Clinical trial results:
A PHASE I/IIa STUDY OF THE SAFETY, TOLERABILITY AND BIOLOGICAL EFFECT OF SINGLE AND REPEAT ADMINISTRATION OF THE SELECTIVELY REPLICATION-COMPETENT HERPES SIMPLEX VIRUS HSV1716 INTO THE TUMOUR-BEARING PLEURAL CAVITY (INTRAPLEURAL) IN PATIENTS WITH INOPERABLE MALIGNANT PLEURAL MESOTHELIOMA.

Summary

EudraCT number	2010-024496-37
Trial protocol	GB
Global end of trial date	14 November 2016

Results information

Result version number	v1 (current)
This version publication date	28 June 2018
First version publication date	28 June 2018

Trial information

Trial identification

Sponsor protocol code	1716-12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01721018
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Virttu Biologics Limited
Sponsor organisation address	BioCity Scotland, Bo'Ness Road, Newhouse, United Kingdom, ML1 5UH
Public contact	Clinical Trial Department, Virttu Biologics Limited, 0141 4451716,
Scientific contact	Clinical Trial Laboratory, Virttu Biologics Limited, 0141 4451716,

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	27 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2016
Global end of trial reached?	Yes
Global end of trial date	14 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine the safety and tolerability of HSV1716 given by single and repeat intrapleural administration in patients with inoperable malignant pleural mesothelioma. The secondary objective was to obtain evidence of HSV1716 replication and lysis of MPM cells and of patient immune responses through analysis of pleural fluid and serum samples for evidence of cell death, HSV1716 replication, changes in appropriate biomarkers and cytokine/chemokines.
A subsidiary endpoint was tumour measurement as recorded by CT scans and assessed using the modified RECIST criteria for MPM.

Protection of trial subjects:

Only patients who met the inclusion and exclusion criteria for the study were enrolled. These patients received a patient information leaflet that explained the procedures and any risks that may be involved. The patients were allowed at least 24 hours to read the information and ask any questions before consenting to the study. The safety and tolerability of HSV1716 was assessed at various time points during the study by review of pre- and post-dose clinical data including: physical examinations, full blood count, biochemical profile (urea, electrolytes, liver function tests, bilirubin, AST/ALT, serum creatinine, LDH, alkaline phosphatase, albumin, calcium) and immunological status. Reviews of this data were carried out two weeks after each patients' final dose and recruitment of another patient was based on whether or not any dose limiting toxicities were experienced. The administration procedure was designed to utilise the patients' indwelling catheters and this was done during an outpatient appointment at a time convenient to the patient.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	21 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	2
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment period for the study was 21st January 2013 to 14th November 2016.
The study was conducted at two sites in the United Kingdom - site 01 in Sheffield and site 02 in Glasgow.

Pre-assignment

Screening details:

A screening assessment was carried out within one week of the planned treatment day. This involved the patient giving consent, providing medical history, undergoing a chest x-ray, CT scan and giving samples of blood and pleural fluid. Relevant data including histology details were reviewed and approved by a third party Medical Monitor.

Period 1

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

Arms

Arm title	HSV1716 treatment

Arm description:

Single arm study - all patients received HSV1716.

Arm type	Experimental
Investigational medicinal product name	HSV1716
Investigational medicinal product code	
Other name	Herpes simplex virus lacking infected cell protein 34.5, Seprehvir
Pharmaceutical forms	Solution for injection
Routes of administration	Intrapleural use

Dosage and administration details:

Patients received 1, 2 or 4 doses of 1x10^7 infectious units (iu) HSV1716 at weekly intervals, followed by a 50ml saline flush, by intrapleural administration via an Indwelling Pleural Catheter. The investigational product was provided in glass vials each containing approximately 1.2 ml of compound sodium lactate and 10% glycerol in which HSV1716 was diluted at a concentration of 2 x 10^6 iu/ml. Five vials were used for each dose and a total of 5ml drawn from the vials and administered to provide each dose of 1x10^7iu of HSV1716.

Number of subjects in period 1	HSV1716 treatment
Started	13
Completed	12
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

All patients who enrolled on to the study and received at least one administration of HSV1716.

Reporting group values	Overall trial	Total	
Number of subjects	13	13	
Age categorical			
The study enrolled adult patients aged 18 or over.			
Units: Subjects			
Adults (18-64 years)	2	2	
From 65-84 years	11	11	
Gender categorical Units: Subjects			
Female	3	3	
Male	10	10	

Subject analysis sets

Subject analysis set title	Completed study visits
Subject analysis set type	Full analysis

Subject analysis set description:

This set of patients completed all study treatments and follow-up visits.

Reporting group values	Completed study visits		
Number of subjects	12		
Age categorical			
The study enrolled adult patients aged 18 or over.			
Units: Subjects			
Adults (18-64 years)	2		
From 65-84 years	10		
Gender categorical Units: Subjects			
Female	3		
Male	9		

End points

End points reporting groups

Reporting group title	HSV1716 treatment
Reporting group description:	
Single arm study - all patients received HSV1716.	
Subject analysis set title	Completed study visits
Subject analysis set type	Full analysis
Subject analysis set description:	
This set of patients completed all study treatments and follow-up visits.	

Primary: Safety

End point title	Safety[1]
End point description:	
The primary objective of the study was to determine the safety and tolerability of HSV1716 given by single and repeat intrapleural administration in patients with inoperable malignant pleural mesothelioma. Safety results: • No 'Dose Limiting Toxicities' or other issues were identified and in all cases, it was concluded that recruitment could proceed to the higher dose level or in the case of Part B Group 2, recruitment could be expanded to include an additional three patients in the 4 dose cohort. • One 'Serious Adverse Event' reported (pleural infection) which was determined to be unlikely related to HSV1716.	
End point type	Primary
End point timeframe:	
Patients were evaluated for safety and tolerability of the procedure from the day of the first administration of HSV1716 through to the end of the 4th week from their final administration of HSV1716.	
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: Safety data were summarised using descriptive summary statistics at each dose level of HSV1716 (1 dose, 2 doses and 4 doses) and overall (all dose levels combined). Study drug administration, compliance and tumour response were summarised by dose level only. No statistical comparison of dose levels was performed. The biological effects data were listed only.	

End point values	Completed study visits			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Patients	12			

Statistical analyses

No statistical analyses for this end point

Secondary: Biological

End point title	Biological
End point description:	
The secondary objective was to obtain evidence of HSV1716 replication and lysis of MPM cells through analysis of pleural fluid and serum samples for evidence of cell death and/or HSV1716 replication and/or changes in appropriate biomarkers.	

Biological results:
• 11/12 patients were seropositive for HSV-1 pre-treatment, whereas 1 patient was seronegative and seroconverted
• In 7/9 patients with detectable HSV DNA in pleural fluid samples, HSV-1 genomes were persistent for ≥ 14 days after the final administration, consistent with replication in tumour cells
• Viral shedding was observed in 1/12 patients, no genotyping was performed to confirm whether this was HSV1716
• In 9/12 patients strong virus neutralisation by pleural fluid was observed
• Pleural fluid levels of the cytokines IL-2, TNFalpha and IFNgamma increased after HSV1716 administration by 5-10-fold, and robust Th1 responses of these 3 cytokines to HSV1716 administration were observed in 8/11 patients

End point type	Secondary

End point timeframe:

Patient samples were assessed for biological activity from the day of the first administration of HSV1716 through to the last study visit.

End point values	Completed study visits			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Exploratory analysis				
number (not applicable)	12			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Tumour measurement

End point title	Tumour measurement

End point description:

A subsidiary endpoint was tumour measurement as recorded by CT scans and assessed using the modified RECIST criteria for MPM.
Response assessment results:
• Tumour response was obtained by CT scanning (screening, day 29 and day 57) using the modified RECIST criteria developed for malignant mesothelioma. Six patients were reported as having stable disease and 6 were reported as having progressive disease at day 57.

End point type	Other pre-specified

End point timeframe:

Tumour measurements were obtained and assessed at screening, day 29 and day 57.

End point values	Completed study visits			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Response assessment				
number (not applicable)	12			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the time of consent to the final study visit.

Adverse event reporting additional description:

Listing includes all Serious Adverse Events (1 unlikely related).
Listing includes only those non-serious adverse events that were possibly or probably related to the investigational product.
Additional non-serious adverse events were reported but were deemed to be unlikely or not related to the investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	HSV1716 treatment arm

Reporting group description:

All patients in study.

Serious adverse events	HSV1716 treatment arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Pleural infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	HSV1716 treatment arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 13 (100.00%)		
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	2		

Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Nervous system disorders Lethargy subjects affected / exposed occurrences (all)	 2 / 13 (15.38%) 2		
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Chills subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	 3 / 13 (23.08%) 3 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	 1 / 13 (7.69%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2012	To include an additional exclusion criterion as requested by the Gene Therapy Advisory Committee during their review of the study.
14 October 2013	To clarify the dose escalation scheme and confirm that a Contract Research Organisation had been contracted to provide Pharmacovigilance, Medical Monitoring and Data Management services.
04 March 2014	To include an additional site for enrolment of patients as recruitment had been slower than anticipated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported