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# Reply to “Exploring the long-term effects of biologic initiation in severe asthma: Insights from the International Severe Asthma Registry”

Wenjia Chen, PhD [a](#) Trung N. Tran, MD, PhD [b](#) Mohsen Sadatsafavi, MD, PhD [c](#) Ruth B. Murray, PhD [d](#) Nigel Chong Boon Wong, BSocSci (Hons) [a](#) Nasloon Ali, PhD [d](#), [e](#) Con Ariti, MSc [d](#), [e](#) Lakmini Bulathsinhala, MPH [d](#), [e](#) Esther Garcia Gil, MD [f](#) J. Mark FitzGerald, MD, FRCPC [g](#) Marianna Alacqua, MD, PhD [h](#) Mona Al-Ahmad, MBBCh, FRCPC [i](#), [j](#) Alan Altraja, MD, PhD [k](#) Riyadh Al-Lehebi, MD, FRCPC [l](#), [m](#) Mohit Bhutani, MD, FRCPC, FCCP [n](#) Leif Bjermer, MD, PhD [o](#) Anne-Sofie Bjerrum, MD, PhD [p](#) Arnaud Bourdin, MD, PhD [q](#) Anna von Bülow, MD, PhD [r](#) John Busby, PhD [s](#) Giorgio Walter Canonica, MD [t](#), [u](#) Victoria Carter, BSc [d](#), [e](#) George C. Christoff, MD, PhD, MPH [v](#) Borja G. Cosio, MD, PhD [w](#) Richard W. Costello, MB, MD, FRCPI [x](#) Jo~ao A. Fonseca, MD, PhD [y](#) Peter G. Gibson, MBBS, FRACP [z](#), [aa](#) Kwang Ha Yoo, MD, PhD [bb](#) Liam G. Heaney, MD [cc](#) Enrico Heffler, MD, PhD [t](#), [u](#) Mark Hew, MBBS, PhD, FRACP [dd](#), [ee](#) Ole Hilberg, MD, DMSc [ff](#) Flavia Hoyte, MD [gg](#) Takashi Iwanaga, MD, PhD [hh](#) David J. Jackson, FRCP, PhD [ii](#) Rupert C. Jones, MD [jj](#) Mariko Siyue Koh, MBBS, MRCP (UK), FCCP [kk](#) Piotr Kuna, MD, PhD [ll](#) Désirée Larenas-Linnemann, MD, FAAAAI, Dist.Intl.FACAAI [mm](#) Sverre Lehmann, MD, PhD [nn](#), [oo](#) Lauri Lehtimäki, MD, PhD [pp](#), [qq](#) Juntao Lyu, PhD [rr](#) Bassam Mahboub, MD [ss](#), [tt](#) Jorge Maspero, PhD [uu](#), [vv](#) Andrew N. Menzies-Gow, PhD, FRCP [ww](#), [xx](#) Anthony Newell, PhD [e](#), [yy](#) Concetta Sirena, PhD [zz](#) Nikolaos G. Papadopoulos, MD, PhD, FRCP [aaa](#), [bbb](#) Andriana I. Papaioannou, MD, PhD [ccc](#) Luis Perez-de-Llano, MD, PhD [ddd](#) Diahn-Warng Perng (Steve), MD, PhD [eee](#), [fff](#) Matthew J. Peters, MD, PhD [ggg](#), [hhh](#) Paul E. Pfeffer, MRCP (UK), PhD [iii](#), [jjj](#) Celeste M. Porsbjerg, MD, PhD [kkk](#) Todor A. Popov, MD, PhD [lll](#) Chin Kook Rhee, MD, PhD [mmm](#) Sundeep Salvi, MD, PhD [nnn](#) Camille Taillé, MD, PhD [ooo](#) Christian Taube, MD [ppp](#) Carlos A. Torres-Duque, MD [qqq](#), [rr](#) Charlotte Ulrik, MD, DMSc, FERS [sss](#) Seung Won Ra, MD, PhD [ttt](#) Eileen Wang, MD, MPH [gg](#), [uuu](#) Michael E. Wechsler, MD [vvv](#) David B. Price, FRCGP [d](#), [e](#), [www](#)

[a](#) Saw Swee Hock School of Public Health, National University of Singapore, Singapore

[b](#) AstraZeneca, Gaithersburg, Md

[c](#) Respiratory Evaluation Sciences Program, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

[d](#) Optimum Patient Care Global, Cambridge, United Kingdom

[e](#) Observational and Pragmatic Research Institute, Singapore

[f](#) AstraZeneca, Barcelona, Spain

[g](#) Department of Medicine, the University of British Columbia, Vancouver, BC, Canada

[h](#) CSL Behring S.p.A, Milan, Italy

[I](#) Microbiology Department, College of Medicine, Kuwait University, Kuwait City, Kuwait

j Al-Rashed Allergy Center, Ministry of Health, Kuwait City, Kuwait

k Department of Pulmonology, University of Tartu and Lung Clinic, Tartu University Hospital, Tartu, Estonia

l Department of Pulmonology, King Fahad Medical City, Riyadh, Saudi Arabia

m Alfaisal University, Riyadh, Saudi Arabia

n Division of Pulmonary Medicine, Department of Medicine, University of Alberta, Edmonton, AB, Canada

o Respiratory Medicine and Allergology, Department of Clinical Sciences, Skåne University Hospital, Lund University, Lund, Sweden

p Department of Respiratory Medicine and Allergy, Aarhus University Hospital, Aarhus, Denmark

q PhyMedExp, Univ Montpellier, CNRS, INSERM, CHU Montpellier, Montpellier, France

r Respiratory Research Unit, Bispebjerg University Hospital, Copenhagen, Denmark

s Centre for Public Health, Queen's University Belfast, Belfast, United Kingdom

t Personalized Medicine, Asthma and Allergy, Humanitas Clinical and Research Center IRCCS, Rozzano, Milan, Italy

u Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy

v Medical University-Sofia, Faculty of Public Health, Sofia, Bulgaria

w Son Espases University Hospital-IdISBa-Ciberes, Mallorca, Spain

x Clinical Research Centre, Department of Respiratory Medicine, Smurfit Building Beaumont Hospital, RCSI, Dublin, Ireland

y Department of Community Medicine, Information and Health Decisions (MEDCIDS), Health Information and Decision Sciences Department (MEDCIDS) & Center for Health Technology and Services Research (CINTESIS), Faculty of Medicine of University of Porto, Porto, Portugal

z Australian Severe Asthma Network, Priority Research Centre for Healthy Lungs, University of Newcastle, Newcastle, NSW, Australia

aa Department of Respiratory and Sleep Medicine, Hunter Medical Research Institute, John Hunter Hospital, New Lambton Heights, NSW, Australia

bb Division of Pulmonary, Allergy and Critical Care Medicine, Department of Internal Medicine, Konkuk University School of Medicine, Seoul, South Korea

cc Wellcome-Wolfson Centre for Experimental Medicine, Queen's University Belfast, Belfast, United Kingdom

dd Allergy, Asthma & Clinical Immunology Service, Alfred Health, Melbourne, VIC, Australia

ee Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

ff Medical Department, Vejle University Hospital, Vejle, Denmark

gg Division of Allergy & Clinical Immunology, Department of Medicine, National Jewish Health, Denver, Colo

hh Kindai University Hospital, Osakasayama, Japan

ii Guy's Severe Asthma Centre, Guy's Hospital, King's College London, UK

jj Research and Knowledge Exchange, Plymouth Marjon University, Plymouth, United Kingdom

kk Respiratory & Critical Care Medicine, Singapore General Hospital, Singapore

ll Division of Internal Medicine, Asthma and Allergy, Medical University of Lodz, Lodz, Poland

mm Centro de Excelencia en Asma y Alergia, Hospital Médica Sur, Ciudad de México, Mexico

nn Section of Thoracic Medicine, Department of Clinical Science, University of Bergen, Bergen, Norway

oo Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

pp Allergy Centre, Tampere University Hospital, Tampere, Finland

qq Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

rr Griffith University, Centre for Applied Health Economics, Nathan, Australia

ss Rashid Hospital, Dubai Health Authority, Dubai, United Arab Emirates

tt Dubai Academic and Health Corporation, Dubai, United Arab Emirates

uu Clinical Research for Allergy and Respiratory Medicine, CIDEA Foundation, Buenos Aires, Argentina

Vv University Career of Specialists in Allergy and Clinical Immunology, Buenos Aires University School of Medicine, Buenos Aires, Argentina

ww AstraZeneca, Cambridge, United Kingdom

xx Lung Division, Royal Brompton & Harefield Hospitals, London, United Kingdom

yy Optimum Patient Care, Brisbane, QLD, Australia

zz Severe Asthma Network in Italy (SANI), Milano, Italy

aaa Division of Infection, Immunity & Respiratory Medicine, University of Manchester, Manchester, United Kingdom

bbb Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

ccc 2nd Respiratory Medicine Department, National and Kapodistrian University of Athens Medical School, Attikon University Hospital, Athens, Greece

ddd Pneumology Service, Lucus Augusti University Hospital, EOXI Lugo, Monforte, Cervo, Lugo, Spain

eee School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

fff Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

ggg Department of Thoracic Medicine, Concord Hospital, Sydney, NSW, Australia

hhh Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia

iii Department of Respiratory Medicine, Barts Health NHS Trust, London, United Kingdom

jjj Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

kkk Department of Respiratory Medicine and Infectious Diseases, Research Unit, Bispebjerg Hospital, Copenhagen, Denmark

lll University Hospital “Sv. Ivan Rilski,” Sofia, Bulgaria

mmm Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul St. Mary’s Hospital, College of Medicine, the Catholic University of Korea, Seoul, South Korea

nnn Pulmocare Research and Education Foundation, Pune, India

ooo Department of Respiratory Diseases, Bichat Hospital, AP-HP Nord-Universit\_e de Paris, Paris, France

ppp Department of Pulmonary Medicine, University Medical Center Essen-Ruhrlandklinik, Essen, Germany

qqq CINEUMO, Respiratory Research Center, Fundaci\_ on Neumol\_ogica Colombiana, Bogota, Colombia

rrr Universidad de La Sabana, Chia, Colombia

sss Department of Respiratory Medicine, Copenhagen University Hospital-Hvidovre, Hvidovre, Denmark

ttt Department of Internal Medicine, Division of Pulmonology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, South Korea

uuu Division of Allergy & Clinical Immunology, Department of Medicine, University of Colorado School of Medicine, Aurora, Colo

vvv NJH Cohen Family Asthma Institute, Department of Medicine, National Jewish Health, Denver, Colo

www Centre of Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Aberdeen, United Kingdom.

**Corresponding author:**

David B. Price, FRCGP, Observational and Pragmatic Research Institute, 22 Sin Ming Lane, #06 Midview City, Singapore 573969.

**E-mail:**

[dprice@opri.sg](mailto:dprice@opri.sg).

## To the Editor:

We agree with many points made by Cheng et al<sup>1</sup> and offer our clarifications. We agree that severe asthma is heterogeneous, and unraveling asthma phenotypes and endotypes can pave the way for precision medicine in asthma management, which is within the scope of the International Severe Asthma Registry (ISAR). The referenced GLITTER study was focused on a more severe subgroup of patients who had guideline-defined severe asthma and high exposure to oral corticosteroids (OCS).<sup>2</sup> The study has investigated the phenotypes of OCS-dependent and frequent OCS users with severe asthma, in particular treatment effect variations with regard to biologic-associated reductions in exacerbations across various demographic, clinical, and phenotypic parameters. Figure 4, as depicted in the reference paper, showed a consistent reduction in exacerbations after biologic initiation; the reductions were observed across categories such as age, sex, smoking status, body mass index, and, notably, eosinophilic phenotypes, characterized by type 2 inflammation, allergic predisposition, the presence of nasal polyps, and responsiveness to various asthma treatments. These findings demonstrated treatment efficacy across asthma phenotypes. However, the extent of reduction indeed slightly varied. A pertinent study of Chen et al<sup>3</sup> demonstrated that a combination of core prognostic factors has the capacity to predict multi-domain treatment responses to mepolizumab, in particular, to identify a small subset of patients with severe asthma who will not benefit as much from the treatment. As we move forward, ongoing studies with ISAR are delving deeper into the subject matter. The Effectiveness of biologics in patients with different combinations of T2 biomarkers (IGNITE) study, for instance, seeks to assess the impact of several T2 biomarkers on the treatment effects of various types of biologic therapy in severe asthma. These studies may continue to offer valuable insights into the nuances of precision medicine strategies for asthma management.

Regarding the consistency and representativeness of study findings, it is important to emphasize that ISAR stands as the largest and most comprehensive database dedicated to this complex medical condition. The commitment to quality assurance and continuous improvement has laid the foundation for the establishment and ongoing success of ISAR. The utilization of the Delphi process,<sup>4</sup> a widely recognized approach to reach consensus among experts, enabled ISAR to harness the collective expertise of professionals worldwide, which ensures that data collection, categorization, and analysis adhere to the rigorous standards in clinical guidelines. All participating sites, individually or as part of a local or national registry, gather data for submission to ISAR that is of the highest quality achievable. The clinical care provided at centers is also of high quality as reflected in improved outcomes seen in the non-initiating subjects of the GLITTER study.<sup>2</sup> The database's extensive reach has facilitated pioneering research in severe asthma management and precision medicine and has yielded numerous scientific breakthroughs.

Therefore, it is important to clarify that the multi-centered settings in the referenced study are, in fact, an advantage rather than limitation. Earlier evidence on the real-world effectiveness of biologics in patients with asthma mainly came from single settings such as the United Kingdom, the United States, and Japan.<sup>5-7</sup> In contrast, ISAR's multi-centered approach offers a more diverse and comprehensive perspective, which improves the generalizability of findings.

Lastly, although we agree that the use of biologic therapies may not be universally cost-effective in patients with moderate-to-severe asthma, it is important to clarify that ISAR was not designed to address questions related to the cost-effectiveness of medications due to the nature of registry data. Moreover, the referenced GLITTER study was tailored to a more severe subset of patients with severe asthma,<sup>2</sup> which did not cover the entire target population for cost effectiveness analyses of biologics. Rather, the core clinical implication of the GLITTER study is that we confirmed that the identified treatment benefits of biologics in the restricted, artificial environment of randomized controlled trials can be replicated in real-world clinical practice, which provides an evidence base for payers and funders of more costly health care interventions to make informed decisions.

This study was conducted by the Observational and Pragmatic Research Institute (OPRI) Pte Ltd and was partially funded by Optimum Patient Care Global and AstraZeneca Ltd. No funding was received by the OPRI for its contribution.

### **Conflicts of interest:**

T. N. Tran is an employee of AstraZeneca and may own stock or stock options in AstraZeneca. M. Sadatsafavi has received honoraria from AstraZeneca, Boehringer Ingelheim, Teva, and GlaxoSmithKline for purposes unrelated to the content of this manuscript and has received research funding from AstraZeneca and Boehringer Ingelheim directly into his research account from AstraZeneca for unrelated projects. R. B. Murray is a consultant for Observational and Pragmatic Research Institute (OPRI), which conducted this study in collaboration with Optimum Patient Care and AstraZeneca. N. Ali was an employee of OPRI at the time this research was conducted. OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca. C. Ariti was an employee of the OPRI. OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca. L. Bulathsinhala is an employee of the OPRI. OPRI conducted this study in collaboration with Optimum Patient Care and AstraZeneca. E. G. Gil was an employee of AstraZeneca at the time this research was conducted. AstraZeneca is a co-funder of the International Sociological Association Registry. J. M. FitzGerald previously declared grants from AstraZeneca, GlaxoSmithKline, Sanofi Regeneron, and Novartis paid directly to UBC, and has received personal fees for lectures and attending advisory boards from AstraZeneca, GlaxoSmithKline, Sanofi Regeneron, and Teva. M. Alacqua was an employee of AstraZeneca at the time of manuscript development and is currently employed at CSL Behring SpA. M. Al-Ahmad has received advisory board and speaker fees from AstraZeneca, Sanofi, Novartis, and GlaxoSmithKline, and received a grant from Kuwait Foundation for the Advancement of Sciences (KFAS). A. Altraja has received lecture fees from AstraZeneca, Berlin-Chemie, Menarini, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, Orion, Sanofi, and Zentiva; sponsorships from AstraZeneca, Berlin-Chemie Menarini, Boehringer Ingelheim, GlaxoSmithKline, MSD, Norameda, Novartis, and Sanofi; and has participated in advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, MSD, Novartis, Sanofi, and Teva. R. Al-Lehebi has given lectures at meetings supported by AstraZeneca, Boehringer Ingelheim, Novartis, GlaxoSmithKline, and Sanofi, and received advisory board fees from GlaxoSmithKline, AstraZeneca, Novartis, and Abbott. M. Bhutani has received speaker and consultant fees from AstraZeneca, GlaxoSmithKline, Sanofi, Covis, Boehringer Ingelheim, and Valeo. L. Bjermer has (in the last 3 years) received lecture or advisory board fees from Alk-Abello, Astra-Zeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis, Sanofi, Genzyme/Regeneron, and Teva. A. Bjerrum has received



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