# Clinical trial results:
# PEPtalk 2: Pilot of a randomised controlled trial to compare VZIG and aciclovir as post-exposure prophylaxis against chickenpox in children with cancer.

## Summary

| | |
|---|---|
| EudraCT number | 2013-001332-22 |
| Trial protocol | GB |
| Global end of trial date | 22 February 2016 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 March 2017 |
| First version publication date | 12 March 2017 |
| Summary attachment (see zip file) | PEPTalk2 Clinical Trial Summary Report 17 Jan 2017 (PEPTalk2_Clinical Trial Summary Report_v1.0 vd17-Jan-2017.pdf) |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | RG_12-201 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN48257441 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | CAS Code: XX2001 |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Edgbaston, Birmingham, United Kingdom, B15 2TT |
| Public contact | Trial Team, University of Birmingham, 44 0121 415 8211, PEPtalk2@trials.bham.ac.uk |
| Scientific contact | Trial Team, University of Birmingham, 44 0121 415 8211, PEPtalk2@trials.bham.ac.uk |

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 | 17 August 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 30 June 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 22 February 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this pilot trial was to establish the likely rate of patient recruitment in a projected full-scale Phase III trial and to gather data which will allow for an informed sample size calculation for the main trial.

This will enable a full-scale trial to compare the efficacy, safety and acceptability of varicella zoster immunoglobulin (VZIG) and aciclovir as post-exposure prophylaxis (PEP) for chickenpox in children receiving treatment for cancer. This would address the urgent need for evidence on how best to prevent chickenpox in children receiving treatment for cancer who are exposed to the virus. The proposed definitive study will be a multi-centre randomised controlled trial to compare aciclovir with VZIG.

Protection of trial subjects:

No specific measures were employed to protect the trial subjects, however both drugs are in standard use as prophylaxis for immunocompromised patients experiencing chickenpox exposure and it is in that same context that the drugs were used in this trial. VZIG use relates to licensed indication, dosage and form; aciclovir is used off-label per established paediatric practice.

Background therapy:

None

Evidence for comparator:

There are no comparators in this study as there is no defined standard of treatment. The main objective of this pilot study was to determine the likely rate of patient randomisation and to facilitate sample size calculation, in order to inform the design of a larger trial. If, for example, the pilot study was successful in recruiting 50 patients from up to seven UK centres over a 12-month period, then a larger trial that recruited from twice as many centres over a 24-month period could recruit about 200 patients.

| | |
|---|---|
| Actual start date of recruitment | 09 May 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 32 |
| Worldwide total number of subjects | 32 |
| EEA total number of subjects | 32 |

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) | 5 |
| Children (2-11 years) | 26 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment between 9th May 2014 and 30th June 2015 at 6 treatment sites in the UK. Patients were screened (482) of which 32 were registered and 3 subsequently randomised.

### Pre-assignment

Screening details:

A blood test confirming VZV seronegativity either at cancer diagnosis or within 3 months prior to registration. Patients with a previous VZV serostatus result taken greater than 3 months prior to trial registration were eligible to be registered if a repeat VZV serostatus (negative) obtained.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 482[1] |
| Intermediate milestone: Number of subjects | Screening: 482 |
| Intermediate milestone: Number of subjects | Registration: 32 |
| Number of subjects completed | 32 |

### Pre-assignment subject non-completion reasons

| | |
|---|---|
| Reason: Number of subjects | Seropositive screening result: 337 |
| Reason: Number of subjects | Indeterminate screening result: 47 |
| Reason: Number of subjects | Declined - Travel distance: 23 |
| Reason: Number of subjects | Declined registration: 22 |
| Reason: Number of subjects | Declined - additional blood samples: 8 |
| Reason: Number of subjects | Declined - additional oral medication: 6 |
| Reason: Number of subjects | Declined - no reason given: 6 |
| Reason: Number of subjects | Allergic to aciclovir: 1 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Of those patients screened (482) only those that were eligible and had not declined (32) where registered.

