Spesolimab Efficacy and Safety in Patients with Moderate-to-Severe Palmoplantar Pustulosis – a Multicentre, Double-Blind, Randomised, Placebo-Controlled, Phase IIb, Dose-Finding Study

Authors: A. David Burden[1], Robert Bissonnette[2], Alexander A. Navarini[3], Masamoto Murakami[4], Akimichi Morita[5], Thomas Haeufel[6], Binqi Ye[7], Frank Baehner[8], Tadashi Terui[9]

Affiliations

[1]School of Infection and Immunity, University of Glasgow, Glasgow, UK; [2]Innovaderm Research Inc., Montreal, Quebec, Canada; [3]Department of Dermatology, University Hospital Basel, Basel, Switzerland; [4]Department of Dermatology, Ehime University Graduate School of Medicine, Ehime, Japan; [5]Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [6]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [7]Boehringer Ingelheim (China) Investment Corporation Limited, Shanghai, People's Republic of China; [8]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [9]Division of Cutaneous Science, Department of Dermatology, Nihon University School of Medicine, Tokyo, Japan

ORCID iDs: A. David Burden: 0000-0001-7395-9931; Robert Bissonnette: 0000-0001-5927-6587; Alexander A Navarini: 0000-0001-7059-632X; Masamoto Murakami: 0000-0003-3923-5096; Akimichi Morita: 0000-0001-8372-3754; Binqi Ye: 0000-0003-2276-1217; Tadashi Terui: 0000-0002-0275-4311

Corresponding author: A. David Burden
David.Burden@glasgow.ac.uk
School of Infection and Immunity, University of Glasgow, Glasgow, UK

Target journal: Dermatology and Therapy

SUPPLEMENTARY MATERIAL

Table S1 Independent ethics committees and institutional review boards that granted approval for participating centres in the clinical trial

Australia
Bellberry Limited, 123 Glen Osmond Road, Eastwood SA 5063
Melbourne Health Human Research Ethics Committee, Office for Research, The Royal Melbourne Hospital, Level 2 South West, 300 Grattan Street, Parkville VIC 3050
Belgium
AZ Delta, Commissie Medische Ethiek, Rode-Kruisstraat 20, Roeselare, 8800
Canada
Advarra Inc., 372 Hollandview Trail – Unit 300, Aurora, Ontario, L4G 0A5
HREBA – Health Research Ethics Board of Alberta, Clinical Trials Committee, #1500-101004 103 Avenue, Edmonton, Alberta, T5J 0H8
Czechia
Ethics Committee for Multi-centric Trials, Faculty Hospital in Motol, V Úvalu 84, 150 06, Praha 5 – Motol
France
CPP Sud Méditerranée 1, Hôpital Ste. Marguerite, Pavillon 9, 270 Bld Sainte Marguerite, 13274 Marseille Cedex 9
Germany
Ethikkommission der Medizinischen Fakultät der Christian-Albrechts-Universität zu Kiel, Universitäts-Kinderklinik, Schwanenweg 20, 24105 Kiel
Hungary
Medical Research Council Ethics Committee for Clinical Pharmacology, Szechenyi Istvan Square 7-8, 1051 Budapest
Japan
Sagamihara National Hospital Institutional Review Board, 18-1 Sakuradai, Minami-ku, Sagamihara, Kanagawa, 252-0392

Nihon University Hospitals' Joint Institutional Review Board, 30-1, Ohyaguchi Kami-cho, Itabashi-ku, Tokyo, 173-8610

Tokyo Medical University Hospital Institutional Review Board, 6-7-1 Nishishinju-ku, Shinjuku-ku, Tokyo, 160-0023

Nagoya City University Hospital Institutional Review Board, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya, Aichi, 467-8602

Fukuoka University Hospital Institutional Review Board, 7-45-1, Nanakuma, Jonan-ku, Fukuoka, 814-0180

Teikyo University Hospital Institutional Review Board, 2-11-1, Kaga, Itabashi-ku, Tokyo, 173-8606

University Hospital, Kyoto Prefectural University of Medicine Institutional Review Board, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto, 602-8566

Shinshu University Hospital Institutional Review Board, 3-1-1 Asahi, Matsumoto, Nagano, 390-8621

Tohoku University Hospital Institutional Review Board, 1-1 Seiryomachi, Aoba-ku, Miyagi, Sendai, 980-8574

Dr Mano Medical Clinic Institutional Review Board, 1-8-1 Ebisu, Shibuya-ku, Tokyo, 150-0013

Asahikawa Kosei General Hospital Institutional Review Board, 24-111, 1-Jodori, Asahikawa, Hokkaido, 078-8211

Kumamoto University Hospital Institutional Review Board, 1-1-1, Honjo, Chuo-ku Kumamoto, Kumamoto, 860-8556

Asahikawa Medical University Hospital Institutional Review Board, 1-1-1 Midorigaokahigashi 2-jo, Asahikawa, Hokkaido, 078-8510

Osaka City University Hospital Institutional Review Board, 1-5-7 Asahi-machi, Abeno-ku Osaka, 545-8586

Jichi Medical University Hospital Institutional Review Board, 3311-1 Yakushiji, Shimotsuke, Tochigi, 329-0498

Gifu University Hospital Institutional Review Board, 1-1 Yanagido Gifu, Gifu, 501-1194

Ehime University Hospital Institutional Review Board, Shitsukawa, Toon, Ehime, 791-0295

Osaka University Hospital Institutional Review Board, 2-15, Yamadaoka, Suita, Osaka, 565-0871

The Central Institutional Review Board for the Fujita Health University Hospitals, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi, 470-1192

Shiga University of Medical Science Hospital Institutional Review Board, Seta, Tsukinowa-cho, Otsu, Shiga, 520-2192

Kindai University Hospital Institutional Review Board, 377-2, Ohno-higashi Osaka-sayama, Osaka, 589-8511

Institutional Review Board of Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku Okayama, Okayama, 700-8558

Sapporo Dermatology Clinic Institutional Review Board, 2-1-1 Minami 3-Jo Nishi, Chuo-ku, Sapporo, 060-0063

Tokyo Dental College Ichikawa General Hospital Institutional Review Board, 5-11-13 Sugano, Ichikawa, Chiba, 272-8513

University of the Ryukyus Hospital Institutional Review Board, 207 Uehara, Nishihara-cho, Nakagami-gun, Okinawa, 903-0215

Nohonbashi Sakura Clinic Institutional Review Board, 1-9-2 Nihonbashikayaba-cho, Chuo-ku, Tokyo, 103-0025

Wakayama Medical University Institutional Review Board, 811-1 Kimiidera Wakayama, Wakayama, 641-8510

Takamatsu Red Cross Hospital Institutional Review Board, 4-1-3 Bancho Kagawa, Takamatsu, Kagawa, 760-0017

Republic of Korea

Seoul National University Bundang Hospital Institutional Review Board / 82 Gumi-ro, 173 Beon-gil Seongnam, 13620

Gachon University Gil Medical Center Institutional Review Board/ 21, Namdong-daero 774 Beon-gil, Namdong-gu, Incheon, 21565

Seoul National University Hospital Institutional Review Board/ 101 Daehak-ro, Jongno-gu Seoul, 03080

Netherlands

Stichting Beoordeling Ethiek Biomedisch Onderzoek, Dr Nassaulaan 10, Assen, 9401 HK

Poland

Bioethical Commission at the Medical University in Lublin, Al. Racławickie 1, 20-059 Lublin

Russia

Ethical Council of Ministry of Healthcare of Russian Federation, Rakhmanovskyi Lane 3, Moscow, 127994

Independent Ethics Committee of St. Petersburg State Budget, Healthcare Institution 'Dermatovenerologic dispensary No.10 – Clinic of dermatology and venereology', 29 Liter A, Parkhomenko Prospect, St Petersburg, 194021

Local Ethics Committee of Federal State Budget Educational Institution of Higher Education, 'Kazan State Medical University' of Ministry of Healthcare of Russian Federation, 49 Butlerova str., Kazan, 420012

Local Ethics Committee of State Budget Healthcare Institution, 'Chelyabinsk regional clinical dermatovenerologic dispensary', 24 Yablochkina str., Chelyabinsk, 454048

Switzerland

Ethical Committee of North Western and Central Switzerland, Hebelstrasse 53, Basel, 4053

Taiwan

Research Ethics Committee A, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan 100

UK

London – Hampstead Research Ethics Committee and Medicines and Healthcare Products Regulatory Agency, 10th Floor, 10 South Colonnade, Canary Wharf, London, E14 4PU

USA

University of Utah Institutional Review Board, 75 S 2000 E, Salt Lake City, UT 84112

Washington University IRB, 660 S. Euclid Ave MS08089-2300, St Louis, MO 63110

Alpha IRB, 1001 Avenido Pico, Suite C # 497, San Clemente, CA 92673

Table S2 Full inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• 18–75 years of legal age (according to local legislation) at screening. • Diagnosis of PPP, defined as the presence of primary, persistent (>3 months duration), sterile, macroscopically visible pustules on the palms and/or soles, with or without plaque psoriasis elsewhere on the body. • Presence of white or yellow pustules on palms and/or soles at screening and baseline. • Pustular severity score ≥2 in at least one region and ≥10 well-demarcated pustules (white or yellow pustules) across all regions at screening and baseline. • PPP PGA of at least moderate severity (≥3) at screening and baseline. • A minimum PPP ASI score of 12 at screening and baseline. • Male or female. Women of childbearing potential were to be prepared and able to use highly effective methods of birth control, per ICH M3 (R2), that	• Reduction of ≥5 in PPP ASI total score from screening visit to baseline (randomisation visit). • Worsening of plaque psoriasis within the last 3 months prior to screening. • Skin conditions that affected ability to score area and severity of PPP components (such as dyshidrotic eczema, calluses, tinea, xerotic scaling on heels or maceration of interdigital areas). • Women who were pregnant, nursing or who planned to become pregnant while in the trial. • A severe, progressive or uncontrolled condition such as renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurological, cerebral or psychiatric disease, or signs and symptoms thereof. • Presence or known history of anti-tumour necrosis factor-induced PPP-like disease. • Patient with a transplanted organ (except for a corneal transplant >12 weeks prior to screening) or who had ever received stem cell therapy (e.g. Prochymal). • Known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.

resulted in a failure rate of <1% per year when used consistently and correctly. • Signed and dated written informed consent in accordance with ICH Good Clinical Practice and local legislation prior to admission to the trial.	• Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or *in situ* carcinoma of the uterine cervix. • Use of any restricted medication (see Table S3), or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator. • Plans for administration of live vaccines during the study period or within 6 weeks prior to randomisation. • History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients. • Active systemic infections (except for a common cold) during the last 2 weeks prior to randomisation, as assessed by the investigator. • Chronic or relevant acute infections including human immunodeficiency virus, viral hepatitis and/or active or latent TB: QuantiFERON® TB test was performed at screening. If the result was positive, the patient was allowed to participate in the study if further work up (according to local practice/guidelines) established conclusively that the patient had no evidence of active TB. Patients with active TB were excluded. If latent TB was established, treatment was initiated and maintained according to local country guidelines.

	• Major surgery (according to the investigator's assessment) performed within 12 weeks prior to randomisation or planned within 52 weeks after randomisation (e.g. hip replacement, aneurysm removal, stomach ligation). • Surgical treatment of focal infection (e.g. tonsillectomy or dental therapy) within 6 months of randomisation. • Total white blood cell count <3000/μL, or platelets <100 000/μL, or neutrophils <1500/μL, or haemoglobin <8.5 g/dL at screening. • Aspartate aminotransferase or alanine aminotransferase >2× the upper limit of normal, or total bilirubin >1.5× the upper limit of normal (patients with Gilbert's syndrome were not excluded) at screening. • Currently enrolled in another investigational device or drug study, or <30 days since ending another investigational device or drug study or receiving other investigational treatment(s). • Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, made the patient an unreliable trial participant or unlikely to complete the trial. • Not expected to comply with the protocol requirements or not expected to complete the trial as scheduled. • Previous randomisation in this trial.

ICH International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, *PGA* Physician Global Assessment, *PPP* palmoplantar pustulosis, *PPP ASI* Palmoplantar Pustular Area and Severity Index, *TB* tuberculosis

Table S3 Medications restricted before randomisation. These were not allowed to be taken for the time periods specified, for washout

Medication or class of medication	Duration of restriction
IL-36R inhibitors (other than study drug)	Not allowed
Biologic treatment, e.g. secukinumab, ustekinumab, guselkumab, ixekizumab, tildrakizumab, brodalumab, adalimumab, infliximab, natalizumab or agents that deplete B or T cells (e.g. rituximab, alemtuzumab, visilizumab)	12 weeks or 5 half-lives, whichever is greater, prior to randomisation
Investigational products for psoriasis	12 weeks or 5 half-lives, whichever is greater, prior to randomisation
Etanercept Live virus vaccinations[a]	6 weeks prior to randomisation
Other systemic immunomodulating treatments (e.g. corticosteroids[b], methotrexate, fumaric acid esters, acitretin, ciclosporin, apremilast) Any investigational device or product (excluding psoriasis products)	4 weeks prior to randomisation
Phototherapy (e.g. ultraviolet A, ultraviolet B), topical treatment for psoriasis or any other skin condition affecting palms/soles (e.g. corticosteroids[c], vitamin D analogues, salicylic acid, tar, anthralin)	14 days prior to randomisation
Anakinra	7 days prior to randomisation

[a]Live virus vaccination was restricted until the end of the trial

[b]There was no restriction on corticosteroids with only topical effects (e.g. inhaled corticosteroids to treat asthma or corticosteroid drops administered in the eye or ear)

[c]Exceptions were topical steroids for use on the face, axilla and/or genitalia with a restriction of use within 24 hours prior to trial visit in which PPP ASI was assessed

IL interleukin, *PPP ASI* Palmoplantar Pustular Area and Severity Index

Table S4 Safety summary post Week 16

Adverse event, n (%)	Spesolimab low (*n* = 21)	Spesolimab medium–low (*n* = 20)	Spesolimab medium–high (*n* = 20)	Spesolimab high (*n* = 40)	Placebo to spesolimab (*n* = 38)
Patients with any AE	19 (90.5)	17 (85.0)	18 (90.0)	36 (90.0)	29 (76.3)
Investigator-defined, treatment-related AEs	5 (23.8)	8 (40.0)	8 (40.0)	18 (45.0)	15 (39.5)
SAEs	2 (9.5)	4 (20.0)	2 (10.0)	2 (5.0)	3 (7.9)
Investigator-defined, treatment-related SAE	0	0	0	2 (5.0)	0
Resulted in death	0	0	0	0	0
AEs leading to treatment discontinuation[a]	0	0	2 (10.0)	1 (2.5)	1 (2.6)
Severe AEs (RCTC grade 3 or 4)	2 (9.5)	4 (20.0)	3 (15.0)	3 (7.5)	2 (5.3)
Investigator-defined AESIs	1 (4.8)[b]	1 (5.0)[c]	0	1 (2.5)[d]	1 (2.6)[e]
Local tolerability[f]	*n* = 22	*n* = 21	*n* = 22	*n* = 44	*n* = 43
Any symptom	5 (22.7)	7 (33.3)	8 (36.4)	23 (52.3)	8 (18.6)
Swelling	3 (13.6)	4 (19.0)	4 (18.2)	12 (27.3)	3 (7.0)
Induration	2 (9.1)	4 (19.0)	4 (18.2)	5 (11.4)	1 (2.3)
Heat	2 (9.1)	3 (14.3)	3 (13.6)	9 (20.5)	1 (2.3)
Redness	5 (22.7)	5 (23.8)	6 (27.3)	21 (47.7)	5 (11.6)

Pain	1 (4.5)	4 (19.0)	2 (9.1)	4 (9.1)	3 (7.0)
Other	3 (13.6)	2 (9.5)	5 (22.7)	15 (34.1)	3 (7.0)
Missing	0	0	0	0	5 (11.6)

[a]AEs led to treatment discontinuation in four patients: malignant neoplasm (n = 1, spesolimab medium–high group); worsening pustulotic arthro-osteitis (n = 1, spesolimab medium–high group); worsening PPP, pustular psoriasis and dyshidrotic eczema (n = 1, spesolimab high group) and psoriatic arthritis (n = 1, placebo-to-spesolimab group)

[b]Herpes zoster; no action taken with the study treatment and the event resolved with treatment

[c]Herpes zoster and latent tuberculosis, herpes zoster assessed by the investigator to be treatment-related; no action taken with the study treatment and the event resolved with treatment

[d]Bacterial pneumonia, assessed by the investigator to be treatment-related; no action taken with the study treatment and the event resolved with treatment

[e]Herpes zoster; no action taken with the study treatment and the event resolved with treatment

[f]Data are presented for the entire study duration (0–52 weeks), except for the placebo-to-spesolimab group (post Week 16 only)

Only AEs starting or worsening post-Week 16 are included. If patients skipped treatment at Week 16, only AEs starting after the first treatment post Week 16 are included.

AE adverse event, *AESI* AE of special interest, *RCTC* Rheumatology Common Toxicity Criteria, *SAE* serious adverse event.

Table S5 Common AEs post Week 16, by PT

Adverse event, n (%)	Spesolimab low (*n* = 21)	Spesolimab medium–low (*n* = 20)	Spesolimab medium–high (*n* = 20)	Spesolimab high (*n* = 40)	Placebo to spesolimab (*n* = 38)
Any AEs (in ≥7 patients overall)					
Nasopharyngitis	2 (9.5)	2 (10.0)	1 (5.0)	1 (2.5)	3 (7.9)
Diarrhoea	3 (14.3)	2 (10.0)	1 (5.0)	0	1 (2.6)
Arthralgia	2 (9.5)	0	1 (5.0)	1 (2.5)	4 (10.5)
Back pain	3 (14.3)	0	2 (10.0)	2 (5.0)	0
Injection site reaction	3 (14.3)	5 (25.0)	4 (20.0)	14 (35.0)	4 (10.5)
Investigator-defined treatment-related AEs (in ≥2 patients overall)					
Injection site reaction	3 (14.3)	5 (25.0)	4 (20.0)	14 (35.0)	4 (10.5)
Injection site erythema	0	1 (5.0)	1 (5.0)	0	2 (5.3)
Injection site pain	0	2 (10.0)	0	0	2 (5.3)
Diarrhoea	2 (9.5)	0	0	0	0
Nasopharyngitis	0	0	0	0	2 (5.3)
Sinusitis	0	0	2 (10.0)	0	0

[a]AE of PPP denotes a worsening of disease under study

Only AEs starting or worsening post Week 16 are included. If patients skipped treatment at Week 16, only AEs starting after the first treatment post Week 16 are included

AE adverse event, *PPP* palmoplantar pustulosis, *PT* preferred term, *SOC* system order class

Table S6 Patients with potentially clinically significant abnormalities[a] in neutrophil, eosinophil and liver enzyme levels, and mean neutrophil and eosinophil levels, at Week 16 and post Week 16

	Week 16					
	Spesolimab low	**Spesolimab medium–low**	**Spesolimab medium–high**	**Spesolimab high**	**Spesolimab combined**	**Placebo**
ALT and/or AST ≥3 × ULN, *n* [*N*]	0 [22]	0 [21]	0 [22]	0 [44]	0 [109]	0 [43]
ALT and/or AST ≥3 × ULN, plus total bilirubin ≥2 × ULN, plus alkaline phosphatase ≥2 × ULN, *n* [*N*][b]	0 [22]	0 [21]	0 [22]	0 [44]	0 [109]	0 [43]
Patients with abnormalities among patients without those abnormalities at baseline, *n* (%) [*N*]						
Neutrophils [*N*]	[21]	[21]	[20]	[43]	[105]	[42]
Low	0	0	0	0	0	0
High	0	1 (4.8)	2 (10.0)	2 (4.7)	5 (4.8)	1 (2.4)
Eosinophils, high	0 [22]	0 [20]	0 [22]	0 [43]	0 [107]	0 [42]
AST, high	0 [22]	0 [21]	0 [21]	0 [44]	0 [108]	0 [43]
ALT, high	0 [22]	0 [21]	0 [21]	0 [44]	0 [108]	0 [43]
Alkaline phosphatase, high	0 [22]	0 [21]	0 [21]	0 [44]	0 [108]	0 [43]
Gamma glutamyl transferase, high	0 [21]	0 [21]	2 (9.5) [21]	0 [44]	2 (1.9) [107]	0 [41]
Bilirubin, high	0 [22]	0 [21]	0 [22]	0 [44]	0 [109]	0 [43]
Patients with abnormalities among patients with those abnormalities at baseline, *n* (%) [*N*]						
Neutrophils [*N*]	1	0	2	0	3	1

