Supplemental Material

Title: Efficacy and safety of ixekizumab through 5 years in moderate-to-severe psoriasis: Long-term results from the UNCOVER-1 and UNCOVER-2 Phase 3 randomized controlled trials

Running Heading (short version of the title): 5-year efficacy and safety of ixekizumab in psoriasis

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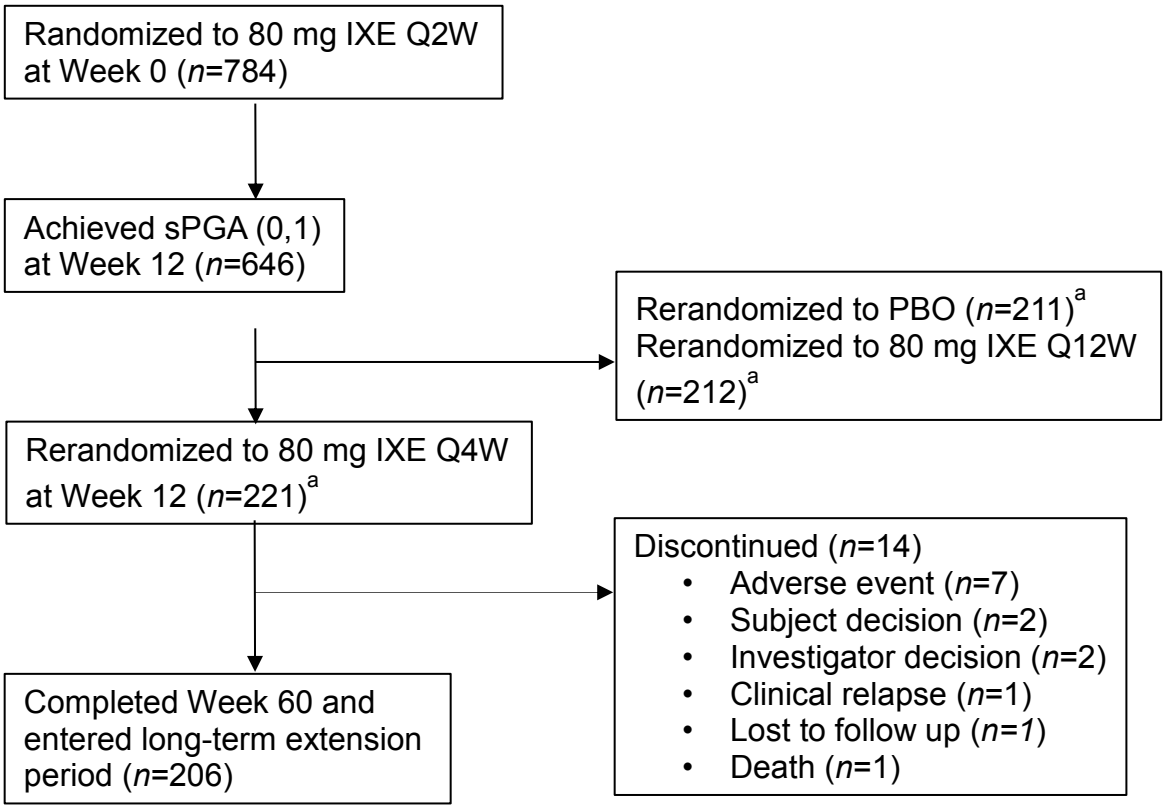
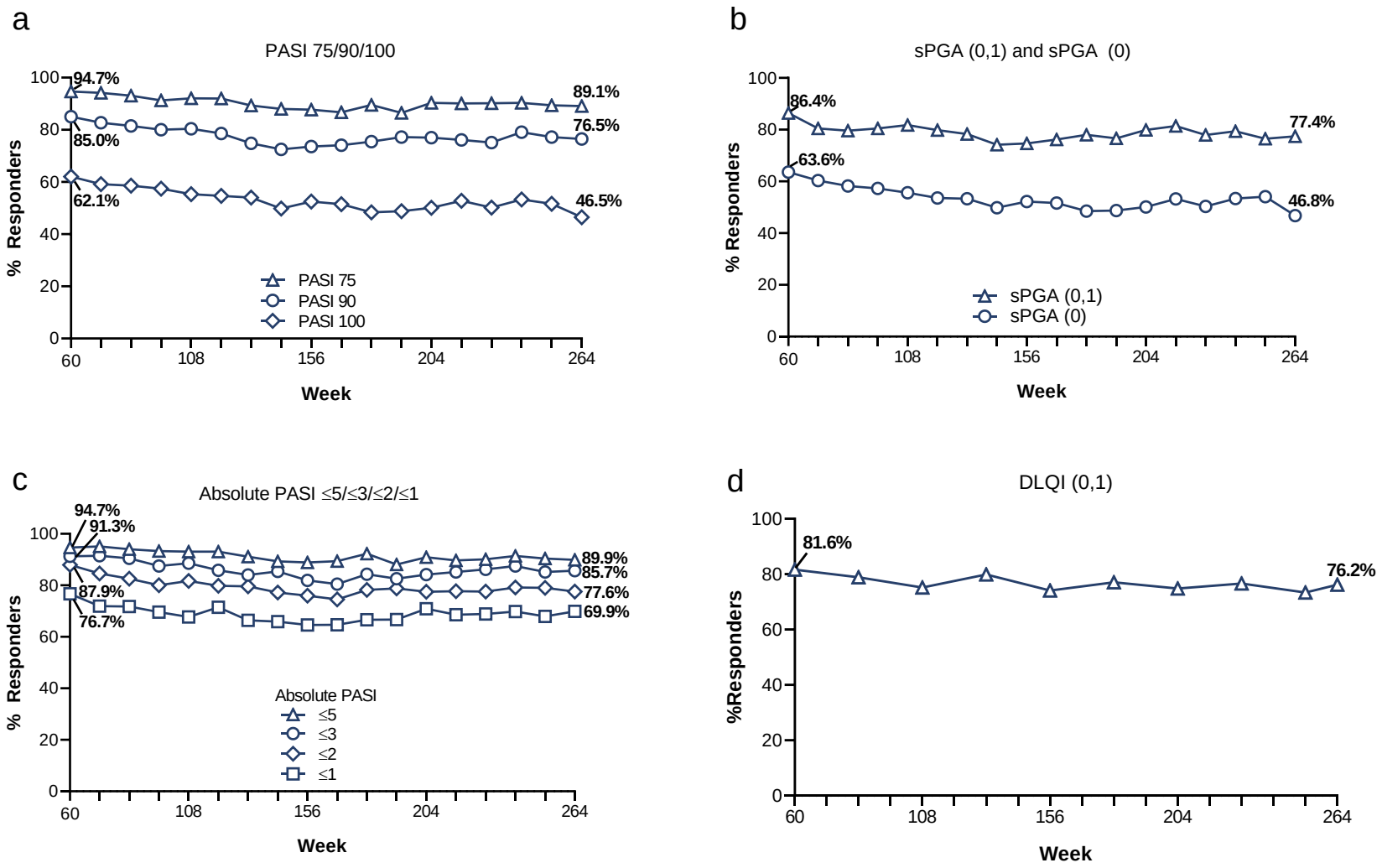


Supplemental Fig. 1 Disposition of patients: approved dosing regimen patient population

IXE Q2W ixekizumab every 2 weeks, *IXE Q4W* ixekizumab every 4 weeks, *IXE Q12W* ixekizumab every 12 weeks, *n* number of patients in the specified category, *PBO* placebo, *sPGA (0,1)* static Physician's Global Assessment score of 0 or 1

[a]Of the 646 patients who achieved sPGA (0,1) at Week 12, 6 discontinued at Week 12 before entering the maintenance dosing period (3 due to adverse events, 2 due to patient decision, 1 due to investigator decision). A total of 644 patients rerandomized into the maintenance dosing period; 4 patients who did not achieve sPGA (0,1) at Week 12 rerandomized at Week 12 due to randomization errors.

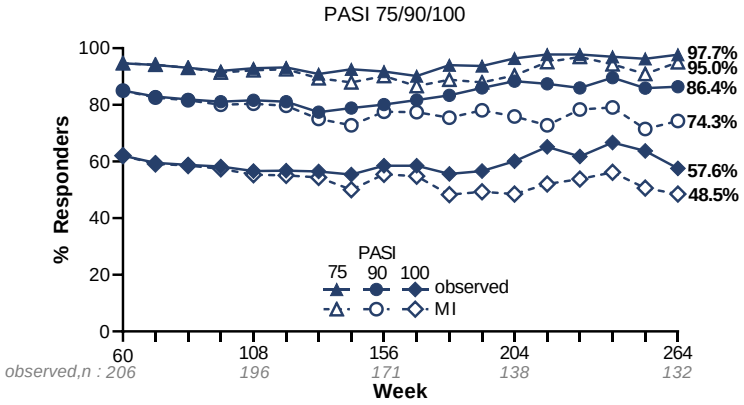
An additional patient in the IXE Q4W group was considered to not have entered the long-term extension period. This patient attended the Week 60 visit but was then lost to follow up and did not provide the study treatment exposure record to prove the subject had taken study treatment in the long-term extension period.



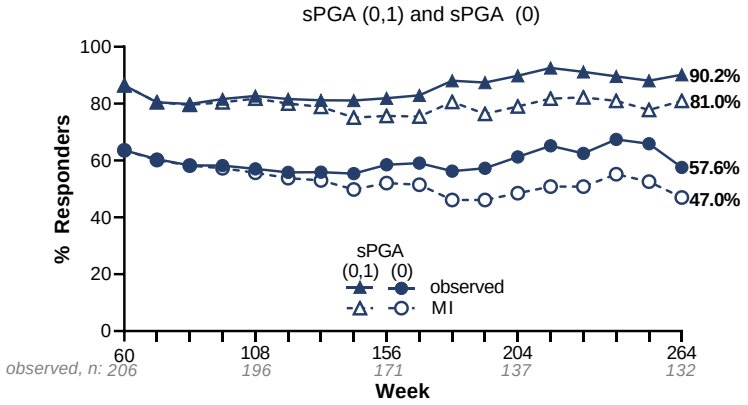
Supplemental Fig. 2 Treatment effects on response rates (modified nonresponder imputation analysis) for efficacy outcomes including both 80 mg ixekizumab every-4-week and every-2-week escalation visit: a. Psoriasis and Severity Index (PASI) 75/90/100; b. static Physician's Global Assessment (sPGA) 0 or 1 and sPGA 0; c. absolute PASI ≤5/≤3/≤2/≤1; d. Dermatology Life Quality Index (DLQI) scores of 0 or 1 for efficacy outcomes through 5 years of treatment. Data

include patients who escalated to every-2-week dosing during the long-term extension period. Percentages listed on the graphs are the percentage of patients achieving response at Week 60 and Week 264. Each consecutive tick mark after Week 60 on the x-axis represents 12 weeks.

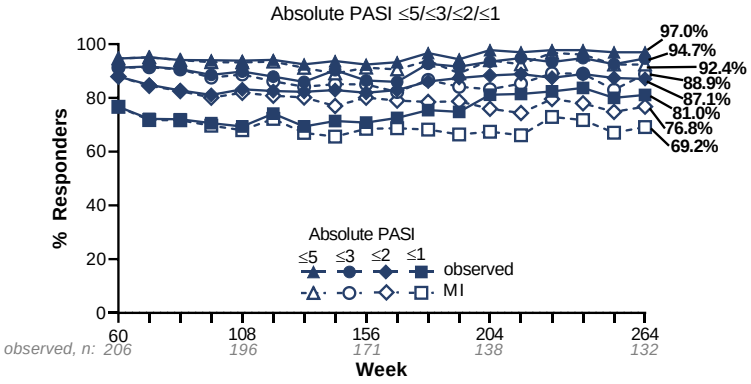
a


PASI 75/90/100
% Responders
100
80
60
40
20
0
97.7%
95.0%
86.4%
74.3%
57.6%
48.5%
PASI
75 90 100
observed
MI
60 108 156 204 264
observed,n : 206 196 171 138 132
Week

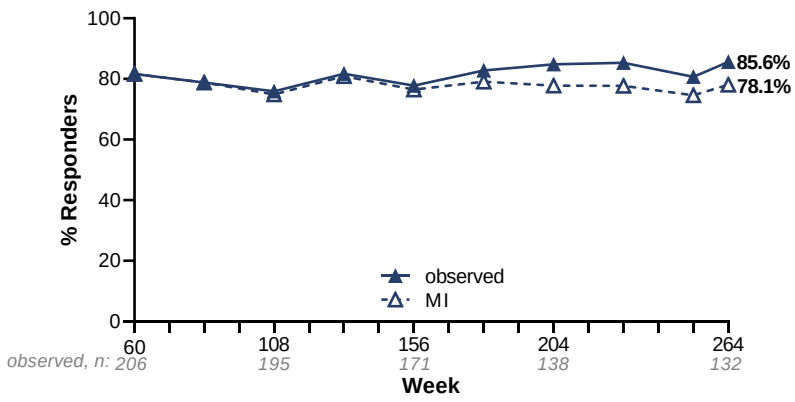
b


sPGA (0,1) and sPGA (0)
% Responders
100
80
60
40
20
0
90.2%
81.0%
57.6%
47.0%
sPGA
(0,1) (0)
observed
MI
60 108 156 204 264
observed, n: 206 196 171 137 132
Week

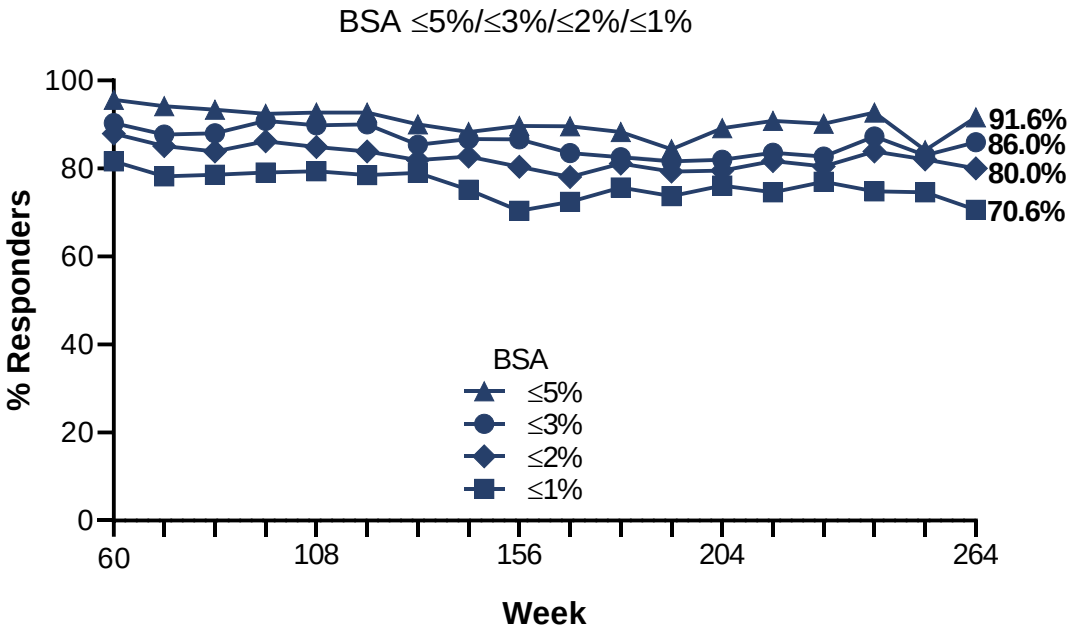
c


Absolute PASI ≤5/≤3/≤2/≤1
% Responders
100
80
60
40
20
0
97.0%
94.7%
92.4%
88.9%
87.1%
81.0%
76.8%
69.2%
Absolute PASI
≤5 ≤3 ≤2 ≤1
observed
MI
60 108 156 204 264
observed, n: 206 196 171 138 132
Week

d


DLQI (0,1)
% Responders
100
80
60
40
20
0
85.6%
78.1%
observed
MI
60 108 156 204 264
observed, n: 206 195 171 138 132
Week

Supplemental Fig. 3 Observed case and multiple imputation (MI) analyses: response rates in patients receiving 80 mg ixekizumab every 4 weeks achieving a. Psoriasis and Severity Index (PASI) 75/90/100; b. static Physician's Global Assessment (sPGA) 0 or 1 and sPGA 0; c. absolute PASI ≤5/≤3/≤2/≤1; and d. Dermatology Life Quality Index (DLQI) scores of 0 or 1 for efficacy outcomes through 5 years of treatment. Data include patients who escalated to every-2-week dosing during the long-term extension period. Percentages listed on the graph in panels a, b, and d are the percentages of patients achieving response at Week 264. Each consecutive tick mark after Week 60 on the x-axis represents 12 weeks.



Supplemental Fig. 4 Response rates (modified nonresponder imputation) of patients receiving 80 mg ixekizumab every 4 weeks with body surface area (BSA) involvement ≤5/≤3/≤2/≤1% through 5 years of treatment. Data exclude patients who escalated to every-2-week dosing during the long-term extension period. Percentages listed on the graph are the percentages of patients achieving response at Week 264. Each consecutive tick mark after Week 60 on the x-axis represents 12 weeks.

Supplemental Table S1 Treatment response at visit prior to every-2-week (Q2W) dose escalation in patients who escalated to IXE Q2W dosing

Parameter	IXE Q2W/IXE Q4W 80 mg *N* = 206
IXE Q2W escalators/ approved dose regimen patient population	43/206 (20.9%)
PASI	*N* = 43
Mean (SD)	7.3 (9.1)
Percent improvement, mean (SD)	66.7 (28.9)
PASI 50, n (%)	35 (81.4)
PASI 75, n (%)	20 (46.5)
PASI 90, n (%)	4 (9.3)
PASI 100, n (%)	0
sPGA, n (%) patients with:	*N* = 43
0, n (%)	0
1, n (%)	2 (4.7)
2, n (%)	12 (27.9)
3, n (%)	26 (60.5)
4, n (%)	3 (7.0)
5, n (%)	0

IXE Q2W ixekizumab every 2 weeks, *IXE Q4W* ixekizumab every 4 weeks, *N* number of patients in the analysis population, *n* number of patients in the specified category, *PASI* Psoriasis Area and Severity Index, *SD* standard deviation, *sPGA* static Physician's Global Assessment

Supplemental Table S2 Serious adverse events during the long-term extension period (Week 60 to Week 264)

Serious Adverse Events		IXE Q2W/IXE Q4W[a] 80 mg 604.3 PY
		n (IR)
Any SAE[b]		41 (6.8)
Infections and infestations[c]	Cellulitis	3 (0.5)
	Erysipelas	3 (0.5)
	Pneumonia	3 (0.5)
	Subcutaneous abscess	2 (0.3)
	Herpes zoster	1 (0.2)
	Necrotizing fasciitis	1 (0.2)
	Tooth abscess	1 (0.2)
	Esophageal candidiasis	1 (0.2)
Nervous system disorders	Carpal tunnel syndrome	1 (0.2)
	Ischemic stroke	1 (0.2)
	Presyncope	1 (0.2)
	Seizure	1 (0.2)
	Subarachnoid hemorrhage	1 (0.2)
Musculoskeletal and connective tissue disorders	Bursitis	1 (0.2)
	Intervertebral disc protrusion	1 (0.2)
	Osteoarthritis	1 (0.2)
Gastrointestinal disorders	Esophageal achalasia	2 (0.3)
	Abdominal pain	1 (0.2)
General disorders and administration site conditions	Chest pain	1 (0.2)
	Drug withdrawal syndrome	1 (0.2)
Injury, poisoning, and procedural complications	Ankle fracture	1 (0.2)
	Concussion	1 (0.2)
	Fall	1 (0.2)
	Head injury	1 (0.2)
	Ligament rupture	1 (0.2)
	Meniscus injury	1 (0.2)
Benign, malignant, and unspecified neoplasms	Laryngeal squamous cell carcinoma	1 (0.2)
	Prostate cancer	1 (0.3)[d]
	Pyogenic granuloma	1 (0.2)
Reproductive system and breast disorders	Endometriosis	1 (0.5)[e]

	Ovarian cyst	1 (0.5)[e]
	Vaginal hemorrhage	1 (0.5)[e]
Blood and lymphatic system disorders	Anemia	1 (0.2)
Cardiac disorders	Myocardial infarction	1 (0.2)
	Myocardial ischemia	1 (0.2)
	Palpitations	1 (0.2)
Ear and labyrinth disorders	Positional vertigo	1 (0.2)
Psychiatric disorders	Anxiety	1 (0.2)
	Depression	1 (0.2)
	Psychotic disorder	1 (0.2)
	Schizophrenia	1 (0.2)
	Suicide attempt	1 (0.2)
Surgical and medical procedures	Gastrectomy	1 (0.2)
	Hernia hiatus repair	1 (0.2)
Skin and subcutaneous tissue disorders	Psoriasis	1 (0.2)
Investigations	Abnormal electrocardiogram	1 (0.2)
Vascular disorders	Femoral artery aneurism	1 (0.2)

IR incidence rate per 100 patient years, *IXE Q2W* ixekizumab every 2 weeks, *IXE Q4W* ixekizumab every 4 weeks, *n* number of patients in the specified category, *PY* patient years, *SAE* serious adverse event

[a]Patients were allowed to escalate to Q2W dosing after Week 60 during the long-term extension period. Patients who increased dosing to 80 mg IXE Q2W remained on this dose until they completed or discontinued from the study. These data comprise all patients in the approved dosing regimen patient population, including those who escalated to every-2-week dosing during the long-term extension period.

[b]Patients with multiple SAEs were counted once for each category and may have been counted in more than 1 category.

[c]The most frequently reported SAEs were infections and infestations (14 patients; IR: 2.3).

[d]Denominator adjusted for male-specific event: number of males = 140; PY = 392.1.

[e]Denominator adjusted for female-specific event: number of females = 66; PY = 212.1.

Supplemental Table S3: List of Ethics Review Boards for Studies UNCOVER-1 and UNCOVER-2

UNCOVER-2	
Local Ethics Committees	
USA	Western Institutional Review Board (WIRB) 1019 39th Avenue SE Suite 120 Puyallup, Washington 98374-2115, USA University of Connecticut Institutional Review Board 263 Farmington Ave Munson Bldg - 2nd Floor, Farmington, Connecticut 06030-3926, USA
Canada	Research Review Board, Inc 19-13085 Yonge St Ste 203 Richmond Hill, Ontario L4E 0K2, Canada Research Review Board, Inc 1500-10104 103 Ave NW Edmonton, Alberta T5J 4A7, Canada
Germany	Ethics Committee of Westphalia-Lippe Medical Association and the Medical Faculty of the WWU Münster Gartenstr. 210-214, 48147 Münster, Germany Ethikkommission der Medizinischen Hochschule Hannover Carl-Neuberg-Str. 1 Hannover 30625, Germany Ethics Committee of Hessen State Medical Association Im Vogelsgesang 3 60488 Frankfurt am Main, Germany Ethikkommission der Medizinischen Fakultät der Eberhard-Karls-Universität Tübingen Gartenstraße 47 72074, Tübingen, Germany

	Ethikkommission der Medizinischen Fakultät der Georg-August-Universität Göttingen Von-Siebold-Straße 3 37075, Göttingen, Germany Ethikkommission des Landes Berlin, Landesamt für Gesundheit und Soziales Fehrbelliner Platz 1 10707 Berlin, Germany Ethikkommission der Friedrich-Schiller-Universität Jena Bachstraße 18 7740 Jena, Germany Ethics Committee of the Medical Faculty of Dresden University of Technology Fetscherstrasse 74 01307, Dresden, Germany Ethikkommission der Medizinischen Fakultät der Universität Duisburg-Essen, Robert-Koch-Str. 9-11, 45147 Essen, Germany Ethikkommission zur Beurteilung medizinischer Forschung am Menschen der Aerztekammer Niedersachsen Berliner Allee 20, 30175 Hannover, Germany
United Kingdom	R&D Department Corporate Services Bldg Monklands Hospital, Monkscourt Ave. ML6 0JS Airdrie, United Kingdom NRES Committee East of England - Cambridge South R&D Department Salford Royal NHS Foundation Trust Stott Lane, The Mayo Building, Level 3, Salford M6 8HD, United Kingdom Medical School Bldg, Royal Free London NHS Foundation Trust Royal Free Hospital, Pond St, R&D Office, Admin Corridor Room G649, Medical School Building, London NW3 2QG, United Kingdom R&D Management Office Western Infirmary, Tennent Institute, 1st Floor, 38 Church St, Glasgow G11 6NT, United Kingdom

	Tayside Medical Science Centre, Ninewells Hospital & Medical School TASC Research & Development Office, Residency Block, Level 3, George Pirie Way, Dundee, DD1 9SY, United Kingdom Research & Development Dept, Northern Lincolnshire and Goole Hospitals NHS Foundation Trust, Scunthorpe General Hospital, Cliff Gardens Scunthorpe, North Lincolnshire, DN15 7BH, United Kingdom Sheffield Teaching Hospital NHS Foundation Trust, Glossop Rd, Royal Hallamshire Hospital, Sheffield S10 2JF, United Kingdom
Australia	Eastern Health Research and Ethics Sub-Committee 5 Arnold St, Box Hill Victoria 3128, Australia Cabrini Human Research Ethics Committe183 Wattletree Rd Malvern East, Victoria 3145, Australia Human Research Ethics Committee of North Sydney Central Coast Health, Level 13 Kolling Bldg, Royal North Shore Hospital St Leonards New South Wales 2065, Australia
Austria	Ethics Committee Vienna Medical University Borschkegasse 8b/6 1090 Vienna, Austria Ethikkommission des Landes Vorarlberg Rathausstrasse 15 6900 Bregenz, Austria Ethics Committee of Innsbruck Medical University Innrain 43 6020 Innsbruck, Austria

Czech Republic	Etická komise Fakultni nemocnice u sv. Anny v Brne Pekarska 53 656 91 Brno, Czech Republic Etická komise pro multicentricke klinicke hodnoceni Fakultní nemocnice v Motole V Uvalu 84 150 06 Praha 5 -Motol, Czech Republic
Spain	Comité Ético de Investigación Clínica Hospital Universitari Germans Trias i Pujol Secretaría del CEIC – Planta baja, pasillo de archivo Edificio Materno-Infantil Ctra. del Canyet, s/n 08916 Badalona – Barcelona, Spain Comité Ético de Investigación Clínica – Área 7 Hospital Clínico San Carlos Servicio de Farmacología Clínica Unidad de Coordinación de Ensayos Clínicos 1.ª planta, Ala norte, puerta G 28040 Madrid, Spain Comité Ético de Investigación Clínica Hospital de la Santa Creu i Sant Pau Servicio de Farmacología Clínica Edificio HC, planta 1ª - izquierda. Av. Sant Antoni Mª Claret, 167 08025 Barcelona, Spain Comité Coordinador de Ética de la Investigación Biomédica de Andalucía Avda. Innovación, s/n Consejería de Salud Edificio Arena I Sevilla 41020, Spain

