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Izokibep for the treatment of moderate-to-severe plaque psoriasis: a phase II, randomized, placebo-controlled, double-blind, dose-finding multicentre study including long-term treatment

Sascha Gerdes,[1] Petra Staubach,[2] Thomas Dirschka,[3] Dieter Wetzel,[4] Oliver Weirich,[5] Johannes Niesmann,[6] Rodrigo da Mota,[7] Alex Rothhaar,[8] Michael Ardabili,[9] Gerda Vlasitz,[10] Joachim Feldwisch,[10] Lisa Osterling Koskinen,[10] Sven Ohlman,[10] Paul M. Peloso,[11] Nikolai C. Brun[10] and Fredrik Y. Frejd[10,12]

[1]Psoriasis Center, Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany
[2]Department of Dermatology, Medical Center, Medical University Center, Mainz, Germany
[3]Germany Private Practice for Dermatology, Wuppertal, Germany
[4]toclinco GmbH, Freiburg, Germany
[5]Rosenpark Research, Darmstadt, Germany
[6]Private Practice for Dermatology, Bochum, Germany
[7]Private Practice Dr. Hilton & Partner for Dermatology, Düsseldorf, Germany
[8]Rothhaar Studien GmbH, Berlin, Germany
[9]Derma-Centro-Bochum, Bochum, Germany
[10]Affibody AB, Solna, Sweden
[11]ACELYRIN Inc., Agoura Hills, CA, USA
[12]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden
Correspondence: Nikolai C. Brun. Email: nikolai.brun@affibody.com

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Abstract

Background Monoclonal antibodies to interleukin (IL)-17 have shown strong efficacy in patients with psoriasis. Izokibep is a unique IL-17A inhibitor with a small molecular size and favourable distribution to sites of inflammation.

Objectives To evaluate the dose response, efficacy and safety of izokibep in patients with plaque psoriasis.

Methods In this double-blind, randomized, phase II dose-finding study (AFFIRM-35) in adults with moderate-to-severe plaque psoriasis and inadequate response to two or more standard therapies, patients were randomized (1:1:1:1:1) to placebo or izokibep 2, 20, 80 or 160 mg every 2 weeks for 12 weeks. During the remainder of the 52-week core study, patients given placebo were switched to izokibep 80 mg, and dosing intervals were adapted based on Psoriasis Area and Severity Index (PASI) scores for all patients. The core study was followed by two optional consecutive 1-year extension periods for a total duration of 3 years. The primary endpoint was a 90% reduction in PASI score (PASI 90) at week 12. Additional efficacy outcomes and adverse event (AE) rates were evaluated.

Results In total, 109 patients were randomized [safety set, $n=108$ (one exclusion criteria failure); full analysis set, $n=106$]. At week 12, PASI 90 response rates were 0%, 5%, 19%, 71% and 59% for the placebo, 2-, 20-, 80- and 160-mg izokibep groups, respectively. Rapid dose-dependent improvements were also observed across other efficacy outcomes. During the placebo-controlled period, AEs in the izokibep groups were similar to placebo except for mild injection site reactions. AEs were generally mild to moderate and the drug was well tolerated. Izokibep maintained efficacy at the higher dosage groups for up to 3 years, with no new safety signals.

Conclusions Data from this phase II study indicate that izokibep is well tolerated and efficacious in the treatment of plaque psoriasis. Higher doses or more frequent dosing could be explored to further enhance response rates.

What is already known about this topic?

- Monoclonal antibodies that inhibit interleukin (IL)-17 have demonstrated robust efficacy in patients with plaque psoriasis.
- Izokibep is a unique, subcutaneously administered IL-17A inhibitor with a small molecular size designed to overcome the limitations of monoclonal antibodies, such as poor tissue distribution.
- An albumin-binding domain extends the izokibep half-life and helps direct distribution to sites of inflammation.

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What does this study add?

- Izokibep at 80 mg or 160 mg every 2 weeks demonstrated a high level of efficacy compared with placebo at 12 weeks in patients with moderate-to-severe plaque psoriasis, and efficacy was sustained for up to 3 years.
- Izokibep was safe and well tolerated over up to 3 years of exposure.
- No dose-limiting toxicity was observed at the tested doses, suggesting that exploration of higher doses may be appropriate.

Interleukin (IL)-17 plays a central role in the immunopathogenesis of psoriasis.[1,2] This cytokine family, which includes several structurally related proteins designated IL-17A to IL-17F, stimulates T-cell-mediated inflammation and keratinocyte proliferation and helps drive the psoriasis inflammatory cascade.[1–3] Blocking IL-17 activity results in a rapid reduction in psoriatic disease severity.[3] Most anti-IL-17 agents in clinical use are monoclonal antibodies. Monoclonal antibodies are effective therapeutic agents, but are limited by their large size, relative instability and manufacturing costs.[4]

Izokibep is a unique, subcutaneously (SC) administered IL-17A inhibitor with a small molecular size designed to overcome the limitations of monoclonal antibodies, such as poor tissue distribution.[5,6] This agent was developed using Affibody® molecules (Affibody, Solna, Sweden), consisting of small, triple-helical high-affinity protein domains.[7] Izokibep combines two IL-17A-specific Affibody domains with one albumin-binding domain (ABD) (Albumod®; Affibody) to create an 18.6 kDa IL-17A ligand trap (Figure 1a).[6] Izokibep's ABD results in a long half-life and favourable biodistribution to sites of inflammation, while its reduced molecular size allows it to reach high drug exposure levels through SC injection.[7,8] Pharmacodynamic studies indicate that izokibep is more potent in inhibiting IL-17A than secukinumab or ixekizumab.[6] Izokibep has four orders of magnitude higher affinity for the IL-17AA homodimer than for the IL-17AF heterodimer,[6] which could potentially decrease the risks associated with IL-17F inhibition, such as *Candida* spp. infections.[4,9] A phase I study supported the rationale for further exploration of izokibep in patients with inflammatory diseases.[5,6]

We report the results of a phase II study of izokibep in patients with plaque psoriasis. The goals of the study were to evaluate the efficacy and safety of izokibep at various doses in adults with moderate-to-severe plaque psoriasis and to gain insights into potential strategies for treatment optimization.

Patients and methods

Study design

This prospective, randomized, parallel-group, double-blind, placebo-controlled dose-finding study was conducted in adults with moderate-to-severe plaque psoriasis at 16 study sites in Germany (Appendix S1; see Supporting Information). The first/last visits for the core study and extension periods were 7 March 2018/26 February 2020 and 16 May 2019/3 December 2021, respectively. The study was registered in the EudraCT database (2017-001615-36) on 7 September 2017 and subsequently registered with ClinicalTrials.gov (NCT03591887).

Following screening and confirmation of eligibility, patients entered a 52-week core study consisting of the following periods (Figure 1b).

Induction period (weeks 0–12)

Patients were randomized to placebo or one of four izokibep dose groups (2 mg, 20 mg, 80 mg or 160 mg) administered every 2 weeks (Q2W). Izokibep and placebo doses were administered as two SC injections of 1.0 mL.

Optimization period (weeks 12–24)

Patients administered placebo were switched to izokibep 80 mg every 4 weeks (Q4W). Patients receiving izokibep during the induction period had their dose adjusted based on Psoriasis Area and Severity Index (PASI) score (Figure 1b). Patients receiving izokibep Q4W received a double-dummy placebo to maintain blinding.

Individualization period (weeks 24–48+ 4 weeks of follow-up)

The dose interval was switched to Q4W for all treatment groups. Patients randomized to receive 2 mg with a PASI score $\geq$3 had their dose escalated to 80 mg. From week 32 onward, the dose interval was modified based on PASI scores (Figure 1b).

Patients were seen every 2 weeks during the induction and optimization period, and every 4 weeks during the individualization period.

The study design was chosen to provide information on the efficacy, safety and maintenance of response of izokibep at different doses, and to allow for insights into possible treat-to-target strategies, with the aim of obtaining the highest possible treatment response in each patient and maintaining this response at the lowest possible exposure.

The core study was followed by an optional 52-week extension period and a further optional 52-week prolongation of extension period (Figure 1b). The prolongation of extension period was discontinued by sponsor decision on 8 July 2021 as sufficient safety and efficacy data for up to 3 years of izokibep exposure had been obtained. Patients entered the extension period at the optimized dose and dosing interval they received at week 48 of the core study. The initial design of the extension periods specified no changes in dose or dosing interval, but a subsequent amendment modified this restriction to allow changes in dose or dosing interval based on PASI response to achieve full disease control (Figure 1b). Patient visits during the extension and prolongation of extension periods were scheduled every 4 weeks.

Patients were randomized, using an interactive web response system administered by Almac (Dundalk, Ireland), to the five treatment groups (1:1:1:1:1) using a block size of 5. The core study was double-blinded with respect to

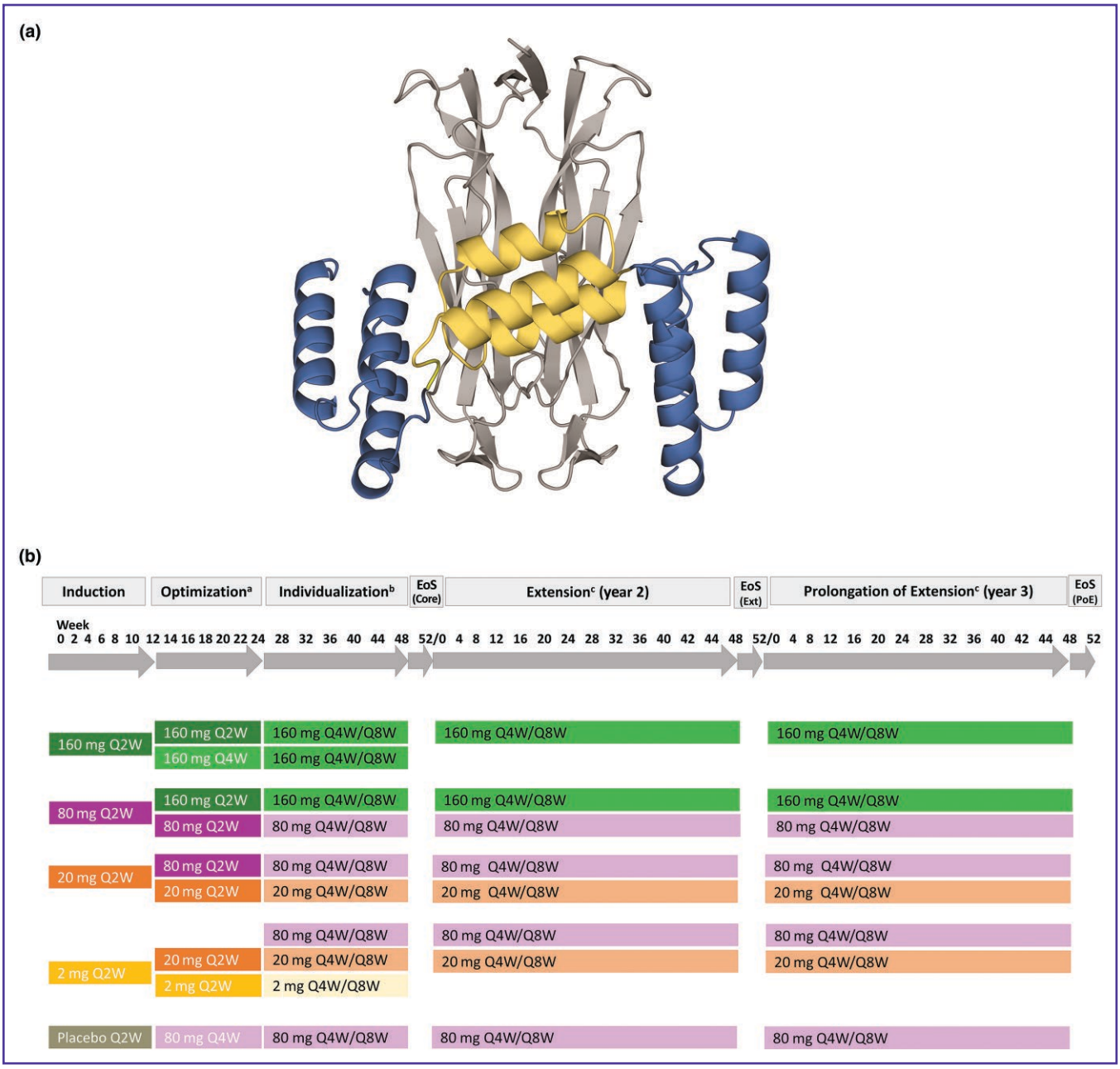

Figure 1 (a) Molecular model of izokibep. The proposed binding mode of izokibep involves simultaneous binding of two interleukin (IL)-17A Affibody® affinity domains (blue) on each side of the homodimeric IL-17A target protein (grey), thus improving potency. The albumin binding domain (yellow) enables high-affinity binding to albumin, extending plasma half-life. (b) Study design for the core study and extension (Ext) periods of AFFIRM-35. [a]Participants with a Psoriasis Area and Severity Index (PASI) score of ≥ 3 received escalated doses; participants with a PASI score < 3 maintained the same dose, with the exception that those in the izokibep 160-mg group with a PASI score ≥ 3 maintained izokibep 160 mg every 2 weeks (Q2W) and those with a PASI score < 3 switched to izokibep 160 mg every 4 weeks (Q4W). [b]All participants received dosing Q4W at the start of this period. Participants in the initial izokibep 2-mg group with a PASI score ≥ 3 at week 24 received the izokibep 80-mg dose. From week 32, the dose interval changed to every 8 weeks (Q8W) if a participant's PASI score was ≤ 1 on two consecutive visits, and returned to Q4W dosing if they had a PASI score ≥ 3. [c]Dose level increased or dose interval shortened for participants with a PASI score > 1 at two consecutive visits. EoS, end of study; PoE, prolongation of extension.

sponsor, contract research organization, investigators and patients. As different concentrations varied in appearance, izokibep/placebo preparation and administration was performed by unblinded personnel not involved in any other study activities. Blinded study staff performed all medical assessments. The study was unblinded after completion of the core study. All doses were administered by study personnel, thereby ensuring treatment adherence.

Patients

This study enrolled adults (aged 18–75 years) with moderate-to-severe plaque psoriasis, defined as psoriasis involving $\geq 10\%$ of the body surface area (BSA), a PASI score ≥ 12 and a static Physician Global Assessment (sPGA) score ≥ 3. Patients had to be diagnosed with plaque psoriasis at least 6 months prior to screening, have stable disease (no clinically

significant flares during the 12 weeks before randomization), have failed or have a contraindication or intolerance to at least two standard therapies (systemic or phototherapy), and be willing to use adequate contraception. Previous biologic and nonbiologic disease-modifying antirheumatic drug therapy with agents other than anti-IL-17 therapies was allowed with an appropriate washout period. Patients with low active psoriatic arthritis were eligible if they had not received systemic treatment within the last 12 months. Concomitant topical and systemic antipsoriatic medications were prohibited during the study.

Exclusion criteria included other forms of psoriasis; prior exposure to anti-IL-17 biologic therapies; history of recurrent/medically important infections in the last 12 months, including *Staphylococcus aureus* skin infections or *Candida* spp. infections; history of or current autoimmune diseases other than psoriasis [including inflammatory bowel disease (IBD)] requiring treatment within the past 12 months; pregnancy; and other major medical conditions.

Endpoints and assessments

The primary efficacy endpoint was the proportion of patients with a 90% reduction in PASI score from baseline (PASI 90 response) at week 12. Additional evaluations of efficacy were explored as secondary endpoints, including supplementary PASI analyses [75% reduction in PASI score (PASI 75), 100% reduction in PASI score (PASI 100), PASI ≤ 1, PASI < 3], sPGA of 0 or 1, Dermatology Life Quality Index (DLQI), Nail Psoriasis Severity Index for a prespecified target nail representing the worst nail psoriasis involvement (or a randomly chosen nail for patients with no baseline involvement) and 100-mm visual analogue scale (VAS) scores for itch and pain.

Adverse events (AEs) and serious AEs (SAEs) were coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 20.1). Treatment-emergent AEs (TEAEs) were defined as those starting after first dose administration. AEs of special interest included *Candida* spp. infection, staphylococcal skin infections, IBD and injection site reactions. Antidrug antibody (ADA) blood levels against izokibep were determined by immunoassay (Appendix S2; see Supporting Information).

Statistical analysis

No formal sample size estimation was made, as the expected variability of measurements associated with the primary objective was unknown. The enrolment goal was 20 patients per treatment group, which is in the general range of other phase II dose-finding psoriasis trials for anti-IL-17 agents.[10–12]

Efficacy analyses were conducted on the full analysis set (FAS), defined as all randomized patients who received at least one dose of study drug and had at least one post-baseline PASI result. The planned logistic regression model to assess differences between izokibep treatment groups and placebo in proportions achieving PASI 90 at week 12 was not performed, because there were no PASI 90 responders in the placebo group at week 12. Therefore, the proportion of patients with a PASI 90 response at week 12 was only presented by descriptive statistics (i.e. number of patients with PASI 90 response divided by the total number of patients in the FAS population). For secondary efficacy analyses, statistical evaluations were based on descriptive statistics; analyses of continuous endpoints were based on observed data and binary endpoints (e.g. responder analyses) were presented as proportion of responders in the FAS.

Descriptive statistics of safety endpoints were based on the safety set of all patients who received at least one dose of the study drug.

Results

Patients in the core study

A total of 134 patients were screened and 109 were randomized. One patient did not receive treatment due to violation of an exclusion criterion; the safety set therefore included 108 patients. Two patients did not have PASI results after the baseline visit, resulting in a FAS of 106 patients (Figure 2); both discontinued the study during the induction period (one lost to follow-up and one due to violation of an exclusion criterion). As a result, the numbers of patients in each treatment group were the same for the safety set and FAS in the optimization and individualization periods. Six patients discontinued from the FAS during the induction period, 2 patients during the optimization period and 10 during the individualization period (Figure 2). Eighty-eight of 109 randomized patients (81%) completed the 52-week core study.

Baseline demographic and disease characteristics in the FAS were generally similar across treatment groups (Table 1), but patients in the izokibep 80-mg Q2W group had a lower mean body mass index (BMI) and greater disease severity, particularly with respect to PASI, BSA and pain VAS scores.

PASI 90 responses in the core study

At week 12, PASI 90 data were missing for seven patients (one each in the izokibep 2-, 20- and 160-mg groups, and four in the 80-mg group). The primary endpoint (PASI 90 response at week 12) was achieved by up to 71% of patients (15/21 in the izokibep 80-mg Q2W group) in the izokibep treatment groups but by none of the patients in the placebo group (Figure 3). A dose–response curve was observed over 2–80 mg Q2W [izokibep 2 mg (5%), izokibep 20 mg (19%) and izokibep 80 mg (71%)]. The PASI 90 response rate in the izokibep 160-mg group was 59% (Figure 3). Slightly higher response rates [up to 88% ($n = 15/17$) in the izokibep 80-mg Q2W group] were observed in the subgroup of patients with a PASI assessment at week 12.

During the core study, PASI 90 response rates were maintained over the optimization period in patients who initially received higher doses of izokibep [14 of 16 (87%) patients in the izokibep 80-mg Q2W to 80-mg Q2W group and in 14 of 17 (82%) patients in the izokibep 160-mg Q2W to 160-mg Q4W group at 24 weeks] and increased in patients who were initially treated with placebo or low doses of izokibep

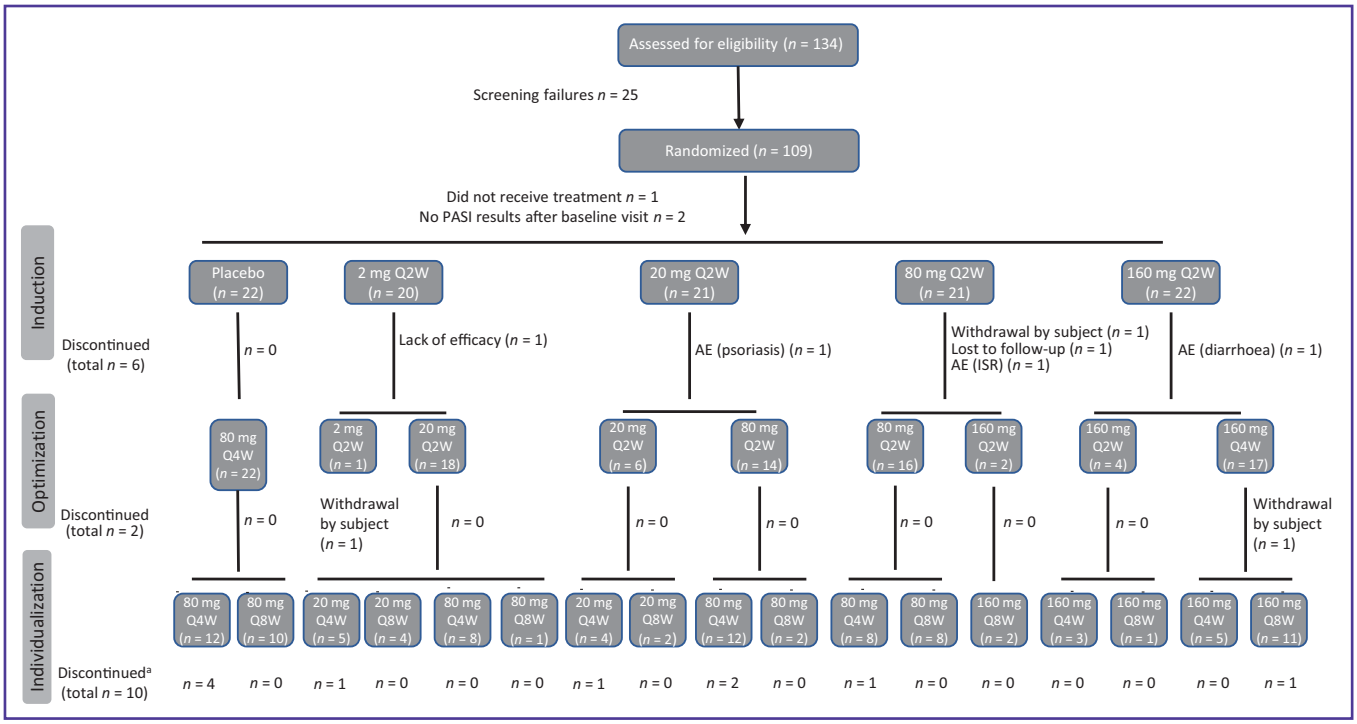

Figure 2 Patient disposition in the full analysis set (FAS) during the core study. The induction period extended from weeks 0 to 12, the optimization period from week 12 to 24 and the individualization period from week 24 to 48+4 weeks of follow-up. [a]Reasons for discontinuation in the placebo to 80-mg every 4 weeks (Q4W) group: withdrawal by participant (n=2); lack of efficacy; adverse event (AE; atopic dermatitis). Reason for discontinuation in the izokibep 2-mg to 20-mg Q4W group: withdrawal by participant. Reason for discontinuation in the izokibep 20-mg Q2W to 20-mg Q4W group: AE (psoriasis). Reasons for discontinuation in the izokibep 20-mg Q2W to 80-mg Q4W group: physician's decision; withdrawal by participant. Reason for discontinuation in the izokibep 80-mg Q2W to 80-mg Q4W group: AE (pustular psoriasis). Reason for discontinuation in the izokibep 160-mg Q2W to 160-mg every 8 weeks (Q8W) group: AE (psoriatic arthropathy). ISR, injection-site reaction.

Table 1 Baseline characteristics of participants in the full analysis set in the phase II dose-finding AFFIRM-35 study

		Izokibep				
Characteristic	**Placebo (n=22)**	**2 mg Q2W (n=20)**	**20 mg Q2W (n=21)**	**80 mg Q2W (n=21)**	**160 mg Q2W (n=22)**	**All patients (n=106)**
Age (years), mean (SD)	38.4 (13.0)	40.5 (13.1)	45.0 (12.5)	42.0 (13.8)	43.2 (11.4)	41.8 (12.7)
Female	7 (32)	8 (40)	6 (28)	7 (33)	10 (45)	38 (36)
White	20 (91)[a]	20 (100)	21 (100)	20 (95)[a]	22 (100)	103 (97)[a]
Weight (kg), mean (SD)	90.1 (16.5)	90.7 (18.3)	91.8 (21.8)	77.3 (12.7)	86.6 (21.1)	87.3 (18.8)
BMI (kg/m^2), mean (SD)	29.3 (5.4)	30.2 (5.5)	29.8 (6.2)	26.0 (3.6)[b]	28.5 (6.7)	28.8 (5.7)
Psoriasis duration (years), mean (SD)	15.4 (9.7)	18.8 (13.1)	15.2 (13.0)	16.6 (12.8)	20.5 (12.4)	17.3 (12.2)
Psoriatic arthritis	1 (4)	0	1 (5)	1 (5)	3 (14)	6 (6)
BSA, mean (SD)	24.8 (13.4)	23.8 (12.6)	29.5 (17.2)	33.2 (20.2)	28.2 (15.8)	27.9 (16.1)
PASI, mean (SD)	18.9 (8.2)	18.0 (6.9)	20.2 (8.6)	22.7 (10.1)	17.9 (6.6)	19.5 (8.2)
DLQI, mean (SD)	11.4 (5.8)	12.7 (5.7)	13.3 (7.6)[c]	14.3 (6.3)	12.1 (5.8)	12.7 (6.2)
Pain VAS, mean (SD)[d]	30.4 (32.1)	29.0 (27.3)	34.8 (32.6)	50.2 (30.8)	44.0 (33.1)	37.7 (31.8)
Itch VAS, mean (SD)[d]	54.8 (29.6)	62.3 (27.2)	49.5 (33.0)	63.8 (22.3)	61.0 (30.8)	58.2 (28.8)
Prior medications[e]						
Topical antipsoriatics	14 (64)	16 (76)	17 (77)	14 (67)	13 (59)	74 (68)
Systemic antipsoriatics	12 (54)	14 (67)	16 (73)	15 (71)	15 (68)	72 (67)
Topical corticosteroids	20 (91)	16 (76)	15 (68)	18 (86)	17 (77)	86 (80)
Oral corticosteroids	2 (9)	2 (9)	2 (9)	2 (9)	2 (9)	2 (9)
csDMARDs	9 (41)	10 (48)	4 (18)	6 (29)	11 (50)	40 (37)
bDMARDs	3 (14)	1 (5)	2 (9)	4 (19)	4 (18)	14 (13)

Data are presented as n (%) unless otherwise indicated. bDMARDs, biologic disease-modifying antirheumatic drugs; BMI, body mass index; BSA, body surface area; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; Q2W, every 2 weeks; VAS, visual analogue scale. [a]One Black (placebo) and two Asian (one each in the izokibep 80-mg and placebo groups) patients were included; [b]missing data for one patient; [c]missing data for two patients; [d]100 mm VAS (0=none and 100=worst imaginable); [e]data based on safety set (n=108).

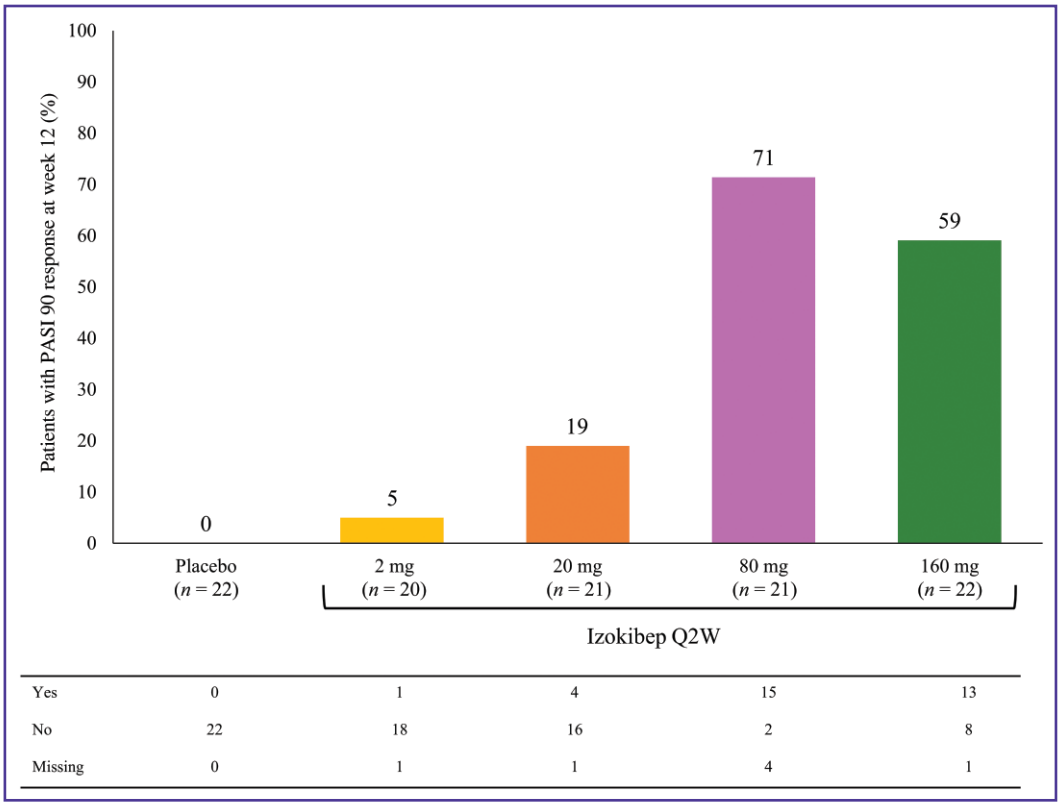

Figure 3 Proportion of participants in the full analysis set who achieved a 90% reduction in Psoriasis Area and Severity Index (PASI 90) at week 12. FAS, full analysis set. Q2W, every 2 weeks.

(2 or 20 mg) (Table S1; see Supporting Information). During the individualization period, extending the dosing interval from Q2W to Q4W did not appear to have a negative effect on response in patients in the izokibep 160-mg group, but it did result in lower response rates in patients in the izokibep 80-mg group [from 14 of 16 patients (87%) for Q2W at week 24 to 3 of 8 patients (37%) for Q4W at week 48] (Table S1).

Additional efficacy evaluations during the core study

Rapid decreases in mean PASI scores were observed in the izokibep 80- and 160-mg groups by week 2; the lowest scores were reached at week 20 (Figure 4). Low scores were maintained in these groups throughout the core study period. PASI scores decreased in patients in the placebo, izokibep 2-mg and izokibep 20-mg groups following the introduction or dose escalation of izokibep, and began to converge with scores observed in patients initially treated and maintained on higher doses by the end of the core study (Figure 4).

Other efficacy outcomes during the core study (e.g. PASI ≤ 1, PASI < 3, sPGA, DLQI and pain VAS) mirrored the PASI 90 responses (Tables 2, 3). Rapid dose-dependent improvements in psoriasis outcomes were observed in izokibep-treated patients and responses were generally maintained. PASI 100 responses were achieved by 38% of patients in the izokibep 80-mg Q2W group and by 23% of patients in the izokibep 160-mg Q2W group at 12 weeks.

Safety during the core study

Izokibep was well tolerated during the core study. Nasopharyngitis was the most common AE. During the 12-week placebo-controlled induction period, overall TEAE rates in the izokibep 2-, 20- and 80-mg groups were generally comparable to placebo, but injection site reactions and gastrointestinal disorders occurred at higher rates in patients in the izokibep groups (Table 4). Patients in the izokibep 160-mg group had higher overall rates of TEAEs. Four SAEs occurred during the placebo-controlled phase, one each in the izokibep 80-mg (meniscus injury) and 160-mg (osteoarthritis) group, and two in the placebo group (atrial fibrillation and fibroadenoma of the breast, respectively).

During the optimization and individualization periods of the core study, the rates of injection site reactions, diarrhoea and fatigue decreased in patients in the izokibep groups (Table S2; see Supporting Information). Overall TEAE rates decreased in the izokibep 160-mg group.

The AE profile over 52 weeks was generally similar to the first 12 weeks; no new safety signals were observed (Table S3; see Supporting Information). Overall numbers of AEs were low and there were no clear differences across active treatment groups. Seven patients experienced SAEs (all assessed as not being related to treatment) from week 12 to 52 (Table S3). There were no deaths or cases of IBD reported. Seven patients discontinued the core study due to AEs: two in the izokibep 20-mg group (both psoriasis flare), two in the izokibep 80-mg group (pustular psoriasis and injection site reaction, respectively), two in the izokibep

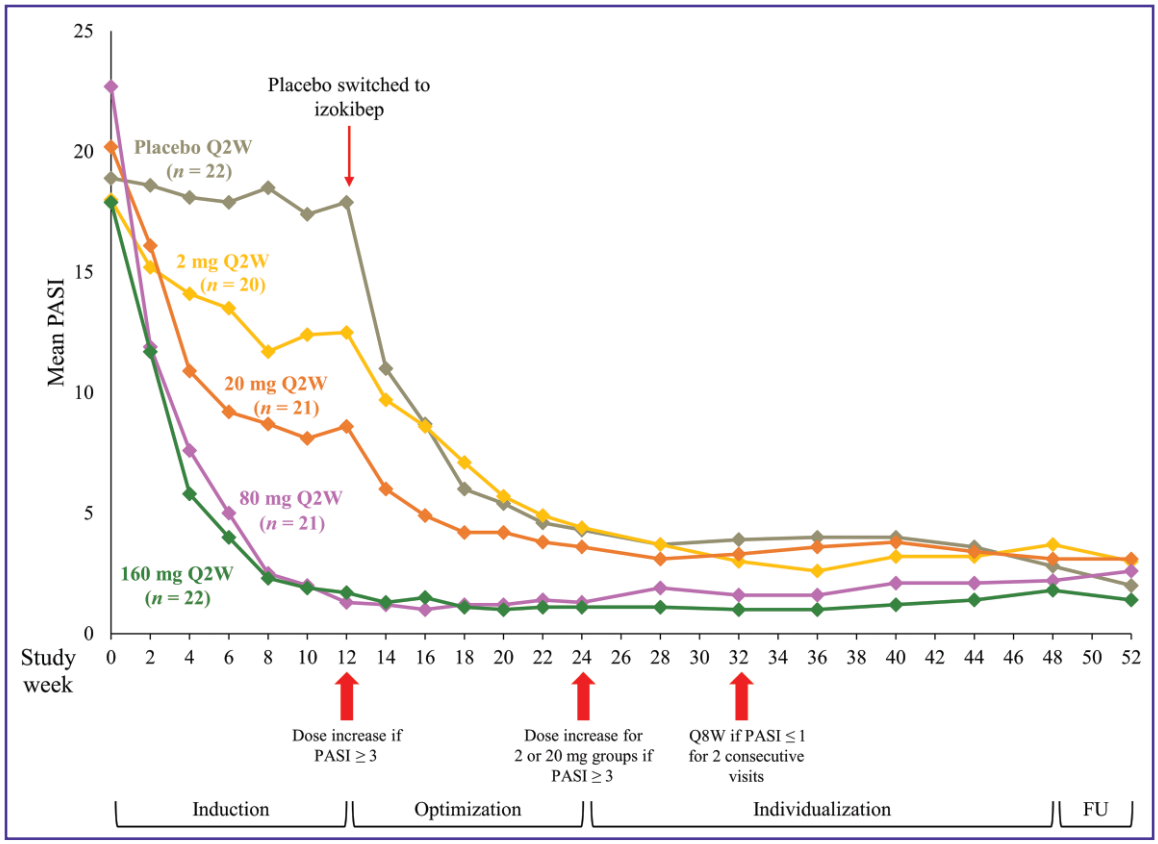

Figure 4 Mean Psoriasis Area and Severity Index (PASI) scores over time by induction period treatment group. FU, follow-up period; Q2W, every 2 weeks; Q8W, every 8 weeks.

Table 2 Secondary efficacy outcomes (binary endpoints) in the full analysis set (FAS) by induction period dose group in the phase II dose-finding AFFIRM-35 study

				Izokibep							
		Placebo (*n*=22)		2 mg Q2W (*n*=20)		20 mg Q2W (*n*=21)		80 mg Q2W (*n*=21)		160 mg Q2W (*n*=22)	
Outcome	**Period/week**	***N*[a]**	***n* (%)**	***N*[a]**	***n* (%)**	***N*[a]**	***n* (%)**	***N*[a]**	***n* (%)**	***N*[a]**	***n* (%)**
PASI 75	Induction/12	22	0	19	2 (10)	20	7 (33)	17	17 (81)	21	19 (86)
	Optimization/24	22	15 (68)	18	10 (50)	20	13 (62)	18	17 (81)	20	19 (86)
	Individualization/52/EoS	18	16 (73)	17	14 (70)	16	11 (52)	17	15 (71)	19	16 (73)
PASI 90	Induction/12	22	0	19	1 (5.0)	20	4 (19)	17	15 (71)	21	13 (59)
	Optimization/24	22	9 (41)	18	7 (35)	20	9 (43)	18	16 (76)	20	16 (73)
	Individualization/52/EoS	18	12 (54)	17	7 (35)	16	6 (28)	17	9 (43)	19	15 (68)
PASI 100	Induction/12	22	0	19	0	20	2 (9)	17	8 (38)	21	5 (23)
	Optimization/24	22	4 (18)	18	2 (10)	20	5 (24)	18	6 (28)	20	8 (36)
	Individualization/52/EoS	18	3 (14)	17	3 (15)	16	1 (5)	17	3 (14)	19	6 (27)
PASI < 3	Induction/12	22	0	19	1 (5)	20	6 (28)	17	15 (71)	21	17 (77)
	Optimization/24	22	12 (54)	18	9 (45)	20	12 (57)	18	16 (76)	20	18 (82)
	Individualization/52/EoS	18	15 (68)	17	13 (65)	16	10 (48)	17	10 (48)	10	15 (68)
PASI ≤ 1	Induction/12	22	0	19	1 (5)	20	3 (14)	17	10 (48)	21	11 (50)
	Optimization/24	22	6 (27)	18	6 (30)	20	7 (33)	18	11 (52)	20	13 (59)
	Individualization/52/EoS	18	7 (32)	17	3 (15)	16	4 (19)	17	7 (33)	19	11 (50)
sPGA 0 or 1	Induction/12	22	0	19	1 (5)	20	5 (24)	17	13 (62)	21	14 (64)
	Optimization/24	22	11 (50)	18	7 (35)	20	10 (48)	18	16 (76)	20	17 (77)
	Individualization/52/EoS	18	11 (50)	17	9 (45)	16	5 (24)	17	10 (48)	19	13 (59)
DLQI 0 or 1	Baseline/0	22	0	20	1 (5)	19	1 (5)	21	0	22	0
	Induction/12	22	1 (4)	19	2 (10)	20	10 (48)	17	12 (57)	21	15 (68)
	Optimization/24	22	11 (50)	18	7 (35)	19	13 (62)	18	14 (67)	20	16 (73)
	Individualization/52/EoS	18	11 (50)	17	8 (40)	16	5 (24)	17	11 (52)	19	13 (59)

N is the number of patients in the FAS population. Patients given placebo were switched to izokibep after week 12. See Figure 1(b) for an overview of dose changes occurring in the optimization and individualization periods. DLQI, Dermatology Life Quality Index; EoS, end of study; PASI, Psoriasis Area and Severity Index; PASI 75, 75% reduction in PASI; PASI 90, 90% reduction in PASI; PASI 100, 100% reduction in PASI; Q2W, every 2 weeks; sPGA, static Physician Global Assessment. [a]Number of patients with a result for the respective endpoint.

Table 3 Secondary efficacy outcomes (continuous endpoints) in the full analysis set by induction period dose group in the phase II dose-finding AFFIRM-35 study

				Izokibep							
		Placebo ($n=22$)		2 mg Q2W ($n=20$)		20 mg Q2W ($n=21$)		80 mg Q2W ($n=21$)		160 mg Q2W ($n=22$)	
Outcome	**Period/week**	***n*[a]**	**Mean (SD)**	***n*[a]**	**Mean (SD)**	***n*[a]**	**Mean (SD)**	***n*[a]**	**Mean (SD)**	***n*[a]**	**Mean (SD)**
PASI	Baseline/0	22	18.9 (8.2)	20	18.0 (6.9)	21	20.2 (8.6)	21	22.7 (10.1)	22	17.9 (6.6)
	Induction/12	22	17.9 (7.5)	19	12.5 (5.0)	20	8.6 (7.5)	17	1.3 (2.1)	21	1.7 (2.1)
	Optimization/24	22	4.3 (4.7)	18	4.4 (4.4)	20	3.6 (4.0)	18	1.3 (1.7)	20	1.1 (1.8)
	Individualization/52/EoS	18	2.0 (2.8)	17	3.0 (3.9)	16	3.1 (2.7)	17	2.6 (2.4)	19	1.4 (1.8)
sPGA	Baseline/0	22	3.2 (0.4)	20	3.2 (0.4)	21	3.4 (0.5)	21	3.4 (0.5)	22	3.4 (0.5)
	Induction/12	22	3.2 (0.5)	19	2.9 (0.6)	20	2.3 (1.1)	17	0.8 (1.0)	21	1.1 (0.9)
	Optimization/24	22	1.5 (1.0)	18	1.8 (1.0)	20	1.5 (1.1)	18	0.8 (0.6)	20	0.8 (0.8)
	Individualization/52/EoS	18	1.3 (1.0)	17	1.5 (1.0)	16	1.9 (0.9)	17	1.4 (0.9)	19	1.2 (1.1)
DLQI	Baseline/0	22	11.4 (5.8)	20	12.7 (5.7)	19	13.3 (7.6)	21	14.3 (6.3)	22	12.1 (5.8)
	Induction/12	22	10.4 (6.8)	19	8.9 (5.2)	20	4.8 (5.9)	17	1.0 (1.2)	21	3.0 (5.3)
	Optimization/24	22	3.5 (4.1)	18	5.1 (5.5)	19	2.9 (4.8)	18	1.7 (3.5)	20	2.3 (5.5)
	Individualization/52/EoS	18	2.4 (4.5)	17	4.1 (4.6)	16	3.7 (4.1)	17	3.0 (5.3)	19	2.2 (4.6)
NAPSI	Baseline/0	20	2.5 (2.3)	18	2.9 (2.6)	20	3.5 (3.2)	20	3.1 (2.4)	21	2.7 (2.6)
	Induction/12	21	2.6 (2.6)	17	2.2 (2.2)	20	2.1 (2.5)	17	1.5 (1.4)	20	2.0 (2.5)
	Optimization/24	20	1.6 (2.1)	16	1.3 (1.6)	20	1.2 (1.8)	17	0.8 (0.9)	18	0.8 (1.3)
	Individualization/52/EoS	17	0.6 (1.4)	15	0.9 (1.5)	15	0.7 (1.6)	15	0.7 (1.2)	17	0.6 (1.3)
Pain VAS[b]	Baseline/0	22	30.4 (32.1)	20	29.0 (27.3)	21	34.8 (32.6)	21	50.2 (30.8)	22	44.0 (33.1)
	Induction/12	22	32.1 (31.6)	19	30.6 (29.1)	20	9.5 (18.9)	17	4.9 (10.2)	21	13.1 (26.8)
	Optimization/24	22	6.0 (13.2)	18	14.2 (19.7)	20	8.3 (18.2)	18	5.2 (9.6)	20	8.3 (19.3)
	Individualization/52/EoS	18	3.4 (5.4)	17	13.9 (25.9)	16	2.2 (2.4)	17	10.9 (23.6)	19	6.1 (10.6)
Itch VAS[b]	Baseline/0	22	54.8 (29.6)	20	62.3 (27.2)	21	49.5 (33.0)	21	63.8 (22.3)	22	61.0 (30.8)
	Induction/12	22	48.8 (33.1)	19	41.5 (31.1)	20	16.8 (25.5)	17	8.4 (18.6)	21	16.0 (25.4)
	Optimization/24	22	12.1 (19.5)	18	23.8 (25.1)	20	9.5 (16.8)	18	11.3 (20.2)	20	12.2 (24.5)
	Individualization/52/EoS	18	7.3 (9.5)	17	18.1 (24.0)	16	7.1 (9.5)	17	14.6 (25.0)	19	12.1 (15.7)

Placebo-receiving patients were switched to izokibep after week 12. See Figure 1(b) for an overview of dose changes occurring in the optimization and individualization periods. DLQI, Dermatology Life Quality Index; EoS, end of study; NAPSI, Nail Psoriasis Severity Index; PASI, Psoriasis Area and Severity Index; sPGA, static Physician Global Assessment; Q2W, every 2 weeks; VAS, visual analogue scale. [a]Number of patients with a result for the respective endpoint; [b]100 mm VAS (0 = none and 100 = worst imaginable).

160-mg group (psoriatic arthropathy and diarrhoea, respectively) and one in the placebo group (atopic dermatitis).

Four *Candida* spp. infections were recorded during the core study, one each in the izokibep 160-mg group (not specified) and placebo group (genital) during the placebo-controlled period, one in the izokibep 160-mg group (oral thrush) during the optimization period and one in the switched placebo group (balanitis) during the individualization period. All were mild-to-moderate in nature and resolved during study treatment.

One hundred patients had a baseline ADA sample and at least one postbaseline sample. The prevalence of baseline ADA was 49% ($n=49$) and a treatment-emergent ADA response (induced or boosted) was detected in 55% ($n=55$) of patients up to 52 weeks (Table S4; see Supporting Information). No clear difference in mean PASI scores was observed among patients with treatment-emergent, reduced or unaffected, or negative ADA responses (Figure 5). The presence of ADA was not associated with AEs.

Table 4 Number of participants with treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) in the safety set during the 12-week placebo-controlled induction period in the phase II dose-finding AFFIRM-35 study

		Izokibep				
AE by preferred term	**Placebo ($n=22$)**	**2 mg Q2W ($n=21$)**	**20 mg Q2W ($n=22$)**	**80 mg Q2W ($n=21$)**	**160 mg Q2W ($n=22$)**	**All patients ($n=108$)**
Any TEAE	15 (68)	14 (67)	14 (64)	15 (71)	22 (100)	80 (74)
Injection site reaction	3 (14)	4 (19)	2 (9)	8 (38)	15 (68)	32 (30)
Nasopharyngitis	7 (32)	3 (14)	4 (18)	3 (14)	9 (41)	26 (24)
Diarrhoea	0	2 (9)	1 (4)	2 (9)	5 (23)	10 (9)
Headache	0	3 (14)	3 (14)	1 (5)	2 (9)	9 (8)
Fatigue	0	1 (5)	0	1 (5)	4 (18)	6 (5)
Any SAE	2 (9)	0	0	1 (5)	1 (4)	4 (4)
AF	1 (4)	0	0	0	0	1 (1)
Fibroadenoma of the breast	1 (4)	0	0	0	0	1 (1)
Meniscus injury	0	0	0	1 (5)	0	1 (1)
OA	0	0	0	0	1 (4)	1 (1)

TEAEs are shown for preferred terms occurring at a frequency of ≥ 10% in any izokibep dosing group. AF, atrial fibrillation; OA, osteoarthritis; Q2W, every 2 weeks.

Long-term outcomes: efficacy and safety

Eighty-eight patients completed the core study, 83 entered the 52-week extension period and 68 entered the 52-week prolongation of extension period (Figure S1, Appendix S3; see Supporting Information). Three-year data were available for 41 patients.

Over half the patients ($n=51/83$; 61%) entered the extension period at a dose of izokibep 80 mg. When the amendment to allow treatment intensification for patients with an inadequate response was introduced, most patients had completed the initial extension period, so only six received intensified treatment during this period (three with dose escalations and three with interval shortening). During the prolongation of extension period, most patients received izokibep 160 mg as their highest dose ($n=45/68$; 66%) and therapy was intensified in 37 patients.

Efficacy outcomes were generally well maintained in patients in the izokibep 80- and 160-mg groups during the 52-week extension period. Fluctuations in PASI 90 response rates were observed during the extension and prolongation of extension periods (Figure S2; see Supporting Information), likely to be related to modifications in dose and dosing intervals, but the numbers were too small to draw firm conclusions from. In the prolongation of extension period, patients in the izokibep 80-mg every 8 weeks (Q8W) and izokibep 160-mg Q8W groups were highly responsive to treatment, as indicated by the highest rates of PASI 90 responses [$n=3/3$ (100%) and $n=4/6$ (67%), respectively].

Patients who intensified treatment during either period showed marked improvements in mean PASI scores (Table S5; see Supporting Information). Overall, the data indicated maintenance of izokibep efficacy over 3 years, but small numbers precluded a confident assessment of trends in efficacy outcome by dose or dosing interval.

TEAEs during the extension period and prolongation of extension period were limited and generally balanced across groups (Tables S6, S7; see Supporting Information). There were no reports of *Candida* spp. infection, IBD or death.

Discussion

In this study of patients with moderate-to-severe plaque psoriasis, IL-17A inhibition with the novel SC agent izokibep resulted in rapid and robust reductions in disease activity in patients in the higher dosage groups (izokibep 80 or 160 mg Q2W). The primary endpoint (PASI 90 at week 12) was achieved by 71% of patients in the izokibep 80-mg Q2W group vs. no patients in the placebo group. Marked decreases in PASI scores were observed as early as week 2 and maintained throughout the core study. Secondary efficacy outcomes showed similar rapid improvements.

A clear dose-dependency was observed in efficacy outcomes from izokibep 2 mg to 80 mg Q2W at week 12. The lower PASI 90 response rates in patients in the izokibep 160-mg vs. the izokibep 80-mg group at week 12 may have been due to differences in baseline disease activity. Furthermore,

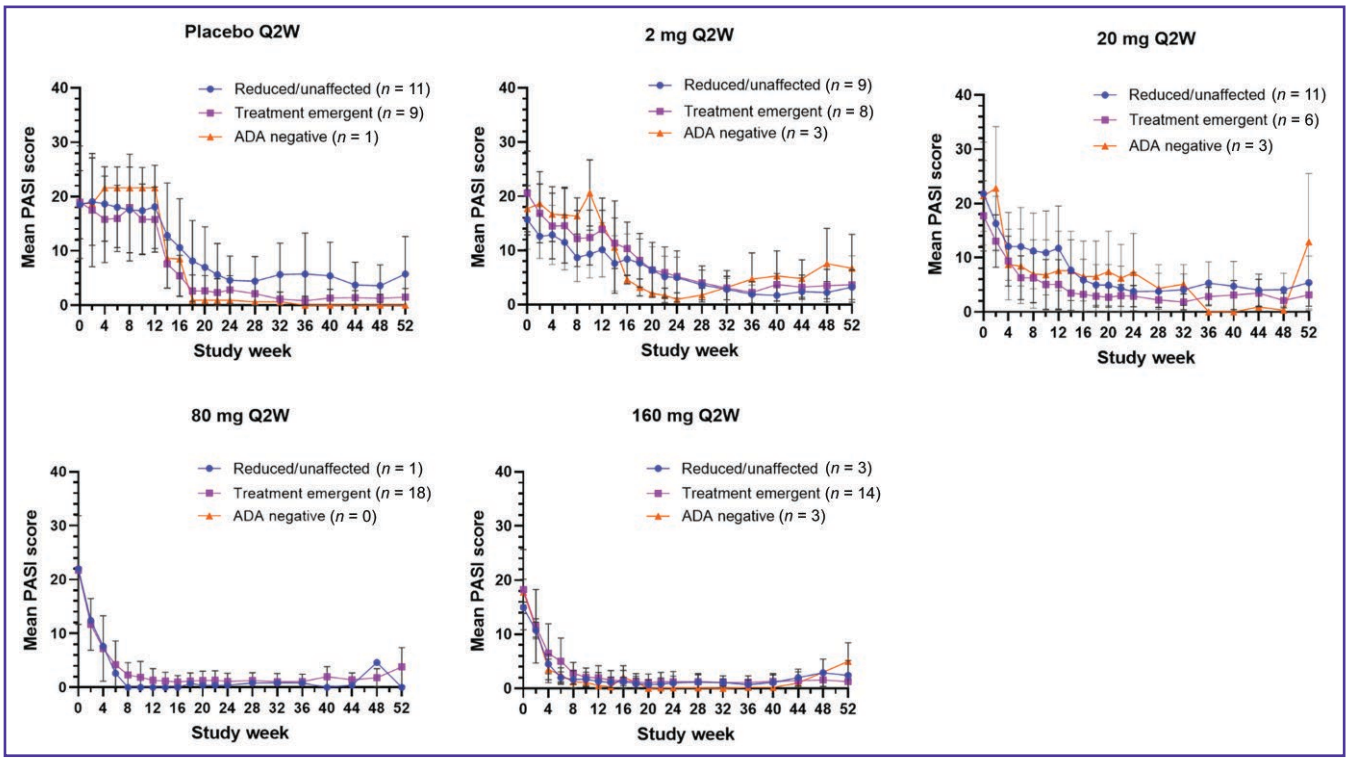

Figure 5 Mean Psoriasis Area and Severity Index (PASI) score over time stratified by antidrug antibody (ADA) status. Patients were grouped according to treatment during the induction period (0–12 weeks). During the remainder of the 52-week core study, those receiving placebo were switched to izokibep 80 mg and, for all patients, doses and dosing intervals were adapted based on PASI scores. ADA negative: patients negative for pre-existing ADA and treatment-emergent ADA throughout the core study. Treatment emergent: participants with treatment-induced or treatment-boosted ADA (defined as a twofold or higher increase in any postdose titre vs. the predose titre). Reduced/unaffected: pre-existing ADA-positive participants whose titres did not increase by twofold or higher following izokibep exposure. Q2W, every 2 weeks.

in the izokibep 80-mg group the mean BMIs and proportion of female patients were lower than in the izokibep 160-mg group. These factors could potentially influence the PASI response.[13–15] For patients who completed full treatment in the core study, the PASI 90 response rate at week 52 was lower for those randomized to izokibep 80 mg Q2W ($n=9/17$; 53%) vs. izokibep 160 mg Q2W ($n=15/19$; 79%).

The safety profile of izokibep was generally comparable to placebo at week 12 except for certain AEs, including injection site reactions and diarrhoea. These AEs decreased after the first 12 weeks of the study. There were no cases of IBD and a very low incidence of *Candida* spp. infection, comparable to placebo.

Although head-to-head trials are required for accurate comparisons of therapeutic agents, efficacy data from the 12-week placebo-controlled part of the study are comparable with those from anti-IL-17 monoclonal antibodies used to treat patients with psoriasis, including bimekizumab, ixekizumab and secukinumab. Randomized trials with these agents show PASI 90 response rates at week 12 ranging from approximately 60% to 80%, depending on the agent and study.[10–12,16–19] The safety profile of izokibep compares favourably with anti-IL-17 monoclonal antibodies, particularly with respect to candidiasis and IBD. An increased risk of these conditions has been reported in patients with psoriasis treated with anti-IL-17 monoclonal antibodies;[20,21] higher rates of candidiasis may be related to the additional inhibition of IL-17F.[4,9]

The efficacy of izokibep observed during the first year was largely maintained over the second year; the highest PASI 90 response rates were observed in the izokibep 160-mg treatment groups followed by the izokibep 80-mg treatment groups. Lower response rates were observed in the izokibep 20-mg group, and treatment intensification was mainly confined to patients in the izokibep 20-mg group or those with extended interval (Q8W) treatment. During the third year of treatment, the efficacy of izokibep was maintained or further improved during response-guided treatment. Patients who required treatment intensification had an excellent response to higher doses and shorter intervals. These observations suggest that izokibep doses $\geq$ 80 mg and more frequent dosing may provide optimal treatment and that treatment intensification may be able to improve outcomes. No obvious association between ADA and PASI scores was observed during the core study. At present, the most likely reason in cases of reduced efficacy is the dosing regimen (i.e. dose and frequency). Izokibep was safe and well tolerated over 3 years of exposure, and there were no dose-limiting safety concerns, suggesting that higher or more frequent doses of izokibep may be an option.

Study limitations include the small number of patients in the dosing subgroups, which complicated the interpretation of differences in response in groups with varying doses and/or dosing intervals. The population in the study had limited diversity. The exclusion of patients with a history of *Candida* spp. infections and IBD may have resulted in lower rates of these AEs.

In conclusion, SC izokibep demonstrated rapid and robust efficacy at dosages of 80 or 160 mg Q2W in patients with moderate-to-severe plaque psoriasis. Efficacy was generally maintained with longer dosing intervals (Q4W) following the initial induction period and izokibep showed a favourable safety profile for up to 3 years. No dose-limiting toxicities were observed, suggesting that higher doses and/or more frequent dosing could be explored. Our data suggest that izokibep has the potential to be a valuable therapeutic option for plaque psoriasis and may also be useful in other immune-mediated inflammatory disorders, including psoriatic arthritis.[22]

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Conflicts of interest

S.G. has received grants, contracts, honoraria, support for meetings/travel and/or participated in advisory or data safety monitoring boards for AbbVie, ACELYRIN, Affibody, Akari Therapeutics, Almirall-Hermal, Amgen, argenx, Aristea Therapeutics, Biogen Idec, Bioskin, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, Hexal, Incyte, Janssen-Cilag, Johnson & Johnson, Klinge Pharma, Kymab, LEO Pharma, Medac, MSD, Neubourg Skin Care, Novartis, Pfizer, Pierre Fabre, Principia Biopharma, Regeneron Pharmaceutical, Sandoz Biopharmaceuticals, Sanofi-Aventis, Trevi Therapeutics and UCB Pharma; and has received equipment, materials, drugs, medical writing or other services from AbbVie, Almirall-Hermal, Amgen, Celgene, Eli Lilly, Janssen-Cilag, LEO Pharma, Medac, Novartis, Pfizer, Sanofi-Aventis and UCB Pharma. P.S. has received grants, contracts, honoraria, support for meetings/travel and/or has participated in advisory or data safety monitoring boards for AbbVie, Allergika, Almirall-Hermal, Amgen, Beiersdorf, Biocryst, BMS, Boehringer Ingelheim, Celgene, CSL-Behring, Eli Lilly, Galderma, Hexal, Janssen, Klinge, Klosterfrau, LEO Pharma, LETI Pharma, L'Oréal, Novartis, Octapharma, Pfizer, Pflüger, Pharming, Regeneron, Shire, Takeda, Regeneron, Sanofi-Genzyme und UCB Pharma. D.W. has received consulting fees from Affibody and ACELYRIN. M.A. has received grants, contracts and/or consulting fees from Arbeitsgemeinschaft Dermatologische Prävention (ADP) Education of Referees for certificate "Hautkrebs-Screening" issued by Zentralinstitut für Kassenärztliche Versorgung, Lumenis and various companies involved in laser treatments in dermatology. G.V. has received consulting fees from Affibody. J.F. is an employee of Affibody, owns stock in Affibody and is a patent holder of five patents

involving interleukin-17A-binding and albumin-binding polypeptides. L.O.K., S.O. and N.C.B. are employees of Affibody and have stock options for Affibody. P.P. is an employee of ACELYRIN and has stock options for ACELYRIN. F.Y.F. is an employee of Affibody, owns stock in Affibody and has stock options for Affibody. T.D., O.W., J.N., R.d.M, and A.R. declare no conflicts of interest.

Data availability

The data that support the findings of this study are available for collaborative research upon reasonable request.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and approved by a lead ethics committee (Ethik-Kommission der Medizinischen Fakultät der Christian-Albrechts-Universität zu Kiel; reference number 129/17) and by each local ethics committee for participating sites. All patients provided written informed consent.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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