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### ► To cite this version:

Wenjia Chen, Trung Tran, Mohsen Sadatsafavi, Ruth Murray, Nigel Chong Boon Wong, et al.. Reply to “Exploring the long-term effects of biologic initiation in severe asthma: Insights from the International Severe Asthma Registry”. *Journal of Allergy and Clinical Immunology: In Practice*, 2024, 12 (2), pp.536-539. 10.1016/j.jaip.2023.12.008 . hal-04450320

**HAL Id: hal-04450320**

**<https://hal.science/hal-04450320>**

Submitted on 10 Feb 2024

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

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## **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



lecture fees from AstraZeneca, GlaxoSmithKline, and Novartis. A. Bourdin has received industry sponsored grants from AstraZeneca/MedImmune, Boehringer-Ingelheim, Cephalon/ Teva, GlaxoSmithKline, Novartis, and Sanofi-Regeneron, and consultancies with AstraZeneca/ MedImmune, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Regeneron-Sanofi, Med-in-Cell, Actelion, Merck, Roche, and Chiesi. A. von Bülow reports speaker fees and consultancy fees from AstraZeneca and Novartis, outside the submitted work. She has also attended advisory board for Novartis and AstraZeneca. J. Busby has received research grants from AstraZeneca and personnel fees from NuvoAir, outside the submitted work. G. W. Canonica has received research grants, as well as lecture or advisory board fees, from A. Menarini, Alk-Albello, Allergy Therapeutics, Anallergo, AstraZeneca, MedImmune, Boehringer Ingelheim, Chiesi Farmaceutici, Circassia, Danone, Faes, Genentech, Guidotti Malesci, GlaxoSmithKline, Hal Allergy, Merck, MSD, Mundipharma, Novartis, Orion, Sanofi Aventis, Sanofi, Genzyme/Regeneron, Stallergenes, UCB Pharma, Uriach Pharma, Teva, Thermo Fisher, and Valeas. V. Carter is an employee of Optimum Patient Care (OPC). OPC is a co-funder of the International Severe Asthma Registry. B. G. Cosio declares grants from Chiesi and GlaxoSmithKline; personal fees for advisory board activities from Chiesi, GlaxoSmithKline, Novartis, Sanofi, Teva, and AstraZeneca; and payment for lectures/speaking engagements from Chiesi, Novartis, GlaxoSmithKline, Menarini, and AstraZeneca, outside the submitted work. R. W. Costello has received honoraria for lectures from Aerogen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Teva. He is a member of advisory boards for GlaxoSmithKline and Novartis, has received grant support from GlaxoSmithKline and Aerogen, and has patents in the use of acoustics in the diagnosis of lung disease, assessment of adherence, and prediction of exacerbations. J. A. Fonseca reports grants from research agreements with AstraZeneca, Mundipharma, Sanofi Regeneron, and Novartis, and received personal fees for lectures and attending advisory boards from Astra-Zeneca, GlaxoSmithKline, Mundipharma, Novartis, Sanofi Regeneron, and Teva. P. G. Gibson has received speaker fees and grants to his institution from AstraZeneca, GlaxoSmithKline, and Novartis. L. G. Heaney has received grant funding, participated in advisory boards, and given lectures at meetings supported by Amgen, Astra- Zeneca, Boehringer Ingelheim, Chiesi, Circassia, Hoffmann la Roche, GlaxoSmithKline, Novartis, Theravance, Evelo Biosciences, Sanofi, and Teva; he has received grants from MedImmune, Novartis UK, Roche/Genentech Inc, and GlaxoSmithKline, Amgen, Genentech/Hoffman la Roche, AstraZeneca, MedImmune, GlaxoSmithKline, Aerocrine, and Vitalograph; he has received sponsorship for attending international scientific meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Napp Pharmaceuticals; he has also taken part in asthma clinical trials sponsored by AstraZeneca, Boehringer Ingelheim, Hoffmann la Roche, and GlaxoSmithKline for which his institution received remuneration; he is the Academic Lead for the Medical Research Council Stratified Medicine UK Consortium in Severe Asthma, which involves industrial partnerships with a number of pharmaceutical companies including Amgen, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Hoffmann la Roche, and Janssen. E. Heffler declares personal fees for advisory boards participation and/or speaker activities from Sanofi, Regeneron, GlaxoSmithKline, Novartis, AstraZeneca, Stallergenes-Greer, Circassia, Bosch, Celltrion-Healthcare, Chiesi, and Almirall. M. Hew declares grants and other advisory board fees (made to his institutional employer) from AstraZeneca, GlaxoSmithKline, Novartis, Sanofi, Teva, and Seqirus, for unrelated projects. O. Hilberg declares lecture and advisory board fees from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, TEVA, Chiesi, Novartis, MSD, and Sanofi. F. Hoyte declares honoraria from AstraZeneca and Genentech. She has been an investigator on clinical trials sponsored by GlaxoSmithKline, Genentech, Teva, and Sanofi, for which her institution has received funding. T. Iwanaga received speaker bureau fees from

Kyorin, GlaxoSmithKline, Novartis, Boehringer Ingelheim, AstraZeneca, and Sanofi. D. J. Jackson has received speaker fees and consultancy fees from AstraZeneca, GlaxoSmithKline, Sanofi Regeneron, and Boehringer Ingelheim, and research funding from AstraZeneca. R. C. Jones declares grants from AstraZeneca, GlaxoSmithKline, Novartis, and Teva, and personal fees for consultancy, speaker fees or travel support from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and OPRI. M. S. Koh reports grant support from AstraZeneca and honoraria for lectures and advisory board meetings paid to her hospital (Singapore General Hospital) from GlaxoSmithKline, AstraZeneca, Novartis, Sanofi, and Boehringer Ingelheim, outside the submitted work. P. Kuna reports personal fees from Adamed, AstraZeneca, Berlin Chemie Menarini, FAES, Glenmark, Novartis, Polpharma, Boehringer Ingelheim, Teva, and Zentiva, outside the submitted work. D. Larenas-Linnemann reports personal fees from ALK-Abello, AstraZeneca national and global, Bayer, Chiesi, Grunenthal, Grin, GlaxoSmithKline national and global, Viatris, Menarini, MSD, Novartis, Pfizer, Sanofi, Siegfried, UCB, and Carnot; and grants from Abbvie, Bayer, Lilly, Sanofi, AstraZeneca, Pfizer, Novartis, Circassia, UCB, and GlaxoSmithKline, outside the submitted work. S. Lehmann declares receipt of lecture (personal) and advisory board (to employer) fees from AstraZeneca, Boehringer Ingelheim, and Novartis. He has participated in research with AstraZeneca and GlaxoSmithKline for which his institution has been remunerated. L. Lehtimäki has received personal fees from ALK, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, Novartis, Orion Pharma, and Sanofi. J. Lyu was an employee of OPC. OPC is a co-funder of the International Severe Asthma Registry. J. Maspero reports speaker fees, grants, or advisory boards for AstraZeneca, Sanofi, GlaxoSmithKline, Novartis, Immunotek, Menarini, and Noucor. A. N. Menzies-Gow is an employee of AstraZeneca and may own stock or stock options in AstraZeneca. A. Newell was an employee of OPC at the time this research was conducted. OPC is a co-funder of the International Severe Asthma Registry. N. G. Papadopoulos has been a speaker and/or advisory board member for Abbott, Abbvie, ALK, Asit Biotech, AstraZeneca, Biomay, Boehringer Ingelheim, GlaxoSmithKline, HAL, Faes Farma, Medscape, Menarini, MSD, Novartis, Nutricia, OM Pharma, Regeneron, Sanofi, Takeda, and Viatris. A. I. Papaioannou has received fees and honoraria from Menarini, GlaxoSmithKline, Novartis, Elpen, Boehringer Ingelheim, AstraZeneca, and Chiesi. L. Perez-de-Llano reports grants, personal fees, and non-financial support from AstraZeneca; personal fees and non-financial support from GlaxoSmithKline; grants, personal fees, and non-financial support from Teva; personal fees and non-financial support from Chiesi; grants, personal fees, and non-financial support from Sanofi; personal fees from MSD; personal fees from Techdow Pharma; grants, personal fees, and non-financial support from Faes Farma; personal fees from Leo-Pharma; grants and personal fees from Gebro; and personal fees from Gilead, outside the submitted work. D. Perng (Steve) received sponsorship to attend or speak at international meetings, honoraria for lecturing or attending advisory boards, and research grants from the following companies: AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Daiichi Sankyo, Shionogi, and Orient Pharma. M. J. Peters declares personal fees and nonfinancial support from AstraZeneca, GlaxoSmithKline, and Sanofi. P. E. Pfeffer has attended advisory boards for AstraZeneca, GlaxoSmithKline, and Sanofi; has given lectures at meetings supported by AstraZeneca and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi, for which his institution received remuneration; and has a current research grant funded by GlaxoSmithKline. C. M. Porsbjerg has attended advisory boards for AstraZeneca, Novartis, TEVA, and Sanofi-Genzyme; has given lectures at meetings supported by AstraZeneca, Novartis, TEVA, Sanofi-Genzyme, and GlaxoSmithKline; has taken part in clinical trials sponsored by AstraZeneca, Novartis, MSD, Sanofi-Genzyme, GlaxoSmithKline, and Novartis; and has received educational and research

grants from AstraZeneca, Novartis, TEVA, GlaxoSmithKline, ALK, and Sanofi- Genzyme. T. A. Popov declares relevant research support from Novartis and Chiesi Pharma. C. K. Rhee received consulting/lecture fees from MSD, AstraZeneca, GlaxoSmithKline, Novartis, Takeda, Mundipharma, Boehringer Ingelheim, Teva, Sanofi, and Bayer. S. Salvi declares research support and speaker fees from Cipla, Glenmark, and GlaxoSmithKline. C. Taillé has received lecture or advisory board fees and grants to her institution from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi and Novartis, for unrelated projects. C. A. Torres-Duque has received fees as an advisory board participant and/or speaker from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sanofi-Aventis; has taken part in clinical trials from AstraZeneca, Novartis, and Sanofi-Aventis; has received unrestricted grants for investigator initiated studies at Fundacion Neumologica Colombiana from AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Grifols, and Novartis. C. S. Ulrik reports personal fees for talks, participation in advisory boards, etc from AstraZeneca, GlaxoSmithKline, Teva, Boehringer Ingelheim, Orion Pharma, Sanofi Genzyme, TFF Pharmaceuticals, Covis Pharma, Berlin-Chemie, Takeda, Chiesi, and Pfizer, outside the submitted work. S.W. Ra has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Novartis. E. Wang has received honoraria from AstraZeneca, GlaxoSmithKline, and Genentech. She has been an investigator on studies sponsored by AstraZeneca, GlaxoSmithKline, Genentech, Sanofi, Novartis, and Teva, for which her institution has received funding. M. E. Wechsler reports grants and/or personal fees from Novartis, Sanofi, Regeneron, Genentech, Sentien, Restorbio, Equillium, Genzyme, Cohero Health, Teva, Boehringer Ingelheim, Astra- Zeneca, Amgen, GlaxoSmithKline, Cytoreason, Cerecor, Sound Biologics, Incyte, and Kinaset. D. B. Price has advisory board membership with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatrix, Teva Pharmaceuticals; consultancy agreements with AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Viatrix, and Teva Pharmaceuticals; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute Pte Ltd) from AstraZeneca, Chiesi, Viatrix, Novartis, Regeneron Pharmaceuticals, Sanofi Genzyme, and UK National Health Service; payment for lectures/ speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Commune Digital, GlaxoSmithKline, Medscape, Viatrix, Novartis, Regeneron Pharmaceuticals and Sanofi Genzyme, and Teva Pharmaceuticals; payment for travel/accommodation/ meeting expenses from AstraZeneca, Boehringer Ingelheim, Novartis, Medscape, and Teva Pharmaceuticals; stock/stock options from AKL Research and Development Ltd, which produces phytopharmaceuticals; owns 74% of the social enterprise Optimum Patient Care Ltd (Australia and UK) and 92.61% of Observational and Pragmatic Research Institute Pte Ltd (Singapore); 5% shareholding in Timestamp, which develops adherence monitoring technology; is peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation Programme, and Health Technology Assessment Programme and was an expert witness for GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.

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