### Period 1

| | |
|---|---|
| Period 1 title | Registration |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | Registration |

Arm description:

Patients available for randomisation

| | |
|---|---|
| Arm type | Randomisation pool |

No investigational medicinal product assigned in this arm

| Number of subjects in period 1 | Registration |
|---|---|
| Started | 32 |
| Completed | 3 |
| Not completed | 29 |
| Not exposed to VZV | 29 |

## Period 2

| | |
|---|---|
| Period 2 title | Randomisation |
| Is this the baseline period? | Yes[2] |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

## Arms

| | |
|---|---|
| **Arm title** | Aciclovir |

Arm description:

High dose oral aciclovir

| | |
|---|---|
| Arm type | Post Exposure Prophylaxis (PEP) |
| Investigational medicinal product name | Aciclovir |
| Investigational medicinal product code | PR49, PR50 |
| Other name | |
| Pharmaceutical forms | Dispersible tablet, Syrup, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

High dose oral aciclovir given for 14 days, from Day 7 to Day 21 following exposure.

Aciclovir dose is per British National Formulary (BNF) for Children:

- Under 2 years age 200 mg four times daily
- 2-6 years age 400 mg four times daily
- Over 6 years age 800 mg four times daily

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Only registered patients who had had a significant exposure to varicella (VZV) were eligible for randomisation.

| Number of subjects in period 2[3] | Aciclovir |
|---|---|
| Started | 3 |
| Completed | 3 |

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Only registered patients who had had a significant exposure to varicella (VZV) were eligible for randomisation.

## Baseline characteristics

### Reporting groups

| Reporting group title | Randomisation |
|---|---|

Reporting group description: -

| Reporting group values | Randomisation | Total | |
|---|---|---|---|
| Number of subjects | 3 | 3 | |
| Age categorical<br>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) | 3 | 3 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 2 | |
| Male | 1 | 1 | |

### Subject analysis sets

| Subject analysis set title | Full end of trial analysis |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:
Randomised patients

| Reporting group values | Full end of trial analysis | | |
|---|---|---|---|
| Number of subjects | 3 | | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 3 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |

| Gender categorical<br>Units: Subjects | | | |
|---|---|---|---|
| Female | 2 | | |
| Male | 1 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Registration |
| Reporting group description: Patients available for randomisation | |
| Reporting group title | Aciclovir |
| Reporting group description: High dose oral aciclovir | |
| Subject analysis set title | Full end of trial analysis |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Randomised patients | |

### Primary: Randomised patients

| | |
|---|---|
| End point title | Randomised patients[1] |

End point description:

The number of patients randomised within 12 months of the trial opening to recruitment. Considered in relation to the number of patients registered and the number of patients screened, this has allowed an informed evaluation of the trial enrolment rate amongst eligible patients.

Data has therefore been collected on the number of patients screened for the study at each centre and the number of eligible patients at each centre who agreed to registration and to randomisation. Reasons for not participating in the study have been collated, so far as reasonably possible, by means of a Screening Log (Pre-Registration) and, where relevant, a Screening Form (Pre-Randomisation).

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

End point timeframe:

Within 12 months of the trial opening to recruitment

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: As only 3 patients were exposed to varicella and subsequently randomised and therefore no meaningful analysis could be completed.

| End point values | Aciclovir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Patients | 3 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Seroconversion

| | |
|---|---|
| End point title | Seroconversion |

End point description:

Seroconversion within 12 (+/- 2) weeks of administration of PEP will be assessed in this pilot study as asymptomatic seroconversion has been documented in previous uncontrolled studies. It is routine clinical practice in most hospitals to obtain a blood sample for confirmation of VZV serology prior to PEP administration. An aliquot (1-2ml) from the blood sample (3-5ml) that is taken prior to PEP administration will be stored locally. A further blood sample (2-3ml) will be obtained at 12 (+/- 2) weeks

after PEP and the 2 samples will be sent in batches to the national reference laboratory for analysis. It is proposed that the current national test, the Binding site assay, will be the basis for this analysis. This test has been validated by the Public Health England and other investigators.

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

End point timeframe:

Serconversion at 12 +/- 2 weeks post administration of PEP

| **End point values** | Aciclovir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Patients | 0 | | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of breakthrough Varicella

| End point title | Incidence of breakthrough Varicella |
|---|---|

End point description:

Incidence of clinical varicella up to 12 (+/- 2) weeks following administration of PEP will be established. Local clinicians and the patient's family were expected to notify the coordinator if varicella occured during this period. Details of any episodes of varicella were to be obtained from the clinical notes, parent diary and/or at study visits.

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

End point timeframe:

At 12 +/- 2 weeks after administration of PEP

| **End point values** | Aciclovir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3[2] | | | |
| Units: Patients | 0 | | | |

Notes:

[2] - There were no incidences or breakthrough Varicella

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Compliance with allocated treatment

| End point title | Compliance with allocated treatment |
|---|---|

End point description:

Compliance with allocated treatment

| End point type | Other pre-specified |
|---|---|

End point timeframe:
Completion of allocated treatment

| End point values | Aciclovir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Patients | 3 | | | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Adherence to study follow up

| End point title | Adherence to study follow up |
|---|---|

End point description:
Adherence to study follow up

| End point type | Other pre-specified |
|---|---|

End point timeframe:
On completion of follow up

| End point values | Aciclovir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Patients | 3 | | | |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: QoL surveys completed

| End point title | QoL surveys completed |
|---|---|

End point description:

Quality of Life assessment is expected to be documented by the following methods.

EQ-5D
The EQ-5D-3L or EQ-5D-Y (depending on patient age) will be administered on three occasions:
(i) when PEP is initiated;
(ii) at 2 weeks (included in the PEPtalk2 Treatment Diary);
(iii) at the 12-week (+/- 2 weeks) follow-up appointment.

The EQ-5D-Y is designed for children aged 7 to 12. It can be completed by proxy (by the patient's parent/legal representative) for children less than 7 years old. The EQ-5D-3L is designed for patients aged 13+.

| End point type | Other pre-specified |
|---|---|

End point timeframe:

1, At administration of PEP
2, At 2 weeks post PEP administration
3, At 12 +/- 2 weeks post PEP administration

| **End point values** | Aciclovir | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3[3] | | | |
| Units: Forms | 7 | | | |

Notes:

[3] - when PEP is initiated;
at 2 weeks
at 12 (+/- 2 weeks)

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Health care resource use

| End point title | Health care resource use |
|---|---|

End point description:

The proportion of patients for whom health care resource use and caregiver costs are collected

| End point type | Other pre-specified |
|---|---|

End point timeframe:

At completion of follow up

### Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information[1] | |
|---|---|
| Timeframe for reporting adverse events: SAEs were documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment. | |
| Assessment type | Systematic |

| Dictionary used | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 4 |

Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There were no Adverse Events (AEs) or Adverse Reactions (ARs) reported during the trial.

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 16 December 2013 | Change of Principal Investigators at:<br><br>St Georges Healthcare NHS Trust, London<br>The Royal Hospital for Children, Bristol |
| 31 October 2014 | Change to the patient eligibility trial inclusion criteria allowing patients who were up to 6 months post immunosuppressing treatment to be registered into the trial in light of the guidance given in the Green Book v2.0, Chapter 34 - Varicella, Page 430 – Management of immunosuppressed patients<br><br>Change to the screening guidelines prior to randomisation which now stipulates that a further test for seronegativity is not required if a seronegativity test has been carried out in the preceding 28 days<br><br>Addition of a further 6 data acquisition forms to the Case Report Form, as listed in the protocol.<br><br>Amendment to the section 15.5 Finance which details that no incurred expenses will be paid to the participants for attending follow-up appointment at 12 (+/-) 2 weeks<br><br>In addition, the Parent Information Sheet and Informed Consent Form (Registration) have been amended to reflect the changes in the protocol. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitations due to:
Rate of seronegativity (16%) was lower than predicted (50%)
High rates of "indeterminate" serostaus results (13%).
No patients were randomised to the VZIG arm.

There were no AEs reported.

Notes: