# Clinical trial results:
# A Clinical Study of Enadenotucirev: Dose Finding and Proof of Concept in Platinum-Resistant Epithelial Ovarian Cancer.

## Summary

| | |
|---|---|
| EudraCT number | 2013-001276-38 |
| Trial protocol | ES |
| Global end of trial date | 18 October 2019 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 05 May 2021 |
| First version publication date | 05 May 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | ColoAd1-2001 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02028117 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | PsiOxus Therapeutics Limited |
| Sponsor organisation address | PsiOxus House, 4-10 The Quadrant, Barton Lane,, Abingdon, United Kingdom, OX14 3YS |
| Public contact | Chief Medical Officer, PsiOxus Therapeutics Limited, 44 01235 835328, enquiries@psioxus.com |
| Scientific contact | Chief Medical Officer, PsiOxus Therapeutics Limited, 44 01235 835328, enquiries@psioxus.com |

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 | 13 May 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 October 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 October 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Phase Ia:
•To determine the MTD and/or the dose of enadenotucirev recommended for further studies when given by intraperitoneal (IP) administration as a monotherapy in patients with ovarian cancer

Phase Ib:
•To determine the MTD and/or the dose of enadenotucirev recommended for further studies when given by IP administration or intravenous (IV) infusion in combination with paclitaxel in patients with ovarian cancer

Dose Expansion Phase and Phase Ib patients treated at the dose for Dose Expansion Phase:
•To evaluate the Progression Free Survival (PFS) of enadenotucirev, using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, when given by IV infusion in combination with paclitaxel in patients with recurrent platinum-resistant ovarian cancer

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and other applicable regulatory requirements. All personal data collected and processed for the purposes of this study were managed by the Investigator and study staff with adequate precautions to ensure confidentiality of those data, and in accordance with national local laws and regulations on personal data protection.

The Investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorised parties. PsiOxus will maintain confidentiality standards by assigning a unique coded identification number to each subject included in the study. Patient names will never be included in data sets that are transmitted to PsiOxus or their representatives or to third parties as permitted by the Informed Consent Form.

Background therapy:

In phase 1b and the Dose Expansion phase of the study, patients were treated with enadenotucirev in combination with paclitaxel.

Enadenotucirev is an Ad11/Ad3 chimeric group B adenovirus virus developed by a process of bio-selection on colorectal cancer cells. The result is a virus that is dependent upon the malignant carcinoma phenotype for replication, demonstrates enhanced potency in tumour cells, kills tumour cells by a rapid non-apoptotic necrolytic mechanism, has poor or absent replication in normal cells and is stable in human blood. Unlike most other oncolytic vaccines, enadenotucirev has no additional engineered gene inserts. There are also no engineered deletions other than those directly produced in the bio-selection process.

Enadenotucirev kills tumour cells by a mechanism, which more closely resembles necrosis than apoptosis. This has a number of potential effects:
• Enadenotucirev has been shown to be potent in multi-drug resistant cancer cell lines and in cancer stem-cell like cells, which are known to have a resistance to apoptosis
• An inflammatory necrotic cell death may be more suitable for the generation of a specific anti-tumoural immune response
• Enadenotucirev exits tumour cells very rapidly, even before target cell death, and may thus have enhanced ability to spread within the tumour

Evidence for comparator:

This was a single arm study with no comparator arm.

| | |
|---|---|
| Actual start date of recruitment | 18 November 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 | Spain: 22 |
| Country: Number of subjects enrolled | United Kingdom: 16 |
| Worldwide total number of subjects | 38 |
| EEA total number of subjects | 22 |

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) | 25 |
| From 65 to 84 years | 13 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited at nine study centres in Europe (four in the UK and five in Spain). Not all sites recruited patients.

Patients who complete screening procedures and meet all eligible criteria may be enrolled into the study using the enrolment procedure established by the Sponsor

### Pre-assignment

Screening details:

The following information was collected at screening. Demographic data; medical history, including all prior cancer therapies and procedures; all medications used by the patient in the 14 days before the first administration of enadenotucirev; serum pregnancy test and a check of the screening data against eligibility criteria.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | IP Monotherapy (1 x 10e12 vp) |

Arm description:

Enadenotucirev IP monotherapy (1 x 10e12 vp)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Enadenotucirev |
| Investigational medicinal product code | |
| Other name | ColoAd1 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intraperitoneal use |

Dosage and administration details:

Administered a dose of 1e12 vp on days 1, 8, 15, 29, 36 and 43

| | |
|---|---|
| **Arm title** | IP Monotherapy (6 x 10e12 vp) |

Arm description:

