Safety and Efficacy of Multiple Ascending Doses of Subcutaneous M1095, an Anti-Interleukin-17A/F Bispecific Nanobody®, in Patients with Moderate-to-Severe Psoriasis

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Background and Methods

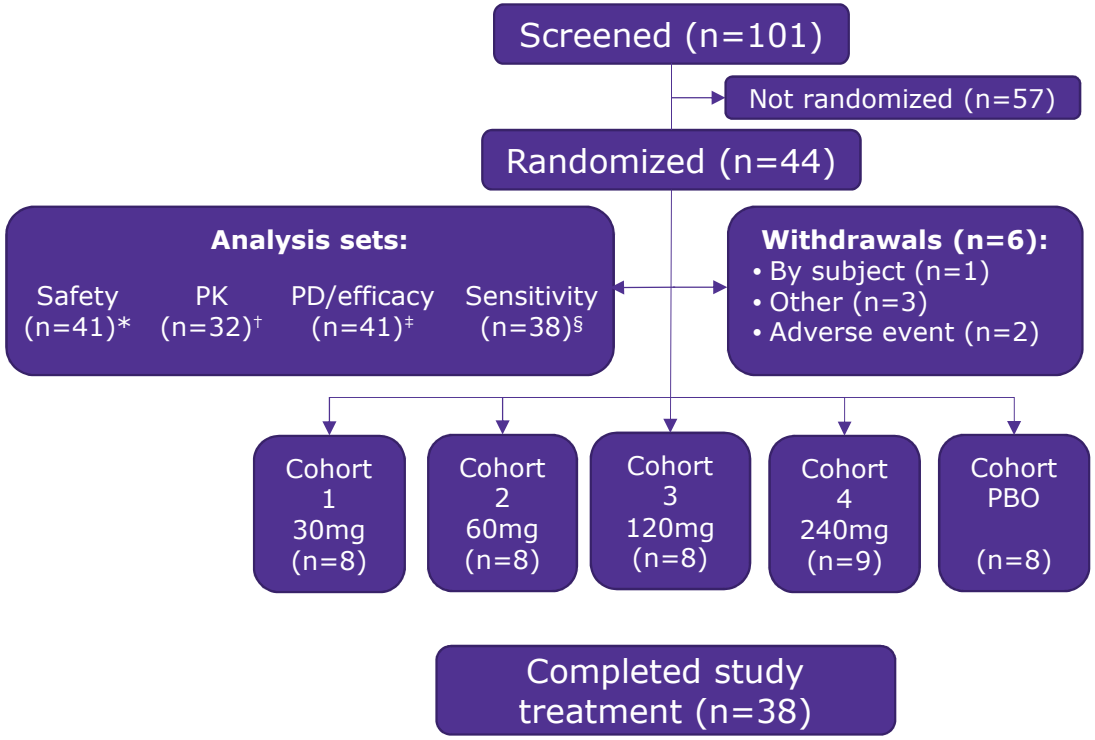
- Targeting the interleukin (IL)-17 pathway is an effective treatment approach for patients with plaque psoriasis[1-2]
- M1095 is an anti-interleukin (IL)-17A/F Nanobody®* that neutralizes the pro-inflammatory cytokines IL-17A and IL-17F
- This multicenter, phase I, randomized, double-blind trial was conducted in adults with moderate to severe, chronic plaque psoriasis (≥10% BSA affected, PASI ≥12 and sPGA ≥3)
  - Primary objective: safety, tolerability, immunogenicity and pharmacokinetics of multiple SC doses of M1095 vs placebo (pharmacodynamics and efficacy were secondary objectives)
  - Patients (10 per cohort) were randomized (4:1) to receive M1095 (30, 60, 120, or 240 mg) or PBO SC every 2 weeks for 6 weeks

	Treatment period						Follow up period				
Site visits (day) Treatment (day)	1, 2, 4 and 5 1	8 and 14	15, 16, 18 and 19 15	22 and 28	29, 30, 32, 33 29	36	43†	50	63	73	85

1. Mease PJ, et al. *N Engl J Med* 2015;373:1329–39;
2. Papp KA, et al. *Br J Dermatol* 2013;168:412–21;
3. http://www.ablynx.com/technology-innovation/understanding-nanobodies/

*Nanobodies® are a novel class of proprietary therapeutic protein based on single-domain antibody fragments that contain the unique structural and functional properties of naturally-occurring heavy chain only antibodies[3]; †Early termination according to protocol; BSA, body surface area; PBO, placebo; PASI, Psoriasis Area and Severity Index; SC, subcutaneous; sPGA, static Physician's Global Assessment

Patient Disposition and Demographics

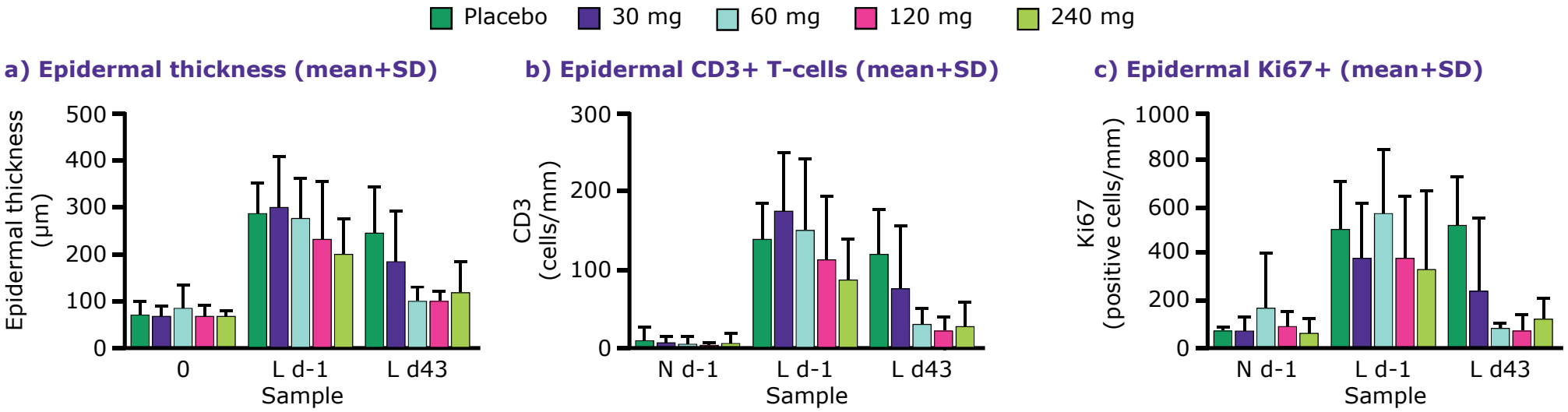


	Total active dose cohorts (n=33)	Total placebo cohort (n=8)	Total (n=41)
Male/Female, n	29/4	6/2	35/6
Age (years), mean	44.8	46.1	45.1
BMI (kg/m²), mean	28.9	27.3	28.6

*Received at least one dose of M1095 or PBO; †received active treatment without protocol deviations affecting PK, and who provide evaluable PK data; ‡based on the safety analysis set; §based on the safety analysis set, but excluding 3 subjects who were discontinued after treatment initiation

Pharmacodynamics: Histological Response

- M1095 treatment led to complete reversal of disease pathology in skin biopsies of the majority of patients in the higher dose groups*
- Dose-dependent reductions were observed in:
  - Epidermal thickness
  - Dermal and epidermal $CD3^+$ T-cell counts
  - Epidermal Ki67+ cell counts in psoriatic plaques



*based on histological analysis of lesional and non-lesional skin on days -1 and 43

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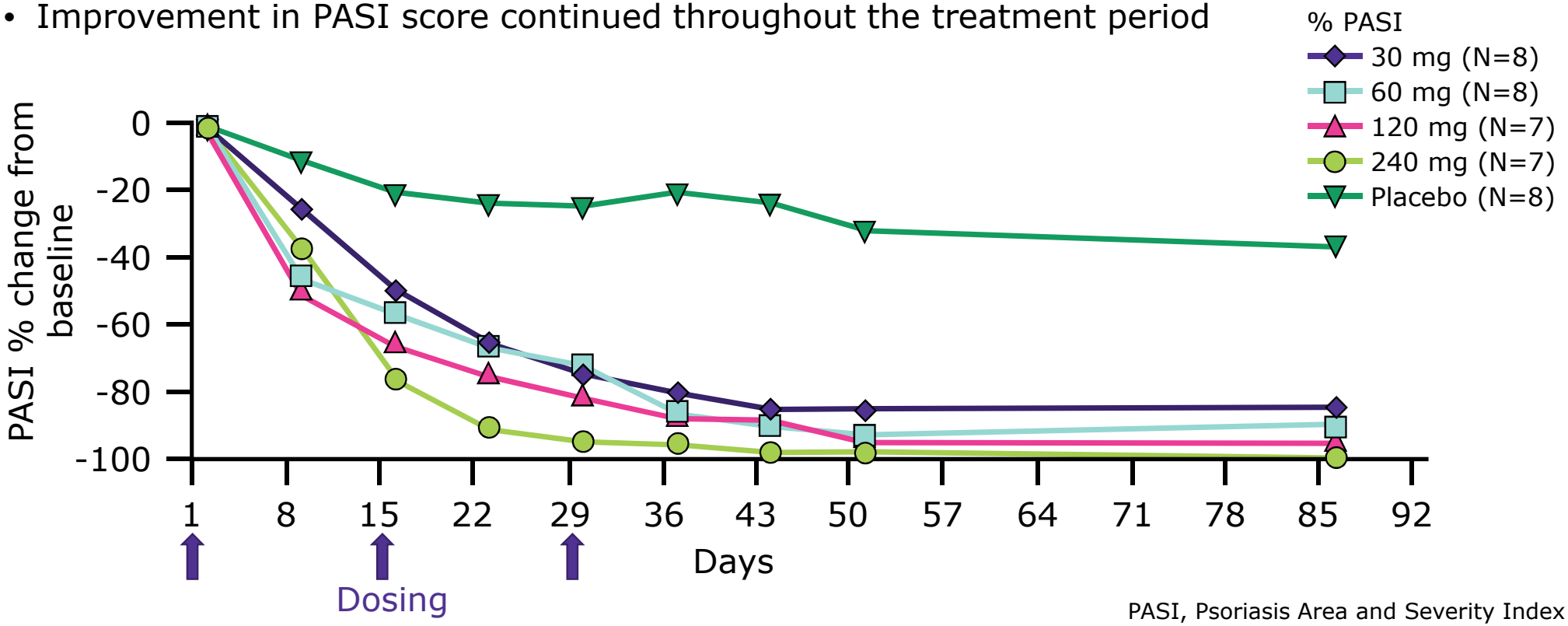
Efficacy: Mean Change from Baseline in PASI Score over Time

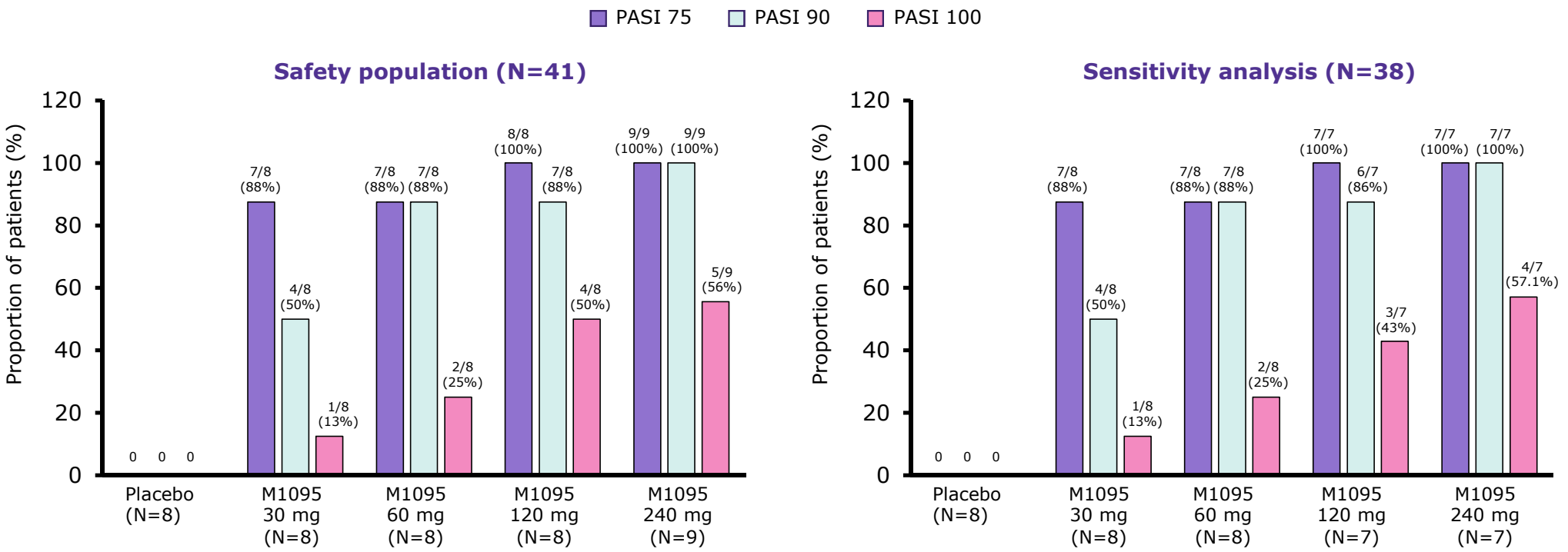
- Marked dose-dependent decrease in PASI score vs placebo within 7 days of first M1095 dose in all 4 cohorts
- Improvement in PASI score continued throughout the treatment period



PASI, Psoriasis Area and Severity Index

Efficacy: Patients with PASI-75, PASI-90 and PASI-100 at Day 85 (Week 12)

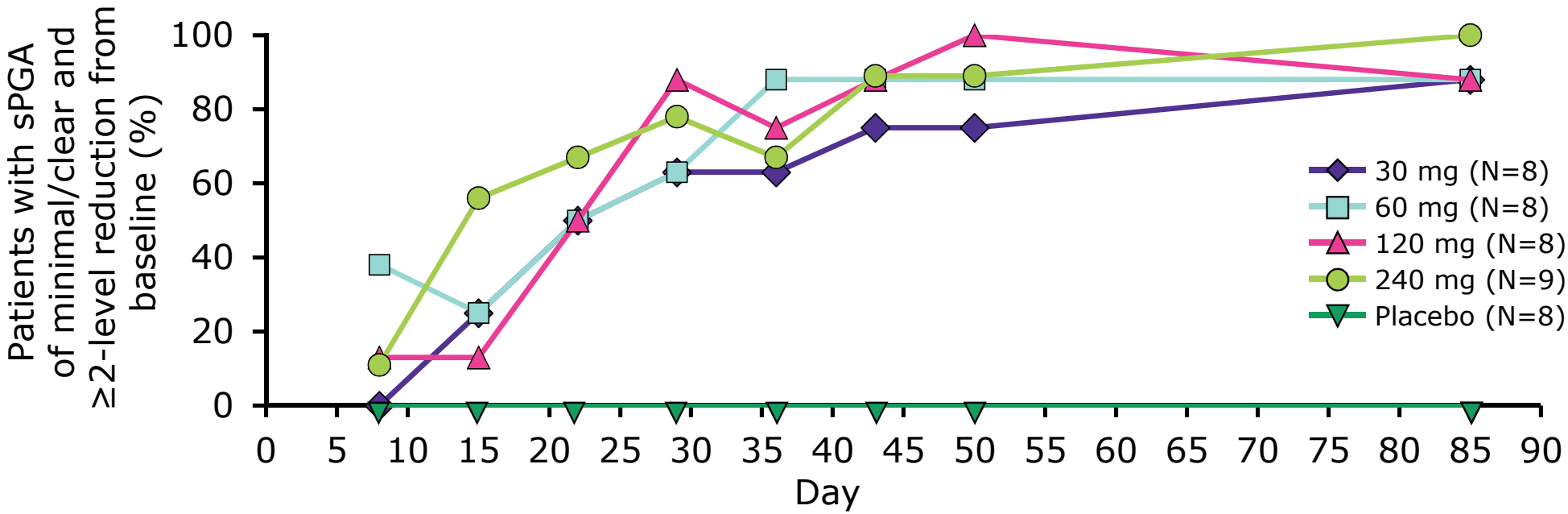
- No patient in the PBO group achieved PASI-75, PASI-90 or PASI-100
- PASI-100 was achieved in ≥50% of patients receiving either 120 or 240mg M1095



PASI, Psoriasis Area and Severity Index

Efficacy: Patients with sPGA of Minimal or Clear and with ≥2-Level Reduction from Baseline*

- Lesion severity improved in all M1095-treated patients
- By Day 85, 30/33 (91%) M1095-treated patients had achieved a sPGA of minimal/clear with ≥2-level reduction from baseline, compared with 0/8 (0%) placebo-treated patients



*Safety population; sPGA, Static Physician's Global Assessment

Safety: Incidence of TEAEs by Treatment and Severity

	Relationship by Severity							
	Mild		Moderate		Severe		All TEAEs	
Treatment	n	%	n	%	n	%	n	%
Placebo (N=8)	6	75	3	38	2	25	6	75
Cohort 1 30 mg (N=8)	4	50	4	50	0	0	6	75
Cohort 2 60 mg (N=8)	5	63	3	38	0	0	5	63
Cohort 3 120 mg (N=8)	5	63	2	25	0	0	5	63
Cohort 4 240 mg (N=9)	5	56	2	22	0	0	6	67
Total (N=41)	25	61	14	34	2	5	28	68

- Multiple SC doses of M1095 were well tolerated up to a dose level of 240 mg
- Most TEAEs were of mild severity, 4 events were graded 'severe', all occurred in the placebo group
- Incidence of TEAEs did not appear to be dose dependent
- Two subjects discontinued treatment: one due to an AE of injection site reaction and one to an AE of elevated liver enzymes
- One serious AE of acute vestibular syndrome was reported; the episode resolved in 7 days and was considered unrelated to M1095 by the investigator

AE, adverse event; N, number of subjects exposed per treatment; n, number of subjects that experienced the AE per treatment; %, percentage of subjects that experienced the AE per treatment; (n/N)*100%; TEAE, treatment emergent adverse event

SEE BACK-UP SLIDES FOR A SUMMARY OF MOST FREQUENT TEAEs AND IMMUNOGENICITY

Safety: Summary of TEAEs Reported in ≥ 2 Subjects (Total)

TEAEs, n (%)	Cohort 1 30 mg (N=8)	Cohort 2 60 mg (N=8)	Cohort 3 120 mg (N=8)	Cohort 4 240 mg (N=9)	Total M1095 (N=33)	Placebo (N=8)
Pruritus	2 (25)	1 (13)	0	1 (11)	4 (12)	1 (13)
Headache	0	2 (25)	0	1 (11)	3 (9)	0
Hypertension	0	1 (13)	1 (13)	0	2 (6)	1 (13)
Nasopharyngitis	0	0	1 (13)	1 (11)	2 (6)	1 (13)
Pruritus generalised	1 (13)	0	0	1 (11)	2 (6)	1 (13)
Somnolence	1 (13)	1 (13)	0	0	2 (6)	0
Bronchitis	0	2 (25)	0	0	2 (6)	0
Fibrin D-dimer increased	1 (13)	0	0	0	1 (3)	1 (13)
Arthralgia	0	1 (13)	0	0	1 (3)	1 (13)
Blood creatine phosphokinase increased	0	1 (13)	0	0	1 (3)	1 (13)
Glucose urine	1 (13)	0	0	0	1 (3)	1 (13)
Psoriasis	0	0	0	0	0	2 (25)

Summary

- Biopsy assessment of lesional skin showed complete reversal of disease pathology in majority of patients in high dose groups
- All patients attained PASI-75 at the highest M1095 doses; half attained PASI-100
- Lesion severity by sPGA improved from moderate/severe at baseline to mostly clear/minimal by end of study in >90% of patients
  - No sPGA improvement observed in patients receiving PBO
- Multiple ascending doses of M1095 were well tolerated in patients with moderate to severe plaque psoriasis
  - Similar incidence of TEAEs in M1095 and placebo groups
- No apparent dose dependency of the incidence or severity of TEAEs
  - One subject withdrew due to an injection site reaction and one due to elevated liver enzymes

PASI, Psoriasis Area and Severity Index;
sPGA, Static Physician's Global Assessment

Conclusions

- M1095 is a novel anti-IL-17A/F Nanobody® with the promise of anti-disease activity in psoriasis
- Multiple ascending doses of M1095 (up to 240 mg) were well tolerated in patients with moderate-to-severe psoriasis
- Significant skin improvement was demonstrated by histological analysis of skin biopsies

Acknowledgments and Disclosures

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- ML, HM, RG, DW and EH, are employees of EMD Serono, a business of Merck KGaA, Germany. DS has no COIs to disclose
- OS was an employee of EMD Serono at the time of the study