Real-World Biologics Response and Super-Response in the International Severe Asthma Registry cohort (LUMINANT)

Observational & Pragmatic Research Institute

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Eve Denton, Mark Hew, Matthew J. Peters, John W. Upham, Lakmini Bulathsinhala, Trung N. Tran, Neil Martin, Celine Bergeron, Mona Al-Ahmad, Alan Altraja, Désirée Larenas-Linnemann, Ruth Murray, Carlos Andrés Celis-Preciado, Riyad Al-Lehebi, Manon Belhassen, Mohit Bhutani, Sinthia Z. Bosnic-Anticevich, Arnaud Bourdin, Guy G. Brusselle, John Busby, Giorgio Walter Canonica, Enrico Heffler, Kenneth R. Chapman, Jérémy Charriot, George C. Christoff, Chung, Li Ping, Borja G. Cosio, Andréanne Côté, Richard W. Costello, Breda Cushen, James Fingleton, João A. Fonseca, Peter G. Gibson, Liam G. Heaney, Erick Wan-Chun Huang, Takashi Iwanaga, David J. Jackson, Mariko Siyue Koh, Lauri Lehtimäki, MD, Jorge Máspero, Bassam Mahboub, Andrew N. Menzies-Gow, Patrick D. Mitchell, Nikolaos G. Papadopoulos, Andriana I. Papaioannou, Luis Perez-de-Llano, Diahn-Warng Perng (Steve), Paul E. Pfeffer, Todor A. Popov, Celeste M. Porsbjerg, Chin Kook Rhee, Nicolas Roche, Mohsen Sadatsafavi, Sundeep Salvi, Johannes Martin Schmid, Chau-Chyun Sheu, Concetta Sirena, Carlos A. Torres-Duque, Laila Salameh, Pujan H. Patel, Charlotte Suppli Ulrik, Eileen Wang, Michael E. Wechsler, and David B. Price, on behalf of the ISAR LUMINANT Working Group.

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Methods

- **Objective**
  - Describe responsiveness to biologic asthma therapies in real-world patients with severe asthma
- **Study population**
  - Data from the International Severe Asthma Registry (www.isar.opcglobal.org)
  - Includes electronic medical records from 20,000 patients in 28 countries
- **Inclusion criteria**
  - Uncontrolled asthma on GINA Step 4 treatment or on GINA Step 5 treatment (ISAR inclusion criteria)
  - Age ≥18 years
  - ≥24 weeks of follow-up
- **Study groups**
  - Patients prescribed biologic medication after their baseline visit
  - Patients with baseline impairment in predefined outcome domains but who did not initiate biologics
- **Outcome domains**
  - Forced expiratory volume in 1 second (FEV_1)
  - Improved asthma control (controlled, partial, uncontrolled)
  - Annualized exacerbation rate reduction
  - Long-term OCS dose reduction.

ISAR, International Severe Asthma Regstry; GINA, Global Initiative for Asthma; OCS oral corticosteroids.

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Sub-analyses

- **Bronchodilator reversibility in biologics initiators**
  - Defined as ≥12% and ≥200 mL FEV_1 improvement following short-acting bronchodilator administration
- **Type 2 inflammation gradient in the total cohort**
  - Defined by criteria modified by *Heaney et al:*[1] Type 2 phenotypes classified as Grade 3 (most likely eosinophilic), Grade 2 (likely eosinophilic), Grade 1 (least likely eosinophilic), and Grade 0 (non-eosinophilic)
- **Eligibility for randomized controlled trials**
  - Defined as severe asthma and all three of: bronchodilator reversibility on high dose ICS and a second controller; FEV_1 <80% predicted; and smoking history of <10 pack years

FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids.

1. Heaney L, et al. *Chest*. 2021;160:814-830. doi: 10.1016/j.chest.2021.04.013

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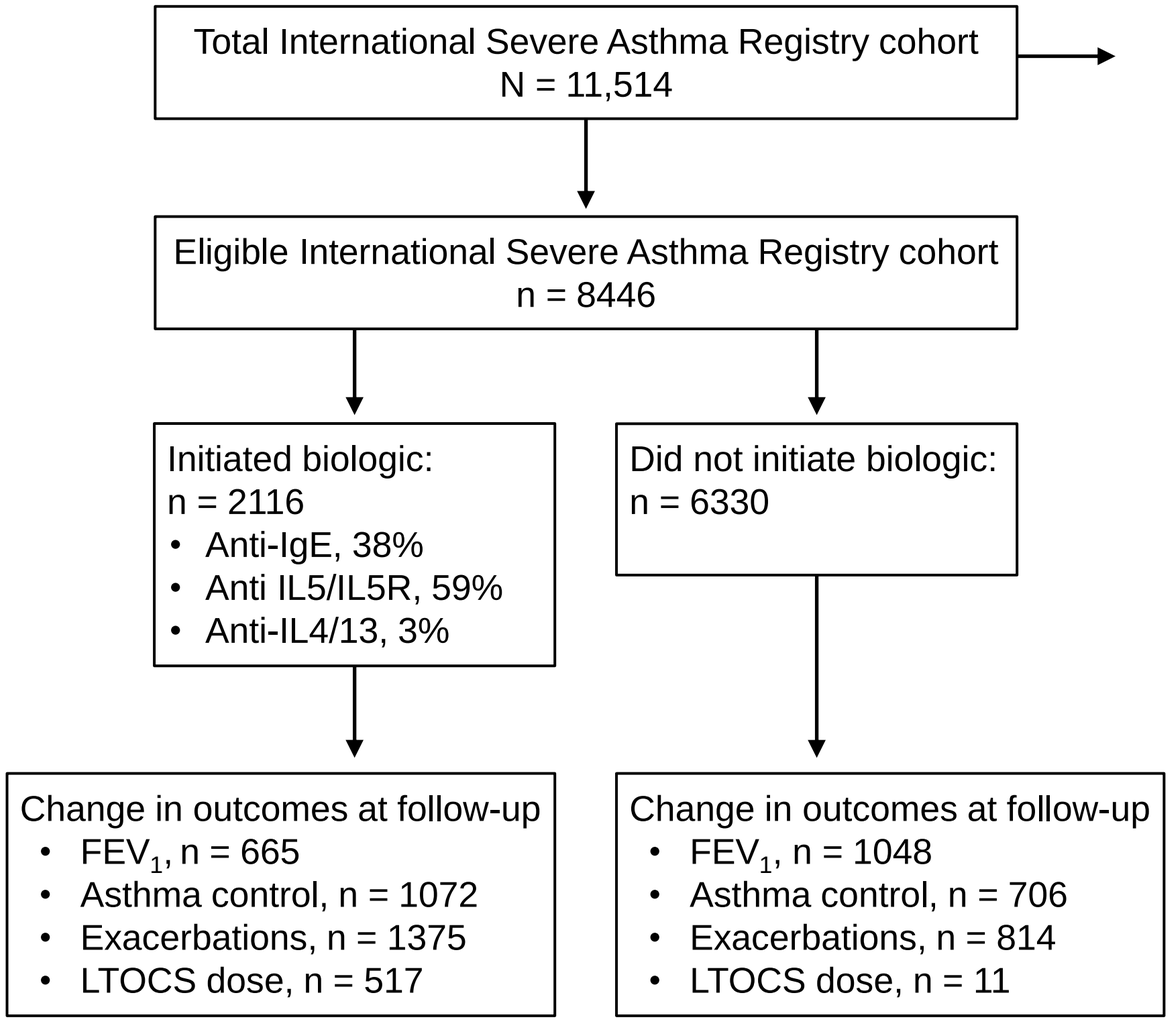
LUMINANT study population flow



Excluded:
- Ceased biologic <24 weeks, n = 118
- On biologic at baseline visit, n = 2767
- Inadequate follow-up data, n = 183

IgE, immunoglobulin E; IL5, interleukin 5; IL5R, IL5 receptor; IL 4/13 interleukin 4/13; FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

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Response domains and criteria

Single-domain definitions of response and super-response in patients with severe asthma between baseline and 12-month visit

Outcome domain	Definition of responders	Definition of super-responders	Excluded from analysis if[a]:
Asthma exacerbations	≥50% reduction in annualized exacerbation rate	Exacerbation elimination	No exacerbations at baseline
FEV_1	≥100 mL improvement in post-bronchodilator FEV_1	≥500 mL improvement in post-bronchodilator FEV_1	Not applicable
Asthma control	Improved asthma control by category (controlled, partial, uncontrolled)	New achievement of well-controlled asthma	Well-controlled asthma at baseline
LTOCS burden	Any reduction in LTOCS dose (mg)	Cessation of LTOCS or tapering to ≤5 mg/day	Not on LTOCS at baseline

FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

[a]Patients who had incomplete data (ie, no follow-up data related to the outcome domain of interest) or no capacity to respond in a particular domain, eg, who had no exacerbations at baseline, had well-controlled asthma, or were not on LTOCS, were excluded from the analysis relating to that particular domain; however, they remained in analyses related to other domains.

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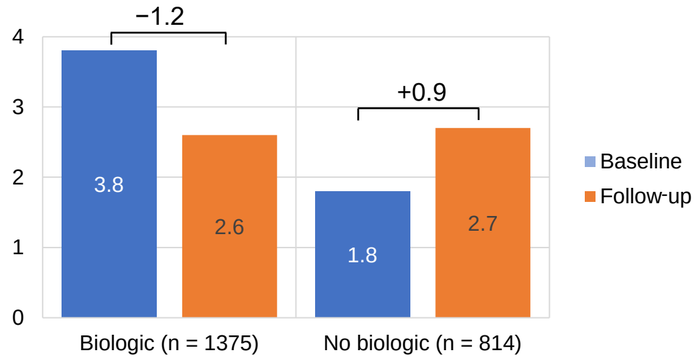
Changes from baseline in single outcome domains

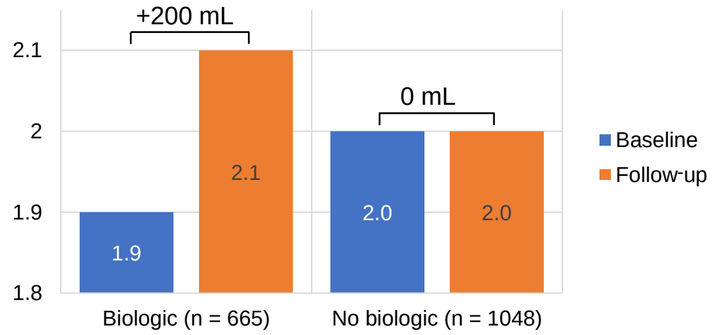
- Biologic initiators had greater improvements from baseline than non-initiators[a,b]

[a]The increase in annual exacerbations among non-biologic users was largely seen in EMR data, where there the 'baseline' may potentially be misclassified, as a patient's first visits in EMR may not fully capture exacerbations; this would lead to an apparent increase in the first year of follow-up.

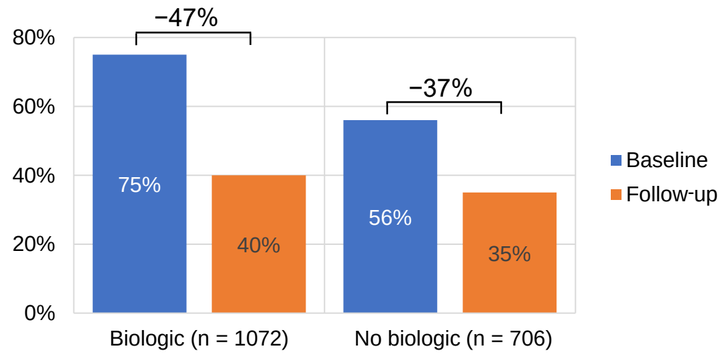
Annualized exacerbations



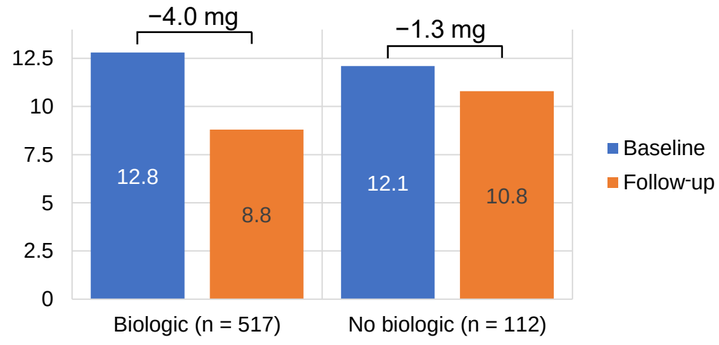
FEV_1 (liters)



Proportion with poor asthma control



Oral corticosteroid dose (mg)



FEV_1, forced expiratory volume in 1 second.

[b]Baseline differences between biologic initators and non-initiators were not adjusted for by matching or multivariable adjustment methods.

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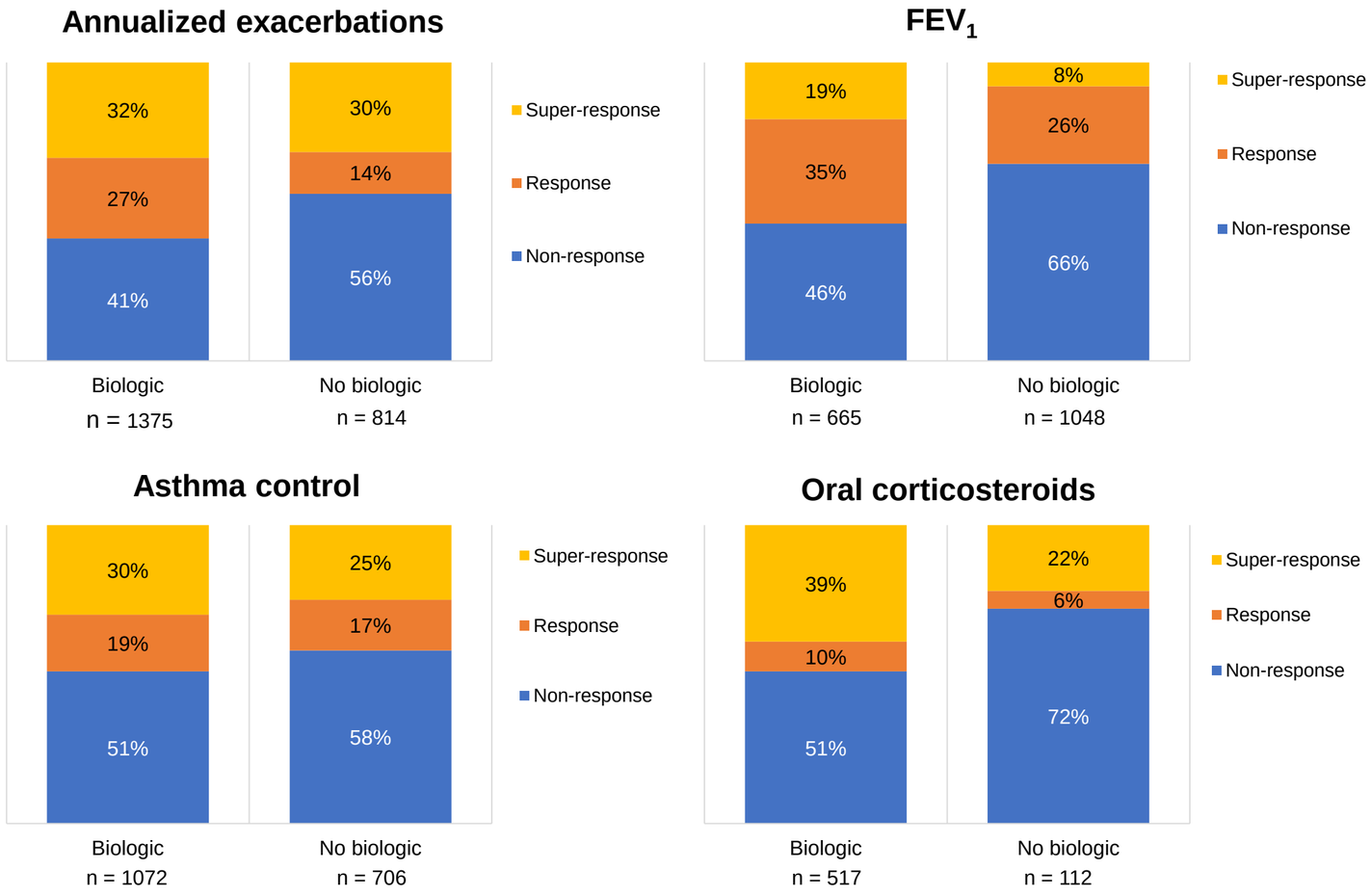
Responses to biologic or non-biologic asthma treatments

- More frequent responses/super-responses in biologic initiators than in non-initiators[a]



- Biologic initiators had more frequent super-responses than responses (except FEV_1)
- **However, 40-50% of biologic initiators did not meet response criteria**

FEV_1, forced expiratory volume in 1 second.

[b]Baseline differences between biologic initators and non-initiators were not adjusted for by matching or multivariable adjustment methods.

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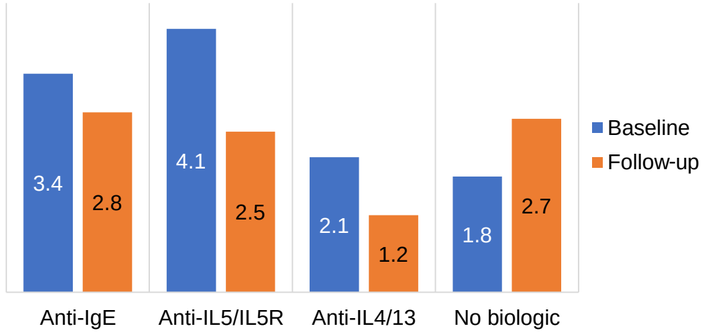
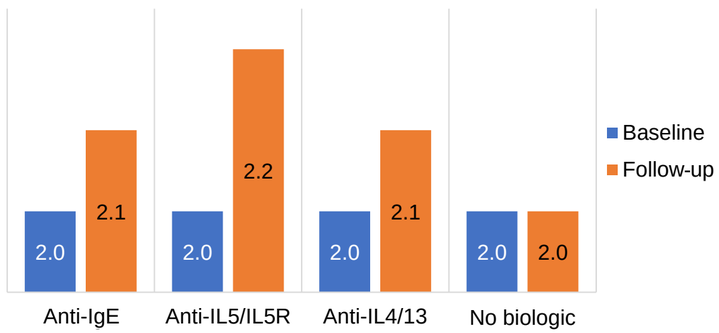
Changes from baseline (unadjusted) by biologic class

- Biologic treatments were associated with asthma improvement in all domains assessed

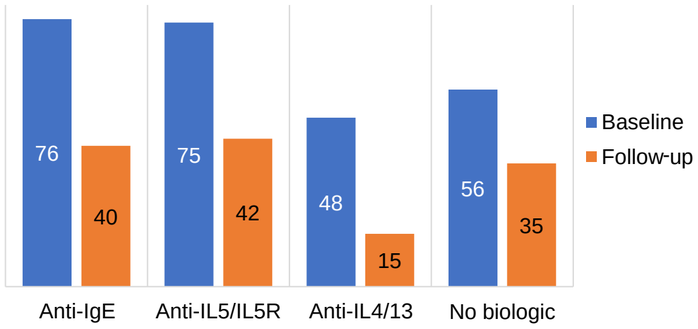
Annualized exacerbations



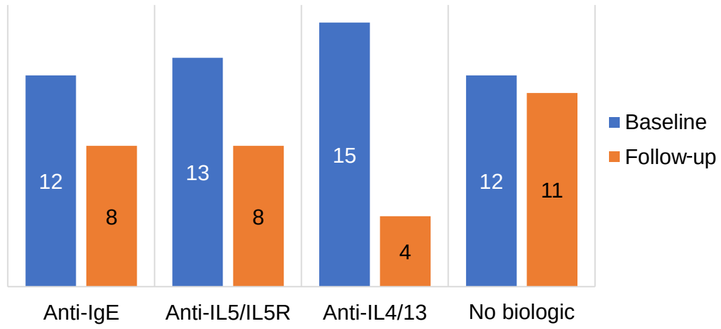
FEV$_1$ (liters)



Poor asthma control (%)



Long-term OCS dose (mg)



FEV$_1$, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL, interleukin; IL-5R, IL5 receptor; OCS, oral corticosteroids.

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Treatment responsiveness by biologic class

- Anti-IL5/IL5R initiators had greater improvement in AER than anti-IgE initiators despite worse baseline impairment

Proportions of responders and super-responders in single outcome domains, by biologic class

	Anti-IgE n = 809	Anti-IL5/IL5R n = 1244	Anti-IL4/13[a] n = 63	P-value
Response				
AER reduced ≥50%, % (number)	52% (253/489)†	62% (542/874)†	69% (18/26)	<0.001
FEV_1 pre improved ≥100 mL, % (number)	49% (144/292)	58% (212/369)	67% (10/15)	<0.001
Asthma control improved, % (number)	49% (215/437)	48% (293/616)	75% (18/24)	0.001
LTOCS dose reduced, % (number)	40% (37/92)	52% (125/240)	50% (2/4)	<0.001
Super-response				
Exacerbation elimination, % (number)	22% (134/618)†	31% (303/987)†	32% (10/31)	<0.001
FEV_1 pre improved ≥500 mL, % (number)	15% (44/292)	22% (80/369)	27% (4/15)	<0.001
New well-controlled asthma, % (number)	27% (116/437)†	31% (188/616)‡	58% (14/24)†‡	<0.001
LTOCS ceased or tapered to <5 mg/day, % (number)	34% (31/92)	43% (103/240)	25% (1/4)	<0.001

AER, annualized exacerbation rate; IgE, immunoglobulin E; IL, interleukin; IL5R, IL5 receptor; IL 4/13, interleukin 4/13; FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

†, ‡ denote columns with significant difference on post-hoc testing ($p < 0.05$).

[a]Note small numbers of patients on anti-IL4/13 therapy limit interpretation of data from this group.

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Treatment responsiveness by biologic class

- Anti-IL4/13 initiators had the highest proportions of responders in all outcome domains
  - 75% achieved improved asthma control and 58% new well-controlled asthma

Proportions of responders and super-responders in single outcome domains, by biologic class

	Anti-IgE n = 809	Anti-IL5/IL5R n = 1244	Anti-IL4/13[a] n = 63	P-value
Response				
AER reduced ≥50%, % (number)	52% (253/489)†	62% (542/874)†	69% (18/26)	<0.001
FEV_1 pre improved ≥100 mL, % (number)	49% (144/292)	58% (212/369)	67% (10/15)	<0.001
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AER, annualized exacerbation rate; IgE, immunoglobulin E; IL, interleukin; IL5R, IL5 receptor; IL 4/13, interleukin 4/13; FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

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[a]Note small numbers of patients on anti-IL4/13 therapy limit interpretation of data from this group.

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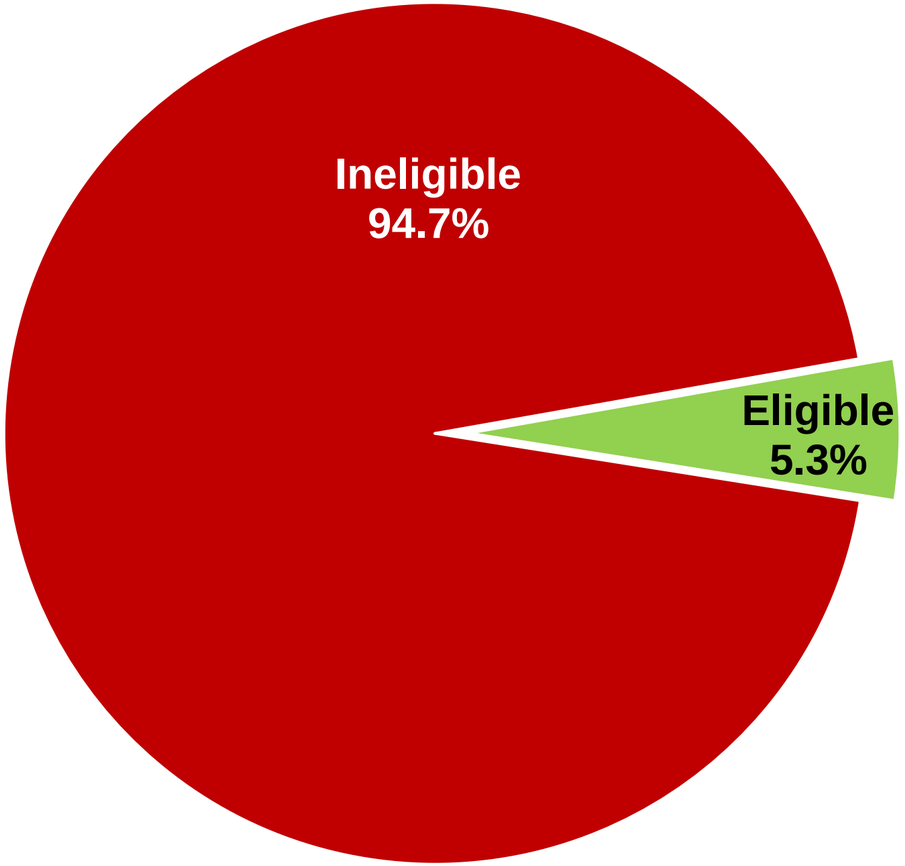
Eligibility for randomized controlled trials

- 5.3% (211) among 4001 subjects with enough data to determine potential RCT eligibility, fulfilled all criteria[a] at baseline



RCT, randomized controlled trial; FEV_1, forced expiratory volume in 1 second.

[a]FEV_1 reversibility on high-dose inhaled corticosteroid; FEV1 <80%; smoking history of <10 pack years).

Denton E, et al. *Allergy.* 2024. doi: 10.1111/all.16178

Bronchodilator FEV_1 reversibility

- FEV_1 response was more likely in biologics initiators with FEV_1 reversibility at baseline than in those without reversibility

Table S3. Responses in single outcome domains in patients who initiated a biologic, by FEV_1 reversibility

	FEV_1 reversibility		
Response domain	**Present**	**Absent**	**P-value**
Annualized exacerbations reduced by ≥50%, % (number)	57 (69/138)	61 (366/599)	0.36
FEV_1 improved ≥100 mL, % (number)	72 (68/94)	52 (223/427)	<0.001
Asthma control improved, % number)	48 (47/99)	45 (208/463)	0.66
LTOCS dose reduced, % (number)	14 (2/14)	43 (46/107)	0.08

Abbreviations: FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids.

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Type 2 inflammation gradient

- Most patients (85%) were T2 gradient Grade 3
  - Patients with T2 grade 3 more frequently had a longitudinal exacerbation improvement

Table S4. Responses in single outcome domains in the LUMINANT cohort, by T2 inflammation gradient grade

	T2 inflammation gradient grade[a]				
Response domain	**0** (n = 84)	**1** (n = 195)	**2** (n = 76)	**3** (n = 2050)	**P-value**
AER reduced by ≥50%	26%	33%	44%	58%	<0.001
Exacerbation elimination	10%	12%	15%	25%	<0.001
FEV_1 improved by ≥100 mL	43%	44%	37%	53%	NS
LTOCS dose reduced	33%	33%	29%	49%	NS

Abbreviations: AER, annualized exacerbation rate; FEV_1, forced expiratory volume in 1 second; LTOCS, long-term oral corticosteroids; NS, not significant.

[a]Phenotypes classified as grade 3 (most likely eosinophilic), grade 2 (likely eosinophilic), grade 1 (least likely eosinophilic), and grade 0 (non-eosinophilic), according to Heaney, et al. Eosinophilic and Noneosinophilic Asthma: An Expert Consensus Framework to Characterize Phenotypes in a Global Real-Life Severe Asthma Cohort. Chest. 2021;160:814-830. doi: 10.1016/j.chest.2021.04.013

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Key insights from LUMINANT

- Only 5.3% of ISAR patients met usual RCT inclusion criteria[a]
- Biologic initiators had worse baseline impairment than non-initiators, despite similar biomarker levels
- Responses/super-responses were more frequent in biologic initiators than in non-initiators
- 40–50% of biologic initiators did not meet response criteria
- Patients initiating anti-IL5/IL5R agents had significantly greater improvement in AER than those initiating an anti-IgE agent despite worse baseline impairment

ISAR, International Severe Asthma Registry; RCT, randomized controlled trial; IgE, immunoglobulin E; IL, interleukin; IL5R, IL5 receptor, AER, annualized exacerbation rate.

[a]Severe asthma and all 3 of: bronchodilator reversibility on high-dose ICS and a second controller, FEV_1 <80% predicted, and smoking history of <10 pack years.

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