



## 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
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##### 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:

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**Results analysis stage**

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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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**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:

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**Subjects enrolled per age group**

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In utero	0
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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 <sup>[1]</sup>
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) were 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 <sup>[2]</sup>
Allocation method	Randomised - controlled
Blinding used	Not blinded

## Arms

<b>Arm title</b>	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 <sup>[3]</sup>	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
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Reporting group description: -

Reporting group values	Randomisation	Total	
Number of subjects	3	3	
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)	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			
Units: Subjects			
Female	2	2	
Male	1	1	

### Subject analysis sets

Subject analysis set title	Full end of trial analysis
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Subject analysis set type	Full analysis
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Subject analysis set description:

Randomised patients

Reporting group values	Full end of trial analysis		
Number of subjects	3		
Age categorical			
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			
Units: Subjects			
Female	2		
Male	1		

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## 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 <sup>[1]</sup>
End point description:	
<p>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.</p> <p>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).</p>	
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.

<b>End point values</b>	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:	
<p>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</p>	

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	

<b>End point values</b>	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 occurred 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	

<b>End point values</b>	Aciclovir			
Subject group type	Reporting group			
Number of subjects analysed	3 <sup>[2]</sup>			
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

<b>End point values</b>	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	

<b>End point values</b>	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	

<b>End point values</b>	Aciclovir			
Subject group type	Reporting group			
Number of subjects analysed	3 <sup>[3]</sup>			
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

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### Adverse events information<sup>[1]</sup>

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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.

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Assessment type	Systematic
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### Dictionary used

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Dictionary name	CTCAE
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Dictionary version	4
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Frequency threshold for reporting non-serious adverse events: 1 %

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#### 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:  St Georges Healthcare NHS Trust, London The Royal Hospital for Children, Bristol
31 October 2014	<p>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</p> <p>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</p> <p>Addition of a further 6 data acquisition forms to the Case Report Form, as listed in the protocol.</p> <p>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</p> <p>In addition, the Parent Information Sheet and Informed Consent Form (Registration) have been amended to reflect the changes in the protocol.</p>

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" serostatus results (13%).  
No patients were randomised to the VZIG arm.

There were no AEs reported.

Notes: