rather rapidly absorbed, with t_{max} between 1 to 3 hours post-dose and the concentration decreased rather rapidly with a multi-compartmental elimination curve. On average, the C_{max} increased from 181 to 291 µg/L (1.6 fold) and the corresponding AUC_{0-12h} increased from 331 to 629 hr* µg/L (1.9-fold) after administering 400 or 800 mg AXP107-11.

Conclusions Phase IIa (modified)

Primary objective:

- The effect of the combination treatment (AXP107-11 and gemcitabine) showed a partial response in 2 patients (13%). The response was noted on the liver metastases and the pancreatic tumour and on the liver and lymph node metastases, respectively. A response duration of 7.1 months was noted in 1 patient, whose liver metastases responded fairly well to the treatment.

Secondary objectives:

- Overall survival after combination therapy with AXP107-11 and gemcitabine was 4.9 months. The outcome for women appeared considerably poorer than for the men: their mOS was 2.3 months *versus* 6.3 months in men.
- Overall survival rate at 6 months after start of combination therapy with AXP107-11 and gemcitabine was 44%, 7 patients survived longer than 6 months, and 3 patients (19%) were still alive at the 1-year follow-up.
- Time to progression after combination therapy with AXP107-11 and gemcitabine was 2.6 months. The outcome for women appeared considerably poorer than for the men: their time to progression was 2.1 months *versus* 4.4 months in men.
- Palliation, defined as the percentage of patients who showed CR, PR or stable disease (SD) after combination therapy with AXP107-11 and gemcitabine occurred in 9 of 16 patients (56%). In 7 patients, the disease was classified as stable, which meant a progression free period of at least 10 weeks. At progression, the most common progression site was the liver, 13 patients had progression observed in the liver. The overall survival appeared slightly better for patients without non-target lesions (mOS 6.3 months) compared to the patients who had non-target lesions (mOS 4.4 months).
- The survival was slightly better for the patients who had a Karnofsky index ≥90 at the start of the study (although only 2 patients had a Karnofsky index lower than 90). A couple of patients temporarily gained weight above the inclusion weight but no 1 was scored as positive. The majority of patients decreased in weight during the study (10 patients), and 6 patients more or less kept their weight. The overall survival was to some extent better for the patients who had lost ≥5 kg, with a median overall survival of 6.8 months, compared to 3.6 months for the patient who last <5 kg.