Oryx GmbH und Co. KG

CLINICAL TRIAL REPORT

Phase I/IIa study of intratumoral/intracerebral or intravenous/intracerebral administration of Parvovirus H-1 (ParvOryx) in patients with progressive primary or recurrent glioblastoma multiforme

Trial product	Parvovirus H-1 (ParvOryx)
Indication	Progressive primary or recurrent glioblastoma multiforme
Phase of development	I / IIa
Sponsor	Oryx GmbH & Co. KG Marktplatz 1 85598 Baldham
Study period	Beginning of study (first patient enrolled) 21st. October 2011 End of study (last patient, last visit) 15th. July 2015
Study protocol number	ParvOryx01
EudraCT number	2011-000572-33

Sponsor's contact person:	Sponsor's signatory:
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Date of this report: Febuary 17th. 2016

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	18.2.2016	
Chief Executive Officer	Date	Signature

for Oryx GmbH & Co. KG.

2. SYNOPSIS

Name of Sponsor/Company Oryx 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

Phase I/IIa study of intratumoral/intracerebral or intravenous/intracerebral administration of Parvovirus H-1 (ParvOryx) in patients with progressive primary or recurrent glioblastoma multiforme

Indication

Progressive primary or recurrent glioblastoma multiforme

Principal investigator and Study Centre

Prof. Dr. Andreas Unterberg

Neurochirurgische Klinik

Im Neuenheimer Feld 400

69120 Heidelberg, Germany

Test substance

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

Reference substance

None

Dosing schedule and mode of administration:

Group I:

Increasing total doses of ParvOryx:

- Dose escalation level 1: total dose $1x10^6$ pfu
- Dose escalation level 2: total dose $5x10^7$ pfu
- Dose escalation level 3: total dose $1x10^9$ pfu

administered in two equal fractions:

- 1st fraction, half of the total dose, intratumorally on Day 1,
- 2nd fraction, half of the total dose, intracerebrally on Day 10.

Group II:

Increasing total doses of ParvOryx:

- Dose escalation level 1: total dose $1x10^6$ pfu (optional; see below)
- Dose escalation level 2: total dose $5x10^7$ pfu
- Dose escalation level 3: total dose $1x10^9$ pfu

administered in six fractions:

- 1st–5th fraction, each one-tenth of the total dose, intravenously on Day 1, 2, 3, 4, 5 over 2 hours,
- 6th fraction, half of the total dose, intracerebrally on Day 10.

In Group II the lowest dose level was to be omitted if there were no dose-limiting events in Group I. Since there were none, dosing at this level in Group II was not performed.

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Group III (amended 4th dose level, administration schedule as for Group I):

- Dose escalation level 4: total dose $5x10^9$ pfu

administered in two equal fractions:

- 1st fraction, $2.5x10^9$ pfu, intratumorally on Day 1,
- 2nd fraction, $2.5x10^9$ pfu, intracerebrally on Day 10.

Duration of study for each patient

Treatment and observation for primary analysis, 28 days; including follow-up, 6 months

Study objectives

Primary: To investigate the safety and tolerability of the study treatment

Secondary: To investigate the efficacy of the study treatment

Study population

Patients with progressive primary or recurrent glioblastoma multiforme (GBM) scheduled for neurosurgery, i.e. for a complete/subtotal tumour resection.

Principal inclusion criteria:

- Age equal to or over 18 years,
- Written informed consent including sampling and processing of biological specimens,
- Recurrent or progressive glioblastoma multiforme,
- Indication for complete or subtotal tumour resection,
- Good clinical condition and sufficient main organ function,
- Negative serology for HIV, HBV and HCV and negative pregnancy test in women; commitment to use the adequate contraception and to adhere to the pre-defined hygienic measures.

Principal exclusion criteria:

- Multifocal disease or evidence of distant tumour metastases,
- Active infection within 5 days, chemotherapy within 4 weeks and/or radiotherapy within 90 days before study inclusion,
- Treatment with antiangiogenic substances within 21 days before therapy,
- Contraindications for use of ParvOryx (known allergy, thyreotoxicosis, decompensated congestive heart failure),
- Immunosuppressive treatment within 60 days prior to therapy.

Number of subjects planned and analysed

Planned: In total, up to 21 subjects
(Group I, up to 9 subjects; Group II, up to 9 subjects; Group III, up to 3 subjects)

Analysed: In total, 18 subjects
(Group I, 9 subjects; Group II, 6 subjects; Group III, 3 subjects)

Only 6 subjects were treated in Group II because of omission of the lowest dose level (see above, ‘Dosing schedule’).

