Oryx GmbH und Co. KG

CLINICAL TRIAL REPORT

A non-controlled, single-arm, open-label, Phase II study of intravenous and intratumoral administration of ParvOryx in patients with metastatic, inoperable pancreatic cancer

Trial product	Parvovirus H-1 (ParvOryx)
Indication	Stage IV pancreatic cancer with at least one hepatic metastasis
Phase of development	I / IIa
Sponsor	Oryx GmbH & Co. KG Marktplatz 85598 Baldham
Study period	Beginning of study (first patient enrolled) 17th. February 2016 End of study (last patient, last visit) 21st. February 2018
Study protocol number	ParvOryx02
EudraCT number	2015-001119-11

Sponsor's contact person:	Sponsor's signatory:
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Date of this report: 19th. February 2019

This study, including the archiving of essential documents, was performed in compliance with Good Clinical Practice (GCP) and with all relevant laws and regulations

Sponsor's Signature Page

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

Dr. Bernard Huber

Chief Executive Officer

20.2.2019

Date

Signature

for Oryx GmbH & Co. KG

2. SYNOPSIS

Name of Sponsor/Company Oryx GmbH & Co. KG Marktplatz 1 85598 Baldham, Germany	Individual study table referring to part of the Dossier Volume Page	*(For National Authority use only)*
Name of finished product ParvOryx		
Name of active ingredient Parvovirus H-1		

Study title

A non-controlled, single arm, open-label, Phase II study of intravenous and intratumoral administration of ParvOryx in patients with metastatic, inoperable pancreatic cancer

Indication

Stage IV pancreatic cancer with at least one hepatic metastasis

Principal investigator and Study Centre

Prof. Dr. med. Dr. rer. nat. Guy Ungerechts
Medical Oncology
NCT Heidelberg
Im Neuenheimer Feld 350
69120 Heidelberg, Germany

Test substance

Parvovirus H-1 (ParvOryx) in Visipaque/Ringer solution

Reference substance

None

Dosing schedule and mode of administration:

Dose level I:

- Intravenous: 1×10^8 pfu (2-hour infusion) per day over 4 days
- Intratumoral: 6×10^8 pfu (slow infusion)
- $\Rightarrow$ Total dose: 1×10^9 pfu

Dose level 2:

- Intravenous: 5×10^8 pfu (2-hour infusion) per day over 4 days
- Intratumoral: 3×10^9 pfu (slow infusion)
- $\Rightarrow$ Total dose: 5×10^9 pfu

Dose level 3:

- Intravenous: 1×10^9 pfu (2-hour infusion) per day over 4 days
- Intratumoral: 6×10^9 pfu (slow infusion)
- $\Rightarrow$ Total dose: 1×10^{10} pfu

Duration of study for each patient

Screening, treatment and follow-up: Upper limit of 7.5 months

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Study objectives

Primary: To investigate the safety and tolerability of the ParvOryx as well as the associated virus distribution, shedding and elimination

Secondary: To provide proof of concept for ParvOryx in the treatment of pancreatic cancer assessed by laboratory and clinical characteristics

Study population

Patients with stage IV pancreatic ductal adenocarcinoma and at least one hepatic metastasis.

Principal inclusion criteria:

- Age equal to or over 18 years,
- Written informed consent including sampling and processing of biological specimens,
- Histologically confirmed pancreatic ductal adenocarcinoma with at least one measurable hepatic metastasis,
- Disease progression despite first-line therapy,
- Eligibility for second-line chemotherapy with gemcitabine,
- Adequate clinical condition and main organ function.

Principal exclusion criteria:

- Eligibility for surgical treatment,
- Symptomatic cerebral, pulmonal, and/or osseous metastases,
- Peritoneal carcinosis with clinically apparent ascites,
- Liver cirrhosis, splenectomy, relevant respiratory impairment, signs of active, systemic infection,
- Recent chemotherapy or radiotherapy.

Number of subjects planned and analysed

Planned: In total, 7 subjects
(dose level 1, 1 subject; dose levels 2 and 3, 3 subjects each)

Analysed: 7 subjects
(dose level 1, 1 subject; dose levels 2 and 3, 3 subjects each)

Methods

This open, Phase I/IIa, non-randomised, non-controlled clinical study was performed at a single centre.

Patients eligible for study treatment received ParvOryx as described above on an in-patient basis. They were observed closely (partly in-patient) until 28 days after the first administration of ParvOryx. Thereafter, gemcitabine was also administered and if disease progression occurred, also nab-paclitaxel. Follow-up examinations were performed after 2, 4 and 6 months.

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Criteria for evaluation

Safety: Adverse events, physical examination, vital signs, 12-lead electrocardiography, haematology and clinical chemistry, haemostasis, determination of antibodies against parvovirus, assessment of viral shedding in blood (pharmacokinetics), urine, saliva and faeces.
The treatment with ParvOryx was to be considered safe and well-tolerated if none of the following events occurred: Elevation of transaminases, alkaline phosphatase or bilirubin to >3 times the baseline value up to Day 28; elevation of C-reactive protein to >3 times the baseline value up to Day 28; neutrophil count $< 1.0 \times 10^9$/L **or** $> 12.0 \times 10^9$/L up to Day 28; Haemoglobin < 7.5 g/L up to Day 28; platelet count $< 50 \times 10^9$/L; international normalised ratio > 2.5, activated partial thromboplastin time > 50 s up to Day 28; neurological symptoms with no other explanation than the administration of ParvOryx (e.g. brain metastasis) up to Day 28; thromboembolic event(s), i.e. deep vein thrombosis, myocardial infarction or stroke up to Day 28; any serious adverse event classified as at least 'possibly' related to ParvOryx; any deterioration in medical monitoring parameters (laboratory values, electrocardiography etc.) that were rated as at least 'possibly' related to ParvOryx and required countermeasures in order to avert conditions fulfilling at least one of the 'seriousness' criteria; medical need to interrupt the scheduled treatment or to terminate it prematurely.

Efficacy: Treatment response assessment, aided in particular by magnetic-resonance imaging (complete response, partial response, progressive disease, stable disease). Change of the largest cross-sectional area and changes in non-measurable lesions were evaluated. Patients were monitored for assessment of progression-free and overall survival.

Other: Biological samples for basic research were obtained.

Statistical methods

Demography, adverse events, findings in physical examinations and 12-lead electrocardiography were listed and tabulated, including breakdowns by, system organ class and preferred term. Continuous variables were tabulated by basic descriptive statistics where appropriate. Progression-free and overall survival were listed and displayed by using Kaplan–Meier plots. Other study variables were listed and/or tabulated as appropriate. No hypothesis-testing was performed.

Results: Study population and compliance with treatment

As planned, 7 patients were treated between 17th. February 2016 (first screening examination) and 21st February 2018 (last study visit). There were no deviations from the study protocol that might have had any effect upon the patients' safety or the study result. All patients were included in the Full Analysis Set (FAS), and only one patient was excluded from the Per Protocol Set (PPS) because of premature withdrawal from the study (withdrawal of consent). The patients' mean age (± standard deviation) was 55.1 ± 10.6 years, ranging from 35 to 69 years. Baseline disease marker CA19-9 ranged from 17.8 to 12200 U/ml (median 499 U/ml).

All patients received all administration of ParvOryx according to the study protocol.

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Results: Efficacy

Median progression-free survival was 72 days in the FAS and 58 days in the PPS. Median overall survival was 175 days in the FAS and 175.5 days in the PPS. The longest periods of survival were 326 days and >426 days. Target lesions increased in size for four of the six assessable patients, for whom assessment according to the RECIST 1.1 criteria revealed progressive disease. For the other two assessable patients, target lesions disappeared, shrank or remained constant; the RECIST 1.1 assessment revealed partial response in the course of the trial. In one of these patients partial response was apparent already at Month 2; the other showed partial response only at Month 6, after stable disease had been diagnosed at Months 2 and 4.

Owing to limitations of tumour amount obtained by biopsies, no sound pathological conclusions were possible. For some patients a time-dependent increase in T cells was observed in the tumour biopsies. In a fraction of patients a virotherapy-induced reactivity pattern in the adaptive and the innate arm of the immune system could be detected.

The two patients with the longest survival times (see above) developed an immunological pattern in blood and in tumour tissue that was considered to be associated with their relatively favourable clinical response to treatment with ParvOryx.

Results: Safety

According to the safety criteria listed above, ParvOryx was very well tolerated and showed a favourable safety profile. Apart from elevated C-reactive protein in four patients that could potentially have been related to the study treatment, no adverse reactions to ParvOryx were detected.

All other adverse events, and also the physical examination, vital signs, electrocardiography, laboratory values, antibody analysis and viral shedding likewise indicated a favourable safety profile for ParvOryx.

Conclusions

ParvOryx was well tolerated by all the study patients, with only one kind of adverse event (elevated C-reactive protein, in four out of seven study patients) considered possibly related to this treatment.

The safety of the treatment was underlined by the clinical and laboratory investigations and by the pharmacokinetics and shedding pattern of the virus.

Two of the seven patients showed a favourable clinical response to treatment (‘partial response’) after administration of ParvOryx and gemcitabine followed by an overall survival time (326 and >426 days) that was longer than those of the other patients (72–176 days, with a median of 118 days). The latter patient first showed stable disease, then partial response. Both of these patients developed an immunological pattern that may have contributed to their clinical response.

Overall, the results of this study indicate that ParvOryx can continue to be regarded as a suitable candidate for further clinical investigation.

DATE OF REPORT: 19th. February 2019