CONFIDENTIAL

CLINICAL STUDY REPORT - SYNOPSIS

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

Study code:	POL7080-002	Study development phase:	Phase II
EudraCT number:	2013-002202-31	Investigational medicinal product:	POL7080
Indication:	Acute exacerbation of non-cystic fibrosis bronchiectasis due to *Pseudomonas aeruginosa* infection requiring intravenous treatment		
First subject enrolled/first visit:	3 February 2014	Last subject completed/last visit:	26 November 2014
Version:	Final Version	Date of early termination	08 October 2015
		Date:	29 December 2016

Coordinating/Principal Investigator:	Dr Adam Hill Royal Infirmary of Edinburgh, Edinburgh, UK Dr Eva Polverino Hospital Clínic, Barcelona, Spain
Sponsor	Polyphor Ltd 411 Tower Bridge Business Centre, 46-48 East Smithfield London, E1W 1AW, United Kingdom
Sponsor signatory:	Leon Hooftman, M.D. Chief Medical Officer
Clinical Study Report Author	Marta Muñoz, Ph.D

This study was performed in compliance with Good Clinical Practice (E6), including the archiving of essential documents.

This Clinical Study Report contains privileged or confidential information which is the property of the Sponsor. Information may not be disclosed to a third party without written authorisation from the Sponsor.

2 SYNOPSIS

Name of the Sponsor/Company: Polyphor Ltd (The sponsor) **Name of Finished Product:** POL7080 **Name of Active Ingredient:** POL7080	**Individual Study Table Referring to Module 5 of the Dossier** **Volume:** **Page:** **Study No.:**	**(For National Authority Use only)**

STUDY CODE:
POL7080-002

TITLE OF STUDY:
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 subjects with acute exacerbation of non-cystic fibrosis bronchiectasis due to *Pseudomonas aeruginosa* infection requiring intravenous treatment.

INVESTIGATORS:
Dra. Polverino, Dra. Menéndez Villanueva, Dr. Dorca, Dr. Oriol Sibila, Dr. Garcia Olivé, Dr. Barbé and Dr. Hill.

STUDY CENTRES:
This study was conducted at 7 sites in Europe, from which 4 sites recruited subjects.
Hospital Clínic i Provincial de Barcelona (Spain), Hospital Universitario y Politécnico La Fe (Valencia, Spain), Hospital de Bellvitge (Barcelona, Spain), Hospital de la Santa Creu i Sant Pau (Barcelona, Spain), Hospital Germans Trias i Pujol (Barcelona, Spain), Hospital Arnau de Vilanova (Lleida, Spain) and Royal Infirmary of Edinburgh (UK).

PUBLICATION (REFERENCE):
None

STUDY PERIOD (YEARS):
Date of first enrolment/first subject first visit: 3 February 2014
Date of last completed/last subject last visit: 26 November 2014

PHASE OF DEVELOPMENT:
Phase II

OBJECTIVES:
The primary objective was to investigate the efficacy of POL7080 administered for 10 to 14 days in the treatment of subjects with acute exacerbation of non-cystic fibrosis bronchiectasis due to *Pseudomonas aeruginosa* infection.

The secondary objectives were to investigate POL7080 for the following parameters:

- Safety and tolerability.
- Pharmacokinetics/pharmacodynamics of POL7080.

METHODOLOGY:
This was an open-label multi-centre phase II study. A total of 20 subjects were planned for inclusion in this study, however, a minimum of 15 subjects with documented (by quantitative sputum culture growing ≥10^5 Colony Forming Units (CFU)/mL) *Pseudomonas aeruginosa* at inclusion and who met all the inclusion/exclusion criteria were to be enrolled. Subjects received 10 to 14 days of intravenous treatment with POL7080.
The objectives of the study were to assess the tolerability, safety, efficacy, pharmacokinetics/pharmacodynamics of POL7080 in the treatment of exacerbation of non CF bronchiectasis.

NUMBER OF SUBJECTS (planned and analysed):

	Treatment
No. planned:	20
No. treated:	12
No. analysed for efficacy (mITT population):	5
No. analysed for pharmacokinetics (PK population):	12
No. analysed for safety:	12

Name of the Sponsor/Company: Polyphor Ltd (The sponsor)	**Individual Study Table Referring to Module 5 of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: POL7080		
Name of Active Ingredient: POL7080	**Volume:** **Page:** **Study No.:**	

No. completed the study: 4

No.treated: number of subjects who received at least one dose of POL7080.
No. completed the study: number of subjects who completed between 10-14 days of treatment.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Main inclusion criteria:

- Male and female aged ≥18 to <80 and suffering from documented non-cystic fibrosis bronchiectasis.
- Subjects who were currently having an exacerbation with:
  - Increased cough.
  - Increased volume of sputum production.
  - Increase in sputum purulence.
- Subjects with documented *Pseudomonas aeruginosa* infection for the current episode or a positive rapid test for *Pseudomonas aeruginosa* in the sputum at inclusion or known to be chronically infected with *Pseudomonas aeruginosa* in the past or isolation of *Pseudomonas aeruginosa* in the sputum culture at least twice in the last 12 months prior to inclusion (from subject records).
- Sputum sample collected for quantitative culture before starting treatment.

Main exclusion criteria:

- Subjects suffering from cystic fibrosis, active pulmonary mycobacterial infection, end stage chronic obstructive pulmonary disease on long term oxygen therapy, severe uncontrolled asthma, active sarcoidosis and active allergic broncho-pulmonary aspergillosis.
- Current exacerbation of bronchiectasis was associated with lung abscess or empyema.
- Current exacerbation episode was suspected or documented to be due to pathogens other than *Pseudomonas aeruginosa*.
- Patients who received more than 24 hours of systemic anti-pseudomonas antibiotic(s) for the current exacerbation of NCFB (patients on maintenance inhalation antipseudomonas antibiotics without increase in the dose or addition of new antipseudomonas antibiotics during 4 weeks prior to inclusion can be enrolled).
- Creatinine clearance <60mL/min. If the subject develops renal insufficiency (with creatinine clearance of <50mL/minute in 2 consecutive measurements within 24 hours) after the inclusion, the POL7080 treatment was discontinued and the subject treated with different anti pseudomonas antibiotic(s) as per the discretion of the investigator.

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

POL7080 was provided as a lyophilised powder for injection after reconstitution in a colorless 20R glass vial with lyophilisation rubber stopper, sealed with a flip-off cap (aluminum with plastic disc).

The reconstitution solvent was supplied in a colorless 20R glass vial with serum rubber stopper, sealed with a flip-off cap (aluminium with plastic disc).POL7080 was administered as sterile intravenous infusion at a dose of 2.5mg/kg, 2h infusion; t.i.d for 10 to 14 days.

DURATION OF TREATMENT:

POL7080 was administered at a dose of 2.5mg/kg during 2-h infusion, three times daily (t.i.d), for 10 to 14 days.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER:

No reference therapy was used in this study.

CRITERIA FOR EVALUATION:

SAFETY:

The safety evaluations included vital signs (blood pressure, heart rate and body temperature), electrocardiogram (ECG) parameters, hematology, blood chemistry, urinalysis and adverse events.

EFFICACY:

Efficacy was assessed by sputum bacterial clearance (reduction in the daily quantitative viable counts

Name of the Sponsor/Company: Polyphor Ltd (The sponsor)	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use only)
Name of Finished Product: POL7080		
Name of Active Ingredient: POL7080	Volume: Page: Study No.:	

(CFU/ mL) of *Pseudomonas aeruginosa* by at least 1-log [Primary efficacy end point]). Additional secondary efficacy end points were (as compared to baseline): time to log reductions in CFU/mL of *Pseudomonas aeruginosa*, microbiology results, 24-h sputum volume, sputum purulence score, total WBC count, serum C-reactive protein (CRP), Procalcitonin (PCT) and lung function tests: forced expiratory volume in the first second (FEV_1) (% predicted), forced vital capacity (FVC) (% predicted) and FEV_1/FVC ratio).

PHARMACOKINETICS/PHARMACODYNAMICS:
The following pharmacokinetic parameters were assessed for POL7080 on day 3: maximum plasma concentration (C_{max}), the area under the plasma concentration versus time curve during a dosing interval (AUC_{tau}), terminal elimination half-life ($t_{½}$), systemic plasma clearance (CL), volume of distribution at steady state (V_{ss}), volume of distribution based on the terminal phase following intravenous administration (V_z), and mean residence time (MRT).

STATISTICAL METHODS:
SAFETY PARAMETERS:

Adverse events were tabulated and summarised according to the current version of Medical Dictionary for Regulatory Activities (MedDRA version 18.1). The total number of subjects with at least 1 AE (adverse event)/1 TEAE (treatment emergent adverse event) and the total number of AEs/TEAEs were presented. The number of subjects and the number of AEs/TEAEs were tabulated by system organ class (SOC) and by preferred term (PT). TEAEs were also tabulated versus worst severity and worst relationship to treatment. Subjects with serious adverse events (SAEs) including those leading to death were likewise summarised. All vital signs, hematology, blood chemistry, urinalysis and ECG data were listed by subject. All values outside the normal reference ranges and clinically significant abnormal values were flagged in this listing.

Summary statistics (mean, median, standard deviation and range) were calculated for all parameters and for changes from baseline and were presented by time windows (Day4, Day 10, EOT and TOC). Shift tables for each assessed laboratory parameter were presented to summarize the change from baseline to Day4, Day10, EOT and TOC.

EFFICACY PARAMETERS:

The efficacy parameters were summarised descriptively. Evolution of these parameters as compared to baseline and time to event were analysed where appropriate.

PHARMACOKINETIC PARAMETERS:

Descriptive statistics (arithmetic and geometric means, ranges, standard deviations and coefficient of variance [%]) were generated. For maximum observed plasma concentration (T_{max}), median values were reported.

SUMMARY AND CONCLUSION(S):
EFFICACY RESULTS:
Twelve subjects with an acute exacerbation of non-CF bronchiectasis were included in the study and comprised the safety and PK populations. Five (41.7%) subjects had a documented *Pseudomonas aeruginosa* infection at baseline (≥ 1 x 10^5 CFU/ mL sputum) and were included in the mITT population. Overall, four (33.3%) subjects completed the study as scheduled, two (16.7%) in the mITT population.

The primary efficacy objective was defined as the assessment of sputum bacterial clearance, measured as a minimum 1-log reduction of *Pseudomonas aeruginosa* for at least two consecutive days post baseline. Two subjects (40.0%) achieved sputum bacterial load reduction, in the case of three subjects there was no reduction in bacterial load but it remained static. Individual *Pseudomonas*

Name of the Sponsor/Company: Polyphor Ltd (The sponsor)	Individual Study Table Referring to Module 5 of the Dossier	(For National Authority Use only)
Name of Finished Product: POL7080		
Name of Active Ingredient: POL7080	Volume: Page: Study No.:	

aeruginosa CFU counts were generally only collected for all subjects at baseline and on days 2-5 of treatment. Therefore, at TOC there was a high degree of imprecision regarding the mean CFU estimate and as a consequence no significant change in mean CFU count was demonstrated in this study population.

Improvement of clinical status was documented in two (40.0%) subjects (201-003 and 201-005) of the mITT population at treatment visit 10; these subjects continued to show this improvement until after the TOC visit. In these two subjects there was no 1-log reduction of *Pseudomonas aeruginosa* recorded, however in the unchanged clinical status cohort, two subjects experienced a 1-log reduction of *Pseudomonas aeruginosa* within a mean of 3.5 days. None of the subjects in the mITT group experienced a deterioration of their clinical status. With regard to the efficacy parameters (sputum volume, sputum purulence, WBC, CRP and PCT values) there was no notable difference between patient clinical status strata or change in mITT mean values over the course of treatment or follow-up. Despite insufficient data to compare lung function between patient clinical status strata, a trend towards improvement in lung function was observed over the treatment period and EOT visit, however, this was not maintained at the TOC visit. Furthermore, complete MIC profiles were documented for four subjects. Combined with the incomplete MIC profiles, the data suggest that there was no resistance development to POL7080 during treatment or follow-up. Finally, results from the patient-reported outcome (PRO) questionnaires Leicester cough questionnaire (LCQ) and St. George's respiratory questionnaire (SGRQ) did not indicate any mean change in quality of life after treatment when compared to baseline.

Individual pharmacokinetic analysis of POL7080 administration revealed comparable profiles with moderate interindividual variability. T_{max} of POL7080 was achieved at the end of the 2-hour infusion and the geometric C_{max} (7248.8 ng/mL) was similar to that from heathy volunteers. Trough levels of POL7080 were approximately 2500 ng/mL, higher than the 1400 ng/mL predicted trough level for this dosing regimen.

SAFETY RESULTS:
No SAEs or deaths were reported for any subject.

From the 12 subjects included in the study, eight (66.7%) presented with at least one TEAE and seven (58.3%) subjects experienced at least one treatment-related TEAE. The majority of the 25 documented TEAEs were mild (88.0%), treatment related (64.0%) and had recovered (80.0%) by the test of cure visit. Three (25.0%) subjects had moderate TEAEs; infusion site phlebitis, proteinuria, and pleural effusion. The most common treatment-related TEAEs were infusion site pain (four [16%] events in two patients), infusion site phlebitis (three [12%] events in three patients), and oral paraesthesia (three [12%] events in twopatients). The three subjects with unresolved TEAEs at the TOC visit consisted of one subject with proteinuria of moderate severity and rectal haemorrhage of mild severity; one subject with pleural effusion of moderate severity; and one subject with dizziness and neck pain, both of mild severity. All unresolved TEAEs were considered to be unrelated to the study drug.

One (8.3%) subject permanently discontinued the study due to decreased creatinine CL_R of mild severity (serum creatinine change from 86 to 122 µmol/L and thus an estimated glomerular filtration rate change from 59 to 40 mL/min/1.73 m^2). Furthermore, one (8.3%) subject temporarily discontinued due to phlebitis and subsequently permanently discontinued due to mild-severity infusion site pain on the 13th day of treatment. All discontinuations were considered to be related to POL7080 treatment by the investigator.

There were no other noteworthy treatment-related trends related to clinical laboratory, vital signs, or physical finding parameters.

CONCLUSION(S):
Five patients were included in the mITT population. Two of the five (40.0%) patients in the mITT population met the primary endpoint, i.e., a reduction in the daily quantitative viable counts of

Name of the Sponsor/Company: Polyphor Ltd (The sponsor)	**Individual Study Table Referring to Module 5 of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: POL7080		
Name of Active Ingredient: POL7080	**Volume:** **Page:** **Study No.:**	
(CFU/mL) *Pseudomonas aeruginosa* by at least 1-log. Although the majority of the patients in this trial appeared to benefit from POL7080 monotherapy, judged by clinical assessment, it proved difficult to document CFU reductions. An important factor may have been that a fair number of patients were entered into the study with a low CFU count, possibly influenced by routinely administered inhalational antibiotics.		