



Inhibition of local and systemic inflammatory responses by POLB 001, a novel p38 MAPK inhibitor, following in vivo LPS administration in healthy volunteers

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Introduction Inhibition of the p38 mitogen-activated protein kinase (MAPK) pathway is a potential therapeutic strategy for certain acute and chronic inflammatory conditions. POLB 001 is a selective p38 MAPK inhibitor, proven to be effective in suppressing selected ex vivo inflammatory responses. In this study, the effect of POLB 001 on inflammation was evaluated in healthy volunteers via subsequent *in vivo* challenges with intradermal (ID) and intravenous (IV) lipopolysaccharide (LPS).

Aim To evaluate the effect of POLB 001 on LPS-driven inflammatory responses following a local and systemic LPS challenge in healthy volunteers.

Methods and results A randomized, double-blind, placebo-controlled, parallel-group, single center, multiple ascending dose study in 36 healthy male volunteers was conducted.

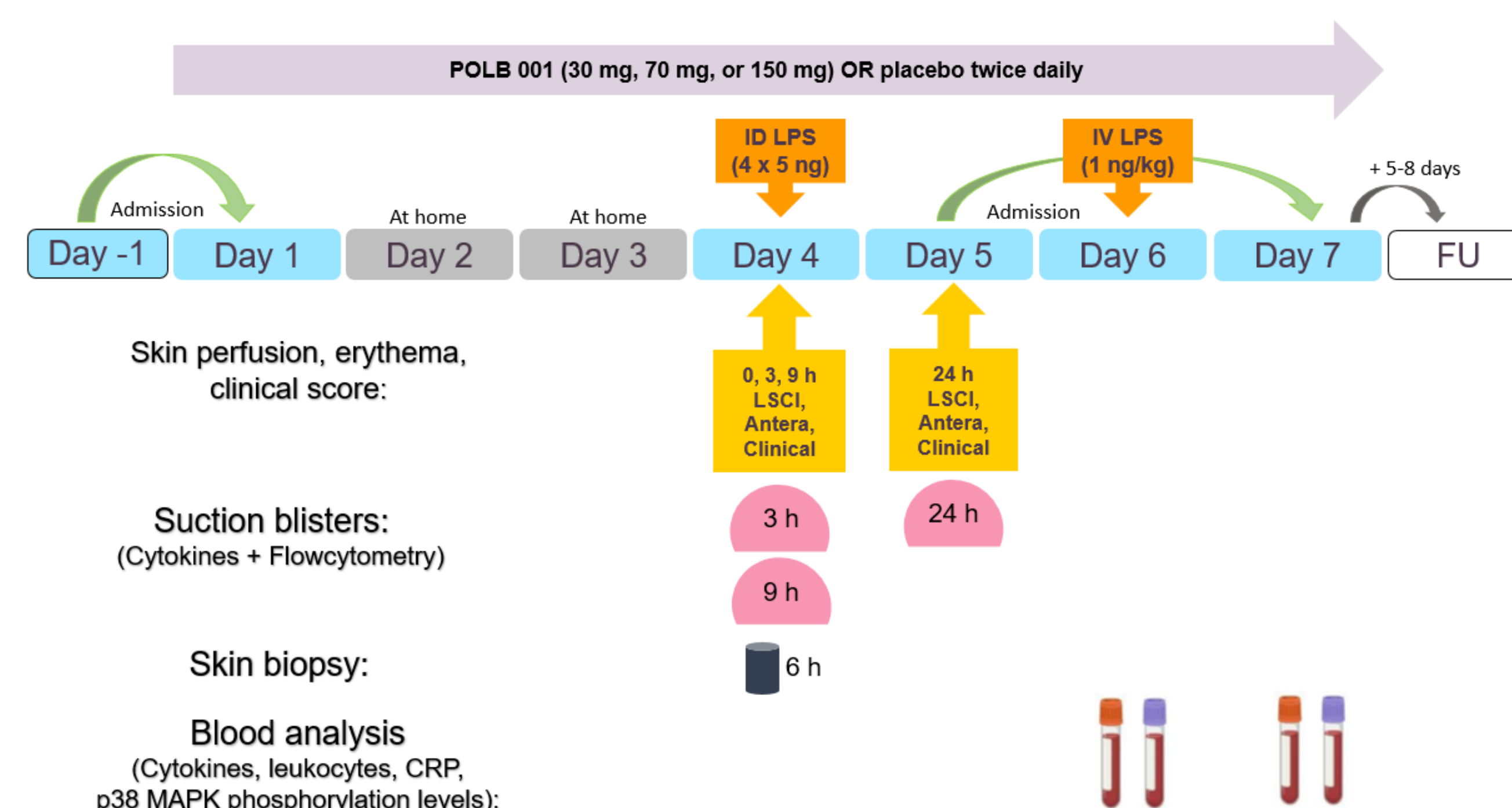


Fig 1: Study design Participants were randomized to receive POLB 001 (30, 70, or 150 mg) or placebo twice daily for seven consecutive days and were challenged with intradermal (4 injections of 5 ng) and intravenous (1 ng/kg via bolus injection) LPS. The LPS response was evaluated by several (non-)invasive assessments.

Local responses following intradermal LPS administration (selected endpoints)

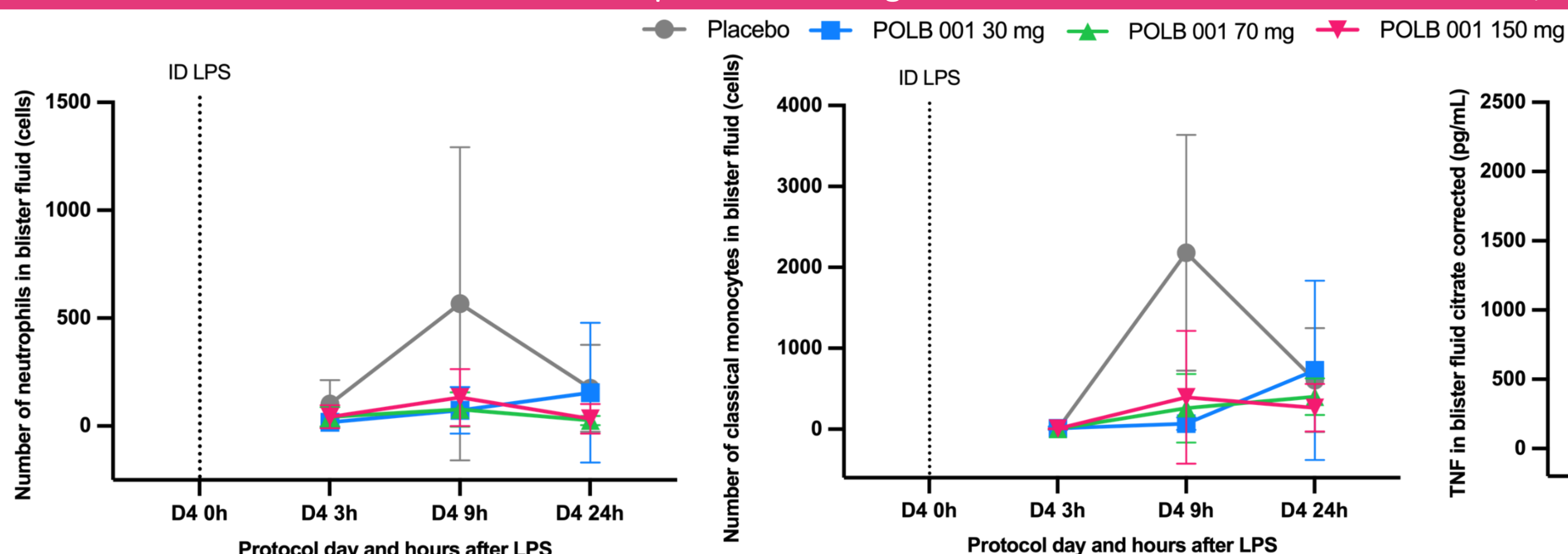


Fig 2: POLB 001 reduced the LPS-driven influx of neutrophils (left graph) (72-82%, $P = 0.02$) and classical monocytes (right graph) (68-74%, $P < 0.01$) in blister fluid compared to placebo.

Fig 3: POLB 001 suppressed the increase in TNF in blister fluid following local LPS administration (35-65%, $P < 0.01$) compared to placebo.

Systemic responses following intravenous LPS administration (selected endpoints)

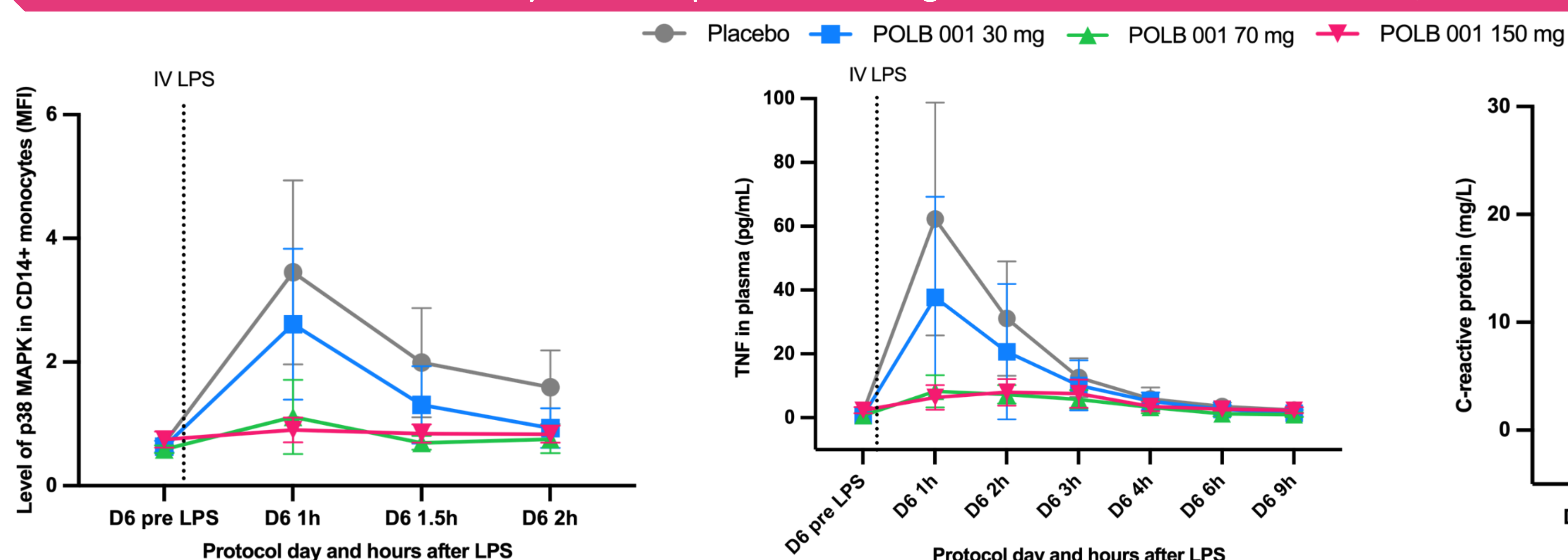


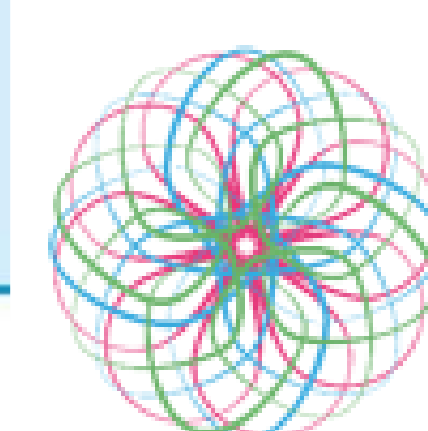
Fig 4: LPS-induced p38 MAPK phosphorylation in CD14+ monocytes was significantly reduced by POLB 001 (inhibition range 32-61%, $P < 0.01$) compared to placebo.

Fig 5: POLB 001 suppressed the increase in TNF in plasma following systemic LPS administration (47-74%, $P < 0.01$) compared to placebo.

Fig 6: A significant reduction was observed in LPS-driven CRP levels for POLB 001 70 mg (33% reduction, $P = 0.03$) and 150 mg (33% reduction, $P = 0.02$) compared to placebo following systemic LPS administration.

Conclusions

POLB 001 has the potential to effectively inhibit specific local and systemic inflammatory responses via suppression of the MAPK activity in humans. Further research is envisaged to evaluate the efficacy of POLB 001 in patients with certain acute and chronic inflammatory conditions.



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