Synoptic Clinical Study Report

A multicenter, open-label, sponsor-blinded, randomized, active-controlled, parallel group, pivotal study to evaluate the efficacy, safety, and tolerability of murepavadin given with ertapenem versus an anti-pseudomonal-β-lactam-based antibiotic in adult subjects with nosocomial pneumonia suspected or confirmed to be due to *Pseudomonas aeruginosa*

PRISM-UDR Study

Report Status: Final
Report Date: 08 November 2019

Investigational Product: Murepavadin

Protocol Reference: POL7080-010
EudraCT Number: 2018-001159-11
IND Number: 120996

Clinical Phase: 3
First Subject Enrolled: 14 April 2019
Date of Last Subject's Last Visit: 11 June 2019
Date of Study Termination: 17 July 2019

This study was conducted in accordance with Good Clinical Practice.

2. SYNOPSIS

Sponsor: POLYPHOR LTD.

Investigational product: Murepavadin

Title of study: A multicenter, open-label, sponsor-blinded, randomized, active-controlled, parallel group, pivotal study to evaluate the efficacy, safety, and tolerability of murepavadin given with ertapenem versus an anti-pseudomonal-β-lactam-based antibiotic in adult subjects with nosocomial pneumonia suspected or confirmed to be due to *Pseudomonas aeruginosa*

Investigators: It was planned to open approximately 100 sites across 15 countries in order to randomize approximately 250 subjects. At the time the study was stopped, 13 sites were open across 4 countries.

Two sites in Israel enrolled the 2 subjects into this study.

Publications: None

Period of study: 14 APRIL 2019 (date of first informed consent) to 11 JUNE 2019 (date of last subject's last visit).

Phase of development: Clinical Phase 3.

Background and rationale for the study: Murepavadin (POL7080, a synthetic cyclic peptide consisting of 14 amino acids) is an antimicrobial peptidomimetic with a novel, non-lytic mechanism of action. Murepavadin functions by binding to the lipopolysaccharide transport protein D (LptD), an outer membrane protein involved in lipopolysaccharide biogenesis in Gram-negative bacteria. By binding to LptD, murepavadin causes lipopolysaccharide alterations in the outer membrane of the bacterium and ultimately, cell death. Murepavadin's activity is specific to LptD of *Pseudomonas aeruginosa* (*P. aeruginosa*) and has no activity against other Gram-negative bacteria.

Non-clinical studies have demonstrated the selective and potent antimicrobial activity of murepavadin against *P. aeruginosa in vitro*, including multi-drug resistant strains. When tested against over 1200 *P. aeruginosa* isolates from the United States, Europe, and China, including multi-drug resistant (MDR) isolates, the minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90}) was 0.12-0.25 mg/L.

Murepavadin had a low propensity to induce resistance *in vitro*.

All treatment-emergent adverse events reported in Phase 1 and Phase 2 with murepavadin were reversible and the majority of adverse events (AEs) were of mild or moderate severity. Murepavadin's dose needed to be adjusted according to the renal function.

Overall, the safety profile of murepavadin in Phase 1 and Phase 2 studies was acceptable and the benefit/risk ratio of murepavadin for the treatment of subjects with severe and life-threatening infections due to *P. aeruginosa* was considered positive.

Murepavadin was being developed for the treatment of nosocomial pneumonia (NP) known or suspected to be caused by *P. aeruginosa*. Study POL7080-010 was to evaluate subjects with NP i.e., hospital-acquired bacterial pneumonia (HABP) and VABP, due to *P. aeruginosa*. Another study (i.e., POL7080-011) was conducted in subjects with VABP to explore the efficacy of murepavadin combined with another anti-pseudomonal antibiotic versus 2 anti-pseudomonal antibiotics.

Objectives:

Primary Efficacy Objective:

- To demonstrate the non-inferiority (NI) in 28-day all-cause mortality (ACM) rate of intravenous (IV) murepavadin given with ertapenem compared to an anti-pseudomonal-β-lactam-based antibiotic (either piperacillin-tazobactam or meropenem) in the microbiological modified intention-to-treat (micro-MITT) analysis set in subjects with NP due to *P. aeruginosa.*

Safety Objective:

- To evaluate the safety profile of murepavadin given with ertapenem and an anti-pseudomonal-β-lactam-based antibiotic (either piperacillin-tazobactam or meropenem).

Methodology:

This was a prospective, multicenter, Phase 3, open-label, sponsor-blinded, randomized, active-controlled, parallel group, global, pivotal study. Adult subjects with NP, suspected or confirmed to be caused by *P. aeruginosa,* were randomized to receive either murepavadin + ertapenem or an anti-pseudomonal-β-lactam-based antibiotic (either piperacillin-tazobactam or meropenem). Safety data were to be reviewed by the independent Data Monitoring Committee after data from 20 subjects were available. Additional interim safety reviews were planned after 60 and 150 subjects had been enrolled. An interim analysis for futility was planned when 52 subjects per arm (i.e., 50% of subjects) were evaluable for the primary efficacy outcome.

Number of subjects (planned and analyzed):

A total of approximately 250 subjects were planned to be enrolled to reach 210 subjects in the micro-MITT analysis set. Randomization ratio was to be 1:1.

Two subjects were enrolled and both were randomized to the active comparator arm to receive either piperacillin-tazobactam or meropenem.

Diagnosis and main criteria for inclusion and exclusion:

Inclusion Criteria

Subjects who met all the following diagnostic and clinical criteria were eligible for the study:

1. Provided written informed consent prior to any study-related procedure not part of normal medical care. Surrogate consent/use of a legally authorized representative could have been provided, if permitted by local country and institution-specific guidelines
2. Male or female subjects, ≥ 18 years of age

   Women of childbearing potential were eligible only if the following applied:

   - Negative serum pregnancy test at baseline (a urine pregnancy test could have been used at the time of screening, but the result was to be confirmed by a serum test)
   - Agreement to undertake a urine pregnancy test at the End-of-Study Visit (30-33 days after last dose)
   - Agreement to use one of the methods of birth control described in the protocol from screening up to at least 30 days after study treatment discontinuation

   Non-vasectomized men were eligible only if they were willing to use a condom during study treatment and for at least 7 days after the last dose.
3. Subjects hospitalized for ≥ 48 hours or those with prior hospital admission of ≥ 48 hours if they were discharged within the last 7 days
4. Intubated (via naso- or endotracheal tube, including tracheostomy subjects) and had received mechanical ventilation for ≥ 48 hours, and acute changes were made in the ventilator support to maintain adequate partial pressure of oxygen (PaO_2) or oxygen saturation (SpO_2)

   OR

   At least 2 of the following signs or symptoms were present within 24 hours prior to randomization:

   - New onset of cough or worsening of baseline cough
   - Auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (e.g., dullness on percussion, bronchial breath sounds, or egophony)
   - Dyspnea, tachypnea (respiratory rate > 25 breaths/minute), particularly if any or all of these signs or symptoms were progressive in nature
   - Hypoxemia (e.g., PaO_2 < 60 mmHg while the subject was breathing on room air as determined by arterial blood gas or SpO_2 < 90% while the subject was breathing on room air as determined by pulse oximetry, or worsening [decline from any earlier finding] of the ratio of the partial pressure of oxygen to the fraction of inspired oxygen [PaO_2/FiO_2], or respiratory failure requiring intubation and mechanical ventilation, or increased ventilator demand if on mechanical ventilation for < 48 hours prior to randomization)
   - New onset of sputum or suctioned respiratory secretions characterized by purulent appearance indicative of bacterial infection or a worsening in character of purulent appearance

5. Chest radiograph showed the presence of new or progressive infiltrate(s) characteristic of bacterial pneumonia (based on Investigator's evaluation). A chest computed tomography scan may have been used in place of a chest x-ray
6. At least 1 of the following was present within 24 hours prior to randomization:
    - Documented fever (oral ≥ 38.0° C [100.4° F] or a tympanic, temporal, rectal or core temperature ≥ 38.3° C [101.0° F], axillary or forehead scanner ≥ 37.5° C [99.5° F]), OR
    - Hypothermia (rectal/core body temperature ≤ 35.0° C [95.2° F]), OR
    - Total peripheral white blood cell count (WBC) ≥ 10,000 cells/mm^3, OR
    - Leukopenia with WBC ≤ 4,500 cells/mm^3
7. Acute Physiology and Chronic Health Evaluation (APACHE II) score between 8 and 25, inclusive, within 24 hours prior to randomization
8. Strong clinical suspicion of pneumonia due to *P. aeruginosa*. Such evidence could have been the following criteria, but was not limited to:
    - a surveillance culture from a respiratory sample positive for *P. aeruginosa*
    - a Gram stain performed within 36 hours prior to randomization using an acceptable respiratory sample (protected brush specimen [PBS], broncho-alveolar lavage [BAL], mini-BAL, endotracheal aspirate [ETA], sputum) showing Gram-negative rods (with or without Gram-positive bacteria)
    - History of previous *P. aeruginosa* infection or colonization of a respiratory sample within the previous 12 months

      A rapid diagnostic test (RDT), performed within 36 hours prior to randomization on respiratory secretions, may further support the suspicion based on the above clinical criteria.

      AND
    - At least one risk factor, including the following, but not limited to:
        - Broad-spectrum antibiotics (carbapenems, broad-spectrum cephalosporins, aminoglycosides, fluoroquinolones) administered within 90 days prior to randomization,
        - Current hospitalization of ≥ 5 days,
        - Late onset (> 4 days after intubation) of VABP,
        - History of chronic obstructive pulmonary disease,
        - Immunosuppressive disease/therapy (e.g., steroid use).

Exclusion Criteria

Subjects who met any of the following criteria were not eligible to participate in this study:

1. Known or suspected community-acquired, viral, fungal, or parasitic pneumonia
2. Any of the following health conditions:

- Confirmed legionella infection (*Legionella pneumophila* pneumonia), *Aspergillus spp.* pneumonia (testing was not required)
- Cystic fibrosis
- Known or suspected *Pneumocystis jirovecii* pneumonia
- Known or suspected active tuberculosis
- Lung abscess
- Solid organ transplant within 6 months prior to randomization
- Pleural empyema.

3. Bronchial obstruction or a history of post-obstructive pneumonia (this did not exclude subjects with pneumonia who had an underlying chronic obstructive pulmonary disease)
4. Expected survival < 72 hours
5. Burns > 40% of total body surface area
6. Current or anticipated neutropenia with absolute neutrophil count < 500 cells/mm^3
7. Severe renal disease defined as the estimated glomerular filtration rate per the 6-point Modification of Diet in Renal Disease (eGFR-MDRD-6) < 30 mL/min/1.73 m^2, or requirement for peritoneal dialysis, hemodialysis, hemofiltration, or a urine output < 20 mL/hour over a 24-hour period
8. Alanine aminotransferase or aspartate aminotransferase ≥ 5 times upper limit of normal or Child-Pugh B and C in subjects with chronic hepatic function impairment
9. Received systemic or inhaled anti-pseudomonal antibiotic therapy within 72 hours prior to randomization as follows:
    - > 5 IV doses of an antibiotic administered 4 times per day (q.i.d.; e.g., piperacillin-tazobactam)
    - > 4 IV doses of an antibiotic administered 3 times per day (t.i.d.; e.g., meropenem)

    Exceptions:

    - Progression of disease on the prior antibacterial regimen for this episode of pneumonia after > 72 hours of treatment, provided prior respiratory or blood culture did not grow an anti-pseudomonal-β-lactam-resistant *P. aeruginosa* pathogen, or only a Gram-positive pathogen. Required microbiological confirmation of a Gram-negative pathogen, OR
    - Subject developed symptoms of pneumonia and a new infiltrate while they received the prior antibacterial regimen for reasons other than the current pneumonia; if the pneumonia had occurred while the subject was receiving antibiotics as prophylaxis or for treatment of an unrelated infection, the antibacterial therapy was to be considered ineffective, irrespective of the susceptibility profile of the study qualifying pathogen, OR
    - Subject received systemic antibacterial therapy that did not cover *P. aeruginosa*, OR

- Prior therapy with a non-absorbed antibiotic therapy used for gut decontamination or to eradicate *Clostridium difficile.*

10. Investigator's opinion of clinically significant electrocardiogram (ECG) finding with immediate potential for a fatal outcome such as ischemia, infarct, ventricular arrhythmia, or prior to the current infection, a history of New York Heart Association Class IV cardiac failure
11. Stroke (ischemic or intracerebral hemorrhage) within 5 days prior to randomization and there was an increased risk of fatal brain edema as indicated by a major early computerized tomography hypodensity exceeding 50% of the middle cerebral artery territory
12. Women who were pregnant or nursing
13. Persisting hypotension requiring sympathomimetic agents (> 0.2 µg/kg/min norepinephrine or a total of all vasopressors > 0.2 µg/kg/min norepinephrine equivalents) to maintain a mean arterial pressure (MAP) ≥ 65 mmHg despite adequate fluid administration
14. Evidence of co-infection with ertapenem-resistant Gram-negative pathogen(s). Evidence of infection with meropenem- AND piperacillin-tazobactam-resistant *P. aeruginosa* or co-infection with meropenem- AND piperacillin-tazobactam-resistant Gram-negative pathogen(s)
15. Former exposure to murepavadin
16. Subjects with known hypersensitivity to any component of ertapenem, meropenem or to other drugs in the same class or demonstrated anaphylactic reactions to β-lactams or a history of allergic reactions to any of the penicillins, cephalosporins, or β-lactamase inhibitors
17. Known or suspected neuro-muscular disease, e.g. myasthenia gravis
18. Subjects who were currently enrolled in or had not yet completed at least 30 days since ending another investigational device or drug trial or were receiving other investigational agents
19. Subjects with other severe acute or chronic medical or laboratory abnormality that could have, in the Investigator's opinion, interfered with the assessment of safety, tolerability, or efficacy or interfered with the conduct or interpretation of the study
20. Not willing to comply with all study procedures

Investigational product, dose and mode of administration, batch number:

Murepavadin: 230 mg t.i.d. was infused over 2 hours in subjects with an eGFR-MDRD 6 ≥ 60 mL/min/1.73 m^2. Throughout the course of the study, murepavadin dosing regimen was to be adjusted (either increased or decreased) based on the eGFR-MDRD-6.
Batch number = F18114

Ertapenem: 1 g twice daily (b.i.d.) infused over 30 minutes
Batch number = N034897

Reference therapies, dose and mode of administration:

Meropenem: 1 g t.i.d. infused over 30 minutes, or

Piperacillin-tazobactam: 4.5 g q.i.d. infused over 30 minutes.

Duration of treatment:

The planned treatment duration per subject was 7 to 14 days.

Endpoints:

The planned primary efficacy endpoint variable was:

- ACM rates within 28 days after randomization in the micro-MITT analysis set.

The planned secondary efficacy variables were:

- ACM rates within 14 days after randomization
- Clinical outcome on Day 3, 5, 7, 10, at End of Treatment (EoT), and Test of Cure (ToC)
- Change from baseline in (i) Sequential Organ Failure Assessment score to Days 3, 5, 7, 10, EoT, ToC; (ii) in modified Clinical Pulmonary Infection Score ([CPIS], intubated subjects) to ToC, (iii) in PaO_2/FiO_2 ratio
- Number of subjects experiencing development of resistance to *P. aeruginosa*

Safety:

Safety was to be evaluated in the safety population through the assessment of treatment exposure, AEs, vital signs (blood pressure, heart rate, and body temperature), clinical laboratory evaluations (chemistry, hematology, and urinalysis), concomitant medications, renal function tests, and ECGs.

In addition, pharmacokinetic and pharmacoeconomic variables were also planned.

Statistical methods:

A total of approximately 250 subjects were planned to be enrolled to allow for drop-outs, negative *P. aeruginosa* culture results and incomplete data. Approximately 125 subjects were to be randomized in each arm. None of the planned efficacy endpoints were analyzed due to safety concerns that arose during the course of the study POL7080-011, leading to the premature termination of the Phase-3 program.

Summary - Conclusions: The POL7080-010 study was planned as a multicenter, open-label, sponsor-blinded, randomized, active-controlled, parallel group, pivotal study to evaluate the efficacy, safety, and tolerability of murepavadin in combination with ertapenem versus an anti-pseudomonal-β-lactam-based antibiotic in adult subjects with NP suspected or confirmed to be due to *P. aeruginosa*.

The primary aim of the study was to demonstrate the NI in 28-day ACM rate of IV murepavadin given with ertapenem compared to an anti-pseudomonal β-lactam-based antibiotic (either piperacillin-tazobactam or meropenem) in the micro-MITT analysis set in subjects with NP due to *P. aeruginosa.*

The study had initially planned to enroll 250 randomized subjects to reach 210 subjects in the micro-MITT analysis set. However, only 2 subjects were enrolled and both were randomized to the active comparator arm.

Post this enrollment, the POL7080-010 was terminated and enrollment was suspended because of the acute kidney injury (AKI) event observed in subjects in the parallel POL7080-011 study. As the POL7080-011 study used the same murepavadin dosing scheme (e.g., dosing regimen, treatment duration) as the POL7080-010 study, there was a high probability that the POL7080-010 study would have shown the same AKI event.

There was no efficacy data available for this study. The safety data of the 2 enrolled subjects have been provided in the subject summaries.