



## 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:

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**Results analysis stage**

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|                                                      |                  |
|------------------------------------------------------|------------------|
| 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:

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**General information about the trial**

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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.

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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.

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Background therapy:

Not applicable

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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:

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**Population of trial subjects**

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**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:

| <b>Subjects enrolled per age group</b>    |    |
|-------------------------------------------|----|
| 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  $1 \times 10^7$  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  $2 \times 10^6$  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  $1 \times 10^7$  iu of HSV1716.

|                                       |                   |
|---------------------------------------|-------------------|
| <b>Number of subjects in period 1</b> | 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:<br>Single arm study - all patients received HSV1716.                              |                        |
| Subject analysis set title                                                                                     | Completed study visits |
| Subject analysis set type                                                                                      | Full analysis          |
| Subject analysis set description:<br>This set of patients completed all study treatments and follow-up visits. |                        |

### Primary: Safety

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Safety <sup>[1]</sup> |
| End point description:<br>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.<br>Safety results: <ul style="list-style-type: none"><li>• 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.</li><li>• One 'Serious Adverse Event' reported (pleural infection) which was determined to be unlikely related to HSV1716.</li></ul> |                       |

|                                                                                                                                                                                                                                 |         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|
| End point type                                                                                                                                                                                                                  | Primary |
| End point timeframe:<br>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:<br>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  $\geq 14$  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.

|                             |                        |  |  |  |
|-----------------------------|------------------------|--|--|--|
| <b>End point values</b>     | 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.

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

## **Statistical analyses**

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported