Definition, aims, and implementation of GA2LEN/HAEi Angioedema Centers of Reference and Excellence

Maurer, Marcus; Aberer, Werner; Agondi, Rosana; Al-Ahmad, Mona; Al-Nesf, Maryam Ali; Anstotegui, Ignacio; Arnout, Rand; Arruda, Luisa Karla; Asero, Riccardo; Aygören-Pürsü, Emel; Banerji, Aleena; Bauer, Andrea; Ben-Shoshan, Moshe; Berardi, Alejandro; Bernstein, Jonathan A.; Betschel, Stephen; Bindslev-Jensen, Carsten; Bizjak, Mojca; Boccon-Gibod, Isabelle; Bork, Konrad; Bouillet, Laurence; Boysen, Henrik Balle; Brodsgki, Nicholas; Broesby-Olsen, Sigurd; Busse, Paula; Buttgerit, Thomas; Bygum, Anette; Caballero, Teresa; Campos, Régis A.; Cancian, Mauro; Cherréz-Ojeda, Ivan; Cohn, Danny M.; Costa, Célia; Craig, Timothy; Criado, Paulo Ricardo; Criado, Roberta F.; Csuka, Dorottya; Dissemond, Joachim; Du-Thanh, Aurélie; Ensina, Luis Felipe; Ertas, Ragip; Fabiani, José E.; Fantini, Claudio; Farkas, Henriette; Ferrucci, Silvia Mariel; Figueras-Nart, Ignasi; Fili, Natalia L.; Fomina, Daria; Fukunaga, Atsushi; Gelincik, Asli; Giménez-Arnau, Ana; Godse, Kiran; Gompels, Mark; Gonzalo, Margarida; Gotua, Maia; Gower, Richard; Grumach, Anete S.; Guidos-Fogelbach, Guillermo; Hide, Michihiro; Illina, Nataliya; Inomata, Naoko; Jakob, Thilo; Josviack, Dario O.; Kang, Hye Ryun; Kaplan, Allen; Kasperska-Zając, Alicja; Katelaris, Constance; Kessel, Aharon; Kleinheinz, Andreas; Kocatürk, Emek; Košnik, Mitja; Krasowska, Dorota; Kulthan, Kanokvalai; Kumar, M. Sendhil; Larco Sousa, José Ignacio; Longhurst, Hilary J.; Lumry, William; MacGinnitie, Andrew; Magerl, Markus; Makris, Michael P.; Malbrán, Alejandro; Marsland, Alexander; Martinez-Saguer, Inmaculada; Medina, Iris V.; Meshkova, Raisa; Metz, Martin; Nasr, Imran; Nicolay, Jan; Nishigori, Chikako; Ohssawa, Isao; Ozyurt, Kemal; Papadopoulos, Nikolaos G.; Parisi, Claudio A.S.; Peter, Jonathan Grant; Pfützner, Wolfgang; Popov, Todor; Prior, Nieves; Ramon, German D.; Reich, Adam; Reshef, Avner; Riedl, Marc A.; Ritchie, Bruce; Röckmann-Helmbach, Heike; Rudenko, Michael; Salman, Andaç; Sanchez-Borges, Mario; Schmid-Grendelmeier, Peter; Serpa, Faradiba S.; Serrabaldrich, Esther; Sheikh, Farrukh R.; Smith, William; Soria, Angèle; Staubach, Petra; Steiner, Urs C.; Stobiecki, Marcin; Sussman, Gordon; Tagka, Anna; Thomsen, Simon Francis; Treudler, Regina; Valle, Solange; van Doorn, Martijn; Varga, Lilian; Vázquez, Daniel O.; Wagner, Nicola; Wang, Liangchun; Weber-Chrysochoou, Christina; Ye, Young Min; Zalewska-Janowska, Anna; Zanichelli, Andrea; Zhao, Zuoqiao; Zhi, Yuxiang; Zuberbier, Torsten; Zwiener, Ricardo D.; Castaldo, Anthony

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Definition, aims, and implementation of GA\textsuperscript{2}LEN/HAEi Angioedema Centers of Reference and Excellence

To the Editor,

GA\textsuperscript{2}LEN, the Global Allergy and Asthma European Network, and HAE international (HAEi), the global umbrella organization for the world’s hereditary angioedema (HAE) patient groups, have launched their joint ACARE (Angioedema Center of Reference and Excellence) program, within GA\textsuperscript{2}LEN’s center of reference and excellence (CORE) initiative. Angioedema is a common, heterogeneous, often debilitating and chronic condition and is frequently a challenge for physicians and affected patients, especially patients suffering from recurrent attacks. Additionally, it can be a challenge for some patients to understand the underlying etiology of their angioedema (Table 1). GA\textsuperscript{2}LEN’s CORE networks, such as UCARE for urticaria and ADCARE for atopic dermatitis, help to improve the management of difficult-to-treat conditions. Here, we describe the aims, requirements, provisions, application process, audit, and accreditation protocol for GA\textsuperscript{2}LEN/HAEi ACAREs. ACAREs aim to provide excellence in angioedema management, increase the knowledge of angioedema through research and education, and promote advocacy activities that raise angioedema awareness. To become a certified ACARE, angioedema centers must fulfill 32 requirements, defined by specific provisions that will be assessed during an audit visit. The ACARE program will result in a strong network of angioedema specialists, promote angioedema research and awareness, and harmonize and improve angioedema management globally. ACAREs will expand access to modern angioedema medicines in countries where they are available and help to bring them to countries where they are not.\textsuperscript{1}

This document summarizes the aims of GA\textsuperscript{2}LEN/HAEi Angioedema Centers of Reference and Excellence (ACAREs) and elaborates the requirements that ACAREs must fulfill to become certified.

### TABLE 1

<table>
<thead>
<tr>
<th>Classification of angioedema</th>
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<tr>
<td><strong>Bradykinin-mediated angioedema</strong></td>
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<tr>
<td>C1-INH deficiency/defect</td>
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<tr>
<td>Inherited</td>
</tr>
<tr>
<td>HAE-1 AAE-C1-INH</td>
</tr>
<tr>
<td>HAE-2 HAE nC1-INH</td>
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</tbody>
</table>

**Abbreviations:** AAE-C1-INH, acquired angioedema due to C1-inhibitor deficiency; ACEI-AE, angiotensin-converting enzyme inhibitor-induced angioedema; BK, bradykinin; HAE nC1-INH, hereditary angioedema with normal C1-inhibitor levels, either due to a mutation in factor XII (F12), angiopoietin-1 (ANGPT1), plasminogen (PLG), kinogen-1 (KNG1), or unknown (UNK) (HAE-FXII, HAE-ANGPT1, HAE-PLG, HAE-KNG1, HAE-UNK); HAE-1, hereditary angioedema due to C1-inhibitor deficiency; HAE-2, hereditary angioedema due to C1-inhibitor dysfunction.
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Certified. It also provides (see Appendix S1) background information on GA2LEN and HAEi, including HAEi member organizations and regional patient advocates, on why we need an Angioedema Center of Reference and Excellence (ACARE) program and network, and on the accreditation and certification process, governance and funding, and on the interaction with other GA2LEN networks of centers of reference and excellence. The protocols, aims, requirements, and provisions related to becoming a certified ACARE are based on (a) the experience of the GA2LEN UCARE network and (b) input from angioedema patients, general practitioners, and angioedema specialists.

What are the aims of GA2LEN/HAEi ACAREs? The aims of ACAREs are to set the global standard for excellence in comprehensive angioedema care through research, education, advocacy, and interaction among ACAREs. By serving as referral centers for the diagnosis and management of patients with angioedema, ACAREs will complement the local healthcare system. ACAREs aim to increase knowledge and awareness of angioedema.

What are the requirements for GA2LEN/HAEi ACAREs? ACAREs are required to demonstrate excellence in the management of angioedema, research activities, efforts in education, and advocacy activity. ACAREs need to fulfill 32 requirements, which are explained in the audit checklist (Figure 1A). This checklist includes specific deliverables for each requirement. For example, the requirement to know and follow international guidelines and consensus documents for angioedema (Requirement #16) entails that physicians and other ACARE healthcare professionals have read and understood the current versions of these guidelines and consensus documents and that their recommendations are implemented in their center.

These guidelines and consensus documents include, for example, the international WAO/EAACI guideline for HAE, the EAACI/GA2LEN/EDF/WAO guideline for urticaria, the International/Canadian hereditary angioedema guideline,2-5 the international consensus on the diagnosis and management of pediatric patients with hereditary angioedema with C1 inhibitor deficiency,6 the international consensus on the use of genetics in the management of HAE,6 and the international consensus and practical guidelines on the gynecologic and obstetric management of female patients with hereditary angioedema caused by C1 inhibitor deficiency.7 The deliverables for this requirement are that (a) current guideline and consensus document versions are present (paper or electronic version), (b) ACARE staff can answer questions on the recommendations these documents provide, and (c) ACARE physicians can show, upon request, by use of a patient file, that patient

**Figure 1** A and B. Audit checklist for GA2LEN/HAEi Angioedema Center of Reference and Excellence (ACARE) certification (A) and certificate awarded to GA2LEN/HAEi ACAREs upon a successful audit (B). A. The list shows and explains the requirements for becoming a GA2LEN/HAEi ACARE and the deliverables that are reviewed during the audit process. B. The certificate is awarded for 2 y and requires successful re-audit to be extended.
management decisions are based on guideline recommendations (Figure 1B).

This publication marks our intent to start the implementation of the GA²LEN/HAEi ACARE initiative. Specialty centers for angioedema have started to apply to become ACAREs, and audits and certifications are ongoing (Figure 1B). We expect that most GA²LEN UCARE centers and many angioedema specialty centers will become ACAREs in the near future. We predict and hope that by 2022, GA²LEN/HAEi ACAREs will be established in every continent. This will result in a strong global network of angioedema specialists, promote angioedema research, and harmonize and improve angioedema management worldwide. GA²LEN and HAEi will measure the impact of ACAREs over time and document and report the benefits of this initiative. ACARE network activities and a current list of ACAREs are posted on the network’s website (www.acare-network.com).

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CONFLICT OF INTEREST
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Dr Caballero reports personal fees and other from BioCryst, personal fees, non-financial support and other from CSL-Behring, personal fees from Merck, personal fees and other from Novartis, personal fees from Octapharma, personal fees, non-financial support and other from Shire HGT, personal fees and other from Pharming NV, outside the submitted work. Dr Campos reports Personal fees for consulting and lectures from Takeda. Dr Cancian served for Scientific Advisory Boards, and received travel grants, for/from CSL Behring and Shire-Takeda. His Institution (Department of Medicine, University of Padua, Italy) received grants from CSL Behring and Shire-Takeda. Dr Cohn reports personal fees from Takeda, personal fees from Pharming, personal fees from CSL, personal fees from BioCryst, outside the submitted work. Dr Craig reports grants, personal fees and other from CSL Behring, grants and personal fees from Dyax, grants, personal fees and other from Takeda, grants and personal fees from BioCryst, grants and personal fees from Pharming, personal fees from Grifols, grants and non-financial support from GSK, grants and non-financial support from Regeneron, grants and non-financial support from Novartis/Genentech, outside the submitted work; and On the Medical Advisory Board for HAE-A of America, AAAAI Board, ALA Mid Atlantic Board. Dr Dissemond reports grants and personal fees from Novartis, outside the submitted work. Dr Du-Thanh reports personal fees from SHIRE/T. Dr Ensina reports personal fees from NOVARTIS, personal fees and non-financial support from TAKEDA, personal fees from SANOFI, outside the submitted work. Dr Farkas reports grants and personal fees from CSL Behring, grants and personal fees from Shire/Takeda, grants and personal fees from Pharming, personal fees from BioCryst, personal fees from Kalvista, outside the submitted work. Dr Gimenez-Arnau reports grants and personal fees from URIACH, grants and personal fees from NOVARTIS, personal fees from DSANOIF, grants from CARLOS III FEDER, personal fees from FAES, personal fees from GSK, personal fees from ALMIRALL, personal fees from ASTRA ZENECA, outside the submitted work. Dr Fukunaga reports personal fees from A Takeda company (Shire), personal fees from CSL Behring, outside the submitted work. Dr Gompels reports other from Speaker at Novartis Urticaria conference 2019, outside the submitted work; and A member of the Immunology Clinical reference group. Dr Gower reports grants,
personal fees, research grants and other from Takeda/Shire/Dyax, research grants and other from BioCryst Pharmaceuticals, other from CSL Behring, other from Pharming, other from Fresenius kabi, outside the submitted work. Dr Grumach reports grants, personal fees and other from Shire/Takeda, personal fees and other from CSL Behring, outside the submitted work. Dr Hide reports grants and personal fees from Shire/Takeda, Mitsubishi-Tanabe, Taiho-yakuhin, personal fees from CSL-Behring, BioCryst, Novartis, Teikoku-Seiyaku,Eizai, Kaken, Kyowahakkou-Kirin, grants from Glaxo-Smith-Klein, outside the submitted work. Dr Jakob reports grants, personal fees and non-financial support from Novartis, personal fees and non-financial support from Thermo Fisher Scientific, grants and personal fees from ALK-Abello, personal fees from Celgene, personal fees and non-financial support from Bencard/Allergy Therapeutics, personal fees from Allergopharma, outside the submitted work. Dr Kaplan reports other from Genentech, other from Novartis, other from Sanofi Aventis, other from BioCryst, outside the submitted work. Dr Katelaris reports grants and personal fees from CSL Behring, grants and personal fees from Takeda, grants from BioCryst, during the conduct of the study. Dr Kleinheinz reports personal fees from Novartis, during the conduct of the study; personal fees from Abbvie, personal fees from Leo GmbH, personal fees from Janssen, personal fees from Medac, personal fees from Galderma, personal fees from Celgene, personal fees from Bencard, outside the submitted work. Dr Kocatürk reports personal fees from Novartis, personal fees from Sanofi, outside the submitted work. Dr Longhurst reports grants and personal fees from BioCryst, grants, personal fees and non-financial support from CSL Behring, grants from Ionis, grants from Kalvista, personal fees from Pharming, grants, personal fees and non-financial support from Takeda, personal fees from GSK, personal fees from Octapharma, outside the submitted work. Dr MacGinnitie reports personal fees from BioCryst, personal fees from Shire, outside the submitted work. Dr Magerl reports personal fees from CSL Behring, personal fees from Shire/part of Takeda, personal fees from Novartis, personal fees from BioCryst, personal fees from Kalvista, personal fees from Pharming, outside the submitted work. Dr Makris reports personal fees from Novartis, outside the submitted work. Dr Marsland reports grants and personal fees from Novartis, personal fees and non-financial support from Sanofi, personal fees from Galderma, personal fees from Roche, non-financial support from Almirall, outside the submitted work. I. Martínez Saguer has received honoraria, research funding, and travel grants from BioCryst, CSL Behring, Pharming, and Takeda/Shire, KalVista and/or served as a consultant and/or participated in advisory boards for these companies. Dr Metz reports personal fees from Moxie, personal fees from Novartis, personal fees from Roche, personal fees from Sanofi, personal fees from Shire, outside the submitted work. Dr Papadopoulos reports personal fees from Novartis, personal fees from Nutricia, personal fees from HAL, personal fees from MENARINI/FAES FARMA, personal fees from SANOFI, personal fees from MYLAN/ MEDA, personal fees from BIOMAY, personal fees from AstraZeneca, personal fees from GSK, personal fees from MSD, personal fees from ASIT BIOTECH, personal fees from Boehringer Ingelheim, grants from Gerolymatos International SA, grants from Capricare, outside the submitted work. Dr Reich reports personal fees from Abbvie, personal fees from Bioderma, personal fees from Chema Elektromet, personal fees from Galderma, personal fees from Bausch Health, personal fees from Janssen, personal fees from Leo Pharma, personal fees from Medac, grants and personal fees from Menlo Therapeutics, personal fees from Novartis, personal fees from Pierre-Fabre, personal fees from Trevi, personal fees from Kymab Limited, personal fees from MSD, personal fees from Metriopharm, personal fees from Drug Delivery Solutions, personal fees from Eli Lilly, outside the submitted work. Dr Riedl reports grants and personal fees from CSL Behring, grants and personal fees from Shire/Takeda, grants and personal fees from BioCryst, grants and personal fees from Pharming, personal fees from Pharvaris, personal fees from Adverum, personal fees from Sanofi, personal fees from Sanofi Genzyme, personal fees from Abbvie, outside the submitted work. Dr Smith reports personal fees from Takeda/Shire, personal fees from CSL/Behring, grants from Takeda/Shire, grants from BioCryst, outside the submitted work. Dr Soria reports personal fees from Novartis, personal fees from Novartis Pharmaceutical, personal fees from Abbvie, outside the submitted work. Dr Sussman reports grants and personal fees from Research grants from pharmaceutical companies. Novartis, Genentech, Amgen, Sanofi, CSL behring, Leo, Kedrion, Green Cross, DBV, Aimmune. D’dConsulting and honoraria from Novartis, Novo, CSL Behring, Amgen., during the conduct of the study; grants from Novartis Pharmaceutical, grants from Genentech, grants from CSL behring, grants from Amgen, grants from Leo, grants from DBV, grants from Aimmune, grants from Sanofi, non-financial support from Novartis, non-financial support from Novo, non-financial support from Novo, non-financial support from Novo, non-financial support from Novo, non-financial support from Takeda/Shire, non-financial support from Sanofi, grants from Kedrion, outside the submitted work. Dr Thomsen reports grants and personal fees from Novartis, grants and personal fees from Sanofi, grants and personal fees from UCB, grants and personal fees from Janssen, grants and personal fees from Abbvie, outside the submitted work. Dr Treudler reports personal fees from Shire-Takeda, personal fees from ALK-Abello, personal fees from Novartis, grants and personal fees from Sanofi-Genzyme, grants from Hautnetz Leipzig e.V., other from Fraunhofer Institut, outside the submitted work.
work. Dr van Doorn reports personal fees from Leopharma, grants and personal fees from Novartis, personal fees from Abbvie, personal fees from BMS, personal fees from Celgene, personal fees from Lilly, personal fees from MSD, personal fees from Pfizer, personal fees from Sanofi-Genzyme, personal fees from Janssen Cilag, outside the submitted work. Dr Weber-Chrysochoou reports personal fees from AstraZeneca, personal fees from AbbVie, personal fees from ALK, personal fees from Almirall, personal fees from Astellas, personal fees from Bayer Health Care, personal fees from Bencard, personal fees from Berlin Chemie, personal fees from FAES, personal fees from HAL, personal fees from Leti, personal fees from Meda, personal fees from Menarini, personal fees from Merck, personal fees from MSD, grants and personal fees from Novartis, personal fees from Pfizer, personal fees from Sanofi, personal fees from Stallergenes, personal fees from Takeda, personal fees from Teva, personal fees from UCB, grants from Henkel, personal fees from Kryolan, personal fees from L’Oréal, outside the submitted work; and Organizational affiliations: Committee member: WHO-Initiative “Allergic Rhinitis and Its Impact on Asthma” (ARIA) Dember of the Board: German Society for Allergy and Clinical Immunology (DGAKI) Dead: European Centre for Allergy Research Foundation (ECARF) Secretary General: Global Allergy and Asthma European Network (GA2LEN) Dember: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO). Other authors declare that they have no conflicts of interest.

Marcus Maurer1
Werner Aberer2
Rosana Agondi3
Mona Al-Ahmad4
Maryam Ali Al-Nesf4
Ignacio Anotegui6
Rand Arnaout7
Luisa Karla Arruda8
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1Department of Dermatology and Allergy, Dermatological Allergology, Allergie-Centrum-Charité, Charité—Universitätsmedizin Berlin, Berlin, Germany
2Department of Dermatology, Medical University of Graz, Graz, Austria
3University of São Paulo, São Paulo, Brazil
4Microbiology Department, Faculty of Medicine, Kuwait University, Safat, Kuwait
5Allergy and Immunology Section, Department of Medicine, Hamad General Hospital, Doha, Qatar
6Department of Allergy and Immunology, Hospital Quiron Bizaia, Bizaia, Spain
7King Faisal Specialist Hospital & Research Center, Al Faisal University, Riyadh, Saudi Arabia
8Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil
9Ambulatorio di Allergologia, Clinica San Carlo, Paderno Dugnano (MI), Italy
10Center for Children and Adolescents, University Hospital Frankfurt, Frankfurt, Germany
11Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, USA
12Department of Dermatology, University Allergy Center, University Hospital Carl Gustav Carus, Technical University, Dresden, Germany
13Division of Allergy, Immunology and Dermatology, Department of Pediatrics, McGill University Health Center, Montreal, QC, Canada
14Instituto de Asma, Alergia y Enfermedades Respiratorias, Corrientes, Argentina
15Allergy Section, Division of Immunology, Department of Internal Medicine, Partner Bernstein Allergy Group, Partner Bernstein Clinical Research Center, University of Cincinnati, Cincinnati, OH, USA
16Division of Clinical Immunology and Allergy, St. Michael’s Hospital, University of Toronto, Toronto, ON, Canada
17Department of Dermatology and Allergy Center, Odense University Hospital, Odense, Denmark
18Division of Allergy, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia
19Clinical Immunology/Internal Medicine Department, National Reference Center for Angioedema, Grenoble University Hospital, Grenoble, France
20Department of Dermatology, Johannes Gutenberg University Mainz, Mainz, Germany
21HAE International (HAEi), Horsens, Denmark
22Skåne University Hospital, Lund University, Lund, Sweden
23Division of Clinical Immunology, Icahn School at Mount Sinai,
LETTERS TO THE EDITOR

