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ARTICLE

The oral IRAK4 inhibitors zabedosertib and BAY1830839 suppress local and systemic immune responses in a randomized trial in healthy male volunteers

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Abstract

This study evaluated and characterized the pharmacological activity of the orally administered interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitors BAY1834845 (zabedosertib) and BAY1830839 in healthy male volunteers. Participants received one of either IRAK4 inhibitors or a control treatment (prednisolone 20 mg or placebo) twice daily for 7 days. Localized skin inflammation was induced by topical application of imiquimod (IMQ) cream for 3 days, starting at Day 3 of treatment. The inflammatory response was evaluated by laser speckle contrast imaging (skin perfusion) and multispectral imaging (erythema). At Day 7, participants received 1 ng/kg intravenous lipopolysaccharide (LPS). Circulating inflammatory proteins, leukocyte differentiation, acute phase proteins, and clinical parameters were evaluated before and after the systemic LPS challenge. Treatment with BAY1834845 significantly reduced the mean IMQ-induced skin perfusion response (geometric mean ratio [GMR] vs. placebo: 0.69 for BAY1834845, 0.70 for prednisolone; both $p < 0.05$). Treatment with BAY1834845 and BAY1830839 significantly reduced IMQ-induced erythema (GMR vs. placebo: 0.75 and 0.83, respectively, both $p < 0.05$; 0.86 for prednisolone, not significant). Both IRAK4 inhibitors significantly suppressed the serum TNF-α and IL-6 responses (≥80% suppression vs. placebo, $p < 0.05$) and inhibited C-reactive protein, procalcitonin, and IL-8 responses to intravenous LPS. This study demonstrated the pharmacological effectiveness of BAY1834845 and BAY1830839 in suppressing systemically and locally induced inflammatory responses in the same range as prednisolone, underlining the potential value of these IRAK4 inhibitors as future therapies for dermatological or other immune-mediated inflammatory diseases.

Stefan J. Jodl and Wouter ten Voorde contributed equally and share first authorship.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Experimental human pharmacology models have been developed to test the pharmacological effects of drugs in development and thereby enable dose finding and de-risking during early investigation of their clinical efficacy and safety.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study investigated the effects of two novel, highly selective inhibitors of interleukin-1 receptor-associated kinase 4 (IRAK4), BAY1834845 (zabedosertib) and BAY1830839, in human in vivo experimental challenge models of topical and systemic inflammation. The challenge models, which incorporated active (prednisolone) and non-active (placebo) controls, characterized specific anti-inflammatory properties of the two IRAK4 inhibitors to inform their subsequent potential development.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The results of this study confirmed the therapeutic potential of zabedosertib (BAY1834845) and BAY1830839 and supported their further clinical development progressing into phase II.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The study underlined the potential utility of different novel human pharmacological models to assess the immunomodulatory effects of anti-inflammatory molecules in early development.

INTRODUCTION

Interleukin-1 receptor-associated kinase 4 (IRAK4) is a serine/threonine kinase that is a key intracellular signaling component downstream of myeloid differentiation primary response protein 88-associated toll-like receptors (TLRs) and the interleukin (IL)-1 receptor (IL-1R) family that are key mediators of human innate immune responses. Inhibition of IRAK4 activity blocks the production of inflammatory cytokines, such as IL-6, tumor necrosis factor (TNF)-α, IL-12, IL-1, and type I interferons (IFNs), which are key drivers in the pathogenesis of multiple autoimmune inflammatory diseases. In mouse models, IRAK4 inhibition was shown to suppress lipopolysaccharide (LPS)-induced TNF-α activation, alleviate collagen-induced arthritis, and block gout formation.[1,2] IRAK4 has thus emerged as an attractive therapeutic target for diseases associated with dysregulated inflammation, such as chronic inflammatory skin conditions, systemic and cutaneous lupus erythematosus, and rheumatoid arthritis. The clinical efficacy of IRAK4 inhibition in rheumatoid arthritis has been demonstrated by a selective, small molecule IRAK4 inhibitor,[3] and studies of other IRAK4-targeting compounds in other indications are ongoing.[4–6]

BAY1834845 (zabedosertib) and BAY1830839 are two oral IRAK4 inhibitors with high potency and selectivity, and good oral availability across preclinical species. Synthesized by Bayer AG, Berlin, Germany,[7] both compounds are drug candidates in development for the treatment of immune-mediated inflammatory diseases. In mice with imiquimod (IMQ)-induced psoriasis, treatment with BAY1834845 or BAY1830839 significantly reduced the severity of psoriasis-like lesions and reduced the extent of erythema, skin thickening, and scaling compared with vehicle. Both compounds dose-dependently blocked IL-1β-induced inflammation in mice.[7] BAY1834845 also strongly inhibited the secretion of TNF-α in isolated murine and rat splenic cells stimulated for 24 h with LPS 1 and 0.1 μg/mL, with half-maximal inhibitory concentration (IC_{50}) values of 385 and 1270 nM, respectively (data on file at Bayer). As part of the initial clinical phase I studies, the ex vivo activity of both compounds was evaluated by whole blood LPS challenges (LPS concentration 0.1 ng/mL, 6 h incubation) in healthy male volunteers. BAY1834845 (daily doses up to 240 mg for 10 days) and BAY1830839 (daily doses up to 400 mg for 10 days) suppressed TNF-α release in a dose-dependent manner, with a mean inhibition of 50% and 70%, respectively (data on file at Bayer).

The purpose of this clinical study was to evaluate and characterize the pharmacological activity of orally administered BAY1834845 and BAY1830839 in the inhibition of IRAK4 pathway-mediated reactions in healthy male volunteers. A conventional immunosuppressive agent (prednisolone) and placebo were used as active and non-active controls, respectively. The study design allowed discrimination between systemic and peripheral inflammation, and between TLR4- and TLR7-mediated responses; in vivo drug activity in a peripheral tissue (skin) was evaluated based on a topical IMQ challenge driving TLR7 activation, while in vivo drug activity in systemic inflammation was investigated by an intravenous (i.v.) LPS challenge driving TLR4 activation. Ex vivo drug activity in circulating immune cells was monitored by whole blood challenges driving TLR4, TLR7/8, and IL-1R. Both the topical IMQ challenge and intravenous LPS challenge are clinically well-characterized models which have been used to demonstrate the pharmacological activity of candidate drugs.[8–11] TLR4, TLR7/8, and IL-1R are all receptors upstream of IRAK4 signaling and, therefore, serve as relevant targets for providing proof of clinical pharmacological activity and exploring the therapeutic potential of BAY1834845 and BAY1830839.

METHODS

General study design

This was a randomized, partial-blind, four-arm study. Healthy male volunteers (12 per study arm) received oral treatment with one of the two study drugs (BAY1834845 or BAY1830839), matching placebo, or prednisolone as an active control, each twice daily (b.i.d.) for 7 days (Figure 1). The effects of these oral treatments on local and systemic IRAK4-driven responses, which were triggered by a topical inflammatory skin challenge conducted from Day 3 to Day 5 after start of treatment and a systemic immune challenge conducted on Day 7, were evaluated over time, while safety/tolerability was monitored closely.

This study (ClinicalTrials.gov identifier: NCT05003089) was conducted in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Sciences International Ethical Guidelines, and the International Conference of Harmonisation Good Clinical Practice Guidelines. The independent Medical Review and Ethics Committee 'Medisch Ethische Toetsingscommissie van de Stichting Beoordeling Ethiek

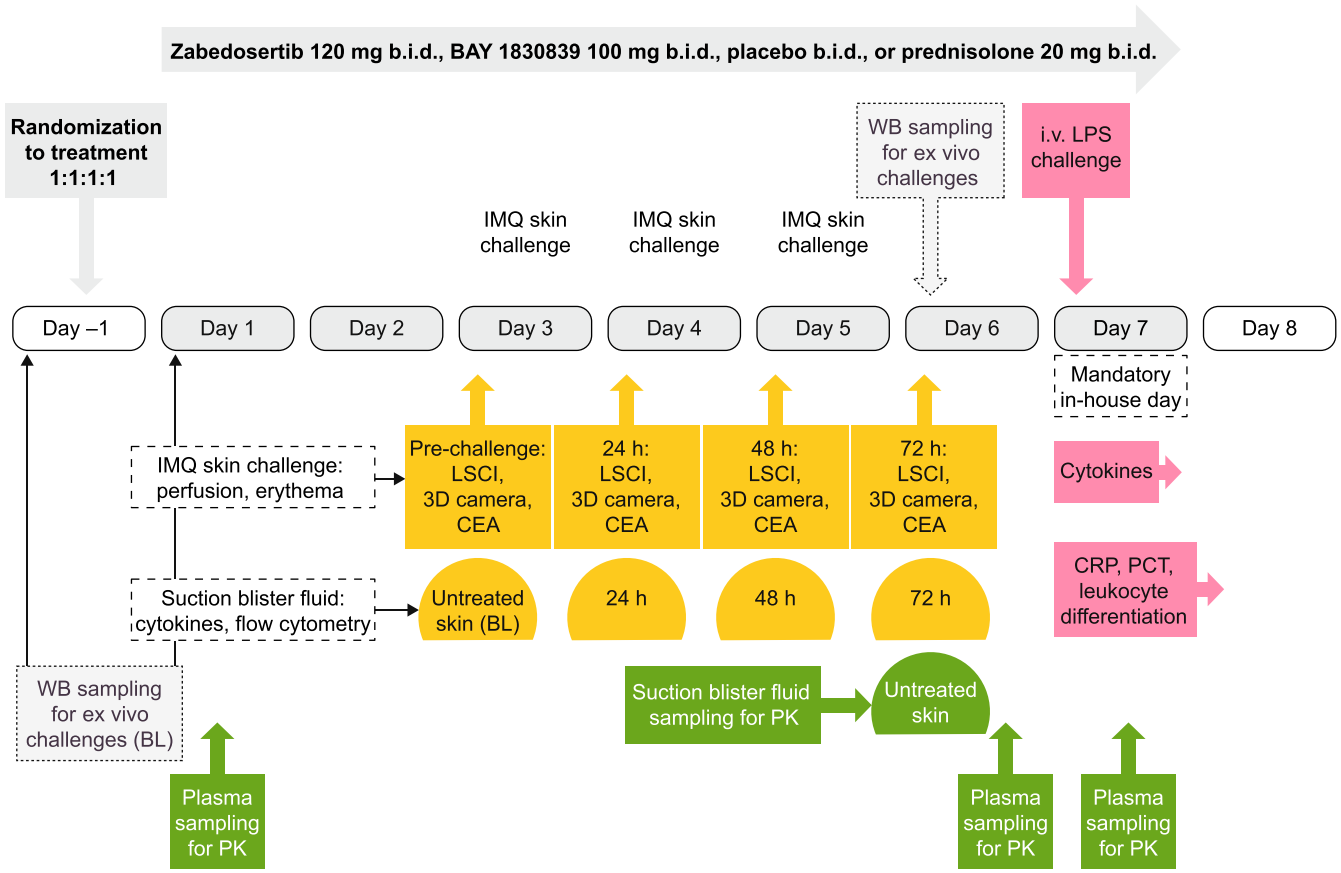

FIGURE 1 Study design. b.i.d., twice daily; BL, baseline; CEA, Clinician Erythema Assessment; CRP, C-reactive protein; IMQ, imiquimod; LCSI, laser speckle contrast imaging; LPS, lipopolysaccharide; PCT, procalcitonin; PK, pharmacokinetics; WB, whole blood.

Biomedisch Onderzoek' (Assen, The Netherlands) reviewed and approved the study prior to clinical study activities. All subjects received oral and written information and provided written informed consent before participation. The study was conducted at the Centre for Human Drug Research, Leiden, The Netherlands, between June 2021 and December 2021.

Study participants

The study included men aged 18–55 years at the time of screening (within 42 days prior to the study treatment period). All provided informed consent and were healthy as determined by medical evaluation based on medical history, physical examination, laboratory tests, electrocardiogram (ECG), and vital signs. Individuals were excluded from the study if they had specified medical conditions, medication or drugs, or evidence of any other clinically relevant findings. Subjects with active infections, who had recently used immune-modulating drugs, or with skin disorders were excluded. Further information regarding the inclusion and exclusion criteria are provided in Data S1.

Dose selection

The selected doses of BAY1834845 (120 mg b.i.d.) and BAY1830839 (100 mg b.i.d.) were based on the drug concentrations and exposures found to exert pharmacological activity in preceding preclinical experiments, which used IL-1β-induced systemic inflammation in mice[7] and mouse collagen antibody-induced arthritis (data on file at Bayer), after taking into account species differences in potency, as well as evidence from initial clinical studies.[12–15] In these clinical studies, BAY1834845 was well tolerated in healthy male volunteers at single oral doses of up to 480 mg and at multiple oral doses of up to 200 mg b.i.d. for 10 days; in male and female patients with plaque psoriasis, a similar safety profile was also reported at 120 mg b.i.d. for 8 weeks (data on file at Bayer). In addition, single oral doses of BAY1830839 of up to 800 mg as well as multiple oral doses of up to 200 mg b.i.d. and 100 mg t.i.d. for 10 days were generally well tolerated (data on file at Bayer). Prednisolone was administered as an active control at a supratherapeutic clinical dose (40 mg daily) for long-term use.

Treatments

Study participants were randomized 1:1:1:1 to receive BAY1834845 120 mg b.i.d. (masked), BAY1830839 100 mg b.i.d. (masked), matching placebo b.i.d. (masked), or 20 mg prednisolone b.i.d. (open label). Study treatments were administered for 7 consecutive days (Days 1–7). Further information regarding the randomization and blinding procedures are provided in Data S1. Prednisolone was administered at 20 mg b.i.d. to mimic the dosing regimen of the two investigational drugs. Treatment compliance during in-house visits and on Day 6 (full day in-house) was monitored at the study site. In the ambulatory phases of the study, direct supervision of drug intake was undertaken by study personnel via a live video call. Clinical evaluations were done by treatment-blinded investigators.

Immune challenges

IMQ skin challenge

For the IMQ skin challenge, commercially available IMQ-containing cream (Aldara™ 5% cream, Meda AB, Solna, Sweden) was used, starting after 2 days of treatment with the study drugs. IMQ cream was applied for 3 days to induce skin inflammation as previously described.[8] IMQ cream 5% (100 mg) was applied daily to tape-stripped skin treatment areas on the back under occlusion by a standard 12-mm Finn chamber (Smart Practice, Phoenix, AZ, USA). The Finn chamber was replaced with a new dose of IMQ after 24 h (treatment areas 2 and 3) and again after 48 h (treatment area 3). This resulted in the following treatment durations and doses – area 1: 24 h IMQ exposure, cumulative dose 5 mg; area 2: 48 h IMQ exposure, cumulative dose 10 mg; area 3: 72 h IMQ exposure, cumulative dose 15 mg; and area 4: no IMQ exposure (untreated control).

At baseline and 24, 48, and 72 h after the start of the IMQ skin challenge, skin reactions were evaluated using three-dimensional (3D) optical skin image capture and analysis (Antera 3D® camera, Miravex, Dublin, Ireland) for erythema and a laser speckle contrast imager (LSCI; Perimed AB, Järfälla, Sweden) for perfusion. Both procedures were performed according to the manufacturer's instructions.[8] In addition, visual assessments of the skin reaction were graded using the Clinician Erythema Assessment (CEA) score.[16]

At baseline and 24, 48, and 72 h after the start of the IMQ skin challenge, suction blisters were generated on the inflamed skin areas using a negative pressure device (NP-4; Electric Diversities, Finksburg, MD, USA).[17] Blister fluid was harvested and used to analyze immune cell subsets via flow cytometry (using Flowlogic 7.3, Inivai Technologies) as well as cytokines and chemokines via multiplex immunoassays (Meso Scale Discovery; Meso Scale Diagnostics, Rockville, MD, USA); see Data S1 for further details.

Systemic LPS challenge

After participants had undergone the IMQ skin challenge, an i.v. LPS challenge was performed on Day 7 after the start of treatment. All participants received 1 ng/kg purified *Escherichia coli* O113 LPS (List Labs, US, Lot #94332B4) reconstituted in 0.5 mL glucose 2.5%–sodium chloride (NaCl) 0.45% and administered as a 2-min infusion. To ensure that participants stayed adequately hydrated, glucose 2.5%–NaCl 0.45% was infused, starting 2 h prior to LPS administration and continuing until 6 h afterwards.[18] Circulating inflammatory proteins (acute phase proteins, cytokines), leukocyte differentiation, and clinical parameters (pulse rate, blood pressure, and temperature) were evaluated over time, starting 0.5 h after the end of the infusion and ending up to 24 h after infusion.

Ex vivo whole blood challenges

Before treatment, two baseline (Day −1 and Day 1) and on Day 6 (Figure 1), ex vivo peripheral blood samples were drawn into TruCulture tubes (Myriad RBM, Austin, TX, USA) according to the manufacturer's instructions. Tubes contained LPS (TLR4 agonist, 0.1 ng/mL) or R848 (TLR7/8 agonist, 0.35 μg/mL). In addition, a third blood sample was incubated with IL-1β (IL-1R agonist, 125 ng/mL) in 4 mL sodium heparin tubes. Blood samples were incubated in duplicate for each challenge agent at 37°C for 24 h. After incubation, cytokine release in culture supernatants was evaluated using multiplex immunoassays; see Data S1 for further details.

PK sample collection (plasma and skin suction blister fluid)

Sample collection for pharmacokinetic (PK) analyses is described in Data S1.

Safety monitoring

Adverse events (AEs) were recorded and assessed for intensity, cause, and potential relationship to study treatments or procedures at each study visit. Assessment of clinical signs and symptoms was particularly thorough during the 48 h after the i.v. LPS challenge on Day 7 to ensure participant safety. For these AEs, their potential relationship to the LPS infusion was specifically documented by the investigator as "infusion-related reactions" (as part of the AE description text) and subsequently rated as "procedure-related" AEs. This approach enabled the evaluation of the effects of the active treatments on LPS-induced adverse reactions.

Study end points

The co-primary end points of the study were the average change from baseline of skin perfusion/basal flow and erythema over 72 h after the start of the IMQ challenge, and the average change in systemic TNF-α and IL-6 levels over 6 h after the systemic LPS challenge. Secondary end points included: skin perfusion/basal flow and erythema at the individual time points (24, 48, and 72 h after the start of the IMQ challenge), CEA scores (24, 48, and 72 h after the start of the IMQ challenge), molecular responses (cytokines and immune cells in skin suction blisters) driven by IMQ; as well as immune responses in blood (e.g., immune cells, C-reactive protein [CRP], cytokines) and clinical responses (body temperature, pulse rate, systolic and diastolic blood pressure) driven by the systemic LPS challenge. Other prespecified end points included concentrations of total and unbound BAY1834845 and BAY1830839 in plasma and suction blister fluid, cytokine release in the ex vivo whole blood challenge assays, and treatment-emergent AEs (TEAEs).

Statistical approach and analyses

Evidence of the pharmacological activity of each treatment was evaluated using a two-step hierarchical decision: step 1 to establish assay sensitivity, and step 2 to establish superiority of the treatments versus placebo. To satisfy step 1 (IMQ skin challenge assay sensitivity), the prednisolone arm was required to show superiority in at least one of the outcome variables (erythema or perfusion) with >95% posterior probability. A sample size of 12 evaluable participants per arm was deemed sufficient to achieve >95% power for success in step 1, assuming a mean reduction versus placebo of 73% (conservative estimate based on available data, with a coefficient of variation [CV] of 15%) in erythema and a mean reduction versus placebo of 71% (with a CV of 25%) in perfusion. Proof of assay sensitivity with an effective anti-inflammatory drug was deemed important due to the limited available data for the challenges. Step 2 (main analysis) required that the active treatments demonstrated superiority versus placebo with >90% posterior probability for erythema as well as perfusion. Twelve participants were calculated as sufficient to achieve >90% power for demonstrating superiority

versus placebo if the treatment effect was at least 70% of the effect of prednisolone. A Bayesian repeated measures analysis of covariance model was fitted to the original log-transformed values for change from baseline (or change from pre-challenge value, if applicable) adjusted for treatment–timepoint interaction and a random subject effect. All statistical analyses were performed using SAS software, release 9.4 or higher (SAS Institute Inc., Cary, NC, USA), R version 3.61 or higher, or JAGS version 4.3 or higher. One-sided p-values <0.05 were considered statistically significant.

RESULTS

Participants and disposition

Fifty-one eligible participants were randomly assigned to one of the four study intervention groups. Two participants were withdrawn early due to AEs (see later) and were replaced to achieve 12 evaluable participants in each treatment group (Table S1). Based on direct supervision at the study site and video call monitoring, treatment compliance was estimated to be 100% in all evaluable patients (Table S2). All randomized participants were Caucasian adult males aged between 19 and 55 years. Baseline characteristics were similar across the four participant groups (Table S1).

IMQ skin challenge

Based on the statistically significant difference ($p=0.02$) in skin perfusion between the active control prednisolone and the placebo group, assay sensitivity was confirmed (step 1; Figure 2b,d, Table 1). Treatment with BAY1834845 and BAY1830839 reduced IMQ-driven erythema, with a GMR of treatment effect versus placebo of 0.75 and 0.83, respectively ($p=0.01$ and $p=0.05$, respectively; Figure 2a,c, Table 1). Treatment with BAY1834845 reduced IMQ-driven increases in skin perfusion as quantified by LSCI, with a GMR of treatment versus placebo of 0.69 ($p=0.02$; Figure 2b,d, Table 1). Clinical evaluation of skin reactions indicated that participants treated with BAY1834845 and BAY1830839 had a less severe inflammatory reaction to the skin challenge than those who received placebo (Figure 2a,b, Figure S1). Overall, the effect size of BAY1834845 on IMQ-driven skin responses was comparable or better than that of prednisolone (Table 1).

Skin suction blister fluid analysis

BAY1834845, BAY1830839, and prednisolone strongly suppressed IMQ-driven IP-10 and interferon-induced myxovirus resistance protein 1 (MxA) in skin suction blister exudate (analysis on Day 6), which were the two biochemical end points showing the strongest response

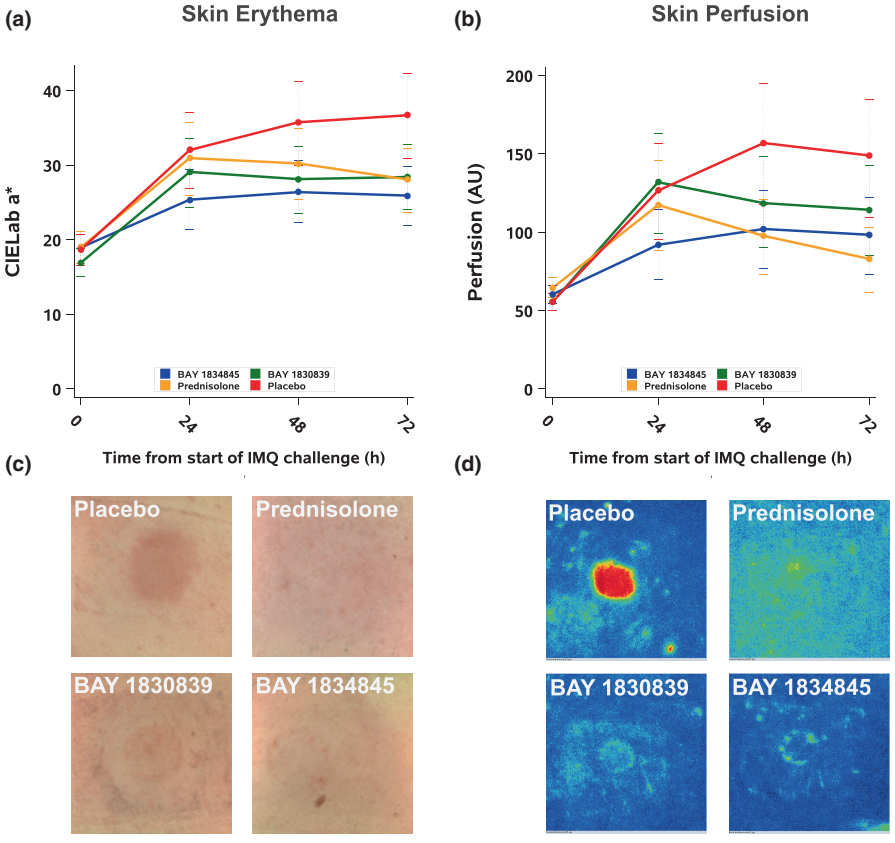

FIGURE 2 Changes over time in (a) skin erythema and (b) skin perfusion after start of imiquimod (IMQ) challenge, both in arbitrary units. Representative images captured 72 h after start of IMQ challenge are also shown for (c) three-dimensional (3D) camera and (d) laser speckle contrast imaging (LSCI). AU, arbitrary units; IMQ, imiquimod.

TABLE 1 Co-primary end point analysis: imiquimod skin challenge and systemic lipopolysaccharide challenge parameters.

Parameter	Placebo ($N=12$)	BAY 1834845 120 mg b.i.d. ($N=12$)	BAY 1830839 100 mg b.i.d. ($N=12$)	Prednisolone 20 mg b.i.d. ($N=12$)
IMQ skin challenge				
Skin perfusion/basal flow				
Geometric mean response (90% CrI; AU)	143.02 (112.05, 172.85)	98.68 (68.65,128.58)	123.00 (85.67,158.90)	100.11 (70.08,129.15)
GMR of treatment effect vs. placebo (90% CrI)	1	0.69 (0.48, 0.90)	0.86 (0.60, 1.11)	0.70 (0.49, 0.90)
Posterior probability of treatment superiority to placebo	—	0.98*	0.82 (n.s.)	0.98*
Erythema				
Geometric mean response (90% CrI; AU)	34.7 (29.9, 39.4)	26.0 (20.89, 30.92)	28.8 (23.08, 34.21)	29.8 (23.98, 35.50)
GMR of treatment effect vs. placebo (90% CrI)	1	0.75 (0.60, 0.89)	0.83 (0.67, 0.99)	0.86 (0.69, 1.02)
Posterior probability of treatment superiority to placebo	-	0.99*	0.95*	0.91 (n.s.)
LPS challenge				
TNF-α (blood)				
Posterior geometric mean response (90% CrI; pg/mL)	17.25 (13.18, 21.49)	3.45 (2.28, 4.61)	2.42 (1.60, 3.26)	5.35 (3.52, 7.12)
GMR of treatment effect vs. placebo (90% CrI)		0.20 (0.13, 0.27)	0.14 (0.09, 0.19)	0.31 (0.20, 0.41)
Posterior probability of treatment superiority to placebo		>0.99*	>0.99*	>0.99*
IL-6 (blood)				
Posterior geometric mean response (90% CrI) (pg/mL)	18.1 (13.7, 22.3)	4.89 (3.31, 6.59)	4.71 (3.04, 6.12)	5.61 (3.71, 7.39)
GMR of treatment effect vs. placebo (90% CrI)		0.27 (0.18, 0.36)	0.26 (0.17, 0.34)	0.31 (0.21, 0.41)
Posterior probability of treatment superiority to placebo		>0.99*	>0.99*	>0.99*

Abbreviations: AU, arbitrary units; b.i.d.; twice daily; CrI, credible interval; GMR, geometric mean ratio; IL, interleukin; IMQ, imiquimod; LPS, lipopolysaccharide; LSCI, laser speckle contrast imaging; TNF, tumor necrosis factor.

*Statistically significant at a one-sided α of 5%

in this test matrix following skin challenge (Figure 3a,b). The IMQ challenge resulted in an increase in CD8+ T cells, dendritic cells, classical monocytes, and natural killer (NK) cells in suction blister fluid. The responses of CD8+ T cells and dendritic cells were suppressed by BAY1834845, BAY1830839, and prednisolone treatment at 72 h after the start of the IMQ challenge. The responses of NK cells and classical monocytes were markedly suppressed by prednisolone at 72 h post-challenge only after a preceding increase of these cell types up to 48 h post-challenge (Figure S2). No changes in systemic markers during or after the IMQ challenge were observed.

Systemic LPS challenge

BAY1834845 and BAY1830839 treatment significantly suppressed the marked and rapid increase in circulating TNF-α and IL-6 following i.v. LPS challenge by ≥80%, averaged over assessments from 0.5 to 6 h after the LPS challenge when compared with placebo ($p<0.01$; Figure 4a,b). LPS-induced increases in IL-8, CRP, and procalcitonin (PCT; Figure 4c,e,f, respectively), as observed in the placebo group, were also inhibited by BAY1834845 and BAY1830839. In contrast to prednisolone, treatment with either BAY1834845 or BAY1830839

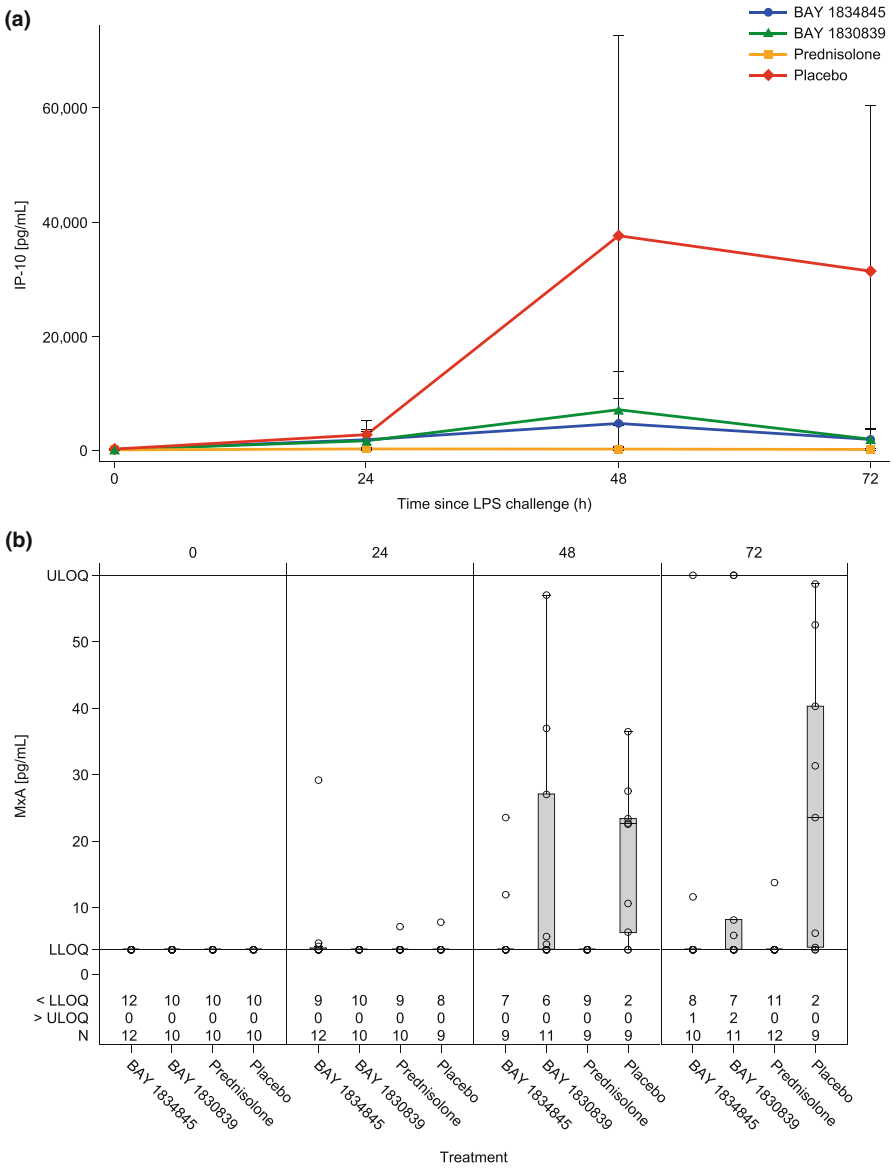

FIGURE 3 Changes over time in (a) IFN-γ-induced protein 10 (IP-10) and (b) myxovirus resistance protein 1 (MxA) in blister fluid after imiquimod (IMQ) challenge. LLOQ, lower limit of quantitation; LPS, lipopolysaccharide; ULOQ, upper limit of quantitation.

did not lead to an increase in the anti-inflammatory cytokine IL-10 compared with placebo (Figure 4d). Furthermore, BAY1834845 and BAY1830839 suppressed LPS-driven increases in systolic blood pressure and pulse rate (Figure S3) compared with placebo without suppressing the mild increase in core temperature 2–6 h after i.v. LPS challenge.

Adverse events related to LPS challenge

The majority of the TEAEs that occurred during the study were reported within 48 h after the start of the LPS challenge. These procedure-related TEAEs, comprising reactions related to the LPS infusion, mostly started within 1 h of beginning the LPS challenge and resolved completely after 2 h. Three of these TEAEs (tachycardia and infusion-related reactions of fever and chills) were of moderate intensity and observed in two participants in the placebo group; all other TEAEs were assessed as mild. Overall, compared with the placebo group, a clear reduction in the number of procedure-related TEAEs occurring within 48 h after the start of the LPS challenge was observed in the BAY1834845 and BAY1830839 treatment groups, in which 7 and 6 (of 12) participants, respectively, reported no procedure-related TEAEs within the assessment period (Figure 5).

Ex vivo whole blood challenges

Incubation of whole blood with different immune challenge agents triggered the secretion of cytokines characteristic of specific signaling pathways activated by the respective agents, thereby serving as a measure of ex vivo pharmacological activity. The cytokines induced by R848,

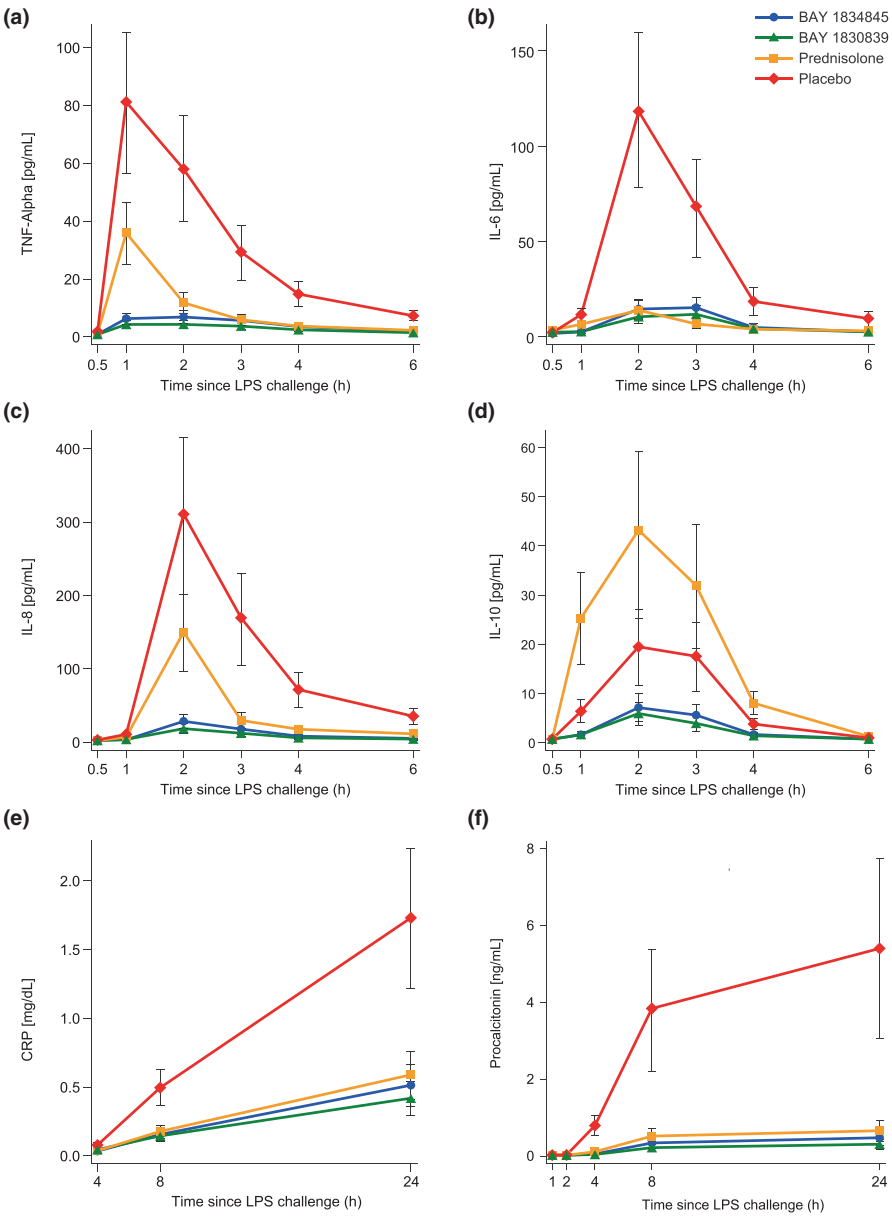

FIGURE 4 Changes in estimated geometric mean response over time in (a) tumor necrosis factor (TNF)-α, (b) interleukin (IL)-6, (c) IL-8, (d) IL-10, (e) C-reactive protein (CRP), and (f) procalcitonin after intravenous lipopolysaccharide (LPS) challenge.

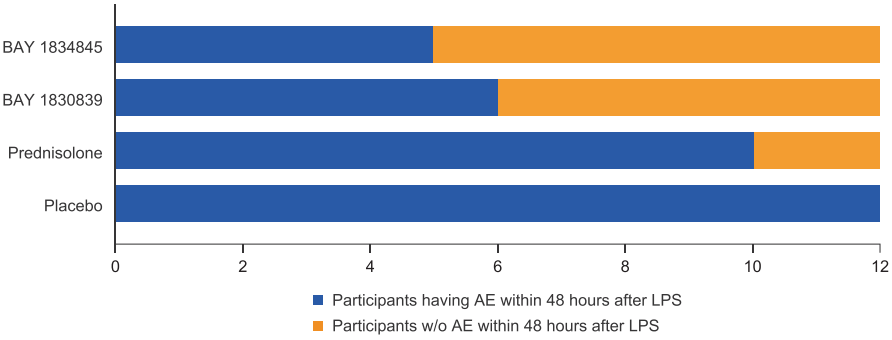

FIGURE 5 Subjects with procedure (lipopolysaccharide [LPS] challenge)-related treatment-emergent adverse effects within 48 h of intravenous LPS administration by treatment group ($N = 12$ per group): BAY 1834845, BAY 1830839, prednisolone, and placebo. AE, adverse effect; LPS, lipopolysaccharide.

LPS, and IL-1β as well as the inhibition of cytokine release per treatment arm are summarized in Table 2. Treatment with BAY1834845 and BAY1830839 resulted in an approximately 80%–95% reduction in R848-driven IL-1β, TNF-α, IL-6, and IFN-γ release; while IL-8 and IL-10, .IP-10 and IFN-α responses had smaller reductions and were mildly impacted by the IRAK4 inhibition. Both IRAK4 inhibitors suppressed LPS-driven IL-1β, TNF-α, IL-6, and IL-8 release with a 50%–80% reduction. Moreover, reductions in IL-1β-driven TNF-α, IL-6, and IL-8 were observed. Overall, BAY1830839 resulted in a stronger suppression of R848-driven responses than BAY1834845. Prednisolone

TABLE 2 Ex vivo pharmacological activity: inhibition of whole blood cytokine release triggered by R848, lipopolysaccharide, and interleukin (IL)-1β.

Challenge agent	Cytokine	BAY 1834845	BAY 1830839	Prednisolone	Placebo
R848	TNF-α	−87	−93	−32	+22
	IL-6	−77	−85	−20	+22
	IL-8	−30	−37	+133	+7
	IL-1β	−87	−92	−2	+19
	IFN-α	+11	−32	n.c.	+18
	IFN-γ	−93	−93	−67	+32
	IL-10	−69	−85	+11	+8
	IP-10	−20	−30	+10	+10
LPS	TNF-α	−51	−75	−56	+38
	IL-6	−52	−73	−71	+34
	IL-8	−60	−79	+13	+14
	IL-1β	−50	−75	−57	+30
IL-1β	TNF-α	n.c.	n.c.	+34	-1
	IL-6	−41	−81	−1	+23
	IL-8	0	−50	+30	0
	IFN-α	n.c.	n.c.	n.c.	n.c.

Note: Data shown are the geometric mean percentage change from baseline stimulation for each cytokine; a negative change indicates a reduction of the respective marker. Some means were not calculated because too many values were below the lower limit of quantitation.

Abbreviations: IFN, interferon; IL, interleukin; IP-10, IFN-γ-induced protein 10; LPS, lipopolysaccharide; n.c., not calculated; TNF, tumor necrosis factor.

treatment was less effective at suppressing most R848- and IL-1β-driven cytokine responses but showed similar potency to the two IRAK4 inhibitors for the attenuation of LPS-stimulated IL-1β, IL-6, and TNF-α release.

Overall safety and tolerability

TEAEs were reported by 9 participants (69.2%) in the BAY1834845 group, 8 (61.5%) in the BAY1830839 group, and 12 (100%) in the prednisolone and placebo groups, respectively (Table S4). An AE leading to withdrawal from the study occurred in one participant in each of the BAY1834845 and BAY1830839 treatment groups. The two discontinuations were due to an asymptomatic and uncomplicated SARS-CoV-2 infection and an upper respiratory tract infection on Day 4, respectively.

Most of the TEAEs that occurred in 36 participants were assessed as being related to study procedures and comprised reactions occurring within 48 h after the start of the i.v. LPS challenge (see Figure 5). These procedure-related AEs were reported in two participants in the BAY1834845 group, three in the BAY1830839 group, four in the prednisolone, and six in the placebo groups, respectively. In the two IRAK4 inhibitor-treated groups, these AEs included nausea, chills, asthenia, spontaneous hematoma, myalgia, headache, and oropharyngeal pain. Two participants in the placebo group reported procedure-related TEAEs of moderate intensity. All other AEs in any of the treatment groups were of mild intensity.

PK of BAY1834845 and BAY1830839

At 3 h post-dose on Day 6, geometric mean (CV) total plasma concentrations were 6.1 (14.9%) mg/L for BAY1834845 and 5.0 (23.6%) mg/L for BAY1830839 (Figure S4). The corresponding geometric mean (CV) total concentrations in blister fluid were 2.6 (32.3%) and 3.0 (28.3%) mg/L. The geometric mean (CV) of individual suction blister fluid versus plasma ratios were 0.43 (22.7%) for BAY1834845 and 0.59 (16.2%) for BAY1830839.

DISCUSSION

This study evaluated the pharmacological activity of the two orally administered IRAK4-specific inhibitors BAY1834845 (zabedosertib) and BAY1830839 in experimental inflammation in healthy volunteers. Pharmacological activity was investigated by ex vivo whole blood challenges and in vivo experimental models of tissue inflammation and systemic inflammation. The data-rich, proof-of-mechanism study design and selection of challenge models were chosen to (a) evaluate

the translation of results obtained from investigations of BAY1834845 and BAY1830839 based on TLR-driven pharmacodynamic cell and animal models; (b) characterize the inhibitory effect of these compounds on different TLR pathways in humans, both systemically and in peripheral tissue; and (c) inform decisions regarding the potential clinical development of both compounds.

The doses of BAY1834845 and BAY1830839 used in this study were based on data from cell-based experiments, animal models, and clinical studies.[7,12–14,19] In multiple ascending dose phase I studies, doses of 120 mg b.i.d. BAY1834845 and 100 mg b.i.d. BAY1830839 resulted in a mean suppression of TNFα of 40% and 70% (TLR4-cytokine release in ex vivo whole blood assay), respectively, at corresponding systemic exposures of 5.2 (19.4%) and 4.3 (42.8%) mg/L. In the present study, average plasma concentrations (total) of 6.2 and 5.0 mg/L were observed on Day 6, 3 h after BAY1834845 and BAY1830839 intake. Drug concentrations in suction blister fluid, which acted as a proxy for dermal drug concentration, were approximately half that of systemically circulating drug concentrations. Based on the literature,[20–22] it is known that the ratio between systemic and interstitial fluid PK differs, and the basement membrane acting as a barrier for compound penetration might cause differences in T_{max}. Although the concentration measured at Day 6 was considerably lower than that in the suction blister fluid, the skin readouts from the IMQ skin challenge suggested efficient exposure to elicit an immunomodulatory effect.

BAY1834845 treatment significantly suppressed the IMQ-induced increase in skin perfusion as quantified by LSCI, and both IRAK4 inhibitors significantly suppressed induction of erythema as quantified by multispectral imaging. These findings were supported by visual grading of erythema and by reductions in biochemical (IP-10 and MxA) and cellular (T cells, dendritic cells, classical monocytes, NK cells) responses in suction blister fluid. The results suggest that, of the two study drugs, BAY1834845 was more effective in the topical inflammatory challenge. Overall, the effect sizes of BAY1834845 and BAY1830839 on IMQ-driven skin responses were comparable or better than that of oral prednisolone (20 mg b.i.d.), which was used as an active control. Of note, prednisolone has been shown to suppress IMQ-induced skin inflammation in mice,[23] and a recent study also demonstrated this suppressive effect in humans.[24]

In addition to the effect on the topical IMQ challenge response, the systemic pharmacological activity of BAY1834845 and BAY1830839 was evaluated by means of an i.v. LPS challenge in the same volunteers. The model is well established for the investigation of physiological mechanisms of systemic inflammation and drug candidates in clinical development. Intravenous administration of purified *E. coli* LPS results in flu-like signs and symptoms and increased levels of inflammatory markers, such as cytokines and acute phase reactants. The extent of the effect of LPS challenge on inflammatory markers in the current study was consistent with that seen in previous studies.[25,26] BAY1834845 and BAY1830839 strongly inhibited the responses driven by LPS; cytokine, CRP, and PCT responses were suppressed, and LPS-driven increases in systolic blood pressure and pulse rate were limited as a result of the IRAK4 inhibition. Oral prednisolone administered at 20 mg b.i.d. had mostly comparable effects, consistent with earlier reports.[27]

Two clear differences between prednisolone and the IRAK4 inhibitors were observed. Prednisolone induced IL-10 systemically after the LPS challenge and also caused a prominent increase in classical monocytes in skin suction blisters within 48 h after the IMQ challenge, whereas BAY1834845 and BAY1830839 did not. An earlier clinical study showed that steroids upregulate constitutive IL-10 production by selectively triggering activation signals on monocytes[27]; this was not evident for BAY1834845 and BAY1830839.

The pharmacological activity of both IRAK4 inhibitors was evaluated ex vivo by means of whole blood challenges with specific triggers of the innate immune system. Treatment with BAY1834845 and BAY1830839 resulted in a reduction in R848-induced TLR7/8 responses, which were most prominent for NF-κB-dependent IL-1β, TNF-α, IL-6, and IFN-γ; and, to a lesser extent, for IL-8 and IL-10. Interferon regulatory factor-dependent responses (IP-10 and IFN-α) were only mildly inhibited by the two IRAK4 inhibitors, which may be explained by the potentially lower sensitivity of the assay platform for IFN-α. Both BAY1834845 and BAY1830839 suppressed LPS-induced TLR4-driven IL-1β, TNF-α, IL-6, and IL-8 release and IL-1β-induced TNF-α, IL-6, and IL-8. Overall, BAY1830839 resulted in a stronger suppression of ex vivo R848-driven responses and slightly higher suppression of LPS-driven responses than BAY1834845 in this assay.

BAY1834845 and BAY1830839 inhibited the IL-1β-driven IL-8 and IL-6 cytokine release by 50%–80% and 0%–40%, respectively. This contrasted with the weak effects on IL-1β-induced cytokines reported for another IRAK4 specific inhibitor (PF-06650833),[28] which even demonstrated an upregulation of these cytokines in comparison with vehicle control. These differences might be compound-dependent or could be explained by differences in experimental assay setup. Our data also suggested a similar level of pharmacological activity compared with an IRAK4 degrader, which suppressed TLR4- and TLR7/8-mediated cytokine release in peripheral blood mononuclear cells from healthy volunteers.[29]

While the clinical relevance of the differences observed between BAY1834845 (zabedosertib) and BAY1830839 in the described suppression of cytokine release remains unclear and warrants further investigation, this

indirect comparison with available data from other IRAK4-targeting molecules clearly suggests a competitive profile for zabedosertib and BAY1830839.

The maximal effect size of BAY1834845 and BAY1830839 differed between experimental models. Both compounds almost completely suppressed (≥80%) TLR4-driven systemic responses of TNF-α and IL-6 release following the i.v. LPS challenge, and the observed effects were comparable or stronger than those observed for prednisolone. In the ex vivo whole blood challenge, inhibition of these cytokines was more pronounced by BAY1830839 (75% for TNF-α; 73% for IL-6) than by BAY1834845 (approximately 50% for both cytokines) if TLR4-driven, but similarly high (80%–90%) for both inhibitors if TLR 7/8-driven. By contrast, the inflammation induced by topical IMQ was more prominently suppressed by BAY1834845 than by BAY1830839, and the effects of both compounds on TLR7-mediated responses to the IMQ skin challenge were less pronounced compared with those in the i.v. LPS challenge. This was not surprising, given the previously reported effects of prednisolone on TLR4-driven inflammatory responses following skin inflammatory challenge with intradermal LPS; although oral prednisolone treatment significantly inhibited LPS-driven increases in skin perfusion and erythema, no full inhibition of the LPS response was observed.[30]

Based on the distinct immunomodulatory effects demonstrated by both IRAK4 inhibitors in this study, combined with favorable comparisons with prednisolone, a known strong immunosuppressant, both compounds may be clinically active and advanced further in clinical development.

Of note, the study was not designed or powered to make a quantitative comparative assessment of the two compounds in the chosen respective dose regimens, because we anticipated only marginal differences based on in vitro and ex vivo findings.

To investigate the effects of BAY1834845 and BAY1830839 in this study, we administered each at one dose level to obtain proof of pharmacological activity and enable decisions on the future development of these compounds. The use of additional dose levels of the two treatments could have allowed for a more extensive characterization of the respective effects in the immune challenge tests via a more detailed exposure–pharmacodynamic response evaluation.

Although the immune challenges used in this study provided clear evidence for the pharmacological activity of BAY1834845 and BAY1830839 in healthy volunteers and were comparable to preclinical data, the therapeutic effects remain to be investigated. A direct translation of the observed pharmacological activity into clinical efficacy in immune-mediated diseases is not possible by extrapolation of these findings. In addition, the immune challenges used target distinct immune mediators (TLR4 in the systemic LPS challenge and TLR7 in the IMQ skin challenge), whereas immune-mediated diseases often result from disordered activity of several interconnected and potentially dynamic signaling pathways; inhibition of one pathway does not necessarily translate into suppression of disease progression or reduction of the associated symptoms.

The combination of the observed suppression of immune responses in this study together with ex vivo and preclinical data served as essential steps in understanding the pharmacological responses in humans and, therefore, contributed to the clinical development of the two tested IRAK4 inhibitors. While model limitations exist, and conclusive evidence for a direct translation into clinical efficacy could not be provided, the results of this study offer proof of pharmacological activity that are important sources to direct the scope of future development of the tested compounds. Moreover, study outcomes and efficacy data of subsequent clinical trials with patients may be hard to interpret without human pharmacology data. It is certain that a lack of evidence for the pharmacological activities of the two molecules tested in this study would have precluded further clinical development. That being said, the pharmacological effects demonstrated in this study and data from preceding phase I studies fully supported the selection of doses for phase II studies.

In addition to the beneficial immunomodulatory effects in chronic inflammatory diseases, the fast onset of action of these compounds suggests a potential application in acute conditions requiring an anti-inflammatory intervention. Notably, the observed effects in the skin challenge also underpin the potential of these compounds as future therapies for inflammatory diseases in other peripheral tissues.

Taken together, the investigations conducted in this mechanistic clinical phase I study showed that BAY1834845 (zabedosertib) 120 mg b.i.d. and BAY1830839 100 mg b.i.d. administered for 7 days achieved a rapid and distinct anti-inflammatory effect in a human skin challenge model with IMQ, as well as in a human systemic LPS challenge model. For several end points, the immunosuppressive effect of both IRAK4 inhibitors was more pronounced than the effect of prednisolone 20 mg b.i.d. The onset of action of both treatments occurred within 3 days of starting oral treatment. Both IRAK4 inhibitors achieved approximately 50% systemic exposure in suction blister fluid (as a proxy for skin exposure). No safety signals were observed during the 7 days of treatment. The human challenge methodologies used in this study (skin and systemic challenges) were well tolerated by the study participants.

The current study demonstrated proof-of-mechanism for targeted IRAK4 inhibition by BAY1834845 (zabedosertib)

and BAY1830839, supporting their suitability as drug candidates for efficacy studies in appropriately selected patient populations. Results were indicative of potential immunomodulatory effects in chronic and acute inflammatory settings as well as a beneficial steroid-sparing effect for chronic autoimmune conditions (e.g., systemic and cutaneous lupus erythematosus). The outcomes of both treatments following a topical inflammatory challenge were particularly encouraging in respect of the applicability of these IRAK4 inhibitors to dermatological inflammatory diseases. In line with this, a clinical study investigating zabedosertib in patients with moderate to severe atopic dermatitis, NCT05656911, is currently ongoing.[31]

AUTHOR CONTRIBUTIONS

S.J.J. and W.t.V. contributed equally to this work. S.J.J., W.t.V., S.K., A.W., F.S.Z., M.F., N.B.K., D.T.d.B., M.A.A.J., R.R., B.R., and M.M. wrote the manuscript. S.J.J., W.t.V., S.K., A.W., F.S.Z., M.F., N.B.K., M.A.A.J., R.R., B.R., and M.M. designed the research. W.t.V., N.B.K., D.T.d.B., M.A.A.J., R.R., and M.M. performed the research. S.J.J., W.t.V., S.K., A.W., F.S.Z., M.F., N.B.K., D.T.d.B., M.A.A.J., R.R., B.R., and M.M. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

S.J.J., S.K., A.W., M.F., and B.R. are employees of Bayer AG. All other authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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