Enadenotucirev IP monotherapy (6 x 10e12 vp)

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Enadenotucirev |
| Investigational medicinal product code | |
| Other name | ColoAd1 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intraperitoneal use |

Dosage and administration details:

Administered a dose of 6e12 vp on days 1, 8, 15, 29, 36 and 43

| | |
|---|---|
| **Arm title** | IP + paclitaxel (1 x 10e12 vp) |

Arm description:

Enadenotucirev IP (1 x 10e12 vp) in combination with paclitaxel

| | |
|---|---|
| Arm type | Experimental |

| | |
|---|---|
| Investigational medicinal product name | Enadenotucirev |
| Investigational medicinal product code | |
| Other name | ColoAd1 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intraperitoneal use |

Dosage and administration details:

Administered a dose of 1e12 vp on days 1, 8, 15, 29, 36 and 43.

| | |
|---|---|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered a dose of 80 mg/m2 on days 9, 16, 23, 37, 44 and 51

| | |
|---|---|
| **Arm title** | IV + paclitaxel (1 x 10e12 vp) |

Arm description:

Enadenotucirev IV (1 x 10e12 vp) in combination with paclitaxel

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Enadenotucirev |
| Investigational medicinal product code | |
| Other name | ColoAd1 |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered a dose of 1e12 vp on days 1, 3, 5, 29, 31, 33

| | |
|---|---|
| Investigational medicinal product name | Paclitaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Administered a dose of 80 mg/m2 on days 9, 16, 23, 37, 44 and 51

| **Number of subjects in period 1** | IP Monotherapy (1 x 10e12 vp) | IP Monotherapy (6 x 10e12 vp) | IP + paclitaxel (1 x 10e12 vp) |
|---|---|---|---|
| Started | 7 | 3 | 8 |
| Completed | 1 | 0 | 0 |
| Not completed | 6 | 3 | 8 |
| Consent withdrawn by subject | - | - | - |
| Physician decision | - | - | - |
| Adverse event, non-fatal | - | 1 | 1 |
| Death | 3 | - | 1 |
| Other | - | - | 1 |
| Progressive disease | 3 | 2 | 5 |

| **Number of subjects in period 1** | IV + paclitaxel (1 x 10e12 vp) |
|---|---|

| | |
|---|---|
| Started | 20 |
| Completed | 11 |
| Not completed | 9 |
| Consent withdrawn by subject | 2 |
| Physician decision | 2 |
| Adverse event, non-fatal | - |
| Death | 2 |
| Other | 1 |
| Progressive disease | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | IP Monotherapy (1 x 10e12 vp) |
| Reporting group description: Enadenotucirev IP monotherapy (1 x 10e12 vp) | |
| Reporting group title | IP Monotherapy (6 x 10e12 vp) |
| Reporting group description: Enadenotucirev IP monotherapy (6 x 10e12 vp) | |
| Reporting group title | IP + paclitaxel (1 x 10e12 vp) |
| Reporting group description: Enadenotucirev IP (1 x 10e12 vp) in combination with paclitaxel | |
| Reporting group title | IV + paclitaxel (1 x 10e12 vp) |
| Reporting group description: Enadenotucirev IV (1 x 10e12 vp) in combination with paclitaxel | |

| Reporting group values | IP Monotherapy (1 x 10e12 vp) | IP Monotherapy (6 x 10e12 vp) | IP + paclitaxel (1 x 10e12 vp) |
|---|---|---|---|
| Number of subjects | 7 | 3 | 8 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 3 | 2 | 6 |
| From 65-84 years | 4 | 1 | 2 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 65.9 | 59.7 | 60.5 |
| full range (min-max) | 54 to 77 | 47 to 68 | 53 to 70 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 7 | 3 | 8 |
| Male | 0 | 0 | 0 |
| Race<br>Units: Subjects | | | |
| White | 7 | 3 | 8 |
| Ethnicity<br>Units: Subjects | | | |
| Not Hispanic or Latino | 7 | 2 | 7 |
| Hispanic or Latino | 0 | 1 | 1 |
| height<br>Units: cm | | | |
| arithmetic mean | 163.7 | 158.7 | 160.3 |

| | | | |
|---|---|---|---|
| standard deviation | ± 4.03 | ± 6.03 | ± 4.33 |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 68.59 | 69.63 | 62.16 |
| standard deviation | ± 10.651 | ± 2.214 | ± 9.705 |
| BMI | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 25.590 | 27.706 | 24.268 |
| standard deviation | ± 3.8955 | ± 1.5378 | ± 4.0781 |

| **Reporting group values** | IV + paclitaxel (1 x 10e12 vp) | Total | |
|---|---|---|---|
| Number of subjects | 20 | 38 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 14 | 25 | |
| From 65-84 years | 6 | 13 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 59 | | |
| full range (min-max) | 36 to 76 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 20 | 38 | |
| Male | 0 | 0 | |
| Race | | | |
| Units: Subjects | | | |
| White | 20 | 38 | |
| Ethnicity | | | |
| Units: Subjects | | | |
| Not Hispanic or Latino | 15 | 31 | |
| Hispanic or Latino | 5 | 7 | |
| height | | | |
| Units: cm | | | |
| arithmetic mean | 159.7 | | |
| standard deviation | ± 7.78 | - | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 67.63 | | |
| standard deviation | ± 11.034 | - | |
| BMI | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 26.727 | | |
| standard deviation | ± 5.0031 | - | |

## Subject analysis sets

| Subject analysis set title | Full Analysis Set |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis set (FAS) will include all patients in the safety analysis set who have at least one baseline and one post-treatment efficacy measurement

| Subject analysis set title | Safety Analysis Set |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety analysis set will include all patients who receive at least one dose of study treatment.

| Subject analysis set title | Per Protocol Set (PPS) |
|---|---|
| Subject analysis set type | Per protocol |

Subject analysis set description:

Per Protocol Set (PPS):
For the IP cohort, the PPS included all patients in the FAS who tolerated a minimum of five IP administrations of enadenotucirev or discontinued treatment with enadenotucirev before their fifth administration due to death, toxicity, consent withdrawal or loss to follow-up and did not have any major protocol violations that were deemed to affect the assessment of efficacy.
For the IV cohort, the PPS included all patients in the FAS who tolerated a minimum of five IV administrations of enadenotucirev or discontinued treatment with enadenotucirev before their fifth administration due to death, toxicity, consent withdrawal or loss to follow-up and did not have any major protocol violations that were deemed to affect the assessment of efficacy.

| Subject analysis set title | PK Set (PKS) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

PK Set (PKS): The PKS included all patients in the SAS who had at least one baseline and one corresponding post-treatment kinetics measurement

| Subject analysis set title | PD Set (PDS) |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

The PDS included all patients in the SAS who had at least one baseline and one corresponding post-treatment shedding, cytokine or antibody measurement.

| Subject analysis set title | All IP treated patients |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

All patients who received enadenotucirev via IP administration (either monotherapy or in combination with paclitaxel)

| Subject analysis set title | Enadenotucirev IP Monotherapy |
|---|---|
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Enadenotucirev IP Monotherapy

| Reporting group values | Full Analysis Set | Safety Analysis Set | Per Protocol Set (PPS) |
|---|---|---|---|
| Number of subjects | 38 | 38 | 30 |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | 25 | 25 | |
| From 65-84 years | 13 | 13 | |
| 85 years and over | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 60.6 | 60.6 | 60.3 |
| full range (min-max) | 36 to 77 | 36 to 77 | 36 to 76 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 38 | 38 | 30 |
| Male | 0 | 0 | 0 |
| Race<br>Units: Subjects | | | |
| White | 38 | 38 | 30 |
| Ethnicity<br>Units: Subjects | | | |
| Not Hispanic or Latino | 31 | 31 | 23 |
| Hispanic or Latino | 7 | 7 | 7 |
| height<br>Units: cm | | | |
| arithmetic mean | 160.4 | 160.4 | 159.3 |
| standard deviation | ± 6.47 | ± 6.47 | ± 1.75 |
| Weight<br>Units: kg | | | |
| arithmetic mean | 66.81 | 66.81 | 67.48 |
| standard deviation | ± 10.260 | ± 10.260 | ± 10.128 |
| BMI<br>Units: kg/m2 | | | |
| arithmetic mean | 26.077 | 26.077 | 26.570 |
| standard deviation | ± 4.4480 | ± 4.4480 | ± 4.5210 |

| **Reporting group values** | PK Set (PKS) | PD Set (PDS) | All IP treated patients |
|---|---|---|---|
| Number of subjects | 20 | 35 | 18 |
| Age categorical<br>Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |

| | | | |
|---|---|---|---|
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | | | 11 |
| From 65-84 years | | | 7 |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 62 | 61.5 | |
| full range (min-max) | 47 to 77 | 45 to 77 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 20 | 35 | 18 |
| Male | 0 | 0 | 0 |
| Race | | | |
| Units: Subjects | | | |
| White | 20 | 35 | 18 |
| Ethnicity | | | |
| Units: Subjects | | | |
| Not Hispanic or Latino | 18 | 28 | 16 |
| Hispanic or Latino | 2 | 7 | 2 |
| height | | | |
| Units: cm | | | |
| arithmetic mean | 161.1 | 160.0 | |
| standard deviation | ± 4.64 | ± 6.15 | ± |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 66.13 | 67.29 | |
| standard deviation | ± 9.168 | ± 10.135 | ± |
| BMI | | | |
| Units: kg/m2 | | | |
| arithmetic mean | 25.529 | 26.418 | |
| standard deviation | ± 3.6018 | ± 4.4404 | ± |

| **Reporting group values** | Enadenotucirev IP Monotherapy | | |
|---|---|---|---|
| Number of subjects | 10 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | |
| Preterm newborn infants (gestational age < 37 wks) | | | |
| Newborns (0-27 days) | | | |
| Infants and toddlers (28 days-23 months) | | | |
| Children (2-11 years) | | | |
| Adolescents (12-17 years) | | | |
| Adults (18-64 years) | 5 | | |
| From 65-84 years | 5 | | |
| 85 years and over | | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| full range (min-max) | | | |

| | | | |
|---|---|---|---|
| Gender categorical<br>Units: Subjects | | | |
| Female | 10 | | |
| Male | 0 | | |
| Race<br>Units: Subjects | | | |
| White | 10 | | |
| Ethnicity<br>Units: Subjects | | | |
| Not Hispanic or Latino | 9 | | |
| Hispanic or Latino | 1 | | |
| height<br>Units: cm | | | |
| arithmetic mean | | | |
| standard deviation | ± | | |
| Weight<br>Units: kg | | | |
| arithmetic mean | | | |
| standard deviation | ± | | |
| BMI<br>Units: kg/m2 | | | |
| arithmetic mean | | | |
| standard deviation | ± | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | IP Monotherapy (1 x 10e12 vp) |
| Reporting group description: | |
| Enadenotucirev IP monotherapy (1 x 10e12 vp) | |
| Reporting group title | IP Monotherapy (6 x 10e12 vp) |
| Reporting group description: | |
| Enadenotucirev IP monotherapy (6 x 10e12 vp) | |
| Reporting group title | IP + paclitaxel (1 x 10e12 vp) |
| Reporting group description: | |
| Enadenotucirev IP (1 x 10e12 vp) in combination with paclitaxel | |
| Reporting group title | IV + paclitaxel (1 x 10e12 vp) |
| Reporting group description: | |
| Enadenotucirev IV (1 x 10e12 vp) in combination with paclitaxel | |
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| The full analysis set (FAS) will include all patients in the safety analysis set who have at least one baseline and one post-treatment efficacy measurement | |
| Subject analysis set title | Safety Analysis Set |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| The safety analysis set will include all patients who receive at least one dose of study treatment. | |
| Subject analysis set title | Per Protocol Set (PPS) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Per Protocol Set (PPS):<br>For the IP cohort, the PPS included all patients in the FAS who tolerated a minimum of five IP administrations of enadenotucirev or discontinued treatment with enadenotucirev before their fifth administration due to death, toxicity, consent withdrawal or loss to follow-up and did not have any major protocol violations that were deemed to affect the assessment of efficacy.<br>For the IV cohort, the PPS included all patients in the FAS who tolerated a minimum of five IV administrations of enadenotucirev or discontinued treatment with enadenotucirev before their fifth administration due to death, toxicity, consent withdrawal or loss to follow-up and did not have any major protocol violations that were deemed to affect the assessment of efficacy. | |

| | |
|---|---|
| Subject analysis set title | PK Set (PKS) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| PK Set (PKS): The PKS included all patients in the SAS who had at least one baseline and one corresponding post-treatment kinetics measurement | |

| | |
|---|---|
| Subject analysis set title | PD Set (PDS) |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| The PDS included all patients in the SAS who had at least one baseline and one corresponding post-treatment shedding, cytokine or antibody measurement. | |

| | |
|---|---|
| Subject analysis set title | All IP treated patients |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| All patients who received enadenotucirev via IP administration (either monotherapy or in combination | |

with paclitaxel)

| | |
|---|---|
| Subject analysis set title | Enadenotucirev IP Monotherapy |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Enadenotucirev IP Monotherapy

## Primary: Primary: Determine MTD and/or dose of enadenotucirev in patients with ovarian cancer

| | |
|---|---|
| End point title | Primary: Determine MTD and/or dose of enadenotucirev in patients with ovarian cancer[1][2] |

End point description:

The MTD assessed using the incidence of dose limiting toxicities (DLTs) and/or the dose of enadenotucirev recommended for further studies of enadenotucirev (when given by IP administration as a monotherapy or by IP administration or IV infusion in combination with paclitaxel)

| | |
|---|---|
| End point type | Primary |

End point timeframe:

End of study

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: No statistical analysis available due to the low number of patients

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The CEC took the decision to discontinue the IP administration route from the study based on practical issues with administration of the IP dose (see Section 10.1). A MTD for enadenotucirev by IP administration was not determined.
A MTD was only determmined for the arm : Enadenotucirev IV + Paclitaxel

| End point values | IV + paclitaxel (1 x 10e12 vp) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: viral particles (vp) | | | | |
| number (not applicable) | 1000000000000 | | | |

## Statistical analyses

No statistical analyses for this end point

## Primary: Primary: Evaluate PFS of enadenotucirev when given IV in combination with paclitaxel

| | |
|---|---|
| End point title | Primary: Evaluate PFS of enadenotucirev when given IV in combination with paclitaxel[3][4] |

End point description:

To evaluate the progression free survival (PFS) of enadenotucirev, using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1, when given by IV infusion in combination with paclitaxel in patients with recurrent platinum-resistant ovarian cancer.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Patients in full analysis set who were event-free at 16 weeks.

Notes:

[3] - 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: No statistical analysis available due to the low number of patients

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only related to the Arm selected : Enadenotucirev IV + Paclitaxel

| **End point values** | IV + paclitaxel (1 x 10e12 vp) | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 20 | | | |
| Units: Weeks | | | | |
| geometric mean (confidence interval 95%) | 63.8 (36.1 to 82.1) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Secondary: Evaluate PFS of enadenotucirev when administered by IP monotherapy or with paclitaxel

| End point title | Secondary: Evaluate PFS of enadenotucirev when administered by IP monotherapy or with paclitaxel[5] |
|---|---|

End point description:

To evaluate the PFS of enadenotucirev, using RECIST v1.1, when given by IP administration as a monotherapy and in combination with paclitaxel in patients with ovarian cancer. Data presented are the percentage of patients event-free (95% CI) at 16 weeks.

| End point type | Secondary |
|---|---|

End point timeframe:

16 weeks

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point is related to two arms (IP + paclitaxel (1 x 10e12 vp), IV + paclitaxel (1 x 10e12 vp) )and a combination of 2 arms Enadenotucirev IP Monotherapy. This last one includes the two arms below: IP Monotherapy (1 x 10e12 vp) and IP Monotherapy (6 x 10e12 vp)

| **End point values** | IP + paclitaxel (1 x 10e12 vp) | IV + paclitaxel (1 x 10e12 vp) | Enadenotucirev IP Monotherapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 8 | 20 | 10 | |
| Units: Percentage of patients event-free | | | | |
| arithmetic mean (confidence interval 95%) | 66.7 (19.5 to 90.4) | 63.8 (36.1 to 82.1) | 11.1 (0.6 to 38.8) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the time of informed consent until 28 days after the last administration of enadenotucirev.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety Analysis Set |

Reporting group description:

The Safety Analysis Set included all patients who received at least one dose of study treatment. An incorrect treatment schedule or study treatment administration, or an early termination of treatment, did not result in exclusion of patients from this population.

| | |
|---|---|
| Reporting group title | IP Monotherapy (1 x 10e12 vp) |

Reporting group description:

Enadenotucirev IP monotherapy (1 x 10e12 vp)

| | |
|---|---|
| Reporting group title | IP Monotherapy (6 x 10e12 vp) |

Reporting group description:

Enadenotucirev IP monotherapy (6 x 10e12 vp)

| | |
|---|---|
| Reporting group title | IP + paclitaxel (1 x 10e12 vp) |

Reporting group description:

Enadenotucirev IP (1 x 10e12 vp) in combination with paclitaxel

| | |
|---|---|
| Reporting group title | IV + paclitaxel (1 x 10e12 vp) |

Reporting group description:

Enadenotucirev IV (1 x 10e12 vp) in combination with paclitaxel

| Serious adverse events | Safety Analysis Set | IP Monotherapy (1 x 10e12 vp) | IP Monotherapy (6 x 10e12 vp) |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 38 (36.84%) | 4 / 7 (57.14%) | 1 / 3 (33.33%) |
| number of deaths (all causes) | 14 | 0 | 0 |
| number of deaths resulting from adverse events | 2 | 0 | 0 |
| Cardiac disorders | | | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 7 (14.29%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 7 (28.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| abdominal pain | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 2 / 7 (28.57%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal Obstruction | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 7 (14.29%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 7 (14.29%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatic Haemorrhage | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 7 (14.29%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site infection | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 1 / 3 (33.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral Infection | Additional description: Viral Infection/ Acute Inflammatory Response To Virus | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic Shock | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abscess | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal Skin Infection | | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | IP + paclitaxel (1 x 10e12 vp) | IV + paclitaxel (1 x 10e12 vp) | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 8 (75.00%) | 3 / 20 (15.00%) | |
| number of deaths (all causes) | 1 | 1 | |
| number of deaths resulting from adverse events | 1 | 1 | |
| Cardiac disorders | | | |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| abdominal pain | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal Obstruction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic Haemorrhage | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral Infection | Additional description: Viral Infection/ Acute Inflammatory Response To Virus | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic Shock | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 20 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal Skin Infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 20 (5.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | Safety Analysis Set | IP Monotherapy (1 x 10e12 vp) | IP Monotherapy (6 x 10e12 vp) |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 38 / 38 (100.00%) | 7 / 7 (100.00%) | 3 / 3 (100.00%) |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 14 | 0 | 0 |
| Nervous system disorders | | | |
| Lethargy | | | |
| subjects affected / exposed | 7 / 38 (18.42%) | 3 / 7 (42.86%) | 1 / 3 (33.33%) |
| occurrences (all) | 11 | 5 | 3 |
| Headache | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 2 / 7 (28.57%) | 1 / 3 (33.33%) |
| occurrences (all) | 5 | 2 | 1 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 38 (28.95%) | 1 / 7 (14.29%) | 2 / 3 (66.67%) |
| occurrences (all) | 27 | 2 | 7 |
| Fatigue | | | |
| subjects affected / exposed | 8 / 38 (21.05%) | 2 / 7 (28.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 11 | 2 | 0 |

| | | | |
|---|---|---|---|
| Asthenia | | | |
| subjects affected / exposed | 7 / 38 (18.42%) | 0 / 7 (0.00%) | 1 / 3 (33.33%) |
| occurrences (all) | 10 | 0 | 1 |
| Chills | | | |
| subjects affected / exposed | 7 / 38 (18.42%) | 2 / 7 (28.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 10 | 2 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 2 / 7 (28.57%) | 0 / 3 (0.00%) |
| occurrences (all) | 7 | 3 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 7 (14.29%) | 1 / 3 (33.33%) |
| occurrences (all) | 9 | 4 | 2 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 19 / 38 (50.00%) | 4 / 7 (57.14%) | 2 / 3 (66.67%) |
| occurrences (all) | 36 | 4 | 2 |
| Neutropenia | | | |
| subjects affected / exposed | 10 / 38 (26.32%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 23 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 16 / 38 (42.11%) | 5 / 7 (71.43%) | 2 / 3 (66.67%) |
| occurrences (all) | 25 | 7 | 3 |
| Nausea | | | |
| subjects affected / exposed | 16 / 38 (42.11%) | 5 / 7 (71.43%) | 2 / 3 (66.67%) |
| occurrences (all) | 28 | 7 | 9 |
| Abdominal pain | | | |
| subjects affected / exposed | 12 / 38 (31.58%) | 3 / 7 (42.86%) | 2 / 3 (66.67%) |
| occurrences (all) | 15 | 3 | 2 |
| Vomiting | | | |
| subjects affected / exposed | 10 / 38 (26.32%) | 4 / 7 (57.14%) | 1 / 3 (33.33%) |
| occurrences (all) | 26 | 9 | 7 |
| Constipation | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 7 | 0 | 0 |
| Ascites | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 7 (14.29%) | 0 / 3 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 2 / 7 (28.57%) | 1 / 3 (33.33%) |
| occurrences (all) | 7 | 3 | 1 |
| Cough | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 0 / 7 (0.00%) | 0 / 3 (0.00%) |
| occurrences (all) | 6 | 0 | 0 |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 2 / 7 (28.57%) | 1 / 3 (33.33%) |
| occurrences (all) | 5 | 2 | 1 |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 7 (14.29%) | 0 / 3 (0.00%) |
| occurrences (all) | 10 | 2 | 0 |

| **Non-serious adverse events** | IP + paclitaxel (1 x 10e12 vp) | IV + paclitaxel (1 x 10e12 vp) | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 20 / 20 (100.00%) | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 20 (10.00%) | |
| occurrences (all) | 4 | 10 | |
| Nervous system disorders | | | |
| Lethargy | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 2 | 1 | |
| Headache | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 20 (5.00%) | |
| occurrences (all) | 1 | 1 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 4 / 20 (20.00%) | |
| occurrences (all) | 12 | 6 | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 4 / 20 (20.00%) | |
| occurrences (all) | 4 | 5 | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 6 / 20 (30.00%) | |
| occurrences (all) | 0 | 9 | |
| Chills | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 20 (15.00%) | |
| occurrences (all) | 5 | 3 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 1 / 20 (5.00%) | |
| occurrences (all) | 3 | 1 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 3 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 10 / 20 (50.00%) | |
| occurrences (all) | 6 | 24 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 8 / 20 (40.00%) | |
| occurrences (all) | 2 | 21 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 5 / 20 (25.00%) | |
| occurrences (all) | 5 | 10 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 7 / 20 (35.00%) | |
| occurrences (all) | 4 | 8 | |
| Abdominal pain | | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 3 / 20 (15.00%) | |
| occurrences (all) | 7 | 3 | |
| Vomiting | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 8 (25.00%) | 3 / 20 (15.00%) | |
| occurrences (all) | 5 | 5 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 4 / 20 (20.00%) | |
| occurrences (all) | 2 | 5 | |
| Ascites | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 20 (5.00%) | |
| occurrences (all) | 3 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 20 (10.00%) | |
| occurrences (all) | 1 | 2 | |
| Cough | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 2 | 2 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 4 / 20 (20.00%) | |
| occurrences (all) | 2 | 4 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 20 (10.00%) | |
| occurrences (all) | 0 | 2 | |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 20 (10.00%) | |
| occurrences (all) | 2 | 6 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 October 2014 | Version 3.0 dated 21 Oct 2014<br><br>Patient Population<br><br>• To allow for patients to be included in Phase Ia and for the first three Phase Ib to reflect usual Phase I population criteria e.g. patients who exhausted all other treatment options, with no measurable disease acceptance of other malignancies in the 3 years prior to study entry<br>• To accept prior weekly paclitaxel monotherapy if there had been a 6 months between last weekly paclitaxel administration and first administration enadenotucirev<br>• To better define the exclusion criterion relating to intestinal subocclusion<br>• To allow nonsymptomatic central nervous system metastasis<br>• To remove the time window between last administration of prior systemic treatment for cancer and the first dose of study treatment as long had recovered from side effects to NCI CTCAE Grade 1 or less<br>• To not restrict the choice of IP catheter<br>• To allow for the IP catheter to be removed at any time post last administration study treatment according to the Investigator’s clinical judgement<br><br>Study Design<br>To extend the screening period to 21 days and mandate for the screening eligibility<br>procedures to be completed before insertion of the catheter |
| 23 March 2015 | Version 4.0 dated 23 Mar 2015<br><br>Patient Population<br>To refine the eligibility criteria relating to tolerance of administration procedures for enadenotucirev, to only select patients likely to tolerate the procedures<br><br>Safety<br>To allow for no or partial drainage of ascites prior to enadenotucirev administration in patients who had not tolerated the procedure during prior enadenotucirev administration or who were unlikely to further tolerate it |
| 25 January 2016 | Version 5.0 dated 25 Jan 2016<br><br>Patient Population<br>To remove the eligibility criterion excluding patients who had received a weekly regimen of paclitaxel in the previous 6 months |

| | |
|---|---|
| 01 November 2016 | Version 6.0 dated 01 Nov 2016<br><br>Patient Population:<br>The requirement for having historical biopsy samples was removed from a specific inclusion criterion and included as a study requirement<br><br>Safety:<br>• The use of acetaminophen/paracetamol and ibuprofen was amended to be administered according to the Investigator's normal prescribing practices and their discretion<br>• The DLT definition was amended to specify that the causality of an adverse event must be considered at least possibly attributed to enadenotucirev (whether it is given as a monotherapy or in combination with paclitaxel), in order to be considered a DLT<br><br>Study Design:<br>To add an IV dosing arm to the study to evaluate the safety and tolerability, PFS, anti-tumour activity, immune responses and exploratory objectives in patients with platinum-resistant ovarian cancer receiving IV enadenotucirev in combination with paclitaxel. Since the initiation of the study investigating the IP dosing route, two other clinical studies had investigated the IV administration of enadenotucirev (Study ColoAd1-1001 and ColoAd1-1002). The safety and tolerability profile had been outlined for a range of doses, dosing schedules and dosing regimens of enadenotucirev administered IV to more than 70 patients with a variety of epithelial derived cancers. A dose level of enadenotucirev for IV administration was identified to take forward in development that had both an acceptable tolerability profile and demonstrated delivery to an epithelial derived tumour type (colon cancer). The objective of this study changed to investigate administration of enadenotucirev by IP injection alongside IV infusion, the latter providing a potentially more convenient and acceptable route of administration in these patients. |
| 04 April 2017 | Version 7.0 dated 04 Apr 2017<br>Study Design<br>• An exploratory objective of Phase I of this study was added to measure a panel of cytokines in peripheral blood samples to explore the safety, the mechanism of action and the activity of enadenotucirev<br>• The cytokine sampling for Phase Ib IV administration was amended to be taken at pre-dose and 6 hours post-dose and 12 hours post-dose. This was to be consistent with another active study with IV enadenotucirev administration (ColoAd1-1003) |
| 14 December 2017 | Version 8.0 dated 14 Dec 2017<br><br>Safety:<br>Procedures were implemented as part of an urgent safety measure to increase monitoring of kidney function. This was in response to a Grade 4 SAE of acute renal injury in a single patient with Stage IV colon cancer in Study ColoAd1-1003 with enadenotucirev and nivolumab combination therapy. The event was assessed to be related to enadenotucirev.<br>For the two ongoing patients in the Dose Expansion Phase (both had completed Cycle 1 and were due to enter Cycle 2 at the time of this amendment):<br>• To make all safety laboratory tests mandatory (when previously optional based upon clinical judgement)<br>• To add urinalysis assessments at the following timepoints: Day 37, Day 44 and to correct an inconsistency and include urinalysis on Day 51<br>• To specify that any proteinuria detected on urinalysis must have been confirmed by repeat testing. If the patient presented any indication of decreased renal function on clinical assessment, then the Sponsor must have been contacted and a renal consultation arranged immediately. |

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| 05 February 2018 | Version 9.0 05 Feb 2018<br>Safety Following the implementation of an urgent safety measure to increase monitoring of kidney function in Version 8.0 of the protocol, in response to a treatment-related SAE of Grade 4 acute renal injury in a single patient with Stage IV colon cancer in a separate study with enadenotucirev and nivolumab combination therapy (Study ColoAd1-1003). Although this patient met the eligibility criteria for study entry (with adequate renal function) he had a past history of methotrexate-related renal injury and chronic kidney disease that was not declared at study entry.<br>In the overall context of three patients out of around 100 treated with enadenotucirev presenting with significant renal injury and in the context of risk:benefit of treatment, measures were implemented in ongoing studies to exclude those potentially at higher risk of renal injury (e.g. those with past history of renal disease, reduced renal function or proteinuria), monitoring patients more closely (at least weekly urinalysis assessment with appropriate confirmation of dipstick results with spot albumin creatinine ratios and 24-hour urinary protein if necessary) in turn with a view to early specialist intervention for investigation and treatment if decline in renal function should be detected. In addition, prophylactic hydrocortisone therapy was to be given with each administration of enadenotucirev to minimise any potential for renal damage as a result of cytokine-release mediated vascular leak syndrome. |
| 14 December 2018 | Version 10.0 14 Dec 2018<br>Safety:<br>The status, findings and recommendations following investigation into the renal injury signal were updated, including the risk: benefit assessment |
| 08 April 2019 | Version 11.0 08 Apr 2019<br>Safety:<br>• This protocol amendment comprised an urgent safety measure to exclude all patients from this study who had suspected, or evidence of, pulmonary lymphangitic carcinomatosis. This urgent safety measure followed an SAE of Grade 4 hypoxia in a patient treated with enadenotucirev at a dose of 1 x 1012 vp on Day 1 followed by 3 x 1012 vp on Days 3 and 5 in Study ColoAd1-1003. This patient was noted to have pre-existing pulmonary lymphangitic carcinomatosis. The cause of the profound hypoxia in this case was thought to be due to viral replication in tumour cells that had diffusely infiltrated the pulmonary lymphangitic channels with associated inflammation leading to impairment of diffusion capacity. This patient was treated with the antiviral medication cidofovir with some clinical improvement.<br>• When treatment with cidofovir should be considered was outlined.<br><br>Patient Population:<br>An exclusion criterion was added 'Clinically or radiologically suspected, or evidence of, lymphangitic carcinomatosis |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported