Clinical trial results:
A phase II, open-label, multi-center study to assess the tolerance, safety, efficacy and pharmacokinetics/pharmacodynamics (PK/PD) of POL7080 in the treatment of patients with acute exacerbation of non-cystic fibrosis bronchiectasis due to Pseudomonas aeruginosa infection requiring intravenous treatment.

Summary

EudraCT number	2013-002202-31
Trial protocol	GB ES DE
Global end of trial date	08 October 2015

Results information

Result version number	v1 (current)
This version publication date	08 June 2017
First version publication date	08 June 2017
Summary attachment (see zip file)	Synopsis_CSR_2013-002202-31 (ESPOL003 (POL7080-002)_CSR_Synopsis_Final Version_29 Dec 16.pdf)

Trial information

Trial identification

Sponsor protocol code	POL7080-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02096315
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Polyphor Ltd
Sponsor organisation address	411 Tower Bridge Business Centre, 46-48 East Smithfield, London, United Kingdom, E1W 1AW
Public contact	Leon Hooftman, M.D., Polyphor Ltd, +41 615671600, Leon.Hooftman@polyphor.com
Scientific contact	Leon Hooftman, M.D., Polyphor Ltd, +41 615671600, Leon.Hooftman@polyphor.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	19 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2014
Global end of trial reached?	Yes
Global end of trial date	08 October 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of POL7080 administered for 10 to 14 days in the treatment of patients with acute exacerbation of non-cystic fibrosis bronchiectasis due to Pseudomonas aeruginosa infection.

Protection of trial subjects:

The patient health status was closely monitored throughout the study. If changes in their well-being or laboratory results or other findings develop during the course of the trial which indicated that their health had been impaired and was at risk, the Study Doctor was obliged to take all medically necessary measures to restore their previous state of health and to keep the changes under control until they had normalized again.
As a precaution, male patients were to practice contraception during the treatment period and up to 75 days after the end of treatment. Currently, the effects of POL7080 on the embryo/foetal development of pregnant woman and fertility in man are not known. If the patient was a woman of child bearing potential (capable of becoming pregnant) she had to practice a reliable method of contraception (such as continuation of contraception pills, abstinence, double protection i.e. condom and diaphragm).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 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: 6
Country: Number of subjects enrolled	United Kingdom: 6
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	6
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

It was planned to included 20 patients. FPFV: Feb 3, 2014, LPLV: Nov 26, 2014. Recruitment was temporarily halted in December 2014 due to discordance between clinical improvement and microbiological response, and terminated on October 8, 2015 due to futility in achieving a positive microbiological response in this particular study setting.

Pre-assignment

Screening details:

Inclusion criteria: adults ≥18 to <80 with non-cystic fibrosis bronchiectasis, with exacerbation with increased cough, sputum production or sputum purulence, current infection/chronically infected with Pseudomonas aeruginosa, and sputum sample collected for quantitative culture. All screened patients were enrolled, there were not screening failure.

Pre-assignment period milestones

Number of subjects started	12
Number of subjects completed	12

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Treated with POL7080

Arm description:

All screened and enrolled patients received treatment with POL7080

Arm type	Experimental
Investigational medicinal product name	POL7080
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

POL7080 was administered as intravenous infusion at a dose of 2.5mg/kg, 2-hour infusion, three times daily for 10 to 14 days.

Number of subjects in period 1	Treated with POL7080
Started	12
Completed	4
Not completed	8
Absence of Pseudomonas aeruginosa infection	3
Abnormal laboratory value	1
Due to proteinuria	1

Low Pseudomonas aeruginosa count	2
Absence of symptom improvement	1

Baseline characteristics

Reporting groups

Reporting group title	Treatment period

Reporting group description: -

Reporting group values	Treatment period	Total	
Number of subjects	12	12	
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)	6	6	
From 65-84 years	6	6	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	64.6		
standard deviation	± 11.05	-	
Gender categorical Units: Subjects			
Female	11	11	
Male	1	1	
Race Units: Subjects			
Caucasian	12	12	
Black	0	0	
Asian/Oriental	0	0	
Other	0	0	
Weight (kg) Units: Subjects			
<60kg	7	7	
60 to <80 kg	5	5	
80 to <100 kg	0	0	
>=100 kg	0	0	

Subject analysis sets

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

All enrolled patients who received at least one dose of POL7080.

Subject analysis set title	PK population

Subject analysis set type	Sub-group analysis

Subject analysis set description:

All enrolled patients who received at least one dose of POL7080 and at least one valid post infusion pharmacokinetic assessment.

Subject analysis set title	mITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All enrolled patients with documented Pseudomonas aeruginosa infection (i.e., 105 cfu/mL) at baseline and who received at least one dose of POL7080.

Reporting group values	Safety population	PK population	mITT population
Number of subjects	12	12	5
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)	6	6	2
From 65-84 years	6	6	3
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	64.6	64.6	64.6
standard deviation	± 11.05	± 11.05	± 15.87
Gender categorical Units: Subjects			
Female	11	11	5
Male	1	1	0
Race Units: Subjects			
Caucasian	12	12	5
Black	0	0	0
Asian/Oriental	0	0	0
Other	0	0	0
Weight (kg) Units: Subjects			
<60kg	7	7	4
60 to <80 kg	5	5	1
80 to <100 kg	0	0	0
>=100 kg	0	0	0

End points

End points reporting groups

Reporting group title	Treated with POL7080
Reporting group description:	
All screened and enrolled patients received treatment with POL7080	
Subject analysis set title	Safety population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled patients who received at least one dose of POL7080.	
Subject analysis set title	PK population
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All enrolled patients who received at least one dose of POL7080 and at least one valid post infusion pharmacokinetic assessment.	
Subject analysis set title	mITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled patients with documented Pseudomonas aeruginosa infection (i.e., 105 cfu/mL) at baseline and who received at least one dose of POL7080.	

Primary: Sputum Bacterial clearance of Pseudomonas aeruginosa

End point title	Sputum Bacterial clearance of Pseudomonas aeruginosa[1]
End point description:	
The primary efficacy variable is the Sputum Bacterial clearance [reduction in the daily quantitative viable counts (cfu/mL) of Pseudomonas aeruginosa by at least 1-log] in subjects with baseline P. aeruginosa ≥ 100,000 cfu/mL.	
End point type	Primary
End point timeframe:	
Test of Cure (TOC) was the time of the primary endpoint assessment at 4±1 day after EOT (end of treatment).	

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: The number and percentage (plus 95% CI) of patients in the mITT analysis set with reduction in the quantitative viable counts (cfu/mL) of Pseudomonas aeruginosa by at least 1-log at TOC was presented. Evolution of bacterial viable counts was summarised for the absolute and change from baseline values by visit. Confidence intervals for point estimates where appropriate were 95% (i.e. using a 5% significance level). No adjustment for multiple comparisons or corrections for multiplicity was planned

End point values	mITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: number of patients				
Patients with 1-log reduction	1			
Patients with no 1-log reduction	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 1-log reduction of Pseudomonas aeruginosa as compared to baseline

End point title	Time to 1-log reduction of Pseudomonas aeruginosa as compared to baseline

End point description:

Time to 1 log reduction of Pseudomonas aeruginosa as compared to baseline:
In patients who had at least 1X100,000 P. aeruginosa grown in the baseline quantitative culture of the sputum, the time difference between the baseline culture and the first of the 2 consecutive samples with 1-log reduction will be calculated as the time to log reduction.

End point type	Secondary

End point timeframe:

Any time (to 1 log reduction) compared to baseline

End point values	mITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: days				
arithmetic mean (standard deviation)	3.5 (± 2.12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical status assessment

End point title	Clinical status assessment

End point description:

Clinical status assessment was based on the clinical signs and symptoms of the patient and was assessed at treatment visits 4 and 10, EOT, and TOC. During the earlier treatment visit 4 there was no documented change in clinical status whereas at treatment visit 10 and EOT there were two (40.0%) subjects who exhibited improved status (three
[60.0%] subjects had missing status. At TOC, two (40.0%) subjects exhibited improved clinical status, while the remaining three (60.0%) subjects had an unchanged status. No subject in the mITT group showed a worsening of clinical status.

End point type	Secondary

End point timeframe:

It was assessed at visit 4 (day 4), visit 10 (day 10), end of treatment (EOT), and test of cure (TOC).

End point values	mITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: number of patients				
Visit 4 - returned to preexacerbation state	0			
Visit 4 - Improved	0			
Visit 4 - Unchanged	4			
Visit 4 - Worsened	0			
Visit 4 - Missing	1			
Visit 10 - returned to preexacerbation state	0			
Visit 10 - Improved	2			
Visit 10 - Unchanged	0			
Visit 10 - Worsened	0			
Visit 10 - Missing	3			
EOT - Returned to preexacerbation state	0			
EOT - Improved	2			
EOT - Unchanged	0			
EOT - Worsened	0			
EOT - Missing	3			
TOC - Returned to preexacerbation state	0			
TOC - Improved	2			
TOC - Unchanged	3			
TOC - Worsened	0			

Statistical analyses

No statistical analyses for this end point

Secondary: 24-hour sputum volume

End point title	24-hour sputum volume

End point description:

End point type	Secondary

End point timeframe:

This was assessed at visits 4, 10, EOT and TOC.

End point values	mITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: mL				
arithmetic mean (standard deviation)				
Screening visit	18.8 (± 11.09)			
Treatment visit 4	20.8 (± 19.43)			
Treatment visit 10	5.5 (± 6.36)			

Treatment visit EOT	5.5 (± 6.36)			
Treatment visit TOC	20.8 (± 13.83)			

Statistical analyses

No statistical analyses for this end point

Secondary: Sputum purulence score

End point title	Sputum purulence score

End point description:

Sputum purulence score is calculated as 3 for purulent sputum, 2 for muco-purulent sputum and 1 for mucoid sputum.

At EOT visit only one patient had sputum purulence score, a zero (0) had added in the SD box due to the inability to leave the value box empty. When SD=0, it has been indicated as 0.0

End point type	Secondary

End point timeframe:

This was assessed at visits 4, 10, EOT and TOC

End point values	mITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Score				
arithmetic mean (standard deviation)				
Screening visit	3 (± 0)			
Treatment visit 4	2.8 (± 0.5)			
Treatment visit 10	2.5 (± 0.71)			
Treatment visit EOT	3 (± 0)			
Treatment visit TOC	3 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in lung function - FEV1

End point title	Change in lung function - FEV1

End point description:

End point type	Secondary

End point timeframe:

It was assessed at screening visit, visit 7, EOT and TOC.

End point values	mITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: % predicted				
arithmetic mean (standard deviation)				
Screening visit (baseline)	72 (± 7.53)			
Visit 7 - change from baseline	2 (± 18.38)			
EOT - change from baseline	15 (± 9.9)			
TOC - change from baseline	-1.3 (± 22.28)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient reported outcome - St George's Respiratory questionnaire (SGRQ)

End point title	Patient reported outcome - St George's Respiratory questionnaire (SGRQ)

End point description:

End point type	Secondary

End point timeframe:

The questionnaire was administered at screening and TOC visits.

End point values	mITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: Score				
arithmetic mean (standard deviation)				
Total score - screening visit	60.3 (± 19.44)			
Total score - TOC	70.3 (± 15.23)			
Total score - change from baseline (screening)	2.7 (± 3.84)			
Symtoms score - screening visit	76 (± 14.98)			
Symptoms score - TOC	69.8 (± 19.4)			
Symptoms score - change from baseline (screening)	-6.2 (± 10.35)			
Activity score - screening visit	63.4 (± 31.53)			
Activity score - TOC	65 (± 33.92)			
Activity score - change from baseline	1.6 (± 4.98)			
Impacts score - screening visit	54.2 (± 18.11)			
Impacts score - TOC	63.8 (± 20.13)			

Impacts score - change from baseline (sceening)	3.9 (± 6.68)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic analysis

End point title	Pharmacokinetic analysis

End point description:

The following pharmacokinetic parameters were assessed for POL7080: maximum plasma concentration (Cmax), the area under the plasma concentration versus time curve during a dosing interval (AUC [0-8h]), terminal
elimination half-life (t½), systemic plasma clearance (CL), volume of distribution at steady state (Vss), volume of
distribution based on the terminal phase following intravenous administration (Vz), and mean residence time (MRT).

End point type	Secondary

End point timeframe:

Pharmacokinetic parameters were assessed for POL7080 on day 3.

End point values	PK population			
Subject group type	Subject analysis set			
Number of subjects analysed	12			
Units: Several units				
arithmetic mean (standard deviation)				
Cmax (ng/mL)	7417 (± 1577.57)			
Tmax (h)	1.87 (± 0.35)			
AUC(0-8h) (h*ng/L)	34418.7 (± 6521.93)			
Mean residence time (min)	357.52 (± 84.57)			
Clearance (L/h)	4.0181 (± 0.6)			
Volume, steady-state (L)	23.602 (± 5.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of clinical signs and symptoms at TOC

End point title	Assessment of clinical signs and symptoms at TOC

End point description:

In each category, it has been indicated the number of patients (from mITT population) for this category. Only data of changed/unchanged status at TOC visit is specified.

End point type	Secondary

End point timeframe:

Clinical status assessment was based on the clinical signs and symptoms of the patient and was assessed at treatment visits 4 and 10, EOT, and TOC.

End point values	mITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: number of patients				
Cough - TOC (N=5) - Improved	2			
Cough - TOC (N=5) - Unchanged	3			
Sputum production - TOC (N=5) - Improved	2			
Sputum production - TOC (N=5) - Unchanged	3			
Sputum colour (purulent) - TOC (N=3) - Improved	1			
Sputum colour (purulent) - TOC (N=3) - Unchanged	2			
Dyspnea - TOC (N=5) - Improved	2			
Dyspnea - TOC (N=5) - Unchanged	3			
Fatigue (Yes) - TOC (N=5) - Improved	2			
Fatigue (Yes) - TOC (N=5) - Unchanged	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event were collected during all the study (screening period, treatment period, EOT and TOC)

Adverse event reporting additional description:

AEs were collected from the time of signing the informed consent to the TOC. Patients were carefully monitored for the occurrence of AEs. All AEs must be recorded in the CRF and should include: brief description of the event, start date, stop date, severity, action taken regarding study drug, opinion on causality, seriousness, and outcome.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Safety population

Reporting group description:

All screened and enrolled patients that received at least one dose of POL7080

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vascular disorders			

Phlebitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Infusion site phlebitis			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Infusion site pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Infusion site pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Paraesthesia oral			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Infections and infestations Oral herpes subjects affected / exposed occurrences (all) Parainfluenzae virus infection subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2014	This substantial amendment (submitted to regulatory authorities in all participating countries) was made in order to allow a total treatment duration of 10 to 14 days for POL7080 instead of a fixed duration of 14 days. The justification for this amendment was that it aligned the study with the current practice of using 10 to 14 days of treatment with co-administered SoC anti-pseudomonas antibiotic(s). Furthermore, it provided greater flexibility to the treating physician whereby the investigator could decide when to stop POL7080 treatment after 10 days at his own discretion and based on the patient's condition.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 October 2015	Temporary interruption: Investigator notification of temporary hold on enrolment (18 December 2014): The letter from the chief medical officer, Dr. Leon Hooftman, informing all investigators of the study's enrolment being placed on a temporary hold. Regulatory authority notification of study temporarily on hold (December 2014): Notification was submitted in Spain on 19 December 2014. The submission to the UK and Germany was delivered on the 22 December 2014 as a substantial amendment, as per the request of the MHRA and BfArM, respectively. Permanent interruption: Investigator notification of study termination (08 October 2015): The letter from the chief medical officer, Dr. Leon Hooftman, informing all investigators of the decision to terminate the study.	-

Notes:

Limitations and caveats

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

The study was early terminated (not initiated in Germany/Netherlands) due to the lack of reduction in CFU (primary end-point), possibly influenced by routine inhalational antibiotics. The majority of patients showed benefits in clinical assessments.

Notes: