Clinical trial results:
A randomised, double-blind, placebo-controlled trial to evaluate the effect of Epstein-Barr virus suppression in chronic obstructive pulmonary disease (EViSCO trial).

Summary

EudraCT number	2017-004686-28
Trial protocol	GB
Global end of trial date	27 May 2020

Results information

Result version number	v1 (current)
This version publication date	31 May 2021
First version publication date	31 May 2021

Trial information

Trial identification

Sponsor protocol code	14143JK-AS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03699904
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health and Social Care Trust
Sponsor organisation address	A Floor, Belfast City Hospital, Lisburn Road, Belfast, United Kingdom, BT9 7AB
Public contact	Dr Joe Kidney, Belfast Health and Social Care Trust , 0044 (0)2895 047531, joe.kidney@belfasttrust.hscni.net
Scientific contact	Dr Joe Kidney, Belfast Health and Social Care Trust , 0044 (0)2895 047531, joe.kidney@belfasttrust.hscni.net

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	12 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2020
Global end of trial reached?	Yes
Global end of trial date	27 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Aim: To establish if an antiviral therapy (valaciclovir) used to treat other herpes viruses is safe in patients with COPD. To examine whether it is possible to supress EBV in the airways of patients with COPD and examine important outcome measures including lung function and markers of airway inflammation in the blood and sputum.

Primary Objective: To evaluate the safety of valaciclovir (1 gram three times daily for 8 weeks) for the suppression of Epstein-Barr virus in patients with COPD. To suppress Epstein-Barr virus shedding in COPD.

Protection of trial subjects:

The risks for the patients in the intervention group included the side effects of the study drug (valaciclovir) and included headache, nausea, diarrhoea, vomiting and photosensitivity reaction. Patients with documented history of allergy or intolerance of the study drug were excluded from the trial. Patients unable to produce sputum samples spontaneously were offered the opportunity to undergo sputum induction this can cause bronchospasm. Therefore, subjects requiring sputum induction received prior nebulised bronchodilator and had serial FEV1 monitoring to ensure no deterioration. An independent data monitoring and ethics committee was also convened for the trial.

Background therapy:

Not Applicable

Evidence for comparator:

The comparator was placebo.

Actual start date of recruitment	02 November 2018
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: 85
Worldwide total number of subjects	85
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	49
From 65 to 84 years	36
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between 02/11/2018 and 12/03/2020 from a single site, the Mater Hospital Belfast. 85 patients out of the planned 88 patients were recruited during this period.
Recruitment to the trial was terminated early (08/04/2020) due to the risks of ongoing recruitment of patients with COPD given the current Covid 19 pandemic.

Pre-assignment

Screening details:

Potentially eligible subjects with COPD were identified and screened by members of the direct care team based on the inclusion/exclusion criteria as specified in the study protocol.
A total of 171 patients were screened, of which 85 patients were recruited.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

This study was a randomised double blind placebo controlled trial with an allocation ratio of 1 : 1.
Randomisation was undertaken by the clinical trials unit using randomised permuted blocks
All researchers were blinded to the treatment allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

The intervention was valaciclovir 1 gram to be taken 3 times daily for 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Valaciclovir 500mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Valaciclovir 1 gram (2 x 500mg) orally three times daily for 8 weeks.

Arm title	Control

Arm description:

The comparator was matched placebo to be taken 3 times daily for 8 weeks.

Arm type	Placebo
Investigational medicinal product name	Matched placebo (Avicel®PH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matched placebo (Avicel®PH) orally three times daily for 8 weeks.

Number of subjects in period 1[1]	Intervention	Control
Started	43	41
Completed	41	40
Not completed	2	1
Lost to follow-up	2	1

Notes:

[1] - 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: One patient was randomised to the trial, this patient subsequently withdrew prior to treatment allocation. 85 patients were randomised, 84 recieved an allocation to a treatment arm.

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description:	
The intervention was valaciclovir 1 gram to be taken 3 times daily for 8 weeks.	
Reporting group title	Control
Reporting group description:	
The comparator was matched placebo to be taken 3 times daily for 8 weeks.	

Reporting group values	Intervention	Control	Total
Number of subjects	43	41	84
Age categorical 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)	23	26	49
From 65-84 years	20	15	35
85 years and over	0	0	0
Age continuous			
Age at randomisation, years			
Units: years			
arithmetic mean	63.1	60.3	
standard deviation	± 8.1	± 9.8	-
Gender categorical Units: Subjects			
Female	29	26	55
Male	14	15	29
Smoking Status Units: Subjects			
Current Smoker	19	24	43
Ex-Smoker	24	17	41
Never Smoked	0	0	0
Presence of EBV Units: Subjects			
Yes	43	41	84
No	0	0	0
Relevant co-morbidities Units: Subjects			
Yes	38	36	74
No	5	5	10
Pre-existing cardiovascular issues Units: Subjects			

Yes	15	14	29
No	28	27	55
Exacerbations in the last 12 months Units: Subjects			
Yes	32	29	61
No	11	12	23
Height Units: Metres			
arithmetic mean	1.7	1.7	
standard deviation	± 0.1	± 0.1	-
Weight Units: Kilograms			
arithmetic mean	77.2	75.4	
standard deviation	± 18.2	± 19.5	-
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	27.3	27.2	
standard deviation	± 5.3	± 6.2	-
Transfer Factor			
Transfer Factor ((TLCO) as a percentage of the predicted value (%))			
Units: Percentage			
arithmetic mean	58.53	62.97	
standard deviation	± 16.30	± 19.28	-
Forced Expiratory Volume			
Forced Expiratory Volume (FEV1 (L))			
Units: Litres			
arithmetic mean	1.60	1.57	
standard deviation	± 0.58	± 0.62	-
Forced Vital Capacity			
Forced Vital Capacity (FVC (L))			
Units: Litres			
arithmetic mean	3.21	3.13	
standard deviation	± 0.92	± 0.94	-
FEV1/FVC Ratio			
FEV1/FVC Ratio (%)			
Units: Percentage			
arithmetic mean	49.44	49.88	
standard deviation	± 9.67	± 10.23	-
Mid Expiratory Flow			
Mid Expiratory Flow (MMEF 25-75% (L/s))			
Units: L/S			
arithmetic mean	0.59	0.67	
standard deviation	± 0.33	± 0.56	-
Peak Expiratory Flow			
Peak Expiratory Flow (PEF (L/s))			
Units: L/S			
arithmetic mean	4.51	4.39	
standard deviation	± 1.68	± 1.60	-
Pack Years Units: Years			
arithmetic mean	55.3	48.3	
standard deviation	± 36.7	± 25.9	-

Quantitative PCR Titre Units: Copies			
median	91000	56400	
inter-quartile range (Q1-Q3)	15200 to 298000	11500 to 315000	-

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description:	
The intervention was valaciclovir 1 gram to be taken 3 times daily for 8 weeks.	
Reporting group title	Control
Reporting group description:	
The comparator was matched placebo to be taken 3 times daily for 8 weeks.	

Primary: Primary Efficacy Outcome (EBV Suppression)

End point title	Primary Efficacy Outcome (EBV Suppression)
End point description:	
End point type	Primary
End point timeframe:	
8 Weeks	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	41	40		
Units: n(%)				
Yes	36	17		
No	5	23		
Not Recorded	0	0		

Statistical analyses

Statistical analysis title	Primary Efficacy ITT
Statistical analysis description:	
The primary efficacy outcome is suppression of Epstein-Barr virus in the sputum of subjects with COPD and was assessed using quantitative PCR at baseline and 8 weeks. EBV suppression is defined as a 90% reduction in the viral load.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	9.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	30

Primary: Primary Safety Outcome (SARs)

End point title	Primary Safety Outcome (SARs)[1]

End point description:

The primary safety outcome is the incidence of serious adverse reactions (SARs).

End point type	Primary

End point timeframe:

Week 8

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: It was planned that the number of patients experiencing SAR in the two groups would be compared using Fisher's exact test, reporting the relative risk and 95% confidence interval. There were no SARs reported and thus it was not possible to carry out the planned analysis.

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	41		
Units: n(%)				
Yes	0	0		
No	43	41		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for this trial begins on enrolment into the trial and ends 28 days following the administration of the study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Intervention

Reporting group description:

The intervention was valaciclovir 1 gram to be taken 3 times daily for 8 weeks.

Reporting group title	Control

Reporting group description:

The comparator was matched placebo to be taken 3 times daily for 8 weeks.

Serious adverse events	Intervention	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Intervention	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 43 (60.47%)	30 / 41 (73.17%)	
Vascular disorders			
Angina Pectoris			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	1 / 43 (2.33%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Hyperhidrosis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Chest Discomfort			
subjects affected / exposed	1 / 43 (2.33%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Cough			
subjects affected / exposed	0 / 43 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Haemoptysis			
subjects affected / exposed	0 / 43 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Mucous plugging			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Pleuritic Pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Upper Respiratory Tract infection			
subjects affected / exposed	2 / 43 (4.65%)	2 / 41 (4.88%)	
occurrences (all)	2	2	
Psychiatric disorders			
Depressed Mood			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Investigations			
Abnormal CT Scan			

subjects affected / exposed	3 / 43 (6.98%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Blood Creatinine			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Blood Potassium Increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Blood Urea Increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Culture Urine Positive			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Cystoscopy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Endoscopy			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
International Normalised Ratio Increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Sputum Cuture Positive			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
White Blood Cell Count Increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Arthropod Bite			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Fall			

subjects affected / exposed	1 / 43 (2.33%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 43 (2.33%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 43 (4.65%)	2 / 41 (4.88%)	
occurrences (all)	2	2	
Eosinophilia			
subjects affected / exposed	3 / 43 (6.98%)	1 / 41 (2.44%)	
occurrences (all)	3	1	
Neutrophilia			
subjects affected / exposed	3 / 43 (6.98%)	3 / 41 (7.32%)	
occurrences (all)	3	3	
Thrombocytopenia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye Pruitus			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Dry Eye			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	4 / 43 (9.30%)	5 / 41 (12.20%)	
occurrences (all)	4	5	

Dry Mouth			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Gastroesophageal Reflux Disease			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	4 / 43 (9.30%)	2 / 41 (4.88%)	
occurrences (all)	4	2	
Vomiting			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Pruritis			
subjects affected / exposed	1 / 43 (2.33%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Subcutaneous Abscess			
subjects affected / exposed	0 / 43 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	2 / 43 (4.65%)	1 / 41 (2.44%)	
occurrences (all)	2	1	
Muscle Spasms			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Thoracic Vertebral Fracture			

subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	2	
Aspergillus Infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Oral Candidiasis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Urinary Tract Infection			
subjects affected / exposed	0 / 43 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
White Blood Cell Count Increased			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 43 (0.00%)	2 / 41 (4.88%)	
occurrences (all)	0	2	
Osteopenia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 41 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2019	Substantial Amendment 1 (Amendment 3) was for the amendment of protocol version 2.0 (28/11/2018) to protocol version 3.0 (22/05/2019). The study sponsor requested that EBV quantitative PCR should be listed as a co-primary outcome as the study sample size was calculated based on this parameter. In addition the wording of the primary safety outcome was amended to: "The primary safety outcome is the incidence of serious adverse reactions (SARs)". This amendment was requested by the sponsor prior to recruitment commencing. Recruitment was permitted to commence and subsequently the amendment was submitted and approved by Ethics and MHRA.
18 March 2020	Substantial Amendment 2 (Amendment 7) was for the amendment of protocol version 3.0 (22/05/2019) to protocol version 4.0 (22/04/2020). This amendment was submitted in light of the Covid19 pandemic lockdown and detailed that study visits would be conducted virtually in order to protect study participants. This was actioned with immediate effect on urgent safety grounds.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 April 2020	The EVISCO trial was terminated early. A total of 85 patients out of the planned 88 patients were recruited. Recruitment to the trial was terminated early (08/04/2020) due to the risks of ongoing recruitment of patients with COPD during the Covid 19 pandemic.	-

Notes:

Limitations and caveats

None reported