Low	0	–	0	–	0	0
High	1 (100)	–	1 (50)	–	2 (66.7)	1 (100)
Eosinophils, high	– [0]	1 (100) [1]	– [0]	– [0]	1 (100) [1]	1 (100) [1]
AST, high	– [0]	– [0]	0 [1]	– [0]	0 [1]	– [0]
ALT, high	– [0]	– [0]	0 [1]	– [0]	0 [1]	– [0]
Alkaline phosphatase, high	– [0]	– [0]	1 (100) [1]	– [0]	1 (100) [1]	– [0]
Gamma glutamyl transferase, high	0 [1]	– [0]	1 (100) [1]	– [0]	1 (50.0) [2]	0 [2]

Post Week 16

	Spesolimab low	**Spesolimab medium–low**	**Spesolimab medium–high**	**Spesolimab high**	**Spesolimab 600 mg q4w SC**	**Placebo to spesolimab**
Among patients without these abnormalities at baseline, *n* (%) [*N*]						
Neutrophils [*N*]	20	20	18	39	96	37
Low	0	0	0	0	0	0
High	0	1 (5.0)	0	1 (2.6)	3 (3.1)	1 (2.7)
Eosinophils, high	0 [21]	0 [19]	0 [20]	0 [39]	0 [95]	0 [37]
AST, high	0 [21]	0 [20]	0 [19]	0 [40]	0 [98]	0 [38]
ALT, high	0 [21]	0 [20]	0 [19]	0 [40]	0 [98]	0 [38]
Alkaline phosphatase, high	1 (4.8) [21]	0 [20]	0 [19]	0 [40]	0 [98]	0 [38]
Gamma glutamyl transferase, high	0 [21]	1 (5.0) [20]	2 (10.5) [19]	1 (2.5) [40]	2 (2.1) [96]	0 [36]
Bilirubin, high	0 [21]	0 [20]	0 [20]	0 [40]	0 [98]	0 [38]

Among patients with these abnormalities at baseline, *n* (%) [*N*]						
Neutrophils [*N*]	1	0	2	0	1	1
Low	0	–	0	–	0	0
High	1 (100)	–	1 (50.0)	–	1 (100)	1 (100)
Eosinophils, high	– [0]	0 [1]	– [0]	– [0]	1 (50.0) [2]	1 (100) [1]
AST, high	– [0]	– [0]	0 [1]	– [0]	– [0]	– [0]
ALT, high	– [0]	– [0]	0 [1]	– [0]	– [0]	– [0]
Alkaline phosphatase, high	– [0]	– [0]	0 [1]	– [0]	– [0]	– [0]
Gamma glutamyl transferase, high	– [0]	– [0]	0 [1]	– [0]	0 [2]	0 [2]
Neutrophil and eosinophil counts						
Neutrophils, × 10^9/L, mean (SD) [*N*]						
Baseline	4.58 (2.24) [22]	5.19 (2.28) [21]	6.12 (4.49) [22]	5.76 (1.92) [43]	5.54 (2.20) [107]	5.49 (2.43) [43]
Week 16	4.33 (1.96) [19]	4.76 (2.45) [19]	4.48 (1.68) [20]	4.94 (1.63) [39]	4.92 (2.07) [96]	4.98 (2.30) [38]
Change at Week 16	–0.12 (0.97) [19]	–0.60 (1.12) [19]	–1.83 (3.89) [20]	–0.68 (1.46) [39]	–0.56 (1.38) [96]	–0.42 (1.43) [38]
Week 52	4.56 (2.97) [19]	4.80 (1.92) [17]	5.06 (2.79) [17]	4.95 (1.95) [32]	4.75 (1.91) [81]	4.52 (1.91) [32]
Change at Week 52	0.15 (1.16) [19]	–0.57 (1.63) [17]	–1.20 (3.76) [17]	–0.69 (1.77) [32]	–0.71 (1.70) [81]	–0.81 (1.72) [32]

Eosinophils, × 10^9/L, mean (SD) [*N*]						
Baseline	0.33 (0.24)	0.44 (0.74)	0.30 (0.21)	0.28 (0.16)	0.33 (0.41)	0.33 (0.36)
	[22]	[21]	[22]	[43]	[107]	[43]
Week 16	0.26 (0.14)	0.27 (0.16)	0.26 (0.14)	0.24 (0.13)	0.28 (0.23)	0.31 (0.32)
	[19]	[19]	[20]	[39]	[96]	[38]
Change at Week 16	–0.05 (0.12)	–0.18 (0.66)	–0.04 (0.11)	–0.02 (0.08)	–0.05 (0.31)	–0.03 (0.15)
	[19]	[19]	[20]	[39]	[96]	[38]
Week 52	0.27 (0.17)	0.35 (0.28)	0.26 (0.17)	0.24 (0.12)	0.29 (0.19)	0.32 (0.19)
	[19]	[17]	[17]	[32]	[81]	[32]
Change at Week 52	–0.04 (0.14)	–0.13 (0.86)	–0.01 (0.13)	–0.003 (0.08)	–0.04 (0.44)	–0.03 (0.34)
	[19]	[17]	[17]	[32]	[81]	[32]

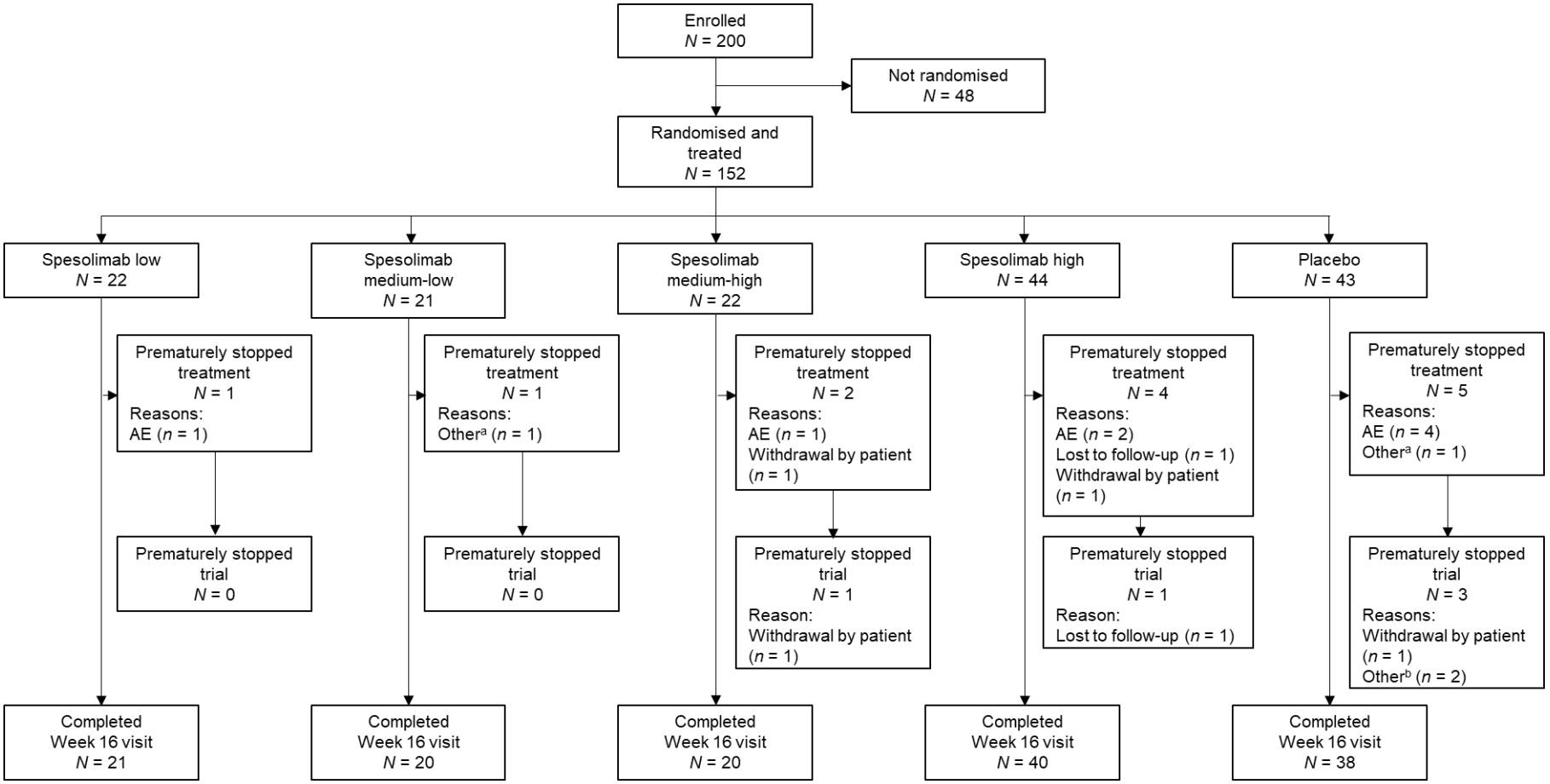
[a]Neutrophils <1 × 10^9/L or >10 × 10^9/L in blood; eosinophils >1 × 10^9/L in blood; AST >3× ULN; ALT >3× ULN; alkaline phosphatase >2× ULN; gamma glutamyl transferase >3× ULN; bilirubin >34 µmol/L

[b]Patients with ALT and/or AST ≥3× ULN plus total bilirubin ≥2× ULN in a 30-day period after ALT and/or AST elevation

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *N* number of patients analysed, *n* number of patients with characteristic, *q4w* every 4 weeks, *SC* subcutaneous, *SD* standard deviation, *ULN* upper limit of normal

Fig. S1 Patient disposition by treatment, (a) up to Week 16 and (b) overall. [a]Reasons included: prostate cancer reported as SAE, patient not willing to travel to site due to COVID-19. [b]Reasons included: investigator decision, patient not willing to attend further visits. [c]Reasons included: prostate cancer reported as SAE, patient not willing to travel to site due to COVID-19, patient did not return to clinic for all study visits, pregnancy, personal/private reasons (*n* = 2), difficulty maintaining visit schedule (*n* = 2), patient decision to discontinue treatment (*n* = 2). [d]Reasons included: investigator decision, patient moved abroad, difficulty maintaining visit schedule, patient decision to discontinue study (*n* = 2), personal/private reasons (*n* = 2), patient unwilling to continue further visits/examinations (*n* = 8). *AE* adverse event, *COVID-19* coronavirus disease 2019, *SAE* serious adverse event

a


Enrolled
N = 200
Not randomised
N = 48
Randomised and treated
N = 152
Spesolimab low
N = 22
Spesolimab medium-low
N = 21
Spesolimab medium-high
N = 22
Spesolimab high
N = 44
Placebo
N = 43
Prematurely stopped treatment
N = 1
Reasons:
AE (n = 1)
Prematurely stopped treatment
N = 1
Reasons:
Other[a] (n = 1)
Prematurely stopped treatment
N = 2
Reasons:
AE (n = 1)
Withdrawal by patient (n = 1)
Prematurely stopped treatment
N = 4
Reasons:
AE (n = 2)
Lost to follow-up (n = 1)
Withdrawal by patient (n = 1)
Prematurely stopped treatment
N = 5
Reasons:
AE (n = 4)
Other[a] (n = 1)
Prematurely stopped trial
N = 0
Prematurely stopped trial
N = 0
Prematurely stopped trial
N = 1
Reason:
Withdrawal by patient (n = 1)
Prematurely stopped trial
N = 1
Reason:
Lost to follow-up (n = 1)
Prematurely stopped trial
N = 3
Reasons:
Withdrawal by patient (n = 1)
Other[b] (n = 2)
Completed Week 16 visit
N = 21
Completed Week 16 visit
N = 20
Completed Week 16 visit
N = 20
Completed Week 16 visit
N = 40
Completed Week 16 visit
N = 38

b

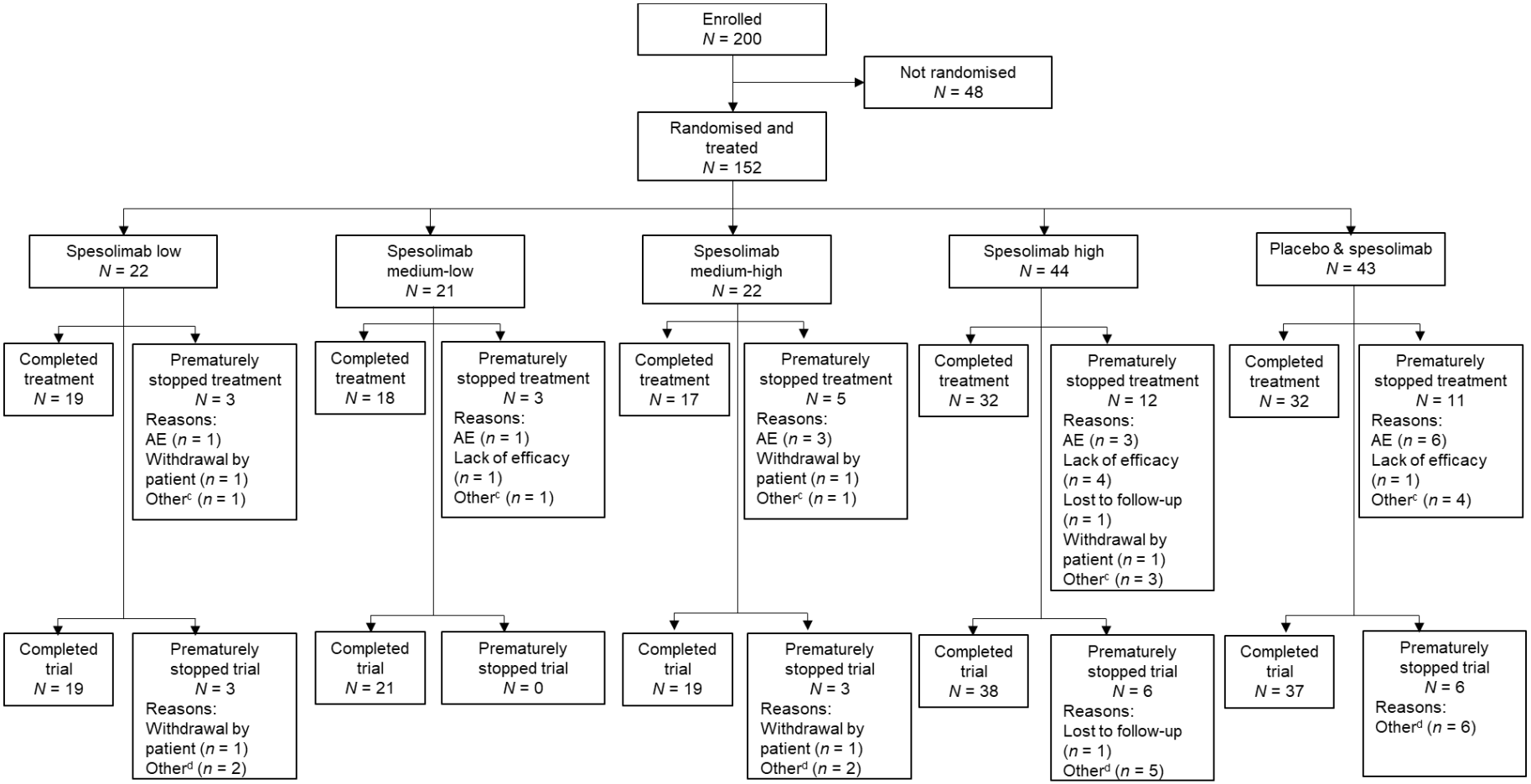

Enrolled
N = 200
Not randomised
N = 48
Randomised and treated
N = 152
Spesolimab low
N = 22
Spesolimab medium-low
N = 21
Spesolimab medium-high
N = 22
Spesolimab high
N = 44
Placebo & spesolimab
N = 43
Completed treatment
N = 19
Prematurely stopped treatment
N = 3
Reasons:
AE (n = 1)
Withdrawal by patient (n = 1)
Other[c] (n = 1)
Completed treatment
N = 18
Prematurely stopped treatment
N = 3
Reasons:
AE (n = 1)
Lack of efficacy (n = 1)
Other[c] (n = 1)
Completed treatment
N = 17
Prematurely stopped treatment
N = 5
Reasons:
AE (n = 3)
Withdrawal by patient (n = 1)
Other[c] (n = 1)
Completed treatment
N = 32
Prematurely stopped treatment
N = 12
Reasons:
AE (n = 3)
Lack of efficacy (n = 4)
Lost to follow-up (n = 1)
Withdrawal by patient (n = 1)
Other[c] (n = 3)
Completed treatment
N = 32
Prematurely stopped treatment
N = 11
Reasons:
AE (n = 6)
Lack of efficacy (n = 1)
Other[c] (n = 4)
Completed trial
N = 19
Prematurely stopped trial
N = 3
Reasons:
Withdrawal by patient (n = 1)
Other[d] (n = 2)
Completed trial
N = 21
Prematurely stopped trial
N = 0
Completed trial
N = 19
Prematurely stopped trial
N = 3
Reasons:
Withdrawal by patient (n = 1)
Other[d] (n = 2)
Completed trial
N = 38
Prematurely stopped trial
N = 6
Reasons:
Lost to follow-up (n = 1)
Other[d] (n = 5)
Completed trial
N = 37
Prematurely stopped trial
N = 6
Reasons:
Other[d] (n = 6)

Fig. S2 Percentage change from baseline in PPP ASI up to Week 52. Means and CI estimated by (REML)-based MMRM including the fixed, categorical effects of treatment at each visit, region and the continuous effect of baseline at each visit as well as random effects of subject. [a]Patients received placebo up to Week 16 before switching to spesolimab. *CI* confidence interval, *MMRM* Mixed Model Repeated Measures, *PPP ASI* Palmoplantar Pustular Area and Severity Index, *REML* restricted maximum likelihood, *SE* standard error

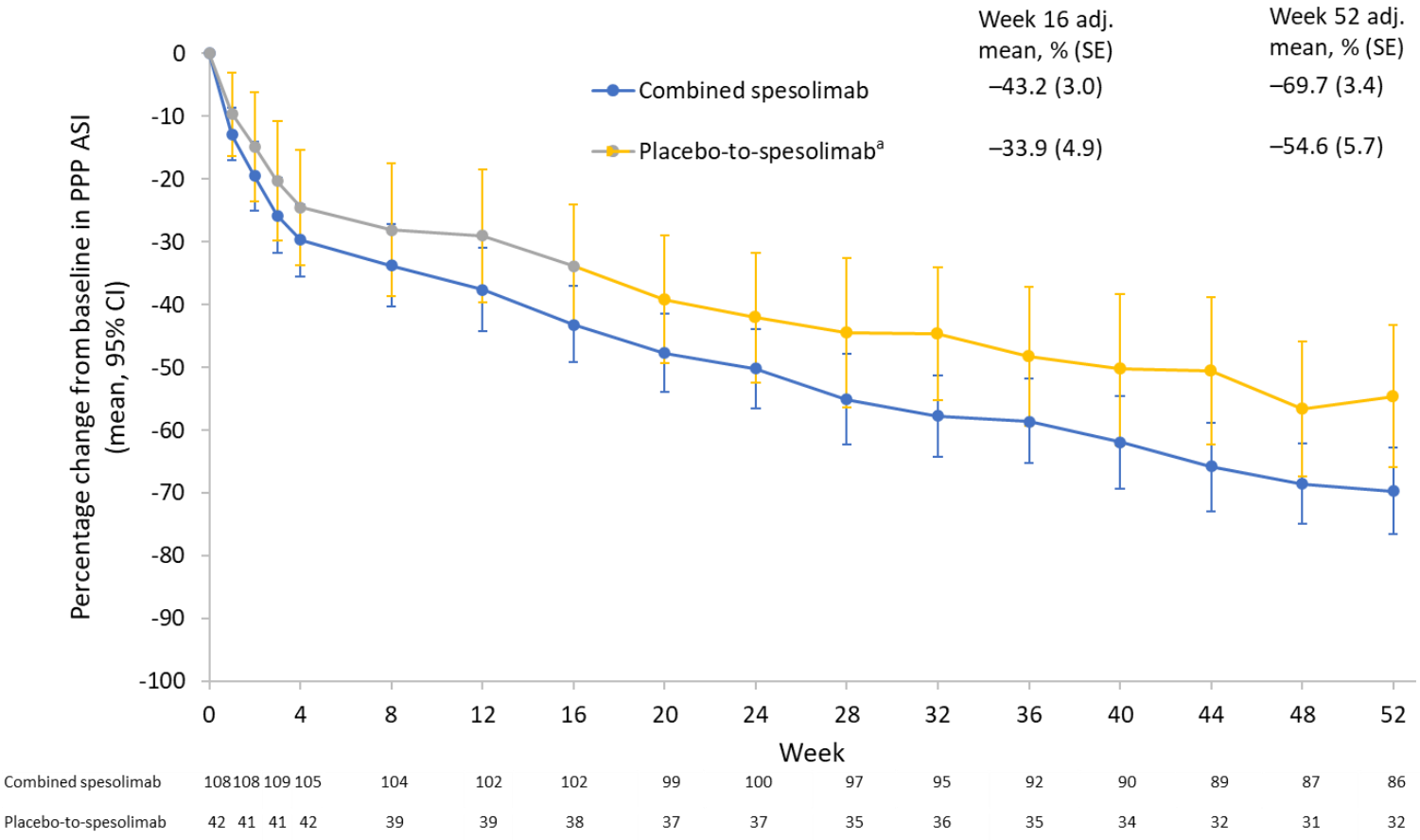
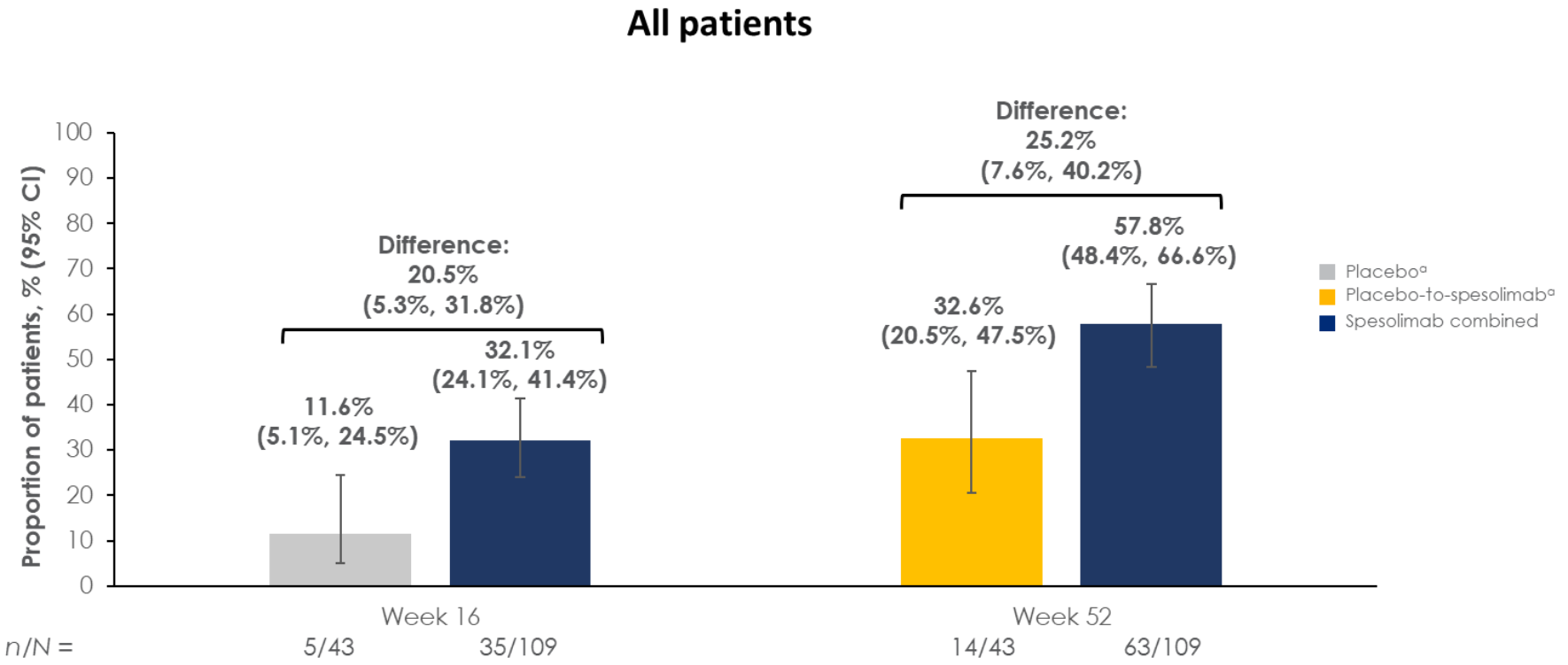
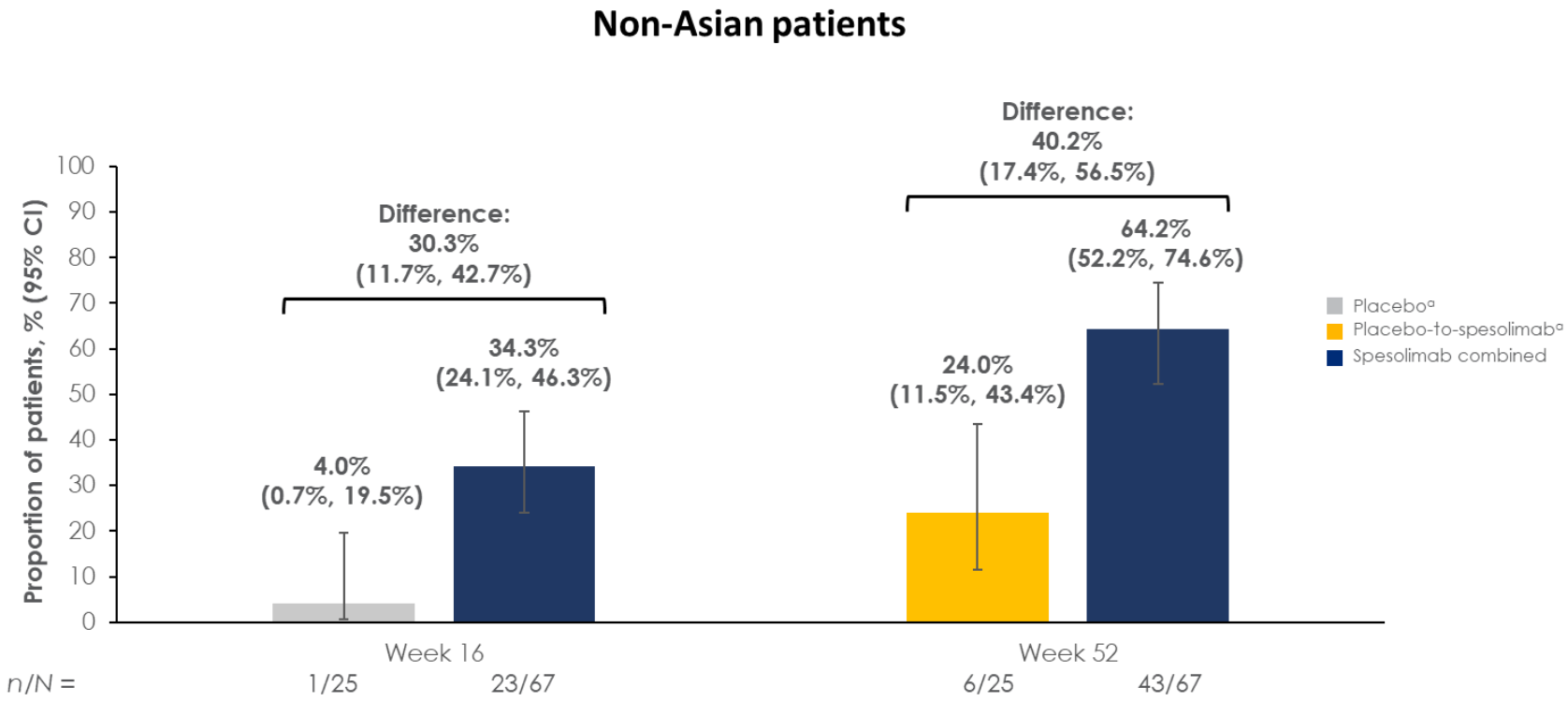


Fig. S3 Proportion of patients achieving PPP PGA pustulation subscore of 0/1 at Weeks 16 and 52 in (a) all patients, (b) non-Asian patients and (c) Asian patients. 95% CIs were calculated by the Wilson method. [a]Patients received placebo until Week 16 before switching to spesolimab. *CI* confidence interval, *n* number of patients achieving PPP PGA pustulation subscore of 0/1, *N* number of patients evaluated, *PPP PGA* Palmoplantar Pustular Physician Global Assessment

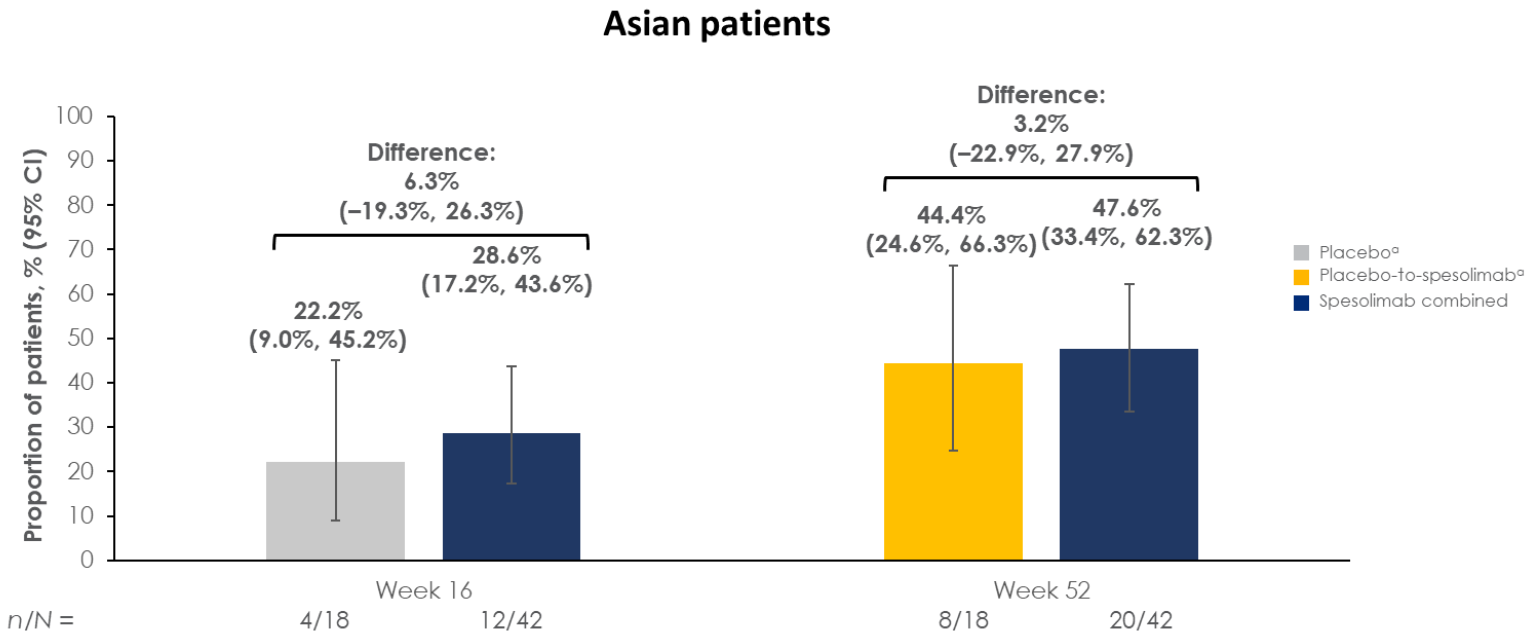
a



b


Non-Asian patients
Difference:
30.3%
(11.7%, 42.7%)
Difference:
40.2%
(17.4%, 56.5%)
34.3%
(24.1%, 46.3%)
64.2%
(52.2%, 74.6%)
4.0%
(0.7%, 19.5%)
24.0%
(11.5%, 43.4%)
Proportion of patients, % (95% CI)
100
90
80
70
60
50
40
30
20
10
0
Placebo[a]
Placebo-to-spesolimab[a]
Spesolimab combined
Week 16
Week 52
n/N =
1/25
23/67
6/25
43/67

c


Asian patients
Proportion of patients, % (95% CI)
100
90
80
70
60
50
40
30
20
10
0
Difference:
6.3%
(–19.3%, 26.3%)
22.2%
(9.0%, 45.2%)
28.6%
(17.2%, 43.6%)
Difference:
3.2%
(–22.9%, 27.9%)
44.4%
(24.6%, 66.3%)
47.6%
(33.4%, 62.3%)
Placebo[a]
Placebo-to-spesolimab[a]
Spesolimab combined
Week 16
Week 52
n/N =
4/18
12/42
8/18
20/42