	Comité Ético de Investigación Clínica - Área 8 Fundación Hospital Alcorcón C/ Budapest, nº1 - Planta Sótano 28922 Alcorcón – Madrid, Spain
	Comité Ético de Investigación Clínica Hospital General Universitario de Alicante Centro de Diagnósticos - 3ª Plta. - Edificio Gris C/ Pintor Baeza, 12 03010 Alicante, Spain Comité Ético de Investigación Clínica Parc de Salut MAR Consorci Mar Parc de Salut de Barcelona Parc de Recerca Biomèdica de Barcelona (dcho. 163.03) C/ Doctor Aiguader, 88, 1ª planta 08003 Barcelona, Spain Hospital Universitario 12 De Octubre Instituto De Investigacion Hospital 12 de Octubre (i+12) Avda. de Cordoba s/n Area de Gestion de Proyectos - Unidad Administrativa CEIC Centro de Actividades Ambulatorias, Bloque D - Planta 6ª 28041 Madrid, Spain Comité Ético de Investigación Clínica Hospital Univ. de Gran Canaria Dr. Negrín 1.° Planta-Al lado de Farmacia C/ Barranco de la Ballena, s/n 35010 Las Palmas de Gran Canaria, Spain Comité Coordinador de Ética de la Investigación Biomédica de Andalucía Avda. Innovación, s/n Consejería de Salud Edificio Arena I Sevilla 41020 Spain

Central Ethics Committees	
USA	Schulman Associates IRB 4445 Lake Forest Dr, Ste 300 Cincinnati, Ohio 45242, USA*
Germany	Ethikkommission der Ärztekammer Hamburg Weidestr. 122 b 22083 Hamburg, Germany
Poland	Komisja Bioetyczna przy Centralnym Szpitalu Klinicznym MSW Ul. Wołoska 137 02-507 Warszawa, Mazowieckie, Poland
Romania	Academy of Medical Sciences National Bioethics Committee of Medicines and Medical Devices 020125 Bucharest 19-21 Stefan Cel Mare Street District 2, Romania
United Kingdom	NRES Committee East of England - Cambridge South The Old Chapel, Royal Standard Ct Nottingham NG1 6FS, United Kingdom
Australia	Bellberry Human Research Ethics Committee (HREC) 129 Glen Osmond Rd Eastwood, South Australia 5063, Australia
France	CPP ile de france IV Hôpital Saint Louis, Porte 5 du carre Historique 1 Avenue Claude Vellefaux 75475 Paris Cedex 10, France
Netherlands	CMO Regio Arnhem-Nijmegen UMC St Radboud Centraal, route 578 Geert Grooteplein 10 6500 HB Nijmegen, Netherlands

Poland	Komisja Bioetyczna przy Centralnym Szpitalu Klinicznym MSW ul. Wołoska 137 02-507 Warszawa, Mazowieckie, Poland
Austria	Ethics Committee Graz Medical University Auenbruggerplatz 2 8036 Graz, Austria
Czech Republic	Etická komise Fakultní nemocnice Kralovske Vinohrady Srobarova 50 100 34 Praha 10, Czech Republic
Spain	Comité Ético de Investigación Clínica Hospital Universitari Germans Trias i Pujol Secretaría del CEIC – Planta baja, pasillo de archivo Edificio Materno-Infantil Ctra. del Canyet, s/n 08916 Badalona – Barcelona, Spain
	Comité Ético de Investigación Clínica Area de Gestion de Proyectos – Unidad Administrativa Hospital Universitario 12 de Octubre Instituto de Investigación Hospital 12 de Octubre (i+12) Centro de Actividades Ambulatorias, 6ª Planta – Bloque D Avda. de Córdoba, s/n 28041 Madrid, Spain

IRB institutional review board, *USA* United States of America