Supplementary Materials

Efficacy and safety of izokibep in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study

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Table of Contents

Supplemental Section S1 Inclusion and exclusion criteria

Inclusion criteria

1. Patient who has given his/her signed declaration of consent and data protection declaration
2. At least 18 years and less than 75 years of age at the screening visit
3. Psoriatic arthritis (PsA) with inflammatory musculoskeletal disease (joint, spine or entheseal) with the presence of ≥3 points from the five categories of the Classification Criteria for Psoriatic Arthritis at any time point in medical history
4. Active PsA defined by:
    a. ≥3 swollen joints out of 66 joints (swollen joint count based on 66 joints [SJC66]) at the screening visit and baseline visit
    b. ≥3 tender joints out of 68 (tender joint count based on 68 joints [TJC68]) at the screening visit and baseline visit
5. Precedent failure or insufficient treatment response to at least one of the following PsA treatments:
    a. Non-steroidal anti-inflammatory drug
    b. Conventional synthetic disease-modifying antirheumatic drug (csDMARD; i.e. methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, cyclosporine A)
    c. Tumour necrosis factor inhibitor (TNFi; e.g. adalimumab, infliximab, etanercept, golimumab, certolizumab)
6. Rheumatoid factor and anti–cyclic citrullinated peptide antibody negative
7. Presence or history of plaque psoriasis (PsO)
8. For females of childbearing potential only: negative serum human chorionic gonadotropin test at screening visit
9. Willingness and capability of using adequate contraceptive methods from the screening visit until 14 weeks after the last izokibep dose
    a. Female of childbearing potential should use a highly efficient method of contraception but this is not necessary for females of non-childbearing potential permanently sterilised or post-menopausal (i.e. at least 12 consecutive months with amenorrhea without other known or suspected medical cause)
    b. Male who has a female partner of childbearing potential should use a highly efficient method of contraception
    c. Adequate contraceptive method defined as the following:
        i. A method with less than 1% failure rate (e.g. permanent sterilisation, hormone implants, hormone injections, some intrauterine devices, vasectomised partner)

    OR

        ii. The use of two methods of contraception (e.g. one barrier method [condom,

diaphragm, cervical/vault caps] with spermicide and one hormonal contraceptive [e.g. combined oral contraceptives, patch, vaginal ring, injectables and implants])

10. Willingness and capability of complying with all trial procedure requirements as per the investigator's judgement

Exclusion criteria

Medical and surgical history

1. Underlying conditions, which in the investigator's opinion significantly immunocompromise the patient and/or place the patient at unacceptable risk for receiving an immunomodulatory therapy
2. History of or current relevant autoimmune diseases (e.g. rheumatoid arthritis, primary ankylosing spondylitis, systemic lupus erythematosus) other than PsO or PsA
3. History of or current fibromyalgia or pain syndrome
4. Uncontrolled inflammatory bowel disease
5. Presence or history of recurrent or medically important infections in the last 6 months prior to the baseline visit (e.g. due to bacterial, mycobacterial, invasive fungal, parasitic, viral other opportunistic infections that required medical/pharmaceutical intervention [i.e. prescription of antibiotics and/or hospitalisation])
6. Clinically relevant *Candida* infection requiring systemic treatment within the last 6 months prior to the baseline visit
7. History or any signs of lymphoproliferative disease or a known malignancy or a history of malignancy within the previous 5 years (with the exception of basal cell or squamous cell carcinoma of the skin that had been fully excised with no evidence of recurrence)
8. Insufficiently controlled heart failure as assessed by the investigator
9. Current uncontrolled arterial hyper- or hypotension

Laboratory examinations and body measurements

10. Positive test for subclinical/latent tuberculosis infection (i.e. positive QuantiFERON-TB® Gold test or equivalent product) or chest X-ray suggestive of tuberculosis at the screening visit
11. Positive test for human immunodeficiency virus (HIV) to hepatitis B (HBV) or hepatitis C (HCV) at the screening visit
    a. HIV antibody (any test)
    b. HBV surface antigen
    c. Anti-HCV antibody
12. Alanine aminotransferase or aspartate aminotransferase level ≥2.5 times the upper limit of normal at the screening visit

13. Estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 according to the Chronic Kidney Disease-Epidemiology Collaboration equation at the screening visit
14. Body mass index (BMI) ≥40 kg/m^2 or <16 kg/m^2

Medication to drug use and special behavioural patterns

15. Previous exposure to izokibep or any other interleukin-(IL)17i or IL-17 receptor inhibitor (e.g. secukinumab, ixekizumab, brodalumab)
16. History of hypersensitivity or allergy to izokibep or its excipients
17. Exposure to IL-12/23 inhibitors within 12 weeks, TNFi within 8 weeks (except etanercept within 2 weeks), csDMARD within 6 weeks and/or systemic and/or intraarticular glucocorticoid and/or Janus kinase inhibitors (JAKi) within 4 weeks prior to the baseline visit (apart from one csDMARD or oral glucocorticoids, if on a chronic and stable dose at the baseline visit)
18. Previous failure to more than two TNFi or any exposure to more than four TNFi
19. Failure to JAKi or previous exposure to more than two JAKi (e.g. tofacitinib)
20. Current use of more than one csDMARD
21. Ongoing or 4 weeks prior to the baseline visit systemic PsO treatments (e.g. biological therapies, mycophenolate mofetil, azathioprine, tacrolimus, retinoids, fumarates, apremilast or phototherapy [e.g. psoralen and ultraviolet A, ultraviolet A, ultraviolet B, (UVB), UVB311])
22. Use of high potency opioid analgesics (e.g. methadone, hydromorphone, morphine)
23. Live vaccination within 12 weeks prior to the baseline visit to or intend to have a live vaccination during the course of the study or within 15 weeks of completing treatment in this clinical trial to or have participated in a vaccine clinical trial within 12 weeks prior to the baseline visit
24. Participation in another clinical trial within 30 days prior to the screening visit or administration of another investigational medicinal product within five half-lives (for biologics, 6 months or five half-lives, whichever is longer) prior to the baseline visit
25. Evidence or indication of drug and/or alcohol abuse or dependence according to the judgement of the investigator

Other exclusion criteria

26. Females who are currently pregnant, who intend to become pregnant during the course of the trial or who are breastfeeding
27. Previous randomisation in the current clinical trial
28. Patient is an investigator to trial site or sponsor personnel directly affiliated with this clinical trial and/or their immediate families (partner, spouse, parent, child or sibling, whether biological or legally adopted)
29. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the patient from adhering to the protocol or completing the clinical trial per protocol

30. Patient is considered to belong to a vulnerable population (e.g. placed under guardianship, imprisoned)

Supplemental Table S1 Study centres and investigators

Country	Study centre (city)	Principal investigator
Austria	LKH Universität Klinikum (Graz)	Dr. Rusmir Husic
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Czech Republic	VESALION s.r.o (Ostrava)	Dr. Libor Novosad
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Germany	Centrum für Diagnostik und Therapy Rheumatologie/Immunologie (Frankfurt)	Prof. Frank Behrens
	Schlosspark Klinik (Berlin)	Prof. Rieke Alten
	Rheumatologische Schwerpunktpraxis (Berlin)	Prof. Jan Brandt-Jürgens
	Universitätsklinikum Freiburg (Freiburg)	Dr. Stephanie Finzel
	Rheumazentrum Ruhrgebiet (Herne)	Prof. Jürgen Braun
	Klinikum der Universität München Rheumatologie (Munich)	Prof. Hendrik Schulze-Koops
	Rheumazentrum Ratingen (Ratingen)	Dr. Siegfried Wassenberg
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	CRU Hungary Ltd (Miskolc)	Dr. Katalin Fazekas
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Supplemental Table S2 Additional pre-specified efficacy outcomes during the placebo-controlled study period (up to week 16, observed data)

Outcome	Week	PBO (N=44)			Izokibep 40 mg (N=44)				Izokibep 80 mg (N=47)			
		n	Mean	SD	n	Mean	SD	*P* value vs PBO*	n	Mean	SD	*P* value vs PBO*
Musculoskeletal and inflammatory endpoints												
TJC68 score	8	41	10.5	7.5	42	9.0	10.5	0.0108	46	7.4	7.2	0.0014
	12	42	10.9	8.7	43	8.1	8.9	<0.0001	46	6.0	6.7	<0.0001
SJC66 score	8	41	6.0	6.2	42	3.5	4.1	0.0002	46	3.7	4.7	<0.0001
	12	42	5.1	5.2	43	2.6	3.4	<0.0001	46	2.3	3.4	<0.0001
ESR (mm/h)	8	41	23.0	16.4	43	16.4	17.0	0.0135	47	14.8	10.0	0.0013
	12	42	21.9	16.0	43	16.4	15.1	0.0847	46	13.8	10.0	0.0017
	16	43	23.6	16.3	42	16.3	19.4	0.0081	46	14.7	10.1	0.0003
CRP (mg/L)	8	40	8.36	9.18	42	4.20	5.57	<0.0001	47	3.05	3.13	<0.0001
	12	42	9.47	11.75	43	4.09	4.89	<0.0001	46	3.48	4.18	<0.0001
	16	43	8.33	9.13	42	5.76	9.89	0.0098	44	3.15	3.78	<0.0001
Psoriasis-related endpoints												
NAPSI score (target nail)	8	35	2.9	1.9	35	1.9	1.8	0.0132	39	2.1	2.0	0.0591
Patient-reported outcomes												
Worst Itch NRS score	16	43	3.6	2.9	42	2.2	2.5	0.0048	46	3.0	2.3	0.0194
DLQI sum score	16	43	7.1	7.8	42	3.0	3.5	0.6412	46	3.9	4.1	0.5907
Composite and global disease activity outcomes												
DAPSA clinical score	16	43	25.77	16.06	42	16.51	14.81	<0.0001	46	14.08	11.47	<0.0001
DAS28-ESR score	16	43	4.27	1.26	42	3.11	1.36	<0.0001	46	3.15	1.07	<0.0001

*Adjusted for previous TNFi exposure, concomitant csDMARD use, country, treatment, visit and treatment by visit interaction. Two-sided *P* values <0.05 were considered statistically significant.

CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28, Disease Activity Score in 28 joints; DLQI, Dermatology Life Quality Index; ESR, erythrocyte sedimentation rate; NAPSI, Nail Psoriasis Severity Index; NRS, numerical rating scale; PBO, placebo; SD, standard deviation; SJC66, swollen joint count based on 66 joints; TJC68, tender joint count based on 68 joints; TNFi, tumour necrosis factor inhibitor.

Supplemental Table S3 Selected efficacy outcomes at weeks 32 and 46 (observed data)

Outcome	Placebo→Izokibep 80 mg*				Izokibep 40 mg				Izokibep 80 mg			
	Week 32		Week 46		Week 32		Week 46		Week 32		Week 46	
	n	Value	n	Value	n	Value	n	Value	n	Value	n	Value
Musculoskeletal endpoints												
LDI-B for patients with LDI-B >0 at baseline	8	0.64 (1.81)	5	0.00 (0.00)	6	0.00 (0.00)	4	0.00 (0.00)	4	0.00 (0.00)	3	0.00 (0.00)
LDI-B=0 for patients with LDI-B >0 at baseline†	8	7 (88%)	5	5 (100%)	6	6 (100%)	4	4 (100%)	4	4 (100%)	3	3 (100%)
SPARCC EI in patients with SPARCC EI >0 at baseline†	24	1.6 (2.4)	16	0.8 (1.8)	26	0.6 (0.9)	13	0.5 (0.9)	26	1.0 (2.1)	18	0.9 (2.1)
LEI in patients with LEI >0 at baseline†	8	0.3 (0.7)	5	0.4 (0.9)	12	0.4 (0.7)	6	0.3 (0.8)	15	0.3 (0.7)	9	0.2 (0.7)
Psoriasis-related endpoints												
PASI90‡	13	8 (62%)	11	10 (91%)	17	13 (76%)	9	6 (67%)	19	15 (79%)	14	11 (79%)
NAPSI score (target nail)	25	1.3 (1.7)	17	0.5 (1.1)	29	0.7 (1.2)	12	0.7 (1.3)	27	1.1 (1.4)	16	1.0 (2.1)
Patient-reported outcomes												
PsAID-9	31	3.15 (2.12)	21	2.25 (2.12)	32	3.11 (2.16)	17	3.21 (2.53)	33	2.67 (1.89)	21	2.28 (2.00)
HAQ-DI	31	0.87 (0.67)	21	0.77 (0.72)	32	0.76 (0.65)	17	0.74 (0.66)	33	0.79 (0.65)	21	0.77 (0.64)
Patient's pain assessment	31	35.0 (21.9)	21	21.0 (23.2)	32	33.2 (26.3)	17	37.4 (30.1)	33	27.4 (21.6)	21	19.0 (20.3)

Outcome	Placebo→Izokibep 80 mg*				Izokibep 40 mg				Izokibep 80 mg			
	Week 32		Week 46		Week 32		Week 46		Week 32		Week 46	
	n	Value	n	Value	n	Value	n	Value	n	Value	n	Value
Patient's global assessment	31	32.9 (21.2)	21	18.6 (20.2)	32	33.1 (26.0)	17	38.1 (31.5)	33	25.8 (21.4)	21	19.1 (21.2)
Average Itch NRS	31	1.6 (1.9)	21	1.6 (2.0)	32	2.2 (2.4)	17	2.9 (2.6)	33	2.4 (2.1)	21	1.7 (2.0)
Composite and global disease activity outcomes												
DAPSA composite score	31	16.92 (11.86)	21	11.55 (10.68)	32	14.74 (13.03)	17	15.69 (13.18)	33	13.30 (9.38)	20	10.91 (9.35)
DAPSA clinical score	31	13.40 (11.84)	21	8.91 (10.80)	32	11.50 (12.01)	17	12.90 (12.46)	33	9.75 (8.36)	21	7.15 (7.40)
DAS28-CRP	31	2.71 (0.88)	21	2.20 (0.86)	32	2.52 (1.00)	17	2.50 (1.01)	33	2.48 (0.91)	20	2.09 (0.89)
DAS28-CRP ≤2.6 (remission)†	31	17 (55%)	21	16 (76%)	32	17 (53%)	17	10 (59%)	33	20 (61%)	20	15 (75%)
DAS-ESR score	31	2.98 (1.04)	21	2.37 (0.97)	31	2.72 (1.26)	17	2.76 (1.16)	33	2.59 (1.10)	21	2.15 (1.04)
Physician's global assessment	31	16.5 (14.2)	21	10.7 (13.0)	32	13.7 (13.1)	17	17.5 (18.1)	33	10.2 (9.8)	21	7.5 (9.1)

Values are presented as n (%) or mean (SD).

*Placebo patients were switched to izokibep 80 mg Q2W at week 16.

†Subgroup analyses not pre-specified in the study protocol.

‡In patients with >3% BSA at baseline.

BSA, body surface area; DAPSA, Disease Activity in Psoriatic Arthritis; DAS, Disease Activity Score; DAS28-CRP, Disease Activity Score in 28 joints with C-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; LDI-B, Leeds Dactylitis Index-Basic; LEI, Leeds Enthesitis Index; NAPSI, Nail Psoriasis Severity Index; NRS, numerical rating

scale; PASI, Psoriasis Area Severity Index; PsAID, Psoriatic Arthritis Impact of Disease; Q2W, every two weeks; SD, standard deviation; SPARCC EI, Spondyloarthritis Research Consortium of Canada Enthesitis Index.

Supplemental Table S4 Serious adverse events

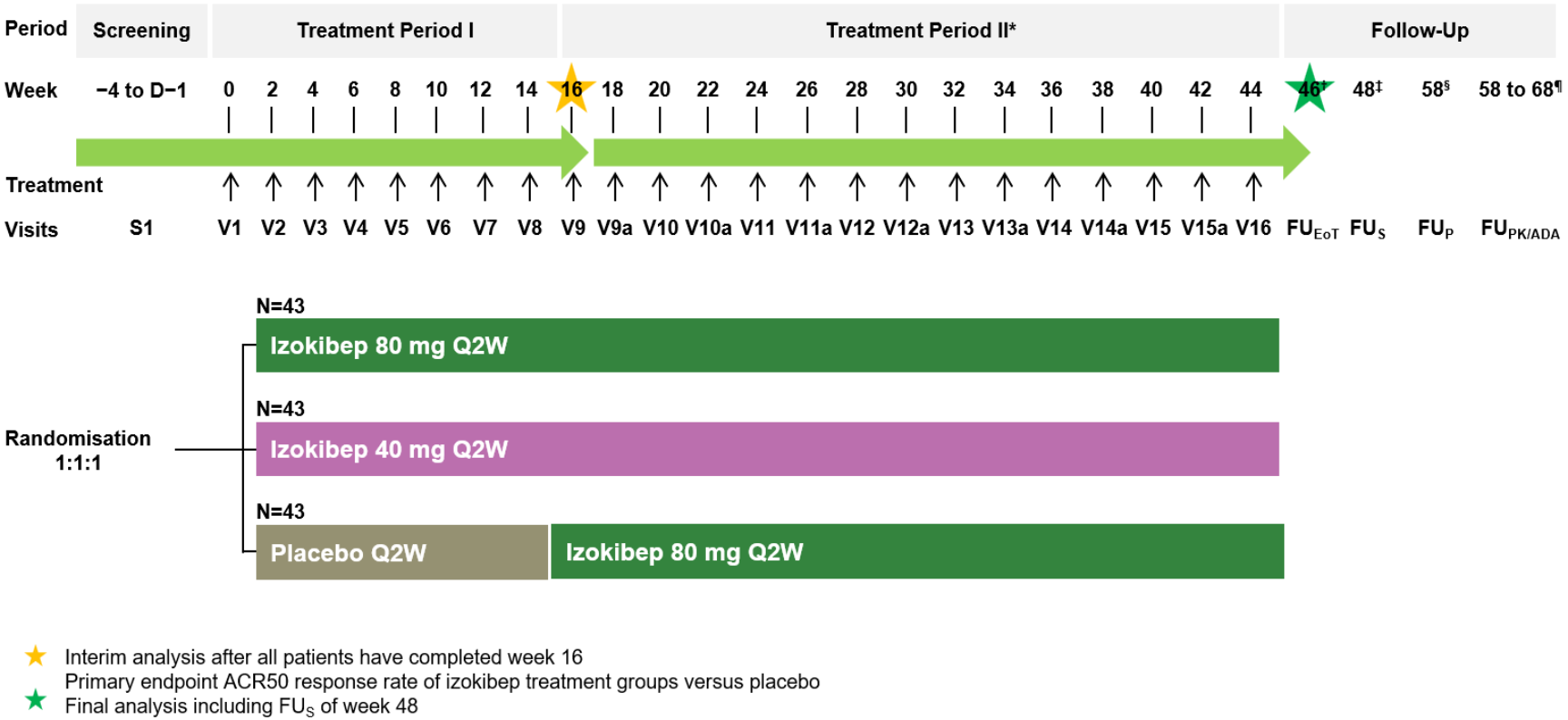
Serious adverse event	Number of patients	Treatment	Trial period	Outcome
Unstable angina	1	Izokibep 40 mg	16 to 46 weeks	Recovered/resolved
Hepatitis E infection	1	Placebo to izokibep 80 mg	16 to 46 weeks	Recovered/resolved
Intercostal neuralgia	1	Placebo to izokibep 80 mg	16 to 46 weeks	Recovered/resolved
Concussion*	1	Placebo to izokibep 80 mg	16 to 46 weeks	Recovered/resolved
Ulna fracture*	1	Placebo to izokibep 80 mg	16 to 46 weeks	Recovered/resolved
COVID-19–associated pneumonia	1	Izokibep 80 mg	16 to 46 weeks	Recovered/resolved
Ligament injury	1	Izokibep 80 mg	16 to 46 weeks	Recovered/resolved
Vulval cancer†	1	Izokibep 80 mg	16 to 46 weeks	Unknown

*The same patient experienced both a concussion and fracture of the ulna.

†57-year-old female with longstanding PsA treatment. The event was initially reported as early-stage, highly differentiated, squamous human papillomavirus–associated cell carcinoma of the vulva (pT1a, G1, L0, V0). After laser excision, the event was downgraded to vulval intraepithelial neoplasia (uVIN3). After approximately 4 months of izokibep exposure, this latency period is considered too short to be a treatment-related effect.

COVID-19, coronavirus disease 2019; PsA, psoriatic arthritis.

Supplemental Figure S1 Clinical trial design.



*Premature termination of the trial during treatment period II affecting approximately up to 75 of 135 randomised patients.

†FU_{EoT}.

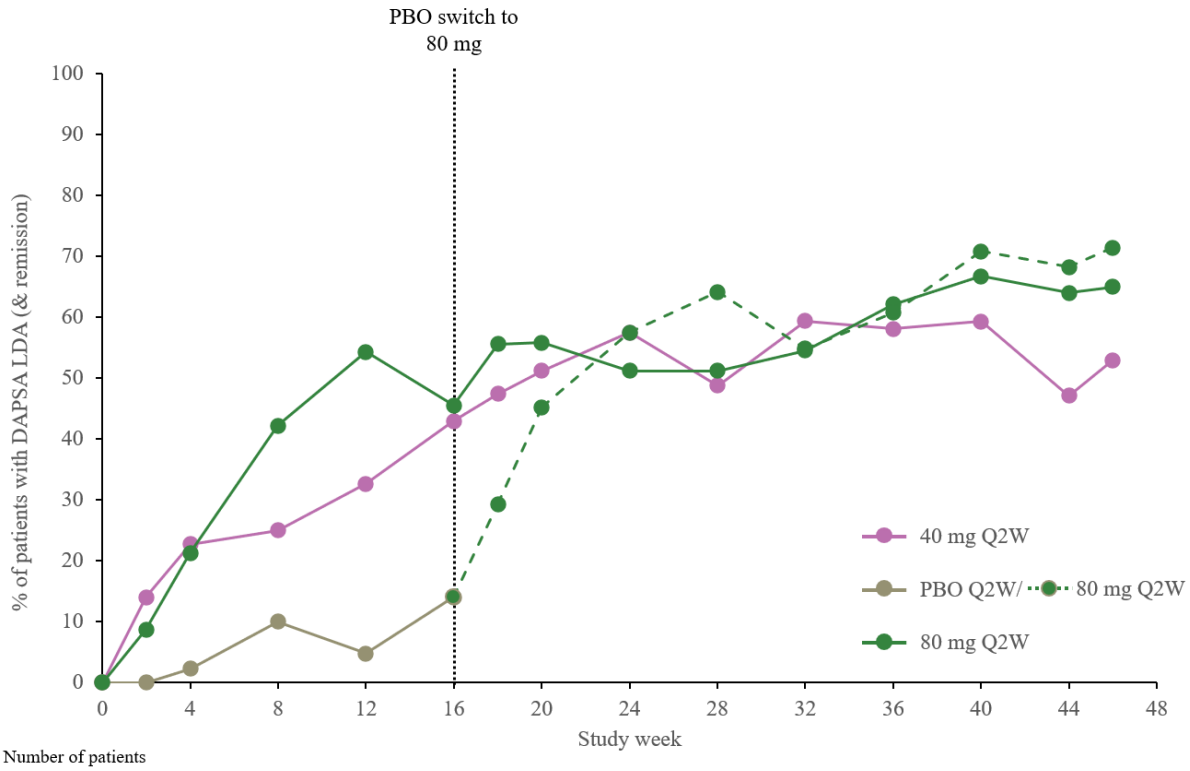
‡FU_S via phone call.

§F_{UP} in females of childbearing potential.

¶$FU_{PK/ADA}$ at trial completion visit.

ACR50, ≥50% improvement from baseline based on American College of Rheumatology criteria; D, day; FU_{EoT}, end of treatment visit; $FU_{PK/ADA}$, follow-up of pharmacokinetics and anti-drug antibodies; FU_S, follow-up of safety; FU_{UP}, follow-up visit for pregnancy test; Q2W, every 2 weeks; S, screening; V, visit.

Supplemental Figure S2 DAPSA LDA (including remission) responses over 46 weeks (observed data).



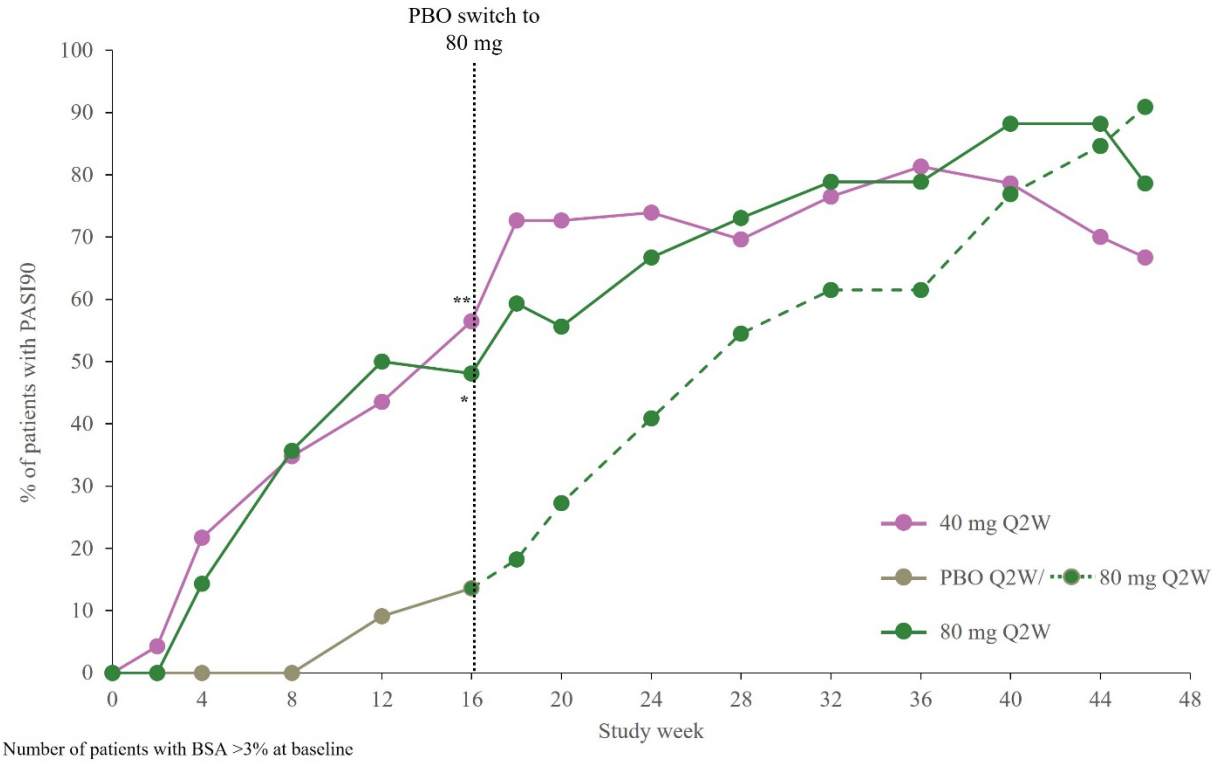
Number of patients

	Observed									Observed					
Week	**0**	**2**	**4**	**8**	**12**	**16**	**18**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**46**
40 mg	44	43	44	40	43	42	38	41	40	41	32	31	27	17	17
PBO/80 mg	44	44	44	40	42	43	41	42	40	39	31	28	24	22	21
80 mg	46	46	47	45	46	44	45	43	41	43	33	29	24	25	20

DAPSA LDA and remission were defined as scores ≤14; analyses were conducted post hoc.

DAPSA LDA, Disease Activity in Psoriatic Arthritis low disease activity; PBO, placebo; Q2W, every 2 weeks.

Supplemental Figure S3 PASI90 responses over 46 weeks in patients with >3% BSA at baseline (observed data).



Number of patients with BSA >3% at baseline

Week	0	2	4	8	12	16	18	20	24	28	32	36	40	44	46
40 mg	23	23	23	23	23	23	22	22	23	23	17	16	14	10	9
PBO/80 mg	23	23	23	22	22	22	22	22	22	22	13	13	13	13	11
80 mg	28	28	28	28	28	27	27	27	27	26	19	19	17	17	14

*Two-sided $P<0.05$; **$P<0.001$ in analyses of modelled data for izokibep versus placebo.

BSA, body surface area; PASI90, 90% reduction from baseline in Psoriasis Area and Severity Index; PBO, placebo; Q2W, every two weeks.