A randomized, double-blind, placebo-controlled phase 1 study of multiple ascending doses of subcutaneous M1095, an anti–interleukin 17A/F nanobody, in moderate-to-severe psoriasis

Danka Svecova, MD, PhD,[a] Martin W. Lubell, MD,[b] Florence Casset-Semanaz, MSc,[b] Harald Mackenzie, MBChB,[b] Roland Grenningloh, PhD,[b] and James G. Krueger, MD[c]
Bratislava, Slovakia; Billerica, Massachusetts; and New York, New York

Background: Interleukin 17 is involved in the pathogenesis of psoriasis, a chronic debilitating disease.

Objectives: To evaluate the safety/tolerability, immunogenicity, pharmacokinetics/pharmacodynamics, and efficacy of M1095, an anti–interleukin 17A/F nanobody, in moderate-to-severe plaque psoriasis.

Methods: This multicenter, double-blind, placebo-controlled dose escalation phase 1 study randomized 44 patients 4:1 to treatment with subcutaneous M1095 (30, 60, 120, or 240 mg) or placebo biweekly for 6 weeks, in 4 ascending dose cohorts.

Results: The most frequent treatment-emergent adverse events with M1095 were pruritus (n = 4) and headache (n = 3); 2 patients withdrew owing to adverse events (injection site reaction and elevated liver enzyme levels). The terminal half-life of M1095 was 11 to 12 days. The area under the curve/maximum concentration was dose proportional. Of 10 M1095-treated patients positive for antidrug antibodies, 5 showed treatment-emergent antidrug antibody responses. There was no effect on M1095 exposure. Marked decreases in psoriasis inflammatory markers were observed with M1095. By day 85, 100% and 56% of patients receiving M1095, 240 mg, achieved psoriasis area and severity index 90 and 100, respectively. Improvements in static Physician's Global Assessment and affected body surface area were also seen.

Limitations: Interpretation of efficacy data is limited by the small sample size.

Conclusion: Multiple subcutaneous doses of M1095 showed a favorable safety profile with dose-dependent improvements in psoriasis. (J Am Acad Dermatol 2019;81:196-203.)

Key words: ALX-0761; interleukin 17; M1095; nanobody; phase 1; psoriasis.

From the Faculty of Medicine of Comenius University, Bratislava, Slovakia[a]; EMD Serono Research and Development Institute, Billerica[b]; and Rockefeller University, New York.[c]

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Correspondence to: Roland Grenningloh, PhD, EMD Serono Research and Development Institute, 45A Middlesex Turnpike, Billerica 01821, MA. E-mail: roland.grenningloh@emdserono.com.

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Increasing evidence demonstrates that interleukin 17 (IL-17) plays a vital role in psoriasis pathophysiology.[1] IL-17 is a mediator of autoimmunity and inflammation produced by type 17 helper T cells among other leukocytes.[2] IL-17 inhibition modulates inflammation primarily by reducing production of many feed-forward inflammatory products made by keratinocytes in psoriasis lesions.[3] These products include chemokines that regulate trafficking of neutrophils, T cells, and dendritic cells (C-X-C motif chemokine ligands 1 to 8 and C-C motif chemokine ligand 20), antimicrobial proteins (lipocalin 2, beta-defensin, cathelicidin/LL37), psoriasin (S100A7), and cytokines that potentially drive keratinocyte proliferation (IL-19 and IL-36), thus inducing keratin 16 and Ki-67).[4] The IL-17 family includes 6 cytokines (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E/IL-25, and IL-17F).[5] IL-17A and IL-17F homodimers or heterodimers[5] bind to the IL-17R (formed by IL-17RA and IL-I7RC subunits)[6] and drive inflammation via effects on multiple cell types.[7-9] For example, through IL-8 induction by various cell types, including fibroblasts and synoviocytes, both IL-17A and IL-17F indirectly recruit neutrophils.[7] This has been demonstrated in vitro through dual neutralization of IL-17A and IL-17F, leading to greater IL-8 inhibition than IL-17A inhibition alone.[10] Therefore, neutralizing both IL-17A and IL-17F may provide a more effective way to block inflammatory responses in psoriasis. Monoclonal antibodies targeting IL-17A or IL-17RA are effective in treating plaque psoriasis,[11-13] and secukinumab, ixekizumab, and brodalumab have been US Food and Drug Administration—approved. Whereas secukinumab and ixekizumab neutralize IL-17A alone, brodalumab prevents binding of IL-17A, IL-17F, and IL-25 to the shared IL17RA receptor.[11-13] Recently, dual blockade of both IL-17A and IL-17F by using bimekizumab (which binds to a common region shared by IL-17A and IL-17F) was shown to be effective in patients with psoriasis.[14]

Nanobodies are derived from the variable domain of the camelid heavy-chain-only antibodies. Several nanobodies can be linked by using glycine-serine linkers to obtain molecules with multiple specificities.[15] The novel trivalent, bispecific anti—IL-17A/F nanobody comprises 3 sequence-optimized, monovalent camelid nanobodies that are specific for (1) human IL-17F, (2) both human IL-17A and IL-17F, and (3) human serum albumin (for half-life extension) (Fig 1).[15] M1095 contains humanized sequences to reduce immunogenicity, and because of its smaller size (40 kDa), it may potentially have better tissue penetration than conventional antibodies do,[15] although this remains unconfirmed.

To our knowledge, M1095 is the first bispecific nanobody to be studied in psoriasis. The objectives of this study were to (1) assess the safety, tolerability, pharmacokinetics, and immunogenicity and (2) evaluate the pharmacodynamic profile and efficacy of multiple subcutaneous doses of M1095 in patients with moderate-to-severe psoriasis.

CAPSULE SUMMARY

- To our knowledge, this is the first study in moderate-to-severe psoriasis to utilize a nanobody (M1095) that targets both interleukin 17A and interleukin17F.
- This randomized, double-blind phase 1 trial showed a favorable safety profile for M1095, as well as promising efficacy. The M1095 nanobody offers the potential to neutralize multiple targets in psoriasis.

METHODS

Study design

This randomized, double-blind, placebo-controlled phase 1 study evaluated M1095 in multiple ascending subcutaneous doses of 30, 60, 120, and 240 mg in patients with moderate-to-severe psoriasis over 15 weeks: a 3-week screening period, 6-week treatment period (dosing every other week for 3 doses), and a 6-week follow-up period, at 9 sites in Slovakia, the Czech Republic, Hungary, and Poland. The protocol was approved by the independent ethics committee(s) or institutional review board(s) of the participating centers. The study was conducted in accordance with the ethical principles of the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki and all applicable local regulations. Written informed consent was obtained from each patient. The study's ClinicalTrials.gov identifier is NCT02156466 (study no. EMR200574-003); it was registered on June 5, 2014, with the first patient screened on August 12, 2014.

Study participants

The participants were male and female patients who were 18 to 70 years of age and had chronic plaque psoriasis for at least 6 months before screening, plaques on at least 10% of their body surface area (BSA), a Psoriasis Area and Severity Index (PASI) score of 12 or higher, and a static Physician's Global Assessment (sPGA) score of 3 or higher. Patients were excluded if they had

Abbreviations used:

ADA: antidrug antibody
AE: adverse event
BSA: body surface area
IL: interleukin
PASI: Psoriasis Area and Severity Index
sPGA: Static Physician's Global Assessment
TEAE: treatment-emergent adverse event

drug-induced psoriasis, had a clinically significant exacerbation of psoriasis during the 4 weeks before randomization, or were taking/had taken nonpermitted medications, including the following: biological therapy; systemic immunosuppressants; corticosteroids or phototherapy; some topical corticosteroids; and treatment targeting IL-17, IL-12, and/or IL-23. However, certain low-potency topical steroids could be used on the face and groin area during the trial.

Randomization and masking

Randomization into the 4 ascending M1095 dose cohorts (30, 60, 120, or 240 mg) or placebo was performed, and allocation was concealed by using a central interactive voice and web response system. Patients were randomized 4:1 (M1095:placebo). The patient, investigator, sponsor, and laboratory personnel were blinded to the study drug assignment through use of randomized lists.

Treatment

Over 6 weeks, M1095 or placebo (10 mM phosphate buffer [pH 7.5], 8% sucrose, and 0.01% pharmacopeia-grade Polysorbate 80) were administered via subcutaneous injection into the abdominal wall on days 1, 15, and 29. On the basis of blinded data (day 43), a safety monitoring committee decided whether protocol-defined dose escalation to the next dose level was appropriate.

Outcomes

The primary outcomes evaluated the safety, tolerability, pharmacokinetics, and immunogenicity of multiple subcutaneous doses of M1095 versus placebo in patients with moderate-to-severe psoriasis. Safety and tolerability were assessed throughout the study by incidence of treatment-emergent adverse events (TEAEs). Local tolerability of the injection was assessed by pain using a visual analogue scale of 0 to 100 mm and investigator-assessed injection site reactions (eg, redness, swelling, indurations, bruising or itching) were classified as no, mild, moderate, or severe reaction. Safety laboratory parameters, vital signs, electrocardiogram result, and physical examination findings were also assessed. Serum samples were taken before each administration of the study drug; at prespecified intervals up to 336 hours after the dose; and on days 43, 50, 63, 73, and 85. Serum M1095 levels were quantified by using a validated enzyme-linked immunosorbent assay. Pharmacokinetic parameters were derived from M1095 serum concentrations by noncompartmental methods with use of the validated computer program Pharsight Phoenix WinNonlin (version 6.3.1, Certara LP, Princeton, NJ). Dose proportionality was assessed by analysis of variance and a power model. A tiered approach was used to assess immunogenicity and determine the percentage of patients with antidrug antibodies (ADAs) and ADA titer. Samples were screened by using an ADA assay; ADA-positive samples were evaluated in a confirmatory assay and titrated to quantify the ADA response. Samples from patients who presented with pre-existing antibodies to M1095 were further characterized in a modified ADA assay, which identifies ADAs that are not specific for the known pre-existing antibody epitope and are therefore considered to be treatment emergent.

Secondary outcomes evaluated the pharmacodynamic profile and efficacy of multiple subcutaneous doses of M1095. Blood samples and skin biopsy specimens were analyzed throughout the study to evaluate IL-17–induced proteins, gene expression, and psoriasis markers. Efficacy was assessed as the mean percentage change from baseline in PASI score on days 43 and 85, and the proportion of patients achieving a 75% or greater, 90%, or 100% improvement in PASI (PASI 75, PASI 90, or PASI 100, respectively) compared with baseline at each time point and overall. Clinical response was determined by the proportion of patients achieving an sPGA score of 0 or 1 (minimal or clear) and a 2-level or greater reduction from baseline at each time point, as well as the mean percentage BSA change from baseline at each time point.

Statistical analysis

The number of patients in each dose cohort considered safety assessments, and the overall sample size was typical for a dose escalation study. Given the exploratory nature of this trial, the sample size was not based on power calculations. All statistics were descriptive. Analyses of clinical response and pharmacodynamic end points were based on the safety analysis population (all patients who had received $\geq$1 dose of the planned study treatment). Three patients randomized to M1095 discontinued treatment or were excluded from the trial after

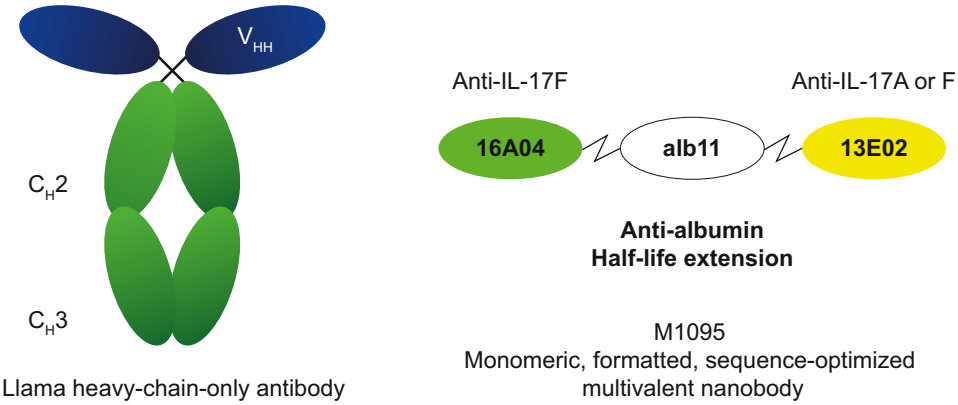

Fig 1. Schematic representation of the IL-17– and albumin-binding domains of M1095. M1095 is a recombinant, sequence-optimized, trivalent monomeric protein that comprises 3 nanobody building blocks connected by glycine-serine linkers. Nanobodies are based on the smallest functional fragments of heavy-chain-only antibodies that occur naturally in the camelid family.

treatment was initiated. Given the small sample size, and to more accurately assess treatment effect, additional completed-patients sensitivity analyses were performed. Statistical analyses were performed by using SAS System for Windows software (version 9.1.3, SAS Institute Inc, Cary, NC).

RESULTS

Of the 44 patients who were randomized, 41 received at least 1 dose of the planned study treatment (33 received M1095 and 8 received placebo [safety analysis population]). Six patients discontinued from the study prematurely owing to protocol deviation (n = 2), adverse events (AEs) (n = 2), withdrawal of consent (n = 1), or other reasons (n = 1). Most patients were male, the mean age was 45.1 years (range, 21-69 years), and all patients were white (Table I). The treatment groups were comparable in terms of baseline characteristics except for PASI, with the observed baseline mean score higher in the placebo group (25.49) than in the total active treatment group (19.56). In all, 21 patients received concomitant medication for pre-existing conditions, including hypertension, psoriasis, and diabetes. Concomitant treatment for psoriasis was limited to low-potency topical steroids. A total of 3 patients (2 in the placebo group and 1 in the 240-mg group) were treated for psoriasis-related AEs (new lesions or pruritus of lesions) with the permitted comedications according to the criteria predefined in the study protocol.

Multiple subcutaneous doses of M1095 up to 240 mg were generally well tolerated. A total of 94 TEAEs were reported; they were experienced by 67% or 75% of patients receiving M1095 or placebo, respectively. The majority (95%) of TEAEs were mild or moderate in severity. A total of 4 severe TEAEs were reported by 2 patients receiving placebo: increased fibrin D-dimer and peripheral swelling in 1 patient, and increased blood creatine phosphokinase and blood creatine phosphokinase MB levels in the other. The most frequently reported TEAEs for patients receiving M1095 were pruritus, headache, hypertension, nasopharyngitis, generalized pruritus, somnolence, and bronchitis (Table II). On day 79, 1 serious AE was reported in a patient administered 30 mg of M1095 (moderate acute vestibular syndrome that was not considered treatment related). Of the 65 TEAEs occurring in patients receiving M1095, 22 were regarded as treatment-related, with no apparent dose dependency. Two patients withdrew because of treatment-related AEs that were moderate in severity; one had an injection site reaction (induration, redness, and swelling) on day 18 following the second dose of M1095, 120 mg, and 1 had an elevation in hepatic enzyme levels on day 16 following the second dose of M1095, 240 mg, which resolved by day 28. No overall trends in liver enzyme levels, other clinical laboratory parameters, or clinically significant findings regarding vital signs, electrocardiogram result, body weight, or physical examination were observed, and no deaths occurred.

Local tolerability was satisfactory. Reports of some bruising and itching, redness, induration, and swelling were observed with M1095; they were mostly mild, sporadic, transient, and of little or no clinical significance. Minimal pain (between 1 and 16 mm on the visual analogue scale) was reported by 10 patients receiving M1095 and 1 receiving placebo.

Table I. Baseline demographics (safety analysis population)

Demographic characteristic	M1095 dose level				Total active (n = 33)	Total placebo (n = 8)
	30 mg (n = 8)	60 mg (n = 8)	120 mg (n = 8)	240 mg (n = 9)		
Male/female, n (%)	7 (88)/1 (13)	8 (100)/0 (0)	6 (75)/2 (25)	8 (89)/1 (11)	29 (88)/4 (12)	6 (75)/2 (25)
White race, n (%)	8 (100)	8 (100)	8 (100)	9 (100)	33 (100)	8 (100)
Mean age, y (SD)	48.6 (13.24)	42.1 (19.57)	43.8 (13.59)	44.8 (15.65)	44.8 (15.15)	46.1 (14.57)
Range	23-64	21-69	24-60	23-65	21-69	22-62
Mean height, cm (SD)	176.6 (9.33)	178.8 (5.57)	171.9 (8.41)	176.8 (5.61)	176.0 (7.46)	174.6 (7.29)
Range	157-187	168-186	160-185	170-185	157-187	164-186
Mean weight, kg (SD)	78.24 (11.21)	89.49 (11.64)	94.46 (12.73)	93.77 (17.01)	89.13 (14.42)	83.14 (16.68)
Range	62.0-91.9	70.0-104.1	78.0-121.0	75.0-119.0	62.0-121.0	59.9-113.3
Mean body mass index, kg/m^2 (SD)	25.28 (4.36)	28.04 (3.55)	32.20 (5.50)	30.04 (5.56)	28.92 (5.27)	27.33 (5.77)
Range	17.7-29.7	21.1-32.9	25.6-42.9	23.5-39.8	17.7-42.9	20.0-39.7
Mean PASI score* (SD)	16.91 (5.75)	19.76 (4.79)	23.35 (6.60)	18.38 (6.07)	19.56 (6.06)	25.49 (5.58)
Range	12.4-24.6	12.0-26.8	12.2-42.0	12.8-30.6	12.0-42.0	13.0-36.6
sPGA score*						
0 (clear)	0	0	0	0	0	0
1 (minimal)	0	0	0	0	0	0
2 (mild)	0	0	0	0	0	0
3 (moderate)	7 (88)	5 (63)	4 (50)	5 (56)	21 (64)	4 (50)
4 (severe)	1 (13)	3 (38)	4 (50)	4 (44)	12 (36)	4 (50)
5 (very severe)	0	0	0	0	0	0

PASI, Psoriasis Area and Severity Index; *SD*, standard deviation; *sPGA*, static Physician's Global Assessment.
*Values at day −1.

Table II. TEAEs occurring in 2 or more patients (safety analysis population)

TEAE, n (%)	With M1095 (n = 33)	With placebo (n = 8)
Pruritus	4 (12)	1 (13)
Headache	3 (9)	0
Hypertension	2 (6)	1 (13)
Nasopharyngitis	2 (6)	1 (13)
Pruritus, generalized	2 (6)	1 (13)
Somnolence	2 (6)	0
Bronchitis	2 (6)	0
Fibrin D-dimer level increased	1 (3)	1 (13)
Arthralgia	1 (3)	1 (13)
Blood creatine phosphokinase level increased	1 (3)	1 (13)
Glucose present in urine	1 (3)	1 (13)
Psoriasis	0	2 (25)

TEAE, Treatment-emergent adverse event.

No association between local tolerability and dose or injection volume was noted.

A dose-proportional increase in area under the serum concentration−time curve and maximum concentration observed within 1 dosing interval was seen in patients following the first and third administrations of M1095 (>30 to 240 mg). The terminal half-life of M1095 was approximately 11 to 12 days, with the maximum M1095 serum concentration reached after 31 to 84 hours. Pharmacokinetic results will be reported in detail elsewhere.

Of 13 ADA-positive patients, 5 out of 10 receiving M1095 had treatment-emergent ADA responses that were not pre-existing but developed following M1095 administration. No effect of ADAs on M1095 exposure was observed for ADA-positive patients.

Pharmacodynamic analysis revealed no effect of multiple ascending doses of M1095 on plasma levels of IL-17−induced circulating proteins (IL-6, IL-8, lipocalin-2, and MCP-1) compared with placebo. M1095 administration resulted in a dose-dependent decrease in numbers of dermal and epidermal $CD3^+$ cells, epidermal thickness, and numbers of epidermal $Ki67^+$ cells in psoriasis plaques (Supplementary Fig 1; available at https://doi.org/10.17632/ckz2ss9njx.3).

The proportions of patients achieving PASI 75, PASI 90, and PASI 100 on day 85 were dose related (Fig 2). All patients who received 240 mg of M1095 achieved PASI 90 on day 85; 56% of these patients achieved PASI 00. All PASI findings were consistent in the completed-patient sensitivity analysis (Fig 2). sPGA scores on day 85 are shown in Table III. All patients (100%) treated with M1095, 240 mg, achieved an sPGA result of minimal or clear with at least a 2-level reduction in sPGA from baseline. In

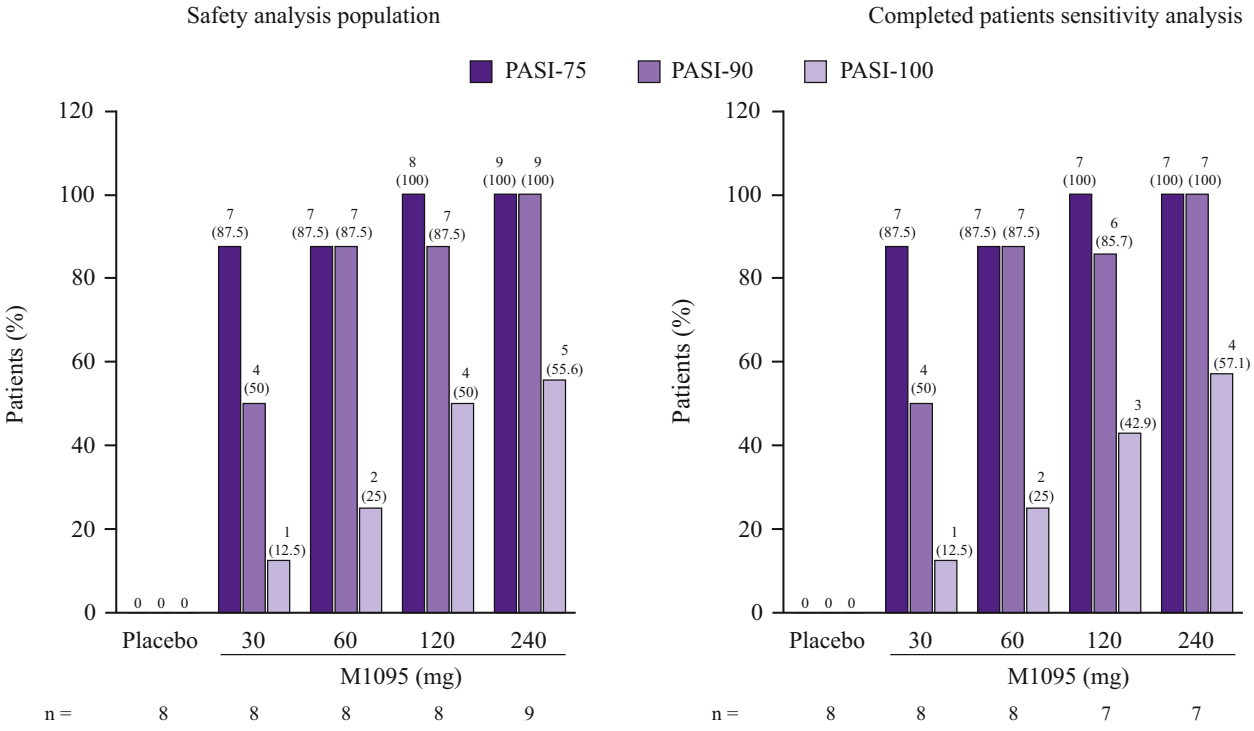

Fig 2. Psoriasis. Proportion of patients with a 75%, 90%, and 100% improvement in PASI score on day 85 (safety analysis population). The safety analysis population comprised all patients who received at least 1 dose of the planned study treatment. The completed-patients' sensitivity analysis included patients who completed the trial and received all 3 doses of M1095. Data in the graph are expressed as n (%). *PASI*, Psoriasis Area and Severity Index.

Table III. Proportion of patients achieving an sPGA result of minimal or clear and a 2-level or greater reduction (safety analysis population)

	M1095 dose level					
Visit	**30 mg (n = 8)**	**60 mg (n = 8)**	**120 mg (n = 8)**	**240 mg (n = 9)**	**Total active (n = 33)**	**Total placebo (n = 8)**
Day 8	0 (0)	3 (38)	1 (13)	1 (11)	5 (15)	0 (0)
Day 15	2 (25)	2 (25)	1 (13)	5 (56)	10 (30)	0 (0)
Day 22	4 (50)	4 (50)	4 (50)	6 (67)	18 (55)	0 (0)
Day 29	5 (63)	5 (63)	7 (88)	7 (78)	24 (73)	0 (0)
Day 36	5 (63)	7 (88)	6 (75)	6 (67)	24 (73)	0 (0)
Day 43	6 (75)	7 (88)	7 (88)	8 (89)	28 (85)	0 (0)
Day 50	6 (75)	7 (88)	8 (100)	8 (89)	29 (88)	0 (0)
Day 85	7 (88)	7 (88)	7 (88)	9 (100)	30 (91)	0 (0)

Data are n (%).
sPGA, Static Physician's Global Assessment.

addition, the largest decrease (~95%) in BSA scores was observed in the cohort receiving M1095, 240 mg.

By day 43, assessment of histological changes in lesional skin revealed a dose-dependent reversal of pathologic hyperplasia that was quantified by histological improvement scores (data not shown). In patients who received M1095, a largely dose-dependent decrease to normal skin levels was observed in the expression of interleukin 17A gene (*IL17A*), interleukin 17F gene (*IL17F*), C-C motif chemokine ligand 20 gene (*CCL20*), C-X-C motif chemokine ligand 1 gene (*CXCL1*), defensin beta 4A gene (*DEFB4A* [also know by the alias symbol *HBD2*]), C-X-C motif chemokine ligand 8 gene (*CXCL8* [previously known by the symbol IL8]), lipocalin 2 gene (LCN2), cathelicidin antimicrobial peptide gene (*CAMP* [also known by the alias symbol *LL37*]), and keratin 16 gene KRT16 [also known by

the alias symbol *K16*]) in psoriasis plaques (Supplementary Fig 2; available at https://doi.org/10.17632/ckz2ss9njx.3).

DISCUSSION

To our knowledge, this is the first study of patients with moderate-to-severe psoriasis treated with M1095 and the first to demonstrate a marked clinical effect with a nanobody in psoriasis. No unanticipated safety findings were noted; the most frequent AEs were consistent with those observed with other subcutaneously administered anti–IL-17 psoriasis agents.[16] Multiple doses of up to 240 mg of M1095 were well tolerated, with clear dose-dependent skin improvement in all clinical indices of psoriasis studied. The greatest improvement in efficacy was with the highest M1095 dose (240 mg), indicating a dose-response relationship. Patients who received M1095 experienced a rapid onset of improvement, as early as the first week of treatment. Meaningful clinical efficacy was indicated by PASI 75 and PASI 90 improvement, a minimal or clear sPGA score, plus a 2-level or greater reduction from baseline 8 weeks after the last dose and a reduction in mean percentage of total BSA with psoriasis. M1095 was associated with dose-dependent reductions in dermal and epidermal $CD3^+$ cell counts, epidermal thickness, and epidermal Ki 67^+ cell counts in psoriasis plaques. The drug was also associated with reversal of pathologic hyperplasia in lesional skin and decreased RNA levels of IL-17A, IL-17F, and various IL-17–induced proinflammatory and/or antimicrobial genes that are up-regulated in psoriatic plaques. However, interpretation is limited by the small sample size inherent to phase 1 studies.

Previous phase 3 studies have demonstrated PASI 75 response rates of approximately 77% to 90% with the IL-17–targeting agents secukinumab, ixekizumab, and brodalumab and PASI 90 response rates of approximately 54% to 71% with secukinumab and ixekizumab. In this study, treatment with M1095 showed PASI 75 or PASI 90 response rates of 100% and a PASI 100 response rate of 56% in the 240-mg group. The results presented here are consistent with the effects on epidermal thickness, Ki67 expression, infiltrating T cells, and IL-17–induced genes observed with other IL-17/IL-17R–targeting agents such as ixekizumab and brodalumab used to treat psoriasis.[4,13]

The bispecific antibodies bimekizumab and NI-1401, both of which inhibit IL-17F and IL-17A, have been investigated in mild plaque psoriasis/psoriatic arthritis and healthy volunteers, respectively.[10] Bimekizumab has achieved PASI 100 in up to approximately 87% of patients treated with the highest doses at week 8.[10] This result is comparable to that in our study. However, the low number of patients included in the bimekizumab study warrants confirmation in larger trials.[10] Several other dual-targeting agents, including ABT-122 (which is specific to tumor necrosis factor-α and IL-17) and the bispecific tumor necrosis factor-α/IL-17A inhibitor COVA322, underwent early investigation[17]; however, these clinical trials have not been continued.

M1095 and BI 836880 (a vascular endothelial growth factor/Ang2 inhibitor under investigation in solid tumors) are currently the only 2 bispecific nanobodies in clinical trials.[15] Given the flexible platform of nanobodies, which allows multiple antigenic targets, generation of trivalent or even quadrivalent nanobodies is possible.[15] To our knowledge, M1095 is the only example of a trivalent nanobody used in humans.

In summary, a favorable safety profile with multiple doses of up to 240 mg of M1095 was observed in patients with moderate-to-severe psoriasis. Clear dose-dependent skin improvement across all indices of psoriasis was observed. In several patients, complete disappearance of psoriasis plaques after administration of the highest dose of M1095 (240 mg) was seen. A phase 2 study (NCT03384745) to further evaluate the safety and efficacy of M1095 in patients with plaque psoriasis is planned.

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