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ARTICLE

First-in-human study of deucravacitinib: A selective, potent, allosteric small-molecule inhibitor of tyrosine kinase 2

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Abstract

This randomized, double-blind, single- and multiple-ascending dose study assessed the pharmacokinetics (PKs), pharmacodynamics, and safety of deucravacitinib (Sotyktu™), a selective and potent small-molecule inhibitor of tyrosine kinase 2, in 100 (75 active, 25 placebo) healthy volunteers (NCT02534636). Deucravacitinib was rapidly absorbed, with a half-life of 8–15 h, and 1.4–1.9-fold accumulation after multiple dosing. Deucravacitinib inhibited interleukin (IL)-12/IL-18-induced interferon (IFN)γ production ex vivo in a dose- and concentration-dependent manner. Following in vivo challenge with IFNα-2a, deucravacitinib demonstrated dose-dependent inhibition of lymphocyte count decreases and expression of 53 IFN-regulated genes. There were no serious adverse events (AEs); the overall frequency of AEs was similar in the deucravacitinib (64%) and placebo (68%) groups. In this first-in-human study, deucravacitinib inhibited IL-12/IL-23 and type I IFN pathways in healthy volunteers, with favorable PK and safety profiles. Deucravacitinib is a promising therapeutic option for immune-mediated diseases, including Crohn's disease, psoriasis, psoriatic arthritis, and systemic lupus erythematosus.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Targeting IL-12 and/or IL-23 has been clinically validated in the treatment of Th17-driven diseases, including Crohn's disease, psoriasis, and systemic lupus erythematosus.

WHAT QUESTIONS DID THIS STUDY ADDRESS?

This healthy volunteer study assessed the PKs, pharmacodynamics, and safety of deucravacitinib, a potent, highly selective, allosteric small-molecule inhibitor of TYK2 with a novel mechanism of action.

*Lars Hansen, Yali Liu, Di Bei at the time of analysis.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
In this first-in-human study, deucravacitinib inhibited IL-12/IL-23 and type I IFN pathways in healthy volunteers, with favorable PK and safety profiles.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
The novel assay technique used here allowed for in vivo assessment of the inhibition of IFN-responsive gene expression in healthy volunteers and may be useful in future studies. Deucravacitinib was approved in September 2022 for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy[1] and holds promise for the treatment of other immune-mediated diseases, such as Crohn's disease, psoriatic arthritis, and systemic lupus erythematosus.

INTRODUCTION

Tyrosine kinase 2 (TYK2) activates signal transducer and activator of transcription protein-dependent transcription and functional responses downstream of critical immune mediators of inflammatory disease, such as interleukin (IL)-12, IL-23, and type I and III interferon (IFN) receptors.[2-5] Studies of a partial loss-of-function TYK2 polymorphism result in impairment of type I IFN, IL-12, and IL-23 signaling.[6] Targeting IL-12 and/or IL-23 has been clinically validated in the treatment of T helper 17 cell (Th17)-driven diseases, including Crohn's disease and psoriasis,[7,8] although promise in a phase II trial in systemic lupus erythematosus (SLE)[9] was not fulfilled at phase III.[10] Furthermore, following phase II studies of anifrolumab, a type I IFN receptor antagonist, a phase III study in patients with SLE, demonstrated a higher proportion of patients had a response with anifrolumab versus placebo.[11,12] Based on this phase III data, anifrolumab was approved for the treatment of SLE.[13]

Deucravacitinib (BMS-986165) is a potent, highly selective, allosteric, small-molecule inhibitor of TYK2 that acts through a novel mode of binding to the JH2 pseudokinase domain, which locks the kinase in an inactive state. This binding site is more diverse among Janus kinases (JAKs) compared to the ATP binding pocket of the active site where the approved JAK inhibitors (JAKi) bind, which is highly conserved.[14,15] Thus, JAKi are ATP competitive active site inhibitors with pharmacologic activities against JAK1, JAK2, and JAK3 in differing proportions depending upon the drug.[16] Notably, to date, all JAKi have some activity against JAK2, which carries specific liabilities.[17] Deucravacitinib has 200-fold greater selectivity for TYK2 inhibition over JAK1/JAK3 inhibition, and 3000-fold greater selectivity for TYK2 inhibition over JAK2 inhibition in cell-based assays.[18,19] A more recent analysis of the selectivity profile of deucravacitinib also demonstrated highly selective inhibition of TYK2 and not JAK 1/2/3.[19] Although TYK2 is a JAK family member, TYK2 is only involved in specific immune-regulating cytokines. In patients with psoriasis treated with nonselective JAKi, typical laboratory changes are observed, including decreased hemoglobin levels, decreased lymphocyte or neutrophil counts, and increases in cholesterol levels and liver transaminases.[20-22] These changes were not observed in patients with psoriasis or psoriatic arthritis treated with deucravacitinib, and demonstrate that the in vitro selectivity profile is borne out in the clinical profile.[23,24] The efficacy observed in psoriasis is evidence of effective inhibition of IL-23 and the downstream Th17 pathway.

Based on preclinical data,[18] deucravacitinib, an oral, selective TYK2 inhibitor, was predicted to inhibit signaling downstream of the type I IFN receptor, and inhibition of the type I IFN pathway. Additional preclinical studies, including animal toxicology, and in vitro assessments of deucravacitinib potency using human whole blood assays and pharmacokinetic (PK) parameters, were performed to establish the in vitro PK/target engagement relationship.[25-27] Current treatments for psoriasis include the application of topical corticosteroids, methotrexate, ciclosporin, hydroxycarbamide, fumarates, retinoids for systemic treatment, and apremilast, which targets specific aspects of the immune response in psoriasis. In addition, there are several biologics that are approved for the treatment of psoriasis (e.g., infliximab, adalimumab, etanercept, ixekizumab, ustekinumab, and guselkumab); however, the majority must be administered intravenously or by subcutaneous injection. Deucravacitinib has shown efficacy in both phase II and III trials. In a phase II trial, 67%–75% of patients with plaque psoriasis treated with deucravacitinib achieved ≥75% reduction from baseline in Psoriasis Area and Severity Index at 12 weeks (vs. placebo $p < 0.001$).[28] Deucravacitinib has also achieved phase II trial primary (improvement of 20% in American College of Rheumatology criteria [ACR 20] response) and key secondary objectives (including improvement from baseline

in the Health Assessment Questionnaire–Disability Index and Short Form-36 Physical Component Score) at week 16 in patients with active psoriatic arthritis.[24] Furthermore, recent phase III trials (POETYK PSO-1 and POETYK PSO-2) in patients with psoriasis showed deucravacitinib was well-tolerated and superior to placebo for both co-primary end points in each trial.[29,30] Based on these data, deucravacitinib was recently approved by the US Food and Drug Administration (FDA) for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1] Oral agents, such as deucravacitinib, may provide a more convenient alternative therapy for several immune-mediated diseases.

The primary objective of this study was to assess the PKs, pharmacodynamics (PDs), effects on biomarkers of target engagement, and safety of deucravacitinib in healthy volunteers.

METHODS

Study design

A randomized, double-blind, placebo-controlled, phase I study was performed to assess the PK, PD, target engagement, safety, and tolerability of deucravacitinib in healthy volunteers (NCT02534636). Here, we report the data from the single-ascending dose (SAD) and multiple-ascending dose (MAD) cohorts. The study was conducted in accordance with Good Clinical Practice (as defined by the International Conference on Harmonization) and in line with the ethical principles of the Declaration of Helsinki, European Union Directive 2001/20/EC, and the United States Code of Federal Regulations, Title 21, Part 50. The protocol was approved by the Alfred Hospital Ethics Committee (Victoria, Australia) prior to study initiation, and all volunteers provided written informed consent before beginning any study procedures.

Study population and dose regimen

Volunteers aged 18–50 years with a body mass index of 18–40 kg/m^2, inclusive, who were healthy, as determined by medical history, physical examination, 12-lead electrocardiogram (ECG), and clinical laboratory evaluations, were eligible to participate in the study. Women of childbearing potential were required to have a negative serum or urine pregnancy test prior to enrollment and were excluded from participation in the study if pregnant or breastfeeding. Volunteers with serious or recurrent infection or a recent history of serious infection, and those with a significant history of cardiovascular disease, chronic or active infection, or any other illness, condition, or significant laboratory anomalies that the investigator felt may put the volunteer at unacceptable risk, were also excluded. All volunteers were screened to evaluate their eligibility within 21 days prior to study drug administration, and safety, target engagement, and PK data from each dosage panel were reviewed with the Principal Investigator before escalation to the next higher dosage level. Volunteers and medical staff were blinded to treatment assignment. Randomization schedules were provided to pharmacists or other personnel responsible for the dispensing of blinded study drugs and not involved in any other aspect of study conduct; randomization schedules were maintained in a secure location.

Single-ascending dose cohort

Eight healthy volunteers were randomized to each sequential dose panel (deucravacitinib 1, 3, 10, 20, and 40 mg) and, within each dose panel, were randomized in a 3:1 ratio to receive a single oral dose of deucravacitinib as a liquid formulation or matching placebo according to a computer-generated randomization scheme supplied by the sponsor. Volunteers were admitted to the facility on the day before study drug administration and were required to fast and avoid drinking (excluding water) from ~10 h prior to and 4 h following administration of the single dose of study drug on day 1; volunteers remained at the facility until discharge on study day 5. Blood samples for the PK analysis and assessment of target engagement were collected predose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 10, 16, 24, 36, 48, 60, 72, and 96 h postdose; urine samples for the PK analysis were collected at intervals (0–10, 10–24, 24–48, 48–72, and 72–96 h).

Multiple-ascending dose cohort

Twelve healthy volunteers were randomized to each sequential dose panel (deucravacitinib 2 mg twice daily [b.i.d.], 4 mg b.i.d., 6 mg b.i.d., 12 mg b.i.d., or 12 mg once daily [q.d.]) and, within each dose panel, were randomized in a 3:1 ratio to receive oral deucravacitinib as a liquid formulation or matching placebo for 12 days. Volunteers were admitted to the facility the day before study drug administration and received doses of study drug at 12-h intervals (24-h intervals in the 12 mg q.d. group) on days 1–12, and remained at the facility until discharged on day 19. Volunteers were required to fast prior to the morning dose and water was not permitted within 1 h of dosing. A standard lunch was served ~4 h postdose, a standard dinner at ~8 h postdose, and a light snack was provided ~12 h

postdose. Blood samples for PK analysis and the assessment of target engagement were collected predose on days 1, 5, 8, and 12, and at 1, 2, 3, 4, 6, 8, and 12 h following the first dose on day 1 and day 12. Additional blood samples for the assessment of IFNα-2a (Roferon; Roche) and PD effects on IFN-regulated gene expression were collected prior to IFNα administration on days 1 and 13, and then at 2, 2.5, 3, 5, 8, 11, 14, 24, 26, 50, and 72 h following IFNα administration.

Pharmacokinetic assessment

All blood samples were collected through an indwelling catheter or by direct venipuncture. Blood samples for PK analyses were collected into a 4 ml tube containing K_2EDTA and immediately mixed by gentle inversion and placed on ice. Samples were centrifuged at 1100–1300×*g* for 10 min at 4–6°C and the plasma transferred to a clean tube. Samples were shipped to the analyzing laboratory at −20°C. PK parameters were derived from plasma concentrations of deucravacitinib as assessed by a qualified mass spectrometry method with a lower limit of quantification (LLOQ) of 0.2 ng/ml.

Assessment of target engagement

Inhibition of the IL-12 pathway by deucravacitinib was monitored by ex vivo stimulation of whole blood (1 ml) drawn into two tubes (TruCulture tubes; Myriad RBM) with either IL-12 (plus IL-18 adjuvant) or no stimulant (null), and assessment of IFNγ production. The tubes were incubated for 24 h at 37°C in a dry heat block. IFNγ in the plasma supernatant was measured by enzyme-linked immunosorbent assay (ELISA; LabCorp). Inhibition of the IL-12 pathway was calculated relative to the predose baseline sample with background subtraction (null tube).

Challenge with IFNα-2a (MAD cohort only)

The type I IFN pathway when activated results in upregulation of the expression of multiple interferon-responsive genes (IRGs).[31] To assess the effects of deucravacitinib on IRG expression in healthy volunteers in whom the type I IFN pathway would not normally be activated, an IFNα-2a challenge was given to induce IRG expression.

For the assessment of IRG expression over time, samples were drawn into PreanalytiX PaxGene Blood RNA tubes (BD Diagnostics) prior to administration of deucravacitinib (predose) on day 1, and pre-challenge on day 13 and at 0.5-, 1-, 3-, 6-, 9-, and 24-h post-challenge. On day 13, 2-h post-morning deucravacitinib dose, 3 million units of IFNα-2a were administered by subcutaneous injection. This dosage has previously been shown to produce a consistent biologic PD response, including signs and symptoms of IFN exposure that were suitable for evaluation as additional PD end points.[32,33]

For the assessment of IFNα-2a, blood samples were collected into 5 ml serum separating tubes and immediately mixed by gentle inversion. The tubes were stored upright and the blood allowed to clot for 30 min at room temperature. Samples were then centrifuged at 1500–2000×*g* for 15 min at 4°C and the serum was transferred to clean tubes. Samples were stored at −70°C and analyzed using an ELISA, performed as validated prior to study sample analysis.

Expression of 53 IFN-regulated genes and three housekeeping genes were assessed by quantitative reverse transcription polymerase chain reaction (QPS). Gene expression was calculated as fold-change relative to the level on day 1 prior to administration of deucravacitinib (predose level). Gene expression for each volunteer receiving deucravacitinib was expressed as a percentage of the group mean for placebo-treated volunteers on a time-matched basis.

PD effects of IFNα-2a exposure and inhibition by deucravacitinib were also evaluated through physiologic assessments, including body temperature, heart rate, blood pressure (see Safety assessments), and complete blood cell (CBC) counts. Samples for CBC counts were collected pre-challenge with IFNα-2a and then at 1-, 3-, 6-, 9-, 12-, 24-, and 48-h post-challenge.

Safety assessments

Safety assessments included recording of adverse events (AEs) and serious AEs (categorized according to Medical Dictionary for Regulatory Activity preferred term and system organ class), clinical laboratory results, vital signs, blood pressure, and 12-lead ECG telemetry (Holter monitoring). Telemetry was initiated on day −1, ~18 h prior to administration of the first dose of study drug.

Statistical analysis

PK parameters were derived from the plasma concentration of deucravacitinib at the prespecified timepoints, and from urinary excretion data by analyte and collection interval. maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and minimum plasma concentration (C_{min}; recorded at the end of the

dosing interval and immediately prior to the next dose, where applicable) were tabulated as observed. Other individual PK parameter values were derived by noncompartmental methods using Phoenix version 1.4 (Pharsight). Actual sampling times were used for PK calculations, and nominal times were used for the generation of mean plasma concentration time plots and summaries. Predose concentrations, and concentrations prior to the first quantifiable concentration that were below the LLOQ, were set to zero for the purpose of calculating PK parameters but were treated as "missing" for the calculation of summary statistics. All other concentrations below the LLOQ were set to "missing" for the calculation of PK parameters and summary statistics.

The terminal half-life ($t_{1/2}$) was calculated as ln2/λ, where λ is the absolute value of the slope of the terminal log-linear phase. The area under the concentration–time curve (AUC) was calculated by mixed log-linear trapezoidal summations, and AUC to infinity (AUC_{INF}) was estimated by summing AUC from time zero to the time of the last quantifiable concentration (AUC_{0-t}) and the extrapolated area, computed using the quotient of the last observable concentration and λ. The apparent total body clearance (CLT/F) was calculated by dividing AUC_{INF} (single dose) or AUC over one dosing interval (AUC_{TAU}; multiple dose) by the dose. Dose proportionality in the MAD cohort was assessed on days 1 and 12 through generation of scatter plots of C_{max} and AUC_{TAU} versus dose, with estimation of a regression line from the power model overlaid on the individual points in the corresponding scatter plot.

Although the number of volunteers was not based on statistical power considerations, administration of deucravacitinib to six or nine volunteers in each panel provides an 80.7% or 91.5% probability, respectively, of observing at least one occurrence of any AE that would occur with 24% incidence in the population from which the sample was drawn.

RESULTS

The study was conducted between October 14, 2015, and November 22, 2016, at Nucleus Network (Victoria, Australia). A total of 40 volunteers were randomized (6 given deucravacitinib and 2 given placebo, in 5 sequential dose panels) in the SAD cohort, all of whom completed the study with no withdrawals. Of the 60 volunteers who were randomized (9 given deucravacitinib and 3 given placebo, in 5 sequential dose panels) in the MAD cohort, 51 volunteers (85%) completed the study and there were nine withdrawals: seven (12%) volunteers discontinued due to AEs, and two (3%) volunteers withdrew consent to participate in the study. Volunteers were aged between 19 and 39 years, and the majority of volunteers were White, with sex well-balanced among the treatment groups. A summary of volunteer demographics is shown in Table S1.

Pharmacokinetic in healthy volunteers

After administration, deucravacitinib was rapidly absorbed and exhibited an apparent elimination $t_{1/2}$ of 7.9–15.0 h following a single dose, and a mean effective $t_{1/2}$ of 7.5–13.1 h after multiple dosing (Figure 1, Table 1). The C_{max} and AUC_{INF} showed a greater than proportional increase with ascending doses following a single dose of deucravacitinib (up to 10 mg in the SAD cohort) but showed an apparent dose proportionality at doses ≥10 mg. A similar PK profile was seen following multiple doses in the MAD cohort, with dose proportionality at doses ≥4 mg b.i.d. Modest accumulation (1.4–1.9-fold) was observed after multiple dosing, with steady-state reached by day 5, the first day on which C_{min} samples were collected. Urinary recovery of unchanged deucravacitinib was assessed in the SAD cohort only, and ranged from 10% to 15% across all doses; renal clearance of deucravacitinib ranged from 27.5 to 54.2 ml/min across the dose range.

Target engagement and pharmacodynamics

As TYK2 is bound to the IL-12Rb chain, which is used by both IL-12 and IL-23 for signal transduction, an IL-12–dependent assay was used for the direct assessment of the effects of deucravacitinib on IL-12–mediated signaling, and served as a surrogate for IL-23–mediated signaling.[18,34] IL-12-mediated IFNγ production was inhibited by deucravacitinib in a dose- and concentration-dependent manner across all SAD and MAD dose groups, with no observed hysteresis (i.e., no time-dependent change in exposure-response relationship was observed; Figure 2).

Challenge with IFNα-2a

Interferon-responsive genes expression following IFNα-2a challenge

IRG induction began ~3 h following in vivo challenge with a clinical dose of IFNα-2a given 2 h after the morning dose of deucravacitinib or placebo, as demonstrated by induction of the oligoadenylate synthetase-like (OASL) gene, a typical IRG (data not shown). IRG induction was robust in placebo-administered volunteers, with most genes being

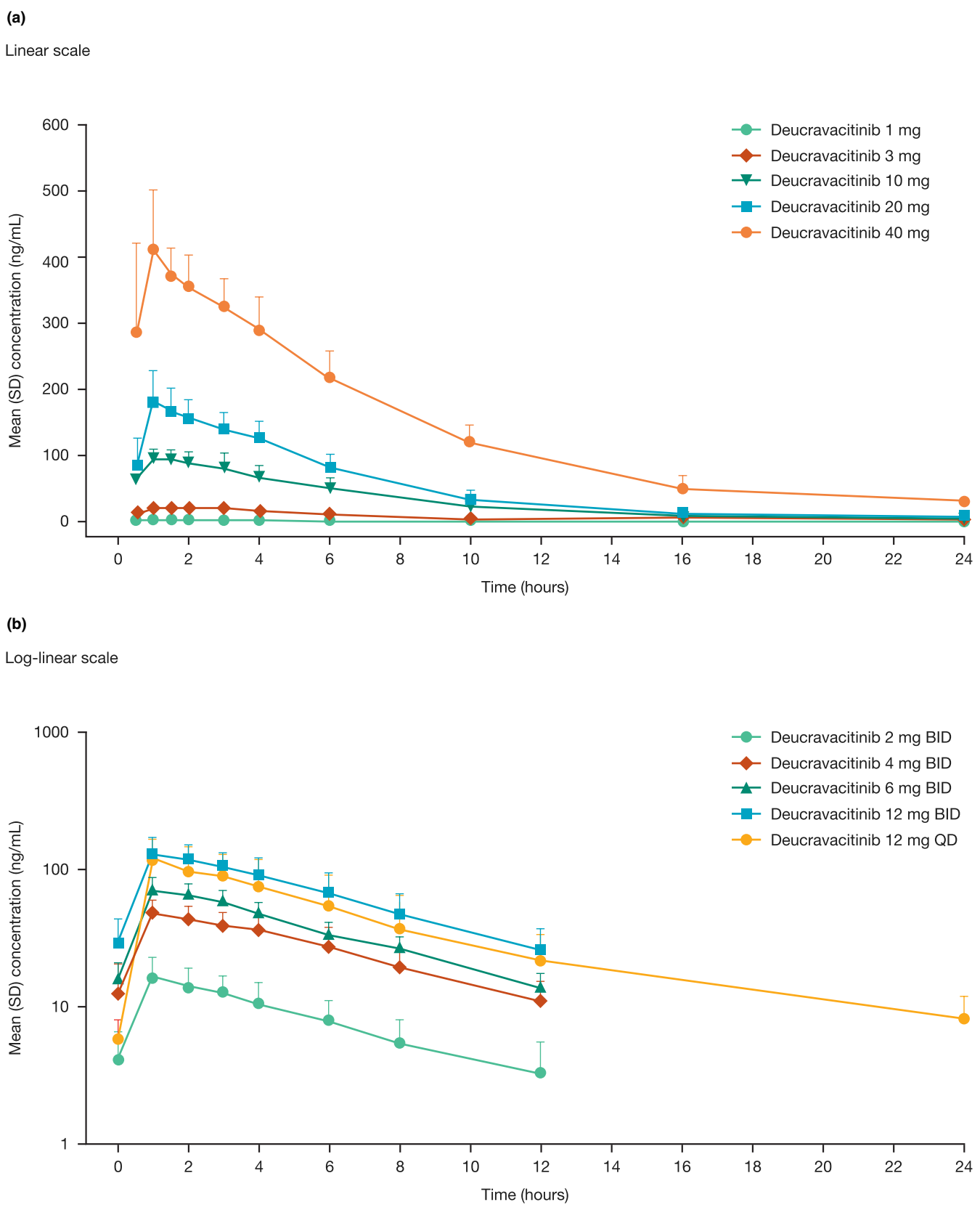

FIGURE 1 Pharmacokinetics of deucravacitinib in healthy subjects (a) over 24 h following administration of a single-dose and (b) over one dosing interval at steady-state on day 12 following multiple-doses. Lower limit of quantitation = 0.200 ng/ml. Error bars represent SD. BD, twice daily; QD, once daily; SD, standard deviation. Panel (b) was previously presented at EULAR 2017 (poster SAT0226); copyright the authors.

TABLE 1 Pharmacokinetics of deucravacitinib following administration of a single dose and at steady-state on day 12 following multiple doses

SAD cohort						
Dose	C_{max}, ng/ml Geo mean (CV%)	T_{max}, h median (min, max)	AUC_{0-t}, Geo mean (CV%)	AUC_{IFN}, ng*h/ml Geo mean (CV%)	CLR	Apparent $t_{1/2}$, h Mean (SD)
1 mg ($n = 6$)	3.33 (18)	2.00 (0.50–4.00)	28.2 (20)	31.6 (18)	54.2 (23)	7.93 (1.94)
3 mg ($n = 6$)	19.6 (21)	1.00 (0.67–2.00)	143 (33)	150 (32)	40.0 (31)	11.0 (2.99)
10 mg ($n = 6$)	102 (9)	1.17 (0.85–1.50)	752 (29)	756 (6)	27.5 (25)	9.87 (3.45)
20 mg ($n = 6$)	185 (23)	1.25 (1.00–2.00)	1175 (20)	1183 (20)	34.2 (21)	14.9 (17.15)
40 mg ($n = 6$)	410 (21)	1.25 (1.00–1.50)	3460 (21)	3473 (21)	28.5 (25)	15.0 (5.83)
MAD cohort						
Dose	C_{max}, ng/ml Geo mean (CV%)	T_{max}, h Median (min, max)	C_{avg}, ng/mlGeo mean (CV%)	AUC_{TAU}, ng*h/ml Geo mean (CV%)	AI AUC mean	Effective $t_{1/2}$, h Mean (SD)
2 mg b.i.d. ($n = 8$)	15.2 (40)	1 (1–3)	7.59 (43)	90.5 (43)	1.60	8.63 (2.91)
4 mg b.i.d. ($n = 8$)	49.6 (21)	1 (1–2)	26.5 (29)	315 (29)	1.85	10.7 (2.68)
6 mg b.i.d. ($n = 8$)	70.0 (26)	1 (1–2)	36.0 (23)	429 (23)	1.50	9.12 (1.89)
12 mg b.i.d. ($n = 8$)	126 (30)	1 (1–2)	66.2 (34)	789 (34)	1.49	7.46 (1.97)
12 mg q.d. ($n = 8$)	117 (38)	1 (1–3)	33.6 (37)	803 (37)	1.39	13.1 (4.71)

Abbreviations: AI, accumulation index; AUC, area under the curve; AUC_{0-t}, AUC from $t = 0$ to the last estimable timepoint; AUC_{TAU}, area under the curve for one dosing interval; AUC_{IFN}, AUC to infinity; b.i.d., twice daily; CLR, renal clearance; C_{avg}, average concentration; C_{max}, maximum concentration; CV, coefficient of variation; Geo, geometric; h, hours; MAD, multiple-ascending dose; Max, maximum; Min, minimum; q.d., once daily; SAD, single-ascending dose; SD, standard deviation; $t_{1/2}$, terminal half-life; T_{max}, time to peak concentration.

induced by more than 10-fold. Of the 53 target genes assessed, 52 were included in the analysis, as complement component 1q (C1Q) was found not to be induced immediately by IFN administration but was induced at the 26-h timepoint, and thus was considered unlikely to be a direct target for IFN-induced gene expression. Compared with the placebo group, the expression of all 52 genes included in the aggregation was robustly inhibited in a dose-dependent manner by prior administration of deucravacitinib (Figure 3); C1Q expression was inhibited 26 h after challenge. Exposures of IFNα-2a increased in a deucravacitinib dose-dependent manner, thus, consumption of IFNα-2a was inhibited by blocking signal transduction. This paradoxical increase in IFNα-2a appears to be an additional PD measure of deucravacitinib (data not shown).

Physiological effects of IFNα-2a challenge

Following administration of IFNα-2a, induction of physiological markers (i.e., increased body temperature, heart rate, and blood pressure), decreases in circulating lymphocyte counts, and increases in monocyte and granulocyte counts were seen (data not shown). Deucravacitinib inhibited the IFN-mediated decrease in lymphocytes seen in placebo-administered volunteers in a robust and dose-dependent manner (Figure 4). Effects on monocyte and granulocyte counts were modest and not dose responsive (data not shown).

Safety

In the SAD cohort, AEs were reported in 11 volunteers (36.7%) who received deucravacitinib and four volunteers (40%) who received placebo; the most frequently reported AE by preferred term was headache (deucravacitinib: 5 volunteers, 16.7%; placebo: 2 volunteers, 20.0%). A total of seven (23.3%) gastrointestinal disorder AEs (system order class) were reported in volunteers receiving deucravacitinib versus no volunteers in the placebo group, with the most common being dyspepsia reported in three volunteers (10%). All AEs were mild in severity, with the exception of one event of presyncope of moderate severity in the placebo group. The most common all-cause AEs in the SAD cohort are summarized in Table 2.

In the MAD cohort, all AEs were mild to moderate in severity, and the overall frequency of AEs was similar in the deucravacitinib (37 volunteers, 82%) and placebo (13 volunteers, 87%) groups. For the deucravacitinib and placebo groups, respectively, the most frequently reported AEs by preferred term were headache (11 volunteers,

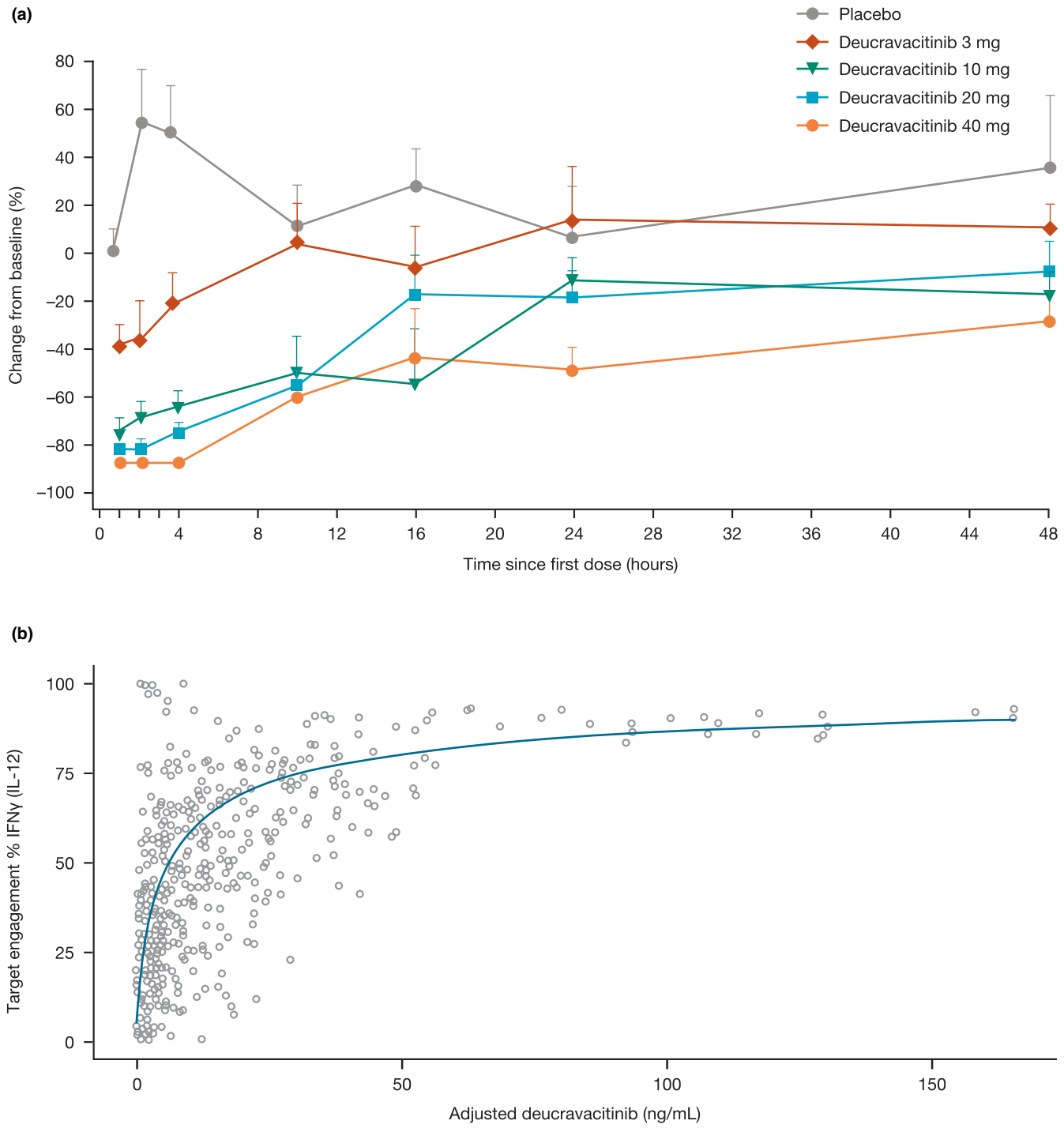

FIGURE 2 (a) Mean IFNγ production over time following stimulation with IL-12 (plus IL-18 adjuvant; single-ascending dose cohort). (b) Relationship between target engagement, measured as inhibition of IL-12/IL-18–mediated IFNγ production, and steady-state plasma concentration of deucravacitinib (multiple-ascending dose cohort). Adjusted concentration is shown as a three-fold dilution of the blood sample was performed prior to ex vivo stimulation. IFN, interferon; IL, interleukin. Panel b has been adapted from a figure that was previously presented at EULAR 2017 (poster SAT0226); copyright the authors.

24.4%; 5 volunteers, 33.3%), rash (9 volunteers, 20%; 2 volunteers, 13.3%), upper respiratory tract infection (8 volunteers, 17.8%;. 3 volunteers, 20.0%), acne (6 volunteers, 13.3%; 0 volunteers), and nausea (6 volunteers, 13.3%; 2 volunteers, 13.3%). The most common all-cause AEs in the MAD cohort are summarized in Table 2. All AEs resolved except for one case of urticaria of moderate severity, which occurred in the deucravacitinib 6 mg b.i.d. group, and was considered unrelated to study treatment. A total of seven volunteers discontinued due to AEs: six

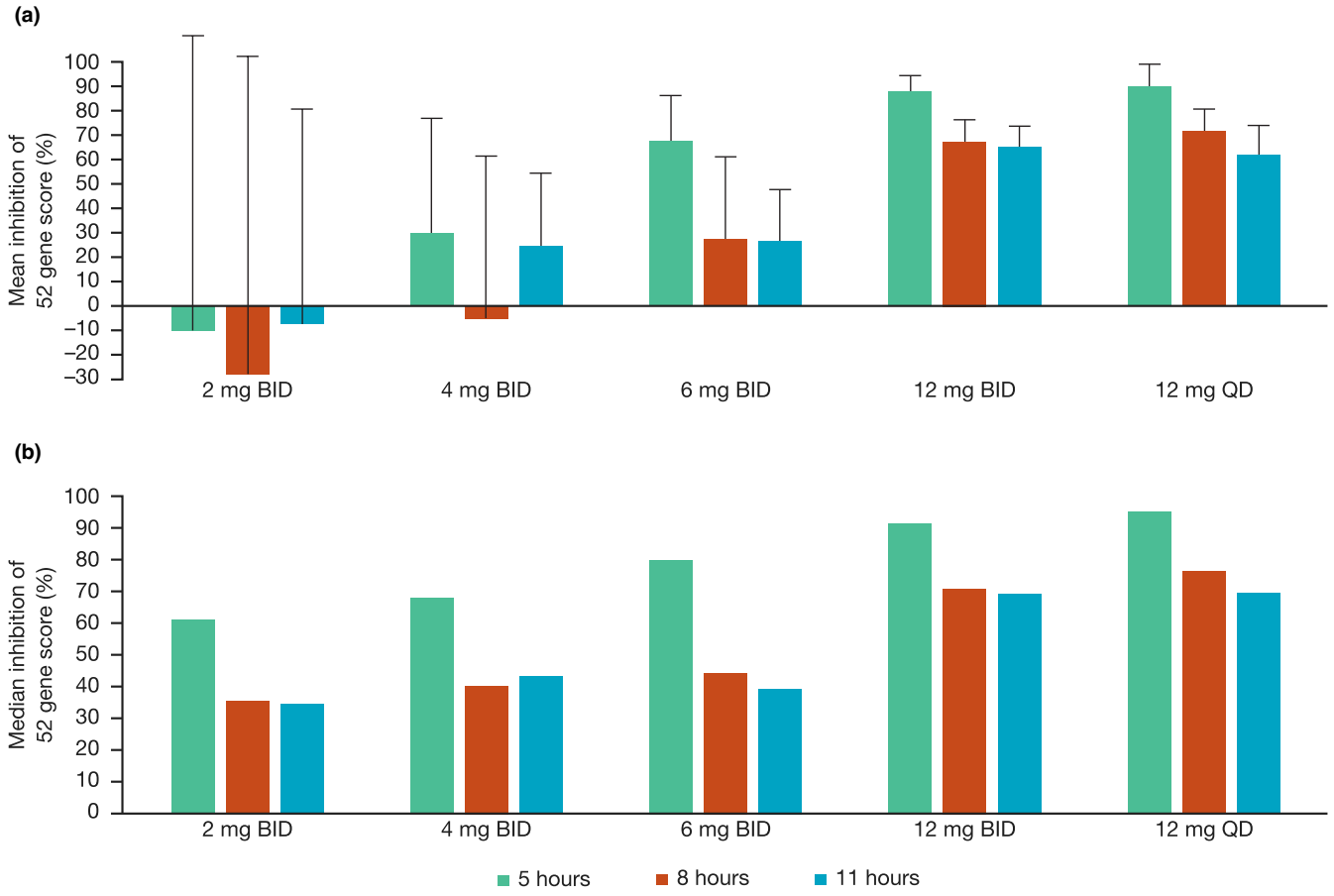

FIGURE 3 Deucravacitinib inhibition of IFN-regulated gene expression after IFNα-2a challenge, based on an aggregated panel of 52 selected genes. (a) Mean percentage of inhibition, (b) Median percentage of inhibition. Error bars represent standard error of the mean. BID, twice daily; IFN, interferon; QD, once daily. Previously presented at EULAR 2017 (poster SAT0226); copyright the authors.

following administration of deucravacitinib (2 mg b.i.d.: 1 volunteer, chest pain; 4 mg b.i.d.: 1 volunteer, rash; 6 mg b.i.d.: 2 volunteers, urticaria; 12 mg b.i.d.: 1 volunteer, tonsillitis; 12 mg q.d.: 1 volunteer, furuncle) and one volunteer in the placebo group (decreased consciousness).

Deucravacitinib was associated with an increased incidence of skin rashes and acne- and urticaria-like skin reactions versus placebo, particularly at the highest dosage of 24 mg/day (12 mg b.i.d. dose panel). Skin rash/acne AEs were of mild or moderate severity, responded well to topical treatment (corticosteroid cream for urticaria-like rash and benzoyl peroxide cream, clindamycin solution, or chlorhexidine ointment for acne) if required, and rarely led to discontinuation.

White blood cell counts were monitored by a standard automated cell count and further enumeration of major white blood cell populations using TBNK flow cytometry identified no abnormalities in T, B, or natural killer (NK) cell subsets following exposure to deucravacitinib (data not shown).

There were no dose-related trends in the occurrence of any clinical laboratory marked abnormalities or ECG abnormalities, including out-of-range ECG intervals, in any part of the study, and no effect of deucravacitinib on heart rate or body temperature was observed.

DISCUSSION

This was the first-in-human study of deucravacitinib, and the dose range selected for investigation in this trial was expected to provide a broad range of exposures and target engagement, projected from animal PK studies, the in vitro PK/target engagement relationship, and the safety margins established from animal toxicology studies. In healthy volunteers, deucravacitinib showed predictable PK, with PD effects and inhibition of IRG expression following dosing.

Following oral administration as a liquid formulation, deucravacitinib was rapidly absorbed into the systemic circulation and steady-state was achieved within 5 days, which was the earliest timepoint that trough samples were collected in volunteers in the MAD cohort. Steady-state is likely to have been achieved earlier based on the drug's half-life. Peak plasma concentrations

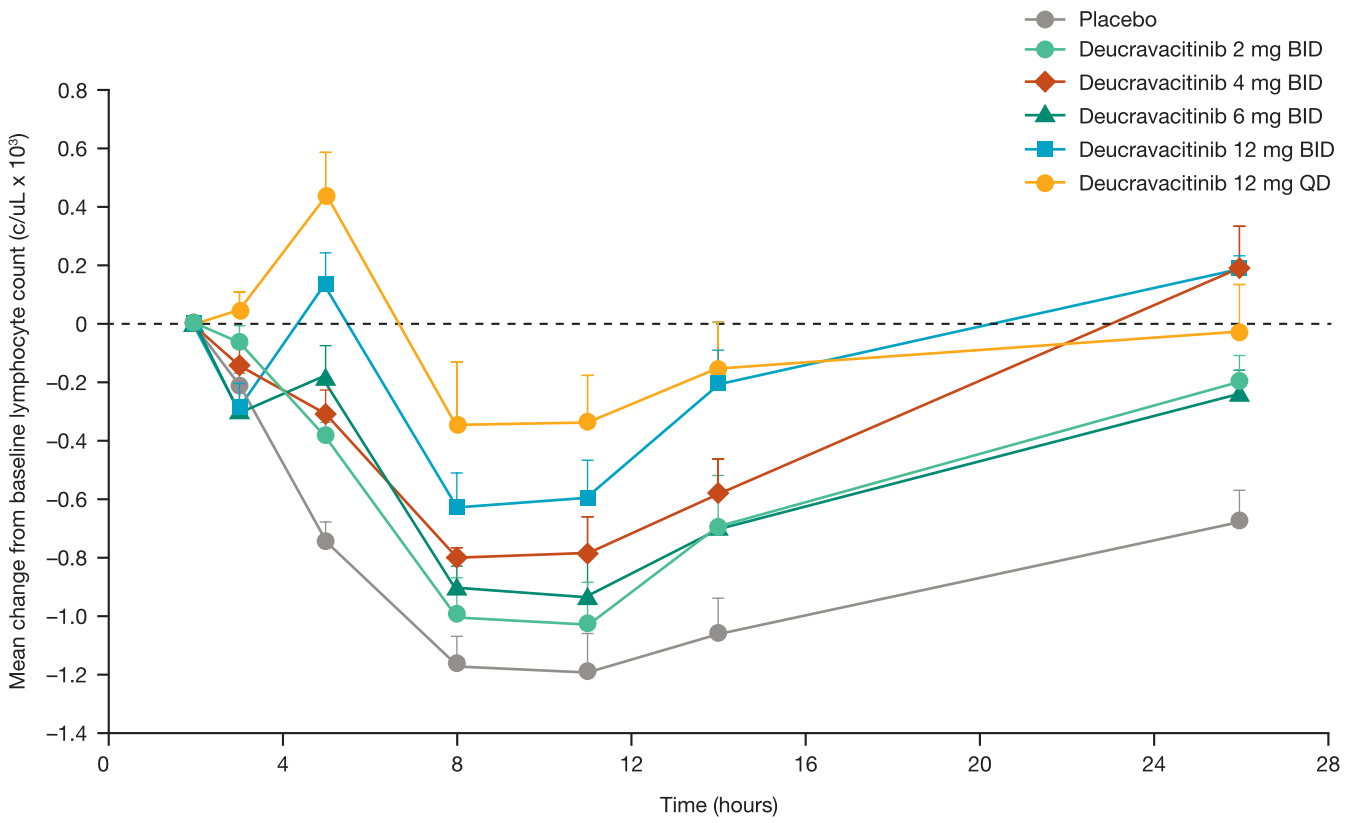

FIGURE 4 Changes in lymphocyte count upon in vivo IFNα-2a challenge. Error bars represent standard error of the mean. BID, twice daily; IFN, interferon; QD, once daily. Previously presented at EULAR 2017 (poster SAT0226); copyright the authors.

and deucravacitinib exposure increased in a more than dose-proportional manner at lower dosages, and dose-proportional at single dosages above 10 mg, or at dosages above 4 mg b.i.d. following repeat dosing. Consistent with the dose proportionality observations, the incremental difference in apparent clearance reduced with increasing dosage. The mechanism behind these observations is unknown at this time, but these findings related to saturation of an efflux drug transporter, such as P-glycoprotein, at the intestinal epithelium above a certain dosage. However, as this study was not designed nor powered to measure dose proportionality, this should be interpreted with caution.

The ability of deucravacitinib to inhibit TYK2 signaling was assessed by investigating the effects on ex vivo IL-12-induced IFNγ production and effects on IFNα-induced gene expression. A common issue with studies of immunomodulatory molecules in healthy volunteers is the fact that the pathways of interest are not active. The typical approach is to stimulate blood samples ex vivo with agonists for the pathways of interest and to measure a convenient outcome. In this healthy population, deucravacitinib demonstrated potent inhibition of IL-12–mediated IFNγ production in ex vivo assessments.

In addition to this approach, in vivo physiologic effects and molecular responses were assessed to provide additional confidence that the target would be effectively inhibited. Prior administration of deucravacitinib inhibited IFNα-regulated gene induction following in vivo challenge with IFNα-2a in a dose- and concentration-dependent manner, and IFNα-2a-induced reductions in lymphocyte counts were also inhibited by deucravacitinib in a robust manner across all dosages tested. This finding is of particular interest with respect to SLE and other autoimmune diseases; in SLE, IFNα promotes lymphocyte migration to the lymph nodes,[35,36] thereby decreasing counts in peripheral blood, resulting in lymphopenia. Further, SLE is characterized by a highly elevated expression of IRGs, which is thought to be of pathophysiologic importance. Thus, deucravacitinib inhibited the induction of two hallmarks of SLE disease. Although this approach may seem somewhat artificial, it is known that a lupus-like reaction can be elicited in patients receiving IFNα as a therapy for other diseases (e.g., cancer or hepatitis C infection). Inhibition of IRG expression has been demonstrated in SLE and is associated with clinical response.[11,37,38] This approach provides a rigorous test for the compound and support for the dosages assessed in phase II.

Deucravacitinib was generally well-tolerated in single and multiple doses administered for up to 12 days. All AEs were mild to moderate in severity, and no serious or severe

TABLE 2 Summary of all-cause adverse events by system order class and preferred term

SAD cohort	Any deucravacitinib ($n = 30$)	Placebo ($n = 10$)	Deucravacitinib				
			1 mg ($n = 6$)	3 mg ($n = 6$)	10 mg ($n = 6$)	20 mg ($n = 6$)	40 mg ($n = 6$)
Total volunteers with any event	11 (36.7)	4 (40.0)	1 (16.7)	3 (50.0)	3 (50.0)	0	4 (66.7)
Nervous system disorders	5 (16.7)	3 (30)	0	2 (33.3)	1 (16.7)	0	2 (33.3)
Headache	5 (16.7)	2 (20)	0	2 (33.3)	1 (16.7)	0	2 (33.3)
Gastrointestinal disorders	7 (23.3)	0	0	2 (33.3)	3 (50.0)	0	2 (33.3)
Dyspepsia	3 (10)	0	0	1 (16.7)	1 (16.7)	0	1 (16.7)
Constipation	2 (6.7)	0	0	0	1 (16.7)	0	1 (16.7)
Nausea	2 (6.7)	0	0	1 (16.7)	0	0	1 (16.7)
Skin and subcutaneous tissue disorders	2 (6.7)	1 (10)	1 (16.7)	0	0	0	1 (16.7)
Respiratory, thoracic, and mediastinal disorders	1 (3.3)	1 (10)	0	0	1 (16.7)	0	0
Cardiac disorders	1 (3.3)	0	0	0	0	0	1 (16.7)
Musculoskeletal and connective tissue disorders	1 (3.3)	0	0	1 (16.7)	0	0	0
Reproductive system and breast disorders	0	1 (10)	0	0	0	0	0

MAD cohort	Any deucravacitinib ($n = 45$)	Placebo ($n = 15$)	Deucravacitinib				
			2 mg b.i.d. ($n = 9$)	4 mg b.i.d. ($n = 9$)	6 mg b.i.d. ($n = 9$)	12 mg b.i.d. ($n = 9$)	12 mg q.d. ($n = 9$)
Total volunteers with any event	37 (82.2)	13 (86.7)	7 (77.8)	8 (88.9)	5 (55.6)	9 (100)	8 (88.9)
Nervous system disorders	15 (33.3)	8 (53.3)	2 (22.2)	3 (33.3)	3 (33.3)	2 (22.2)	5 (55.6)
Headache	11 (24.4)	5 (33.3)	1 (11.1)	3 (33.3)	3 (33.3)	1 (11.1)	3 (33.3)
Dizziness	2 (4.4)	2 (13.3)	1 (11.1)	0	0	0	1 (11.1)
Presyncope	1 (2.2)	2 (13.3)	0	0	0	0	1 (11.1)
Skin and subcutaneous tissue disorders	19 (42.2)	4 (26.7)	0	4 (44.4)	3 (33.3)	7 (77.8)	5 (55.6)
Rash	9 (20.0)	2 (13.3)	0	2 (22.2)	1 (11.1)	2 (22.2)	4 (44.4)
Acne	6 (13.3)	0	0	0	1 (11.1)	5 (55.6)	0
Gastrointestinal disorders	17 (37.8)	3 (20.0)	6 (66.7)	1 (11.1)	3 (33.3)	5 (55.6)	2 (22.2)
Nausea	6 (13.3)	2 (13.3)	3 (33.3)	0	1 (11.1)	0	2 (22.2)
Abdominal pain	4 (8.9)	1 (6.7)	1 (11.1)	1 (11.1)	0	2 (22.2)	0
Diarrhea	3 (6.7)	1 (6.7)	2 (22.2)	0	0	1 (11.1)	0
Dyspepsia	2 (4.4)	1 (6.7)	2 (22.2)	0	0	0	0

(Continues)

TABLE 2 (Continued)

MAD cohort	Any deucravacitinib ($n = 45$)	Placebo ($n = 15$)	Deucravacitinib				
			2 mg b.i.d. ($n = 9$)	4 mg b.i.d. ($n = 9$)	6 mg b.i.d. ($n = 9$)	12 mg b.i.d. ($n = 9$)	12 mg q.d. ($n = 9$)
Infections and infestations	11 (24.4)	3 (20.0)	1 (11.1)	4 (44.4)	1 (11.1)	3 (33.3)	2 (22.2)
Upper respiratory tract infection	8 (17.8)	3 (20.0)	1 (11.1)	3 (33.3)	1 (11.1)	2 (22.2)	1 (11.1)
General disorders	9 (20.0)	4 (26.7)	3 (33.3)	0	0	4 (44.4)	2 (22.2)
Influenza-like illness	2 (4.4)	2 (13.3)	1 (11.1)	0	0	1 (11.1)	0
Fatigue	1 (2.2)	2 (13.3)	1 (11.1)	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	6 (13.3)	2 (13.3)	2 (22.2)	1 (11.1)	0	3 (33.3)	0
Oropharyngeal pain	3 (6.7)	1 (6.7)	1 (11.1)	1 (11.1)	0	1 (11.1)	0
Musculoskeletal and connective tissue disorders	3 (6.7)	1 (6.7)	0	0	0	2 (22.2)	1 (11.1)

Note: All values are *n* (%). All events are reported by system order class. Events occurring in >1 volunteer in the SAD cohort or >2 volunteers in the MAD cohort by preferred term are reported.

Abbreviations: b.i.d., twice daily; MAD, multiple-ascending dose; q.d., once daily; SAD, single-ascending dose.

AEs occurred during the study. Among volunteers in the MAD cohort receiving the highest dosage of deucravacitinib (12 mg b.i.d.), 80% had AEs of mild-to-moderate severity skin rashes or skin reactions that were managed with topical treatments.

The PK profile of deucravacitinib indicates that it is readily absorbed following oral administration, and elicits PD effects over 24 h, allowing for daily dosing. Further, because of the relationship between deucravacitinib PK and PD, low daily doses are sufficient to provide varying amounts of inhibition at trough level and elicit a sustained pharmacologic effect. Prolonged PD is expected in some of the targeted pathways (e.g., IL-23 signaling) and is observed in patients with psoriasis treated with risankizumab.[39]

Deucravacitinib was associated with robust inhibition of signaling pathways downstream of receptors for the inflammatory cytokines IL-12/IL-23 and type I IFN and was generally well-tolerated in this healthy population following single and multiple doses up to 12 days. One phase II and two phase III studies of deucravacitinib in patients with moderate-to-severe psoriasis have been reported,[28-30] leading to FDA approval for adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1] Along with the results reported here, these findings support further evaluation of deucravacitinib in other immune-mediated diseases; in addition to the phase II results in patients with active psoriatic arthritis,[24] deucravacitinib recently showed clinical efficacy and was generally well-tolerated in a phase II study in patients with SLE.[40]

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript, designed the research, and analyzed the data. I.M.C., U.A., L.H., Y.L., and I.G.G. performed the research.

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CONFLICT OF INTEREST

I.M.C., U.A., I.G.G., and B.M. are employees of Bristol Myers Squibb and receive salaries and stock commensurate with employment. L.H., Y.L., and D.B. were employees of Bristol Myers Squibb at the time this research was conducted.

DATA AVAILABILITY STATEMENT

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html.

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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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