POLB 001, AN ORAL BROAD-SPECTRUM ANTI-INFLAMMATORY WITH THE POTENTIAL TO PREVENT CYTOKINE RELEASE SYNDROME (CRS)

E Searle[1,2], LF Tremble[3], R Popat[4,5,6], DT de Bruin[7,8], M Moerland[7,8], B Buckley[3]

1. The University of Manchester, United Kingdom; 2. The Christie NHS Foundation Trust, United Kingdom; 3. Poolbeg Pharma, Ireland; 4. University College London Hospitals NHS Foundation Trust, United Kingdom; 5. NIHR UCLH Clinical Research Facility, University College London Hospitals NHS Foundation Trust,, United Kingdom; 6. University College London, United Kingdom; 7. Centre for Human Drug Research (CHDR), Leiden, Netherlands; 8. Leiden University Medical Center (LUMC), Leiden, Netherlands

INTRODUCTION

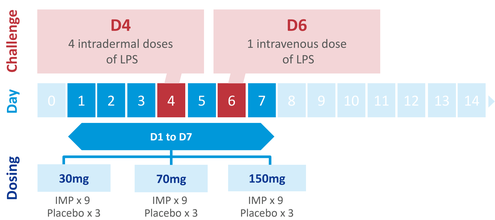
Cytokine Release Syndrome (CRS) is a well-recognized toxicity that occurs with high frequency following treatments such as T-cell engaging antibodies, Chimeric Antigen Receptor (CAR) T cells and other T-cell boosting immunotherapies. In addition to patient mortality and morbidity, the high frequency of CRS associated with these treatments is a major challenge for healthcare institutions, which can often require ICU step up availability prior to administration. The need for inpatient management of CRS adds to the costs of treatment and constrains their availability. CRS is currently treated by reactive administration of tocilizumab, steroids or anakinra[1].

POLB 001 is a Phase 2 ready p38 MAPK inhibitor in development for severe influenza infections and CRS[2]. In vivo, POLB 001 acts as a broad-spectrum anti-inflammatory by potently inhibiting the expression of proinflammatory cytokines such as IL-1β, IL-6, IL-8, IL-10, TNFα, COX-2.

AIM

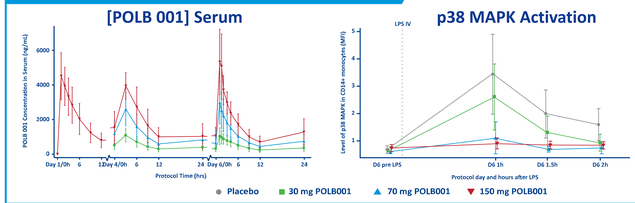
The aim of the study was to evaluate the ability of POLB 001 to suppress Lipopolysaccharide (LPS) driven local, and systemic immune responses. Safety and pharmacokinetics of POLB 001 were also observed.

METHODS



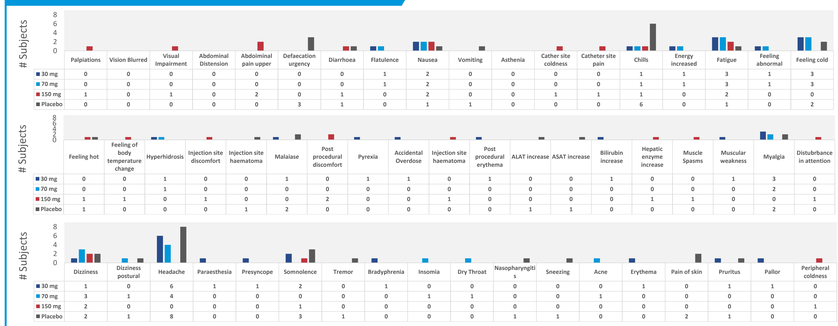
This was a single-center, randomized, double blinded, placebo-controlled, multiple dose study (NCT05765955). 36 healthy volunteers were orally administered 30, 70 or 150mg POLB 001 or placebo BD (3:1 active to placebo) for 7 days. Each subject was then challenged with intradermal lipopolysaccharide (LPS) (4x5 ng) and intravenous LPS (1 ng/kg) which drive local and systemic inflammation, respectively. Venous blood samples were collected to measure target inhibition and inflammatory markers. 4 intradermal LPS challenges were applied to the forearm of each volunteer and a single blister exudate sample was collected from each blister to prevent interference from multiple sampling. Volunteers were followed-up 12-16 days after the first dose of POLB 001. The exploratory pharmacodynamic analysis presented was performed using repeated measures mixed model (RMMM) statistics in SAS.

EFFECTIVE TARGET INHIBITION



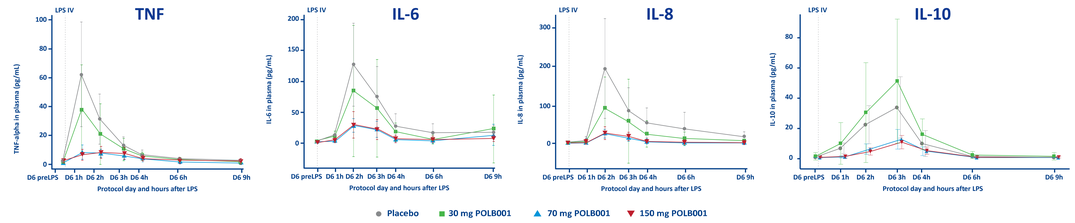
Steady-state levels of POLB 001 in serum were reached after approx. 3 days of dosing. Inhibition of p38 MAPK activation in $CD14^+$ monocytes following IV LPS challenge appeared to be dose dependent.

ADVERSE EVENTS



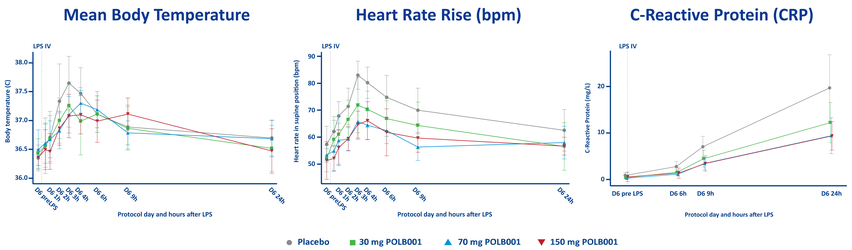
No SAEs occurred during the study. The highest number of adverse events was observed in the placebo group (50 events), followed by the POLB 001 30 mg group (45 events), the POLB 001 70 mg group (25 events), and the POLB 001 150 mg group (25 events). The most commonly reported AE was headache, with the highest number of participants and events in the placebo group (8/9 [88.9%] participants and 14 events) followed by the POLB 001 30 mg group (6/9 [66.7%] participants and 11 events). Headache is a known effect of LPS challenge[3]. Out of range alanine aminotransferase (ALT) values were observed in the POLB 001 150 mg and placebo groups on Day 4 (two participants and one participant, respectively) and Day 6 (one participant in both groups), and at the EOS visit for POLB 001 150 mg (one participant, 3005)

SERUM CYTOKINES



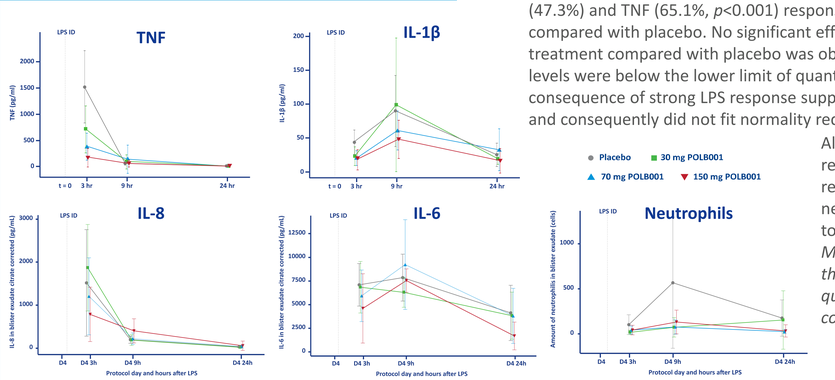
A significant, dose-dependent reduction was observed in the LPS-driven IL-6 response in plasma for active treatments compared with placebo (inhibition range: 37.7-63.5%). Also, a significant reduction in IL-8 and TNF in plasma was observed in all active treatments compared with placebo. Maximal inhibition appeared to be reached at a dose of 70 mg (80.7% for IL-8 and 73.5% for TNF). For IL-10, a significant reduction was observed for POLB 001 70 mg and 150 mg compared with placebo (of 62.4% and 62.7%, respectively; all p<0.001). IL-1β levels in plasma were below the LLOQ, the distribution of the data was not normal or log-normal, and so the requirements for analysis were not met. Nevertheless, graphical presentation appeared to show a trend towards suppression with POLB 001 150 mg.

CLINICAL PARAMETERS



A significant reduction was observed in LPS-driven CRP levels for POLB 001 70 mg and 150 mg compared with placebo (33.1% and 33.3% reduction). HR during the IV LPS challenge was significantly lower in participants receiving active treatment compared with placebo (4.0-9.3 bpm lower [5.8-13.4%]). Maximal inhibition appeared to be reached at POLB 001 70 mg.

LOCAL IMMUNE RESPONSE



POLB 001 150 mg significantly reduced LPS-driven IL-1β (47.3%) and TNF (65.1%, $p<0.001$) responses in blister exudate compared with placebo. No significant effect of active treatment compared with placebo was observed for IL-8. IL-6 levels were below the lower limit of quantification as a consequence of strong LPS response suppression by POLB 001 and consequently did not fit normality required for analysis. All treatment groups resulted in a significant reduction of neutrophils compared to placebo. *Measurements outside the limits of quantification were corrected.*

CONCLUSIONS

- POLB 001 was well tolerated with a favorable safety profile in healthy participants at all dose levels tested in this study.
- Both local and systemic immune responses to LPS were suppressed by POLB 001 compared with placebo:
  - POLB 001 suppressed tissue cytokine and cellular responses upon intradermal LPS injection.
  - POLB 001 suppressed systemic cytokine, CRP, and p38 MAPK phosphorylation levels upon IV LPS administration.
- Clinical trial design is planned to demonstrate the ability of POLB 001 to treat CRS in patients receiving T cell engaging multi-specific antibodies for the treatment of haematological malignancies.
- Further preclinical work is ongoing to demonstrate the potent ability of POLB 001 to treat CRS in humanised mouse models of CAR T cell therapy and CD28 super agonist-induced cytokine storm.

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