New York, NY, USA

24 HAE Centre, Odense University Hospital, Odense, Denmark
25 Allergy Department, Hospital Universitario La Paz, IdiPaz, CIBERER U754, Madrid, Spain
26 Universidade Federal da Bahia, Salvador, Brazil
27 Serviço de Imunologia, Hospital das Clínicas Professor Edgard Santos, Salvador, Brazil
28 Department of Systems Medicine, University Hospital of Padua, Padua, Italy
29 School of Medicine, Universidad de Especialidades Espíritu Santo, Samborondón, Ecuador
30 RespiraLab, Research, Guayaquil, Ecuador
31 Department of Vascular Medicine, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
32 Immunology Department, Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte (CHLN), EPE, Lisbon, Portugal
33 Department of Medicine and Pediatrics, Penn State University, Hershey, PA, USA
34 Faculdade de Medicina do ABC, Santo André, Brazil
35 Alergoskin Alergia e Dermatologia SS Ltda, Santo André, Brazil
36 UCARE Center, São Paulo, Brazil
37 Faculdade de Medicina do ABC (FMABC), Santo André, Brazil
38 3rd Department of Internal Medicine, Hungarian Angioedema Reference Center, Semmelweis University, Budapest, Hungary
39 Department of Dermatology, Venereology and Allergology, University of Essen, Essen, Germany
40 Service de Dermatologie-allergologie, CHU Montpellier, Montpellier Cedex 5, France
41 Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil
42 Department of Dermatology, Kayseri City Education and Research Hospital, Kayseri, Turkey
43 Private Practice, Lomas de Zamora, Argentina
44 Servicio de Alergia e Inmunología—Hospital Alende y Clínica Colón, Mar del Plata, Argentina
45 Ambulatorio di Dermatologia Allergologica e Professionale, Fondazione IRCCS Co’ Granda Ospedale Maggiore Policlinico, Milano (MI), Italy
46 The Dermatology Department of the Hospital de Bellvitge, Universitat de Barcelona, Barcelona, Spain
47 Unidad Alergia e Inmunología Clínica, Hospital Público Materno Infantil, Salta, Argentina
48 Center of Allergy and Immunology, City Clinical Hospital No. 52, Moscow Ministry of Healthcare, Moscow, Russian Federation
49 Department of Allergology and Clinical Immunology, I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation
50 Division of Dermatology, Graduate School of Medicine, Kobe University, Kobe, Japan
51 Division of Immunology and Allergic Diseases, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey
52 Department of Dermatology, Hospital del Mar, IMIM, Universitat Autònoma, Barcelona, Spain
53 Department of Dermatology, D Y. Patil University School of Medicine, Mumbai, India
54 Department of Immunology, North Bristol NHS Trust, Southmead Hospital, Bristol, UK
55 Clinica de Dermatologia, Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal
56 Center of Allergy and Immunology, Tbilisi, Georgia
57 Marycliff Clinical Research, Spokane, WA, USA
58 Clinical Immunology, Medical School, University Center Health ABC, Santo Andre, Brazil
59 National School of Medicine, Instituto Politécnico Nacional, Mexico City, Mexico
60 Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan
61 NRC Institute of Immunology FMBA, Moscow, Russia
62 Department of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, Yokohama, Japan
63 Department of Dermatology and Allergy, University Medical Center Giessen (UKGM), Justus-Liebig-University Giessen, Giessen, Germany
64 Instituto de Medicina Respiratoria—Rafaela, Santa Fe, Argentina
65 Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, Korea
66 Medical University of South Carolina, Charleston, SC, USA
67 European Center for Diagnosis and Treatment of Urticaria, Zabrze, Poland
68 Immunology & Allergy Unit, Department of Medicine, Campbelltown Hospital, Campbelltown, NSW, Australia
69 Division of Allergy & Clinical Immunology, Rappaport Faculty of Medicine, Bnai Zion Medical Center, Technion, Haifa, Israel
70 Clinic for Dermatology, Elbe Kliniken Buxtehude, Buxtehude, Germany
71 Department of Dermatology, School of Medicine, Koç University, Koc, Turkey
72 Department of Dermatology, Venerology and Pediatric Dermatology, Medical University of Lublin, Lublin, Poland
73 Department of Dermatology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand
74 Department of Dermatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
75 Clinica San Felipe, Lima, Peru
76 Department of Immunology, Addenbrookes Hospital Cambridge University NHS Foundation Trust, Cambridge, UK
77 UCLH, London, UK
78 Addenbrooke’s Hospital Cambridge and University College Hospital, London, UK
79 Allergy/Immunology Division, Department of Internal Medicine, University of Texas Southwestern Medical School,
Correspondence
Marcus Maurer, Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité—Universitätsmedizin Berlin, Berlin, Germany.
Email: marcus.maurer@charite.de

ORCID
Marcus Maurer https://orcid.org/0000-0002-4121-481X
Mona Al-Ahmad https://orcid.org/0000-0003-3720-7032
Maryam Ali Al-Nesf https://orcid.org/0000-0001-9354-0214
Luisa Karla Arruda https://orcid.org/0000-0002-7505-210X
Riccardo Asero https://orcid.org/0000-0002-3524-9952
Ana Giménez-Arnau https://orcid.org/0000-0001-9548-5423
Maia Gotua https://orcid.org/0000-0003-0327-3963
Atsushi Fukunaga https://orcid.org/0000-0003-2026-8154
Asli Gelincik https://orcid.org/0000-0003-2497-4128
Andrew MacGinnitie https://orcid.org/0000-0002-9451-3733
Martin Metz https://orcid.org/0000-0002-4070-9976
Iman Nasr https://orcid.org/0000-0003-0346-9675
Nikolaos G. Papadopoulos https://orcid.org/0000-0002-4448-3468

REFERENCES


SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.