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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; the first half of the dose was injected intratumorally on Day 1 or infused in equal fractions on Days 1 to 5, and resection was performed on Day 10; following the operation, the second half of the dose was applied intracerebrally (i.e., into the walls of the resection cavity around the resected tumour area). The patients were observed daily during the entire period; this observation was continued for a month (discharge on Day 18 and examination on Day 28 ± 2), and thereafter at less frequent intervals for up to six months.

Criteria for evaluation

Safety: Adverse events, physical and neurological examination, vital signs, 12-lead electrocardiography, haematology and clinical chemistry, haemostasis, serum protein electrophoresis, determination of antibodies against parvovirus, assessment of viral shedding in blood, urine, saliva and faeces.

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, changes of non-measurable lesions, extent of steroid therapy and results of the neurological examination were evaluated. Patients were also 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 ECG were listed and tabulated, including breakdowns by, system organ class and preferred term. Continuous variables were tabulated by basic descriptive statistics. Progression-free and overall survival were listed and also displayed by using Kaplan–Meier plots.

A decision tree was constructed to allow a prospectively determined decision on any reduction of dose levels required by the occurrence of dose-limiting event(s). However, no such event occurred.

Results: Study population and compliance with treatment

As planned, 18 patients were treated between October 2011 (first enrolment) and July 2015 (last study visit). There were no major deviations from the study protocol that had any effect upon the further conduct or the analysis of the study, and no patient was excluded from the efficacy analysis because of them.

Patients' mean age (± standard deviation) was 57.8 ± 10.6 years, ranging from 41.6 to 76.1 years. Karnofsky performance status was 100% for 8 patients, 90% for 5 patients, 80% for 3 patients and 70% and 60% for 1 patient each. Initial tumour sizes ranged from 1.08 cm^2 to 33.0 cm^2.

Results: Efficacy

Median post-operative progression-free survival was 110 days (~3.7 months). Any realistic estimate of this within the dose groups was not meaningful because of the smallness of the patient population. Overall survival was much longer; its median could not be estimated, as 14 of the 18 patients survived until after the end of observation. Six months after treatment, progression-free survival was 27% and overall survival was 72%.

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Results: Safety

Among the patients in dosage levels 1–3 there was no apparent association between dose and the frequency of the various adverse events and types of adverse events. A higher rate of adverse events overall among the patients receiving dose level 4 was attributed to these patients' generally poorer state of health, as a higher incidence of individual event types in this cohort was not apparent.

Six patients died during or shortly after the study: four during the actual study period, one a few days after the end of the six-month follow-up period and one after having withdrawn prematurely from the study because of a high tumour burden. Four of these deaths were due to disease progression, one was due to pneumonia (considered unlikely to be related to the study treatment) and one was due to hydrocephalus, for which a relationship to the study treatment could not be excluded and was therefore classified as possibly related to it. Other reasons for premature termination were disease-related. All serious adverse events (by patient) were: cerebrospinal fistula and post-operative wound infection; deep vein thrombosis, pneumonia and pulmonary embolism; cystitis and urosepsis; wound dehiscence and upper-limb fracture; fall, head injury, subdural hygroma, depressed level of consciousness and (fatal) pneumonia; depressed level of consciousness, device occlusion and hydrocephalus (of unclear neurological outcome; the patient was multimorbid and died); depressed level of consciousness and convulsion. [Disease progression was not classified as a serious adverse event.] No adverse events were assessed as being dose-limiting.

Haematological, clinico-chemical and haemostatic measurements, vital signs and physical and neurological examinations did not lead to any observations suggesting a dose-relationship or and risk entailed by the administration of ParvOryx.

Viral genome levels in blood varied very greatly after intratumoral or intracerebral administration and at the lower dose levels they were mostly below the lower limit of quantification. Inter-individual variability was high; this variability was considered possibly related to the degree of individual alteration of the blood–brain barrier due to tumour burden. The absence of a strong correlation between the dose and the systemic bioavailability of the virus suggests that ParvOryx did not itself substantially influence the blood–brain barrier. After intravenous administration of ParvOryx a clear dose-dependence of systemic exposure was seen, suggesting a very good predictability of the treatment in respect of pharmacokinetics.

Conclusions

This study did not bring to light any clear sign of poor tolerability of the study treatment with ParvOryx or of any risk associated with this treatment. The only safety issue was a case of hydrocephalus, for which a relationship with ParvOryx could not be ruled out and was therefore rated as ‘possible’ (event with unclear neurological outcome; the patient was multimorbid and died). The clinical response showed promising results with progression free and overall survival rates above those known from literature data; however, this result is still tentative. The results of the accompanying *ex vivo* basic research (proof of concept) confirmed that the virus crosses the blood–brain barrier and replicates in glioma cells while being cleared rapidly from the bloodstream and exhibiting no sign of cytokine storm or of eco-toxicity. The next step will be to identify the optimum mode of treatment with ParvOryx.

DATE OF REPORT: January 15th. 2016