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ARTICLE

Pharmacokinetics, safety, and efficacy of cedirogant from phase I studies in healthy participants and patients with chronic plaque psoriasis

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Abstract

Cedirogant is an inverse agonist of retinoic acid-related orphan receptor gamma thymus (RORγt) developed for the treatment of moderate to severe chronic plaque psoriasis. Here, we report the results from two phase I studies in which the pharmacokinetics (PK), safety, and efficacy of cedirogant in healthy participants and patients with moderate to severe chronic plaque psoriasis were evaluated. The studies consisted of single (20–750 mg) and multiple (75–375 mg once-daily [q.d.]) ascending dose designs, with effect of food and itraconazole on cedirogant exposure also evaluated. Safety and PK were evaluated for both healthy participants and psoriasis patients, and efficacy was assessed in psoriasis patients. Following single and multiple doses, cedirogant mean terminal half-life ranged from 16 to 28 h and median time to reach maximum plasma concentration ranged from 2 to 5 h across both populations. Cedirogant plasma exposures were dose-proportional after single doses and less than dose-proportional from 75 to 375 mg q.d. doses. Steady-state concentrations were achieved within 12 days. Accumulation ratios ranged from approximately 1.2 to 1.8 across tested doses. Food had minimal effect and itraconazole had limited impact on cedirogant exposure. No discontinuations or serious adverse events due to cedirogant were recorded. Psoriasis Area and Severity Index (PASI) and Self-Assessment of Psoriasis Symptoms (SAPS) assessments demonstrated numerical improvement with treatment of cedirogant 375 mg q.d. compared with placebo. The PK, safety, and efficacy profiles of cedirogant supported advancing it to phase II clinical trial in psoriasis patients.

Roberto Carcereri De Prati: No longer employed by Abbvie, but contributed to this work at the time of his employment.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

The interleukin (IL)-23/IL-17 signaling pathway plays a pivotal role in the pathogenesis of psoriasis. Retinoic acid-related orphan receptor gamma thymus (RORγt) is a key transcription factor responsible for IL-17 synthesis, and RORγt expression is driven by IL-23. Therapeutics that target RORγt have the potential to provide a unique mechanism for intervention in this pathway for the treatment of psoriasis.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study assessed, for the first time, the pharmacokinetics (PK), safety, and efficacy of cedirogant, an inverse agonist of RORγt, in healthy participants and psoriasis patients. This study also evaluated the effect of co-administration of food or CYP3A inhibitors on cedirogant plasma exposures.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Cedirogant plasma exposures were dose-proportional after single doses and less than dose-proportional after multiple daily doses between 75 and 375 mg. The observed PK profiles support once-daily dosing of cedirogant. No relevant food effect and limited effect from CYP3A inhibitors on cedirogant exposure are expected. Cedirogant was well tolerated for the doses and duration tested in the study. Numerically greater efficacy of cedirogant relative to placebo was observed in psoriasis patients.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE

This study provides the first characterization of the PK, safety, and efficacy of cedirogant, an oral inverse agonist of RORγt. The reported results can help inform future development for drugs with similar mechanism of action.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that is prevalent in approximately 3% of adults in the United States.[1] Psoriasis impacts all facets of an individual's quality of life and significant investments in measuring these improvements in addition to physical improvements have advanced our ability to assess clinical benefits from therapeutic treatments.[2–4] It has been shown that an increased level of interleukin-17 (IL-17) plays an essential role in the pathogenesis of psoriasis.[5] IL-17 is produced by T helper 17 (Th17) cells in response to IL-23. Therefore, disruption of the IL-23/IL-17 signaling pathway is expected to provide therapeutic benefits to patients with psoriasis. Such benefits have been confirmed by the Food and Drug Administration approval of biologics targeting either the IL-17 (e.g., secukinumab,[6] ixekizumab,[7] and brodalumab[8]) or the upstream IL-23 (e.g., tildrakizumab,[9] guselkumab,[10] and risankizumab[11]) for the treatment of psoriasis. Neutralization or blockade of IL-17 secretion by biologics has demonstrated robust efficacy[12]; however, no clinical response within the initial treatment timeframe, loss of drug effectiveness after initial remission, and the length of time until discontinuation of a drug remains a challenge for these biologics.[13,14] Furthermore, patient adherence, accessibility, and reluctance due to concern about potential side effects of biologics prevent systemic treatment, leaving patients undertreated.[15,16] Thus, there remains an unmet need for therapeutic intervention of the Th17 cell lineage with an orally bioavailable, small molecule medication.

Retinoic acid-related orphan receptor gamma thymus (RORγt) is a key transcription factor responsible for IL-17 synthesis in vivo and the master regulator of the Th17 cell lineage program.[17] RORγt expression is driven by IL-23 and directly supports IL-17 production in multiple immune cell types, particularly Th17 cells; thus, RORγt bridges the gap between these two important cytokines. Targeting RORγt has the potential to directly block cellular function (i.e., RORγt-dependent genes), a different strategy from the neutralization of effector molecules (such as IL-17 and IL-23) by biologics.[18,19]

Cedirogant is an inverse agonist of RORγt developed for the treatment of psoriasis. Here, we report results from the first-in-human single-ascending dose (SAD) and multiple-ascending dose (MAD) studies in healthy

participants and a multiple-dose study in patients with chronic plaque psoriasis, which evaluated the pharmacokinetics (PK), safety and tolerability, and preliminary efficacy of cedirogant. Food effect and drug–drug interaction (DDI) of cedirogant with itraconazole are also reported.

METHODS

Study designs

Two clinical studies were conducted (Study 1 and Study 2). Study 1 was conducted between November 07, 2018 and May 5, 2019; Study 2 was conducted between June 11, 2019 and April 13, 2021. The studies reported herein were conducted in accordance with the International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. The study protocols were approved by the Institutional Review Boards/Ethics Committees boards (Study 1: Quorum, Seattle, WA, USA; Study 2: Quorum, Seattle, WA, USA and Advarra, Columbia, MD, USA) of the study sites (see Table S1), and all the participants gave written informed consent prior to participation in the studies.

Study 1 was a first-in-human, randomized, double-blind, placebo-controlled, single-center study of single-ascending oral doses of cedirogant (Study 1A) and an open-label food effect/DDI study (Study 1B) in healthy participants. In Study 1A, single oral doses of 20, 75, 225, 395, and 750 mg cedirogant were administered in five dosing groups (Groups 1–5, respectively) consisting of eight participants each. Within each group, participants were randomized to receive cedirogant at the specified dose or matching placebo in a 3:1 ratio. Participants received study drug after a minimum of 10 h fasting and approximately 4 h before lunch.

The cedirogant dose range evaluated in Study 1A (20–750 mg) was based on in vitro and in vivo pharmacology, and preclinical toxicology studies. These data supported the human PK projections, predicted human efficacious doses, and calculations of safety margins relative to exposures which were found to be safe in preclinical species.

In Study 1B, food effect (Periods 1 and 2, crossover design) and DDI with itraconazole (Period 3) were evaluated in an additional 12 participants. Participants received a single dose of 225 mg cedirogant under either fasting or non-fasting (with a high-fat breakfast) conditions in either Period 1 or Period 2 depending on the randomized sequence. In Period 3, all participants received itraconazole 200 mg twice on Day 1 followed by 200 mg once-daily (q.d.) for 7 days using itraconazole oral solution (10 mg/mL). A single dose of 225 mg cedirogant was administered under fasting conditions on Day 4. A 7-day washout separated the three study periods. The 225 mg cedirogant dose was selected based on predicted pharmacologic activity and to maintain exposures within the range explored in Study 1A in the case that food effect or a DDI led to increased cedirogant exposures.

Study 2 was a randomized, double-blind, placebo-controlled evaluation of multiple oral doses of cedirogant in healthy adult participants (Study 2A) and in patients with moderate to severe chronic plaque psoriasis (Study 2B). Study 2A was conducted in three sequential groups (Groups 1–3; $N=12$ per group) in which healthy participants in each dose group (75, 225, or 375 mg, respectively) were randomized in a 3:1 ratio to receive cedirogant or placebo, respectively, q.d. for 14 consecutive days. Dose selection for this study was based on observed PK, pharmacodynamic, and safety results from Study 1, findings from preclinical studies, and accounting for potential accumulation with multiple daily dosing. In Study 2B, patients were randomized in a 2:1 ratio to receive 375 mg q.d. cedirogant or placebo, respectively, for 28 consecutive days and total enrollment was capped at 30 patients. Study 2B was designed as an exploratory, proof-of-concept study, and a total sample size of 30 patients was deemed to be sufficient to gain an understanding of the safety, PK, biomarkers, and early efficacy outcomes in this patient population.

In Study 2A, standard meals were provided to participants, and the study drug was administered under non-fasting conditions. In Study 2B, drug was administered without regard to food except on Days 1 and 28 (intensive PK assessment days), on which patients were fasted for at least 8 h before and 1 h after dosing. Participants in Study 1 and Study 2A were confined at the clinical sites throughout the study period. Psoriasis patients in Study 2B were not confined, and patients visited the clinical sites on study Days 1, 2, 7, 14, 21, 28, 29, and 38. A schematic of the study designs is provided in Figure S1.

Participants

Healthy male and female adult participants in the two phase I studies were eligible to enroll if they were 18–55 years of age inclusive, with a body mass index (BMI) within 18.0–29.9 kg/m^2 and judged to be in good general health. Male and female adult patients with chronic plaque psoriasis in Study 2 were eligible to enroll if they were 18–75 years of age inclusive; had a BMI within 18.0–40.0 kg/m^2 at screening; had a clinical

diagnosis of moderate to severe chronic plaque psoriasis for at least 6 months; had a Psoriasis Area and Severity Index (PASI) score of ≥12, a static Physician's Global Assessment (sPGA) score ≥3, a body surface area (BSA) affected by psoriasis ≥10%; and had discontinued use of treatment for chronic plaque psoriasis for topical therapies at least 2 weeks prior to Day 1, phototherapy at least 2–4 weeks prior to Day 1, and systemic therapies at least 4 weeks prior to Day 1. Participants had to be candidates for systemic therapy defined as having moderate to severe chronic plaque psoriasis considered inadequately controlled by topical treatments, and/or phototherapy, and/or previous systemic therapy. Topical therapies were not allowed over the study period in Study 2B. Additional eligibility criteria are provided in the Supplemental Methods.

PK sampling and bioanalytical methods

In Study 1, intensive PK blood samples for cedirogant assay were collected prior to dosing (0 h) and at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16, 24, 36, 48, 72, 96, and 120 h (only collected in Study 1B) after single-dose administration. Intensive PK sampling days were Day 1 for Study 1A and Study 1B (Period 1 and 2) and Day 4 for Study 1B (Period 3). Additional PK samples were collected to assess trough concentrations on all study days following the intensive PK sampling day.

In Study 2A, intensive PK blood samples were collected on Days 1, 7, and 14 prior to dosing (0 h) and at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 16, and 24 h after dose administration. Additional blood samples were collected on Day 14 at 48, 72, 96, and 120 h after dose administration and on Days 5–6, 10, and 12–13 prior to dosing. Urine samples for cedirogant analysis were also collected on Days 14 and 15 (see Supplemental Materials). For Study 2B, intensive PK blood samples were collected on Days 1 and 28 prior to dosing (0 h) and at 1, 2, 3, 4, 5, 6, and 24 h after dose administration. Additional PK blood samples were collected on Days 7, 14, and 21 prior to dosing.

Plasma concentrations of cedirogant were determined using a validated liquid chromatography method and tandem mass spectrometry detection (LC–MS/MS). Additional information on blood sample collection and analysis can be found in the Supplemental Methods.

Efficacy and safety assessments

Efficacy was evaluated in patients with moderate to severe chronic plaque psoriasis in Study 2B by assessing the percentage change from baseline (Day 1) of the Psoriasis Area and Severity Index (PASI) score to Days 7, 14, 21, and 28. Changes in Self-Assessment of Psoriasis Symptoms (SAPS)[20] score were calculated from values obtained on Days 1, 14, and 28.

Safety was monitored throughout the studies with clinical and laboratory evaluations including collection of adverse events (AEs), physical examinations, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory testing, and ophthalmologic evaluation. Treatment-emergent AEs (TEAEs; i.e., any event that began or worsened in severity after initiation of study drug through 30 days post-study drug dosing) were tabulated by the primary System Organ Class and MedDRA preferred term with a breakdown by dose level. TEAEs considered by the investigator to have reasonable possibility of relationship to study drug or no reasonable possibility of relationship to study drug are referred to as "study drug-related" or "not study drug-related," respectively.

PK and statistical analyses

PK parameters of cedirogant were determined using non-compartmental analyses with Phoenix software (Certara). The calculated parameters included maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), trough plasma concentration (C_{trough}; for Study 2), area under the plasma concentration–time curve (AUC) (from time 0 to the time of the last measurable concentration [AUC_{last}] and from time 0 to infinite time [AUC_{inf}] for single doses, and over a 24-h dosing interval [$AUC_{0\text{-}24}$] for multiple doses), apparent oral clearance (CL/F), and terminal elimination half-life ($t_{1/2}$). For Study 2, PK analyses were performed on data collected from Days 1, 7, and 14 for healthy participants and Day 1 and 28 for patients with psoriasis. Accumulation ratios for C_{max} and $AUC_{0\text{-}24}$ were calculated as the ratios of respective parameter values on last dosing day (Day 14 for Study 2A and Day 28 for Study 2B) to Day 1.

Statistical analyses were performed using SAS (SAS Institute Inc.). Dose proportionality of cedirogant was assessed using an ANCOVA on the PK parameters. Analyses were performed on the natural logarithms of dose-normalized C_{max}, dose-normalized AUC_{last}, and dose-normalized AUC_{inf} for Study 1, and on the natural logarithms of dose-normalized C_{max}, C_{trough}, and $AUC_{0\text{-}24}$ on Day 14 for Study 2A. To assess the attainment of steady state of cedirogant in Study 2A, for each dose group, a repeated measures ANOVA was performed on the pre-dose concentration measurements on Days 2, 5, 6, 7, 8, 10, 12, 13, and 14. To assess the effect of food and co-administration of itraconazole on the bioavailability of cedirogant (Study 1B), a repeated measures ANOVA was performed for the natural logarithms of C_{max}, AUC_{last}, and AUC_{inf}.

RESULTS

Participant demographics and disposition

A summary of participant demographics for the studies reported herein is provided in Table 1. In Study 1, 50 of 51 enrolled participants in the study completed the study; one participant discontinued for unspecified reasons after receiving one dose of cedirogant 225 mg under non-fasting conditions in Study 1B. In Study 2, 35 healthy participants were enrolled into Study 2A, and 34 completed the study. One participant, who received only placebo, prematurely discontinued from the study due to an AE of tooth abscess, assessed as not study-drug related, after dosing on study Day 11. In Study 2B, 30 patients with psoriasis were enrolled, and 26 participants completed the study. Four participants discontinued prematurely due to COVID-19 logistical restrictions ($N=2$; one participant after dosing on Day 17 and the other participant after dosing on Day 23), not meeting eligibility criteria ($N=1$; one participant after dosing on Day 3), and withdrawal of consent ($N=1$, one participant after dosing on Day 9). In addition, one participant received incorrect doses for the first 14 days and another participant had inconsistent documentation of dosing records. Data from these six participants were excluded from efficacy analyses.

PK results

Study 1 (SAD and food effect/DDI)

Data of all participants who received cedirogant ($N=42$) were included in the PK analyses. The mean plasma concentration–time profiles from Study 1A are presented in Figure 1. A summary of the single-dose PK parameters of cedirogant in healthy participants in Study 1A is presented in Table 2. Following single oral doses of cedirogant ranging from 20 to 750 mg, the harmonic mean $t_{1/2}$ ranged from 16 to 23 h and the median T_{max} ranged from 2 to 4 h. Geometric mean (GM; mean, percentage coefficient of variation [%CV]) dose-normalized C_{max} and AUC_{inf} after single-dose administration of cedirogant are presented in Table 2 and Figure 3.

From the SAD data, assessments of dose-proportionality of cedirogant showed that there were no statistically significant trends ($p \geq 0.453$) in any of the dose-normalized PK parameters with cedirogant dose in the range studied (20 to 750 mg). Cedirogant exposures (C_{max} and AUC) increased in a dose-proportional manner across the 20 mg through 750 mg dose range. The ratio (90% confidence interval) for cedirogant C_{max} was 0.843 (0.728–0.982) when administered with a high-fat meal relative to fasting conditions, while there was no change in cedirogant AUC due to high-fat meal administration (Table S2). Co-administration of itraconazole had no effect on cedirogant C_{max} but increased cedirogant AUC by approximately 50% relative to cedirogant administered alone (Table S3).

Study 2 (MAD)

Data of all participants who received cedirogant were included in the PK analyses in healthy participants ($N=27$; Study 2A). Data of all patients with psoriasis who received cedirogant ($N=19$; Study 2B) were included in the PK analyses except for the patient who had inconsistent dosing documentation; thus, data for 18 of 19 patients with psoriasis (Study 2B) were utilized for PK analyses. The mean plasma concentration–time profiles are presented in Figure 2a,b for healthy participants and patients with psoriasis, respectively. A summary of the PK parameters of cedirogant in healthy participants and patients with psoriasis is presented in Table 3. In healthy participants, cedirogant plasma concentrations reached peak levels at approximately 4 to 5 h (mean T_{max}) after dosing, and the harmonic mean $t_{1/2}$ ranged from 26 to 28 h. Repeated measures ANOVA indicated steady-state concentrations in healthy participants were attained by Day 5, Day 2, and Day 12 for the 75, 225, and 375 mg q.d. doses, respectively. Following administration of cedirogant 75 mg through 375 mg q.d. for 14 days to healthy participants, the C_{max} and $AUC_{0\text{-}24}$ median accumulation ratios were ~1.8 for the 75 mg, ~1.4 for the 225 mg, and ~1.2 for the 375 mg (Table 3). In patients with psoriasis, plasma concentrations reached peak levels at approximately 2 h after dosing. The C_{max} and $AUC_{0\text{-}24}$ median accumulation ratios were ~1.2 for patients with psoriasis following administration of 375 mg q.d. cedirogant for 28 days.

The mean dose-normalized C_{max} and $AUC_{0\text{-}24}$ at steady state after multiple-dose administration of cedirogant for healthy participants (Day 14) and psoriasis patients (Day 28) are presented in Figure 3. A statistically significant decreasing trend was observed for dose-normalized $AUC_{0\text{-}24}$ on Day 14 (p-value = 0.002), C_{max} (p-value = 0.002), and C_{trough} (p-value <0.001) across the 75 to 375 mg q.d. range in healthy participants. For the comparison of the 225 mg q.d. dose to the 75 mg q.d. dose, dose-normalized $AUC_{0\text{-}24}$ (p-value <0.001) and C_{max} (p-value =0.045) were statistically significantly lower for the 225 mg q.d. dose; however, there was no statistical difference in dose-normalized $AUC_{0\text{-}24}$ (p-value = 0.367) and C_{max} (p-value = 0.274) for the comparison of the 375 mg q.d. dose to the 225 mg q.d. dose. Dose-normalized C_{trough} was statistically significantly lower (p-value < 0.001) for

TABLE 1 Participant demographics.

	Mean ± SD	Min–Max
Study 1: Single-ascending dose ($N=51$)		
Study 1A: Healthy participants ($N=39$)		
Age (years)	37.6 ± 11.9	20–56
Weight (kg)	74.4 ± 12.6	51.9–101
Height (cm)	174 ± 8.71	154–191
BMI (kg/m^2)	24.4 ± 2.98	19.2–29.9
Sex	29 males (74%), 10 females (26%)	
Race	23 White (59%), 11 Black (28%), 4 Asian (10%), 1 multi-race (3%)	
Study 1B: Food effect/DDI in healthy participants ($N=12$)		
Age (years)	38.9 ± 11.0	26–55
Weight (kg)	78.2 ± 8.53	65.8–93.1
Height (cm)	169 ± 7.14	158–183
BMI (kg/m^2)	27.2 ± 1.97	23.4–29.7
Sex	11 males (92%), 1 females (8%)	
Race	7 White (58%), 4 Black (33%), 1 Multi-race (8%)	
Study 2: Multiple-ascending dose study ($N=65$)		
Study 2A: Healthy participants ($N=35$)		
Age (years)	39.3 ± 9.93	21–56
Weight (kg)	79.5 ± 12.8	56.3–98.2
Height (cm)	174 ± 8.27	158–188
BMI (kg/m^2)	26.1 ± 3.05	19.7–29.9
Sex	30 males (86%), 5 females (14%)	
Race	20 White (57%), 15 Black (43%)	
	Mean ± SD (min–max) Placebo ($N=11$)	**Mean ± SD (min–max) Cedirogant 375 mg QD ($N=19$)**
Study 2B: Patients with moderate to severe psoriasis ($N=30$)		
Age (years)	44.6 ± 17.41 (21–72)	45.4 ± 13.26 (20–65)
Weight (kg)	90.2 ± 15.38 (64.9–119.9)	91.2 ±13.17 (60.8–114.1)
Height (cm)[a]	176.6 ±6.48 (165.1–188.0)	172.0 ± 8.21 (157.0–187.0)
BMI (kg/m^2)[a]	29.1 ± 5.47 (19.9–37.2)	30.6 ± 4.86 (19.6–38.1)
Sex	11 males	17 males, 2 females
Race	10 White (91%), 1 Black (9%)	17 White (89.5%) 2 Black (10.5%)
Baseline BSA with Psoriasis (%)	20.89 ± 15.083 (10.00–64.00)	26.16 ± 15.980 (10.00–70.00)
Baseline sPGA-score	3.09 ± 0.302 (3.00–4.00)	3.37 ± 0.496 (3.00–4.00)
Baseline PASI score	17.69 ± 6.072 (12.4–33.4)[b]	18.23 ± 6.902 (12.0–38.2)[c]
Baseline SAPS score	41.1 ± 19.79 (1–65)[d]	46.6 ± 16.50 (18–67)[e]

Abbreviations: BMI, body mass index; BSA, body surface area; DDI, drug-drug interaction; PASI, Psoriasis Area and Severity Index; QD, once daily; SD, standard deviation; SAPS, Self-Assessment of Psoriasis Symptoms; SD, standard deviation; sPGA, static Physician's Global Assessment.

[a] $N=29$.

[b] $N=11$ total; $N=8$ moderate (PASI < 20), $N=3$ severe (PASI ≥ 20).

[c] $N=13$ total; $N=10$ moderate (PASI < 20); $N=3$ severe (PASI ≥ 20).

[d] $N=11$ total; $N=1$ moderate (PASI < 20); $N=10$ severe (PASI ≥ 20).

[e] $N=13$ total; $N=1$ moderate (PASI < 20); $N=12$ severe (PASI ≥ 20).

the 225 mg q.d. dose compared with the 75 mg q.d. dose. Despite being statistically significant, the difference in mean dose-normalized C_{trough} between 375 and 225 mg q.d. was only 14% (Table 3). Results indicated that cedirogant plasma exposures increased in a less than dose-proportional manner between 75 and 225 mg q.d. but

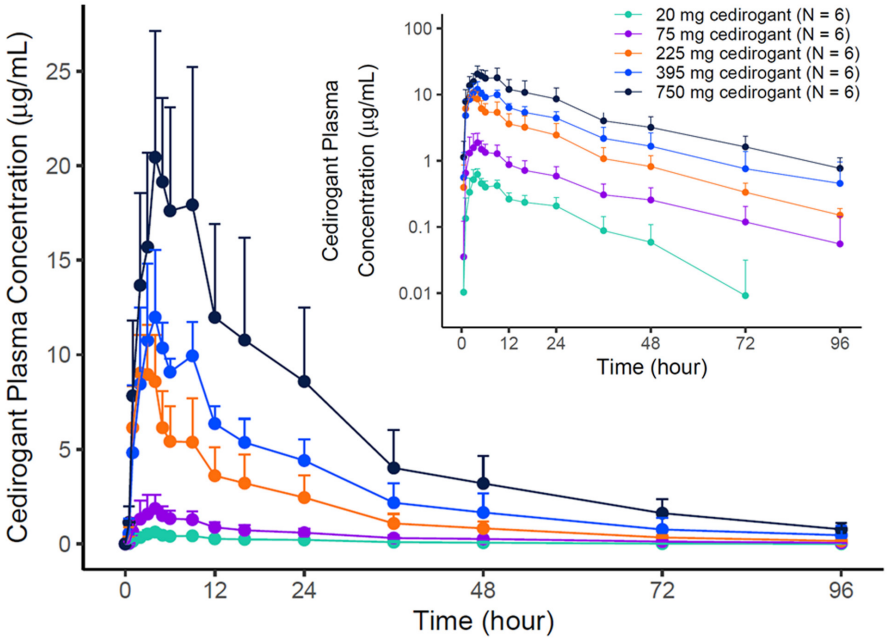

FIGURE 1 Study 1: Cedirogant plasma concentration–time profiles after administration of single-ascending cedirogant doses in healthy participants. Datapoints represent mean (±standard deviation). Inset shows log-linear scale. *N*, number of participants.

TABLE 2 Geometric mean (mean, percentage coefficient of variation) pharmacokinetic parameters of cedirogant after single-ascending doses (Study 1A) under fasting conditions.

PK parameters (units)	Group 1: 20 mg cedirogant	Group 2: 75 mg cedirogant	Group 3: 225 mg cedirogant	Group 4: 395 mg cedirogant	Group 5: 750 mg cedirogant
N	6	6	6	6	6
C_{max} (µg/mL)	0.627 (0.636, 19)	1.74 (1.93, 38)	9.10 (9.35, 26)	13.0 (13.1, 10)	23.0 (23.6, 24)
T_{max}[a] (h)	3.5 (2.0–4.0)	4.0 (3.0–9.0)	2.0 (2.0–4.0)	4.0 (2.0–9.0)	4.0 (4.0–9.0)
$t_{1/2}$[b] (h)	16.1 (3.36)[c]	21.3 (5.49)	20.7 (4.77)	20.4 (5.17)	22.6 (5.46)
AUC_{last} (µg•h/mL)	11.0 (11.2, 21)[c]	35.6 (37.8, 39)	148 (158, 39)	263 (272, 29)	481 (511, 35)
AUC_{inf} (µg•h/mL)	12.7 (12.9, 21)[c]	38.4 (41.0, 42)	154 (163, 38)	277 (290, 35)	507 (538, 34)
C_{max}/dose (µg/mL/mg)	0.0313 (0.0318, 19)	0.0232 (0.0258, 38)	0.0404 (0.0416, 26)	0.0329 (0.0330, 10)	0.0307 (0.0315, 24)
AUC_{inf}/dose (µg•h/mL/mg)	0.633 (0.644, 21)	0.513 (0.547, 42)	0.682 (0.724, 38)	0.701 (0.733, 35)	0.676 (0.718, 34)

Abbreviations: AUC_{inf}, area under the plasma concentration–time curve from time 0 to infinite time; AUC_{last}, area under the plasma concentration–time curve from time 0 to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; *N*, number of participants; PK, pharmacokinetic; T_{max}, time to reach C_{max}; $t_{1/2}$, terminal elimination half-life.

[a]Median (minimum–maximum).

[b]Harmonic mean (pseudo-standard deviation).

[c]$N = 5$.

were approximately dose-proportional between 225 and 375 mg q.d. at steady state.

In addition, urine analysis for assessment of renal clearance showed that cedirogant was mostly undetectable in urine, indicating that renal elimination has negligible contribution to cedirogant systemic clearance.

Efficacy of cedirogant in patients with moderate to severe psoriasis

Efficacy was assessed in 24 of 30 enrolled patients during Study 2B. Among these 24 patients, 13 received cedirogant and 11 received placebo. PASI scores and percentage change from baseline of the PASI and SAPS scores were tabulated by visit. PASI and SAPS results are presented in Figure 4. The mean percentage changes in PASI scores on Day 28 were −18.7% and −33.2% for placebo ($N = 11$) and cedirogant (375 mg q.d.; $N = 13$), respectively. The mean percentage changes in SAPS scores on Day 28 were 2.0% and −46.5% for placebo and cedirogant, respectively. Compared with placebo, treatment with cedirogant demonstrated greater numerical improvement in both mean percentage PASI and SAPS scores at Day 28. The percentage of patients who achieved 50% reduction in PASI score from baseline (PASI-50) at Week 4 was 46% for cedirogant compared with 9% for placebo.

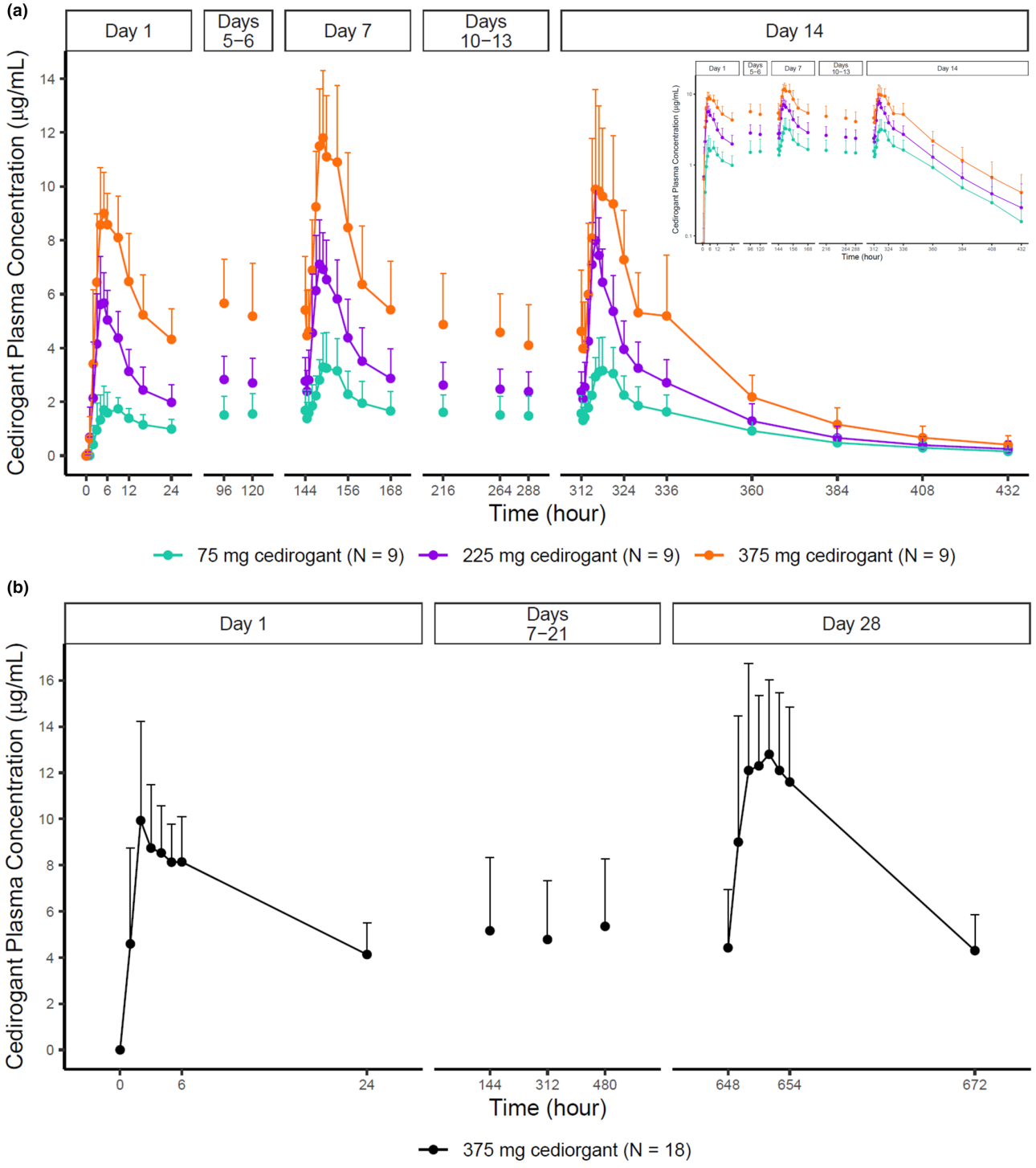

FIGURE 2 Study 2: Cedirogant plasma concentration–time profiles after administration of multiple-ascending cedirogant doses in (a) healthy participants and (b) patients with moderate to severe chronic plaque psoriasis. Cedirogant was administered once-daily in both populations. Datapoints represent mean (+standard deviation). Inset shows log-linear scale. The *x*-axes for Days 5–6, 10–13, and 7–21 are scaled for better visualization. A total of 18 patients were included in panel (b) ($N=13$ for Day 1; $N=16$ for Day 7; $N=14$ for Day 14 and Day 21; $N=11$ for Day 28). *N*, number of participants.

Safety

Across Study 1 and Study 2, a total of 69 healthy participants and 19 patients with psoriasis received cedirogant; a total of 17 healthy participants and 11 patients with psoriasis received placebo. The regimens tested were generally well tolerated by the participants in both studies. No deaths, serious AEs, or significant AEs were reported in either study.

TABLE 3 Geometric mean (mean, percentage coefficient of variation) pharmacokinetic parameters of cedirogant after multiple-ascending doses in healthy participants (Study 2A) and patients with moderate to severe chronic plaque psoriasis (Study 2B) under fed conditions.

			Study 2A		Study 2B
PK parameters (units)		**Group 1: 75 mg q.d.**	**Group 2: 225 mg q.d.**	**Group 3: 375 mg q.d.**	**375 mg q.d.**
			Day 1		**Day 1**
N		9	9	9	13
C_{max}	(μg/mL)	1.94 (2.02, 30)	5.96 (6.10, 23)	9.92 (9.98, 12)	10.7 (11.0, 25)
T_{max}[a]	(h)	5.0 (3.0–9.0)	4.0 (4.0–6.0)	4.0 (4.0–9.0)	2.0 (1.0–6.0)
AUC_{0-24}	(μg•h/mL)	27.4 (28.5, 30)	72.8 (74.8, 26)	139 (141, 17)	150 (154, 24)
C_{max}/dose	(μg/mL/mg)	0.0259 (0.0269, 30)	0.0265 (0.0271, 23)	0.0265 (0.0266, 12)	0.0285 (0.0293, 25)
AUC_{0-24}/dose	(μg•h/mL/mg)	0.365 (0.380, 30)	0.324 (0.333, 26)	0.370 (0.375, 17)	0.400 (0.411, 24)
			Day 7		
N		9	9	9	
C_{max}	(μg/mL)	3.30 (3.49, 36)	7.56 (7.69, 19)	12.3 (12.5, 17)	
T_{max}[a]	(h)	5.0 (3.0–9.0)	4.0 (3.0–9.0)	4.0 (4.0–9.0)	
AUC_{0-24}	(μg•h/mL)	51.7 (54.7, 37)	104 (107, 24)	185 (191, 26)	
C_{trough}	(μg/mL)	1.53 (1.66, 43)	2.70 (2.87, 39)	5.16 (5.42, 34)	
C_{max}/dose	(μg/mL/mg)	0.0440 (0.0465, 36)	0.0336 (0.0342, 19)	0.0328 (0.0333, 17)	
AUC_{0-24}/dose	(μg•h/mL/mg)	0.689 (0.730, 37)	0.463 (0.476, 24)	0.494 (0.509, 26)	
C_{trough}/dose	(μg/mL/mg)	0.0205 (0.0221, 43)	0.0120 (0.0128, 39)	0.0138 (0.0144, 34)	
			Day 14		**Day 28**
N		9	9	9	11
C_{max}	(μg/mL)	3.45 (3.60, 31)	7.99 (8.19, 22)	10.4 (10.8, 29)	13.8 (14.2, 25)
T_{max}[a]	(h)	5.0 (4.0–9.0)	4.0 (4.0–5.0)	5.0 (3.0–9.0)	2.0 (1.0–5.0)
AUC_{0-24}	(μg•h/mL)	50.9 (53.2, 32)	101 (104, 24)	159 (165, 27)	206 (213, 25)
C_{trough}	(μg/mL)	1.53 (1.63, 38)	2.57 (2.71, 32)	4.88 (5.19, 44)	4.50 (4.63, 26)
CL/F	(L/h)	1.47 (1.54, 30)	2.23 (2.30, 28)	2.36 (2.46, 34)	1.82 (1.88, 27)
$t_{1/2}$[b]	(h)	26.2 (7.08)	27.1 (8.85)	27.5 (7.39)	–
C_{max}/dose	(μg/mL/mg)	0.0461 (0.0480, 31)	0.0355 (0.0364, 22)	0.0277 (0.0289, 29)	0.0367 (0.0377, 25)
AUC_{0-24}/dose	(μg•h/mL/mg)	0.679 (0.710, 32)	0.448 (0.460, 24)	0.425 (0.441, 27)	0.550 (0.567, 25)
C_{trough}/dose	(μg/mL/mg)	0.0204 (0.0218, 38)	0.0114 (0.0120, 32)	0.0130 (0.0138, 44)	–
$R_{ac}C_{max}$	(ratio)	1.80 (1.44–2.48)[c]	1.37 (1.05–1.60)[c]	1.09 (0.684–1.47)[c]	1.24 (0.830–2.14)[e]
$R_{ac}AUC_{0-24}$	(ratio)	1.84 (1.54–2.43)[d]	1.38 (1.17–1.67)[d]	1.20 (0.806–1.33)[d]	1.26 (0.934–2.09)[f]

Note: Limited data collection for Study 2B prevented $t_{1/2}$ calculations.

Abbreviations: AUC_{0-24}, area under the plasma concentration–time curve from time 0 to 24 h; Cl/F, apparent oral clearance; C_{max}, maximum plasma concentration; C_{trough}, observed plasma concentration at the end of the dosing interval; *N*, number of participants; PK, pharmacokinetic; q.d., once-daily; T_{max}, time to reach C_{max}; $t_{1/2}$, half-life.

[a]Median (minimum through maximum).

[b]Harmonic mean (pseudo-standard deviation).

[c]Accumulation ratio calculated as the ratio of C_{max} on study Day 14 to C_{max} on study Day 1, median (minimum through maximum).

[d]Accumulation ratio calculated as the ratio of AUC_{0-24} on study Day 14 to AUC_{0-24} on study Day 1, median (minimum through maximum).

[e]$N = 10$; accumulation ratio calculated as the ratio of C_{max} on study Day 28 to C_{max} on study Day 1, median (minimum through maximum).

[f]$N = 10$; accumulation ratio calculated as the ratio of AUC_{0-24} on study Day 28 to AUC_{0-24} on study Day 1, median (minimum through maximum).

No clinically significant vital signs, ECG or laboratory hematology, chemistry, and urinalysis measurements were observed during the course of these studies. There was no pattern to the AEs reported. AEs that were reported by one or more participants in the cedirogant or placebo groups in Study 1 and Study 2 are presented in Table S4.

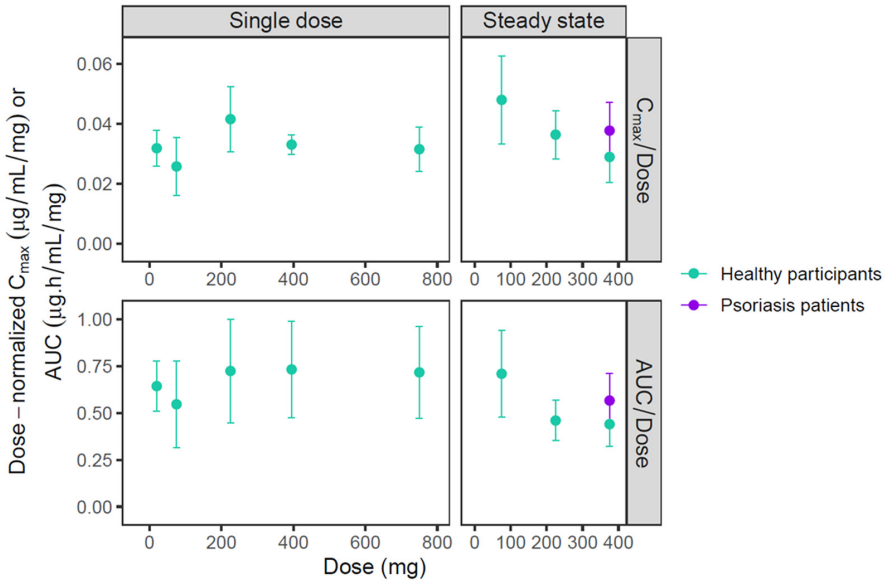

FIGURE 3 Dose-normalized cedirogant maximum plasma concentration (C_{max}) and area under the drug plasma concentration–time curve (AUC) after administration of a single dose in healthy participants and multiples doses in both healthy participants and patients with moderate to severe chronic plaque psoriasis. Datapoints and error bars represent mean and standard deviation. AUC from time 0 to infinity (AUC_{inf}) and AUC from time 0 to 24 h ($AUC_{0\text{-}24}$) were used in the single-dose and steady-state panels, respectively.

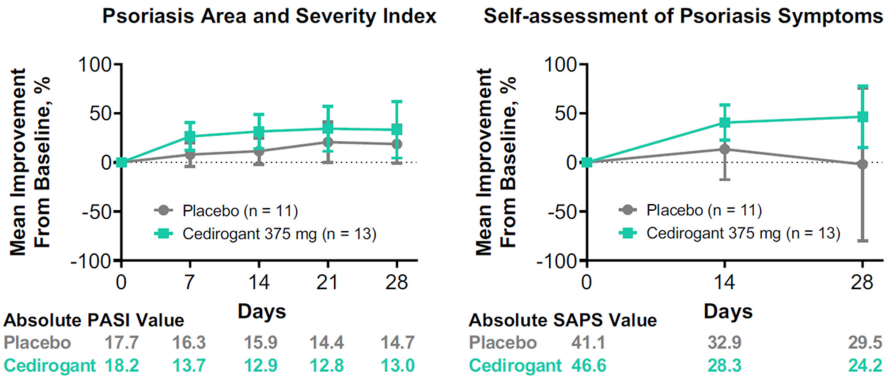

FIGURE 4 Mean (±standard deviation) percentage Psoriasis Area and Severity Index (PASI) and Self-Assessment of Psoriasis Symptoms (SAPS) change from baseline in patients with moderate to severe plaque psoriasis following administration of placebo or cedirogant.

Study 1 (SAD and food effect/DDI)

Data from all participants in Study 1 were included in the safety analysis. Three participants experienced TEAEs during Study 1A. Two participants reported a TEAE of headache, one of which (395 mg group) was assessed as having a reasonable possibility of being study drug-related. An additional TEAE of skin discomfort on the nose was reported in a third participant who received 395 mg cedirogant and was assessed as not study drug-related. All events were considered mild in severity and resolved. In Period 1 and 2 of Study 1B, four participants reported TEAEs (see Table S4). All TEAEs were assessed as not study drug-related and were mild in severity.

Study 2 (MAD)

Data from all participants who received at least one dose of study drug were included in the safety analysis for Study 2A ($N=35$) and Study 2B ($N=30$). A summary of TEAEs for both studies is provided in Table S4. In healthy participants (Study 2A), rates of TEAEs were similar between placebo and the three cedirogant treatment groups, although the sample size was small. No AE was reported more than once. No TEAEs were severe or serious, and the majority of TEAEs were mild in severity. Events of mild anal hemorrhage (felt to be due to a hemorrhoid) and mild infrequent bowel movement occurred in one participant each on cedirogant 225 mg and events of mild abdominal pain and mild aphthous ulcer occurred in one participant each on placebo. No other gastrointestinal events occurred in other cedirogant treatment groups. TEAEs of moderate tooth abscess, mild headache, and mild somnolence ($N=1$ each) were reported for participants who received placebo. The ocular events reported in participants receiving cedirogant (eye irritation, blurry vision, photophobia, abnormal sensation in the eye) were mild, did not lead to discontinuation of study drug, and were attributed to either the post-baseline protocol-specified ophthalmologic examination or the fluorescent lighting/dry air. One event of photophobia was reported in a participant receiving placebo. Three TEAEs assessed by the investigator as having a reasonable possibility of being study drug-related included one event each of mild infrequent bowel movements, mild upper respiratory

tract infection, and mild dizziness for participants who received cedirogant.

In patients with chronic plaque psoriasis (Study 2B, see Table S4), the rate of TEAEs for placebo were numerically higher on placebo than on cedirogant 375 mg, although the numbers are small and should be interpreted with caution. No AE was reported more than once. The majority of TEAEs were mild in severity. No TEAEs were severe or serious, or led to study drug discontinuation. Diarrhea (mild in severity) occurred in one participant each on placebo and cedirogant 375 mg. For participants who received placebo, TEAEs included diarrhea, paraesthesia, and hyperaesthesia ($N=1$ each).Three participants who received cedirogant reported TEAEs assessed as having a reasonable possibility of being study drug-related which included moderate pruritus, moderate skin burning sensation, and mild diarrhea ($N=1$ each).

DISCUSSION

Here, we report the first clinical experience with cedirogant, a RORγt inverse agonist. Cedirogant was generally well tolerated after single doses up to 750 mg and after multiple once-daily doses up to 375 mg. The safety and tolerability profiles were comparable between participants who received cedirogant and placebo. In both studies, there were no discontinuations or serious AEs due to cedirogant.

Based on the observed minimal food effect with a high-fat breakfast, cedirogant can be administered regardless of meals in clinical trials. Accordingly, cedirogant was administered under non-fasting conditions in Study 2A, which was conducted in heathy participants at a specialized phase I site where participants were confined and received standardized meals on the intensive PK sample collection days. Conversely, Study 2B was conducted in psoriasis patients at multiple sites. In this study, psoriasis patients were not confined to the study sites, and it was not feasible to ensure consistency of meals administered across the different clinical sites. Although minimal food effect was expected, fasting was required on intensive PK sample collection days in this study to minimize variability in PK data and provide more robust characterization of PK in patients.

Since CYP3A4 was identified as the major cytochrome P450 (CYP) enzyme responsible for cedirogant metabolism in vitro (data on file with AbbVie), interactions between cedirogant and itraconazole, a known strong CYP3A inhibitor, was evaluated in Study 1B. Itraconazole is a strong CYP3A inhibitor that is recommended by regulatory agencies to be used in drug interaction studies for CYP3A substrates.[21,22] Following co-administration of cedirogant with itraconazole, cedirogant AUC was increased by approximately 50% confirming metabolism by CYP3A as an elimination pathway for cedirogant. Based on the mild magnitude of DDI (i.e., <2-fold increase in cedirogant exposure), cedirogant is not considered as a sensitive substrate for CYP3A. Therefore, weak and moderate CYP3A inhibitors are not likely to cause clinically meaningful DDI with cedirogant.

Nonlinear PK of cedirogant at steady state was observed in the MAD study. This phenomenon may have resulted from auto-induction of CYP3A by cedirogant. As suggested by the DDI study with itraconazole and in vitro findings, cedirogant is a substrate of CYP3A. Moreover, in vitro studies have suggested that CYP3A can be induced by cedirogant with an in vitro half maximum induction concentration (EC_{50}) within the cedirogant concentration ranges observed in the MAD study (data on file with AbbVie). By visual check, the 75 mg q.d. of cedirogant achieved a steady-state dose-normalized $AUC_{0\text{-}24}$ that was comparable to the dose-normalized AUC_{inf} with single doses (Figure 3), indicating a lesser extent of CYP3A induction at low dose. This observation is consistent with the higher drug accumulation at the 75 mg q.d. dose compared with the other two higher doses (i.e., 225 and 375 mg q.d.). Interestingly, the terminal $t_{1/2}$ of cedirogant was not shortened at steady state when compared with the $t_{1/2}$ after a single dose. In addition, the $t_{1/2}$ values were similar across all multiple doses evaluated despite differences in dose-normalized C_{max} and AUC. Therefore, it is possible that the observed nonlinearity in cedirogant steady-state exposures is due to auto-induction of primarily first-pass metabolism by CYP3A.

Following multiple doses of once-daily 375 mg cedirogant in this study, cedirogant PK were generally comparable between healthy participants and psoriasis patients. Cedirogant mean plasma C_{max} and $AUC_{0\text{-}24}$ at steady state were approximately 30% higher in psoriasis patients, which is within the expected study-to-study variability. Although elevated levels of certain cytokines due to inflammatory diseases in psoriasis patients may downregulate the expression of CYP enzymes which may contribute to the differences in drug exposures between patients and healthy participants,[23–27] a recent population PK analysis demonstrated that the disease status of psoriasis was not expected to pose clinically relevant effects on CYP3A activity.[28] Similarly small differences in exposures between healthy participants and psoriasis patients has also been reported for other drugs with CYP-mediated metabolism.[29,30] This difference in exposure was small in magnitude (within 30%) and could be attributed to cohort-to-cohort variability as well as different characteristics in patients compared with healthy participants (e.g., age, renal function, hepatic function).

In patients with moderate to severe chronic plaque psoriasis, cedirogant demonstrated a greater numerical improvement in the percentage change in PASI and SAPS scores compared with placebo at Day 28. Although not statistically tested due to the exploratory nature of the efficacy assessment, the observed numeric improvement versus placebo suggested potential efficacy of cedirogant as a treatment for psoriasis.

One limitation of Study 2B in psoriasis patients was the small sample size, which precluded formal statistical analyses for the efficacy end points. Larger clinical trials would be needed to adequately characterize the efficacy and safety of cedirogant in psoriasis patients. The study duration (i.e., 28 days) was shorter than larger conventional trials conducted for small molecule medications approved for treatment of psoriasis, where the maximum therapeutic effects appeared to be approached within 12–16 weeks after initiation of treatment.[31–34] For Study 2B, a treatment duration of 28 days was selected to enable an early assessment of efficacy and demonstrate proof-of-concept in this patient population before larger studies were conducted to evaluate the long-term effect of treatment. Notably, there are examples[35,36] in the development of moderate-to-severe psoriasis treatments where initial proof-of-concept studies were designed as small, short-term trials which were 4 weeks in duration. Although the full extent of efficacy of cedirogant cannot be extrapolated based on the results from Study 2B, the enrollment of patients with psoriasis in early clinical development still allowed for a preview into the efficacy of cedirogant for early decision-making, and overall study results informed a larger phase IIb trial of cedirogant in psoriasis patients with a treatment duration of 16 weeks (NCT05044234).

In conclusion, cedirogant displayed favorable safety and tolerability profiles over single doses up to 750 mg and multiple doses up to 375 mg once-daily for 14 days in healthy participants, and for 28 days in patients with psoriasis. Cedirogant demonstrated a PK profile suitable for once-daily dosing. A greater numerical improvement in the percentage change in PASI and SAPS scores was demonstrated in psoriasis patients treated with cedirogant compared with placebo after 4 weeks of dosing. The safety and efficacy results of these studies supported further clinical development of cedirogant in patients with psoriasis in a phase II study.

AUTHOR CONTRIBUTIONS

M.-E.F.M., R.D., G.F.L., S.H., W.L., and R.C.D.P. designed the research. M.-E.F.M., R.D., T.S., L.K.F., A.E., G.F.L., S.H., S.G., D.G.R., W.L., S.J., H.S., and R.C.D.P. performed the research. Y.Q., R.D., A.E., G.F.L., S.H., and R.C.D.P. analyzed the data. All authors wrote the manuscript.

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CONFLICT OF INTEREST STATEMENT

M.-E.F.M., Y.Q., R.C.D.P., A.E., G.L., S.H., S.G., D.G.R., and W.L. are employees of AbbVie Inc. and may hold AbbVie stock, stock options, and/or patents. R.C.D.P. is a former employee of AbbVie Inc. and may hold AbbVie stock, stock options, and/or patents. T.S. is an employee of Velocity Clinical Research, who conducts clinical research with AbbVie. She has received consulting fees as a medical advisor and/or consultant for Curon, Nutrilite, Pfizer, and SageMed. She has been an investigator for AbbVie, 4D Pharma, Abbott, Acadia, Acambis, Access Business Group, Acrux, Akros, Alizyme, Allena, Allergan, Almirall, Alpharma, Altana, Amarin, Amgen, Amylin, Amytrx, Anacor, Anika, Antares, AOBiome, Ardelyx, Arena, AZ, Auxillium, Axsome, Bavarian Nordic, Beckman, BI, Biocryst, Biodel, Biohaven, Biomarin, BMS, Centrexion, Cephalon, Chiesi, Clarus, Concert, Cubist, Curon, CymaBay, Daiichi-Sankyo, deCode, DOV, Dr. Reddy's Labs, Elcelyx, Endo, Ferring, Flexion, Foamix, Focus, Forest, Fougera, Furiex, Galderma, Genentech, Gilead, GSK, Glenmark, Great Lakes, Grunthal, Hanmi, Heel, Hemacare, Hoffmann, Hollis Eden, Horizon, Immunodiagnostics Systems, Intarcia, Ironwood, Janssen, Jazz, Kaketsuken, Kiniksa, Kintor, Kowa, Lexicon, Ligand, Lilly, Lipocine, Logical, Mannkind, MediVector, Medimmune, Menarini, Menlo, Merck, Merz, Metabolex, Moderna, MT Group, Mylan, NanoBio, Neurocrine, Novartis, Novavax, Novo Nordisk, NovMetaPharma, Novum, Oneness, Optinose, Oramed, Orexo, Otsuka, P&GP, Paradigm, Pearl, Perrigo, Pfizer, Pharmaco, Pharmasset, Pharmos, Pozen, Promius, Proteus, Purdue, Quinnova, Rapt, RedHill, Regenacy, Regeneron, Renovo, Replidyne, Response, Roche, Sage-Med, Salix, Sanofi, Seikagaku, Shionogi, Shire, SkyePharma, Sol–Gel, Speedel, SpineCare, Strakan, Sun Pharma, Surface Logix, Synergy, Taiwan Liposome, Takeda, Targacept, Taro, Techfields, Teva, Theracos, Tibotec, Tioga, Tobira, Tolmar, Trevi, Trimel, Valeant, Velicept, Ventrus, Vermillion, Vertex, Vibrant, Viking, Vivus, Westward, and Zogenix. L.K.F. has received consulting fees from AbbVie, Arcutis, BMS, Dermavant, Janssen, Lilly, and Pfizer. She has been an investigator for AbbVie, Arcutis, BMS, Celgene/

Amgen, Dermavant, Galderma, Janssen, LEO, Novartis, and Regeneron. S.J. has received honoraria as a speaker for AbbVie and Novartis, and grants as an investigator from AbbVie, Amgen, Athenex, AbGenomics, Bausch Health Americas Valeant, BI, BMS, Coherus, Corrona, DS Biopharma, Galderma, Genentech, Health Analytics, Innovaderm, IQVIA Biotech, Janssen, Kadmon, LEO, Lilly, Novartis, Novella, Pfizer, Regeneron, Tolmar, UCB, Xenoport (Arbor Pharmaceuticals), and Watson. H.S. has served as a scientific adviser and/or clinical study investigator for AbbVie, BI, BMS, Dermavant, Incyte, Janssen, LEO, Lilly, Novartis, Pfizer, Sanofi-Genzyme, Sun, and UCB.

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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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