SPEXIS

Inhaled Murepavadin

Study POL7080-201-01

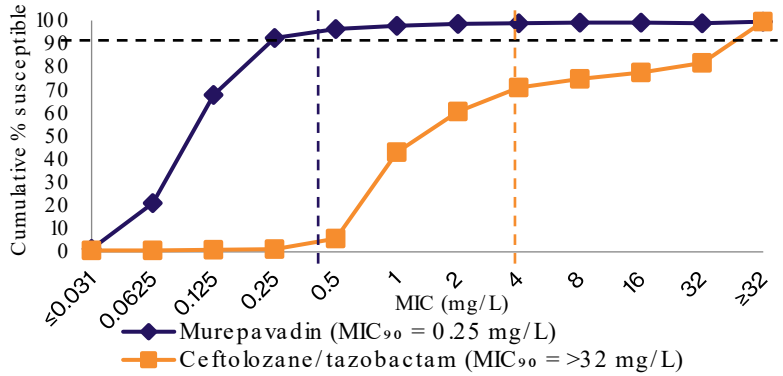
Murepavadin: First P. aeruginosa Selective Antibiotic

Murepavadin targets specifically P. aeruginosa LptD

- New antibiotic class (OMPTA)[1] / new mode of action through targeting the outer membrane protein LptD
- P. aeruginosa specific, preserving microbiome vs broad spectrum antibiotics
- Bactericidal
- Potent activity including MDR[2] / XDR[3]
- Low resistance potential
- No cross-resistance with other antibiotics
- Activity maintained in presence of surfactants and sputum
- Potent activity in lung infection models

Potent activity against XDR P. aeruginosa[4]

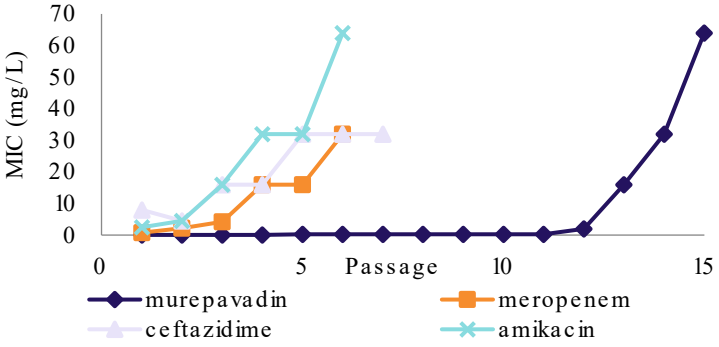
Cumulative susceptibility on 785 XDR isolates



Low propensity of development of resistance

Resistance development: serial passage

Pa ATCC 27853



Notes:

1. Outer Membrane Protein Targeting Antibiotic
2. Multidrug-Resistant
3. Extensively Drug-Resistant
4. Reference: Martin Loeches et al. Expert Review of Anti-Infective Therapy 2018, https://doi.org/10.1080/14787210.2018.1441024

Inhaled Murepavadin ("iMPV")

Pre-Clinical Findings

Male and Female CD-1 Mice:

- Inhaled murepavadin at 1, 5 or 10 mg/kg/day did not cause systemic toxicity after 4 weeks daily dosing
- Adverse pathology in the respiratory tract (atrophy of the olfactory epithelium of the nasal cavity and eosinophilic globules in the nasopharynx, partially recovered after a 4-week free treatment period) prevents to establish a No Observable Adverse Effect Level (NOAEL)

Male and Female Cynomolgus Monkeys

- Inhaled murepavadin at 2, 5 or 14 mg/kg/day did not cause systemic toxicity after 4 weeks daily dosing
- Microscopic pathological findings in the respiratory tract (loss of cilia at the tracheal bifurcation, fully recovered after a 4 weeks free treatment period) were judged as non-adverse and the NOAEL established at 14 mg/kg/day

The low systemic exposure indicates the predicted dose of inhaled murepavadin required for efficacy in P. aeruginosa lung infections is unlikely to result in organ toxicity

Inhaled Murepavadin ("iMPV")

Phase 1/ First-in-Human

Primary Objective:

- to investigate the safety, overall and local tolerability of single-ascending doses of murepavadin by oral inhalation in healthy female and male adult subjects

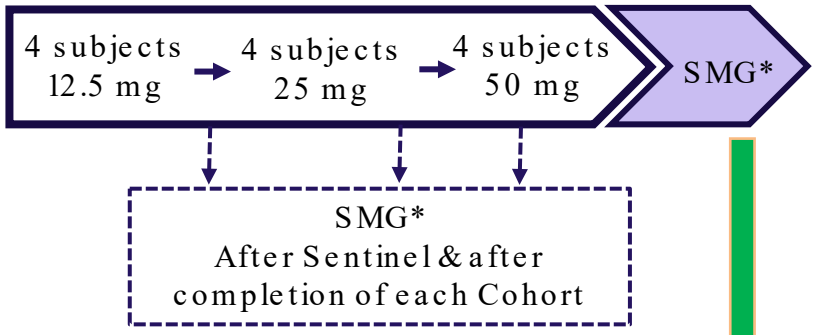
Secondary Objective

- to characterize the systemic and pulmonary pharmacokinetics (plasma, urine, ELF) of murepavadin following inhalation of single-ascending doses in healthy female and male adult subjects

Inhaled Murepavadin

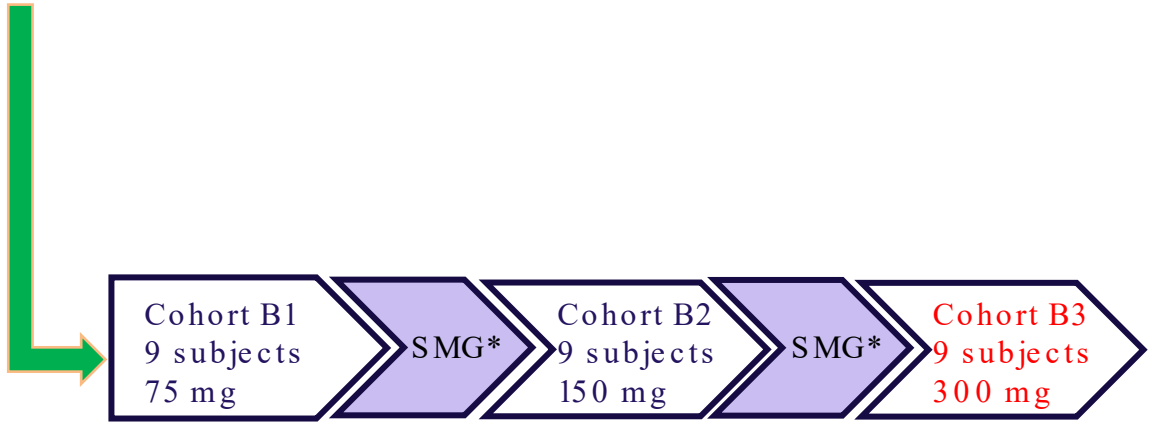
Phase 1 Study POL7080-201-01

Part A
Run-in phase
Double-blind, vs placebo,
Single dose



Volume of the solution to be inhaled: 8mL
Nebulizer: eFlow® with a reservoir of 8 mL

Part B
Double-blind, vs placebo,
Single dose
BAL performed at 3 timepoints: 2, 24,
48 hours after start of inhalation



*SMG: Safety Monitoring Group

Inhaled Murepavadin – POL7080-201-01

Status

- 39 subjects
- FSFD: 14 December 2021
- LSLD: 03 November 2022
- Database locked
- Programming of Tables, Listings, Figures: ongoing

Inhaled Murepavadin – POL7080-201-01
Preliminary, Blinded Results - Safety

- No SAEs
- Excellent local tolerability:
  - No clinically relevant signs of irritation of the upper airways
  - Serial pulmonary function tests were normal and did not show narrowing of the airways after administration of inhaled murepavadin
  - Vital signs, ECGs, and safety laboratory data were within the normal range

Inhaled Murepavadin – POL7080-201-01
Preliminary, Blinded Results - Pharmacokinetics

- Pharmacokinetics:
  - Systemic bioavailability of MPV < 5% compared to equivalent intravenous dose
  - C_{max} observed at 1-2 hours post start of inhalation
  - In the epithelial lining fluid (ELF), the concentration of MPV at the 24-hour timepoint was still above CMI_{90} of P. aeruginosa isolates obtained from people with CF.

This favorable tolerability, safety, and concentration profile of MPV after inhalation in the Phase 1 trial clears the way for further clinical trials of iMPV in people with CF or non-CF bronchiectasis

Inhaled Murepavadin – POL7080-201-01
Preliminary, Blinded Results - Conclusion

This favorable tolerability, safety, and concentration profile of murepavadin after inhalation in the Phase 1 trial clears the way for further clinical trials of inhaled murepavadin in people with CF or non-CF bronchiectasis